PRINCIPLES AND PRACTICE OF

Obstetrics and Gynecology
for Postgraduates

Federation of Obstetric and Gynaecological Societies of India
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As far as possible we have tried to incorporate the Vancouver system of references. However, since we are in transitional phase in some articles, we could not incorporate the same.

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PRINCIPLES AND PRACTICE OF Obstetrics and Gynecology for Postgraduates

Fourth Edition

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Our teachers
for teaching us the Art and Science of Obstetrics and Gynecology and
for their major contribution in making us what we are today

Our patients
for their unstained faith in us, which has helped us to develop
our vast clinical experience and self-confidence

Our students
who continue to stimulate us to be researchers, teachers as well as students

Our families
for their support and for tolerating our repeated stints at various works and
for sharing their personal family time and of course
for supporting us and for always encouraging us

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for giving us an opportunity to express ourself and to serve Science and Humanity
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The popularity of *Principles and Practice of Obstetrics and Gynecology for Postgraduates* has made us come out with the fourth edition.

In the rapidly advancing field of Obstetrics and Gynecology, new techniques, new treatments and modifications are happening rapidly.

A postgraduate student has to read many references, journals, Internet updates to keep abreast with all the rapid changes. This comprehensive multicontributor book, compiled by the members and the examiners of our own Federation of Obstetric and Gynaecological Societies of India (FOGSI), and updated by newly passed postgraduates and young lecturers, provides an in-depth, researched write-up on all the issues of obstetrics and gynecology.

The contributors have thoroughly researched and prepared the chapters along with clinical experiences and situations and cases peculiar to our country.

We are confident that this FOGSI textbook will be the main textbook for postgraduates in the field of obstetrics and gynecology. Not applicable only to students, we feel the textbook will be a referral guide for the busy practitioners also.

With due humility, we present the fourth updated edition of the *Principles and Practice of Obstetrics and Gynecology for Postgraduates*.

Narendra Malhotra
PK Shah
Hema Divakar
Saroj Singh
Jaideep Malhotra
The field of Obstetrics, Gynecology and Family Welfare is a dynamic one. The truisms of yesterday are the questions of today and hopefully, the truths of tomorrow.

In this age of rapidly growing information and technology, there have been many noteworthy advances in the recent years which have had a major impact on the practice of Obstetrics and Gynecology changing social and cultural environment has brought with it different needs and expectations of the society from our specialty.

New technologies for diagnosis, treatment and prevention of disorders of the fetus have burgeoned in modern obstetrics, which has grown from the concept of merely assisting childbirth into a highly specialized field. The fetus as a patient has now become a reality for the obstetricians. Principles and Practice of Obstetrics and Gynecology for Postgraduates is the product of our attempt to advance these objectives.

This book has been written keeping in view the latest concept in the understanding of various obstetrics and gynecological conditions as well as their management, without omitting the basic principles and their applied pathophysiology. The text covers extensively topics relevant to the Indian context, like malaria, jaundice and other infections in pregnancy, which are rampant in the developing countries. Management of obstructed labor and the art instrumental delivery is still pertinent in our set-up. These are dealt with by the masters of these old and dying skills.

The reader is also apprised of the state-of-the-art technology in modern obstetrics and gynecology involving transvaginal ultrasonography, color Doppler, fetal surveillance and intrauterine interventions. The concept of auditing maternal morbidity and mortality has also been introduced to lay a firm foundation of clinical research and promote a logical approach instead of blindly following the traditional and irrational practices.

The authors have done a meticulous survey of the current literature and have amalgamated it with their rich experience to make the text a pleasurable reading. It has been our endeavor to see that the content of the book is both current and comprehensive; and this volume serves as a basic textbook for the postgraduates and as a handy reference for the practitioners.

In order to be a teacher, one must always be a student. Compiling and editing the book has been a personal learning experience.

Kamal Buckshee
Vasant B Patwardhan
Rustom P Soonawala
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Prepregnancy Care
INTRODUCTION
The health care offered before conception in order to optimize the outcome of a given pregnancy constitutes the preconception care. It is the preventive care for women of reproductive age and their partners, including assessment by history and physical examination, counseling, education and intervention. Achieving good health before conception helps women to have healthier pregnancies with fewer complications. The continuity of care and the close physician-patient relationship in primary care offers an opportunity for the physician to assess risk factors and to intervene and modify behaviors that increase pregnancy risk. Education of males is also important since they often influence health risks and behaviors in the female. Preconception care must begin at least 3 months before planning a pregnancy.

EARLY TRENDS
Until 1941, the placental barrier was believed to protect the developing fetus from adverse exposure to environmental hazards. Studies of birth defects caused by rubella infection during pregnancy disproved this theory. Further progress toward protecting neonatal outcomes has included education and close management of insulin dependent diabetic women before and during pregnancy. This was later extended to various high-risk factors existing before pregnancy. The concept was then offered even to normal women as a primary preventive measure because it was realized that a woman’s health prior to pregnancy is important for successful pregnancy outcome.

PRECONCEPTION VISIT
A preconception visit should include:
1. History including medical history, family’s medical background, questions about diet and social habits, such as whether she drinks or smokes, past pregnancies, birth control use, medication and immunizations.
2. General physical examination including height, weight, blood pressure, thyroid, dentition, heart, breasts and signs of asymptomatic underlying disease.
3. Pelvic examination:
   - Infection identification: (1) signs of condylomata or herpes (2) vaginal discharge evaluated for Candida, Trichomonas, and bacterial vaginosis, cervical discharge culture for gonococci and Chlamydia
   - Cervical anomalies
   - Pap smear
   - Bimanual examination to rule out uterine and adnexal abnormalities
   - Ultrasound assessment in case of any clinical suspicion.
4. Laboratory evaluation: Complete blood count (CBC), blood group, Rh type. Infection profile [venereal disease research laboratory (VDRL), rubella, human immunodeficiency virus (HIV) and hepatitis B surface antigen], blood sugar, urine analysis and in indicated cases hemoglobin electrophoresis and cytomegalovirus (CMV) antibody titers.
Counseling Implications

Medical Disorders

Diabetes mellitus, epilepsy and hypertension are amongst diseases where it is worthwhile to bring the disease under optimal control before getting pregnant. In diabetes to prevent early pregnancy loss and congenital malformations, maternal nutrition 90–120 days prior to conception is believed to be as critical, if not more, as the early pregnancy nutrition. Maternal nutrition during Second World War revealed the vital need for good preconception nutrition to ensure healthy newborns.

A balanced, nutritious diet is advisable before conception and throughout pregnancy. Studies of the Dutch famine during Second World War revealed the vital need for good preconception nutrition to ensure healthy newborns. Maternal nutrition 90–120 days prior to conception is believed to be as critical, if not more, as the early pregnancy nutrition.7

Age-related Factors

Pregnancy in an adolescent girl encompasses problems in education, medical and social risks. Pregnancy in elderly encompasses another set of problems. Older women are more likely to have health problems, which could adversely affect pregnancy. In addition, previous gynecologic conditions or abdominal surgery may affect the mother’s ease in carrying or delivering the baby. For couples in their 30s and 40s considering parenthood, a common concern is the risk of having a baby with a genetic defect. The risk of chromosomal anomalies increases from 1 in 1,300 at 24 years to 1 in 100 at 40 years. The patient needs to be counseled regarding the need for invasive diagnostic procedures when pregnancy establishes.

Nutrition and Weight Gain

A balanced, nutritious diet is advisable before conception and throughout pregnancy. Studies of the Dutch famine during Second World War revealed the vital need for good preconception nutrition to ensure healthy newborns. Maternal nutrition 90–120 days prior to conception is believed to be as critical, if not more, as the early pregnancy nutrition.7

Special attention is required regarding intake of calcium and vitamins, and must include a folate supplement. Folate has been shown to reduce the rate of neural tube defects arising in the first few weeks of pregnancy often before a woman realizes she is pregnant.8 Similarly, pantothenate may help in decreasing the incidence of cardiac anomalies.

Young women in the current times are depriving themselves of sound nutritional habits to meet social images of feminine beauty. Primary care attempts to address this problem through education and counseling. However, poor nutrition due to poverty may be the single greatest risk factor for many future mothers. The role of client advocacy clearly comes into focus when the connection between poverty and at risk pregnancy or neonatal outcomes is made.

A woman should attempt to reach her ideal body weight (IBW) before conceiving. Women who weigh less than 90% IBW have increased risk for preterm or low birth weight infants.

Women who weigh more than 120% IBW have increased risk for gestational diabetes or hypertension. Reducing obesity before pregnancy increases the chances of having a healthy pregnancy.9

Eating disorders may cause nutrient deficiencies that should be corrected before pregnancy. The woman must also be informed that vitamin excesses, especially fat-soluble vitamins, may be toxic and possibly teratogenic.

Lifestyle Behaviors

Counseling regarding a woman’s social habits, such as tobacco and alcohol use, is another crucial part of a preconception visit. Discontinuing behaviors, which can be harmful to the developing fetus, including quitting smoking at least 3 months prior to conception is important. Smoking has been shown to influence fertility, cause miscarriage, low birth weight, preterm delivery and is considered a risk factor for sudden infant death syndrome.

Birth defects and growth retardation are known risk factors with alcohol consumption. Drinking alcohol beverages can cause fetal alcohol syndrome, a pattern of birth defects that includes mental retardation, cardiovascular, skeletal and facial abnormalities.10 Lower birth weight has been associated with fathers who drank prior to conception and passive smoking is also harmful to the fetus. Hence, the father to be has to be involved in these lifestyle changes. Intake of caffeine containing beverages must also be reduced, as it may delay conception and increase risk of abortion.11 A discussion regarding illicit, prescription and over-the-counter drug use and understanding the harm is also important.8

Environmental Challenges

Studies of occupational hazards and their effects currently support a much larger environmental risk of birth defects. Hazard protection for the worker often fails to include the
fetus.9 An example of this is the noise protection devices for workers exposed to high levels of noise. Testing of children exposed in utero revealed a threefold increase in development of a high frequency hearing loss greater than 4,000 decibels. The protective device the pregnant woman wears over her ears does not provide any protection for her developing fetus.

Another deficit is the safe levels of chemicals. Heavy metals like lead, copper and mercury, carbon disulfide, acids, and anesthetic gases can affect the developing embryo. With over 50,000 chemicals in the market, including household chemicals and insecticides, there are less than 100 animal studies to determine the effect of chemicals on human development. An adult’s safe level of chemical exposure is believed to be five to ten times higher than fetal tolerances. Fetal vulnerability is due to a high rate of cell division and differentiation, a small relative size, a lack of enzymes to metabolize drugs, and a less efficient excretory system.12

Protection from radiation (X-rays and effect of electromagnetic radiation), including exposure to it by living near high tensions wires and by use of microwave ovens and video display terminals, needs to be discussed. Knowledge of the dangers of physical stresses and strains to pregnancy are also important. Modern amusement park rides can generate high negative G-forces, which cause shearing affects known to cause placental abruptions. The early pregnancy is largely protein embryonic cells. Proteins undergo great changes at increased temperature. Hence, tub bath and infrared heat exposure may be harmful.

Infections
Rubella infection can cause serious birth defects if contracted during pregnancy. If the patient is not immune to rubella due to a prior episode, she can be vaccinated before pregnancy, but pregnancy should be delayed for 3 months after vaccination.9 Toxoplasmosis can seriously affect the fetus. Serological testing to identify immunity is worthwhile in high prevalence areas. A pregnant woman can help to avoid contracting toxoplasmosis by not eating undercooked meat or handling cat litter before she becomes pregnant and during pregnancy. All women must be preferably screened for hepatitis B. Uninfected women, especially those at high risk (such as health care workers who handle blood), can get protection from this infectious disease by vaccination. Local infections must be identified and treated before pregnancy is planned. For example, treatment of condylomata acuminata by podophyllin is contraindicated during pregnancy and hence treatment has to be completed before pregnancy. It is particularly important to screen for and treat bacterial vaginosis since it is associated with an increased risk of premature rupture of membranes, preterm birth, and histologic choriomeningitis. Counseling of HIV-positive couples regarding pregnancy outcome, antiretroviral drugs, breastfeeding and long-term implications is extremely important.

Contraception Usage
Few couples are aware that birth control pills should be discontinued several months in advance of pregnancy to allow at least two regular menstrual cycles to occur before conception. Women who take oral contraceptive agents may gain excessive weight and have an increase in serum cholesterol. An intrauterine device should also be removed a few months prior to pregnancy. Limitations and failure rates of various contraceptive methods must be discussed with the couple.

Drug Usage
Medication use by adult population is extremely common.13 A review of data14 regarding 15,2531 women who delivered between 1996 and 2000 revealed that in 64% of women, a drug other than a vitamin or mineral supplement was dispensed in the 270 days period before delivery. This included category C drugs dispensed to 37.8% and category D drugs dispensed to 4.8% of women. Moreover, drugs which are absolutely contraindicated in women who are pregnant (category X) were given to 4.6% of study population. A planned pregnancy helps in averting problems due to drug usage.

Fertility Treatment
High rate of multifetal gestation in treatments incorporating exogenous gonadotropins and other associated complications and failouts must be discussed.

Genetic Screening
Most couples do not require specific genetic screening before pregnancy. Information about background rate of birth defects needs to be given. However, some couples are at increased risk for genetic problems like thalassemia or Tay Sach’s disease, because of a family history of inherited disease or because of their ethnicity or geographic background. Consanguinity, individuals with abnormal genetic test result and recurrent miscarriage also require genetic counseling. Prepregnancy counseling is quite important in educating couples and helping them make educated decisions about their risk for birth defects or genetic disorders.12

Advantages of Prenatal Care
• Identifying the optimal time to try to conceive.
• Explanation of appropriate testing and procedure options including risks, benefits and limitations.
• The importance of getting adequate folic acid, iron and other nutrients both while trying to conceive and in early pregnancy.
• The dangers of smoking, alcohol and drug use.
• A discussion of the patient’s medical problems and/or those of her partner and its management by team approach.
• Accurate family and genetic history and identification of risk factors may reduce the incidence of birth defects.
Prepregnancy Care

• Updating woman’s immunization status.
• A review of safe activities during pregnancy (e.g. moderate exercise, sex, travel) as well as unsafe ones (e.g. contact sports and first trimester travel).
• Individual participation in health care. The woman can maintain control over her life during the process of conception and pregnancy. Protective environment at work and short-term transfer from job-deemed harmful to pregnancy may be planned.
• Pregnancy planning allows women to optimize their reproductive future. The proportion of infants born with a health disadvantage is significantly lower if the pregnancy was intended than if it was mistimed or not wanted.
• Patient support—facilitation of informed decision-making is available. Assistance in coping with psychosocial issues, education and coordinated patient care is possible.
• Early and complete antenatal care becomes a reality because of the continuum of the care process.

Changing Dynamics of Responsibility

Realistically, although parents want a perfect baby, the physician cannot fulfill this goal every time. Preconception care shifts this responsibility back to the parents. Better reproductive outcomes may be achieved with increased education and intervention on many levels. Average first prenatal visit occurs 10 weeks after conception when most of fetal organogenesis has already been accomplished, greatly reducing chance for outcome intervention. Preconceptual counseling can help to increase the odds for a healthy pregnancy and healthy baby. Preconception planning and a risk screening profile at the initiation of care helps the physician to define the client base by risk level and also the ability to pay for medical care.

Current Status

Many studies\(^8,12\) have found that performance is poor in providing preconception counseling. Deficiencies are noted in providing a healthy woman with information on rubella immunization and family planning or counseling on sexually transmitted diseases and safer sex. This warrants correction. The four components necessary for the successful practice of preventive health care including preconception care, that is, attitude, organization, appropriate knowledge and management skills, needs to be emphasized during the training of the residents in the field of gynecology.

CONCLUSION

Preconception care consists of three main components: (1) risk assessment, (2) health promotion and (3) intervention. Preconception care and early pregnancy care are excellent opportunities to modify the medical, social and behavioral risks on pregnancy outcomes and should be an integral part of primary care practice. Because over 50% of all pregnancies are unplanned, it is imperative that all gynecologists think of themselves as preconception health providers. The benefits are not likely to be fully realized unless primary care physicians include preconception care as a routine intervention for all women of reproductive age in their practice. The need for such care is greater in hospitals that serve large numbers of poor women, since the women most likely to benefit from preconception care, are often those least likely to have access to it.

REFERENCES

From Safe Motherhood to Reproductive Child Health

INTRODUCTION

Maternal mortality (MM) is a truly neglected tragedy. Ninety-nine percent of maternal deaths occur in the developing countries and among women in the most deprived sections of the population. MM remains one of the most daunting public health problems in India. In the global scenario, according to the World Health Organization (WHO) there are about 529,000 maternal deaths per year with a global ratio of 400 maternal deaths per 100,000 livebirths.1

Around 136,000 maternal deaths occur in India (WHO, 2004). National health survey (1998–1999) by International Institute for Population Sciences (IIPS) published from Mumbai in 2000, reported maternal mortality ratio (MMR) at 540, while the Register General Report in 1998 found MMR 470. As high as 80% of MM is preventable. The women in the developing countries have a lifetime risk of death following complications of pregnancy, about 250 times more than that of the developed countries. The lifetime risk of maternal death in the world on the whole is 1 in 74, which varies from country to country and region to region. In the least developed countries the chances are 1 in 17, in the developing countries the risk are 1 in 61 and in the developed countries the chances are 1 in 4,000. Again for every death, there are 10 more that are left with morbidities of various kinds that may have lifelong crippling effects which the women endure in silence (Fig. 1).2–4 It is very rightly stated that MM is only the tip of the iceberg of maternal morbidity and women’s suffering.

DEFINITION AND CAUSES OF MATERNAL MORTALITY

The MMR means the number of death of women while being pregnant or during delivery or within 42 days of termination of pregnancy, irrespective of duration and site of pregnancy, from any cause related to or aggravated by the pregnancy or its management, but not from accidental causes, per 100,000 livebirth. Although this statistics is often called the MM rate, it is not really a rate because the numerator (maternal death) is not a part of the denominator (livebirth). The causes of maternal death are multiple; they are divided into direct and indirect causes (Tables 1 and 2). Other causes contributing to maternal death are listed in Table 3.

Direct obstetric causes (80%)5 are those resulting from obstetric complications of the pregnant state (pregnancy,
SECTION

Prepregnancy Care

Table 1: Direct causes of maternal mortality
- Sepsis including unsafe abortion
- Obstetric hemorrhage
- Eclampsia
- Accident of labor
- Others

*Other direct causes include ectopic pregnancy, anesthesia related causes, embolism, etc.

Table 2: Indirect causes of maternal mortality
- Anemia
- Associated diseases
  - Cardiac
  - Renal
  - Hepatic
  - Metabolic
  - Infectious [including human immunodeficiency virus (HIV)]
- Malignancies
- Accident

Table 3: Contributory causes of maternal mortality
- Poor quality of health services including lack of proper infrastructure
- Inadequate obstetric care and essential supplies
- Poor maternal mortality audit
- Illiteracy, early marriage, poverty and malnutrition
- Unregulated fertility
- Ignorance—causes delay in making decisions during pregnancy
- Multiple demands on woman’s own time

labor and puerperium), from interventions, omissions, incorrect treatment, or from a chain of events resulting from any of the above (Table 1).

Indirect obstetric deaths (Table 2) are those resulting from a previously existing disease or a disease that developed during pregnancy and which was not due to direct obstetric causes, but which was aggravated by physiological effects of pregnancy. Investigators have found that 63–80% of direct maternal deaths and 88–98% of all maternal deaths could probably have been avoided with proper handling. Indian and global scenarios of maternal deaths are shown in Figures 2 and 3, respectively.

SAFE MOTHERHOOD INITIATIVE

It is global effort to reduce MM and morbidity and to reduce maternal deaths by at least half by 2010; safe motherhood initiative (SMI) was conceived in 1987 at Nairobi. It has also aimed to enhance the quality and safety of girls’ and women’s lives through adoption of a combination of health and nonhealth strategies. Partners of SMI are governments, different nongovernment organizations (NGOs), World Bank, United Nations International Children’s Emergency Fund (UNICEF), United Nations Fund for Population Activities (UNFPA), WHO, International Planned Parenthood Federation (IPPF), professional bodies and women’s group. As a matter of fact anybody and everybody can be a partner of this initiative. It lays emphasis on the need for better and more widely available maternal health services, the extension of family planning, education and services and effective measures aimed at improving the status of women. It may take many forms: increasing awareness of the magnitude of the problem and the need for action; strengthening maternal health services; training of health workers and others; facilitating educational and economic opportunities for women and research particularly operational research.

STRATEGIES OF SAFE MOTHERHOOD

If we compare the maternal health scenario between the developed and the developing countries (Tables 4 and 5), it becomes evident at MMR in developed countries is very low compared to developing countries. The reasons for massive reduction of MM in developed countries and very high in developing countries has been described below.

- Keeping the above information in mind, a strategy (Fig. 4) was taken in India in 1992, called child survival and safe motherhood (CSSM).
The tip of the pyramid shows health care programs of women for immediate results. Medium- and long-term goals are also defined.

HEALTH CARE INTERVENTIONS

The medical profession is responsible for delivering the obstetric health to all pregnant women. Obstetric health care means three “Es”.
1. Essential obstetric care for all.
2. Early detection of complications.
3. Emergency obstetric care (EOC).

Protocol for Essential Obstetric Care (Fig. 5)

It includes focused antenatal care with booking between 12 weeks and 16 weeks with at least five visits. Routine blood pressure and weight are recorded, along with obstetrical examination. Mandatory investigations like hemoglobin (Hb) percent, blood grouping and Rhesus (Rh) typing, urine sugar and protein are to be done. Two hours are postprandial blood sugar may be performed. Each woman is prescribed iron, folic acid and deworming agent after 16th weeks. Immunization against tetanus and proper care at birth must be taken. “5 clean” must be followed during birth care, clean hand, clean surface, clean razor blade, clean cord tie and clean cord stump. These services can be provided by auxiliary nurse midwife (ANM) or medical officer (MO) at health center and their local doctor or by trained birth attendant, preferably at the women’s locality. All health care providers must know when to refer the women to the nearest referral unit where EOC is available—this is the most important issue in the management of any obstetric complications, anywhere.

Early Detection of Complications

It is wise to remember that every pregnant woman is at risk of developing complications any time during pregnancy, labor and puerperium, and most complications cannot be predicted, also many complications cannot be prevented. Quality antenatal care can detect some complications early. It is always the first contact health providers who will detect the complications. In rural area, they are trained attendants/nurse midwives, family members and local practitioner. This group must be updated with the knowledge of signs of complications, e.g. bleeding anytime during pregnancy, convulsion, high fever, persistent headache and/or blurring of vision, excessive swelling of the body, less amount of daily urine output, prolonged labor pain and excessive bleeding after delivery, etc. and such cases should be referred to the nearest first referral unit (FRU).

Emergency Obstetric Care

The focus of safe motherhood programs in most developing countries has been on delivery of maternal services. The goal of reducing MM cannot be achieved, if prompt adequate care
is not available for obstetric complications. The challenge now is to shift the focus on EOC in addition to ongoing health care program. EOC includes specific interventions to manage specific emergency complications, which can be fatal within hours. It is agreed that 15% of all pregnant women will develop serious complications. Estimated average intervals from onset of complications to death are given in Table 6.

- No women should ideally deliver in a place which is more than 2 hours away from a referral unit. Apart from hemor rhage, there is usually enough time for a woman to be saved, supposing four frequent causes of delay are limited:
  - Delay in recognizing the problem
  - Delay in seeking care
  - Delay in reaching care
  - Delay in receiving care.

Emergency obstetric care will be of three types:
1. Obstetric first aid
2. Basic EOC
3. Comprehensive EOC.

Functions to define obstetric first aid:
- Oral misoprostol
- Parenteral oxytocics
- Parenteral antibiotics
- Parenteral anticonvulsants.

Functions to define basic emergency obstetric care (include in addition to obstetric first aid):
- Manual removal of placenta
- Forceps or vacuum extraction
- Evacuation of uterus in incomplete abortion
- Intravenous (IV) fluid administration. This can be done in community health centers.

**Comprehensive Emergency Obstetric Care**

It includes, in addition to the above, facilities for surgery, anesthesia and blood transfusion. The first referral hospital forms vital link between rural community and the centralized district hospital. MM can be reduced more by treating the complicated cases earlier and nearer home at first referral hospital either by specialists or by the physicians with 3–5 years experience who possess basic skills in obstetrics and surgery.

**First referral hospital or first referral unit:** It may be an upgraded health center, community health center or may be a district hospital. Staffs here are trained to perform essential obstetric functions. These are follows:
- **Surgical function:** Cesarean section, laparotomy for rupture uterus and tubal pregnancy, dilatation and evacuation, amniotomy, oxytocin infusion for augmentation of labor, repair of vaginal or cervical tears.
- **Anesthetic functions:** General/regional
- **Medical functions:** Treatment of shock, sepsis, hypertension, eclampsia and anemia.
- **Blood transfusion**
- **Manual or assessment functions:** Manual removal of placenta, vacuum extraction, forceps, parthography.
- **Family planning:** Tubectomy, vasectomy, intrauterine device (IUD) insertion, norplant insertion, etc.
- **Management of complicated pregnancy/labor referred from other levels.**
- **Neonatal care:** Resuscitation, thermal control and feeding.

Doctors, policy makers and health planners need to recognize that the objective of SMI to reduce MMR cannot be achieved by the existing services alone the provision of EOC at all level will be essential to bring about a sizeable decline in MM.
REPRODUCTIVE AND CHILD HEALTH PROGRAM

Phase I

The concept of reproductive health (RH), first introduced by Prof Fathalla, received a global acknowledgment during the International Conference on Population and Development (ICPD) (Cairo, 1994). ICPD defines RH as “a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity in all matters relating to the reproductive system, its function and process with a lifetime perspective”. The main issues of reproductive and child health (RCH) program are the integration of all interventions relating to improve facilities of obstetric care, medical termination of pregnancy (MTP), IUD insertion in the public health centers (PHCs), specialist centers for sexually transmitted disease (STD) and reproductive tract infection (RTI) in all district hospitals and number of subdivisional hospitals, setting up of FRU at subdistrict level providing comprehensive EOC, integration of all interventions of fertility regulation, maternal and child health with RH for both men and women. RCH phase I program had incorporated safe motherhood components along with child survivor components including STD and RTI. The RCH program was launched on 15th October, 1997. The RCH program integrated all the services of CSSM and the major interventions like essential obstetric care, 24 hour delivery services at PHCs/community health centers (CHCs), EOC, MTP, prevention of RTI and STD.

Phase II

This phase II began from 1st April 2005 with a focus to reduce maternal and child morbidity and mortality along with an emphasis on rural health center. The major strategies under the RCH phase II are:

- Essential obstetric care
  - Institutional delivery
  - Skilled attendance at delivery
- Emergency obstetric operational FRU
  - Operationalizing PHCs and CHCs for 24 hours delivery services
- Strengthening of the referral system.

Recent initiatives have been taken to provide adequate training of the MBBS doctors in life-saving skills for EOC. This provision of adequate and EOC has been recognized as the most important intervention for saving lives of pregnant women with complications.

ROAD AHEAD OF SAFE MOTHERHOOD

Comparison of Indian and International initiative to reduce MM is shown in Table 7.

Table 7: Initiative to reduce maternal mortality

<table>
<thead>
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<th>International</th>
<th>Indian response</th>
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<tr>
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<td>CSSM 1992</td>
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<td>Target to reduce MMR</td>
<td>Target to reduce MMR from Half by 2000</td>
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<td>ICPD Cairo 1994</td>
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<td>Defined “RH”</td>
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<td>MDG 2000 (Goal 5)</td>
<td>RCH-II Target to reduce</td>
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<td>Target to reduce MMR by 3/4th by 2015</td>
<td>MMR to 150/100,000</td>
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</tbody>
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Making Pregnancy Safer

Making pregnancy safer (MPS) is a health sector strategy launched by WHO (2000) for reducing maternal and perinatal mortality and morbidity.

The MPS strategy builds upon the lessons of SMI, existing national efforts and the consensus reached at the ICPD (Cairo, 1994), world conference on women (Beijing, 1995) and the joint WHO/UNFPA/UNICEF/WORLD Bank Statement (1999).

The universally agreed goals in maternal health include:

- Eighty percent childbirths be assisted by skilled attendants by 2005.
- In areas with very high MMR, at least 40% of births be assisted by skilled attendants by 2005, 50% by 2010 and 60% by 2015.
- Reducing pregnancy related mortality by 75% by 2015.
- Reducing infant mortality rate (IMR) below 35 per 1,000 livebirths by 2015.

Three Making Pregnancy Safer Messages

1. Every pregnancy ought to be wanted.
2. All pregnant woman and their infants should have access to skilled care.
3. Every woman should be able to reach a functioning health facility in good time to obtain appropriate care when complications arise during pregnancy, delivery or the puerperium period.

Making pregnancy safer call for following essential services which could prevent up to 80% of maternal and newborn deaths.

- Family planning information and services
- Postabortion care
- Basic antenatal and postpartum care
- Skilled attendance during pregnancy, delivery and postpartum period
- Referral centers for complications.
Millennium Development Goals

This is described elsewhere.

The Partnership for Maternal, Newborn and Child Health

The partnership is a global health partnership launched in September 2005 and joins the maternal, newborn and child health (MNCH) communities into an alliance of some 130 members to ensure that all women, infants and children not only remain healthy, but also thrive. Ottawa, 21st June 2007—a meeting of Canadian and international health professionals was held to discuss why a half-million mothers are still dying each year. "Certainly, progress has been made in many areas," said Dr Dorothy Shaw, President of the International Federation of Obstetrics and Gynecology. "But it is a humbling experience that on the 20th anniversary of these goals, we still have a half-million women dying every year."

Geneva, 15th May 2007—The 60th World Health Assembly of the WHO gave prominence to the issue of MNCH.

Dar es Salaam, 17th April 2007—Prime Minister of Tanzania called on regional leaders to increase health spending to 15% of national budgets and to strive for achieving health millennium development goals (MDGs).

CONCLUSION

The challenge of reducing maternal morbidity and mortality is substantial and there are no simple solutions. The main priority should be for women to have the choice to deliver in any health center or hospital. Ensuring appropriate provision of EOC is an essential feature of all intrapartum care strategies, but timely access is crucial. Alternative approach to increase effective intrapartum care strategies is the availability of skilled birth attendants at home. During the last 20 years of International and National Advocacy for Safe Motherhood, an estimated 10 million women have died of maternal causes though 88–98% of maternal deaths are preventable. The International Federation of Gynecology and Obstetrics (FIGO) world report 2006 is dedicated to women of all ages and their children, who have lost their lives because their rights were not translated into meaningful action. FIGO, through collaboration with others, is committed to actions that will result in the respect of sexual and reproductive rights and access to health for women throughout the world.

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INTRODUCTION: MAGNITUDE OF THE PROBLEM

Childbirth is a biological function and an integral part of the social environment, bringing joy to the mother and family. This can turn into a tragedy where a woman loses her child or suffers a catastrophe herself, while performing this social obligation.

According to the latest annual report 2007-09 of the Department of Health and Family Welfare (DoFW), Government of India (GOI), the national average of the maternal mortality rate (MMR), i.e. maternal deaths per lakh livebirths, in the country is 212. Each year in India, roughly 30 million women experience pregnancy and 27 million have a livebirth. With an estimated 136,000 deaths, India has the highest burden of maternal mortality in the world. Most of the maternal deaths are concentrated in the age-group of 20–24 years [National Family Health Survey 3 (NFHS-3)]. Forty seven percent of maternal deaths in rural India are attributed to anemia and hemorrhage. Abortions are the third leading single cause of maternal mortality being responsible for 12% of the deaths. According to Sample Registration System (SRS) 1998, sepsis accounts for 16%, obstructed labor for 10% and toxemia for 8% of the total maternal mortality.

Regional disparities in maternal and neonatal mortality are wide. It is also recognized that delays in accessing specialized maternal care happens at all levels. Only 42.5% of all births are attended by skilled health staff. The estimates of maternal mortality at State/Union Territories (UTs) levels not being very robust, MMR can only be used as a rough indicator of the maternal health situation in any given country. Hence, other indicators of maternal health status like antenatal checkup, institutional delivery and delivery by trained personnel, etc. are used for this purpose.

Nearly two-thirds of the maternal deaths occur in the Empowered Action Group (EAG) States including Uttar Pradesh, Uttaranchal, Madhya Pradesh, Chhattisgarh, Rajasthan, Jharkhand, Bihar, Orissa and Assam. The MMR was the lowest in Kerala (81), followed by Tamil Nadu (97), Maharashtra (104), Haryana (153), Gujarat (148), Punjab (172), West Bengal (145), Andhra Pradesh (134), Karnataka (178), Orissa (258), Bihar (261), Madhya Pradesh (269), Assam (390), Rajasthan (318) and Uttar Pradesh (359).

With 16% of the world’s population, India still accounts for over 20% of the world’s maternal deaths. Every 5 minutes a woman dies of pregnancy-related causes. It is estimated that for each woman who dies, 30 others develop chronic, debilitating conditions that seriously affect the quality of life.
TRENDS IN DEVELOPMENT OF HEALTH CARE POLICIES IN INDIA

The Ministry of Health and Family Welfare is the apex executive organization dealing with the issues of health and family welfare in the country. It also lays the National Health Policy in accordance with the policy decisions of the Cabinet. In 1986, World Health Organization (WHO) convened a Technical Working Group to define the essential obstetric care (EOC) necessary at first referral level for the reduction of maternal mortality and morbidity, and to describe the staff, training, supervision, facilities, equipment and supplies needed. This definition of EOC at first referral level has been of invaluable service to health planners of maternity services. However, it has not helped to reverse the polarization that has existed for 25 years between the development of hospital maternity services on the one hand and the training of traditional birth attendants (TBAs) on the other.

Two important milestones of the National Health Program of India to reduce maternal mortality were a policy shift from a vertical immunization program to a comprehensive Child Survival and Safe Motherhood (CSSM) initiative, and the strategic programmatic change from a high-risk approach to implementation of EOC, including the establishment of first referral units (FRUs). Health units which were either community health centers (CHCs) or subdistrict hospitals were identified to function as FRUs throughout the country. Second referral units consist of the district level hospitals and Medical College Hospitals.

Subsequently, India accepted the recommendations of the International Conference on Population and Development (ICPD) (1994) and in 1997 the Reproductive and Child Health (RCH) Programme was initiated, incorporating the components of the CSSM program and including the additional component of sexually transmitted diseases and reproductive tract infections.

RCH II: Strategic Choices to Reduce MMR

The RCH Programme, which was launched on October 15, 1997, draws its mandate from the Programme of Action of the ICPD, 1994. Under the RCH Programme, a comprehensive package of services for family planning (FP), maternal and child health and management of reproductive tract infections, including sexually transmitted diseases is being implemented. The key maternal health strategies under the RCH II phase which began on April 1, 2005, are:

- Essential obstetric care
- Skilled attendance at birth (domiciliary and health facilities)
- Operationalize emergency obstetric care at FRUs
- Strengthen referral systems
- Promote institutional deliveries
- Safe abortion services at primary health center (PHC) level.

The main priority of the RCH-II will be the operationalization of all CHCs and at least 50% of PHCs to provide 24-hour safe delivery and basic emergency obstetric care (BEmOC) by 2010. Emergency obstetric care (EmOC) is generally categorized as BEmOC and comprehensive EmOC (CEmOC) (Table 1). United Nations (UN) guidelines recommend a minimum of one comprehensive EmOC facility and four basic EmOC facilities per 500,000 population. Under the RCH phase II, two levels of institutions will be targeted:

1. PHCs and CHCs for BEmOC
2. FRUs for CEmOC.

**Anesthesia for EmOC Training for MBBS MOs**

One of the principal reasons for the failure of the RCH I Programme to operationalize the planned 1,748 FRUs was the lack of anesthetic services.

Department of Health and Family Welfare has developed a 14-week course in anesthesia for EmOC for MBBS Medical Officers (MOs). The first batch completed training at AIIMS last year. By 2010, 4,000 MOs will be trained to address the acute lack of anesthetic skills for EmOC at FRUs.

**Training MBBS MOs in Cesarean Section**

In view of the nonavailability of obstetricians at FRUs, the Federation of Obstetric and Gynecological Societies of India (FOGSI) has developed an EmOC course including cesarean section for MBBS MOs. This important step in capacity building in CEmOC and operationalization of FRUs will be implemented in a stepwise manner. A pilot phase will be evaluated before scaling up.

The National Population Policy (NPP) adopted by the GOI in 2000 reiterates the Government’s commitment to the safe motherhood program within the wider context of reproductive health. Among the National Socio-demographic Goals for 2010 specified by the policy, several goals pertain to safe motherhood, 80% of all deliveries should take place in institutions by 2010, 100% deliveries should be attended by trained personnel, and the maternal mortality ratio should be reduced to a level below 100 per 100,000 livebirths.

### Table 1: Signal functions of basic and comprehensive emergency obstetric care services

<table>
<thead>
<tr>
<th>Basic EmOC</th>
<th>Comprehensive EmOC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skilled health personnel who can provide:</td>
<td>Skilled health personnel who can provide full basic EmOC plus:</td>
</tr>
<tr>
<td>- Parenteral antibiotics</td>
<td>- Anesthetic services (cesarean section)</td>
</tr>
<tr>
<td>- Parenteral oxytocic drugs</td>
<td>- Surgical services</td>
</tr>
<tr>
<td>- Parenteral anticonvulsants</td>
<td>- Safe blood transfusion services</td>
</tr>
<tr>
<td>- Manual removal of retained products</td>
<td></td>
</tr>
<tr>
<td>- Assisted vaginal delivery</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviation:** EmOC, emergency obstetric care
**THE NATIONAL RURAL HEALTH MISSION (2005–12)**

The National Rural Health Mission (NRHM) (2005–12) seeks to provide effective health care to rural population throughout the country with special focus on 18 states, which have weak public health indicators and/or weak infrastructure. Under this scheme, every village/large habitat will have a female Accredited Social Health Activist (ASHA)—chosen by and accountable to the panchayat—to act as the interface between the community and the public health system. ASHA would act as a bridge between the Auxiliary Nurse Midwife (ANM) and the village, and be accountable to the Panchayat. She will be an honorary volunteer, receiving performance-based compensation for promoting universal immunization, referral and escort services for RCH, construction of household toilets and other health care delivery programs. A key strategy of the Mission is operationalizing 3,222 existing CHCs (30–50 beds) as 24-hour FRUs, including posting of anesthetists.

**COMMUNITY MOBILIZATION STRATEGIES**

Learning from the lessons of RCH I, RCH II has evolved innovative strategies to stimulate demand for safe delivery and other RCH services.

**Janani Suraksha Yojana**

*Janani Suraksha Yojana* (JSY) is a modified version of the National Maternity Benefit Scheme. Its twin objectives are:
- To reduce maternal and infant mortality through promotion of institutional deliveries
- To protect the female fetus and child.

Pregnant women belonging to below poverty line (BPL) are eligible. The pregnant woman choosing institutional delivery receives financial assistance:
- Assistance (₹1,500) is provided for cesarean delivery.
- Transport assistance (₹150) is provided to a rural woman for traveling to a health center for delivery.
- Traditional Birth Attendants who mobilize women for antenatal care, institutional delivery and postnatal care are provided with financial assistance.

**Vande Mataram Scheme**

The Government has recently launched a scheme to involve private sector in safe motherhood/FP activities. Under this scheme, the gynecologist members of FOGSI volunteer are to provide free outpatient care services (antenatal and FP) to pregnant women on a fixed day each month. Doctors who are not members of FOGSI are also welcome. Each enrolled Vande Mataram physician is provided a kit, consisting of iron-folic acid (IFA) tablets, condoms, oral contraceptives (OCs) and intrauterine devices (IUDs) by the government for free distribution to patients. The scheme was launched on February 9, 2004.

**The Integrated Management of Neonatal and Childhood Illnesses Approach**

The objectives of Integrated Management of Neonatal and Childhood Illnesses (IMNCI) plus strategy in RCH II are to:
- Implement by 2010, a comprehensive newborn and child health package at the level of all subcenters (SCs) (through ANMs), PHCs (through MOs, nurse and Lady Health Volunteers (LHVs)) and FRUs (through MOs and nurses).
- Implement by 2010 a comprehensive newborn and child health package at the household level in 250 districts.

**Public-Private Partnerships**

Strong partnerships between the DoFW, GOI, state Government and the NGOs are being encouraged. DoFW will provide technical assistance, the state government will provide leadership to the project, and the private sector will be economically and formally engaged for service delivery to fill in gaps. There is a considerable capacity among private providers [nongovernmental organizations (NGOs), medical practitioners and other agencies] which is being explored and operationalized. Such partnerships are particularly likely to be viable in urban areas.

**RURAL HEALTH CARE SYSTEM: THE STRUCTURE AND CURRENT SCENARIO**

Flow chart 1 shows the rural health care delivery system in India.

**Subcenters**

The subcenter is the most peripheral and first contact point between the primary health care system and the community. Each SC is manned by one ANM and one Multipurpose Worker (Male) [MPW(M)]. One Lady Health Worker (LHV) is entrusted with the task of supervision of six SCs. SCs are assigned tasks relating to interpersonal communication in order to bring about behavioral change and provide services in relation to maternal and child health, family welfare, nutrition, immunization, diarrhea control and control of communicable diseases programs. The Department of Family Welfare is providing 100% central assistance to all the SCs in the country since April 2002. There are 144,988 SCs functioning in the country as on March, 2006.

**Primary Health Centers**

Primary Health Center is the first contact point between village community and the MO. The PHCs were envisaged to provide an integrated curative and preventive health care services.
care to the rural population with emphasis on preventive and promotive aspects of health care. A PHC is manned by a MO supported by 14 paramedical and other staffs. It acts as a referral unit for six SCs. It has 4–6 beds for patients. The activities of PHC involve curative, preventive, primitive and Family Welfare Services. There are 22,669 PHCs functioning as on March, 2006 in the country.

**Community Health Centers**

Community health centers are being established and maintained by the State Government under Minimum Needs Programme (MNP)/Basic Minimum Services (BMS) program. It is manned by four medical specialists, i.e. Surgeon, Physician, Gynecologist and Pediatrician, supported by 21 paramedical and other staffs. It has 30 indoor beds with one operation theater (OT), X-ray, labor room and laboratory facilities. It serves as a referral center for four PHCs, and also provides facilities for obstetric care and specialist consultations. As on March, 2006, there are 3,910 CHCs functioning in the country.

**MATERNAL AND CHILD HEALTH SERVICES AT THE PRIMARY AND SECONDARY LEVEL**

Figure 1 shows the antenatal, intranatal and postnatal services at the PHC and CHC level.

**FUTURE CHALLENGES**

Many systemic problems in the government, in General Health and Family Welfare Department in particular, affect the implementation of most health programs, CSSM or RCH being no exception. The goal is to achieve optimal health for all the people, which would allow them to lead socially and economically productive lives. Despite the commitment to the program, enormous health problems still need to be addressed. The major constraints facing the health sector are a lack of resources, large vacancy of posts and frequent transfer of staff, lack of an integrated multisectoral approach, insufficient information, education and communication (IEC) support, poor involvement of NGOs, poor disease
surveillance and response systems and a manually operated health management information system.

**REFERENCES**


INTRODUCTION

Ancient folklore and medical knowledge emphasize that the mother-child dyad (Fig. 1) is a vulnerable group from a health and nutritional point of view. Nutritionists have shown that these segments not only require more dietary intake but are also more susceptible to adverse health consequences following nutritional deprivation. Global studies have unequivocally demonstrated the association between undernutrition and increased risk of maternal, perinatal and infant mortality and morbidity. Clinical trials of food supplementation to undernourished groups suggest that reduction in morbidity and mortality rates and improvement in birthweight and growth in infancy could be achieved by food supplementation and proper nutrition.

But now it is not only deprivation but preconceptional obesity also which predisposes mother for various complications as well as various fetal complications and development of metabolic syndrome later on in life. So nutrition in mother has changed from scarcity to adiposity and would have to be studied from various angles.

NONCOMMUNICABLE DISEASES

Other new aspect which is developing in relationship to maternal nutrition and nutrition on the whole is the emergence of higher incidence of noncommunicable diseases (NCDs).

A recent analysis of mortality trends suggests that large increases in NCDs have occurred in developing countries, particularly those in rapid transition (e.g. Brazil, China and India). According to these estimates, at least 40% of all deaths in developing countries are attributable to NCDs (versus 75% in industrialized countries). Dietary deficits and excesses, and the lifestyle changes that accompany industrialization and urbanization with economic development make a significant contribution to this epidemic. Maternal deaths per minute, related to pregnancy are shown in Figure 2.

As is well recognized, making reproduction and childbirth safer, benefits not only women, but also newborns, children, families and ultimately the communities and nations!

Fig. 1: Mother-child dyad
MATERNAL MORTALITY

EPIEMIOLOGICAL EVIDENCE

World Health Organization Southeast Asian Region (SEAR) accounts for nearly one-fourth of the world’s population; most countries in the region have very young populations, with nearly 50% in the reproductive age group. Consequently, the number of pregnant women and the number of babies born annually are very large. An estimated 37 million childbirths take place annually. The region has about 180 million children under the age of five. Unfortunately, the region also accounts for more than 170,000 maternal deaths and over 3 million child deaths annually. These account for almost 33% of all maternal deaths worldwide. These statistics make the issue of maternal, newborn and child health a major priority for the region.

However, these deaths are not spread equally across the region, and there are vast intra-country and as well as intra-region variations (Fig. 3), especially in terms of inequity in access to skilled care at birth.

Equally, the proportion of newborn deaths is enormous—of the estimated 4 million neonatal deaths annually, 1.4 million newborns die in the first month after birth in countries of the SEAR (Table 1).

Relatively few reports exist on the relationship between maternal nutrition and preterm birth. Although some studies have reported an association between the two, it appears that maternal nutrition during pregnancy is not an important factor for prematurity. Poor maternal nutrition has however been shown to be one of the major causal determinants of intrauterine growth restriction (IUGR) in both developed and developing countries (Figs 4A and B). In developing countries, many women are short and underweight and the number of low birthweight (LBW) babies is particularly high (more than 30% in South Asia, 10–20% in other regions (Table 2).

Many efforts have been made in order to identify a potential “modifiable” factor for LBW. Maternal nutrition is modifiable in the short term; if it is one of the major environmental causes of IUGR in the developing world, a substantial fraction of LBW could possibly be prevented. In turn this might reduce the prevalence of mortality, morbidity, physical and mental development, factors associated with LBW.

HISTORICAL TRENDS IN RECOMMENDATIONS FOR WEIGHT GAIN DURING PREGNANCY

In the 16th, 17th and 18th centuries much emphasis was placed on the maternal diet since the mother was known to be the only source of nutrients for the fetus. In 19th century the idea that pregnant women should not overeat became a recurrent theme. Overeating was believed to be a cause of
large babies and as a consequence more difficult labors and so when maternal mortality was extremely high and cesarean deliveries were a desperate attempt, limitation of fetal size by restraining maternal food intake was an advice. This formed the basis of first published study of diet and pregnancy and this showed that restricting food intake throughout pregnancy reduced the birthweights of males by 400 g and of females by 500 g.

This formed the basis for the fact that maternal weight gain could be used as an indicator of maternal nutritional status and in turn influenced fetal growth. In 1920, Davis; Mcllroy and Roadway, 1937; Bingham, 1932, all advocated to control

weight gain and some advised even salt-free diets to control toxemia.

But it was in 1970 that a comprehensive report entitled “Maternal Nutrition During the Course of Pregnancy” was published (NRC 1970a) which reviewed problems, practices and research bearing on the relations between nutrition, and the course and outcome of pregnancy, and provided recommendations for weight gain and intake of nutrients.

After publication of this report a number of other studies showed that desirable weight gain during pregnancy varies as a function of prepregnancy weight for height and there was evidence to show that in order to achieve proper fetal weight women with adequate height and weight should gain more weight during pregnancy and overweight women should not gain much weight during pregnancy. So the importance of maternal nutrition with gestational weight gain centered the attention on outcome of birthweight, as in epidemiological studies birthweight is the outcome most frequently examined as its association with infant mortality and morbidity is widely recognized (Tables 3 and 4).


1990 report of the IOM, Nutrition During Pregnancy, was written at a time when concern was focused on insufficient gestational weight gain and concerns about LBW. In the intervening years, the larger context has shifted in light of increasing rates of obesity to create concern about too much weight gain, and prepregnancy overweight.
FACTORS AFFECTING FETAL GROWTH

- Nutrition has many components and energy in the form of carbohydrates is important. Glucose is a critical fetal nutrient, and if its supply is reduced growth restriction may result. Sokol et al. and Langer et al. have confirmed that a flat maternal response to glucose loading is associated with an increased risk for fetal growth restriction.

- In one study, it was proved that protein malnutrition before 26 weeks can cause IUGR.

- There is also an intergenerational effect: Women who were born of LBW mothers are more likely to have a LBW child (and even grandchild). This may be because of a metabolic adjustment to assure a fetal weight that is proportional to maternal size.

- Little work has been conducted to relate prepregnancy micronutrient intakes or status to LBW; however, suggests that acquiring a desirable weight and diet during the weeks before and around conception is highly recommended, especially in industrial populations where only subclinical micronutrient deficiencies exist. In developing countries, where a lifetime of very low intakes of micronutrients may exist, it is important to try to reverse these low intakes long...
before conception, but increasing intakes shortly before and during pregnancy may also help increase birthweight and survival chances of infants.

However, a recent study in the UK found that inadequate maternal micronutrient and fiber intakes early in pregnancy were more important in determining LBWs than low protein or energy intake. In this study, women had intakes of fiber and ten of the micronutrients (riboflavin, niacin, pyridoxine, thiamin, folic acid, iron, magnesium, phosphorus, calcium, and zinc) that were more than 20% below the reference requirement.

**GESTANATIONAL WEIGHT GAIN**

This is an important variable of interest that has been studied extensively but it needs further attention. Gestational weight gain has three components:

1. The products of conception, i.e. the fetus, the placenta, and the amniotic fluid
2. The fluids in the extra tissue gained by the mother to support the pregnancy

Roughly, 70% consists of the pregnancy components and 30% is thought to be attributed to maternal stores.

The largest component of gestational weight gain is water, followed by fat (the most variable of all of the components in the literature), and finally protein.

Patrick Catalano described the pattern of gestational weight gain, which is curved during the first two trimesters and then appears to be linear in the last trimester. Longitudinal studies of changes in fat mass show that as lean women (prepregnancy percentage of body fat of less than 25%) go through pregnancy, they tend to gain more fat compared with women who are obese (prepregnancy percentage body fat greater than 25%).

The IOM recommendations for weight gain in pregnancy reflect the curve of normal weight gain: very low at 0–10 weeks, 7 lb at 10–20 weeks, 10 lb at 20–30 weeks (this is when fat is accruing in the mother), and by 30–40 weeks the pace of weight gain should slow down. According to the average fetal growth curve, until about 28 weeks (the beginning of the third trimester), the average fetus weighs about 2 lb. From 28 weeks until term, there is a 5.5 lb increase in weight that reflects fetal growth. Taken together, about 7.7 lb of weight in late pregnancy is related to the fetus, placenta, and amniotic fluid, not specifically maternal weight. Now recommendations for weight gain are based on prepregnant BMI.

Weight gains outside the IOMs suggested ranges are associated with double the number of poor pregnancy outcomes as weight gains within the ranges.

**Association of Low Prepregnancy Weight with IUGR**

Many researchers have found that using a prepregnancy weight of less than 40 kg is a useful cut-off to predict women who will deliver LBW babies. Tripathi et al. (1987) found 60% of small-for-date Indian infants had mothers with prepregnancy weights less than 40 kg and a weight gain of less than 5 kg. Anderson (1989) estimated Indian women weighing less than 40 kg during the first 6 months postpartum had twice the risk of delivering LBW infants. In industrial countries the proportion of women who weigh less than 40 kg is very low. Gopalan (1985) estimated that only 1% of US women weigh less than 40 kg. Women in Africa probably have mean weights that are higher than women in Asia, in part because they are taller. Table 5 shows mean heights and weights of women from a number of countries.

**Energy Requirements During Pregnancy**

Energy requirements increase in pregnancy by about 12%. This is because of the increase in maternal body weight, an average 10–15% increase in basal metabolic rate and the energy requirements of the growing fetus and maternal physiological changes in pregnancy. Energy requirements are higher in later pregnancy but may be, at least partially, offset by mobilization of fat stored in early pregnancy.

Normally, women require 300 kcal more than their normal prepregnancy requirements during second and 450 kcal in third trimester and not during first trimester unless woman is underweight to start with she should gain about

| Table 5: Mean prepregnancy heights and weights of US and developing countries women |
|---------------------|-----------------|-----------------|-----------------|-----------------|
| Country             | Sample size     | Height (cm)     | Weight (kg)    | Source          |
| Bangladesh          | 2,161           | 141.9           | 40.4           | Huffman et al., 1985 |
| Indonesia           | 643             | 149.0           | 42.4           | Kardjati et al., 1982 |
| Nigeria             | 360             | 159.0           | 52.1           | Morley et al., 1968 |
| Senegal             | 2,088           | 162.5           | 58.3           | Briend, 1985    |
| Brazil              | 85              | 153.0           | 57.0           | Desai et al., 1980 |
| Guatemala           | 572             | 148.9           | 49.0           | Lechtig et al., 1975, 1978 |
| US                  | NA              | 163.7           | 56.6           | WHO, 1983       |

*Note: Developing countries women from these studies are from low socioeconomic backgrounds while US women are from average socioeconomic backgrounds*
400 g/week. Women carrying twins should gain 35–45 pounds or approximately 150 kcal a day more than for a singleton pregnancy. Women pregnant with twins should gain approximately 4–6 pounds during the first trimester and 1.5 lb/week thereafter. This weight gain is associated with a decreased risk of preterm delivery and LBW infants. Only two studies have assessed weight gain in triplet pregnancies. A weight gain of 50 pounds in total, or approximately 1.5 lb/week throughout pregnancy, may be appropriate.

Energy deprivation in pregnancy leads to metabolic syndrome later on in life of the baby.

It is hypothesized that some chronic adult diseases originate in utero as a result of fetal adaptation to optimize survival. LBW has been associated with increased risk of later development of type 2 diabetes mellitus, heart disease, hypertension, obstructive lung disease, hypercholesterolemia and renal damage.

Maternal nutrition has therefore been the focus of considerable research over the last few years and because of strong epidemiological evidence of a relation between maternal nutritional status and birthweight, a number of intervention studies of nutritional supplementation during pregnancy have been carried out both in developing and developed countries. Interest has however been largely restricted to birthweight as an outcome, especially in populations with high prevalence of maternal undernutrition, LBW and perinatal mortality.

**Supplementation Trials**

During pregnancy, the fetus is solely dependent on maternal intake and nutritional stores, mostly fat, for its energy. The best methodological approach for assessing the effect of this factor on birthweight and more specifically on IUGR or prematurity is thus supplementation. Will an increase in food intake increase birthweight? Will the prevalence of LBW and IUGR/premature infants thus be decreased?

Provision of food does not necessarily lead to its consumption. Even if it is consumed, it may replace some of the usual diet or may be shared by the family, however supplementation had a positive effect on birthweight and IUGR.

The effect was greater the more malnourished the mother was before pregnancy. Nutritional supplementation during pregnancy was also shown to be associated with a reduction in the incidence of LBW in developing and developed populations. But regardless of methodological and practical differences, the effect of nutritional supplementation during pregnancy on birthweight has generally been modest, with an average increase of about 100 g.

One study showing a substantial effect was in the Gambia where daily supplements of groundnut based biscuits and vitamin fortified tea were distributed to pregnant women. The mean net increase of energy intake was 431 kcal per day. The resulting significant increase in birthweight was on average 120 g and the overall prevalence of LBW babies decreased significantly from 20% to 6%. There were however marked seasonal differences. Supplementation during the wet season ("hungry" season) led to a significant increase in birthweight of about 200 g and a decrease in the proportion of LBW from 23.7% to 7.5%; in the dry season supplementation had no effect (average increase of 2 g only).

Collated data sets suggested that if 100 kcal per day were supplemented throughout pregnancy, the risk of IUGR would be halved in mothers undernourished prior to pregnancy, but only reduced by one-fifth in well-nourished mothers.

- So women without overt malnutrition or in positive energy balance (Gambia dry season) obtain a limited benefit from nutritional supplementation during one pregnancy.
- Chronically malnourished mothers also supplemented during one pregnancy experience only a modest impact on birthweight of about 100 g.
- When women are however in negative energy balance, food supplementation produces a significant increase in birthweight as in the Gambia (230 g increase).
- The expectation of a dramatic recovery from generations of poverty and food scarcity in a short time is an overly optimistic proposition. It may be that the extra, yet prolonged, intake during pregnancies and lactation, rather than large amounts of supplementation during short periods of a given gestation produces the fetal growth effect.
- So all these studies point to the same thing that overall nutrition of women should be cared for and more so in the adolescents. Therefore, it is concluded that “unless future trials of energy and protein supplementation demonstrate clear reductions in risk for preterm birth, stillbirth, or neonatal death, or improvements in maternal health, focus should be shifted towards potentially more fruitful strategies for improving maternal and child health”.

**Interventions**

**Taking Prepregnant Weight**

Taking prepregnant weight is one way of finding out about the energy needs of a woman and if they are being met or not.

- In countries where it is difficult to reach women before conception in order to measure prepregnancy weight but where utilization of antenatal care programs is good, it is possible to obtain weight as a predictor of risk for LBW early in pregnancy up to the 13th week.
- Those women who are at risk for delivering LBW babies should be given appropriate nutrition education messages. If women are not able to eat more because of limited family resources or national supplies of food, every effort should be made, through the community, to educate family members to share and thus reduce the woman’s workload.
- In countries where women present for antenatal care only after the second or third trimester, a weight measurement
at 5th, 7th or 9th month should be obtained and compared with available references for maternal malnutrition.

- For women who are in their 5th or 7th month of pregnancy, appropriate measures to increase food intake or decrease workload are needed.
- If the woman is close to her delivery date, her weight should be measured, but the effectiveness of an intervention at this point to increase her weight is not great. Instead, if she is identified as “at risk” for delivering a LBW baby, procedures for referring her to a hospital before delivery should be reviewed with her in order to optimize the survival of the infant if it is born below 2.5 kg. Family members, traditional birth attendants, and other community members should be contacted to help make the referral process work smoothly.

### INDIA

Pune Maternal Nutritional Study in Maharashtra, India detailed the relationship between the anthropometry of 2,500 women living in six rural villages (measured every 3 months) and the anthropometry of the 633 full-term infants born to these women over a 3-year period. Mothers were short and underweight (mean height—1.52 m; weight—42 kg; BMI—18 kg/m²) and their infants’ birthweight averaged 2,648 g. When compared to measurements of mothers and infants born at Southampton, the Pune mothers and their infants were smaller in all dimensions. The height and weight of mothers from Pune were lower by almost two standard deviations, as was birthweight and placental weight. There was considerable variation, however, in the degree of deficit seen in the various components of the infants’ weight. Mid-arm and abdominal circumferences were dramatically lower by almost three standard deviations. In contrast, the skin fold thickness was only slightly reduced, and therefore subcutaneous fat was relatively spared. Head and length growth were also relatively preserved, although not to the same degree as fat. Thus, although these underweight babies were very thin in the sense that they had reduced soft tissue mass but they were actually relatively “fat”. It may be that fat is preserved as a neonatal survival mechanism. This neonatal phenotype, with reduced muscle mass and relatively increased fat, resembled the phenotype of the adult Indian patient with insulin resistance and diabetes—possibly that phenotype is laid down in utero.

It is thought that average consumption for females in most of rural India is less than they need. At ages 13–16, girls receive a higher percentage of their requirements than boys.

The possibility remains that girls aged 12 or younger are undernourished relative to boys of the same ages; since the National Nutrition Monitoring Bureau (NNMB) does not publish food consumption data separately by gender at these ages, the possibility cannot be tested with these data. However, the NNMB does provide anthropometry, a nutritional outcome indicator by gender for children. The prevalence of underweight for both boys and girls is very high, but there is no female disadvantage.

The bottom line is that gender differences in anthropometry shown for India do not support the notion of substantial dietary discrimination against females in early childhood.

But anthropometric evidence is available only for surviving children. India has been known as one of the few populations in which males outlive females, and this reversal of the usual female advantage in life expectancy has itself been interpreted as evidence of poorer nutrition for females. If this pattern persists, however, these comparisons of food consumption and nutritional status suggest that the explanation does not lie in dietary but rather in healthcare discrimination against females.

Females appear to receive less than a fair share of household food supplies in some regions of India. The data suggest, however, that dietary discrimination against females does not apply to the country as a whole—the situation varies from state to state, across age groups, and across social classes. The only reliable generalizations are that females who are neither pregnant nor lactating take in more relative to their requirements than do men, but that, during pregnancy and lactation, women are at a strong disadvantage relative to men.

The more favorable intakes of reproductive-aged women who are neither pregnant nor lactating argues against generalized discrimination and indicates that (Fig. 5):

- The nutritional needs during pregnancy, particularly while breastfeeding, are either not well understood by women and their households or (for other reasons, including poverty) not addressed. Not just caloric needs but also micronutrient requirements vary among individuals within the same household, especially growing children and pregnant and lactating women in comparison with most other adults.

![Fig. 5: Caloric adequacy of the diet by reproductive status, women ages 16–44, rural Punjab, India](source: Das Gupta, 1995)
• *Nutrition is not proper:* The effect of other possible contributing factors, such as consumption of foods that are not *sufficiently nutrient dense*, might be countered by greater awareness of increased need as well.

• *Energy expenditure is more:* Given that data on women’s energy expenditures are generally unavailable, we must understand that women’s caloric needs are underestimated by common methodologies. The energy needs of women whose domestic and/or paid work is particularly arduous are especially likely to be underestimated. Interventions that target these women and improve understanding of their increased needs may also be appropriate. During pregnancy 300 kcal/day are required more than routine requirement but if women are doing hard labor at home and at work outside then their requirements are more.

• *Less spacing:* Reproduction is a great nutritional stress and if they bear many children and if each child is breastfed for many months, they would be malnourished and is responsible for high incidence of LBW in India. Normally spacing should be minimum of 2 years. Similarly, inadequate intake during lactation may limit breast milk production and thus the growth of children for whom breast milk is an important part of the diet.

• *Discrimination:* Discrimination results from some members being deemed more valuable than others. Although some discrimination is a household-level manifestation of inequitarian attitudes pervasive in the society as a whole (e.g. women are less valuable than men, children are not fully human until after their first birthday, elderly people deserve higher honor. So the fact that average Indian woman weighs 25% less than American woman is because of food and not race, as they are fed last in the household from girlhood to womanhood.

**Gender Differences**

“Hypothesis of female nutritional disadvantage” has been proved to be wrong in Africa and it is concluded that the different roles of African (as compared with South Asian) women provide them with greater control over food and enable them to avoid nutritional deprivation for themselves and their children. Proportions of children underweight, stunted, or wasted appeared to be slightly higher for males than for females in four studies in Africa.

The conclusion, that females are discriminated against in access to food, rests disproportionately on studies from South Asia. The social status of women is especially low in South Asia. Their job opportunities are less and their income-earning potential is far lower than men’s. They take resources (labor and bride-price) out of their natal households. These factors explain why females are perceived as less valuable than males in the region. The female advantage in life expectancy that applies in most countries is reversed in Bangladesh, Bhutan, Nepal, and Pakistan. A female disadvantage in mortality is generally explained in terms of preferential treatment of males, with poorer nutrition for females often specifically cited as a likely part of such a pattern of discrimination. So nutritional discrimination is prevalent here.

Although average figures on calorie consumption have remained nearly unchanged since the mid-1970s, it is likely that household food security among the poorest social groups may have improved given the reported reductions in people living below the poverty line, and the fact that food consumption per caput of landless agricultural workers has risen. This is in line with reductions in underweight prevalence of 0.5 percentage points per year in preschool children.

Regionally, as well as the differences discussed with regard to agriculture, there are also highly significant state-by-state variations in many other nutrition-related variables discussed here, with many factors associated with nutritional problem areas clustering particularly in the states of Rajasthan, Uttar Pradesh, Madhya Pradesh, Bihar and Orissa. Anti-female bias in food provisioning, health care utilization, and general care may be particularly severe also in these northern states, and reflected in the regional differences in juvenile sex ratio. By contrast in Kerala where education and literacy rate is 100% there nutritional indices are highest for women.

Anemia is one of major factors responsible for maternal and fetal mortality and morbidity.

The Consequences of Iron Deficiency and Anemia in Pregnancy on Maternal Health, the Fetus and the Infant.

The health-conscious world community has come to realize that anemia, the majority of which is due to iron deficiency, has serious health and functional consequences.

It is widespread especially among tropical-low income populations and that most of its nutritional component is controllable with a very high benefit/cost ratio. Women of fertile age and pregnant-lactating as well as their infants and young children are particularly affected. The cut-off values for anemia among pregnant woman both non-smokers and smokers are shown in Tables 6 and 7.

In response to the overwhelming evidence to this effect, world authorities have agreed that a minimal goal is that by the end of this century, anemia in pregnant women must be reduced by one-third. The more aggressive groups believe that with new approaches for the control of iron deficiency a

<table>
<thead>
<tr>
<th>Table 6: Cut-off values for anemia for women¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy status</td>
</tr>
<tr>
<td>------------------</td>
</tr>
<tr>
<td>Nonpregnant</td>
</tr>
<tr>
<td>Pregnant</td>
</tr>
<tr>
<td>Trimester 1</td>
</tr>
<tr>
<td>Trimester 2</td>
</tr>
<tr>
<td>Trimester 3</td>
</tr>
</tbody>
</table>

Source: ¹From CDC (ICMR level is 11 g even in 2nd trimester)
reachable goal is to reduce iron deficiency anemia to overall levels below 10% in most populations.

Background

It is estimated that about 2,150 million people are iron deficient, and that this deficiency is severe enough to cause anemia in 1,200 million people globally. About 90% of all anemias have an iron deficiency component.

In the developing world, nearly half of the population is iron deficient. However the industrial world is not free from it: 11% of its population has iron deficiency.

High-risk of women of fertile age and pregnant women for incurring negative balance and iron deficiency is due to their increased iron needs because of menstruation and the substantial iron demands of pregnancy.

Median requirements of absorbed iron are estimated to be 1.36 and 1.73 mg per day among adult and teen-age menstruating females. However, 15% of adult menstruating women require more than 2.0 mg per day, and 5% require as much as 2.84 mg per day. The superimposition of menstrual losses and growth in menstruating teenage girls increases the demands for absorbed iron; 30% need to absorb more than 2.0 mg per day; 10% as much as 2.65 mg, and 5% 3.21 mg. These requirements are very difficult, if not impossible to satisfy even with good quality, iron-fortified diets.

Iron needs exhibit a marked increase during the second and especially during the third trimesters when median daily needs increase up to an average of 5.6 mg per day (that is, 4.1 mg above median prepregnancy needs). The approximate range would be 3.54 and 8.80 mg per day. This amount of absorbed iron needs cannot be met from food iron even if iron fortification is in place.

Factors affecting iron stores:
- Birth spacing favors iron nutrition among fertile-age women because each pregnancy has a high cost in terms of iron.
- However, the use of intrauterine devices almost doubles the iron menstrual loss.
- Women using anovulatory contraceptive methods reduce menstrual loss by almost half.
- Importantly, multiparous women tend to have greater menstrual losses that increase with parity.

Thus the importance of two factors: Prepregnancy iron reserves upon which to draw; and iron supplementation during pregnancy.

Iron deficiency during lactation is mostly a residual from that resulting from pregnancy and delivery and can be partially alleviated because of lactational amenorrhea. However, once menstruation returns, if lactation continues, iron requirements become higher to reach a median of about 1.81 mg/day. Dietary iron absorption in most populations of the developing world may not be sufficient to fulfill these needs.

In conclusion, iron deficiency during pregnancy is extremely common even among otherwise well-nourished populations because of the reasons reviewed above. The risk of iron deficiency in pregnancy and lactation begins with inadequate prepregnancy iron reserves among women of fertile age.

Folic Acid

Folic acid is required for the nucleic acid metabolism and for cell division and growth. Its deficiency causes megaloblastic anemia, neural tube defects, homocystanemia. It also prevents isolated cleft lip congenital anomalies.

Sources of folic acid: Green leafy vegetables, fruits, liver, kidney. RDA for adolescent girls is 500 µg/day.

Folate deficiency has also been documented during pregnancy, often leading to a combined iron-folate deficiency anemia, particularly among lower socioeconomic groups consuming mostly cereal-based diets (poor in folate) aggravated by:
- Prolonged cooking
- Food reheating of liquid preparations.
- Folate requirements double in the second half of pregnancy and are requirement increased by processes that involve hemolysis, such as malaria and hemoglobinopathies.

<table>
<thead>
<tr>
<th>Cigarettes per day</th>
<th>10–20</th>
<th>21–40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy status</td>
<td>Hgb(^{c}) (g/dL)</td>
<td>Hct(^{d}) (%)</td>
</tr>
<tr>
<td>Nonpregnant</td>
<td>12.3</td>
<td>37</td>
</tr>
<tr>
<td>Pregnant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trimester 1</td>
<td>11.3</td>
<td>34</td>
</tr>
<tr>
<td>Trimester 2</td>
<td>10.8</td>
<td>33</td>
</tr>
<tr>
<td>Trimester 3</td>
<td>11.3</td>
<td>34</td>
</tr>
</tbody>
</table>

\(^{a}\) From CDC
\(^{b}\) No adjustment is necessary for women who smoke less than 10 cigarettes daily
\(^{c}\) Hgb = hemoglobin
\(^{d}\) Hct = hematocrit
Changing Trends in Maternal Nutrition and Interventions

Malabsorption processes, common among tropical, low socioeconomic groups, impair folate absorption.

Hookworm infestation

Antifolate treatment as antiepileptic drugs can cause deficiency of folic acid.

Body reserves of folic acid are low.

Intake of goat’s milk which is low in folic acid could be cause of deficiency in rural areas.

Simple things like toilet and latrine facilities are not available in India.

Folic acid supplementation should be given to all adolescent girls preconceptionally. 500 microgram/day in low risk cases and in the high risk cases with H/O previous neural tube defect should be given in the dose of 5 mg/day. Minimum one month before conception. Iron and folate should be given together.

The overall proportion of women and pregnant women with below-standard hemoglobin is highest in South Asia and Africa, followed by Oceania, East Asia, and then Latin America (Fig. 6).

**SUPPLEMENTATION DURING PREGNANCY**

**Iodine Supplementation and Vitamin A Supplementation**

If mother is malnourished then she needs vitamin A supplementation.

Reasonably compelling evidence that nutrition interventions can prevent both infant (iodine supplementation) and maternal (vitamin A or β-carotene supplementation) deaths, is available from randomized trials, and informal analysis suggests that the cost-effectiveness of nutrition interventions would be comparable and in some cases markedly superior to several standard antenatal interventions. The impact of nutrition interventions could be profound. In Nepal vitamin A or β-carotene supplementation trials have been found to be effective and if they can be generalized to the wider developing world, as many as 200,000 maternal deaths per year might be preventable through this simple intervention. Likewise, if severe iodine deficiency were prevalent in one-half of the developing world, iodine supplementation might prevent over 100,000 neonatal and early childhood deaths annually, so iodine supplementation is being done in the form of iodized salt through India.

**Essential Fatty Acids**

Essential fatty acids, needed for neural tissue growth, in fetal tissue and blood correlate with weight and head circumference of the infant at birth (Hackney Hospital, 1991). More work is needed to determine if maternal fatty acid intake or status prior to conception or early in pregnancy is related to birthweight of her infant. DHA supplementation of 300 mg/day is required for retinal and cognitive development in fetus.

**Calcium**

The RDA for calcium is 1,200 mg/day. There is increase in 1,25-dihydroxyvitamin D levels (up to twice postpartum values), which leads to an increase in intestinal calcium absorption. The increase is so large that it exceeds the calcium needs and results in 2.5 times higher urinary calcium excretion during pregnancy than postpartum. If spacing of more than 2 years is there in two deliveries then depleted stores of calcium are replenished.

Multiparous women with poor calcium intake may develop clinical osteomalacia, and the fetal bone density may be similarly affected. Leg cramps during pregnancy may reflect altered calcium or magnesium metabolism.

Calcium supplementation of 1–2 g/day during pregnancy may reduce the risk of developing the hypertensive disorders of pregnancy, including pregnancy-induced hypertension, pre-eclampsia, and eclampsia.

**Zinc**

The RDA for zinc for pregnant women is 11 mg/d, 3 mg more than that allotted for the nonpregnant woman, although up to 40 mg/d is considered safe. The RDA is doubled for vegetarians because less zinc is absorbed with this diet. Without supplementation, zinc levels normally decrease during pregnancy, especially between weeks 14 and 35. Even with adequate supplementation, zinc levels decrease by 20–35% below prepregnancy levels, possibly the result of increases in blood volume, gestational estrogens, fetal needs, and the gestational decrease in albumin, which binds zinc.
Plasma zinc concentrations decline more precipitously when iron is supplemented orally as a result of competition for absorption by these two ions.

Populations at risk for zinc deficiency include:
- Vegetarians
- Alcoholics
- Smokers
- Teenagers
- Multigravidas with impaired intestinal absorption of zinc
- Women receiving diuretics
- Those with an acute stress response to infection or trauma.

Zinc deficiency has been associated with:
- Fetal intrauterine growth retardation
- Congenital malformations
- Premature and postmature births
- Low birthweight
- Perinatal death
- Abnormal delivery with dystocia and placenta abruption
- Gestational zinc deficiency can impair the development of the fetal immune system and impair neurogenesis and subsequent cognitive development, thereby influencing activity, attention, and neuropsychologic performance.

**PROBLEMS OF OVERWEIGHT**

There is a growing epidemic of obesity in the United States and all over world, in USA nearly one-third of all adults are classified as obese, and this proportion has dramatically increased during the last two decades. Women are leading the epidemic at a current prevalence rate of obesity of 33%. Given the environment of overweight and obesity in the United States, the implications of this epidemic for women of childbearing age are of a concern. Data from the March of Dimes Perinatal Data Center indicates that in 2003, 19.6% of US women of reproductive age were obese. Obesity in women can cause serious pregnancy-related complications.

Past efforts to advise women on weight for pregnancy (before, during, and after) have focused little on maternal obesity. Rather, most of the attention has been devoted to concerns about LBW deliveries in addition to other maternal and infant outcomes. Maternal Nutrition and the Course of Pregnancy, a 1970 report of the Food and Nutrition Board of the National Research Council (NRC), had laid stress on undernutrition.

**Obesity** is defined as having a BMI of 30 or greater (Fig. 7). Body mass index is a measure that appears throughout this report as the ratio of weight to height squared (kg/m² or lb/in² × 703) (National Heart, Lung, and Blood Institute, 1998).

**Maternal Weight Definitions (Figs 8 and 9)**
- **Prepregnancy weight:** A woman’s actual weight prior to pregnancy up to the point that pregnancy is identified (Table 8).
- **Prepregnancy weight gain:** A woman’s increase in weight from some prior time until pregnancy.
- **Gestational weight gain:** Amount of weight gained during the pregnancy.
Postpartum weight retention: Amount of weight gained during pregnancy (i.e. gestational weight gain) that the woman has at a given time point postpartum.

Postpartum weight gain: Weight that is gained following pregnancy.

Gestational Weight Gain

The recommendations of the 1990 IOM report specify weight gain ranges during pregnancy for singleton term births based on prepregnancy BMI (Table 9). National birth certificate data include maternal weight. However, data allow for a comparison between very low gestational weight gain groups (less than 15 lb) and very high gestational weight gain groups.

Influence of Pregnancy Overweight on Health

Initially it was maternal undernutrition and malnutrition that was problem so in 1974, the US Department of Agriculture established the Special Supplemental Food Program for Women, Infants, and Children to address the needs of women and children at nutritional risk, and in the intervening years it was realized that not undernutrition but obesity and overweight had also become a problem. Women were leading the epidemic of obesity at a current prevalence rate of obesity of 33%.

It was in 1990 the IOM report Nutrition During Pregnancy recommended guidelines for weight gain during pregnancy based on prepregnancy maternal BMI. Two other reports quickly followed—Nutrition During Lactation (1991) and Nutrition During Pregnancy and Lactation: An Implementation Guide (1992). By this time, the Maternal and Child Health Bureau of the US Department of Health and Human Services had also begun to address concerns about maternal weight gain. Since publication of the 1990 IOM recommendations for weight gain during pregnancy, tremendous changes have occurred in the demographic and epidemiological profile of women experiencing pregnancy. More women entering pregnancy are either overweight or obese, and more women are entering their pregnancies with chronic conditions that lead to increased morbidity during their postpregnancy years. High rates of overweight and obesity are especially common in minority populations that may be already at risk for poor maternal and child health outcomes.

Collectively, these trends have changed the direction of thinking about weight gain during pregnancy, particularly for women who are overweight, underweight, short in stature, or adolescents. In 1998 National Heart and Lung and Blood Institute (NHLBI) gave a revised BMI chart.

Nutrition in pregnancy in this millennium is very important now as the dietary habits of young women are changing in many societies and pregnant women are increasingly entering pregnancy as overweight. This increase in overweight was accompanied by a fivefold increase in gestational diabetes within 15 years in Norway, together with an unprecedented increase in the prevalence of large babies. This is accompanied by increasing risks of fetal malformations, damage to mother and child during parturition, and an increased risk of both obesity and type 2 diabetes in mother and the adolescent child. The prevalence of overweight girls is therefore a public health challenge with intergenerational implications.

Even in developing societies like India as they industrialize and urbanize, and as standards of living continue to rise, weight gain and obesity are beginning to pose a growing threat to the health of the citizens. According to the WHO’s global database, India has a preschool childhood obesity Prevalence of about 1%.

In 1998, 77% of the total number of deaths attributable to NCDs occurred in developing countries, and 85% of the disease burden was borne by low-income and middle-income countries.

The complex range of factors that interact to determine the nature and course of this epidemic needs to be understood in order to adopt preventive strategies to help developing countries.

A recent study of gestational weight gain and preeclampsia was done by Cedergren (2006). The adjusted odds ratio of developing pre-eclampsia for women with weight gains of less than 18 lb was substantially reduced for all women with a BMI more than 20 when compared with women who gained

### Table 8: Criteria for classification of prepregnancy weight status

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt; 19.8</td>
<td>&lt; 18.5</td>
</tr>
<tr>
<td>Normal</td>
<td>19.8–26.0</td>
<td>18.5–24.9</td>
</tr>
<tr>
<td>Overweight</td>
<td>&gt; 26.0–29.0</td>
<td>25.0–29.9</td>
</tr>
<tr>
<td>Obese</td>
<td>&gt; 29.0</td>
<td>30.0+</td>
</tr>
</tbody>
</table>

Source: Institute of Medicine (1990); National Heart, Lung, and Blood Institute (1998)

### Table 9: Distribution of body mass index (BMI) of rural and urban adults of both sexes from a nationally representative survey covering 187 district in 18 states (n = 142220 rural and 35621 urban adults)

<table>
<thead>
<tr>
<th>BMI distribution (%)</th>
<th>Rural</th>
<th>Urban</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>&lt; 18.5 kg/m²</td>
<td>29.3</td>
<td>38.2</td>
</tr>
<tr>
<td>18.5–25.0 kg/m²</td>
<td>66.7</td>
<td>57.7</td>
</tr>
<tr>
<td>25.0–30.0 kg/m²</td>
<td>3.7</td>
<td>3.6</td>
</tr>
<tr>
<td>&gt; 30.0 kg/m²</td>
<td>0.3</td>
<td>0.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 18.5 kg/m²</td>
<td>38.2</td>
<td>29.1</td>
</tr>
<tr>
<td>18.5–25.0 kg/m²</td>
<td>68.7</td>
<td>64.8</td>
</tr>
<tr>
<td>25.0–30.0 kg/m²</td>
<td>5.4</td>
<td>5.4</td>
</tr>
<tr>
<td>&gt; 30.0 kg/m²</td>
<td>0.3</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Source: District Nutrition Profiles Survey 1998, Ministry of Human Resources, Government of India
between 18 lb and 35 lb. Women in all BMI groups who gained more than 35 lb were at greater risk of developing preeclampsia than women who gained between 18 lb and 35 lb. Even societies like India are dealing with problems of overweight.

**Gestational Diabetes Mellitus**

It is seen that the weight gain ratio (observed weight gain over the IOM recommended weight gain) was higher for women with gestational diabetes when compared statistically with women with normal glucose tolerance. The statistical likelihood of developing gestational diabetes was increased by both prepregnancy overweight and obesity status, while the interaction with weight gain during pregnancy was only marginal.

**Obesity Before Pregnancy Linked to Childhood Weight Problems**

“Prevention of childhood obesity needs to begin before a woman becomes pregnant”

—National Institutes of Health (NIH)

The study done by NIH showed a significant relationship between a mother’s weight prior to pregnancy and her child’s weight. If a woman was overweight before she became pregnant, her child was nearly three times more likely to be overweight by age 7 compared to a child whose mother was not overweight or obese, according to the study.

“Smoking during pregnancy causes a host of serious problems, there is growing body of evidence which suggests that smoking during pregnancy may be a key risk factor that increases a child’s chances of being overweight”.

Breastfeeding had a slight effect on weight at each measurement. As much as 5% fewer children who were breastfed were also overweight, compared to bottlefed babies.

**Fetal Origin of Disease Hypothesis**

The fetal origins of disease hypothesis states that susceptibility to adulthood cardiovascular disease (CVD), non-insulin-dependent diabetes mellitus (NIDDM), and the insulin resistance syndrome (IRS) is programmed in utero and is a response to fetal undernutrition. The hypothesis is also referred to as the thrifty phenotype hypothesis.

Over 15 years ago, Barker and colleagues published findings suggesting that fetal growth impairment is associated with CVD.

Numerous studies have now shown an inverse relationship between markers of fetal growth and the later development of CVD and IRS. Evidence is remarkably consistent for adult men and women.

In the Rancho Bernardo Study (depicted), women that had a LBW and were obese as adults had the highest prevalence of the metabolic syndrome (about 30%) (Fig. 10).

Investigators found that birthweight was inversely related to subsequent development of diabetes only among infants that were not breastfed. These studies suggest that the relationship between birthweight and the adult metabolic syndrome may be modified substantially by the presence of other risk factors, findings that are important for identifying opportunities for prevention.

Pregnancy, on the other hand, may be an optimal time to examine the fetal origins of disease hypothesis. Pregnancy can provoke conditions that are established or suspected precursors to the adult metabolic syndrome. For example, women who develop gestational diabetes are at an elevated risk for developing type 2 diabetes. Some studies suggest the risk of type 2 diabetes among women that have had gestational diabetes may be as high as 40%.

In a report from the Medical Birth Registry of Norway, women’s own birthweight was inversely related to their later risk for gestational diabetes (Fig. 11). The U-shaped curve presented here has been identified in other studies and is most likely attributed to the increased birthweight and increased diabetes risk of offspring of diabetic mothers.

These findings suggest that IUGR and not prematurity is the important predictor for later risk for gestational diabetes.

**Role of Nutrition in Pregnancy**

Human epidemiological studies and appropriately designed dietary interventions in animal models have provided considerable evidence to suggest that maternal nutritional imbalance and metabolic disturbances, during critical time windows of development, may have a persistent effect on the health of the offspring and may even be transmitted to the next generation.
Changing Trends in Maternal Nutrition and Interventions

Fig. 11: Risk for gestational diabetes by women’s own birthweight

Animal studies provide the best evidence to date. In rats, protein restrictive diets during pregnancy led to lower birthweight offspring and to higher blood pressure and reduced insulin secretion in adulthood (Fig. 12). Other studies of guinea pigs and sheep also have found that undernutrition during pregnancy altered insulin responses in offspring. These studies provide the best evidence that maternal nutrition can program the offspring physiologically in such a way as to influence disease susceptibility in adulthood.

Alternative Hypothesis, Genetic Influences

According to this hypothesis by Hattersley and Tooke fetal genetics would determine glucose sensing and insulin secretion by the fetal pancreas and thereby influence insulin mediated growth of the fetus. Defects in glucose sensing and insulin secretion would result in LBW, and lead to insulin resistance in adulthood.

Fig. 12: Animal studies


Fig. 13: Fetal insulin hypothesis

Dietary Consumption and Lifestyle Changes during the Nutrition Transition in India

Food balance data from the Food and Agriculture Organization (FAO) show that the change in energy intake in Asian countries has been small, but there have been large changes in consumption of animal products, sugars and fats. The net effect has been a marked shift in the diet with energy from fat (both animal and vegetable) increasing each year. Table 10 presents data from the District Nutrition Profiles Survey, which shows differences particularly in the intakes of vegetables and fruits, and fats and oils between urban and rural populations. The National Family Health Survey (NFHS) provides information on the consumption of specific and selected foods once a week at least and demonstrates, for instance, that the percentage of women consuming meat/chicken/fish once a week is higher in urban than rural locations and not related to standard of living index or educational status except for the illiterate group.

Intake of Fat in the Diet

It has been well documented that the intake of fat in the diet has been increasing in developing countries based on the
food balance analyses carried out by the FAO. Trends based on food balance sheet data show that the per capita supply of animal products has increased from 7.0 g in 1965 to 12.9 g in 1999, thus contributing almost twice the energy content (increased from 104 kcal/capita/day to 192 kcal/capita/day).

The differences in the dietary fat intake between rural and urban, and between lower and higher socioeconomic groups are largely due to large differences in the intakes of visible fats, except in the highest income group (Table 11) where much of it is from animal sources, with the invisible fat intake being similar among these groups. Computations also suggest that 25% of all available fat is consumed by the rural population, while 40% of all edible fat available in India is being consumed by 5% of the total population (i.e. 20% of the urban population that constitutes the “urban-rich”).

### Consumption of Fruits and Vegetables and Dietary Fiber

India has a prominent share in the global production of fruits and vegetables. However, much of this does not seem to be reflected in increases in the consumption of fruits and vegetables—perhaps largely the result of their production as cash crops for export and sale.

### Pollution of Food by Chemicals

There are several other factors likely to contribute to the emerging burden of chronic diseases in India for women and men and for pregnant women. Pollution of food sources by pesticides, chemical fertilizers and toxic contaminants is common in rapidly industrializing societies.

The specific objectives of nutrition in pregnancy are:
- To prevent malnutrition by promoting appropriate infant and young child feeding practices
- To reduce micronutrient malnutrition (particularly in children, adolescents and women of reproductive age)
- To promote healthy lifestyles and interventions for diet related NCDs. In India to reduce anemia just making people about wearing shoes in the fields and making availability of adequate latrine facilities would go a long way in eradicating anemia (only 18.9% of rural population has access to latrines as compared to 80.7% of urban population)
- To assist HIV/AIDS programs with training for reducing mother to child transmission and nutritional support for people living with HIV/AIDS.

### REACHING WOMEN

To improve nutrition in women we have to reach women but how to reach them for nutritional programs for their own good is not clear.
- Women’s nutrition supplementation studies in Guatemala and the Gambia have obtained good participation rates with measurable anthropometric results for women and children.
- A CARE feeding program in India found women more likely to participate if the food ration were ready to eat and women could pick it up on their way to the fields.
- A World Bank project in Indonesia induced women to eat better diets through a nutrition education program.

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**Table 11: Dietary fat intake by urban and rural socioeconomic groups in India**

<table>
<thead>
<tr>
<th>Income group</th>
<th>Fat intake (g/d)</th>
<th>Visible</th>
<th>Invisible</th>
<th>Total of energy</th>
<th>Fat as %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rural*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 150</td>
<td>25</td>
<td>27.4</td>
<td>53.4</td>
<td>18.5</td>
<td></td>
</tr>
<tr>
<td>90–150</td>
<td>17</td>
<td>25.6</td>
<td>42.6</td>
<td>14.8</td>
<td></td>
</tr>
<tr>
<td>60–90</td>
<td>13</td>
<td>22.8</td>
<td>35.8</td>
<td>13.3</td>
<td></td>
</tr>
<tr>
<td>30–60</td>
<td>9</td>
<td>20.3</td>
<td>28.3</td>
<td>11.0</td>
<td></td>
</tr>
<tr>
<td>&lt; 30</td>
<td>5</td>
<td>18.0</td>
<td>23.0</td>
<td>9.5</td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>9</td>
<td>25.6</td>
<td>34.6</td>
<td>13.7</td>
<td></td>
</tr>
</tbody>
</table>

Source: Computed from dietary intake data of the National Nutrition Monitoring Bureau, 1987.

*Rural income in rupees per month

---

**Table 10: Rural-urban differences in consumption of food items (g/consumption unit (CU)/day) and nutrients in India—based on a recent survey covering 187 districts in 18 states (n = 142220 rural and 35621 urban adults)**

<table>
<thead>
<tr>
<th>Food items</th>
<th>Rural 1998</th>
<th>Urban 1998</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cereals</td>
<td>488.1</td>
<td>419.5</td>
</tr>
<tr>
<td>Pulses and legumes</td>
<td>32.5</td>
<td>54.9</td>
</tr>
<tr>
<td>Leafy vegetables</td>
<td>31.8</td>
<td>23.4</td>
</tr>
<tr>
<td>Other vegetables</td>
<td>70.2</td>
<td>75.1</td>
</tr>
<tr>
<td>Roots and tubers</td>
<td>98.6</td>
<td>126.6</td>
</tr>
<tr>
<td>Fruits</td>
<td>14.7</td>
<td>37.6</td>
</tr>
<tr>
<td>Milk and milk products</td>
<td>125.9</td>
<td>142.5</td>
</tr>
<tr>
<td>Flesh foods</td>
<td>22.0</td>
<td>19.0</td>
</tr>
<tr>
<td>Fats and oils</td>
<td>14.3</td>
<td>21.2</td>
</tr>
<tr>
<td>Sugars and jaggery</td>
<td>20.2</td>
<td>21.9</td>
</tr>
</tbody>
</table>

**Nutrients**

<table>
<thead>
<tr>
<th></th>
<th>Rural 1998</th>
<th>Urban 1998</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy (kcal)</td>
<td>2,321.0</td>
<td>2,259.0</td>
</tr>
<tr>
<td>Protein (g)</td>
<td>70.0</td>
<td>70.0</td>
</tr>
<tr>
<td>Fats (g)</td>
<td>31.3</td>
<td>39.5</td>
</tr>
</tbody>
</table>

Source: District Nutrition Profiles Survey 1998, Ministry of Human Resources, Government of India
Behavioral trials determined that pregnant women were willing to increase their total food intake slightly and to eat more greens but were unwilling to eat extra protein or a great deal of additional food. Compliance with iron supplements was good and the negative side effects (of which they were forewarned) did not reduce compliance. This Indonesian work demonstrates that women can be motivated to improve their nutrition so long as it does not conflict with firmly held beliefs.

**Relations between Women’s Issues and Nutritional Issues**

These two issues are very closely intertwined.

- **Enhanced women’s status benefits nutrition:** Programs intended to improve nutritional conditions for women and their families can only be successful if problems of women are realized (Fig. 15).
  - Many women in poor societies are overworked by too many calls on their time and have too few resources to adequately cope with their circumstances. *Women’s fatigue* is now recognized as a social disease affecting not only their own health and well-being, but also their ability to care for the nutrition of their families.
  - Women’s access to productive resources that means if they start earning then increased income and more importantly increased control over it (both women’s income and total household income) would mean better nutrition.
  - Enhanced educational opportunities, social knowledge and decision-making power are prerequisites for more productivity.
  - Increased time available and devoted to productive tasks as well as enhanced efficiency of production.
  - In other words social, cultural and political empowerment of women must be regarded as prerequisites to solving any nutritional problems.

- **Improved nutrition benefits women’s issues:** Nutrition in pregnancy helps not only for well-being of mother and child but by concentrating on proper nutrition throughout the life cycle of a woman, she would have a much healthier life to pursue her multiple responsibilities for production, reproduction and care of family more efficiently, thereby in turn enhancing her social and economic status.

**Possible Interventions**

The over-riding need even in poor countries is for women empowerment: Equality of status in society and in the family, an equal role in making decisions. In viewing the changes in women’s position in industrialized countries at the start of this introduction, several factors were noted which both helped bring about these changes, and were themselves part of the improvement. In some very basic needs women in poor societies to this day lag far behind, notably in this context in their food security and access to health services.

**Education of Women**

Emphasis on education for women is so clearly correct that we can only reinforce this priority. It is well established that children of better educated women have better nutritional status, usually even allowing for income and other similar effects. Education here, rightly, means broad education, and is not just specific to health, nutrition, and child-rearing practices, essential as these are. A nutrition perspective would give major priority to women’s education, for its direct effects and its role in changing society for the better.

Mother’s education is strongly related to children’s malnutrition. According to NFHS, children of illiterate mothers are twice as likely to be undernourished or stunted as compared to literate mothers.

**Right to Decide about Reproduction**

Women’s ability to decide on the timing of their reproduction is similarly seen by many as fundamental human right. Here again, a nutritional view may help to reinforce this position, pointing out the convincing case that too frequent pregnancies, to too young mothers, lead to malnutrition and
increased maternal and child mortality; and that the reasons, although intuitive, are well understood.

**Time Management and Availability of Household Technologies**

Modern access to energy, as electrification, cooking gas is needed for environmental reasons and to save time and labor of women in collecting fuel.

**Availability of Better Health Services**

Serious deficiencies in health services for women contribute to the high mortality risk of childbearing, and their overall health problems. This not only has direct effects on women’s health, but contributes to the cycle of poverty. Moreover, children and the next generation are disadvantaged by LBW, malnutrition, and compromised caring capacity.

**CONCLUSION**

- There is strong epidemiological evidence of an association between maternal nutritional status, both during and prior to pregnancy (prepregnancy weight and weight gain during pregnancy), and birthweight and IUGR.
- Many trials of nutritional supplementation during pregnancy have been carried out, only to show a modest effect of supplementation on birthweight, even in undernourished women (about 100 g), and, according to one review, no long-term benefits to the child in terms of growth or neurocognitive development.
- Whether the supplementation trials were carried out at the right time during pregnancy still remains doubtful. Future supplementation during pregnancy is probably best targeted at nutritionally disadvantaged populations during all three trimesters of pregnancy.
- One of the major drawbacks of many of the studies carried out has been the failure to distinguish between IUGR and prematurity, and especially between stunted and wasted intrauterine growth retarded infants. Such distinctions would be most beneficial for future trials.
- More research is also needed on the effect of maternal nutrition during pregnancy on preterm delivery, and during consecutive pregnancies and prior to pregnancy.
- In the interim, maternal supplementation may be expected to have some benefit, but alone seems unlikely to make a major difference to LBW and child nutrition and it is overall improvement in women’s nutrition which is more important.
- Analyses using the Pregnancy Nutrition Surveillance System show that the risk of preterm delivery varied by both maternal prepregnancy BMI and gestational weight gain.
- Overweight before during and after pregnancy should be highlighted.

- More research should be done on “in utero origin of adult metabolic syndrome”
- Women should be empowered by education and job availability, time management appliances so that they can have better control on sources of nutrition and supply.

**Summary and Approaches for Alleviation of Maternal Nutritional Depletion**

Too young, too old, too many and too close—this is how UNFPA usefully summarizes the problem of frequent pregnancies and periods of lactation that contribute to nutritional depletion of the mother.

**FOR FUTURE CONSIDERATIONS**

**Adolescent Mothers**

Current consideration of pregnancy in adolescence and what guidance or interventions are appropriate for adolescent mothers with regard to obesity risk may need to be revisited. For example, the 1990 IOM recommendations suggest that very young adolescents gain up to the maximum of the range for their BMI. However, relative to older mothers, postpartum weight retention in young adolescents could be serious, as their lifetime weight retention risk may be far greater. For example, during the discussion, data presented about adolescent mothers suggested a relationship between adolescent growth during pregnancy and higher gestational weight gain and postpartum weight retention. In addition, many adolescent mothers (especially younger adolescents) would be expected to be gaining weight as part of typical development in the absence of a pregnancy. These biological factors, coupled with psychological and sociodemographic characteristics of adolescent mothers, make this a highly specialized population in need of focused attention.

**Obese and Morbidly Obese Women**

As obesity has increased generally, so has its incidence among women of childbearing age as well as among those who become pregnant. Obesity in women can cause serious pregnancy-related complications, but it can also be modified to improve birth outcomes. Additional attention is needed for the population of obese women who become pregnant.

A number of practical issues also arise, especially for morbidly obese patients and those who were morbidly obese but underwent bariatric surgery or similar procedures before becoming pregnant. For example, medical practice and equipment may need to be modified to accommodate very large women during pregnancy and especially during delivery. Finally, obese women with a range of medical conditions in addition to their pregnancy can face additional challenges in the management of their pregnancy.
Whole Person Approach (Fig. 16)

We should give equal attention to physical activity and not only to nutrition to have a whole person approach. It was noted that the 1990 IOM recommendations address weight only. In general, nutrition for pregnant and lactating women is currently focused on caloric intake, without specific attention paid to specific nutritional requirements or guidelines. Caloric intake and good nutrition intersect when women make specific food choices. In addition to nutrition guidance, weight control is also about physical activity. It is also important to understand the biological variability in women. Individual metabolism affects caloric and physical activity outcomes. More stress should be laid on exercise and physical activity during pregnancy.

BIBLIOGRAPHY


INTRODUCTION

We have progressed from an era of bed rest prescription to finally into the 21st century when we are talking about prescription of exercise and even dance therapy in pregnancy. Many women of childbearing age, 42% by one estimate, report exercising during pregnancy and many strongly desire to continue to do so.

The traditional medical advice has been for exercising women to reduce their habitual levels of exertion in pregnancy and for nonexercising women to refrain from initiating strenuous exercise programs. This advice was based on concerns that exercise could affect early and late pregnancy outcomes by increasing core body temperature during embryogenesis, increasing the risk of congenital anomalies, and shifting oxygenated blood and energy substrates to maternal skeletal muscle away from the developing fetus, leading to disturbances in growth.

Early studies focusing on hard physical work combined with undernutrition and on forced exercise in laboratory animals tend to support these concerns. Other concerns included:
- The risk of maternal musculoskeletal injury due to changes in posture and center of gravity
- Fetoplacental injury due to blunt trauma
- Stress effects from sudden motions

But recent investigations, focusing on both aerobic and strength-conditioning exercise regimens in pregnancy have shown:
- No increase in early pregnancy loss
- Late pregnancy complications
- Abnormal fetal growth
- Adverse neonatal outcomes

So, the new evidence suggests that previous recommendations have been overly conservative.

COCHRANE REVIEW

Aerobic exercise is physical activity that stimulates a person’s breathing and blood circulation. The review of 11 trials, involving 472 pregnant women, found that pregnant women, who engage in vigorous exercise at least two to three times per week, improve (or maintain) their physical fitness, and there is some evidence that these women have pregnancies of the same length as those who maintain their usual activities. There is too little evidence from trials to show whether there are other effects on the woman and her baby. The trials reviewed included noncontact exercises such as swimming, static cycling and general floor exercise programs. Most of the trials were small and of insufficient methodological quality. Therefore, larger, better trials are needed before confident recommendations can be made about the benefits and risk of aerobic exercise in pregnancy (The Cochrane Database of Systematic Reviews, 2007, Issue 1).

Low-impact aerobic dance, compared with walking at similar heart rates, results in a lower maternal metabolic rate and increases the transient stress on the fetus but this is just a small study.

So pregnancy should not be a state of confinement and pregnant women should be encouraged to engage in physical
activity, move about, work and exercise, and eat healthy. Exercise has minimal risks and many confirmed benefits for most women.

So in the light of all these and so many other studies and along with support of guidelines from the American College of Obstetricians and Gynecologists, the Royal College of Obstetricians and Gynaecologists (RCOG), [Society of Obstetricians and Gynaecologists of Canada, Canadian Society for Exercise Physiology (SOGC/CSEP)] the latest suggestions are:

- All women should be encouraged to participate in aerobic and strength-conditioning exercise as part of a healthy lifestyle during their pregnancy (II-1, 2B)
- Reasonable goals of aerobic conditioning in pregnancy should be to maintain a good fitness level throughout pregnancy without trying to reach peak fitness level or training for athletic competition (II-1, 2 C)
- Women should choose activities that will minimize the risk of loss of balance and fetal trauma (III-C)
- Women should be advised that adverse pregnancy or neonatal outcomes are not increased for exercising women (II-1, 2B)
- Initiation of pelvic floor exercises in the immediate postpartum period may reduce the risk of future urinary incontinence (II-1C)
- Women should be advised that moderate exercise during lactation does not affect the quantity or composition of breast milk or have an impact on fetal growth (I-A)
- Exertion at altitudes up to 6,000 feet appears to be safe. Engaging in physical activities at higher altitudes carries a risk of hypoxemia.

**WHAT ARE THE BENEFITS OF EXERCISE DURING PREGNANCY?**

Childbirth is among the most physically stressful challenges a woman ever faces. Regular exercise during pregnancy:

- Strengthens muscles needed for labor and delivery
- Helps reduce backaches, constipation, bloating, and swelling
- Improves posture
- Gives energy and improves mood
- Lessens some of the discomforts of pregnancy
- Helps one feel less tired and sleep better; strength and stamina are increased.

**Benefits to the Infants**

- Infants have less body fat at birth
- Infants are less cranky, have a reduction in the incidence of infant colic
- Greater neurodevelopmental scores in oral language and motor areas (tested at age 5).

**RISKS OF SEDENTARY LIFESTYLE IN PREGNANCY**

If women are prescribed bed rest and do not do regular physical activity or exercise, then they are prone to following complications in pregnancy:

- Loss of muscular tone and strength
- Cardiovascular fitness is decreased
- Excessive maternal weight gain
- Higher risk of gestational diabetes
- Higher risk of pregnancy-induced hypertension
- Development of varicose veins
- Development of deep vein thrombosis
- A higher incidence of physical complaints such as dyspnea or low back pain
- Poor psychological adjustment to the physical changes of pregnancy.

**WHEN AND HOW TO START AN EXERCISE PROGRAM?**

- The best time to initiate an exercise program is in the second trimester, when the nausea, vomiting, and profound fatigue of the first trimester have passed and before the physical limitations of the third trimester begin. Concerns about the teratogenic effect of high core body temperatures in the early first trimester have not been demonstrated in studies of exercising women.
- Women who have been exercising prior to pregnancy may continue their exercise regimens throughout pregnancy using the guidelines outlined below (II-1, 2B).

**Conditions Requiring Medical Supervision while Undertaking Exercise in Pregnancy**

- Cardiac disease
- Restrictive lung disease
- Persistent bleeding in the second and third trimesters
- Preeclampsia or pregnancy-induced hypertension
- Preterm labor (previous/present)
- Intrauterine growth restriction
- Cervical weakness/cerclage
- Placenta previa after 26 weeks
- Preterm prelabor rupture of membranes
- Heavy smoker (more than 20 cigarettes a day)
- Orthopedic limitations
- Poorly controlled hypertension
- Extremely sedentary lifestyle
- Unevaluated maternal cardiac arrhythmia
- Chronic bronchitis
- Multiple gestation (individualized and medically supervised)
Maternal Exercises, Yoga and Dance Therapy

CHAPTER

5

Maternal Exercises,
Yoga
and Dance Therapy

39

Poorly controlled thyroid disease
Morbid obesity (body mass index greater than 40)
Malnutrition or eating disorder
Poorly controlled diabetes mellitus
Poorly controlled seizures
Anemia (hemoglobin less than 100 g/L).

Healthcare professionals should use their professional judgment as to what extent and duration, exercise should be undertaken in the above circumstances.

Warning Signs to Terminate Exercise
If any of the following symptoms appear during exercise then patient should immediately stop exercise and seek medical attention:

- Excessive shortness of breath
- Chest pain or palpitations
- Presyncope or dizziness
- Painful uterine contractions or preterm labor
- Leakage of amniotic fluid
- Vaginal bleeding
- Excessive fatigue
- Abdominal pain, particularly in back or pubic area
- Pelvic girdle pain
- Reduced fetal movement
- Dyspnea before exertion
- Headache
- Muscle weakness
- Calf pain or swelling.

WHICH MUSCLE GROUPS ARE MOST IMPORTANT TO EXERCISE?

In addition to heart, the three muscle groups, one should concentrate on during pregnancy are the muscles of abdomen, back, and pelvis.

- Strengthening abdominal muscles will make it easier to support the increasing weight of baby. One will also be able to push with more strength and more effectively during the second stage of labor.
- Strengthening back muscles and doing exercises to improve posture will reduce the strain of pregnancy on lower back. It will help prevent discomfort caused by poor posture.
- Strengthening pelvic muscles will allow vagina to dilate more easily during delivery. This will help prevent urinary problems later on as stress incontinence.

Exercise should be made a part of daily life. Daily tasks can double the exercise sessions if one does the following:

- Tighten abdominal muscles when standing or sitting
- Squat when lifting anything, whether it is light or heavy
- Rotate feet and ankles anytime your feet are elevated
- Check posture each time you pass a mirror

Pilates During Pregnancy
The benefits that have been associated with exercise and pregnancy are based on research done on cardiovascular exercise (aerobic). There has been minimal research done on the independent benefits of pilates. Because the base of pilates is “core” training, we believe that pilates can be a beneficial adjunct to any exercise program. The pregnant woman should make sure she is working with a pilates instructor who is trained in prenatal exercise.

Yoga Exercises in Pregnancy
The benefits that have been associated with exercise and pregnancy are based on research done on cardiovascular exercise (aerobic). There has been minimal research done on the independent benefits of Yoga. We believe that Yoga can be a beneficial adjunct to any exercise program. For the pregnant woman, she should make sure she is working with a Yoga instructor who is trained in prenatal exercise. Pregnant women should avoid exercise in extreme environmental conditions, i.e. hot Yoga should be avoided and avoid inverted positions or positions that require spending long periods of...
time on your back. As always, pregnant women should not stretch past their prepregnancy range of motion.

**Tae-Bo During Pregnancy**

Tae-Bo, like any other exercise that includes a cardio, flexibility and strength component, is a good adjunct to training program while pregnant. One has to be careful with fast, uncontrolled movements and jumping or high bouncing activities. Smaller range of motion should be used when exercising and fast kicks and high leg thrusts should be avoided.

**PROTOCOL OF EXERCISE**

In general, exercise prescriptions or exercise protocols are defined by type, intensity, duration, and frequency of exercise. In addition to these four factors, it is important to consider the likes and dislikes of the individual (i.e. working out at home, in gyms, outside, biking, walking, swimming—swimming is a great activity) to perform while pregnant. This activity uses all of the major muscle groups in the body. The water also supports your extra pregnancy weight and decreases added strain on joints (Figs 1 and 2).

Each day a pregnant woman should take the time to relax and stretch, controlling breathing (inhaling and exhaling) throughout the entire stretch, while avoiding bouncing. At the beginning or end of each exercise session, one should take the time to stretch all muscles. Pregnant women should especially focus on calves and legs to avoid cramping.

**DURATION OF EXERCISE**

When prescribing exercise duration; it is important to also consider the environment during exercise. It is important to not exercise in excess of 45 minutes in an environment which does not provide proper ventilation or air conditioning, dangers of thermoregulation can occur. Proper hydration throughout exercise is important remember. Thirst is not a sign of rehydration, it is a sign you are already dehydrated, drink plenty of fluids throughout the day, as well as during exercise sessions are must (Fig. 3).

**INTENSITY OF EXERCISE DURING PREGNANCY**

The development of an exercise program requires individual adaptation. Prior to advising exercise, physician should assess:
- Fitness status
- Current athletic or exercise activities
- Individual goals of exercise

Most guidelines advocate a maximal heart rate of 60–70% for women who were sedentary prior to pregnancy and the upper range of 60–90% of maximal heart rate for women wishing to maintain fitness during pregnancy (Table 1).

Women who were active prior to gestation can continue their exercise routine as long as there are no contraindications. Women beginning an exercise program during pregnancy should start with short durations, 15 minutes a day, and add 5 minutes every week or 2 weeks they are exercising, until they are achieving 30 minutes of moderate activity a day on most days of the week. Health effects can still be accomplished when exercise is broken up throughout the day. Less is better than nothing at all. Starting to add activity into daily schedule when health of the pregnant woman as well as that of the unborn child is at the forefront of the mind is a perfect style.
of healthy living and staying “fit for two”, and has a higher chance of becoming a real lifestyle change.

Other measures of exercise intensity include the “talk test” and a visual rating of perceived exertion. When using the “talk test”, exercise takes place at a comfortable intensity, allowing the woman to maintain a conversation during exercise. A method of measuring perceived exertion is the Borg’s scale of perceived exertion (Table 2). This approach seems to be effective as, when exercise is self-paced, most pregnant women will voluntarily reduce their exercise intensity as pregnancy progresses. For moderate exercise during pregnancy, ratings of perceived exertion should be 12–14 (somewhat hard) on the 6–20 scale.

**Mode of Activity**

- Although there is no established upper level of safe exercise intensity, regular exercisers before pregnancy should be able to engage in high intensity exercise programs, such as jogging and aerobics, with no adverse effect to mother or fetus. Women who have attained a high level of fitness through exercise prior to pregnancy should exercise caution in engaging in higher levels of fitness activities during pregnancy. They should also expect a decline in overall activity and fitness levels as pregnancy progresses.

  - It is suggested that a warm up and cool down period be included in any exercise regimen.
  - There is less evidence on strength conditioning, weight training and stretching exercises such as Yoga and pilates in pregnancy. Considering complementary and alternative therapies in pregnancy, limited evidence currently exists and attention needs to be given for undertaking high-quality randomized controlled trials in these areas.
  - Women should not scuba dive in pregnancy, as the fetus is not protected for decompression sickness and gas embolism.
  - Women are cautioned about the potential for loss of balance and fetal trauma if they participate in horseback riding, downhill skiing, ice hockey, gymnastics and cycling during pregnancy.
  - Women who have gestational diabetes mellitus must take particular precautions with exercise including monitoring blood glucose, regulating meal times, scheduling rest periods and carefully tracking fetal activity and uterine contractions.
  - No adverse effects on the fetus have been reported to occur during water exercise in pregnancy. The physiology of water exercise offers some compensation for the physiological changes of exercise on land that may beneficially affect pregnancy. If a woman is exercising in water (as in aquanatal classes) the water temperature should not exceed 32°C. 35°C is the recommended maximum while using a hydrotherapy pool.

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**Table 1: Modified heart rate target zones for aerobic exercise in pregnancy**

<table>
<thead>
<tr>
<th>Maternal age (years)</th>
<th>Heart rate target zone (beats/minute)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 20</td>
<td>140–155</td>
</tr>
<tr>
<td>20–29</td>
<td>135–150</td>
</tr>
<tr>
<td>30–39</td>
<td>130–145</td>
</tr>
<tr>
<td>&gt; 40</td>
<td>125–140</td>
</tr>
</tbody>
</table>

**Table 2: Borg’s rating of perceived exertion**

<table>
<thead>
<tr>
<th>Rating</th>
<th>Perceived exertion</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Very, very light</td>
</tr>
<tr>
<td>7</td>
<td>Very, very light</td>
</tr>
<tr>
<td>8</td>
<td>Somewhat light</td>
</tr>
<tr>
<td>9</td>
<td>Fairly light</td>
</tr>
<tr>
<td>10</td>
<td>Somewhat hard</td>
</tr>
<tr>
<td>11</td>
<td>Hard</td>
</tr>
<tr>
<td>12</td>
<td>Very hard</td>
</tr>
<tr>
<td>13</td>
<td>Very hard</td>
</tr>
</tbody>
</table>

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*Fig. 3: Duration of exercise*
**Frequency of Exercise**

Frequency is a relatively simple factor in exercise prescriptions. When there are no contraindications with exercise for a female during pregnancy they should try to achieve the recommendations stated by the American College of Sports Medicine and the Centers for Disease Control and Prevention—achieving 30 minutes a day of exercise on most if not all days of the week.

**Tips for the First Trimester**

Dance as you normally would, but keep a few precautions in mind:

- Remember to warm up beforehand to prepare your joints and muscles for exercise, which also builds up your heart rate slowly. Skipping a warm-up could strain ligaments and joints, leading to injury.
- The intensity of dancing should be adjusted according to how one feels. A good rule of thumb—slow down if one cannot comfortably carry on a conversation.
- Keep workout at low-impact by keeping one foot on the floor at all times, substituting marching or stepping side to side for jumps.

**Tips for the Second and Third Trimesters**

Center of gravity shifts as abdomen enlarges, so pay extra attention to balance.

In Africa, the childbearing woman is said to be the key to the universe. She holds the future generation within her womb, as you do. African dance steals you away from the discomfort you may be feeling and makes you gloriously aware of the miracle happening within you. Simply, naturally, you begin to appreciate the fullness of your body, and the life that you encompass.

**Tribal Effect**

Finally, beyond the physical benefits of dancing during pregnancy, there is also that great thing called having a good time with other women. And it goes beyond just laughing it up while shaking your belly with other moms-to-be. Tribal effect of dancing together has a positive impact on the mother’s experience of pregnancy and helps reduce stress. Cowlin says, “These are psychosocial benefits of group physical activity.” Sounds like another great reason to start dancing.

**Belly Dancing Related to Birth Process**

The connection between belly dancing and birth is not a new one. Work has been done, noticed and unnoticed to bring the dance to the attention of birth educators. The link was forged as early as 1965 by Carolina Varga-Dinicu known as Morocco. She compared childbirth education taught at Mount Sinai Hospital in New York and major books like *Natural Childbirth* by Dr Frederick W Goodrich to her dance movements as she performed them.

In 1976, Gigi Groth Devitt, a member of Birth Day in Boston, collaborated with the dancer Barbara Brandt and demonstrated among other things, that Lamaze and this dance are based on the same method of muscle isolation. Around that same time, Edith Maxwell stressed the importance of movement during labor and showed how the movements of this dance help in *moving the baby down* the birth canal.

**COMPETITIVE ATHLETES AND PREGNANCY**

Elite athletes who continue to train during pregnancy require supervision by an obstetric care provider with the knowledge of the impact of strenuous exercise on maternal and fetal outcomes. All pregnant athletes must be made aware of proper hydration, the additional nutritional requirements of pregnancy and exercise, and the dangers of heat stress. Routine obstetric evaluation must be strongly recommended. Additional evaluation to assess fetal growth and well-being may be appropriate if clinically indicated. Although risks are minimal with moderation, even healthy active women should be examined periodically to assess the effect of their exercise programs on the developing fetus and their regimen should be adjusted and discontinued if necessary. Competitive athletes can expect to experience a reduction in their performance during pregnancy.

**Dance and Music**

Dance is a form of aerobic activity as it involves rhythmic movements of various groups of muscles. So whatever form of dance is performed, if it is not of high impact aerobic type and the performer enjoys the music and motion, then it is relaxing and good fitness and balance exercise.

**Benefits of Dancing During Pregnancy**

Dancing is a fantastic and fun exercise during pregnancy. Not only one gets the thrill of moving body to music one loves, but it will keep one flexible while toning muscles. One can get an aerobic workout from any fast-paced dance, or stretch and maintain muscle tone when holding positions in ballet. For maximum benefit, dance for at least 20 minutes three times a week, whether it’s in living room or in class. In addition to teaching women how to relax better, dance through pregnancy classes teach women to strengthen their core in preparation for the intense work of labor. Students learn to “strengthen against resistance in motions that help prepare for labor and birth, including Kegel’s, abdominal hiss/compress exercises and C-curves, as well as the abdominal core strength, upper back strength, and leg strength in dance-related movements”. These are treated as an integrated and flowing choreography.
In 1983, Wendy Buonaventura published a book, *Belly Dancing*, where she outlined the role of the dance throughout history in many cultures. She showed that the dance has always been a part of the birth process. The most exact comparative work was done by Morgana, in 1981. She compared specific movements of the dance to the phases of birth and the motion of the emergence of the baby. She has shown that the dance movements exercise all the birth muscles, and the rhythms, in fact, match the birth process. Her work leaves the impression that the dance could be none other than a birth dance.

Belly dance helps in strengthening muscles in the following motions:

- The circle is a sacred shape and is the very foundation of the dance. Moving the heart in a circle *strengthens and flexes the upper abdominals*.
- Moving the hips in a circle masses the internal organs, including the pelvic floor, and also *conditions the lower abdominals*.
- *Tension* is released by moving the wrists, shoulders and ankles in circles, and by rotating the spine in small circles.
- *Accents* introduce a faster rhythm and they are the power of the dance because they provide an outlet for inner impulses. Hip thrusting teaches control and builds concentration for focusing on one body part while the rest relaxes.
- *Shimmies*, all the different varieties, are the endurance of the dance. They require intense concentration and control of deep inner muscles. They loosen the back and hips and allow the focus to shift from pain to movement.
- *Body undulations are the flexibility of the dance*. The movements mirror how a woman’s body stretches to allow a baby to grow, and at the same time prepares the birth muscles for the task. Undulations also require concentration and focus, mainly because the muscles that need to be activated are unfamiliar to most people.

All of these qualities—relaxation, focus, endurance, and flexibility are needed in the birth process. Belly dance can be done standing, kneeling, lying down or walking. Lastly, belly dancing while giving birth means movement in general is encouraged while trying to give birth. It gives the power back to the process and allows women to find their way through the pain and fear of giving birth.

**Music Therapy During Pregnancy**

Although music therapy in healthcare settings is not new, bringing live music to the bedside is a new way of extending the caring tradition of nursing practice. Bedside musical care is consistent with a philosophy of holistic nursing practice and can be used during pregnancy, childbirth, and in neonatal care. It is defined as live music at the bedside, which is part of a treatment plan to foster integrity, well-being, and health for varied populations across the lifespan.

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**THE ACTUAL PLAN**

**First Trimester**

**Warm-Up**
Walking 8 minutes at a slow to moderate pace is enough to allow your heart rate to begin to rise.

**Aerobic Activity**
This can be 20–40 minutes of walking at a brisk pace, biking on a stationary bicycle, swimming, aerobics, etc. Remember if exercise is new, start with a shorter duration and slowly add to the amount of time one is exercising until one is able to achieve at least 30 minutes a day. Make sure one is comfortable with the intensity, one should still be able to carry on a conversation, and not use heart rate as an indication of intensity; Borg’s rating of perceived exertion can be used.

**Cool-Down**
Walking, biking, etc. for 5 minutes at a slower pace or lower resistance. This should be followed by 5–10 minutes of stretching. This can include all the stretches. Each stretch should be held for 10–30 seconds at a point of mild discomfort (in the muscle being stretched, if there is pain in the abdomen choose another stretch), one can repeat each stretch 2–3 times, with proper breathing.

**Sample Lifting Workout (Fig. 4)**
Remember days before lifting weights one should still start with a warm-up, enough to get the blood flowing to muscles. It is recommended to perform a total body workout 2–3 days a week.

**Workout 1**

**Upper Body**
- Dumbbell row 2 sets × 12 repetitions
- Incline dumbbell bench press 2 sets × 12 repetitions
- Side raise 2 × 12
- Bicep curl 1 × 12
- Tricep extension 1 × 12.

**Lower Body**
- Ball squat 3 × 15
- Leg extension 3 × 15 each leg (hold each for a count of three)
- Back bridge: 30.

**Workout 2**

**Upper Body**
- Pulldown 2 × 12
**Second Trimester**

**Warm-Up**

Same as first trimester.

**Aerobic Activity**

It is never too late to start. If this is where you are beginning, start slow and slowly increase in duration or intensity.

- **Machine chest press** $2 \times 12$ (remember dumb-bell exercises can be substituted)
- **Front raise** $1 \times 12$
- **Bicep curl** $1 \times 12$
- **Tricep pressdown** $1 \times 12$

**Lower Body**

- **Ball squat** $2 \times 20$
- **Leg extension** $2 \times 20$ each leg (hold each for a count of three)
Continue to use the rating of perceived exertion to measure your intensity, not your heart rate (heart rate is altered due to the physiologic changes of pregnancy and is not an accurate measure of exertion).

**Cool-Down**

Same as first trimester.

**Lifting Workout**

Same as first trimester. Remember that one does not want to increase the intensity in such a manner that lifting weights cause one to hold breath (thus, increasing blood pressure). Continue exercising at a moderate intensity. If certain exercises are uncomfortable then the workout should be altered in such a way that one is able to enjoy the exercises and perform them with no discomfort.

**Third Trimester**

**Warm-Up**

Same as first trimester.

**Aerobic Activity**

Use own body as a judge. Remember one should be able to carry on a conversation while working. Good communication with physician must be kept.

**Cool-Down**

Same as first trimester.

**Lifting Workout**

Same as first trimester. Remember avoid standing in one position for extensive periods of time, so move around. Supine position exercises should be avoided. Physicians should be consulted regularly. Exercise should be continued as long as one feels comfortable. Patient herself is the real judge of her body.

**INSTRUCTIONS FOR PATIENT EDUCATION ON STEPS OF EXERCISES: BODY WEIGHT STRETCHES**

**Upper Body**

**Shoulder Stretch**

- Hold raised elbow above chest
- Pull arm across body with opposite arm
- Keep shoulders square ahead

- Apply enough pressure to feel a stretch in shoulder
- Hold for 10–20 seconds, repeat with both arms (Fig. 5).

**Triceps Stretch**

- Bend your arm and pull it behind your head
- Reach as far down your back with the bent arm
- Apply pressure downward on your elbow with the opposite arm
- You should feel a stretch in the triceps, shoulder, and the middle of your back
- Hold for 10–20 seconds, repeat with both arms (Fig. 6).

**Fig. 5: Shoulder stretch**

**Fig. 6: Triceps stretch**
Seated Shoulder Stretch

- In a seated position, place arms straight behind you and reach as far as you can.
- Lean back slightly until a stretch is felt in the front of your shoulder.
- Hold for 10–20 seconds (Fig. 7).

Butterfly Stretch

- Sit on the ground, with back up tall, pull your heels as close to your body as possible.
- Remain sitting up tall and push out on your knees with your elbows.
- Do not bounce and hold for 10–30 seconds (Fig. 9).

Lower Body

Feet Together (Seated)

- Sitting on the ground, extend your legs out, keeping your feet together, and reach your hands toward your toes, grab your calves if you are unable to reach your toes.
- Relax your lower back to achieve an adequate stretch.
- Do not bounce and hold for 10–30 seconds (Fig. 8).

Modified Hurdler

- Sitting on the ground, bring a heel to the opposite leg.
- Keep leg straight and flat on the ground.
- Reach with both hands toward your toes. If you cannot reach your toes, reach as far as you can and grab under your leg.
- Do not bounce and hold for 10–30 seconds, repeat with other leg (Fig. 10).
STRENGTH TRAINING EXERCISES  
(INSTRUCTION FOR THE PATIENTS IN STEP OF EXERCISES)

Upper Body

Dumb-bell Row

- Place the opposite hand on the bench for support. Place one foot slightly behind your hips on the ground with your knee slightly bent; place the other knee on the bench below your hips. Your back should remain flat and your head should stay focused straight ahead (Fig. 11).
- Grasp the dumb-bell in one hand. Begin the exercise with the weight arm-length away. Slowly pull the weight to the chest while squeezing your shoulder blades together.
- Think of the hand as a hook and pull the weight using your upper back muscles. Pause the weight at the chest and slowly lower the weight to the starting position.
- Do not swing your arm to achieve the movement. Remain under control throughout the full range of motion.
- Perform desired repetitions on one arm then perform the same number on the opposite arm.

Pull Down

- Grasp the bar with an underhand grip (palms facing your body). Make sure your hands are evenly spaced and approximately shoulder width apart.
- Begin the exercise with arms straight. Pull the bar to your chest, attempting to pull the elbows down and backward.
- Remain sitting up tall, with your eyes focused straight ahead.
- Pause the bar at your chest before extending the arms back to the starting position.

Incline Dumb-bell Press

- Sit on a bench (with the back pad at a 45° angle), with your feet flat on the floor.
- Hold a dumb-bell in each hand. Start with the weight at chest level. With palms facing each other, slowly press the dumb-bells straight up.
- Pause with arms fully extended and then slowly lower the weights to starting position.
- When performing this exercise have a spotter standing directly behind you.

Machine Press

- Depending on where you are working out will depend on what type of machine is available.
- Adjust the seat so the handles hit you in the middle of your chest. Press the machine lever arms straight out.
- Pause with arms straight, then slowly lower the weight back to the starting position.
- A machine is a good alternative when there is no one available to spot dumb-bell exercises.

Side Raise

- Begin with arms hanging by the side of the body, thumbs pointed straight ahead.
- Keeping your arms straight, but not locked at the elbow, raise the arms out to your sides until the hands are parallel with your shoulders.
- Pause at the top and lower the weight.
- Do not swing the weight at the top. Remain under control throughout the full range of motion. Stand up tall throughout the exercise, never arching your back (Fig. 12).
Bicep Curl

- Stand tall (or sit on a bench). Hold the dumbbells with your arms fully extended. Slowly curl your arms at the elbows bringing the weights up to your chin.
- Lower the weights under control to the starting position.
- Do not swing or arch your back during the movement (Figs 13A and B).

Tricep Extension

- Sit on the edge of bench
- Hold a dumbbell in your hand
- Elbow straight and upper arm along with head
- Flex at the elbow taking your lower arm at the back of head, do not move elbow
- Bring to starting position. Do 10 repetitions and repeat with opposite arm (Figs 14A and B).

Lower Body

Ball Squat

- Your feet should be shoulder width apart, and a ball (Swiss ball, stability ball, or even a basketball can be used) should be placed between your lower back and the wall.
- You can hold dumbbells or plates in each hand at the sides of your body, or the exercise can be performed with just your body weight.
- Place your feet on the ground at a distance so when you squat your knees will not go over your toes.
- Slowly lower your body to where your upper leg is parallel to the ground (or as low as you can go, not exceeding parallel to the ground). Pause, and then slowly raise your body back to starting position.
- Keep your chest tall throughout the motion. The ball will roll during the exercise and will end at the middle of your back (when in the squat position).
- Do not allow your knees to turn in, but keep them in line with your toes (Fig. 15).
Maternal Exercises, Yoga and Dance Therapy

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Fig. 15: Ball squat

Leg Extension

- Start with both knees and both hands on the ground, with your back flat and your head looking straight ahead.
- Raise one leg up to the point where it forms a straight line from your head to your toes.
- Perform slowly, hold for a three count and then return to the start position, perform desired number of repetitions and then switch legs (Fig. 16).

Back Bridge

Lie on your back on the ground. Place your feet flat on the ground. Raise your hips up, squeezing your buttocks. Hold for a designated amount of time and then relax. This may not be able to be performed in the later stages of pregnancy (Fig. 17).

Pelvic Tilt

This can be performed on the ground or standing against a wall. When lying on the ground with your feet flat you will feel a small curve in the low of your back (the same is felt when standing against a wall). Push your belly button toward the ground or wall, controlling your pelvis. Hold for a count of three and then relax, repeat for the desired number of repetitions (Fig. 18).

POSTPARTUM EXERCISE

Benefits of postpartum exercise include improved cardiovascular fitness, facilitated weight loss, raised positive mood, reduced anxiety and depression and more energy. Postpartum women are able to participate in moderate physical activity without compromise to infant breast milk acceptance or infant growth. By strengthening the pelvic floor muscles, the risk of urinary stress incontinence may be reduced.

Current recommendations suggest that, if pregnancy and delivery are uncomplicated, a mild exercise program consisting of walking, pelvic floor exercises and stretching may begin immediately. However, if delivery was complicated or was by lower segment cesarean section, a medical caregiver should be consulted before resuming prepregnancy levels of physical activity, usually after the first postpartum check-up at 6–8 weeks. Women need to return to prepregnancy exercise levels gradually, not resuming high impact activity too soon.

EXERCISE DURING BREASTFEEDING

Breastfeeding is the best method of providing optimal nutrition, immunology-based protection, and emotional nurturing for the growth and development of infants. Therefore, exercise frequency and intensity should not interfere with a mother’s ability to breastfeed. Although exercise does not negatively affect milk production or composition, lactic acid has been shown to be increased in the breast milk of women exercising at maximal intensity, but not in those exercising at moderate levels. Controversy exists as to whether this short-term increase in lactic acid makes the breast milk less palatable to the nursing infant. Mothers who
find their baby does not feed as well right after exercising may consider feeding the baby right before exercising (which may also make the breasts more comfortable during exercise), postponing feeding until 1 hour after exercising, or expressing milk prior to exercising to be used after exercising. The growth of breastfeeding babies of exercising women is normal, even for the infants whose mothers are losing weight as part of their exercise regimen.

EXERCISES FOR THE WORKING WOMEN

Sometimes working women are working double shift, i.e. doing both the house hold and office work. In that case, they need exercises for keeping strength and tone of the muscles and stretching exercises for providing complete range of motion of joints and relaxation is also important and these exercises should be integrated into their routine lifestyle.

Women who are working should also make sure that their circulation is maintained. Those doing desk job should be circulating around, i.e. after an hour or so they should walk around. Their back should be straight and properly supported. They can use foot rests to prop up their feet. Stretching exercises for the shoulders and upper back can be done in between. Diet should be nutritious.

Labor class workers employed in field jobs or as laborers in construction industry should do work where risk of injury is minimum and in the afternoon rest should be given for 1–1.5 hours. Calorie intake should be increased as per demands of physical work involved.

CONCLUSION

A review of the evidence suggests that, in most cases, exercise is safe for both mother and fetus during pregnancy and women should therefore be encouraged to initiate or continue exercise to derive the health benefits associated with such activities.

BIBLIOGRAPHY

CHAPTER 6

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(Chapter updated by Mohita Pengoria)

Genetic Counseling for Obstetricians

GENETIC COUNSELING

Genetic counseling is defined as "the process by which patients or relatives at risk of a disorder are advised of the consequences of the disorder, the probability of developing and transmitting it, and ways in which this can be ameliorated". An accurate diagnosis of the disorder is very essential for any genetic counseling. A thorough knowledge of the manner, in which a particular disorder is inherited, is essential when giving advice to members of a family regarding the likelihood of their being affected, or having affected children.

PRENATAL DIAGNOSTIC TECHNIQUES

Prenatal diagnostic techniques for diagnosing congenital and genetic disorders in utero have proved to be a major advance in medical genetics and have altered the outlook for families at risk of having an affected child with a serious and untreatable disorder. In this specific setting of "New Obstetrics", Obstetricians should learn to apply basic principles of "Genetic Counseling". The Human Genome Project is an international effort to discern the complete genetic make-up of human beings. The isolation and characterization of genes offer tremendous opportunities for disease detection, diagnosis, screening, prevention and counseling. Advances in genetic research are occurring simultaneously with the development of new techniques for prenatal genetic testing. The obstetric community needs to participate actively in the debate surrounding the ethical and legal implications of the Human Genome Project. Since the science of genetics has become increasingly important in the practice of Medicine, all Obstetricians need to know the basic fundamentals of molecular biological techniques currently used in deoxyribonucleic acid (DNA) diagnostic tests; the practical and clinical aspects of genetics relevant to the discipline. Reproductive genetic counseling offers options to patients related to testing (prenatal or carrier) and child bearing. The focus of the counseling is often on decision making by the patient, including accepting the consequences of the choice(s), as it is the patient and the family who have to live with the decision. The strategy of population screening, offering genetic counseling, prenatal diagnosis (PND) and termination of affected pregnancy has been successfully applied worldwide. Common fetal sampling techniques in utero include chorionic villus sampling (CVS), amniocentesis and fetal blood sampling. Appropriate laboratory analysis is applied for diagnosis, where karyotyping is mainly for chromosome abnormalities and polymerase chain reaction (PCR) is for single gene disorders. Several modern molecular techniques are useful for identification of defects in single genes. Preimplantation genetic diagnosis is an advanced alternative giving the couple the chance to start a pregnancy ensuring that the baby is free from the genetic disease.

Aims of Genetic Counseling

Aims of genetic counseling are to help the individual or family to:
- Comprehend the medical facts including the diagnosis, probable course of the disorder and the available management
- Appreciate the way heredity contributes to the disorder and the risk of recurrence in the specified relatives
- Understand the alternatives for dealing with the risk of recurrence
• Choose a course of action which seems to them appropriate in view of their risk, their family goals, and their ethical and religious standards and act in accordance with the decision.

• Make the best possible adjustments to the disorder in an affected family member and/or to the risk of recurrence of that disorder.

Basic Background and Terms

Basic background and terms with special connotations must be introduced and defined at this point:

• The principles of inheritance were discovered in 1865 by Mendel and were subsequently “rediscovered” around 1900 by others. In 1902, Sutton and Boveri first suggested that chromosomes served as the physical basis of inheritance. DNA is the hereditary matter of all living organisms except certain viruses. Subsequently, several types of ribonucleic acid (RNA) were shown to be required to translate the information inherent in the genes. In 1953, Watson and Crick proposed that DNA existed in the form of a double helix; this structural configuration helped explain how DNA could replicate.

• Genes are recognized by the physical characteristics or traits determined by them.

• Trait is a gene—determined characteristic.

• Pedigree is information about families with an inherited condition stored in a family tree which is a shorthand reference of data.

• Inherited condition is defined when several members are affected in different generations, or in the same generation, or an affected member can pass on the condition to his or her next generation.

• Genotype describes the genetic constitution of an individual.

• Phenotype refers to the observable expression of a specific trait, or characteristics that can be visible or biochemically detectable, e.g. blonde hair, blood group A.

• Dominant trait implies that a single copy of the allele is enough for the condition to be expressed. It is seen in both the heterozygotes and homozygotes.

• Recessive trait is one, which is expressed only when two copies or doses of the gene are present.

• Codominant traits are those in which the effects of both alleles may be seen in the heterozygote, e.g. AB blood group.

• X- or Y-linked refers to genes having loci on either the X- or Y- chromosomes.

• Genetic heterogeneity refers to several genes having one effect, e.g. deafness, microcephaly, etc.

• Consultand, proband: The person seeking counseling is called “consultand or counselee” and the index case or affected child is called “proband.”

CONGENITAL MALFORMATIONS AND GENETIC DISEASE INHERITANCE

They can be grouped into: (1) Mendelian inheritance, (2) chromosomal defects and (3) multifactorial or polygenic disorders.

Mendelian Inheritance

Mendelian inheritance involves gene mutation and the risk of recurrence which will depend on the type of inheritance. The usual patterns of transmission are autosomal dominant (AD), autosomal recessive (AR), X-linked dominant, X-linked recessive (XLR) and Y-linked. There are 5,710 human single gene disorders listed in McKusick’s catalogue “Mendelian inheritance in man” (McKusick VA, 1992) which is a valuable ready reference for counseling. Over half are inherited in an AD fashion, about one-third as recessive and one-tenth as X-linked.

In an AR disorder, risk of recurrence is 25% for the sibling. In AD disorder, the risk of recurrence for the sibling is 50% if one of the parents is affected. If it is a sporadic case (new mutation), risk of recurrence in sibling is very low but gonadal mosaicism cannot be ruled out. In XLR disorders, risk of recurrence for boys is 50% whereas females usually do not manifest.

Structural Malformations

Single gene defects causing malformations that can be detected by ultrasound can be either isolated or multiple/syndromic (Table 1). Recurrence risk for the next pregnancy varies depending upon the inheritance pattern.

Chromosomal Defects

Majority of chromosomal disorders have been associated with mental retardation. For example, Down syndrome (DS), Edward syndrome (trisomy 18), Patau syndrome (trisomy 13), etc. In all de novo numerical and structural chromosomal abnormalities, there is a low risk of recurrence (<1%). Risk is higher if either of the parents is carrying a balanced translocation.

Structural Malformations

Five to seven percent of fetuses with single malformation and 15–30% of fetuses with multiple malformations have chromosomal abnormalities. A number of abnormalities detected on ultrasound examination are indicative of aneuploidies like trisomy 21, 18, 13 and 45, X. Of these, nuchal translucency (NT) is of utmost importance. Presence of other soft markers like pyelectasis, short femur, echogenic bowel, sandal gap, etc. in isolation is markers of less
significance. Presence of these findings with other ultrasound abnormalities is an indication for fetal chromosomal analysis.

**Multifactorial or Polygenic Disorders**

These constitute majority of birth defects. These are mostly isolated or non-syndromic malformations. These can be as follows:
- Cardiac, e.g. atrial septal defect (ASD), ventricular septal defect (VSD), tetralogy of Fallot (TOF), patent ductus arteriosus (PDA)
- Central nervous system (CNS), e.g. anencephaly, spina bifida
- Genitourinary, e.g. renal agenesis
- Others, e.g. talipes, cleft lip (CL)/cleft palate (CP).

### NEURAL TUBE DEFECT

Neural tube defect (NTD) is one of the common malformations. The reported incidence in India varies from 0.5–11 per 1,000 live births. Most cases are straightforward and involve an isolated NTD, either anencephaly or spina bifida, or both. Care is needed to ensure that one is dealing with a primary NTD or NTD is a part of syndrome, teratogenic exposure or chromosomal anomaly. Vertebral anomalies and hydronephrosis are commonly seen in isolated NTDs. It can be uniformly fatal as in anencephaly, iniencephaly, acrania; total craniospinal rachisis or prognosis may be variable depending upon the types of defect. In open defect 5 years survival is 36% and 82% are severely handicapped whereas in closed defect 5 years survival is 60%; but 33% are severely handicapped.

**Etiology**

Neural tube defect can either occur as an isolated defect or as part of a syndrome, as described below.

#### Syndromic Defect

- **Chromosomal:** 10% (22qdel, trisomy 13, 18, triploidy, unbalanced translocation)
- **Autosomal recessive:** Meckel-Gruber syndromes, Jarcho-Levin syndrome, Robert syndrome, Walker-Warburg syndrome.

**Isolated Defect**

- **Genetic defect:**
  - Polygenic: Predisposing genes not known
  - Probable association with C677T polymorphism in methylenetetrahydrofolate reductase (MTHFR) gene
- **Environmental defect:**
  - Drugs: Valproate, alcohol, folic acid antagonists
  - Maternal diabetes mellitus.

### ROLE OF A GENETIC COUNSELOR

Genetic counseling involves an attempt by one or more appropriately trained persons ideally by a team of
professionals that may include physician, genetic counselor, cytogeneticist/biochemical geneticist, social worker, psychologist and preferably a religious leader. In one study, among 145 patients evaluated, 38% (n = 55) had additional genetic risk factors detected by trained genetic counselor (p = 0.01). The maternal demographics and characteristics did not differ between the two groups. The practice of referring high-risk obstetric patients for genetic counseling improves the detection of identifiable genetic risk factors.4

**INDICATIONS OF PRENATAL DIAGNOSIS AND GENETIC COUNSELING**3-7

Common indications for genetic counseling in obstetric practice are as follows:

- Advanced maternal age (AMA)
- Positive maternal serum screen
- Abnormal fetal ultrasound
- Previous child with a de novo chromosomal abnormality or presence of structural chromosomal abnormality in one of the parent
- Family history of a genetic disorder that can be diagnosed or ruled out by DNA or biochemical analysis, like thalassemia, spinal muscular atrophy, hemophilia, congenital deafness, Gaucher disease or other inborn errors of metabolism
- History of unexplained mental retardation/dysmorphism/multiple malformations/lethal skeletal dysplasia/unexplained stillbirths (SB)/neonatal or infantile deaths with or without congenital malformations in previous child or in the family
- Recurrent pregnancy loss/SB
- Infertility
- Maternal disease
- Teratogen exposure
- Parental concern.

Analysis of genetic counseling and antenatal diagnostic services offered by a genetics’ unit in a women’s hospital undertaken to identify genetic needs of the Obstetrician-Gynecologist, and findings derived from a genetic questionnaire administered routinely to obstetric registrants showed that certain well-defined indications for genetic referral were identified, allowing specific educational objectives to be formulated. Potential chromosomal abnormalities constitute the most common indications for referral, particularly AMA and repetitive abortions. A wide range of Mendelian and polygenic/multifactorial disorders was encountered, albeit many individually rare. This suggests that the Obstetrician-Gynecologist should become familiar with principles of these modes of inheritance. However, educational objectives need not stress specific details of rare disorders but rather should emphasize the relatively few disorders that the Obstetrician-Gynecologist is likely to encounter.8

**GENETIC COUNSELING CASE MANAGEMENT PROCEDURE**5

This procedure involves the following:

- **Information gathering:**
  - History with particular emphasis on pedigree construction and analysis (Annexures 1 and 2)
  - Detailed clinical examination
  - Diagnosis
  - Investigations of family members
- **Information giving:**
  - Nature and course of disorder
  - Recurrence risk
  - Possible treatment
  - Availability of further or future testing
  - Prenatal diagnosis if possible
  - Decision making
  - Referral to other specialists, health agencies, support groups
- **Follow-up:**
  - Continuing clinical assessment, especially if no diagnosis
  - Psychological support.

**Pedigree Charting (Annexures 1 and 2)**

Pedigree charting is an important part of history taking. There is tremendous utility of the prenatal three-generation pedigree in assessment of the obstetric patient’s primary medical risks. In a case series out of 250 charts of patients referred for amniocentesis on the basis of AMA, a total of 40 patients (16%) were at significantly increased risk for a primary care disorder. Thirty-eight patients (15.2%) were at increased risk for medical conditions for which early screening, detection and/or interventions are established. For the AMA population, formal genetic risk assessment performed prior to amniocentesis can be beneficial in primary care risk assessment.9 A three-generation pedigree is superior to a questionnaire in genetic risk assessment, the questionnaire may not be sufficiently sensitive to serve independently as an adequate genetic screen or risk assessment tool and may not influence subsequent fetal evaluation.10

**GENETIC COUNSELING AND GOALS OF PRENATAL DIAGNOSIS**

The purpose of PND is not simply to detect abnormalities and perform termination of pregnancy (TOP) when the fetus is found to have a defect. Rather, the goals of PND are:

- To provide a range of informed choice to couples at risk of having a child with an abnormality
- To provide reassurance and to reduce anxiety, especially among high-risk groups
• To allow couples at risk of having a child with a specific birth defect, who might otherwise forego having children, to begin a pregnancy with the knowledge that the presence or absence of the disorder in the fetus can be confirmed by testing

• To allow couples the option of appropriate management for the impending birth of a child with a genetic disorder in terms of psychological preparation, pregnancy/delivery management and postnatal care

• To enable prenatal treatment of the affected fetus.

### Annexure 1: Common pedigree symbols, definitions and abbreviations

**Instructions:**
- Key should contain all information relevant to interpretation of pedigree (e.g. define shading)
- For clinical (non-published) pedigrees include:
  a. Family names/initals, when appropriate
  b. Name and title of person recording pedigree
  c. Historian (person relaying family history information)
  d. Date of intake/update.
- Recommended order of information placed below symbol (below to lower right, if necessary):
  a. Age/date of birth or age at death
  b. Evaluation
  c. Pedigree number (e.g. I-1, I-2, I-3).

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<th>Female</th>
<th>Sex unknown</th>
<th>Comments</th>
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<td></td>
<td></td>
<td>Assign gender by phenotype. Square represents male; circle represents a female; a diamond represents whose sex is not known. Age/date of birth can be given at the bottom right hand corner.</td>
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<td>30 year</td>
<td>4 month</td>
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<td>Fillings can be shading, hatches, dots, lines, etc.</td>
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<tr>
<td>individual</td>
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<td>![symbol]</td>
<td>For ≥ 2, conditions the symbols are partitioned correspondingly, each quadrant with different fillings/patterns representing different features.</td>
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<tr>
<td>Multiple</td>
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<td>6</td>
<td>6</td>
<td>Number of the siblings is written inside the symbols; affected individuals should not be grouped.</td>
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<td>d. 4 month</td>
<td></td>
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<td>Stillbirth (SB)</td>
<td>![symbol]</td>
<td>![symbol]</td>
<td>![symbol]</td>
<td>Birth of a dead child with gestational age noted.</td>
</tr>
<tr>
<td>SB 28 week</td>
<td>SB 30 week</td>
<td>SB 34 week</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Contd...
Annexure 1 (Contd…)

<table>
<thead>
<tr>
<th>Pregnancy (P)</th>
<th>Male</th>
<th>Female</th>
<th>Sex unknown</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>P</td>
<td>P</td>
<td></td>
<td>Gestational age and karyotype (if known) below symbol. Light shading can be used for affected and defined in key/legend.</td>
</tr>
</tbody>
</table>

| Proband | | | | First affected family member coming to medical attention. |

| Consultand | | | | Individual(s) seeking genetic counseling/testing. |

- Two parents are joined by a horizontal line.
- Consanguineous matings are indicated by a double line.
- Two parents joined by a horizontal line from which falls an inverted T to which their offspring are attached by short vertical lines.
- A single child is attached by a long vertical line directly to the parents' horizontal mating line.
- Twins attach at the same spot along the inverted T if nonidentical; if identical they branch from a short vertical line and connected by a line.

Annexure 2: Pedigree symbols and abbreviations for pregnancies not carried to term

**Instructions:**
- Symbols are smaller than standard ones and individual's line is shorter (Even if sex is known, triangles are preferred to a small square/circle; symbol may be mistaken for symbols given in the previous table, especially in hand-drawn pedigrees)
- If gender and gestational age known, write below symbol in that order.

<table>
<thead>
<tr>
<th>Spontaneous abortion (SAb)</th>
<th>Male</th>
<th>Female</th>
<th>Sex unknown</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>Female</td>
<td>ECT</td>
<td></td>
<td>If ectopic pregnancy, write ECT below symbol.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Affected SAb</th>
<th>Male</th>
<th>Female</th>
<th>Sex unknown</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>Female</td>
<td>16 week</td>
<td></td>
<td>If gestational age known, write below symbol. Key/legend used to define shading.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Termination of pregnancy (TOP)</th>
<th>Male</th>
<th>Female</th>
<th>Sex unknown</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>Female</td>
<td></td>
<td></td>
<td>Other abbreviations (e.g. TAb, VTOP, Ab) not used for sake of consistency.</td>
</tr>
</tbody>
</table>

| Affected TOP | Male | Female | | Key/legend used to define shading. |

Abbreviations: ECT, ectopic pregnancy; TAb, threatened abortion; VTOP, voluntary termination of pregnancy; Ab, abortion
The generally accepted guidelines for eligibility of pregnant women for PND by amniocentesis or CVS are based on the evidence that the risk for fetal abnormality is at least as great as the risk of miscarriage from the procedure itself.

**Need for Genetic Studies**
- To plan mode of delivery
- To plan postnatal management
- To prognosticate likelihood of postnatal survival
- To decide on medical termination of pregnancy (MTP).

**Pre-test Counseling**
Preliminary genetic counseling of candidates who desire PND usually deals with the following:
- The risk that the fetus is affected
- The nature and probable consequences of the specific problem
- The risks and limitations of the procedures to be used
- The time required before a report can be issued
- The possible need for a repeat procedure in the event of a failed attempt
- The limitation of a test (in view of laboratory error).

Comparison of 275 consecutive patients referred for genetic counseling and amniocentesis on the basis of AMA were compared with charts of 103 consecutive patients referred for an abnormal maternal serum alpha-fetoprotein (MSAFP) finding. In 35.6% of pedigrees evaluated, a significant genetic risk was discovered during genetic consultation that had not been noted by the referring physician. Furthermore, 9.8% of AMA patients and 10.7% of patients with abnormal MSAFP results underwent additional genetic testing or screening on the basis of genetic counseling. Data supports the importance of genetic counseling before amniocentesis in more accurately ascertaining genetic risk and in maximizing the benefits of genetic evaluation of patients seemingly at low risk for other genetic diseases.

**GENETIC COUNSELING AND PRENATAL DIAGNOSIS FOR GENETIC DISORDERS**

**Mendelian Disorders**
For most of the common genetic single gene disorders, either enzyme based or molecular diagnosis is available, though facilities for diagnosis of all disorders are not available, in India. PND is possible by using the same techniques on fetal tissues—chorionic villus (CV) biopsy or amniotic fluid examination.

**X-Linked Disorders**
In pregnancies at high risk for X-linked disorder, fetal sexing offers the possibility of determining whether the fetus is indeed at risk. However, in most disorders direct molecular PND of an affected male is now possible, and even where it is not, linked DNA markers can often be used. First-trimester fetal sexing, using both DNA and cytogenetic methods, is now feasible with CVS. Where a woman is only a possible carrier, it is vital to estimate the risk before fetal sexing is undertaken and to use methods of carrier detection where applicable. The most successful approach to PND is where no prenatal procedure is required at all, because the carrier state is excluded. As far as possible, this should be approached as a planned procedure.

**Inborn Errors of Metabolism**
More than 100 metabolic disorders like organic acidemias and aminoacidemia’s (phenylketonuria, maple syrup urine disease), carbohydrate disorders (galactosemia), cholesterol metabolism disorder (X-Linked ichthyosis), lysosomal disorder (Hurler syndrome), peroxisomal disorder (chondrodysplasia punctata and Zellweger syndrome), etc. can be diagnosed prenatally in CV tissue or cultured amniocytes or directly by assay of a substance in amniotic fluid, like in methylmalonic acidemias, 21-hydroxylase form of congenital adrenal hyperplasia and congenital nephrosis by raised alpha-fetoprotein (AFP) levels. The following points need to be remembered in PND of a metabolic disorder:
- Most metabolic disorders are rare in the general population, but have a high recurrence risk of 25% (1 in 4) for most being AR in nature. Risks for other relatives are rarely high enough to warrant undertaking PND
- Whenever possible, biochemical assay on direct CV tissue as opposed to cultured tissue is preferred, to avoid delay and misinterpretation of results due to expansion in culture of the number of contaminating maternal cells
- Because each condition is rare, the experience of the laboratory performing the prenatal diagnostic testing is very important, thus referral to specialized centers is often desirable
- Wherever possible, samples from the affected individual should be studied alongside those at risk.

**Chromosomal Disorders**
Prenatal screening for common chromosomal disorders has good sensitivity using maternal serum biochemical markers and ultrasonography (USG). Definitive diagnosis can be provided by chromosomal studies on amniotic fluid, CV biopsy or cord blood sample.

**Ultrasound Scanning in Prenatal Diagnosis**
Fetal anomaly scan is done at 11–14 weeks and 18–20 weeks to look at the major malformations and soft markers.

**First-trimester Scan**
It has been shown that around this time there is strong association between chromosomal abnormality and
abnormal accumulation of fluid behind baby’s neck, referred to as increased “fetal NT”. This applies both to DS and other autosomal trisomy syndromes like trisomy 13 and 18. By combining information on maternal age with results of fetal NT and thickness measurements, it is possible to detect approximately 80% of fetuses with trisomy 21, if invasive testing is offered to the 5% of pregnant women with the highest risk.

**Second-trimester Scan**

Significant sonographic findings are seen in nearly all fetuses with trisomy 13 and in about 77–100% of trisomy 18. Current sonographic criteria can identify 65–75% of fetuses with DS with a false positive rate of 4–15% in second trimester. Presence of multiple abnormalities raises the risk of any chromosomal abnormality to 35% (Table 2). With the combined usage of sonographic markers for DS and maternal serum screening, the vast majority of fetuses with DS could be potentially detected.

**Multifactorial or Polygenic Disorders**

Counseling and risk of recurrence in these disorders is based on empiric risk figures, and many anatomic anomalies indicate a heritable tendency. PND is possible in some defects using fetal USG. After diagnosis of any malformation on fetal anomaly scan, one should apply the knowledge of various genetic disorders and syndromes to provide appropriate nondirective genetic counseling and management. Table 3 shows risk of recurrence of some common malformations. Counseling in multifactorial disorders is to be done carefully, as there is a close overlap between hereditary and non-hereditary disorders. PND of major malformation is possible and the risk prediction can be calculated more accurately. There are guidelines which can help the at-risk families to plan the family or can be of great help in premarriage counseling.

---

**Table 2: Aneuploidy risk with major structural fetal malformation**

<table>
<thead>
<tr>
<th>Malformation</th>
<th>Aneuploidy risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystic hygroma</td>
<td>60–75%</td>
</tr>
<tr>
<td>Hydrops</td>
<td>30–80%</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>3–8%</td>
</tr>
<tr>
<td>Holoprosencephaly</td>
<td>40–60%</td>
</tr>
<tr>
<td>Cardiac defects</td>
<td>5–30%</td>
</tr>
<tr>
<td>Diaphragmatic hernia</td>
<td>20–25%</td>
</tr>
<tr>
<td>Omphalocele</td>
<td>30–40%</td>
</tr>
<tr>
<td>Gastrochisis</td>
<td>None-minimal</td>
</tr>
<tr>
<td>Duodenal atresia</td>
<td>20–30%</td>
</tr>
<tr>
<td>Facial cleft</td>
<td>1%</td>
</tr>
<tr>
<td>Bladder outlet obstruction</td>
<td>Minimal</td>
</tr>
<tr>
<td>Limb reduction</td>
<td>20–30%</td>
</tr>
<tr>
<td>Club foot</td>
<td>8%</td>
</tr>
<tr>
<td>Single umbilical artery</td>
<td>20–25%</td>
</tr>
</tbody>
</table>

---

**Table 3: Empiric risk of recurrence of isolated malformation**

<table>
<thead>
<tr>
<th>Malformation</th>
<th>Frequency per 1,000 births</th>
<th>Recurrence for normal parents of one affected child</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anencephaly/spina bifida</td>
<td>4–5</td>
<td>5%</td>
</tr>
<tr>
<td>Cardiac malformation</td>
<td>6–8</td>
<td>3–4%</td>
</tr>
<tr>
<td>Cleft lip (CL) and cleft palate (CP)</td>
<td>2</td>
<td>4–5%</td>
</tr>
<tr>
<td>CP alone</td>
<td>0.5</td>
<td>2–6%</td>
</tr>
<tr>
<td>Pyloric stenosis</td>
<td>2–3</td>
<td>3%</td>
</tr>
<tr>
<td>Talipes equinovarus</td>
<td>3–4</td>
<td>2–8%</td>
</tr>
<tr>
<td>Dislocation of hip</td>
<td>3–4</td>
<td>3–4%</td>
</tr>
<tr>
<td>Hirschsprung disease</td>
<td>0.1</td>
<td>6%</td>
</tr>
</tbody>
</table>
risks of DS and offered amniocentesis; however, uptake of amniocentesis varies greatly between countries and region, and has been considerably affected by the development of second-trimester maternal serum screening. Availability of first-trimester screen results in more AMA women having early prenatal genetic counseling and choosing some form of genetic testing.13

**Translocation Down Syndrome**

Translocation DS comprises only 5% of all cases of DS. The risks for the offspring of balanced carriers varies from 2.5% to 10% for father and mother as a carrier, respectively for 14/21 and 21/22 translocations and 100% for 21/21 translocation. So precise type can be established from chromosomal analysis of index case, and the relatives at risk should be investigated using blood before pregnancy occurs. Where the parents of a child with translocation DS are both chromosomally normal, the risk of further affected child is also low, probably similar to that for trisomic DS and other autosomal trisomies, i.e. less than 1%.

**Trisomic Down Syndrome and Other Autosomal Trisomies**

Trisomic DS and other autosomal trisomies carry low recurrence risk with the exception of very rare families, possibly because of predisposition to nondisjunction or gonadal mosaicism. In practice, most couples with previous affected child do elect for PND in subsequent pregnancy, with full knowledge of the procedural risks and low probability of recurrence. For other relatives of a child with isolated trisomic DS, there is no evidence of an increased risk in their offspring.

**Structural Malformations**

**Antenatal Screening for Neural Tube Defect**

**Maternal serum screening:** Maternal serum AFP levels are measured at 16–18 weeks of gestation. A cut-off greater than 2.5 multiple of median (MOM) detects greater than 90% cases of anencephaly and 80% cases of spina bifida cystica. Though the specificity of the test is not very high, being increased in abortion, twin pregnancy, exomphalos, etc. yet it has been implemented widely and has led to a striking decline in the incidence of open NTD.

**Ultrasound screening:** Anencephaly is detectable at 10–12 weeks of gestation; spina bifida is detectable at 16 weeks onwards; large defects may be visible earlier.

**Prevention:** Folic acid supplementation (4 mg/day) started 2 months before to 3 months after conception (periconceptional) prevents recurrence in about 72% of cases. Primary prevention (about 50%) by use of 0.4 mg of folic acid periconceptionally has also been recommended.

**Malformation with Uncertain Prognosis**

This is a challenge to the counselor as well as a dilemma for the family. Some of the malformations with uncertain prognosis are ventriculomegaly, meningocoele, omphalocoele, multicystic kidneys, hydronephrosis, urinary bladder obstruction, cystic adenomatoid lung malformation, diaphragmatic hernia, cardiac defects, cyst/calcification inside abdomen, mild limb shortening.

**Maternal Serum Screening for Down Syndrome**

Down syndrome is the most common cause of mental retardation with a prevalence of about 1 in every 800–1,000 births.14,15 The majority of cases of DS occur due to an extra chromosome 21. The spontaneous loss rate of fetuses with DS is approximately 30–43% between the time of CVS in the later first trimester and term, and 18–23% between the time of amniocentesis in mid-to-early second trimester and term. Knowledge of the loss rate of affected fetus is important for counseling prospective parents and for assessing the available screening methods at varying times of gestation.

**First-trimester Screening**

Although many markers have been studied in the first trimester, two robust markers suggested are beta-human chorionic gonadotropin (β-hCG) and pregnancy-associated plasma protein A (PAPP-A). Fetal β-hCG (Fβ-hCG) has been found to be elevated with the median MOM values of 2.15, almost similar to the second trimester. PAPP-A values are low with the median MOM of around 0.45–0.51, this alteration is not seen in the second trimester. Based on the available data, the detection rates using these two markers varies between 60% and 67% with a false positive rate of 5%. Detection of trisomy 18 and 13 has also been reported by first-trimester screening with good detection rates.

**Second-trimester Screening**

**Triple Test/Multimarker Screening**

It includes AFP, human chorionic gonadotropin (hCG) and unconjugated estriol (uE3) estimation in maternal serum. Expressed in MOM values, maternal serum AFP and uE3 are reduced by 25%, whereas hCG levels are doubled in pregnancies with DS. None of these parameters alone gives absolute discrimination but taken together they provide a means of modifying a woman’s prior age-related risk to give an overall probability that the unborn is unaffected. When this probability exceeds 1 in 270 or 1 in 250 (USA and UK respectively) invasive testing in the form of amniocentesis or placental biopsy or cordocentesis is offered. At a risk cut-off level of 1:270, 59% of pregnancies with DS and 5% of unaffected pregnancies are designated as screen positive.
Use of level II ultrasound improves the detection rate to 69% at a false positive rate of 5%. Thus, all cases of DS cannot be diagnosed by triple screening.

Until a decade ago, amniocentesis was reserved for women of greater than or equal to 35 years of age, who produced approximately 20% of fetal DS population. With the advent of maternal serum screening, an additional 30–40% of fetuses with DS became identifiable, still leaving a large cohort of patients who carried fetuses with DS but who were not candidate for invasive testing. Disadvantages of second-trimester screening is that it creates more anxiety and late intervention if fetus is affected posing risk to mother.

**Quadruple Test**

Addition of a fourth biochemical marker, inhibin-A, (increased in DS pregnancies) in the second-trimester screen, increases the sensitivity of screening for DS from 60% to 75%.

**Factors affecting levels of maternal serum markers:** There are numerous factors which can affect levels of maternal serum markers. Many screening programs take these into account while calculating risks. These factors include maternal weight (tendency to decrease due to greater blood volume), number of fetuses, smoking, ethnicity, gravidity and parity, previous screening results, assisted reproduction, pregnancy complications and diabetes (lower levels). Most programs usually include correction for maternal weight and diabetic status.

**OSCAR clinic:** The one stop clinic for assessment of risk for fetal anomaly (OSCAR) is prevalent in western countries. It means that in 1-hour single visit, both the biochemical (FIβ-hCG, PAPP-A) and USG (NT + crown rump length + anomaly scan) is carried out between 11 weeks and 14 weeks. It has a predictive value of 86%.

In conclusion, biochemical screening for aneuploidies has many advantages over age-based screening alone: (1) sensitivity and specificity are improved; (2) chromosomal abnormalities other than DS and trisomy 18 are also detected; and (3) prevention can be offered to younger mothers also. However difficult counseling situations and delayed confirmation of fetal chromosomal abnormalities can create problems. This can be taken care off with the help of proper pre-test and post-test counseling.

**ROLE OF OBSTETRICIANS IN MANAGEMENT OF PATIENTS WITH GENETIC DISORDER AND ANTENATAL DETECTION OF MALFORMATION**

Flow charts 1 and 2 depict management of patients with genetic disorders and antenatal detection of malformation, respectively.

**SPECIAL PROBLEMS IN GENETIC COUNSELING**

In some of the situations, especially known AR and AD disorders, counseling and presentation of risks is relatively straightforward based on the principles of Mendelian inheritance. However, in the presence of reduced penetrance, delayed onset and genetic heterogeneity (a disorder caused by more than one genetic mechanism), extending into different modes of inheritance, the counseling becomes more difficult. There are several situations that can pose problems while counseling.

**PRE-TEST AND POST-TEST COUNSELING FOR BIOCHEMICAL SCREENING**

Before offering antenatal biochemical screening, understanding of some basics to interpret these tests and provide effective genetic counseling are required:

- The tests should be performed at specified gestation (e.g. between 15 weeks and 20 weeks for second-trimester screen and between 11 weeks and 14 weeks for first-trimester screening)
- The values change with gestational age. In the second trimester, AFP and uE3 increase with gestational age while hCG decreases. Ideally each testing laboratory should have its own standards of normal values at different gestations
- Values are expressed in MOM for easier understanding and comparison between laboratories
- The detection rates are not 100% even with multiple markers (as discussed earlier and these are screening tests not diagnostic tests)
- Pre-test and post-test counseling are the biggest challenges and should always be done religiously and cautiously. The most important points to emphasize are—a positive test does not mean that the fetus has DS and a negative test does not rule out DS. Table 1 gives a check list for pre-test and post-test counseling. The screening tests are done to relieve the anxiety, but in most situations if done without counseling can make the couple very anxious. In India as the tests have been introduced recently and pre-test and post-test counseling is inadequate; it creates more confusion than solving the problems in many situations in authors’ experience. It is imperative that the clinicians ordering the test should clearly understand the interpretation
- The interpretation is usually given after calculating the risk by entering the data in available software programs. The usual cut-off risk is taken as 1 in 250. Any values having more risk than this are "screen positive", e.g. if the triple test interpretation gives result of 1 in 500 it means that if 500 women had these test values one will have a baby with DS. This is usually compared with a pre-test risk-based on maternal age.
Consanguinity

Consanguinity implies relationship between blood relatives who have at least one common ancestor, not more remote than a great-great grandparent. In Indian scenario, uncle-niece relationship (second degree) is the most common. The absolute risk of abnormal offspring (SB, neonatal death and congenital malformation) for marriages between first cousins is 3–5%, about double the overall background risk of 2–3% for offspring of unrelated individuals. Similarly, the probability that first cousins will have a child with an AR disorder is approximately 3%, although the risk can be greater if there is a family history of a specific genetic disorder.

Disputed Paternity

Difficulty in genetic counseling may arise if the socially accepted father is not the real biologic father.

PROBLEMS WITH CHROMOSOMAL PRENATAL DIAGNOSIS

Mosaicism

Its likely consequences and severity is often difficult to interpret, especially in CVS samples, where mosaicism is often confined to the placenta.

Culture Failure

Unexpected or Unrelated Adverse Findings

Occasionally, prenatal chromosomal analysis performed to rule out aneuploidy may reveal a common variant, a rare rearrangement, or a marker chromosome. As its significance in fetus is not known, parental chromosomal analysis should be done to rule out a de novo or inherited abnormality. Unbalanced or de novo structural rearrangements may cause serious fetal abnormalities.

POINTS TO REMEMBER

1. Hereditary diseases may manifest at the time of birth or several years later in life.
2. All congenital defects observed at the time of birth are not necessarily inherited. Some of these may be due to teratogenic effect of drugs, infections or irradiation during the first trimester of pregnancy.
3. A degree of clinical variability exists in the presentation of certain genetic disorders. This variable expression of the mutant gene is attributed to the degree of penetration of the gene. Thus one member of the family may show all the features of a genetic disease, while his or her siblings may show only mild forms of the disorders with one or the other sign.
4. Genetic counselor should interpret the anticipated risk of recurrence of the inherited disorder in the future siblings in a meaningful manner so that the family can arrive at a rational decision. The counselor has a particularly important responsibility in reassuring the parents that the risk of recurrence is low in case of disorders with multifactorial inheritance. In sporadic mutations and most of chromosomal disorders, there is only a small or no risk of recurrence.
5. While conveying information to the parents the physician should be extremely cautious. He should take special care not to infuse a sense of guilt in the parents. In case of X-linked disorders, it will be desirable to temper the blame on the mother, lest she is castigated by her husband or in-laws (Indian scenario).

CONCLUSION

Genetic counseling has an integral role in the management of genetic disorders. Counseling should be nondirective,
psychoeducational and involve good communication along with the latest information, confidentiality and truthfulness. Pediatricians and Gynecologists are the primary physicians for the diagnosis, and management of children and high-risk couples with genetic disorders. Also besides treating the patients, physicians should make the parents or couple aware of the genetic disorder, risk of recurrence, prognosis and PND. PND of any malformation is not the end of the diagnosis. It is an unexpected dilemma. It poses a great stress on the family, long-term guilt and need for support. Decision regarding termination or continuation is difficult. So accurate prognosis has to be defined keeping in mind that each pregnancy is precious and there is always a desire for continuation in couples. Establishment of clinical standards and use of professional organizations to act as a resource for clinicians, the public and legislatures is needed. Due to the increased requirement for genetic counseling, an expansion of genetics training for residents, clinicians and the development of computer-based interactive video programs for genetic counseling is recommended.

REFERENCES

SECTION 2

Medical Disorders in Pregnancy
Anemia in Pregnancy

INTRODUCTION

Anemia is a global problem. Its prevalence in India is about 60% and may increase to 80% during pregnancy. It directly or indirectly contributes to a significant proportion (about 40%) of maternal deaths. During pregnancy there is a dramatic increase in plasma volume (50%) and cell mass (18–25%). These differential changes cause a dilution decrease in hemoglobin concentration, known as “physiological anemia in pregnancy”. This physiological anemia often gets corrected following iron therapy so its existence is now questioned. This is maximal at 32 weeks of gestation. Poverty, ignorance, malnutrition, food taboos, repeated pregnancy in a limited period of time, parasitic and helminthic infestation and malaria contribute significantly and hemoglobinopathies in a small proportion, to the causation of anemia in our country. Over 90% of anemia is due to red cell iron deficiency associated with depleted iron stores and deficient intake. Infections inhibit incorporation of iron from stores into hemoglobin. Folate deficiency is a minor cause and vitamin B12 deficiency hardly ever causes anemia in pregnancy.

In the Indian context, the word “MA” means “malnourishment and anemia”. Anemia is the most common medical disorder in pregnancy globally. Its prevalence, etiology and severity differ in different populations, being more common in the nonindustrialized countries (56%) where it is responsible for very high maternal (40–60%) and perinatal mortality rates. In industrialized countries, nearly 18% of women are anemic during pregnancy. In India, this figure is as high as 88%. Girls in our country are deprived of good diet in their childhood, and therefore, enter adulthood with malnutrition, anemia and low iron stores. Anemia antedates pregnancy, is aggravated by increased requirements during pregnancy, blood loss at delivery, and infections in the antenatal and postnatal periods. Rapid succession of pregnancies all the more worsens it.

DEFINITION AND SEVERITY OF ANEMIA IN PREGNANCY

The World Health Organization defines anemia in pregnancy as hemoglobin (Hb) concentration of less than 11 g/dL and a hematocrit of less than 0.33. The cut off point suggested by the Centers for Disease Control (CDC) USA is 10.5 g/dL in the second trimester.

The Indian Council of Medical Research (ICMR) categorizes anemia as mild (10–10.9 g/dL), moderate (7.0–10.0 g/dL), severe (< 7.0 g/dL) and very severe (< 4.0 g/dL). The relative prevalence of mild, moderate, and severe anemia are 13%, 57% and 12% respectively in India (ICMR unpublished data).

CLASSIFICATION

- Physiological anemia of pregnancy
- Pathological:
  I. Deficiency anemias (isolated or combined)
    - Iron deficiency
    - Folic acid deficiency
    - Vitamin B12 deficiency
    - Protein deficiency
  II. Hemorrhagic
    - Acute: Abortions, ectopic pregnancy, hydatidiform mole, antepartum hemorrhage (APH), postpartum hemorrhage (PPH)
    - Chronic: Hookworm infestations, bleeding piles
  III. Hereditary
    - Thalassemias
    - Sickle cell disorders
    - Other hemoglobinopathies
  IV. Hemolytic
    - Extrinsic causes: Acquired immune hemolytic anemia and microangiopathic hemolytic anemia
Medical Disorders in Pregnancy

- **Intrinsic causes** (hereditary): Red blood cell (RBC) membrane defects and RBC metabolism defects
- **V. Bone marrow insufficiency**: Hypoplasia or aplasia due to radiation, drugs (aspirin, indomethacin)
- VI. Anemia of infection (malaria, tuberculosis)
- VII. Chronic disease (renal) or neoplasm.

**PHYSIOLOGICAL ANEMIA OF PREGNANCY**

- There is disproportionate increase in plasma volume, RBC volume and Hb mass during pregnancy leading to hemodilution.
- There is increased demand of iron especially in the second half of pregnancy, which even an adequate diet cannot provide, causing physiological iron deficiency during pregnancy.
- There is fall in Hb, hematocrit value, serum iron levels, an increased iron binding capacity and increased rate of iron absorption in second half of pregnancy.
- Thus, the fall in Hb concentration during pregnancy is both due to hemodilution and negative iron balance.
- The physiological anemia is normocytic and normochromic in type, with Hb 10 g%, RBC 3.2 million/mm³, packed cell volume (PCV) 30% and normal morphology of RBCs with central pallor.
- For proper erythropoiesis iron, folic acid, Vitamin B₁₂, Vitamin C, Vitamin B₆, Vitamin A, riboflavin, erythropoietin, zinc, copper, cobalt, androgens and thyroxine are required in adequate amounts.
- Increased requirements, deficient supply or inadequate reserve of any of these constituents interfere with normal erythropoiesis and thereby anemia.

**EFFECTS OF ANEMIA ON PREGNANCY**

- **Maternal**
  - Mild anemia may not have any adverse effect on pregnancy and labor
  - Moderate anemia causes weakness, fatigue and poor work performance
  - **Causes of severe anemia:**
    - During pregnancy - Preeclampsia (31.2%), Abruptio placentae, Preterm labor (28.2%), Cardiac failure (especially at 30–32 weeks)
    - Infections
    - During labor - Uterine inertia, Postpartum hemorrhage, Cardiac failure, Shock
    - During puerperium - Sepsis, Subinvolution

- **Fetal** - Failing lactation
- - Venous thrombosis
- - Pulmonary embolism
- - Preterm birth
- - Small for gestational age baby/ intrauterine growth retardation (SGA/IUGR)
- - Birth anoxia/Low Apgar score
- - Intrauterine death/still birth
- - Low mean weight
- - Infection
- - Cognitive and affective dysfunctions
- - Iron deficiency anemia
- - Hypertension (in later life).

**EFFECTS OF PREGNANCY ON ANEMIA**

- Pregnancy aggravates any pre-existing anemia
- Severely anemic patients become symptomatic by the end of second trimester.

**RISK PERIODS FOR MATERNAL MORTALITY**

- 30–32 weeks of pregnancy
- During labor
- Immediately following delivery
- Puerperium (pulmonary embolism, cardiac failure).

**IRON DEFICIENCY ANEMIA**

Iron deficiency anemia has been defined as microcytic hypochromic anemia, when body iron store becomes inadequate for the need of normal erythropoiesis. Body iron store must be exhausted before red cell production is reduced; therefore, anemia occurs at a late stage of iron deficiency. Iron store depletion occurs as a result of an imbalance between normal physiological demands such as body growth, menstrual blood loss and pregnancy, and the level of dietary iron intake, the efficiency of iron absorption and utilization (Fig. 1).

- Iron deficiency anemia (IDA) is the most common type of anemia in pregnancy
- Total iron requirements vary with the body weight of the mother and the size and maturity of the fetus
- On an average approximately 1000 mg of iron is required during pregnancy. This is distributed in fetus, placenta, expanded red cell mass, blood loss at delivery and obligatory losses through normal routes
- Iron is also conserved by amenorrhea during pregnancy. After deducting this conserved iron, an additional 500–600 mg of iron is required in pregnancy (i.e. 4–6 mg/day of absorbed iron)
The average daily diet contains 10–20 mg of iron. As iron absorption is only 10%, for 4–6 mg/day absorption, at least 40–60 mg elemental iron should be available in the diet. Iron loss is fairly constant. Thus, the iron balance is mainly dependent on the regulation of iron absorption. Iron levels are maintained in short-term by increased absorption in deficiency states and by the amount of bioavailable iron present in the food, in the long-term. Iron is absorbed in the ferrous form from the duodenum and jejunum and is transported in the blood in combination with transferrin (α-glycoprotein). Iron is transported into the cells through attachment of transferrin to specific membrane-bound receptors. Iron is stored in reticuloendothelial cells in liver, spleen, bone marrow, hepatocytes and myocytes. Dietary iron is present in two forms, i.e. heme and nonheme iron. Heme iron is better absorbed (upto 35%) than nonheme iron (5%), but the heme iron is the smaller fraction of the dietary iron. Nonheme iron is mostly in ferric form; needs to be reduced to ferrous form for absorption. Sources of heme iron are animal blood, flesh and viscera. Sources of nonheme iron are cereals, seeds, vegetables, milk and eggs. Absorption of heme iron is not affected by any other foods simultaneously ingested but that of nonheme iron is affected by several factors (Table 1). Heme iron itself facilitates absorption of nonheme iron in a mixed diet.

**Dietary Sources of Iron**

### Rich Sources
Liver, meat, poultry, fish, eggs, yolk, dry fruits, beans, green leafy vegetables, legumes, nuts, jaggery, apple, banana, etc. are rich sources of iron.

### Poor Sources

**Milk and milk products:**
- Although iron absorption is increased during pregnancy, the absorbed iron and the iron mobilized iron stores are usually inadequate to meet the demands. Iron supplementation, therefore, becomes necessary during pregnancy especially in the nonindustrialized countries.
- The fetus obtains iron from maternal transferrin regardless of maternal iron stores. The placenta traps maternal transferrin, removes the iron, and actively transports it to the fetus, mainly in the last 4 weeks of pregnancy.

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**Table 1: Factors affecting the iron status of a pregnant woman**

<table>
<thead>
<tr>
<th>Iron absorption</th>
<th>Iron loss</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dietary iron (heme and nonheme)</strong></td>
<td>Physiological factors</td>
</tr>
<tr>
<td>Heme iron</td>
<td>Basal losses from desquamation from intestines and skin</td>
</tr>
<tr>
<td>Proteins</td>
<td>Menstruation</td>
</tr>
<tr>
<td>Meat</td>
<td>Delivery</td>
</tr>
<tr>
<td>Ascorbic acid</td>
<td>Lactation</td>
</tr>
<tr>
<td>Fermentation</td>
<td>Pathological factors</td>
</tr>
<tr>
<td>Ferrous iron</td>
<td>Hookworm and other helminths</td>
</tr>
<tr>
<td>Gastric acidity</td>
<td>Hemorrhage from gastrointestinal tract (GIT)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Allergies</td>
</tr>
<tr>
<td>Low iron stores</td>
<td>Occult blood losses</td>
</tr>
<tr>
<td>Increased erythropoietic activity (high altitude, hemolysis, bleeding)</td>
<td></td>
</tr>
<tr>
<td><strong>Enhancers of absorption</strong></td>
<td><strong>Inhibitors of iron absorption</strong></td>
</tr>
<tr>
<td>Heme iron</td>
<td>Phytates</td>
</tr>
<tr>
<td>Proteins</td>
<td>Calcium</td>
</tr>
<tr>
<td>Meat</td>
<td>Tannins</td>
</tr>
<tr>
<td>Ascorbic acid</td>
<td>Tea and coffee</td>
</tr>
<tr>
<td>Fermentation</td>
<td>Herbal drinks</td>
</tr>
<tr>
<td>Ferrous iron</td>
<td>Fortified iron supplements</td>
</tr>
<tr>
<td>Gastric acidity</td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td></td>
</tr>
</tbody>
</table>
Iron deficiency anemia is very much prevalent in the tropics, among women of childbearing age, especially in the low socioeconomic group.

**CAUSES**

- Dietary habits
  - Consumption of low bioavailability diet
  - High phosphate and phytic acid in diet forming insoluble iron compounds
  - Food faddism (due to customs and rituals, pregnant women are not allowed to eat many food items)
  - Pica (ingestion of substances having no dietary value)
  - Loss of appetite
  - Hyperemesis gravidarum
- Faulty iron absorption
  - Worm infestation
  - Amebiasis
  - Giardiasis
  - Hypochlorhydria
- Increased iron loss
  - Menorrhagia
  - Repeated pregnancies
  - Bleeding piles
  - Prolonged lactation
  - Hookworm infestations
  - Excessive sweating
  - Schistosomiasis
  - Chronic malaria
  - Dysentery
- Nonpractice of active management of third stage of labor (domiciliary confinements)
- Infections—(interfere with erythropoiesis, e.g. asymptomatic bacteriuria)
- Prepregnancy poor iron reserve
- Teenage pregnancy.

**CLINICAL FEATURES**

The clinical features depend on the degree of anemia.

**Symptoms**

- Mild and moderate anemia may be either asymptomatic or cause weakness, fatigue, lassitude, indigestion and loss of appetite
- In severe anemia, additionally there may be palpitation, breathlessness, giddiness, edema and general anasarca
- If bleeding is the cause of anemia, the patient will complain of it, e.g. bleeding piles.

**Signs**

- Pallor of varying degree, glossitis, stomatitis, and edema due to hypoproteinemia and preeclampsia
- Soft systolic murmur in mitral area (hyperdynamic circulation)
- Fine crepitations at the bases of lungs (congestion).

**MANAGEMENT**

- Diagnosis
- Treatment
  - Preventive
  - Curative
  *The treatment must be preceded by an accurate diagnosis of the cause and the type of anemia.*

**DIAGNOSIS**

- Detailed history
- Clinical examination
- Hemoglobin estimation (simple, cost effective and practical method)
- Hematocrit is reduced, < 33% (Normal 36–46%)
- Peripheral blood smear
  - Differentiates IDA from megaloblastic and hemolytic anemias
  - In IDA, there is microcytosis, anisocytosis, poikilocytosis, hypochromasia and target cells in blood smear
- RBC count—decreased (Normal 4.0–5.20 million/mm³)
- MCV (mean corpuscular volume)—decreased (Normal 78–100 fl)
- MCH (mean corpuscular Hb)—decreased (Normal 26–34 pg/cell)
- MCHC (mean corpuscular Hb concentration)—decreased (normal 31–37 g/dL)
- Reticulocyte count—increased (Normal 0.5–2.5% red cells).

**Red Cell Distribution Width (RDW) (Fig. 2)**

- An index of anisocytosis
- Increase in IIDA and normal in thalassemia (Table 2).

**Serum Ferritin Level (a High Molecular Weight Glycoprotein Circulating in Plasma)**

- Indicates iron stores
- Decreased in IIDA < 12 mg/L (normal 15–300 mg/L)
- First test to become abnormal in IIDA.

**Transferrin Saturation**

- Indicates iron supply to the tissues
- Decreased in IIDA < 15% (Normal 20–45%)
- Second test to become abnormal in IIDA.

**Serum Iron Levels**

- Decreased in IIDA < 60 mg/dL (normal 60–120 mg/dL)
CHAPTER 7

Anemia in Pregnancy

Total Iron Binding Capacity

- Increased in IDA > 350 mg/dL (normal 300–400 mg/dL).

Free Erythrocyte Protoporphyrin (FEP)

- Indicates iron supply to the developing RBCs
- Increased in IDA; and normal in thalassemia (normal < 35).

Serum Transferrin Receptor (TfR)

- Reflects tissue iron status
- Increased in IDA
  - Very good marker of IDA in pregnancy, (test not available routinely).

Bone Marrow Examination

- Stainable iron seen in erythroblasts as blue granules by potassium ferrocyanate
- Accurate method of knowing iron stores
- Invasive and impractical test (not done routinely).

Indications of Bone Marrow Aspiration

- No response to iron therapy after 4 weeks
- Suspected aplastic anemia
- Kala-azar
  - Stool examination for ova and cysts (for 3 consecutive days) in all cases.

Urine Routine and Microscopic Examination

- For proteins, sugar, pus cells, occult blood and schistosomes (in high prevalence areas)
- Urine culture and sensitivity (for bacteriuria)
- Peripheral blood smear for malarial parasite in all cases
- Renal function tests (in suspected renal disease)
- Serum proteins (in hypoproteinemia).

Table 2: Blood indices in iron deficiency anemia (IDA) and thalassemia

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>IDA</th>
<th>Thalassemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral smear</td>
<td>Microcytic, hypochromic</td>
<td>Microcytic</td>
</tr>
<tr>
<td>Serum iron</td>
<td>Low</td>
<td>Normal or high</td>
</tr>
<tr>
<td>% Saturation</td>
<td>Low</td>
<td>Normal or high</td>
</tr>
<tr>
<td>Serum ferritin</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Hb pattern</td>
<td>Normal</td>
<td>Abnormal</td>
</tr>
<tr>
<td>HbF% and HbA₂ %</td>
<td>Normal</td>
<td>High</td>
</tr>
<tr>
<td>Red cell width</td>
<td>High</td>
<td>Normal</td>
</tr>
<tr>
<td>Free erythrocyte</td>
<td>&gt;50</td>
<td>Normal</td>
</tr>
<tr>
<td>porphyrin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: TIBC, total iron binding capacity.

TREATMENT

Prevention

Prophylaxis in Nonpregnant Women

- Prevention of iron deficiency should start before pregnancy
- The amount of 60 mg of iron along with folic acid (100–200 μg) every day for three months in the prepregnancy stage.

Iron Supplementation During Pregnancy (Flow chart 1)

- The World Health Organization (WHO) recommends universal oral iron supplementation, 60 mg elemental iron and 250 μg of folic acid once or twice daily for 6 months in pregnancy, in countries with a prevalence of anemia < 40% and for an additional 3 months postpartum in countries where the prevalence is > 40%.
- Ministry of Health, Government of India recommends intake of 100 mg of elemental iron with 500 μg of folic acid daily in the second half of pregnancy for a period of 100 days
If the compliance is poor, weekly or twice weekly oral iron supplements may be given.

Two injections of iron dextran (250 mg each) given intramuscularly at 4-week intervals also give good results.

**Treatment of Worm Infestation**
- Albendazole (400 mg) single tablet or
- Mebendazole (100 mg) twice daily for 3 days, given to all anemic pregnant women in the second and third trimesters.
- Change in defecation habits
- Avoidance of walking bare-footed.

**Improvement of Dietary Habits**
- Pregnant women should eat high iron bioavailable diet, which is within their reach
- Cooking of food in iron utensils
- Avoidance of tea, coffee and overcooking of food
- Adding lemon juice to the food
- Consumption of iron-rich natural mineral water.

**Improvement of Sanitation and Personal Hygiene**

**Improvement of Female Literacy Status**

**Food Fortification with Iron (e.g. of Salt)**

**Reproductive Interventions**
- Prevention of teenage pregnancies
- Reducing total number of pregnancies
- Spacing the pregnancies.

**Curative Treatment**

**General Measures**
- Diet rich in iron, protein and vitamins is prescribed
- Treatment of the cause of anemia.

**Specific Therapy**

**Principles:**
- To raise the Hb as near as normal
- To replenish iron stores.

**Choice of Therapy (Depends Upon)**
- Severity of anemia
- Duration of pregnancy
- Associated complications.

**IRON THERAPY**

Ideally all anemic patients should be admitted but due to shortage of bed only severe anemic patients are usually admitted. The management of iron deficiency in pregnancy will be governed by the etiology of the deficiency state and severity of anemia. Iron therapy can be divided into:
- Oral iron therapy
- Parenteral iron therapy.

**Oral Iron Therapy**
- If the woman presents in mid trimester or early third trimester oral iron therapy is started
- Available preparations are ferrous sulfate, ferrous gluconate, ferrous fumarate and ferrous succinate
- Ferrous sulfate (200 mg tablet containing 60 mg elemental iron) is given thrice daily till the blood parameters become...
normal. Maintenance dose—one tablet daily is given for 3 months postpartum

- If the compliance is poor (gastrointestinal side effects)
  - Reduce the dose
  - Give tablet with meals or
  - Give the drug less frequently

- Indications of response to therapy
  - Feeling of well-being
  - Improved looks and appetite
  - Rise in reticulocyte count (within 5–10 days), Hb 1.0 g/dL/week) and hematocrit.

If there is no significant clinical or hematological improvement within 3 weeks, diagnostic re-evaluation should be done. The ability of the patient to tolerate oral preparations will also be a factor. Using iron rich spa water as a prophylaxis against iron deficiency in pregnancy has a good place, because it is well tolerated and provides iron in a highly bioavailable form.

Iron (III) Polymaltose Complex

The iron (III) polymaltose complex dextriferron is one of the few available oral iron (III) compounds and belongs to the class of so-called slow-release iron preparations. Polymaltose acts like a casing around the trivalent iron, ensuring slower release of the iron from the complex. The advantages of this iron preparation are, firstly, its favorable side-effect profile compared to iron (II) salts as a result of the slow release, and, secondly, that it can be taken with meals. Various authors have postulated that iron polymaltose complexes have lower toxicity compared with iron sulfate salts, due to reduced formation of oxygen radicals and thus decreased plasma lipid peroxidation. In studies carried out to date, their bioavailability is comparable to that of iron (II) sulfates and fumarates.

Dosage of the iron (III) polymaltose complex (Maltofer®)
(Fe III= 50 mg);
- Drops: 40–120 drops/day
- Tablets: 200–400 mg/day
This is true either during or after meals—in contrast to iron (II) compounds.

Iron Compounds in Combined Preparations

Additives such as succinic acid, fumaric acid, gluconic acid, glutamic acid, aspartic acid and lactic acid, certain vitamins and trace elements (Cu, Co, Mn) form chelates with iron and thus keep divalent iron available for absorption. Ascorbic acid is a useful adjunct for the stabilization of Fe (II) ions against oxidation. Combining iron (II) salts with ascorbic acid increases the absorption of iron. According to the literature, this can lead to an increased side-effect rate due to the more rapid release of iron. In addition, the combination with ascorbic acid can lead to increased formation of toxic hydroxyl radicals.

Oral iron salts are available in a huge variety of combined preparations; their inclusion in multivitamin and trace element preparations, in particular, offers no advantages over the administration of iron alone. The presence of magnesium, calcium and zinc in combined products can inhibit the absorption of iron. Combining different iron (II) salts in one preparation also offers no advantages. Tetracyclines, antacids such as omeprazole and bile acid sequestrants such as cholestyramine can impair iron absorption. Conversely, the bioavailability of some agents, such as gyrase inhibitors, L-thyroxine and penicillamine, can be reduced by the concomitant oral administration of iron.

Causes of Failure of Response to Oral Iron Therapy

- Noniron deficiency microcytic anemia (e.g. thalassemia, pyridoxine deficiency, lead poisoning)
- Noncompliance
- Faulty iron absorption (gastrointestinal disorders)
- Persistent blood loss (hookworm infestation, bleeding piles)
- Infection that suppresses erythropoiesis
- Concomitant folate deficiency.

Reasons for Failure of Oral Iron Therapy

- Additional complicating disorders
- Drugs that inhibit erythropoiesis (e.g. cytotoxic agents, immunosuppressants).

Parenteral Iron Therapy

Parenteral iron can be used in patients receiving recombinant erythropoietin to guarantee adequate iron delivery. Parenteral iron is available as ferric hydroxide dextran complex (50 mg/mL), ferric gluconate and iron sucrose. Iron can be given by intramuscular injection in small amounts. These injections are painful and can cause skin staining. To prevent skin staining, a “Z”-shaped injection track should be followed. Intermittent intramuscular injection of 1000 mg in 4 divided doses can be given prophylactically during pregnancy to prevent anemia. For the treatment of iron deficiency anemia; the preferred method of parenteral iron administration is total dose infusion by slow intravenous infusion with 0.9% sodium chloride with all precautions to prevent anaphylactic reaction. The amount of iron needed can be calculated as follows: Body weight (kg) × 2.3 × (15-patient’s hemoglobin g/dL) + 500 mg to 10000 mg (for store) = Total dose (mg).
- It has no advantage over oral therapy if oral iron is well tolerated and absorbed
- The rise in Hb concentration is same as with oral iron (i.e. 1 g/dL/week)
- It is expensive and could be “hazardous”
- Advantage of parenteral therapy is certainty of its administration
• Oral iron is to be stopped 24 hours prior to parenteral therapy to avoid toxic reaction.

**Indications**

Indications for administering parenteral iron therapy are tabulated in Table 3.

<table>
<thead>
<tr>
<th>Table 3: Indications for parenteral iron therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Patients are unable to tolerate iron (intolerance of oral iron)</td>
</tr>
<tr>
<td>• Patients suffering from gastrointestinal malabsorption (insufficient absorption of oral iron due to intestinal disease)</td>
</tr>
<tr>
<td>• Noncompliant patients (poor compliance)</td>
</tr>
<tr>
<td>• Severe anemia in advanced pregnancy</td>
</tr>
<tr>
<td>• Insufficient or no response to oral iron</td>
</tr>
<tr>
<td>• The need for rapid efficacy</td>
</tr>
<tr>
<td>• Combination with recombinant human erythropoietin (rhEPO) (for patients with chronic renal disease)</td>
</tr>
</tbody>
</table>

**Preparations for Parenteral Iron Therapy**

1. **Type I complexes (Iron dextrin, iron dextran):** These iron complexes have high molecular weight (> 100000 Dalton) and high stability (e.g. Imferon®). The plasma half-life of the type I complexes is 3–4 days. The dextran component, in particular, can lead to severe allergic reactions. This reaction appears to be less pronounced with the dextrans.

2. **Type II complexes (Iron hydroxide-sucrose complex):** These are complexes of so-called medium stability, with a molecular weight of 30000–100000 Dalton (Venofer®). Maximum plasma concentrations are reached as early as 10 minutes following bolus administration (30 mg/L). The plasma levels return to pretreatment values 24 hours after administration. The half-life is 5.5 hours, and positron emission tomography (PET) studies show immediate accumulation in the bone marrow, occurring in parallel with the fall in plasma levels. In patients, 70–97% of the iron is used for erythropoiesis, depending on the severity of their iron-deficiency anemia. General side effects include: metallic taste, feeling hot, nausea, local irritation and dizziness.

3. **Ferric carboxymaltose (Ferinject®):** Ferric carboxymaltose is a nondextran containing intravenous (IV) iron agent designed to be administered in large doses by rapid (15 minutes) IV infusions. The ability to safely infuse a single dose as large as 1000 mg reduces the need for repeated IV infusions and renders this agent a potentially ideal candidate for various indications in anemia therapy.

4. **Type III complexes (Iron gluconate, iron ammonium citrate, iron hydroxyxide sorbitol complex):** Iron gluconates (e.g. Ferlicit®). They are unstable, labile complexes with molecular weights of less than 50000 Dalton. Low stability compared to iron dextrans and iron sucroses complexes, type III complexes show less binding to transport proteins, with greater quantities of free iron being released in the short term. Maximum transferrin saturation following the administration of iron gluconate has been described in various studies.

Free iron is deposited in the parenchyma of various organs. Free radicals lead to lipid peroxidation and, compared with type I/II complexes, to greater tissue toxicity. The iron gluconates, in particular, are comparable to the iron sucroses with regard to allergic or anaphylactic reactions, and, thus, like the iron sucroses, have a better side effect profile than the iron dextrans.

**Iron Sucrose Complex**

Iron sucrose is effective in pregnant and postpartum patients who do not respond to oral iron, who are noncompliant to oral iron, or who treated with rhHuEPO. In both cases, according to the present data, the expected hemoglobin increase and time for therapy are predictable in responding patients. Whether it is reasonable to wait for a response to oral iron in moderate to severe anemia is therefore questionable. Indications for the use of iron sucrose complex are: preexisting (moderate-severe) anemia; no effect of oral iron; side effects of oral iron; refusal of blood transfusion; limited time until delivery; coexisting risks (e.g. bowel disease, renal diseases); pre- and postoperative period and postpartum anemia.

In accordance with obstetrics clinic guidelines, an incremental treatment plan is used in anemia management. Prerequisites for the use of parenteral iron include diagnostic investigations and fulfillment of the following inclusion criteria:

- Hemoglobin (Hb) < 10 g/dL
- No effect of oral iron therapy (160–200 mg/d) over 2 weeks (i.e. no Hb increase and/or reticulocyte response)
- Proven iron deficiency (serum ferritin < 15 µg/L)
- Exclusion of hemoglobinopathy or other red cell disorders
- Exclusion of acute inflammatory state (C-reactive protein determination)
- Gestational age 16 weeks.

**Practical use of iron sucrose at the Zurich clinic of obstetrics:** The substance is administered through a venous butterfly cannula, once correct positioning in the vein has been tested with NaCl. Iron sucrose can be administered undiluted as a bolus or diluted, e.g. to 100–200 mL of isotonic NaCl solution as a short infusion. Administration of a test dose (1 mL) is required in different countries. The bolus injection may be given over 5–10 minutes; however, a short infusion over approximately 20 minutes is considered safer. The maximum single dose is 200 mg. We generally give two doses a week to achieve a target Hb value of 11 g/dL. The treatment can be given on OPD basis.

**Dosage Calculation**

Elemental iron needed (mg) = Iron deficit (Normal Hb – Patients Hb) × weight (kg) × 2.21 +1000
Anemia in Pregnancy

Parenteral preparations:
i. Iron dextran (Imferon®) IM/IV
   - Complex of ferric hydroxide
   - Colloidal solution containing 50 mg/mL elemental iron
   - 2 mL ampoule (single dose)
   - 10 mL vial (multidose)

Intravenous (IV) Infusion
- Total dose of iron required, is administered by a single IV infusion
- To be given by a doctor in a hospital setting
- Initially a small test dose (0.5 mL) is given and the patient is observed for 1 hour for any adverse reaction
- Measures to manage reaction are to be kept ready (e.g. inj epinephrine, inj hydrocortisone and oxygen).
- If the test dose is tolerated, iron dextran diluted in normal saline or 5% dextrose is given slowly over several hours
- Monitor to see for any adverse reaction (e.g. chest pain, chills, rigors, hypotension, breathlessness, hemolysis and anaphylaxis)
- Stop infusion and manage reaction in the event of such need.

Intramuscular (IM) Route
- More popular
- Lesser side effects.
Dose: Initial test dose (few drops) of iron dextran or iron sorbitol citrate, is given IM, when tolerated, is followed by 2 mL (100 mg) daily or on alternate days, deep IM in gluteal region, using Z technique.

Side Effects
Local
- Pain at injection site
- Skin discoloration
- Abscess formation.

Systemic
- Nausea, vomiting
- Headache
- Fever
- Arthralgia
- Lymphadenopathy
- Flushing
- Palpitation
- Anaphylactic reaction.

Indications of Blood Transfusion
If there is not enough time to achieve a reasonable hemoglobin for delivery, acute blood loss, anemia refractory to iron therapy, associated infection, or severe anemia beyond 36 weeks, then blood transfusion with all its hazards should be considered. Packed red cell transfusion is given with meticulous care to prevent severe circulatory overload and pulmonary edema. Blood transfusion corrects anemia, but more important is that it increases oxygen carrying capacity and stimulates erythropoiesis. Exchange transfusion may be indicated in cases of cardiac failure due to severe anemia, cases of marked anemia requiring surgery or as a safer alternative to blood transfusion. It raises the hemoglobin concentration very effectively in severely anemic women without inducing circulatory overload.
- Severe anemia near term
- Antepartum or postpartum hemorrhage
- Refractory anemia
  - Packed cells are preferred
  - Improvement is expected after 72 hours.

Drawbacks of Blood Transfusion
- Transfusion reaction
- Cardiac failure
- Pulmonary edema
- Preterm labor.

Stimulation of Erythropoiesis with Recombinant Erythropoietin (rhEPO)
The growth factor recombinant human erythropoietin (rhEPO), a glycoprotein (molecular weight: 30,400 Dalton) is identical to endogenous erythropoietin and acts as a selective growth and survival factor for erythroid cells. The combination of rhEPO and parenteral iron is superior to iron treatment alone and can be considered as a good option when treating severe anemia or if the patient refuses donor blood. The effect of rhEPO is dose dependent; single intravenous injection of 150–300 IU/kg are sufficient.

Antenatal Care
- More frequent antenatal check-ups required
- Fetal monitoring for growth and well-being
- Detection and management of complications (Cardiac failure, preterm labor)
- Hospitalization of severely anemic patients.

MANAGEMENT DURING LABOR
First Stage
- Blood cross-matching on admission
- Comfortable position in bed
- Adequate pain relief
- Oxygen inhalation (SOS)
- Digitalization (SOS)
• Antibiotic prophylaxis
• Strict asepsis
• For preterm labor β mimetics and steroids given cautiously (to avoid pulmonary edema).

Second Stage
Prophylactic forceps application.

Third Stage
• Active management (except in very severely anemic patients)
• Postpartum hemorrhage to be managed energetically (these patients tolerate bleeding poorly).³

Puerperium
• Adequate rest
• Iron and folate therapy to continue for 3 months
• Careful watch for failing lactation, subinvolution, thromboembolism and infection.

Contraception
• Sterilization (if family is complete)
• Oral contraceptive pills
• Barrier methods.

MEGALOBLASTIC ANEMIA IN PREGNANCY
In megaloblastic anemia, deoxyribonucleic acid (DNA) synthesis is affected. There is derangement of red cell maturation with production of abnormal precursors (megaloblasts) (Fig. 3) in the bone marrow, which are released into the circulation as macrocytes. Megaloblastic anemia is due to folic acid or vitamin B₁₂ deficiency.³

Folic acid at a cellular level is reduced to dihydrofolate acid and then to tetrahydrofolate acid (folic acid) which is essential for the cell growth and division
• Folic acid requirements are increased during pregnancy for the growth of the fetus, placenta, maternal red cell mass and myometrium³⁹
• Plasma folate levels decrease as pregnancy advances, reaching nearly half of nonpregnant values at term.
• Folate deficiency complicates nearly one-third of all pregnancies in nonindustrialized countries.
• Rich sources are green leafy vegetables (broccoli, spinach), Brussels sprouts, beans, yeast, liver, kidney, fruits, cereals, and nuts (almonds, peanuts).
• Poor source—goat’s milk
• It is heat labile, rapidly destroyed by boiling or steaming
• Absorbed from duodenum and upper jejunum
• Stored in the liver; body reserves of folate are low (10 mg)
• Daily requirements:
  – Nonpregnant women: 50–100 µg/day
  – Pregnant women: 300 µg/day
  – Lactating women: 150 µg/day.

Causes
• Reduced dietary intake (poverty)
• Prolonged cooking of food
• Nausea, vomiting, anorexia
• Malabsorption syndrome/gastrointestinal diseases
• Increased plasma clearance of folate by the kidneys
• Transfer of folate from mother to the fetus
• Uterine hypertrophy
• Expanded red cell mass
• Liver disorders
• Chronic alcoholism
• Antifolate medication—antiepileptic drugs (e.g. phenytoin, primidone), pyrimethamine and trimethoprim

FOLIC ACID (FOLATE) DEFICIENCY ANEMIA³⁹
• Folic acid along with iron is one of the important nutrients during pregnancy

Fig. 3: Megaloblastic anemia. Peripheral blood smear showing neutrophil with segmented nucleus
Anemia in Pregnancy

- Low body reserves
- Vitamin C deficiency
- Increased demand—multiple pregnancy, repeated child-births, hookworm infestations, bleeding piles, hemolytic anemias, hemoglobinopathies, chronic malaria, other infections
- Folate requirements are increased by iron therapy due to hyperplastic bone marrow. Therefore, folate is always given with iron for better results.

Clinical Features
- Asymptomatic patient
- Pallor
- Nausea, vomiting, diarrhea
- Loss of appetite
- Unexplained fever
- Glossitis
- Bleeding spots in skin, conjunctiva
- Hepatosplenomegaly.

Effects on Pregnancy

Maternal
- Abortion
- Preterm labor
- Abruptio placentae
- Preeclampsia.

Fetal
- Intrauterine growth retardation (IUGR)
- Preterm births
- Neural tube defects (NTDs)

- Cleft lip and cleft palate
- Megaloblastic anemia in the neonate.

MANAGEMENT

Diagnosis
- Hb < 10 g/dL
- MCV > 100 fl
- MCH > 33 pg/cell
- MCHC: Normal (31–37 g/dL)
- Peripheral smear:
  - Macrocytosis, anisocytosis
  - Hypersegmentation of neutrophils
  - Giant cell polymorphs
  - Megaloblasts
  - Neutropenia
  - Thrombocytopenia
  - RBCs show basophilic stippling, Howell-Jolly bodies and Cabot ring
- Low serum folate (< 3 ng/dL)
- Low RBC folate (< 150 ng/dL)—more useful test
- Normal or high serum iron levels
- High urinary formiminoglutamic acid (FIGLU) following a loading dose of histidine (obsolete test)
- High serum lactate dehydrogenase (LDH) and homocysteine levels
- Low reticulocyte count
- Bone marrow aspiration—megaloblastic picture (rarely done).

Prophylaxis
- Increased dietary intake
- Folic acid supplementation (recommendations).
WHO: 400 µg/day along with 60 mg elemental iron in antenatal and 3 months postnatal period.

Ministry of Health, Government of India: 500 µg/day with 100 mg elemental iron in antenatal and 3 months postnatal period.

- For prevention of NTD, 400 µg/day in low-risk cases and 5 mg/day in high-risk cases in the periconceptional period
- Food fortification with folic acid

**Treatment**

- Established folate deficiency in pregnancy is treated with 5 mg/day folic acid along with iron orally, to be continued in the postnatal period for 3 months
- Lactation provides an added folate stress, 25 µg/day is secreted in the breast milk
- In undiagnosed vitamin B₁₂ deficiency, however, folate therapy worsens neuropathy so add vitamin B₁₂ with folate therapy.
- Add vitamin C (100 mg thrice daily)—converts folic acid to folinic acid.

**Indicators of Response to Therapy**

- Fall in serum LDH levels (within 3–4 days)
- Rise in reticulocyte count (within 5–8 days)
- Parenteral folate is indicated in: (i) gastric intolerance and (ii) advanced pregnancy
- Blood transfusion is required in severely anemic patients (rare).

**Labor and Delivery**

No specific recommendations of management are there if the patient is hemodynamically stable.

### VITAMIN B₁₂ DEFICIENCY ANEMIA

Vitamin B₁₂ (cobalamin) cannot be synthesized in the human body and only dietary source of cobalamin is animal products, meat and dairy products. Pregnancy does not alter its absorption and does not have vast impact on maternal store. The dietary intake of cobalamin is more than adequate for the body’s requirements; except in the vegetarian and breast fed infants of mothers with significant vitamin B₁₂ deficiency. Deficiency of vitamin B₁₂ is almost due to malabsorption. Addisonian pernicious anemia is due to cessation of secretion of intrinsic factor from gastric mucosa which is very unusual during reproductive years. Vitamin B₁₂ deficiency is associated with infertility and pregnancy is likely only if the deficiency is cured.

- This condition is rare
- Serum, RBC and muscle vitamin B₁₂ concentrations decrease during pregnancy
- Vitamin B₁₂ absorption is unaltered in pregnancy
- Tissue uptake is increased under the influence of estrogens
- Smoking decreases serum vitamin B₁₂ levels
- Plasma vitamin B₁₂ binding capacity increases in pregnancy due to increased levels of transcobalamin II
- There is preferential transfer of absorbed vitamin B₁₂ to the fetus
- Pregnancy does not affect maternal vitamin B₁₂ stores
- Minimal amounts of vitamin B₁₂ are required for fetal development. So, not many fetal problems are seen in vitamin B₁₂ deficiency but breast fed infants of mothers with vitamin B₁₂ deficiency show a syndrome characterized by failure to thrive, developmental regression and anemia
- Addisonian pernicious anemia (due to intrinsic factor deficiency) is unusual in reproductive years, rather it causes infertility
- Deficiency is seen in Crohn’s disease, sprue, resection of distal ileum, gastrectomy cases and pure vegetarians
- Rich sources are liver, kidney, meat, fish, eggs, milk and cheese
- Vitamin B₁₂ is not destroyed by cooking
- Stored in the liver
- The average daily diet contains 5–30 µg of vitamin B₁₂
- Daily absorption is 1–5 µg
- Daily requirements (prepregnancy: 3 µg; during pregnancy and lactation: 4 µg).

**MANAGEMENT**

### Diagnosis

- Serum vitamin B₁₂ levels < 90 µg/L
- Elevated methylmalonic acid and homocysteine levels
- Deoxyuridine suppression test can differentiate vitamin B₁₂ and folic acid deficiency.

### Treatment

- Oral Vitamin B₁₂ (10–30 µg/day) along with folic acid is given in patients with dietary deficiency
- In severe deficiency injectable vitamin B₁₂, 1 mg IM on alternate days is given till improvement of neuropathy.

### Dimorphic Anemia

- In tropical countries deficiency of both iron and folic acid are seen together
- Peripheral film may show macrocytic or normocytic, normochromic or hypochromic picture (finding of one type of anemia dominates)
- Bone marrow is megaloblastic.

### Treatment

- Iron and folic acid supplementation in therapeutic dosage
- Intake of green leafy vegetables and fruits
- Avoidance of too much cooking of food.
Hemoglobinopathies

- Hemoglobinopathies are inherited biochemical disorders of Hb with qualitative or quantitative abnormality of globin chain synthesis.
- Subgroups
  - Sickling disorders
  - Thalassemia syndromes.
- Both homozygous and heterozygous forms occur.
- Multidisciplinary team management is required in women during preconception, antenatal, intranatal and postnatal periods.
- Timely screening of women and their partners to identify carriers and those at risk for having an offspring affected with major hemoglobinopathy is essential.

**Sickle Cell Trait (HbAS)**

- Benign condition
- Reproductive performance is unaltered
- Prepregnancy screening and counseling (both partners)
- Offspring having 25% chance of sickle cell disease (SCD), if male partner is a case of SC trait.

**Sickle Cell Disease (HbSS)**

Effects on Pregnancy (Flow charts 2 and 3)

*Maternal (High Maternal Morbidity and Mortality)*

- Sickle cell crisis (painful vaso-occlusive/hemolytic crisis)

**Flow chart 2: Sickling disorders**

- Sickling disorders (Qualitative disorders)*
  - Homozygous Sickle cell disease (SCD) HbSS
  - Heterozygous Sickle cell trait HbAS

*An amino acid substitution in an alpha or beta chain results in synthesis of abnormal Hb.

**Flow chart 3: Etiopathogenesis of sickle cell anemia**

- **HbA**
  - Point mutation
  - 6th Position of &-globin chain
  - Glutamic acid
  - Valine

- **HbS**
  - Oxygenated
  - Deoxygenated
  - HbS solution (RBC)
  - HbS Polymers (RBC) irreversibly sickled

- **Membrane changes increased adhesiveness**

- **Tissues**
  - Microvascular occlusion by sickle cells (infarctions)
  - Painful vaso-occlusive complications
  - Bones
  - Lungs
  - Kidneys
  - Liver
  - Brain
  - Spleen

- **Spleen**
  - Hemolysis
  - Chronic hyperbilirubinemia
  - Jaundice

- **Infection**
- **Acidosis**
- **Dehydration**
- **Hypoxia**
- **Cooling**
SECTION

Medical Disorders in Pregnancy

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• Acute anemia
• Ischemic injury/organ damage (infarctions, e.g. pulmonary)
• Infections (pulmonary, urinary tract)
• Hypertensive disorders of pregnancy
• Congestive cardiac failure
• Thromboembolism (pulmonary, CVA)
• Postpartum hemorrhage
• Fever, leukocytosis, jaundice.

Fetal (High Perinatal Mortality and Morbidity)

• Abortion
• Preterm birth
• Intrauterine growth retardation.

MANAGEMENT

Diagnosis

• Complete blood count (decreased RBC, increased WBC and platelet counts)
• Blood typing
• Red cell antibody screen
• Low Hb-refractory hypochromic anemia
• Peripheral smear—sickle cells, Howell-Jolly bodies, target cells (Fig. 5)
• Low hematocrit (18–30%)
• Persistent reticulocytosis (10–20%)
• Serum iron levels (high)
• Low serum folate levels
• Hb electrophoresis
• Sickle solubility test
• Liver function tests (increased serum bilirubin)
• Renal function tests
• Serum electrolytes

• Urine culture and sensitivity
• Hepatitis B surface antigen (HBs Ag) test
• HIV test
• Rubella antibody status
• Abdominal ultrasound for gallstones and splenic size.

TREATMENT

Preconception

• Screening (both partners)
• Counseling
  – Counseling against conception until disease status is optimized
  – About the risks of pregnancy
  – About prenatal diagnosis.

Antenatal

• Termination of pregnancy is offered if the fetus is homozygous for SCD (act according to parental wishes)
• Early and frequent antenatal check-ups
• Fetal surveillance and tests for fetal well-being
• Avoidance of air travel
• Antibiotics (when required)
• Folic acid supplementation (5 mg/day)
• Blood transfusion (when required).

Labor and Delivery

• Patient is kept warm
• Good hydration
• Adequate pain relief (epidural analgesia)
• Oxygen inhalation
• Antibiotics
• Continuous cardiotocography (CTG) monitoring
• Avoid prolonged labor (plot partogram)
• Cord blood screening for hemoglobinopathy.

Postnatal

• Good hydration
• Oxygenation
• Monitor for sickle cell crisis
• Early ambulation
• Thromboprophylaxis (when required)
• Contraception
• Neonatal care.

ALPHA THALASSEMA MAJOR
(FLOW CHART 4)

• No alpha chain production
• Fetal hydrops develops (incompatible with life)
• Labor and delivery—problems related to large fetus.
**ALPHA THALASSEMIA MINOR**
- Prepregnancy screening (both partners) and counseling
- Offspring having 25% chance of thalassemia major, if partner is a carrier of alpha thalassemia.
- Definitive diagnosis needs DNA analysis
- Antenatally chorionic villous sampling or amniocentesis done for diagnosis
- Preimplantation blastomere biopsy to select unaffected embryos in IVF cases
- The reproductive performance is not affected
- Folic acid supplementation (5 mg/day)
- Blood transfusion when required.

**BETA THALASSEMIA MAJOR (FLOW CHART 4)**
- Survival beyond teenage years is uncommon.
- If they survive, patients are infertile.

**BETA THALASSEMIA MINOR (FLOW CHART 5)**
- Mild, microcytic, hypochromic anemia (Hb 8–10 μg/dL), not responding to iron therapy
- Diagnosis often missed
- Increased HbA₂ (> 3.5%), normal or increased MCHC and serum iron concentrations (See Table 2)
- Iron overload in tissues
- Increased serum bilirubin (2–3 mg%)
- Reproductive performance unaltered
- Offspring having 25% chance if the partner is also a carrier of beta thalassemia.

**TREATMENT**
- Do not supplement iron
- Folic acid supplementation (5 mg/day)
- Withhold iron chelation therapy in pregnancy

**HEMOLYTIC ANEMIA**

**Causes of Hemolysis**

**Intrinsic**
- Abnormalities of Hb structure and function (e.g. hemoglobinopathies)
- Red cell membrane disorders (e.g. hereditary spherocytosis)
- Red cell metabolism disorders (e.g. pyruvate kinase, G6PD deficiency).

**Extrinsic**
- Red cell directed antibody (acquired immune hemolytic anemia)
- Altered intravascular circulation (microangiopathic hemolytic anemia).

**ACQUIRED IMMUNE HEMOLYTIC ANEMIA (EXTRAVASCULAR HEMOLYSIS)**
- The patient makes antibodies (IgG) against red cell antigens causing hemolysis in reticuloendothelial system.

**Causes**
- Idiopathic
- Diseases
  - Leukemias
  - Lymphomas
  - Viral infections
- Drugs
  - Penicillins
  - Sulfas
  - Quinidine
Collagen vascular diseases [e.g. systemic lupus erythematosus (SLE)].

**Diagnosis**
- Positive direct Coomb’s test
- Raised antinuclear antibody titers (SLE)
- Raised anti-DNA antibody titers (SLE)
- Reticulocytosis (10–30%) (Fig. 6)
- Low Hb
- Splenomegaly.

**Treatment**
- Prepregnancy counseling and optimization of treatment
- Adjustment of steroid therapy (prednisolone 60–100 mg daily)

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**Flow chart 5: Pathogenesis of β-thalassemia**

![Flow chart 5: Pathogenesis of β-thalassemia](image)

- Normal
  - Hb
  - HbA–(α2β2)
  - Normal RBC
- Reduced β-globin Synthesis
- β-Thalassemia
  - Abnormal erythroblasts die in bone marrow
  - α-globin aggregates, Microcytic, Hypochromic RBC
  - Ineffective erythropoiesis
- Dietary iron
  - Stomach
  - Increased absorption of iron
  - Heart
  - Liver
  - Secondary hemochromatosis
  - Increased iron deposition
  - Blood transfusions
  - Tissue anoxia
  - Erythropoietin increase
  - Marrow expansion
  - Skeletal deformities
- Anemia
  - Spleen (Hemolysis)
  - Hepatosplenomegaly
  - Increase serum bilirubin

**Fig. 6: Hemolytic anemia (bone marrow smear)**
- Blood transfusion
- Folic acid supplementation (5 mg daily)
- Splenectomy
- Azathioprine (immunosuppression)
- Remission occurs after delivery but the condition can recur in subsequent pregnancies.

**Microangiopathic Hemolytic Anemia (Intravascular Hemolysis) (Flow Chart 6)**

**Causes**
- Preeclampsia/eclampsia (DIVE)
- Thrombotic thrombocytopenic purpura
- Hemolytic uremic syndrome (rare)
- Herpetic hepatitis.

**Diagnosis**
- Peripheral smear
  - Fragmented RBCs (Fig. 7)
  - Schistocytes
  - Helmet cells
  - Thrombocytopenia is always present
- Fibrinogen deposition in microvasculature, spontaneous correction after delivery
- Moderate to severe anemia

**Flow Chart 6:** Clinicopathologic effects of hemolysis

![Flow Chart 6: Clinicopathologic effects of hemolysis](image)
• Reticulocytosis
• Low haptoglobin levels
• High serum LDH levels
• Hemoglobinemia and hemoglobinuria.

Treatment
• Treatment of the causes
• Blood transfusion.

APLASTIC ANEMIA
(RARE IN PREGNANCY)

Causes
• Idiopathic
• Infections
• Medications/toxins
• Immunological
• Autosomal recessive inheritance
• Pregnancy itself.

Clinical Features
• Pallor
• Fatigue
• Bruising/hemorrhage
• Infections
• Lymphadenopathy
• Hepatosplenomegaly.

Complications
• High maternal morbidity and mortality rates (30%)
• Intrauterine growth retardation
• Intrauterine fetal death.

MANAGEMENT

Diagnosis
• Pancytopenia
• Bone marrow aspiration/biopsy
  - Marked hypocellularity
  - Hemopoietic tissue replaced by fat
  - Cytogenetic study and chromosomal fragility tests.

Treatment
• Termination of pregnancy (in first trimester)
• Bone marrow transplantation (if no spontaneous recovery after termination)
• Repeated blood transfusions until delivery to maintain hematocrit > 20
• Platelet transfusion (to control hemorrhage)
• Granulocyte transfusions (to combat infections)

CONCLUSION

Anemia in pregnancy is one of the most common medical disorders in India and is responsible for increased maternal morbidity and mortality. In developing countries nutritional anemia is most common but there are also non-nutritional causes of anemia that may be seen in pregnancy, the sickle cell disorders, the thalassemias, hemolytic anemia, etc. which are reviewed in a separate chapter. Prenatal care is the preventive obstetrics. The factors responsible for anemia in pregnancy should be identified and eradicated. Iron supplement to prevent anemia in pregnancy is a well known strategy. The National Nutritional Anemia Prophylaxis Program (NNAPP) advised 60 mg of elemental iron and 500 µg of folic acid daily for 100 days to all pregnant women. Inaccessibility of such program, noncompliance and gastrointestinal malabsorption still remain as major causes of anemia in our country. Malaria and hookworm prophylaxis must be considered in endemic areas. Prevention and management of nutritional anemia is easy and cheap. Along
with the support of the Government, the support of the family, social workers, schoolteachers, media, etc. is necessary. But, do not worry! Conquering anemia is an achievable goal. Educating women will help by increasing awareness of the need for better nutritional status and contraceptive usage, thus limiting and spacing the pregnancies.

So friends, let us join hands so that the word “MA” can mean “MOVEMENT AGAINST ANEMIA”. The Federation of Obstetric and Gynaecological Societies of India (FOGSI) in 2007 initiated a movement of 12 x 12 initiative to achieve hemoglobin levels of 12 g/dL by 12 years.

In 2008, FOGSI has strengthened its drive and commitment toward anemia eradication by giving a call “ERADICATE ANEMIA EVERYDAY”; only you can make a difference.

REFERENCES

INTRODUCTION

Pregnancy involves a variety of hematological problems needing shared responsibility from obstetricians, hematologists and neonatologists. The disorders may be harmful or lethal to mother or fetus. Similarly, therapeutic interventions meant to decrease maternal morbidity may harm the fetus. Anemia, hemorrhagic disorders and venous thromboembolism (VTE) are probably the most important hematological conditions during pregnancy. Moreover, a patient of primary hematological disorder may become pregnant. This would include disorders as varied as thalassemia, sickle cell disease, immune thrombocytopenic purpura (ITP) and chronic myeloproliferative disorders.

ANEMIA INCLUDING THALASSEMIA AND SICKLE CELL DISEASE

During pregnancy, mother’s blood volume expands physiologically. However, this expansion consists of 40–60% increase in plasma volume which is approximately twice the expansion in red cell mass (20–30%). This hydremia of pregnancy results in a drop in hematocrit to 30% with hemoglobin dropping up to 10 g/dL which, hence, forms the lowest limit of normal hemoglobin during pregnancy.

Apart from this “physiological anemia of pregnancy”, other important anemias during pregnancy include:

- Nutritional anemia
- Others.

Nutritional Anemia

During pregnancy, approximately 1 g of additional iron is needed. This is to provide iron for fetal hemoglobin synthesis and to compensate for the bleeding during delivery. A woman, who is pregnant often, has insufficient iron stores to meet the demands of pregnancy. Despite iron deficiency, delivery of iron to the placenta continues. A normal woman is unlikely to have more than 500 mg of iron storage pool and hence prophylactic iron supplementation is essential.

Widely prevalent iron deficiency in both rural and urban population in India makes the matter worse and occasional patient has severe morbidity and even mortality secondary to severe anemia. Emergency blood support is lifesaving in such situation. A mean corpuscular volume (MCV) less than 80 mg/dL and hypochromia of the red blood cells (RBCs) should prompt further studies, including total iron-binding capacity, ferritin levels and hemoglobin electrophoresis if iron deficiency is excluded.

Megaloblastic anemia or even pancytopenia secondary to folic acid deficiency is also extremely common as there is similar escalation in the need for this cofactor. Body stores for folic acid are small and short-lived. The nausea and vomiting further impairs its intake. As it is well-known, folate deficiency during first trimester results in neural tube defects and cleft palate formation in the fetus. Hence, administration of prophylactic folate immediately after diagnosis of pregnancy has become mandatory. An increased MCV can be suggestive of folate deficiency. Determination of serum levels of vitamin B₁₂ and folate may be required.

Dimorphic anemia due to combined iron and folic acid deficiency is, hence, very common. Such patients may have normal MCV and mean corpuscular hemoglobin (MCH) but red cell distribution width (RDW) is grossly elevated and RBC histograms show characteristic curves. Smear examination also helps (Table 1).

Others

Of the uncommon anemias, “common” types include the anemia of renal disease, myelodysplastic syndrome and the anemia of chronic disease. These conditions may be
Thrombocytopenia

Thrombocytopenia, defined as a platelet count of less than 150,000/µL, is common during pregnancy and is diagnosed in approximately 7% of women. The most common thrombocytopenic disorders with pregnancy include:

1. Gestational thrombocytopenia (GT)
2. Immune thrombocytopenic purpura (ITP)
3. HELLP syndrome, preeclampsia and eclampsia
4. Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome.

**Gestational Thrombocytopenia**

Gestational thrombocytopenia is common. It almost never produces overt bleeding needing clinical attention. Platelet count seldom drops below 70,000/cu mm. It is not an indication for any therapeutic intervention including fetal blood sampling. However, before GT is diagnosed, other causes of thrombocytopenia have to be investigated and ruled out. GT could recur in future pregnancies. The diagnosis requires normalization of platelet count after delivery and/or documentation of absence of thrombocytopenia prior to pregnancy. The mechanism remains unclear and the prevalence could be up to 6% of pregnancies.

**Immune Thrombocytopenia Purpura**

Immune thrombocytopenia is a common disorder in young adult women. The diagnosis is one of exclusion, although platelet associated immunoglobulin G antibodies are easily detectable in such patients. The reasons for this include non-specificity of such antibodies and methodological problems related to their documentation. Therapy for ITP during pregnancy includes corticosteroids, intravenous (IV) gamma globulin, second trimester splenectomy, care during delivery and postnatal care of the neonatal thrombocytopenia. Corticosteroids (prednisolone) given orally, form the most common modality of effective treatment for majority of such patients, despite their adverse effects. Despite its efficacy, IV gamma globulin is used only if steroids are ineffective, require higher maintenance dose or have unacceptable adverse effects. This relates to the cost of therapy, parenteral mode of administration, need for hospitalization and their short duration of efficacy necessitating repeated administration at two-weekly intervals or so. Intravenous gamma globulin therapy is hence, usually administered just prior to delivery. With availability of these two modalities of treatment, splenectomy, which carries a risk of fetal loss, is rarely required.

*Treatment of ITP:* For patients who do not respond to corticosteroids of IV immunoglobulin as single agents, combinations of these therapies may sometimes be more effective/particularly when steroids are delivered as high-dose pulse therapy, e.g. methyl prednisolone 1 g/day for two consecutive days.

If this approach fails, laparoscopic splenectomy is needed and can be safely performed during mid-second trimester.

In refractory ITP, azathioprine has been safely used during pregnancy in patients with renal transplants and inflammatory bowel disease. Cyclosporine A has also been used safely in pregnancy. These cytotoxic drugs can be used in mid-second trimester and beyond.

Transplacental passage of antiplatelet immunoglobulin G can result in fetal thrombocytopenia. Adverse events secondary to this are unusual in intrauterine life. However, intracranial hemorrhage during delivery and overt bleeding diathesis up to 3 weeks after delivery are known. Fetal scalp vein sampling during labor or umbilical vein sampling before labor is helpful in diagnosing fetal thrombocytopenia which in turn should influence the method of delivery. A fetal platelet count of over 50,000/cu mm is considered adequate for safe vaginal delivery. Previously used maternal antiplatelet antibody level to anticipate fetal thrombocytopenia is obsolete. Newborn’s platelet count from previous pregnancy

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**Table 1: Hematological parameters in different anemias**

<table>
<thead>
<tr>
<th>Anemia type</th>
<th>HCT</th>
<th>RBC mass</th>
<th>MCV</th>
<th>MCH</th>
<th>MCHC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normocytic</td>
<td>↓</td>
<td>↓</td>
<td>(N) or ↑</td>
<td>(N)</td>
<td>(N)</td>
</tr>
<tr>
<td>Microcytic hypochromic</td>
<td>↓</td>
<td>(N)</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Macrocytic</td>
<td>↓</td>
<td>(N) or ↓</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
</tr>
</tbody>
</table>

**Abbreviations:** HCT, hematocrit; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; RBC, red blood cell
is an excellent predictor of the count in subsequent pregnancies. Interestingly, administration of IV gamma globulin to mother does not influence the fetal platelet count but giving of steroids to mother with ITP in the 3 weeks prior to delivery has its positive effect.

**HELLP Syndrome, Preeclampsia and Eclampsia**

HELLP syndrome (hemolysis, elevated liver enzymes and low platelets) may or may not be associated with increased blood pressure, edema or proteinuria. Patients with HELLP syndrome present with malaise and right upper quadrant or epigastric pain.

Preeclampsia and eclampsia are discussed elsewhere at length. Thrombocytopenia forms only a part of the whole syndrome and rarely requires separate management.

**Thrombotic Thrombocytopenic Purpura and Hemolytic Uremic Syndrome**

Thrombotic thrombocytopenic purpura is a rare disorder characterized by the pentad—fever, hemolytic anemia, thrombocytopenia, renal disease and central nervous system manifestations. Nonimmune (Coombs’ negative) hemolytic anemia characterized by RBC fragmentation (schistocytosis) and thrombocytopenia are the hallmarks of this rare entity. Except for fever, all other features of TTP are also present in toxemia. Hence, the management of such patient during last trimester usually requires delivery of the infant. Against this, a classical TTP appearing earlier in pregnancy is best treated by plasma exchange or plasma infusion, corticosteroids, antiplatelet drugs, etc.

Hemolytic uremic syndrome is still rarer, and it is managed on similar lines except that role of plasma exchange is unclear while renal failure necessitating dialysis support is common.

These disorders may require maternal management even after the delivery or uterine evacuation.

**von Willebrand’s Disease and Other Genetic Bleeding Disorders**

The most common inherited coagulopathy with pregnancy is vWD with prevalence rate of 0.8–1.3%. von Willebrand’s disease is a common disorder with several subtypes having variable clinical severity needing different management. Fortunately, majority of such patients have significant rise in factor VIII as well as von Willebrand’s factor (vWF) during pregnancy, and hence safe delivery without specific support is common. This, however, does not apply to the rare type 3 vWD where vWF or cryoprecipitate has to be administered before conducting delivery or a cesarean section. The support has to continue for 5–7 days after the delivery. Prenatal sampling of fetal blood helps in identifying the affected infant, and hence vaginal delivery is permissible for unaffected infant. Another subtype, i.e. type 2B, has an additional complexity in the form of gradually worsening thrombocytopenia during pregnancy. Such patients need vWF/cryoprecipitate and not platelet transfusion to support their delivery. Most of the other subtypes of vWD can be helped by infusing desmopressin, which increases endogenous vWF and factor VIII level.

Patients with vWD have an additional problem of delayed bleeding after delivery because of rapid normalization of vWF and factor VIII levels to a nonpregnant deficient state. Such patients would need desmopressin/vWF/cryoprecipitate support.

Other inherited coagulopathies are relatively rare. Factor concentrates or fresh frozen plasma (FFP) during and up to 5 days after delivery is the usual support needed. Coagulation factor level needs to be monitored to decide the replacement protocol and doses.

Factor XIII deficiency is a special problem as it leads to spontaneous recurrent abortions and marked uterine bleeding. Administration of factor XIII concentrates or FFP at regular intervals during pregnancy is helpful.

**Acquired Hemophilia**

Development of acquired inhibitors of coagulation factors, particularly factor VIII is a rare but important disorder in the postpartum period. Nova VII (activated factor VII), prothrombin complex concentrate, activated prothrombin complex concentrate and porcine factor VIII are some of the options available to treat the bleeding complications. Standard factor VIII concentrates in large quantity may also be effective if the inhibitor level is low. Immunosuppressive therapy is also helpful. The problem can rarely recur after subsequent deliveries.

**Disseminated Intravascular Coagulation**

The most common bleeding disorder of hematological origin in obstetric practice is DIC. A rapid and often fatal form of DIC is a dramatic event which may complicate abruptio placentae, amniotic fluid embolism, eclampsia, septic abortion, hypertonic saline and urea induced abortions, etc. A slow DIC, which is usually nonfatal and nowadays infrequent, is seen following intrauterine fetal death.

Disseminated intravascular coagulation during obstetric practice has its origin in the entrance of the thrombogenic products of conception into the systemic circulation. It leads to a combination of thrombosis affecting microcirculation and hemorrhage. Shock, hypoxemia and acidosis are important trigger factors. Correct bedside diagnosis supported by laboratory findings like thrombocytopenia, schistocytosis, prolonged prothrombin time, activated partial thromboplastin time, thrombin time coupled with hypofibrinogenemia and raised D-dimer (a type of fibrinogen degradation products) helps in quick execution of therapeutic measures to decrease maternal mortality and morbidity.
Therapeutic measures include support to vital organs, correction of trigger events, blood component therapy and above all evacuation of uterus. Heparin therapy is not indicated in most forms of DIC complicating pregnancy (except intrauterine fetal death).

HYPERCOAGULABLE STATES

Pregnancy itself is a hypercoagulable state where concentration of clotting factors increase progressively while fibrinolytic capacity drops. In addition, stasis secondary to obstruction of venous return by enlarging uterus, dramatically increase the incidence of VTE in pregnancy and even more during puerperium. The vessels most commonly involved include iliofemoral system and pelvic veins. Occasional fatality can occur secondary to pulmonary embolism, and hence anticoagulation is indicated. As anticoagulation has its own risk, the diagnosis of thromboembolism must be objective. This includes color venous Doppler studies by duplex technology, impedance plethysmography, contrast venography, etc. for the iliofemoral system and ventilation/perfusion scan or pulmonary angiography for pulmonary embolism. Blood test like D-dimer is also helpful.

Inherited (genetic) thrombophilic disorders with pregnancy lead to significant increase in maternal morbidity and mortality secondary to VTE affecting iliofemoral veins, pelvic veins and causing devastating pulmonary emboli. These disorders also lead to fetal wastage, intrauterine growth retardation and premature deliveries.

Antithrombin-III (AT-III) is probably the most well-studied example in this group. Seventy percent of women develop thrombotic events during pregnancy or after delivery. Low-molecular-weight heparin or unfractionated heparin during the first 4 months of pregnancy, oral anticoagulation in the remainder of pregnancy (until 36th week), reintroduction of heparin during last month, and its withdrawal a day before delivery forms the usual protocol. A single infusion of AT-III, 3,500 units just before delivery followed by heparin in the postdelivery period until oral anticoagulation is effectively introduced, is also a must.

Protein C deficiency and protein S deficiency are similarly associated with maternal VTE and fetal wastage. Twenty-five percent of pregnant women with protein C deficiency develop DVT while the exact incidence with protein S deficiency remains unclear. Such mothers require management similar to those with AT-III deficiency.

Factor V Leiden is the most common cause of activated protein C resistance (APC resistance). This mutation, in heterozygous state, is probably the most common cause of hypercoagulable state both in Caucasians and Indians. Prothrombin mutation and hyperhomocysteinemia secondary to methylenetetrahydrofolate reductase may be co-inherited with APC resistance or other prothrombotic disorders exaggerating the risk of VTE and fetal wastage.

Universal screening of pregnant women for these prothrombotic disorders is not recommended. However, those with a personal history of VTE, family history of VTE or unexplained recurrent fetal wastage are candidates for such screening.

Thrombophilic mothers secondary to genetic predisposition may require lifelong anticoagulation, insertion of inferior vena cava filters and regular monitoring of International Normalized Ratio. Thrombolytic therapy during pregnancy is contraindicated due to risk of severe hemorrhage while antiplatelet drugs (aspirin and others) are ineffective.

ANTIPHOSPHOLIPID ANTIBODY SYNDROME AND SYSTEMIC LUPUS ERYTHEMATOSUS

Lupus anticoagulants (LA) and anticardiolipin antibody (ACA) are the laboratory hallmark of relatively common antiphospholipid antibody (APA) syndrome, the most threatening manifestations of which include first trimester abortions and fetal deaths in second as well as third trimesters.

Lupus anticoagulants are immunoglobulins that prolong phospholipid dependent coagulation tests, the most sensitive of which include Kaolin clotting time and dilute Russell viper venom time. ACA are immunoglobulin G or immunoglobulin M antibodies, which are detectable using immunological techniques, i.e. enzyme-linked immunosorbent assay or radioimmunoassay. Occasionally, Venereal Disease Research Laboratory (VDRL) test, a test for syphilis, is also positive (biological false-positive test).

Patients with antiphospholipid antibody (APA) syndrome may develop both arterial and venous thrombosis as well as thrombocytopenia. The mechanism is complex, and it includes prostacyclin inhibition acquired APC-resistance, reduced annexin V levels, acquired deficiency of protein C and free-protein S, etc. The fetal wastage is secondary to a thrombotic process involving the decidual and placental vessels.

Antiphospholipid antibody syndrome could be primary or secondary with systemic lupus erythematosus (SLE) being the most common systemic collagen vascular disease as an underlying illness. Patients with APA syndrome may go on to develop SLE. Similarly, patients with SLE may develop APA syndrome later on. Those affected by APA syndrome may have only LA or only ACA positivity in vitro, and many of these patients may have either clinical evidence of SLE or only serological tests positivity (e.g. antinuclear antibody, anti-dsDNA antibody, etc.).

It is recommended that all women with more than two abortions (specially beyond first trimester), unexplained stillbirths, intrauterine fetal deaths, etc. should be screened for APA syndrome by both LA and ACA testing (Table 2).
Optimal treatment for pregnant women with APA syndrome is undetermined. The use of aspirin and/or prednisolone to reverse the poor outcome has not been validated in placebo-controlled trials. Use of low-molecular-weight heparin as well as unfractionated heparin is a success story among obstetricians, hematologist and neonatologists. Treatment is successful in delaying delivery until it can be terminated. Occasional patient may avoid therapeutic intervention for chronic myelogenous leukemia until delivery as well.

### LEUKEMIA/LEUKEMOID REACTIONS/LEUKOCYTOSIS

Pregnancy itself can occasionally elevate white blood cell count with even shift to left resulting into occasional metamyelocyte and myelocyte in peripheral blood film. Döhle bodies may also be present, and this may create confusion with respect to infections. The mechanism of elevated leukocyte count is unclear but may be related to alterations in cytokines or steroid metabolism.

Leukemia with pregnancy is a rare event and the management is influenced by the stage of pregnancy and family wish. As the first trimester is the most active stage of organogenesis, pregnancy is usually terminated. Spontaneous abortions and fetal losses are also common in such patients. Chronic leukemias may be managed by leukapheresis as successful delaying device until delivery is possible. Chronic myeloid leukemia may also be manageable with α-interferon. There are case reports where successful deliveries without any complications have occurred despite chemotherapy for leukemia and lymphoma during later part of pregnancy. Surprisingly, compounds like ATRA (all-trans-retinoic acid) for treatment of acute promyelocytic leukemia have also been used without fetal complications. Imatinib mesylate has been tried with successful results for treatment of chronic myelogenous leukemia.

### CHRONIC MYELOPROLIFERATIVE DISORDERS

#### Essential Thrombocythemia

This may lead to development of placental infarcts, fetal growth retardation or fetal loss. Monitoring such pregnancies with Doppler ultrasound studies of placental blood flow may help in deciding the need to reduce platelets. Aspirin with or without dipyridamole has been used with success and so is α-interferon. Plateletpheresis has been performed just prior to delivery as well.

#### Polycythemia Vera

Untreated, polycythemia vera with pregnancy leads to poor perinatal outcome with frequent fetal losses. Phlebotomy and judicious use of iron form the mainstay of treatment. Hematocrit must be kept below 40%. Associated thrombocytosis may also create problem. Aspirin or even heparin in perinatal period have been used with success and so is α-interferon. Plateletpheresis has been performed just prior to delivery as well.

#### Chronic Myeloid Leukemia

Once again, α-interferon has been used as the mainstay of treatment. Pregnancies during first trimester may also be terminated. Occasional patient may avoid therapeutic intervention for chronic myeloid leukemia until delivery.

#### Paroxysmal Nocturnal Hemoglobinuria

Cortical venous thrombosis, hepatic and portal vein thrombosis as well as iliofemoral thrombosis are commonly associated with pregnancy in a patient of paroxysmal
nocturnal hemoglobinuria. Low-molecular-weight heparin or low-dose unfractionated heparin during the period of bed confinement is an effective preventive measure. Both hemolytic crises and marrow aplasia are known to worsen during pregnancy. Packed cells support to maintain hematocrit of 40% is desirable. However, this could lead to neonatal isoimmune hemolysis secondary to maternal sensitization.

REFERENCES

INTRODUCTION

The hemoglobinopathies are red blood cell (RBC) disorders which result either from the synthesis of structurally abnormal Hb chains (the Hb variants) or from the defective synthesis of Hb chains (the thalassemia syndromes). These inherited genetic disorders are inherited in Mendelian recessive manner so that persons with the carrier or traits are generally healthy. Patients manifesting clinically significant disease may be homozygous for any one condition or can be heterozygous for two or more hemoglobinopathy genes which interact.

The hemoglobinopathies are result of mutation and deletion in and around the globin genes on chromosome 16 and 11.

SICKLE CELL HEMOGLOBINOPATHIES

Sickle cell disease is one of the most common monogenic disorders over the world, which is associated with lifelong morbidity and reduced life expectancy. Sickle cell hemoglobinopathies or sickle cell disease is a collective name for group of conditions causing clinical symptoms including all those abnormalities resulting from an alteration in structure, function, or production of hemoglobin. Hemoglobin S (HbS) results from substitution of thymine for adenine in the beta-globin gene, which leads to the substitution of the neutral amino acid valine for the negatively charged glutamic acid at the sixth position from the N-terminus in the beta-chain. Hemoglobin C (HbC) results from a lysine substitution for glutamic acid (Fig. 1).

Major sickle disorders with severe clinical symptoms include sickle cell anemia (HbSS), sickle cell hemoglobin C (HbSC) disease, and sickle cell beta-thalassemia (HbS beta-thalassemia).

Minor disorders include hemoglobin C disease (HbAC), hemoglobin SE (HbSE), hemoglobin SD (HbSD), and hemoglobin S-memphis (HbS-memphis). Heterozygosity for hemoglobin A and hemoglobin S (HbAS) is the most common disorder. HbS is also known as sickle cell trait and occurs in 1 in 625 African Americans. HbS is also found in other populations, such as Greeks, Italians (particularly Sicilians), Turks, Arabs, Southern Iranians, and Asian Indians.

Etiopathogenesis

- Sickle cell hemoglobin (HbS) is a variant of the β-chain of hemoglobin. Sickling of the red cells occurs particularly in response to hypoxia, cold, acidosis and dehydration.
- When deoxygenated, HbS molecules undergo aggregation and polymerization. Initially, the red cell cytosol converts from a freely flowing liquid to a viscous gel as HbS aggregates. With continued deoxygenation, aggregated HbS molecules assemble into long needle-like fibers within red cells, producing a distorted sickle or holly leaf shape. These permanently damaged RBCs are then removed by the reticuloendothelial system, with the average RBC lifespan reduced to 17 days. The result is a chronic compensated anemia, with Hb typically measuring between 6.5 g/dL and 9.5 g/dL.
- The sickle shape also results in altered motion through the microvasculature. This altered motion can predispose the patient to vascular stasis, hypoxia, acidosis, and increased production of 2, 3-diphosphoglycerate, which perpetuates the cycle by resulting in further deoxygenation and thus, more sickling. The microvascular injury can result in ischemic necrosis and end-organ infarction. Organs affected by chronic sickling include the spleen, lungs, kidneys, heart, and brain. Patients with sickle cell anemia are functionally asplenic. Therefore, immunization for
encapsulated organisms should be a consideration. Likewise, aggressive treatment should be instituted when encapsulated bacterial infections are diagnosed in sickle cell disease.

Rate and degree of sickling is affected by following factors:
- Most important is amount of HbS and its interaction with other hemoglobin chains in the cell
- Length of time: red cells are exposed to oxygen tension
- A decrease in pH reduces the oxygen affinity of hemoglobin hence more deoxygenation
- Rate of HbS polymerization is strongly dependent upon the Hb concentration per cell or mean corpuscular hemoglobin concentration (MCHC).

**Clinical Features**

**Effect on Pregnancy (Table 1)**
- In addition, Chakravarty and co-workers (2008) reported that sickle cell disease was associated with significantly increased odds ratios for renal failure, various forms of gestational hypertension, and fetal-growth restriction.
- There is increased incidence of abortion, intrauterine growth restriction and prematurity. Fetal distress and perinatal mortality is increased, four to six folds.
- Close observation is recommended at 32–34 weeks; obtain pregnant patient’s blood cell count, to detect hemoglobin level, infection, and serial ultrasonography to monitor fetal growth.
- Crisis complicates about 35% of pregnancies. Painful crisis during pregnancy should be distinguished from ectopic pregnancy, placental abruption, pyelonephritis, appendicitis, cholecystitis or other serious obstetrical or medical problems that cause pain, anemia or both.
- Anemia is not marked, hemoglobin concentration falls below 7 g/dL only if there is presence of infection or nutritional deficiency. Folate supplementation is recommended due to quick turnover of erythrocytes.
- Increased risk of infection is partly due to loss of splenic function. Urinary tract infection (UTI) is twice as common in sickle cell trait.
- Bacteriuria and pyelonephritis are also increased which can precipitate red cell destruction; hematuria is present in few cases. Cardiac dysfunction is present in most of the pregnant women. Preeclampsia and thrombophlebitis, which also increase maternal morbidity and mortality, is estimated to increase by 2.5%.
- Sickling occurs acutely especially late in pregnancy, labor, delivery and early puerperium.
• Acute chest syndrome, this is characterized by fever, tachypnea, pleuritic chest pain, leukocytosis and pulmonary infiltrates. It may be caused by pulmonary infections or infarction from intravascular sickling or thrombosis.

• Splenic sequestration, retinopathy, leg ulcers, aseptic necrosis of bone, renal papillary necrosis, stroke leading to premature death are also seen in some cases.

Investigations and Diagnosis

Diagnosis of hemoglobinopathies is made by hemoglobin electrophoresis. Laboratory tests that may be helpful to distinguish between sickle cell crisis from other cause of pain, are complete blood count (CBC), lactate dehydrogenase (LDH) levels, blood type and cross match, and arterial blood gas determination, as indicated. Suggested scheme of investigation for structural variants is given in Flow chart 1.

Management

During Pregnancy

1. Antenatal surveillance with fetal monitoring every 2–4 weeks, weekly non-stress test (NST) after 32 weeks.

2. Folic acid (5 mg/day) and penicillin prophylaxis to all women.

3. Hemoglobin and mid stream urine should be checked at every visit. Aim is to keep hemoglobin level above 25%, and concentration of HbS should be kept under 60%.

4. Iron supplementation is recommended only in proven cases of iron deficiency.

5. Prophylactic RBC transfusion: Usefulness of transfusion in pregnancy remains unclear. However, it lowers the incidence of painful crisis, and also women with multiple pregnancy are benefited, but multiple transfusion include risk of infection and alloimmunization. In cases with risk of hemoglobin transfusion reaction (HTR) blood transfusion is withheld, and steroids, intravenous immunoglobulin (IVIG) and large doses of erythropoietin are preferable. These have been shown to decrease morbidity in sickle-cell syndromes when given perioperatively and during pregnancy or to prevent strokes in high-risk children. The use of routine prophylactic transfusions during pregnancy remains controversial (American College of Obstetricians and Gynecologists, 2007). They reported a significant decrease in the incidence of painful sickle-cell crises with prophylactic transfusions but no differences in perinatal outcomes. Current consensus is that management should be individualized. Some clinicians choose prophylactic transfusions in women with a history of multiple vaso-occlusive episodes and poor obstetrical outcomes.

6. Assessment of fetal health: Because of the high incidence of fetal-growth restriction and perinatal mortality, serial fetal assessment is necessary. According to the American College of Obstetricians and Gynecologists (2007), a plan for serial sonographic examinations and antepartum fetal surveillance is reasonable. Anyaegbunam and colleagues (1991) evaluated fetal well-being during 39 sickling crises in 24 women. Almost 60% had nonreactive stress tests, which became reactive with crisis resolution, and all had an increased uterine artery systolic-diastolic (S/D) ratio. At the same time, there were no changes in umbilical artery S/D ratios. These investigators concluded that transient effects of sickle-cell crisis do not compromise umbilical,
CHAPTER 9

Hemoglobinopathies in Pregnancy

and hence fetal, blood flow. At Parkland Hospital, we serially assess these women with sonography for fetal growth and amniotic fluid volume changes. Non-stress or contraction stress tests are not done routinely unless complications such as fetal-growth restriction develop or fetal movement is reported to be diminished.

7. Labor and delivery: If a difficult vaginal or cesarean delivery is contemplated, and the hematocrit is less than 20 volumes present, then packed erythrocyte transfusions are administered. Care must be taken to prevent circulatory overload and pulmonary edema from ventricular failure.

During Labor

- Labor should be managed in the same way as for heart disease
- Avoid dehydration, over sedation and acidosis
- Keep patient warm and well oxygenated (avoid over oxygenation)
- Epidural analgesia is of choice during labor. Some recommend elective cesarean section at 36 weeks after partial exchange transfusion. Otherwise, cesarean section should be done for obstetric indications only

- Compatible blood should be kept ready for severe anemia, splenic sequestration and acute chest syndrome
- Circulatory overload is to be avoided.

CONTRACEPTIVE ADVICE

Barrier method is recommended as oral contraception would predispose to thromboembolism. Sterilization is advocated to limit the number of pregnancies, even at young age in parous woman, due to shorter lifespan. Intrauterine contraceptive device (IUCD) is not indicated due to risk of infection.

Progesterone has been long known to prevent painful sickle-cell crises. Because of this, low-dose oral progesterone, progesterone injections, or implants seem ideal. In one study, de Abood and associates (1997) reported significantly fewer and less intense pain crises in women given depot medroxyprogesterone intramuscularly.

EXPERIMENTAL THERAPY

Introduction of fetal hemoglobin (Hbf) by stimulating gamma-chain synthesis appears to be promising treatment for sickling and some thalassemia syndromes as they inhibit polymerization of HbS. Hydroxyurea, 4-azacytidine, as well as recombinant erythropoietin, increase Hbf and decrease sickling.
Other Therapy

There are several therapeutic schemes for sickle-cell patients, some are still experimental (Stuart and Nagel, 2004). Hemoglobin F induction has been studied for sickling and thalassemia syndromes. There are drugs that stimulate gamma-chain synthesis and thus hemoglobin F, which inhibits polymerization of hemoglobin S and resultant sickling. For patients with moderate to severe disease, hydroxyurea increases hemoglobin F production with fewer clinical sickling episodes (Platt, 2008). It may also reduce red cell membrane damage and decrease adherence to endothelium with less vascular damage. At this time, it is unknown if hydroxyurea increases long-term survival (Brawley and co-workers, 008). Experience with hydroxyurea in pregnancy is limited, but is teratogenic in animals (Briggs and colleagues, 2003).

Another cancer drug, decitabine, has been used in patients who are unresponsive to hydroxyurea (DeSimone and colleagues, 2002). Findings from a placebo-controlled trial of inhaled nitric oxide versus placebo suggested benefit for acute vaso-occlusive crises (Weiner and colleagues, 2003).

Hematopoietic cell transplantation as been used as a “cure” for patients with sickle-cell syndromes as well as with thalassemia major. Oringanje and co-workers (2009) performed a Cochrane review and found that only observational studies have been reported. Bone marrow transplantation has been used to provide normal hemoglobin A erythrocyte precursors in pediatric or adult patients with severe disease, and 5-year survival rates exceed 90 percent (Bhatia and Walters, 2008). Cord blood stem cell transplantation from related donors has shown great promise (Pinto and Roberts, 2008). Prenatal diagnosis of sickle-cell disease may allow for in utero stem cell therapy with hemoglobin A cells (Shaaban and Flake, 1999). Perhaps even more intriguing is the possibility that cells taken for prenatal diagnosis from a fetus destined to have sickle-cell anemia can be conditioned to produce hemoglobin A and used for replacement after birth (Ye and co-workers, 2009). Other experimental therapies include a gene therapy technique using a modified β-globin gene that encodes a sickling-resistant protein, which corrected the globin chain in transgenic hemoglobin SS knock-out mice (Pawluk and colleagues, 2001).

THALASSEMIA4.7-10

Introduction

Thalassemias are autosomal recessive genetic disorders of globin chain synthesis. The disease is found throughout the world, but its highest prevalence is in areas endemic for malaria. The syndrome can belong to either of the two groups, the alpha- or beta-thalassemia depending on whether

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Genotype</th>
<th>Phenotype</th>
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<tbody>
<tr>
<td>Normal</td>
<td>αα/αα</td>
<td>–</td>
</tr>
<tr>
<td>α⁺-thalassemia</td>
<td>αα/α⁺</td>
<td>Silent carrier</td>
</tr>
<tr>
<td>heterozygote</td>
<td></td>
<td></td>
</tr>
<tr>
<td>α⁺-thalassemia</td>
<td>α⁺/α⁻</td>
<td>α-thalassemia minor-mild</td>
</tr>
<tr>
<td>homozygote</td>
<td></td>
<td>hypochromic microcytic</td>
</tr>
<tr>
<td>α⁺-thalassemia</td>
<td>α⁺/α⁺</td>
<td>anemia</td>
</tr>
<tr>
<td>heterozygote</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compound</td>
<td>α⁺/α⁺</td>
<td>Hgb H (β4) with moderate</td>
</tr>
<tr>
<td>heterozygous</td>
<td></td>
<td>to severe hemolytic anemia</td>
</tr>
<tr>
<td>Homozygous</td>
<td>α⁺/α⁺</td>
<td>Hgb Bart (γ4) disease,</td>
</tr>
<tr>
<td>α-thalassemia</td>
<td>α⁺/α⁺</td>
<td>hydrops fetalis.</td>
</tr>
</tbody>
</table>

More common in African-Americans
More common in Asian-Americans

Source: Williams Obstetrics
beta-chain production. HbA is usually absent in these individuals. Elevated levels of HbF can often be found. Beta-thalassemia major, or Cooley anemia, is characterized by precipitation of the excessive alpha chains that results in ineffective erythropoiesis and hemolysis (Fig. 2). The fetus is protected from this because of high levels of HbF; however, after birth, as HbF levels fall, the infant becomes anemic. Although transfusion can prolong life, especially when combined with iron chelation therapy, females with this disorder historically have been infertile. However, with proper care and guidance, pregnancies among women with Thalassemia major are practical and can have successful outcome. These patients require frequent transfusions and chelation treatment with desferrioxamine before pregnancy improves pregnancy outcome. The aim is to achieve a serum ferritin level of 1,000–2,000 ng/mL. Desferrioxamine should be discontinued during pregnancy due to possible harmful effects on the fetus and risk of iron deficiency in the neonate. Vitamin usually given with chelation should also be stopped as it increases the absorption of iron.

**Beta-Thalassemia Minor**
It occurs in individuals who are heterozygous for the gene mutations and therefore have variable production of the beta globin chain. Sickle cell trait may coexist with thalassemia
minor. It presents as profound microcytosis and hypochromia with target cells but only minimal or mild anemia.

Hematological findings
- Mean corpuscular volume rarely more than 75 fL, i.e. low but normal MCHC
- Hematocrit rarely less than 30–33%
- Elevated HbA (3.5–7.5%) with or without raised HbF
- Serum iron and total iron-binding capacity (TIBC) are normal or elevated.

The hemoglobin concentration is typically 8–10 g/dL late in the second trimester. There is no specific therapy for beta-thalassemia minor during pregnancy. The outcomes for the mother and fetus are satisfactory. Blood transfusions are seldom indicated except for hemorrhage. Prophylactic iron and folate are administered in daily doses of 60 mg and 1 mg, respectively. Parenteral iron therapy is contraindicated.

Beta-Thalassemia Intermedia

There is severe mutation on one allele or mild mutation in both. Hemoglobin level is usually between 6 g/dL and 9 g/dL.

Diagnosis

An RBC count higher for a given hemoglobin concentration indicates beta-thalassemia trait. Mean corpuscular volume (MCV) less than 80 fL in pregnancy, and MCH less than 25 rules out beta-thalassemia.

The most common methods for diagnosis are:
- NESTROFT
- Screening by electrophoresis or Hb high performance liquid chromatography (HPLC)
- Complete blood count
- HbA2 estimation: Confirming by Hb electrophoresis or gel electrophoresis or high performance liquid chromatography (HPLC). HbA2 is elevated to > 3.5% in thalassemia trait.
- Reverse dot blot analysis (RDV)
- Amplification refractory mutation system (ARMS).
- Each of the above methods has its own advantages and disadvantages. The choice of method depends on the technical expertise available in the laboratory and the population to be studied. It is best practice to have two alternative methods for detecting each mutation.

NESTROFT

Naked eye single tube red cell osmotic fragility test (NESTROFT) is the test used for screening of patients for thalassemia (in hospitals) based on the fact that red cells with large surface area and volume ratio resist lysis in hypotonic saline indicating lower red cell osmotic fragility, suggesting thalassemia trait. If the tube contents are clear then there is no thalassemia. If it is hazy, it signifies thalassemia. The test has sensitivity of 94.4% and a negative predictive value of 97.6%. It costs about ten rupees per test. It is used in mass screening as well as in an antenatal clinic. Patients positive for this test are subjected to electrophoresis.

The pregnant woman testing positive for the thalassemia trait needs her partner to be tested for the same. If he is also positive, there is a need for prenatal diagnosis as there is a 25% chance of homozygous state in the fetus. If both parents are positive, do confirmatory test followed by genetic testing of the fetus by villous biopsy or amniocentesis before 18 weeks of pregnancy. If the fetus is homozygous, termination of pregnancy is advised.

Prevention

Prenatal diagnosis of thalassemia syndrome is available. DNA diagnosis is mainly based on polymerase chain reaction (PCR) amplification of fetal DNA, obtained from chronic villus sampling (CVS) or cordocentesis, which is followed by hybridization to allele specific oligonucleotide probes.

Prenatal Diagnosis of β-Thalassemia Major

Preimplantation blastomere biopsy has been described by Galvani (2000) and Kanavakis (1999) and their associates. Isolation of single nucleated red blood cells from maternal circulation is being explored for prenatal diagnosis of β-thalassemia (Kolialexi and Colleagues, 2007).

REFERENCES

INTRODUCTION

Hypertension is the most common medical problem encountered in pregnancy and remains an important cause of maternal and fetal morbidity and mortality. It complicates up to 15% of pregnancies and accounts for approximately a quarter of all antenatal admissions. The hypertensive disorders of pregnancy cover a spectrum of conditions, of which preeclampsia poses the greatest potential risk and remains one of the most common causes of maternal death.

NORMAL PHYSIOLOGICAL CHANGE IN BLOOD PRESSURE DURING PREGNANCY

Early in the first trimester there is a fall in blood pressure caused by active vasodilatation, achieved through the action of local mediators such as prostacyclin and nitric oxide. This reduction in blood pressure primarily affects the diastolic pressure and a drop of 10 mm Hg is usual by 13–20 weeks gestation. Blood pressure continues to fall until 22–24 weeks when a nadir is reached. After this, there is a gradual increase in blood pressure until term when prepregnancy levels are attained. Immediately after delivery blood pressure usually falls, then increases. Even women whose blood pressure was normal throughout pregnancy may experience transient hypertension in the early postpartum period, perhaps reflecting a degree of vasomotor instability.

DEFINITION OF HYPERTENSION IN PREGNANCY

Hypertension in pregnancy is diagnosed either from an absolute rise in blood pressure or from a relative rise above measurements obtained at booking. The convention for the absolute value is a systolic more than 140 mm Hg or a diastolic more than 90 mm Hg. The definition for a relative rise in blood pressure incorporates either a rise in systolic pressure of more than 30 mm Hg or rise in diastolic pressure of more than 15 mm Hg above blood pressure at booking. Blood pressure must be elevated on at least two occasions and measurements should be made with the woman seated and using the appropriate cuff size (Table 1). Late in the second trimester and in the third trimester, venous return may be obstructed by the gravid uterus and, if supine, blood pressure should be taken with the woman lying on her side. Korotkoff phase I and V (disappearance) should be used, rather than phase IV (muffling), since it is more reproducible and shows better correlation with true diastolic blood pressure in pregnancy. If phase V is not present, phase IV should be recorded. Automated systems for blood pressure measurement have been shown to be unreliable in severe preeclampsia and tend to under record the true value.

Table 1: How to measure blood pressure during pregnancy?

- Mercury sphygmomanometers are preferable to automated blood pressure monitors
- If automated devices are used, they should be calibrated and checked regularly, against a mercury sphygmomanometer
- Use an appropriate sized-cuff
- Woman should be seated or lying at 45° angle, with arm at level of the heart
- Record blood pressure to the nearest 2 mm Hg
- Use phase V Korotkoff sound (sound disappearance) to measure diastolic blood pressure.
There are three types of hypertensive disorders:
1. Chronic hypertension
2. Gestational hypertension
3. Preeclampsia.

Chronic Hypertension

Chronic hypertension complicates 3–5% of pregnancies, although this figure may rise, with the trend for women to postpone childbirth into their 30s and 40s. The diagnosis of chronic hypertension is based on a known history of hypertension prepregnancy or an elevated blood pressure, i.e. 140/90 mm Hg before 20 weeks gestation. However, there are several caveats to this diagnosis. Undiagnosed hypertensive women may appear normotensive in early pregnancy because of the normal fall in blood pressure, commencing in the first trimester. This may mask the preexisting hypertension and when hypertension is recorded later in the pregnancy it may be interpreted as gestational. Sometimes, the diagnosis is only made several months postpartum, when the blood pressure fails to normalize as would be expected with gestational hypertension. Furthermore, preeclampsia can rarely present before 20 weeks gestation and may be misinterpreted as chronic hypertension.

The presence of mild preexisting hypertension approximately doubles the risk of preeclampsia, but also increases the risk of placental abruption and growth restriction in the fetus. In general, when blood pressure is controlled, such women do well and have outcomes not dissimilar to normal women. However, when chronic hypertension is severe (a diastolic blood pressure > 110 mm Hg before 20 weeks gestation) the risk of preeclampsia is as high as 46% with resultant raised maternal and fetal risks.

Gestational Hypertension

Hypertension occurring in the second half of pregnancy in a previously normotensive woman, without significant proteinuria or other features of preeclampsia, is termed as gestational or pregnancy induced hypertension. It complicates 6–7% of pregnancies and resolves postpartum. The risk of superimposed preeclampsia is 15–26%, but this risk is influenced by the gestation at which the hypertension develops. When gestational hypertension is diagnosed after 36 weeks of pregnancy, the risk falls to 10%. With gestational hypertension, blood pressure usually normalizes by 6 weeks postpartum.

Preeclampsia and Eclampsia

Preeclampsia usually occurs after 20 weeks gestation and is a multi-system disorder. It was classically defined as a triad of hypertension, edema, and proteinuria, but a more modern definition of preeclampsia concentrates on a gestational elevation of blood pressure together with more than 0.3 g proteinuria per 24 hours. Edema is no longer included because of the lack of specificity. Preeclampsia may also manifest, with few maternal symptoms and signs, as isolated intrauterine growth restriction (IUGR). Eclampsia is defined as the occurrence of a grand mal seizure in association with preeclampsia, although it may be the first presentation of the condition.

The incidence of preeclampsia is very much influenced by the presence of existing hypertension, although other risk factors are recognized (Table 3). Overall preeclampsia complicates 5–6% of pregnancies, but this figure increases to up to 25% in women with pre-existing hypertension. Eclampsia complicates 1–2% of preeclamptic pregnancies. An estimated 50,000 women die annually from preeclampsia worldwide and morbidity includes placental abruption, intra-abdominal hemorrhage, cardiac failure, and multi-organ failure. The risks to the fetus from preeclampsia include growth restriction secondary to placental insufficiency, and premature delivery. Indeed, preeclampsia is one of the most common causes of prematurity (accounting for 25% of all infants with very low birth weight, < 1,500 g).

PATHOGENESIS OF PREECLAMPSIA

The pathogenesis and manifestations of preeclampsia can be considered in a two-stage model. The primary stage involves:

**Table 2: Classification of hypertensive disorders of pregnancy**

<table>
<thead>
<tr>
<th>Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic hypertension</td>
<td>Hypertension known to be present before pregnancy or detected before 20 weeks gestation</td>
</tr>
<tr>
<td>Gestational hypertension (pregnancy induced hypertension)</td>
<td>Hypertension detected for the first time after 20 weeks gestation, in the absence of proteinuria, defined as systolic blood pressure &gt; 140 mm Hg or diastolic blood pressure &gt; 90 mm Hg. Resolves within 3 months after the birth.</td>
</tr>
<tr>
<td>Preeclampsia and eclampsia</td>
<td>Hypertension and proteinuria detected for the first time after 20 weeks gestation. Hypertension defined as above. Proteinuria defined as &gt; 300 mg/day or &gt; 30 mg/mmol in a single specimen or &gt; 1+ on dipstick. Eclampsia is the occurrence of seizures superimposed on the syndrome of preeclampsia.</td>
</tr>
<tr>
<td>Preeclampsia superimposed on chronic hypertension</td>
<td>Onset of new signs or symptoms of preeclampsia after 20 weeks gestation in a woman, with chronic hypertension.</td>
</tr>
</tbody>
</table>
Abnormal Placentation

In the first trimester, in a healthy pregnancy, the trophoblast invades the uterine decidua and reaches the inner layer of the myometrium. This migration transforms the small musculoelastic spiral arteries into large (four-fold increase in diameter) sinusoidal vessels resulting in a high capacitance, low resistance blood supply to the intervillous space. Although commencing in the first trimester, the change is completed in the second trimester when another wave of trophoblast migration alters the myometrial segments of the arteries. In preeclampsia, these vascular alterations do not occur or they are limited to vessels in the decidua. In addition to the failure of devascularization, the arteries maintain their response to vasomotor influences and undergo accelerated atherosclerosis, which further impairs perfusion to the intervillous space.

The secondary stage of preeclampsia involves:

Conversion of Uteroplacental Maladaptation to Maternal Systemic Syndrome

Conversion of this uteroplacental maladaptation to the maternal systemic syndrome, results in protean manifestations (Table 4). Failure of the normal cardiovascular changes of pregnancy to take place, which results in hypertension, reduction in plasma volume, and impaired perfusion to virtually every organ of the body. There is vasospasm and activation of platelets and the coagulation system, resulting in microthrombi formation. The link between the placenta and the systemic disorder appears to involve endothelial dysfunction and oxidative stress. The management of preeclampsia essentially focuses on recognition of the condition and ultimately the delivery of the placenta, which is curative. Since preeclampsia may arise with few symptoms, all women are screened during pregnancy through regular antenatal care. Those women who are recognized to be at an increased risk have additional screening and more intensive monitoring.

**Table 3: Risk factors for developing preeclampsia**

- Nulliparity
- Multiple pregnancy
- Family history of preeclampsia
- Chronic hypertension
- Diabetes
- Increased insulin resistance
- Increased body mass index
- Hypercoagulability (inherited thrombophilia)
- Renal disease even without significant impairment
- Low socioeconomic status
- Antiphospholipid syndrome (acquired thrombophilia)
- Previous preeclampsia
- Hydatidiform mole
- Black race

**Table 4: Symptoms and signs associated with preeclampsia**

- Hypertension and proteinuria
- Persistent severe headache
- Persistent new epigastric pain
- Visual disturbances (such as blurred vision, diplopia, or floating spots)
- Vomiting
- Hyperreflexia, brisk tendon reflexes
- Epigastric pain or tenderness
- Severe swelling of hands, face, or feet of sudden onset
- Serum creatinine concentration increased (> 110 ~mol/L)
- Platelet count reduced to < 100 × 10^3/L
- Evidence of microangiopathic hemolytic anemia
- Liver enzyme activity elevated

**MANAGEMENT OF HYPERTENSION IN PREGNANCY**

**Prepregnancy Counseling**

Most of the pregnancies are unplanned and thus prepregnancy counseling may not be feasible. In women with chronic hypertension, assessment before conception permits exclusion of secondary causes of hypertension (for example, renal/endocrine), evaluation of their hypertensive control to ensure it is optimal, discussion of the increased risks of preeclampsia, and education about any drug alterations, which would need to be made in the first trimester should they become pregnant. The majority of women with controlled chronic hypertension will, under close supervision and appropriate management, have a successful outcome. Poorly controlled hypertension in the first trimester will significantly increase maternal and fetal morbidity and mortality. It must be stressed that none of the many antihypertensive agents used in routine practice have been shown to be teratogenic and women can safely conceive while taking medication. However, angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) need to be withdrawn in the first trimester since they are fetotoxic. Women who have experienced poor obstetric outcomes in previous pregnancies because of severe preeclampsia, or those at particular risk need to be counseled about the condition and offered prophylactic treatment with low dose aspirin. Since preeclampsia involves endothelial dysfunction and oxidative stress, there is interest in supplementation, with antioxidant vitamins C and E, in the second trimester. A preliminary trial of antioxidant vitamins, in high-risk women, has reported improvements in biochemical markers of endothelial activation together with a reduction...
in preeclampsia and a large, randomized trial is underway (Table 5).

### ANTENATAL CARE

#### General Maternal Care

Blood pressure assessment and the search for proteinuria form the cornerstone of antenatal screening of all pregnant women for preeclampsia. If “white coat” hypertension is suspected, ambulatory monitoring can be helpful as in the non-pregnant population. Those women who have been defined as at increased risk of preeclampsia are monitored more closely, often in a specialized obstetric clinic. Part of the risk assessment includes Doppler ultrasound evaluation of the uterine arteries around the time of the fetal anomaly scan at 20–22 weeks and blood analysis. Rising blood pressure, deranged blood results, and/or the development of significant proteinuria requires enhanced surveillance. Greater than 1+ proteinuria on dip sticks needs to be formally quantified with a 24 hours urine collection or protein:creatinine ratios. The onset of significant proteinuria, in the absence of renal disease, is among the best indicators of superimposed preeclampsia. Many women are initially asymptomatic, or present with non-specific signs of malaise. However, headache, visual disturbance, or abdominal pain are well recognized signs of severe preeclampsia (Table 4).

#### Doppler Assessment of Uterine Arteries

Pulsed wave and color flow Doppler ultrasound examination of the uterine arteries can demonstrate the increased placental vascular resistance, which results from complete or partial failure of trophoblast invasion of the spiral arteries. Uterine artery “Dopplers” are offered to high-risk women at between 20–24 weeks of pregnancy and have useful predictive power. A woman with normal uterine Doppler assessment at 20–24 weeks can be considered to be at low-risk, whereas those with abnormal Dopplers have approximately a 20% chance of developing preeclampsia and require increased vigilance.

#### Fetal Surveillance

Women with both chronic hypertension and preeclampsia are at risk of IUGR. Such women are offered regular fetal ultrasound scans to assess fetal growth, liquor volume, and umbilical artery blood flow. When preeclampsia is severe, and there is a significant risk of delivery before 34 weeks gestation, intramuscular steroids (dexamethasone or betamethasone) are given to the mother to enhance fetal lung maturity in anticipation of a premature delivery.

### WHEN TO TREAT HYPERTENSION DURING PREGNANCY

Significant hypertension must be treated in its own right, regardless of the assumed underlying pathology, largely to reduce the risk of maternal intracranial hemorrhage. The level at which antihypertensive treatment is initiated for non-severe hypertension remains controversial, depending on whether treatment is focused on maternal or fetal wellbeing. Most physicians commence antihypertensive medication when the systolic blood pressure is more than 140–170 mm Hg or diastolic pressure is more than 90–110 mm Hg. Treatment is mandatory for severe hypertension when the blood pressure is 170/110 mm Hg. Once treatment is started, target blood pressure is also controversial, but many practitioners would treat to keep the mean arterial pressure less than 125 mm Hg—for example, a blood pressure of 150/100 mm Hg. Overzealous blood pressure control may lead to placental hypoperfusion, as placental blood flow is not autoregulated, and this will compromise the fetus. Unfortunately, there is no evidence that pharmacological treatment of chronic or gestational hypertension protects against the development of preeclampsia. Changes in diet or bed rest have not been shown to provide maternal or fetal benefit.

All antihypertensive drugs have either been shown, or are assumed, to cross the placenta and reach the fetal circulation. However, as previously stated, none of the antihypertensive agents in routine use have been documented to be teratogenic, although ACE inhibitors and ARBs are fetotoxic. The objective of treating hypertension in pregnancy is to protect the woman from dangerously high blood pressure and to permit continuation of the pregnancy, fetal growth and maturation.

#### Mild-to-Moderate Hypertension

The evidence base for treatment of mild-to-moderate chronic hypertension in pregnancy resides in maternal benefit rather than fetal benefit.
than clear evidence of an enhanced perinatal outcome for the baby. Some women with treated chronic hypertension are able to stop their medication in the first half of pregnancy, because of the physiological fall in blood pressure during this period. However, this is usually temporary, and women are monitored and treatment resumed as soon as necessary.

**First-line Agent**

**Methyldopa**

Methyldopa is a centrally acting agent and remains the drug of first choice for treating hypertension in pregnancy. It has been the most frequently assessed antihypertensive in randomized trials and has the longest safety track record. Long-term use has not been associated with fetal or neonatal problems and there are safety data for children exposed in utero. Women should be warned of its sedative action and this can limit up the titration. The drug may result in an elevation of liver transaminases (in up to 5% of women) or a positive Coomb’s test (although hemolytic anemia is uncommon). Methyldopa should be avoided in women with a prior history of depression, because of the increased risk of postnatal depression.

**Second-line Agents**

These agents should be used when monotherapy with methyldopa is insufficient or when women are unable to tolerate methyldopa.

**Nifedipine**

Nifedipine is popular for the treatment of hypertension in pregnancy and is widely used. It is safe at any gestation. The use of sublingual nifedipine, however, should be avoided to minimize the risk of sudden maternal hypotension and fetal distress, caused by placental hypoperfusion. Abrupt hypotension is potentiated with concomitant magnesium sulfate (used as a treatment or prophylactic agent against eclamptic seizures with severe preeclampsia). Amlodipine has been used in pregnancy but safety data are lacking.

**Oral Hydralazine**

Hydralazine is safe throughout pregnancy, although the occurrence of maternal and neonatal lupus-like syndromes have been reported. Hydralazine is more frequently used as an infusion for the treatment of acute severe hypertension.

**Third-line Agents**

**Alpha- and Beta-adrenergic Blockers**

In the past, β-adrenergic blockers have been highlighted as a class of antihypertensives associated with an increased risk of IUGR. Atenolol in particular has often been singled out. However, in a recent meta-analysis of published data from randomized trials, the presence of IUGR appeared not to be related to the antihypertensive used. Nevertheless, β-adrenergic blockers are still avoided in the first half of pregnancy because of concerns about growth restriction and are viewed as third-line agents for the treatment of hypertension in pregnancy. α Blockers are safe throughout pregnancy and there is wide experience with oxprenolol and labetalol. The safety and efficacy of prazosin in pregnancy has been demonstrated. Doxazosin appears to be safe, although data are limited.

**Thiazide Diuretics**

Thiazide diuretics are used infrequently in pregnancy. The drugs do not appear to be teratogenic and although such drugs abbreviate the plasma volume expansion associated with normal pregnancy, this has not been proven to impair fetal growth. The obstetric community remains reluctant to use these antihypertensive agents because of concern about potentiating the plasma volume contraction, which occurs with preeclampsia. However, women with chronic hypertension who, before conception, responded well to a thiazide diuretic, could have the drug re instituted in pregnancy but it should be withdrawn if preeclampsia develops.

**Drug Treatment of Severe Hypertension**

Severe hypertensive urgency or emergency first-line treatment:
- Labetalol (IV)
- Hydralazine (IV)
- Beta-blockers (IV)
- Nifedipine (PO)

The mortality and morbidity of women with severe hypertension (> 170/110 mm Hg), usually secondary to severe preeclampsia, remains considerable. Because of the circulating plasma volume contraction, women may be very sensitive to relatively small doses of antihypertensive agents (and diuretics), risking abrupt reductions in blood pressure. Good control of hypertension in severe preeclampsia does not halt the progression of the disease, only delivery can do this, but it can reduce the incidence of complications such as cerebral hemorrhage. Management of severe hypertension involves adequate blood pressure control, often using parenteral agents, and “expectant” management by trying to prolong the pregnancy without unduly risking the mother or fetus. In severe cases, only hours or days may be gained. Different units have their preferences for either parenteral hydralazine or labetalol, and some use oral nifedipine. Hydralazine should be given after a colloid challenge to reduce the reflex tachycardia, and abrupt hypotension, precipitated by vasodilatation of a volume contracted circulation. These
women are on a high-risk and should be managed in a high dependency unit setting. They are very sensitive to fluid overload and are at risk of developing noncardiac pulmonary edema, through capillary leak. Severe forms of preeclampsia require admission to intensive care, frequently for respiratory failure or the development of a severe systemic inflammatory response syndrome (SIRS). Seizure prophylaxis, with intravenous magnesium sulfate, may be required in these cases.

**ANTIHYPTERTENSIVE DRUGS TO AVOID IN PREGNANCY**

Antihypertensive drugs to:
- Avoid in pregnancy
  - Thiazide diuretics
- Contraindicated in pregnancy
  - Angiotensin-converting enzyme inhibitors (PO)
  - Angiotensin receptor blockers (PO)
  - Aldosterone antagonists (PO)

Both ACE inhibitors and ARBs are fetotoxic but there are no data to support teratogenicity. Women can thus be reassured that conceiving while taking such agents, particularly ACE inhibitors where the data are strongest, appears to be safe. However, all women of childbearing age treated with these drugs must be informed of the need for drug discontinuation within the first trimester should they become pregnant. The greatest risk to the fetus appears to be associated with exposure in the third trimester, but the earlier the discontinuation the better, hence the need for patient education. A variety of malformations and adverse events have been reported for both ACE inhibitors and ARBs including:
- Oligohydramnios
- Intrauterine growth restriction
- Joint contractures
- Pulmonary hypoplasia
- Hypocalvaria (incomplete ossification of the fetal skull)
- Fetal renal tubular dysplasia and neonatal renal failure.

**ANTIHYPTERTENSIVE TREATMENT POSTPARTUM AND DURING BREASTFEEDING**

Postpartum hypertension is common. Blood pressure typically rises after delivery over the first 5 days. Thus women who experienced hypertension during pregnancy may be normotensive immediately after the birth, but then become hypertensive again in the first postnatal week. The need to obtain hypertensive control may delay discharge. Methyldopa should be avoided postpartum because of the risk of postnatal depression. Our first-line agent is atenolol, plus nifedipine or an ACE inhibitor if another agent is required. Women with gestational hypertension, or preeclampsia, are usually able to stop all antihypertensives within 6 weeks postpartum. Those with chronic hypertension can resume their prepregnancy drugs. Diuretics, however, are usually avoided if the woman wishes to breast feed because of increased thirst. Proteinuria in preeclamptic women will usually remit by 3 months postpartum, in the absence of any underlying renal abnormality. Persistent proteinuria requires further renal investigation.

An accurate estimation of drug passage into breast milk is difficult to individualize since it is influenced by many factors such as the lipid solubility of the drug, protein binding, ionization, molecular weight, and the constituents of milk itself (fat, protein versus water content). However, most antihypertensive agents used in routine practice are compatible with breastfeeding, but safety data for doxazosin, amlodipine, and ARBs are lacking.

**RISK OF RECURRENCE OF HYPERTENSIVE DISORDERS IN A SUBSEQUENT PREGNANCY**

Women who experience hypertension in first pregnancy are at an increased risk in a subsequent pregnancy. Certain factors influence this risk. The earlier the onset of hypertension in the first pregnancy, the greater the risk of recurrence and the type of hypertensive disorder influences recurrence. One study reported a recurrence risk of 19% for gestational hypertension, 32% for preeclampsia, and 46% for preeclampsia superimposed on preexisting chronic hypertension. In addition, severe isolated IUGR is also a risk factor for developing hypertension in a subsequent pregnancy.

**LONG-TERM CARDIOVASCULAR SEQUELAE OF PREGNANCY-INDUCED HYPERTENSION**

Women who develop gestational hypertension or preeclampsia are at increased risk of hypertension and stroke in later adult life. Furthermore, there is evidence of an increased risk of ischemic heart disease (IHD) in women who have experienced preeclampsia or isolated IUGR, together with increased death rates from IHD. At first an association between preeclampsia and an increased risk of IHD in later adult life may appear rather tenuous. However, both conditions are associated with dyslipidemia, insulin resistance, and endothelial dysfunction. It is of interest that the lipid abnormalities which occur in preeclampsia [raised low density lipoprotein (LDL), very low density lipoprotein (VLDL), free fatty acid, and triglyceride values] pre-date the clinical appearance of the condition and endothelial dysfunction continues to be impaired postpartum.

Although there are methodological concerns with some of the data in this area, these apparent late sequelae may
have important public health implications given the relative frequency of pregnancy induced hypertension and may, in future, dictate screening for cardiovascular disease in previously affected women. At the very least, it would seem prudent for such women to have an annual blood pressure measurement. Interestingly, women who go through a pregnancy without developing hypertension are at a reduced risk of becoming hypertensive in later life, when compared to nulliparous women. Pregnancy may offer a window into the future for cardiovascular health of women, which is unavailable in men.

MANAGING HYPERTENSION IN PREGNANCY: KEY POINTS

- Main categories of hypertensive disease in pregnancy: chronic, gestational, preeclampsia
- Preeclampsia remains an important cause of maternal death in the UK
- No antihypertensive has been shown to be teratogenic, but ACE inhibitors and ARBs are fetotoxic
- First-line antihypertensive during pregnancy: Methyldopa
- First-line antihypertensive post partum: Atenolol
- Pregnancy induced hypertension increases the risk of cerebrovascular disease and ischemic heart disease in later life.

BIBLIOGRAPHY

INTRODUCTION

Pregnant women with normal cardiac function can accommodate many alterations in the cardiovascular system that accompanies pregnancy and labor without difficulty. However, in women with cardiac disease, these changes may lead to heart failure, arrhythmias and stroke. Maternal heart disease complicates 0.2–4% of pregnancies and is responsible for 10–25% of maternal deaths. Uterine congestion, insufficient oxygenation, elevated carbon dioxide content of blood may compromise the fetus and may lead to growth restriction and premature labor and delivery. With advances in surgery and medical therapy, more women with congenital heart disease now reach their adult reproductive years and are becoming pregnant more often. The etiology of heart disease has changed from primarily rheumatic to predominately congenital.

Cardiovascular Adaptation to Pregnancy (Table 1)

During pregnancy, complex biochemical, electric and physiologic changes occur that alter the blood volume, myocardial contractility and resistance of the vascular bed.

Cardiac output and blood pressure increases during labor and delivery as a result of pain and uterine contractions. Immediately after delivery, vena caval and aortic compression is relieved and auto transfusion from the emptied and contracted uterus produces further increase in cardiac output. Most hemodynamic changes resolve by 2 weeks postpartum (Table 2). In the presence of underlying heart disease, above changes can compromise maternal life and that of her unborn child.

ECG Changes

• Atrial and ventricular ectopics
• Q wave and inverted T wave in lead III
• ST depression and T wave inversion inferior and lateral leads
• QRS axis leftward shift.

Maternal risk in relation to cardiac disease in pregnancy is shown in Table 3.

A validated cardiac risk score has been shown to predict a woman’s chance of having adverse cardiac complications during pregnancy (Table 4). Each risk factor was given a value of 1 point. The maternal cardiac event rates for 0, 1, and higher than 1 point are 5%, 27%, and 75% respectively.

Fetal Risks

When a pregnant patient or a first degree family member has a congenital heart disease, then the risk for these diseases increases in the fetus. The incidence is 0–10% depending on the specific lesion when the fetus is affected. Approximately 50% have the same anomaly as the mother. Rate of growth restriction and prematurity is increased in pregnant women with cardiac disease.

Cardiac Murmurs

Early to mid-systolic and soft murmurs (grades I–II) are very common during pregnancy (> 90%). These murmurs are rarely associated with cardiac pathology. Systolic murmurs that are loud or long are frequently associated with cardiac pathology. Late systolic, pansystolic and diastolic murmurs are abnormal and require further evaluation by echocardiography.
Table 1: Cardiovascular adaptation to pregnancy

<table>
<thead>
<tr>
<th>Physiological variable</th>
<th>Direction of change</th>
<th>Degree</th>
<th>Start Weeks</th>
<th>Peak</th>
<th>Plateau</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total body water</td>
<td>↑</td>
<td>6–8 liters</td>
<td>Early pregnancy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium retention</td>
<td>↑</td>
<td>500–900 mg</td>
<td>Early pregnancy</td>
<td></td>
<td></td>
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<tr>
<td>Plasma volume</td>
<td>↑</td>
<td></td>
<td>First trimester, ↑ in</td>
<td>32 weeks</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>second and third</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>trimesters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac output</td>
<td>↑</td>
<td>40%</td>
<td>10 weeks</td>
<td>Second trimester</td>
<td></td>
</tr>
<tr>
<td>Stroke volume</td>
<td>↑</td>
<td>10–20 bpm</td>
<td>First and second</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>trimesters, nadir</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>24–28 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate</td>
<td>↑</td>
<td></td>
<td>Third trimester</td>
<td></td>
<td></td>
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<tr>
<td>Blood pressure</td>
<td>↓</td>
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<tr>
<td>Central venous pressure</td>
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<td></td>
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<tr>
<td>Pulmonary capillary</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>wedge pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic vascular</td>
<td>↓</td>
<td>25–30%</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>resistance and</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>pulmonary vascular</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>resistance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum colloid osmotic</td>
<td>↓</td>
<td>10–15%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Keys: ↑, increased; ↓, decreased; →, unchanged

Table 2: Normal hemodynamic changes during intrapartum and postpartum

<table>
<thead>
<tr>
<th>Hemodynamic parameter</th>
<th>Change during labor and delivery</th>
<th>Change during postpartum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood volume</td>
<td>↑</td>
<td>↓ (autidiuresis)</td>
</tr>
<tr>
<td>Heart rate</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>↑ Additional 50%</td>
<td>↓</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Stroke volume</td>
<td>↑ (300–500 mL/contraction)</td>
<td>↓</td>
</tr>
<tr>
<td>Systemic vascular resistance</td>
<td>↑</td>
<td>↓</td>
</tr>
</tbody>
</table>

Mitral Valve Prolapse

It is prevalent in 21% of women in the reproductive age. Palpitation, arrhythmias, chest pain, syncope, fatigue and panic attacks are reported with this condition. Mitral regurgitation is checked by echocardiography. Observe the patient for cardiac arrhythmias, especially supraventricular tachycardia (SVT). These patients should be advised to avoid caffeine, alcohol, betamimetic drugs and tobaccos.

CARDIOVASCULAR DRUGS

Commonly used cardiovascular drug classes and their potential adverse effects during pregnancy are shown in Table 5.
### MANAGEMENT OPTIONS

#### Prepregnancy
- Obstetrician and cardiologist in collaboration
- Discussion of maternal and fetal risks
- Discussion of safe and effective contraception
- Evaluate current cardiac status
- Optimize medical and surgical management
- Advise against pregnancy with certain conditions.

#### Prenatal
- Assess functional class of heart disease (Table 6)
- Termination is an option with some conditions
- Joint management with a cardiologist
- Optimize medical management
- Avoid or minimize aggravating factors
- Anticoagulation for certain conditions, discuss the risks and benefits of continued warfarin therapy versus changing to subcutaneous heparin
- Anesthesiology

---

### Table 3: Maternal risk in relation to cardiac disease in pregnancy

<table>
<thead>
<tr>
<th>Level</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low Risk</strong></td>
<td>Atrial and ventricular septal defect previously repaired or without pulmonary hypertension</td>
</tr>
<tr>
<td></td>
<td>Pulmonic or tricuspid disease</td>
</tr>
<tr>
<td></td>
<td>Mitral valve prolapse (MVP)</td>
</tr>
<tr>
<td></td>
<td>Patent ductus arteriosus</td>
</tr>
<tr>
<td></td>
<td>Corrected congenital heart disease without residual cardiac dysfunction</td>
</tr>
<tr>
<td></td>
<td>Mitral stenosis: New York Heart Association class I or II.</td>
</tr>
<tr>
<td><strong>Moderate Risk</strong></td>
<td>Mitral stenosis with atrial fibrillation</td>
</tr>
<tr>
<td></td>
<td>MVP with valvular regurgitation or thickened leaflets</td>
</tr>
<tr>
<td></td>
<td>Aortic stenosis</td>
</tr>
<tr>
<td></td>
<td>Artificial valve</td>
</tr>
<tr>
<td></td>
<td>Moderate-to-severe systemic ventricular dysfunction</td>
</tr>
<tr>
<td></td>
<td>History of peripartum cardiomyopathy with no residual ventricular dysfunction</td>
</tr>
<tr>
<td></td>
<td>Coarctation of the aorta</td>
</tr>
<tr>
<td></td>
<td>Tetralogy of Fallot, uncorrected or with residual disease</td>
</tr>
<tr>
<td></td>
<td>Marfan's syndrome with normal aorta.</td>
</tr>
<tr>
<td><strong>High Risk</strong></td>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td></td>
<td>Coarctation of the aorta, complicated</td>
</tr>
<tr>
<td></td>
<td>Marfan's syndrome with aortic involvement</td>
</tr>
<tr>
<td></td>
<td>Any condition with New York Heart Association class III or IV (Table 5)</td>
</tr>
<tr>
<td></td>
<td>History of peripartum cardiomyopathy with residual ventricular dysfunction</td>
</tr>
</tbody>
</table>

### Table 4: Predictors of maternal risk for cardiac complications

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Example</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior cardiac events</td>
<td>Heart failure, transient ischemic attack, stroke before current pregnancy</td>
<td>1</td>
</tr>
<tr>
<td>Prior arrhythmia</td>
<td>Symptomatic sustained tachyarrhythmia or bradyarrhythmia requiring treatment</td>
<td>1</td>
</tr>
<tr>
<td>NYHA III or IV or cyanosis</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Valvular and outflow tract obstruction</td>
<td>Aortic valve area &lt; 1.5 cm², mitral valve area &lt; 2 cm², or left ventricular outflow tract peak gradient &gt; 30 mm Hg</td>
<td>1</td>
</tr>
<tr>
<td>Myocardial dysfunction</td>
<td>LVEF &lt; 40% restrictive cardiomyopathy, or hypertrophic cardiomyopathy</td>
<td>1</td>
</tr>
</tbody>
</table>

*Note: Maternal cardiac event rates for 0, 1, and more than 1 points are 5%, 27%, and 75% respectively.*

• Antibiotics with certain conditions (Table 7)
• Fetal surveillance
  - Growth and fetal surveillance (especially in left-to-right shunt)
  - Detailed fetal cardiac ultrasonography if the patient has congenital heart disease.

## Labor and Delivery

- Elective induction may be necessary for maternal or fetal indications
- Prophylactic antibiotics with certain conditions

### Table 5: Cardiovascular drugs used during pregnancy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Use</th>
<th>Potential side effects</th>
<th>Safe during pregnancy</th>
<th>Safe during breastfeeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenosine</td>
<td>Arrhythmia</td>
<td>None reported</td>
<td>Yes</td>
<td>No data</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>Hypertension arrhythmias, MI, ischemia, HCM, hyperthyroidism, mitral stenosis, Marfan's syndrome, cardiomyopathy</td>
<td>Fetal bradycardia, low birth weight, hypoglycemia, respiratory depression, prolonged labor</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Arrhythmia, CHF</td>
<td>Low birth weight, prematurity</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Hypertension, CHF</td>
<td>Reduced uteroplacental perfusion</td>
<td>Unclear</td>
<td>Yes</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>Arrhythmia, anesthesia</td>
<td>Neonatal CNS depression</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Low-molecular weight heparin</td>
<td>Mechanical valve, hypercoagulable state, DVT, AF, Eisenmenger's syndrome</td>
<td>Hemorrhage, unclear effects on maternal bone mineral density</td>
<td>Limited data</td>
<td>Limited data</td>
</tr>
<tr>
<td>Nitrates</td>
<td>Hypertension</td>
<td>Fetal distress with maternal hypotension</td>
<td>Yes</td>
<td>No data</td>
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<tr>
<td>Procainamide</td>
<td>Arrhythmia</td>
<td>None reported</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Unfractionated heparin</td>
<td>Mechanical valve, hypercoagulable state, DVT, AF, Eisenmenger's syndrome</td>
<td>Maternal osteoporosis, hemorrhage, thrombocytopenia, thrombosis</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Mechanical valve, hypercoagulable state, DVT, AF, Eisenmenger's syndrome</td>
<td>Warfarin embryopathy, fetal CNS abnormalities, hemorrhage</td>
<td>Yes, after week 12 of gestation</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**Abbreviations:** AF, atrial fibrillation; CHF, congestive heart failure; CNS, central nervous system; DVT, deep vein thrombosis; HCM, hypertrophic cardiomyopathy; MI, myocardial infarction


### Table 6: New York Heart Association Cardiac Functional Classification

**Class I:** No limitations of physical activity; ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
**Class II:** Slight limitation of physical activity; ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.
**Class III:** Marked limitation of physical activity less than ordinary activity; results in fatigue, palpitation, dyspnea or anginal pain.
**Class IV:** Inability to perform any physical activity; without discomfort; symptoms of cardiac insufficiency or anginal syndrome may be present even at rest and any physical activity increases discomfort.

### Table 7: American Heart Association recommendation for endocarditis prophylaxis

**High Risk**
- Prosthetic cardiac valves, including bioprosthetic and homograft valves
- Previous bacterial endocarditis
- Complex cyanotic congenital heart disease (e.g. single ventricle states, transposition of the great arteries, Tetralogy of Fallot)
- Surgically constructed systemic pulmonary shunts or conduits.

**Moderate Risk**
- Most other congenital cardiac malformations (other than those listed above and below)
- Acquired valvular dysfunction (e.g. rheumatic heart disease)
- Hypertrophic cardiomyopathy
- Mitral valve prolapse with valvular regurgitation or thickened leaflets.

- Avoid mental and physical stress, consider epidural
- Labor in the left lateral and upright positions
- Monitor electrocardiogram; more invasive monitoring is needed with certain conditions
- Full resuscitation facilities should be available
- Provide continuous fetal heart rate monitoring
• Assisted second stage with certain conditions
• Avoid ergotamine for the third stage.

**Postnatal**

• Vigilance for cardiac failure
• Avoid fluid overload
• Continued intensive care
• Discuss safe and effective contraception.

**CONGENITAL HEART DISEASE**

The incidence of congenital heart disease in pregnancy is increasing as women with more severe defects, who underwent corrective surgery as children, are now able to have children themselves. The most common congenital heart diseases in pregnancy are patent ductus arteriosus (PDA), atrial septal defect (ASD) and ventricular septal defect (VSD). Together these account for about 60% of cases.

**ATRIAL SEPTAL DEFECT**

• Most common congenital heart defect in women
• Usually well tolerated in pregnancy
• Potential risk of paradoxical embolism, but risk is low
• Women may deteriorate and become hypotensive if there is an increase in the left-to-right shunt following blood loss at delivery. This causes a drop in left ventricular output and coronary blood flow
• Supraventricular arrhythmias are uncommon before the age of 40 years but may rarely complicate pregnancy.

**VENTRICULAR SEPTAL DEFECT**

• Increased volume load of left ventricle
• Usually well tolerated in pregnancy unless the woman has Eisenmenger’s syndrome.

**CYANOTIC CONGENITAL HEART DISEASE**

Cyanosis carries significant risks for mother and fetus. Problems include:
• Worsening cyanosis because of increased right-to-left shunting secondary to falling peripheral vascular resistance
• Thromboembolic risk increased because of polycythemia (secondary to hypoxemia)
• Increased risk of fetal loss (especially if oxygen saturation > 80–85%) and increased risk of intrauterine growth restriction. Their chance of a livebirth is more than 20%
• Associated pulmonary hypertension.

*Pregnancy outcome is improved if:*
• Resting oxygen saturation more than 85%
• Hemoglobin less than 18 g/dL
• Hematocrit less than 55%

**EISENMENGER’S SYNDROME**

This results when pulmonary hypertension develops secondary to a large left-to-right shunt such as a VSD, and the shunt is reversed to become right-to-left shunt with consequent cyanosis. Pulmonary hypertension is dangerous and may be primary or secondary to lung disease or Eisenmenger’s syndrome. Maternal mortality is 40%. The danger relates to fixed pulmonary vascular resistance and an inability to increase pulmonary blood flow with refractory hypoxemia. Most deaths can be attributed to thromboembolism, hypovolemia or preeclampsia.

**Management**

Women with severe pulmonary hypertension or Eisenmenger’s syndrome should be advised to avoid pregnancy or, in the event of unplanned pregnancy, to have a therapeutic termination. If such advice is declined, multidisciplinary care and elective admission for bed rest, oxygen and thromboprophylaxis are recommended.

**PULMONARY HYPERTENSION**

Maternal mortality rate is very high (50%) when pulmonary hypertension is associated with pregnancy. It can be primary (idiopathic) or secondary to long standing ASD/VSD, PDA or mitral stenosis. Increase in cardiac output during labor, delivery and postpartum period may lead to right sided heart failure or myocardial ischemia, leading to arrhythmias, ventricular failure and sudden death. Chronic maternal hypoxia leads to intrauterine growth restriction and premature delivery. Pregnancy should be discouraged and permanent sterilization should be considered. If pregnancy occurs, termination should be offered because of maternal risks.

**MARFAN’S SYNDROME**

Marfan’s syndrome is inherited as an autosomal dominant disorder. About 80% of patients with Marfan’s syndrome have cardiac involvement, most commonly:
• Mitral valve prolapse
• Mitral regurgitation
• Aortic root dilatation.

In pregnancy, this syndrome carries the risk of aortic dissection and aortic rupture.

*Predictors for dissection and rupture include:*
• Preexisting or progressive aortic root dilatation (10% risk if root > 4 cm)
• Positive family history of dissection or aortic rupture.

**Management**

• Pregnancy is contraindicated if the aortic root is more than 4–4.5 cm
Patients at high-risk (and particularly if root > 4.5 cm) should be offered aortic root replacement prior to pregnancy. β-blockers have been shown to reduce the rate of aortic dilatation and the risk of complications in patients with Marfan’s syndrome. Regular echocardiograms should be carried out to assess aortic root diameter. Elective cesarean section is usually recommended for women with aortic roots showing progressive enlargement or size more than 4.5 cm.

**PERIPARTUM CARDIOMYOPATHY**

Development of heart failure in the last month of pregnancy and 5 months postpartum in the absence of a known cause and without any heart disease prior to the last month of pregnancy (Fig. 1).

**Risk Factors**
- Multiple pregnancy
- Pregnancy complicated by hypertension
- Multiparity
- Advanced maternal age
- Afro-Caribbean race.

**Signs and Symptoms**
- Dyspnea
- Palpitations
- Pulmonary and/or peripheral edema
- Symptoms relating to peripheral or cerebral emboli
- Tachycardia
- Congestive cardiac failure
- Dysrhythmias
- Signs of pulmonary, cerebral and systemic embolization
- Systemic embolism occurs in 25–40% of those affected by peripartum cardiomyopathy, and ischemic stroke in about 5%.

**Diagnosis**
This requires echocardiography. The diagnostic criteria are:
- Left ventricular ejection fraction (LVEF) less than 45%
- Fractional shortening less than 30%
- Left ventricular end-diastolic pressure (LVDP) more than 2.7 cm/m²

**Management**
- Elective delivery, if antenatal
- Thromboprophylaxis. Anticoagulants are mandatory if there is severely impaired left ventricular dysfunction, intracardiac thrombus or arrhythmias
- Conventional treatment for heart failure including diuretics, vasodilators (hydralazine and/or nitrates), cardioselective β-blockers (bisoprolol) or β-blockers with arteriolar vasodilation action (carvedilol, digoxin, inotropes) and, after delivery, angiotensin converting enzyme (ACE) inhibitors
- Cardiac transplantation may be the only option in severe cases unresponsive to conventional and full supportive management.

**Prognosis and Recurrence**
- Maternal mortality rate is reported to be 20–50%
- About 50% of patients make spontaneous and full recovery
- Prognosis depends on normalization of left ventricular size and function within 6 months after delivery
- Women should be counseled against further pregnancy if left ventricular size or function does not return to normal, since there is a significant risk of recurrence, worsening heart failure (50%) and death (25%) in subsequent pregnancies
- For those whose cardiomyopathy resolves, the recurrence risk is not known but appears to be lower (0–25%).

**MYOCARDIAL INFARCTION**

Myocardial infarction is becoming more frequent as older women are becoming pregnant. The worldwide maternal death rate from acute myocardial infarction is over 20%.

**Risk Factors**
- Smokers
- Diabetes
- Obesity
- Family history of ischemic heart disease
- Hypertension
- Hypercholesterolemia
- Multigravidas older than 33 years.
Acute myocardial infarction occurs most commonly in the third trimester, and affects the anterior wall of the heart. In pregnancy, the underlying cause of infarction is more likely to be due to non-atherosclerotic conditions such as coronary artery thrombosis and dissection of coronary arteries. 

**Management**

- Management for acute ischemia and infarction is as for the nonpregnant woman, with heparin, β-blockers and nitrates.
- Low-dose aspirin (75–150 mg/day) is safe for use in pregnancy and should be continued or commenced in pregnancy for primary and secondary prophylaxis. In the acute management of myocardial infarction, 150–300 mg can be given.
- Thrombolytic (intravenous and intracoronary) therapy has been used successfully.
- Coronary angiography is usually appropriate to determine the underlying cause of the infarction and percutaneous transluminal angioplasty and stenting may be used if appropriate.
- Statins should be discontinued prior to pregnancy as, in human pregnancy, there is an increased risk of central nervous system and limb defects.

**MECHANICAL HEART VALVES**

Women with metal heart valve replacements need life-long anticoagulation and this must be continued in pregnancy because of the increased risk of thrombosis.

**Management**

The interest of the mother and fetus are in conflict. Continuation of warfarin affords the mother the lowest risk of thrombosis, whereas for the fetus warfarin is associated with an increased risk of teratogenesis, miscarriage, stillbirth, and intracerebral bleeding.

High-dose subcutaneous low-molecular-weight heparin (LMWH) is safe for the fetus but is associated with a higher risk of thrombosis for the pregnant woman.

The choice of anticoagulation regimen will depend on:

- Position of the prosthesis
- Type of valve replacement
- The number of mechanical valves. Two valves give a higher risk of thrombosis
- Previous history of embolic events
- The dose of warfarin required to maintain a therapeutic INR. The risk of embryopathy and fetal loss are increased in women requiring more than 5 mg
- Patient’s choice. Some women are unhappy to accept any additional risk to the fetus.

The anticoagulant regimes are:

- Warfarin throughout pregnancy
- Heparin between 6 weeks and 12 weeks gestation followed by warfarin
- Heparin throughout.
  When heparin is used, low-dose aspirin should be added as an adjunctive antithrombotic therapy.
  Subcutaneous heparin should be discontinued for labor and delivery. The dose of intravenous heparin is reduced to prophylactic levels.
  Full anticoagulant doses of heparin should be resumed after delivery.
  Warfarin may be restarted 3–5 days following delivery.
  In the event of an urgent need to deliver a fully anticoagulated patient, warfarin may be reversed with fresh frozen plasma (FFP) and vitamin K, and heparin and LMWH with protamine sulfate.

**ACQUIRED HEART DISEASE**

Worldwide, the acquired heart disease most likely to affect women wishing to have children is rheumatic heart disease. This is caused by rheumatic fever, which damages one or more of the heart valves. Mitral stenosis accounts for 90% of rheumatic heart disease in pregnancy.

**MITRAL STENOSIS**

In pregnancy, women may deteriorate secondary to tachycardia, arrhythmias or the increased cardiac output. The commonest complication is pulmonary edema secondary to increased left atrial pressure and precipitated by increased heart rate or increased volume (such as occurs during the third stage of labor).

**Poor prognostic features for development of pulmonary edema include:**

- Severe mitral stenosis as assessed by valve area less than 1 cm
- Presence of moderate-to-severe symptoms prior to pregnancy.

**Management**

Women with severe mitral stenosis should be advised to delay pregnancy until after balloon, open or closed mitral valvotomy. Beta-blockers decrease heart rate and the risk of pulmonary edema, but if medical therapy fails or for those with severe mitral stenosis, balloon mitral valvotomy can be performed safely in pregnancy. Supine and lithotomy positions should be avoided in labor and delivery.

**ARRHYTHMIAS**

A sinus tachycardia requires investigation for possible underlying pathology such as blood loss, infection, heart failure, thyrotoxicosis or pulmonary embolus, but no treatment is required if such causes are excluded. The most common arrhythmia encountered in pregnancy is SVT. An SVT that does
not respond to vagal maneuvers may be safely terminated in pregnancy with adenosine.

**GENETIC COUNSELING**

- The risk of the fetus having a congenital heart defect is higher, if the mother rather than the father has congenital heart disease. Overall, the risk is about 2–5%
- The level of risk depends on the specific lesion and is higher for outflow tract lesions
- In women with aortic stenosis and ASD, the risk of an ASD in the fetus is about 5–10%, for aortic stenosis, the risk is highest (18–20%)
- Both Marfan’s syndrome and hypertrophic cardiomyopathy (HOCM) have autosomal dominant inheritance.

**HEART DISEASE IN PREGNANCY: KEY POINTS**

- Women with significant heart disease need multidisciplinary care in a specialist center by obstetricians, cardiologists and anesthetists with expertise in the care of heart disease in pregnancy
- Discuss safe and effective contraception, if pregnancy contraindicated
- Assess functional class of heart (New York Heart Association classification)
- Palpitations, extrasystoles and systolic murmurs are extremely common in pregnancy and mostly benign.
- Contraindications to pregnancy include:
  - Dilated aortic root more than 4.5 cm
  - Severe left heart obstruction from critical mitral or aortic stenosis
  - Severe impairment of left ventricular function
  - Pulmonary hypertension and fixed pulmonary vascular resistance.
- Careful prepregnancy counseling is vital for a pregnant woman with mechanical heart valves as anticoagulation in these cases is associated with risks to the mother and/or fetus
- Peripartum cardiomyopathy should be treated with conventional heart failure therapy (including thromboprophylaxis) with the exception that ACE inhibitors are withheld until after delivery
- Fetal surveillance and detailed fetal cardiac ultrasonography if the patient has congenital heart disease
- Serial ultrasound examinations usually begin at 32 weeks unless there is presence of fetal or maternal complications
- Elective induction may be necessary for maternal or fetal indication
- Vigilance for cardiac failure and avoid fluid overload
- Labor should be in left lateral and upright position with continuous fetal heart rate monitoring
- Assisted second stage with certain conditions such as severe mitral stenosis
- Avoid ergotamine for third stage.

**REFERENCES**

INTRODUCTION

Depending on the specific population abnormal maternal glucose regulation occurs in 3–10% of pregnancies and 80–90% of these are detected during pregnancy, while the rest are overt or pregestational. It is the most common medical complication of pregnancy. Diabetes during pregnancy is associated with a high perinatal mortality and morbidity. Infants of mothers with pre-existing diabetes experience double the risk of serious injury at birth, triple the likelihood of cesarean delivery and quadruple the incidence of newborn intensive care unit admissions.

Maternal Fetal Metabolism in Normal Pregnancy

With each feeding the pregnant woman undergoes a series of maternal hormonal actions leading to rise in blood glucose, free fatty acids, ketones and triglycerides in response to glucose. There is secondary secretion of pancreatic insulin, glucagon, somatomedins and adrenal catecholamines, so as to provide glucose to the fetus and mother. Pregnant women tend to develop hypoglycemia (mean plasma glucose, 65–75 mg/dL) between meals and during sleep because fetus continues to draw glucose, even during periods of fasting. This hypoglycemia becomes increasingly marked as pregnancy progresses, because the glucose demand of the fetus increases.

Rising levels of placental steroid and peptide hormones (estrogen, progesterone, chorionic somatomammotropin) during the 2nd and 3rd trimester produce insulin resistance and insulin sensitivity also falls by 50%. Increased binding of insulin to adipocytes and hepatocytes results in insulin resistance. Thus, with each feeding the demand for insulin secretion escalates progressively during pregnancy. If maternal pancreatic insulin response is inadequate then maternal and fetal hyperglycemia results.

Surging maternal and fetal glucose levels are accompanied by episodic fetal hyperinsulinemia which in turn promotes excess nutrient storage, resulting in macrosomia. Conversion of excess glucose into fat causes depletion in fetal oxygen levels, which are accompanied by surges in adrenal catecholamines, which, in turn, cause hypertension, cardiac remodelling and hypertrophy, stimulation of erythropoietin, red blood cell hyperplasia and increased hematocrit which results in vascular sludging, poor circulation, ischemia of vital organs and postnatal hyperbilirubinemia.

During normal pregnancy mean fasting blood sugar (FBS) level decline progressively to a low value of about 74 mg/dL and peak postprandial blood sugar to 120 mg/dL.

Fetal Morbidity with Diabetes during Pregnancy

There is a strong association between the degree of glycemic control prior to pregnancy, 3–6 weeks after conception, 2nd and 3rd trimester of pregnancy and miscarriage, birth defects, macrosomia with central obesity, in utero growth restriction, growth acceleration, etc. extending into childhood and adult life. The rates of various morbidities associated with diabetes in pregnancy are shown in Table 1.
Congenital Malformations

Its rate is about 5–10 times that in nondiabetics and accounts for approximately 10–50% of perinatal mortality. The anomalies may involve skeletal, central nervous system (CNS), cardiac, renal, gastrointestinal and other systems. The most common being cardiac [ventricular septal defect (VSD), atrial septal defect (ASD), etc.]. Risk factors are poor preconceptual glycemic control, early onset of disease, ketoacidosis, vasculopathy and hypoxia. Factors influencing the development of congenital malformations are shown in Table 2.

Growth Acceleration, Fetal Obesity and Central Obesity

Macrosomia (birth weight > 4,000 g or that exceeds 90th percentile for gestational age) occurs in 15–45% of cases. These fetuses have a unique pattern of overgrowth (central obesity). The abdominal circumference growth rises above normal after 24 weeks. These newborns face the risk of hypoglycemia, neonatal jaundice, birth trauma, shoulder dystocia, erb’s palsy, prolonged labor, asphyxia and meconium aspiration. Excessive body fat stores, stimulated by excessive glucose delivery during diabetic pregnancy often extend into childhood and adult life. By 10–16 years, these offspring’s have a 19.3% rate of impaired glucose tolerance, diabetes mellitus (2–3%) in later life, neurological deficit (4%) and childhood obesity (50%).

Growth Restriction

Pregnant diabetic patients with vascular disease (retinal/renal or chronic hypertension) are at risk for growth restriction and preterm birth.

Role of Glucose Levels and Maternal Obesity

Fetal birth weight correlates best, with 2nd and 3rd trimester postparandial blood sugar levels. Maternal obesity has a strong and independent effect on fetal macrosomia.

Maternal Morbidity: Retinopathy, Nephropathy, Chronic Hypertension and Preeclampsia

In women with severe to moderate renal impairment (creatinine > 125 µmol/L) and hypertension there is a significant risk of permanent decline in renal function. There is a 2-fold risk of progression of diabetic retinopathy and the risk is higher for women with type 1 diabetes. Thus, renal function test and full retinal screening is required at booking, 16–20 weeks and at 28 weeks gestation. Chronic hypertension (10%) and preeclampsia (12%) are more frequent among diabetic pregnancies. Patients with chronic hypertension and diabetes are at increased risk of intrauterine growth restriction (IUGR), superimposed preeclamptic toxemia (PET), abruptio placentae and maternal stroke. Additionally, problems like urinary tract infection, vaginal candidiasis, respiratory, endometrial and wound infection complicate diabetic pregnancies. Cesarean section rate is increased to about 60%. Since pregnant women are at a greater risk of severe unannounced hypoglycemia, family members should be educated about the use of glucagon injections. Diabetic ketoacidosis (DKA) is rare in pregnancy but is associated with high fetal mortality (20–50%). Precipitating factors for DKA include hyperemesis, infection and tocolytic therapy with beta-sympathomimetics.

Effects of Pregnancy on Diabetes

- Change in eating pattern
- Increase in the insulin dose requirements
- Greater importance to tight glucose control (ideally HbA1c < 6.1%)
- Increased risk of severe hypoglycemia
- Risk of deterioration of pre-existing retinopathy and established nephropathy
- Lower renal threshold for glycosuria.
Effects of Diabetes on Pregnancy

- Need for pregnancy planning
- Risk of congenital malformations, miscarriage, macroadamia, intrauterine disease (IUD), polyhydramnios (5–26%), preterm labor (three fold increase), birth injuries, preeclampsia, infection and increased cesarean section rate
- Need for regular clinical, biochemical and ultrasound monitoring.

Classification of Diabetes

Table 3 shows classification of diabetes.

WHO Criteria to Diagnose Pre-existing Diabetes Mellitus (Non-pregnant Women)

It is difficult to diagnose type 1 and 2 diabetes during pregnancy. Gestational diabetes mellitus (GDM) in early pregnancy is highly suggestive of occult type 2 diabetes. A pregnancy test is recommended in all reproductive age women admitted to hospital for blood sugar management.

One of the criteria shown in Table 4 must be confirmed by repeated testing on a subsequent day unless the patient is symptomatic in which case a single abnormal value will suffice.

Prediabetes

Prediabetics have either impaired fasting glucose (100–125 mg/dL) or impaired glucose tolerance after a 2 hour oral glucose tolerance test (OGTT) (140–199 mg/dL) or both and are at risk of developing diabetes during pregnancy.

Table 3: Classification of diabetes

- Insulin dependent—type 1
- Noninsulin dependent—type 2
  - Nonobese
  - Obese
- Secondary diabetes
- Impaired glucose tolerance
  - Nonobese
  - Obese
  - Secondary
- Gestational diabetes
  - Diet control
  - Insulin required

Table 4: World Health Organization criteria to diagnose pre-existing diabetes mellitus after 75 g oral glucose tolerance test

<table>
<thead>
<tr>
<th>Fasting plasma glucose</th>
<th>2 hours plasma glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>&gt; 7.0 mmol/L</td>
</tr>
<tr>
<td>Impaired glucose tolerance (IGT)</td>
<td>&lt; 7.0 mmol/L</td>
</tr>
</tbody>
</table>

Table 5: Target blood glucose concentrations in pregnancy

<table>
<thead>
<tr>
<th>Whole blood glucose</th>
<th>Before meals</th>
<th>2 hours postprandial</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.9–5.6 mmol/L</td>
<td>&lt; 7.8 mmol/L</td>
<td></td>
</tr>
</tbody>
</table>
Diet and Exercise

Women with normal body mass index (BMI) (18.5–24.9 kg/m²) are advised to consume about 30 kcal/kg/day and those with BMI higher than 30%, 24 kcal/kg/day. The diet is composed of 45% carbohydrate, 20% protein and 35% fat, distributed between evenly spaced meals and snacks, according to the patient’s needs. Refined sugars are avoided, high fiber and low fat diet is recommended. Three meals and four snacks are recommended with the last snack being taken at bed time to minimize overnight hypoglycemia and ketosis. Normal pregnant women are prone to ketonuria after 12–16 hours of fasting therefore, monitoring of morning fasting ketonuria helps to guide the level of carbohydrate restriction to avoid the risk of ketonuria.

Walking for 20 minutes two times daily aids in achieving good glycemic control and improves cardiovascular function.

Insulin Therapy

If diet therapy does not achieve good metabolic control as shown in Table 6, then insulin therapy is started. OHA are not used because they cross the placenta and there is a theoretical risk of prolonged neonatal hypoglycemia.

Human insulins are the least antigenic and are the insulin of choice in patients who are started on insulin for the first time. The insulin analog, Lispro is particularly beneficial in women with frequent hypoglycemia as it has a shorter time to peak (1 hour) and thus can be taken at the same time rather than before a meal. It appears to be safe in pregnancy and is proven to be more effective than regular human insulin in reducing fetal macrosomia.

Usually, a regimen with four times daily insulin dosing (nocturnal, intermediate acting insulin and three premeal, injections of fast acting insulin) is recommended. No perfect regime exists for all patients. If delivery is necessary before 34 weeks gestation, steroids are given to enhance fetal lung maturity. Patient is hospitalized for blood sugar control (around 40% increase in dose is suggested) for up to 24 hours after the last steroid dose.

Second Prenatal Visit

Previous blood sugar values and glycosylated hemoglobin/fructosamine values are reviewed especially if there is new evidence of nephropathy or retinopathy. When the HbA1c is high, options include:

- Continuation of the pregnancy and then dealing with any fetal/neonatal problems that arise
- Delaying the decision until 18 weeks of gestation when findings from sonographic survey (Level 1 and 2) and biochemical screening (double and triple test) results are available.

Second Trimester: Biochemical Screening

Risk for neural tube defects is high (10-fold increased over the rate in the nondiabetic population). For this reason, maternal serum, alpha fetoprotein (AFP) screening in the diabetic gravida is mandatory between 16 weeks and 18 weeks of gestation. Since diabetic pregnancies are associated with a lower maternal serum AFP as compared to nondiabetic women adjustment has to be made to allow for the difference in mean AFP levels between diabetic and nondiabetic pregnancies.

Ultrasound

First Trimester

Early dating and viability scan, nuchal translucency, nasal bone and ducts flow evaluation at 11–13 weeks gestation.

Second Trimester

Detailed fetal anatomy survey at 18–20 weeks for anomalies, including detailed assessment of fetal heart.

Third Trimester

Growth scan to access fetal size, every 4–6 weeks, from 26 weeks to 36 weeks in women with overt pre-existing diabetes, once at 36–37 weeks in women with GDM.

Fetal Echo

At 22 weeks if HbA_{1c} is elevated in first trimester.

Third Trimester

The major hazards of this trimester are:

- Intrauterine fetal demise and asphyxia
- Obstetric or medical complications necessitating premature delivery
- Potential fetal-maternal trauma during delivery because of fetal macrosomia
- The decision to deliver depends on the gestational age, maternal condition and fetal status.

Fetal Surveillance

Fetal well-being is assessed by fetal kick count at night, cardiotocographic tracing, umbilical and middle cerebral artery Doppler velocimetry, fetal biometry and amniotic fluid index.
Fetal monitoring should commence at regular intervals from 28 weeks gestation in uncomplicated diabetic pregnancies, however, in patients with IUGR, hypertension, oligohydramnios, preeclampsia, or poorly controlled blood sugars, testing should be started from 26 weeks gestation and must be performed more frequently.

Twice weekly nonstress test (NST) in the 3rd trimester is associated with a lower perinatal mortality rate. A reactive NST is as predictive as fetal biophysical profile score (BPP) shown in Table 7.

### Hospitalization Versus Outpatient Care

Good maternal/fetal outcomes have been achieved with outpatient care. Admission is advised for treatment of preeclampsia, premature rupture of membranes, or premature labor and or if there is poor glycemic control at any time during pregnancy so as to evaluate their diet, adjust insulin and look for potential underlying problems such as infection.

Out patient care is continued until 36 weeks of gestation in patients with good glycemic control, reassuring fetal monitoring tests, no evidence of preeclampsia or hypertension, and normal fetal growth, but are seen twice a week, along with their biweekly NST. Patients who do not meet these criteria are admitted to the hospital for closer maternal/fetal monitoring for the remainder of pregnancy.

### Timing of Delivery

Plan delivery between 38 weeks and 39 weeks gestation in the well-controlled diabetics in the absence of maternal and fetal complications. However, decision to deliver should be based on individual patient. It has been suggested that when insulin requirements suddenly fall, delivery should be considered, as this may be a sign of failing placenta.

### Route of Delivery

Spontaneous vaginal delivery is the aim of modern management. Diabetes by itself is not an indication for cesarean section (LSCS) when the estimated fetal weight is above 4,500 g. Shoulder dystocia remains difficult to predict and there is no conclusive evidence that early induction of labor prevents dystocia.

### Delivery Day and Time

Every effort is made to schedule inductions or cesarean sections as the first thing in the morning. Maintain euglycemia (4-8 mmol/L) during labour. Insulin requirements during induction of labor and elective cesarean section are shown in Flow chart 1. Insulin requirement may fall due to uterine contractions. Intravenous (IV) infusions of short acting insulin via a pump (50 units human actrapid in 50 mL normal saline to produce 1 unit of insulin/mL) and dextrose with potassium (500 mL of 10% dextrose and 20 mmol/l of potassium chloride at a rate of 100 mL/hour) are administered throughout labour via separate IV sets. Potassium is added as insulin drives extracellular potassium into the cells. Maternal capillary blood sugars should be checked every hour with a dextrometer and adjusted according to a sliding scale. Stop insulin if blood glucose is less than 4.0 mmol/l and restart if higher than 7.0 mmol/l. Monitor blood glucose every 15 minutes during second stage of labor.

### Postpartum

As soon as the cord is cut the rate of insulin infusion should be halved. Subcutaneous insulin administration is to be resumed once the women starts eating normally, to either the prepregnancy dose (type 1 diabetes) or 25% lower if she intends to breastfeed.

Continue hourly blood sugar monitoring for 2 hours postdelivery and then postprandially for next 48 hours.

Unrecognized postnatal hypoglycemia may lead to neonatal seizures, coma and brain damage. Therefore, frequent blood checks, early oral feeding or infusion of glucose if oral measures prove insufficient so as to avoid neonatal hypoglycemia.

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**Table 7: Biophysical tests of fetal well-being**

<table>
<thead>
<tr>
<th>Test</th>
<th>Frequency</th>
<th>Reassuring result</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal movement count</td>
<td>Every night from 28 weeks</td>
<td>10 movements in &lt; 60 min</td>
<td>Performed in all patients</td>
</tr>
<tr>
<td>Nonstress test</td>
<td>Twice weekly</td>
<td>2 heart rate accelerations in 20 min</td>
<td>Begin at 28–34 weeks with type 1 diabetes, begins at 36 weeks in diet controlled GDM</td>
</tr>
<tr>
<td>Ultrasound biophysical profile</td>
<td>Weekly</td>
<td>Score of 8 in 30 min</td>
<td>3 movement = 2, 1 flexion = 2, 30 second of breathing = 2, 2 cm of amniotic fluid = 2</td>
</tr>
</tbody>
</table>

*Abbreviation: GDM, gestational diabetes mellitus*
Association (ADA-2003). It affects mainly fetal growth rate, but can also cause obesity and slow systemic development of type 2 diabetes. However, there is no increase in the rate of congenital abnormalities.

The perinatal mortality and morbidity are increased in women with untreated GDM.

**Screening for GDM (Flow chart 2)**

Screening is carried out between 26 weeks and 28 weeks gestation, when insulin resistance tends to be at its maximum, but in high-risk women (obese, positive personal or family history of diabetes) it is done in 24–28 weeks.

Clinical characteristics associated with increased risk for GDM are shown in Table 8.

First trimester screening (Table 9) should be performed on patients with risk factors to identify occult type II diabetes. If screening is negative then repeat the screening in the 3rd trimester. The ACOG have suggested that women in the low-risk category could be exempted from universal screening.

The national diabetes data group uses a 50 g oral glucose load followed by a glycemic measure 1 hour later (Table 10). A screening result equal to, or in excess of 140 mg/dL (7.8 mmol/L) is considered abnormal and it is followed by further diagnostic testing with either 100 g OGTT two step or one step 75 g OGTT (Table 11). Both tests are administered after an overnight fast of at least 8 hours but no more than 14 hours and after at least 3 days of unrestricted diet including less than or equal to 150 g of carbohydrate per day. Two or more abnormal values must be measured for the test to be considered positive. Single abnormal value on 3 hour screen if left untreated, are at a high-risk of macrosomia and neonatal morbidity.

**Medical Management**

**Diet and Exercise**

This is the mainstay of treatment. Carbohydrates with a low glycemic index like bran (resulting in sustained slow release of glucose) are advised.
Medical Disorders in Pregnancy

**Table 11: Diagnosis of gestational diabetes mellitus**

<table>
<thead>
<tr>
<th>Test</th>
<th>WHO criteria</th>
<th>National Diabetes Data Group criteria</th>
<th>American Diabetes Association (ADA) criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>75 g OGGTT</td>
<td>7.0 mmol/L</td>
<td>10.0 mmol/L (180 mg/dL)</td>
<td></td>
</tr>
<tr>
<td>Fasting</td>
<td>10.6 mmol/L</td>
<td>10.0 mmol/L (180 mg/dL)</td>
<td></td>
</tr>
<tr>
<td>1 hour</td>
<td>8.0 mmol/L</td>
<td>7.8 mmol/L (140 mg/dL)</td>
<td></td>
</tr>
<tr>
<td>2 hours</td>
<td>8.6 mmol/L</td>
<td>7.8 mmol/L (140 mg/dL)</td>
<td></td>
</tr>
<tr>
<td>3 hours</td>
<td>9.2 mmol/L</td>
<td>7.8 mmol/L (140 mg/dL)</td>
<td></td>
</tr>
<tr>
<td>1 hour</td>
<td>10.6 mmol/L</td>
<td>10.0 mmol/L (180 mg/dL)</td>
<td></td>
</tr>
<tr>
<td>2 hours</td>
<td>8.6 mmol/L</td>
<td>7.8 mmol/L (140 mg/dL)</td>
<td></td>
</tr>
<tr>
<td>3 hours</td>
<td>9.2 mmol/L</td>
<td>7.8 mmol/L (140 mg/dL)</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviation:** OGGTT, oral glucose tolerance test

The ADA recommends that normal weight women consume 30–32 kcal/kg in the second half of pregnancy.

**Insulin**

Persistent postprandial hyperglycemia (> 7.5–8.0 mmol/L) or fasting hyperglycemia (> 6.0 mmol/L) despite, compliance with diet is an indication for introduction of insulin therapy. It is usually given as short acting insulin before meals, although in more severe cases intermediate acting insulin at night may be added.

**Oral Hypoglycemic Agents**

Glyburide: This sulphonylurea enhances insulin secretions and does not significantly cross the placenta. It serves as a suitable alternative to insulin for the treatment of GDM with similar perinatal outcomes.

However, it should not be used in the 1st trimester and has the disadvantage that it sometimes takes more than 1 week to observe the effects of dose titrations.

**Metformin:** In women with polycystic ovary syndrome (PCOS), metformin may be safe and may reduce the risk of
miscarriage and the development of GDM when used for the entire pregnancy.\textsuperscript{11}

**Obstetric Management**

**Antepartum**

Gestational diabetes mellitus is associated with an increased risk of PET and thus women should have regular checks of blood pressure and urine analysis. Regular ultrasound assessment for fetal growth is advisable as this is likely to impact decision regarding insulin therapy and mode and timing of delivery.

Each case should be assessed individually regarding the timing of delivery. However, most obstetricians tend to deliver well-controlled GDM around 39–40 weeks. Emphasis must be laid on two things:

- Avoiding shoulder dystocia
- Glycemic management.

**Intrapartum**

Women on small doses of insulin (< 20 units/day) may be managed without insulin during delivery, as women do not eat much during labor. However, women on larger doses are managed with an insulin sliding scale.

**Postpartum**

The ADA recommends 75 g. OGTT at 6 weeks postpartum and annual FBS to exclude impaired glucose tolerance or diabetes outside pregnancy. Risk of recurrence (33–50% chance of GDM in future pregnancy) should also be explained to the women.\textsuperscript{12}

**Breastfeeding**

Breastfed infants have a much lower risk of developing diabetes. Lactation has beneficial effect on the overall maternal glucose and lipid metabolism.

**Prevention**

Loss of weight prior to pregnancy following appropriate diet and lifestyle modifications and regular exercise result in reduction in the risk of development of type 2 diabetes mellitus, and GDM in some patients but not in very susceptible individuals.

**Medicolegal Pitfalls**

Occurrence of a severe, debilitating congenital anomaly in the infant of a mother with diabetes.

The clinician, when discussing pregnancy plans with a woman with pre-existing diabetes, must mention the preventability of these birth defects with good glycemic control prior to pregnancy and this counselling should be recorded in the patient’s medical record.

Risk of perinatal asphyxia, birth injury (clavicle or humerus fractures, brachial plexus disruption, or less commonly, direct cerebral or cervical spine trauma) permanent palsy of the arm and hand after a difficult delivery of an obese fetus usually leads to litigation. Clinicians managing these patients must obtain an ultrasound based estimation of fetal weight in the last 2–3 weeks prior to delivery and offer cesarean delivery to a patient with an estimated fetal weight of more than 4,500 g and if the labor is prolonged and patient is unable to expel the fetal head spontaneously after 2–3 hours of pushing effort.

**CONCLUSION**

Improved medical and obstetric management of diabetes has resulted in good maternal and neonatal outcomes; however, major challenges remain in preventing congenital anomalies and macrosomia. The solution lies in maintaining metabolic milieu of the diabetic gravida as close as possible to normal with multidisciplinary support.

**REFERENCES**

INTRODUCTION
Knowledge of liver function and its role in various disease processes is essential for the practicing obstetrician. Though severe liver disease is only an occasional complication during pregnancy, it has disproportionately high mortality rates. This chapter focuses on conditions which are specific to pregnancy [acute fatty liver, cholestasis, hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome] and those which are commonly seen in pregnant women (viral hepatitis, gallstones).

ETIOPATHOLOGY
In normal pregnancy, with adequate nutrition, the metabolic changes seem to be without significant effect on hepatic function. Pregnancy can produce some clinical manifestations which are typical of liver diseases. Itching is seen in later pregnancy due to the effect of accumulated bile acids under hormonal effects on the biliary system. Abnormalities on liver function testing suggest primary hepatic disease or complication involving the liver and need to be completely evaluated. A summary of the liver function tests in pregnancy is presented in Table 1.2 In general, levels of bilirubin and transaminases are specific guides to liver dysfunction. They are never altered as a result of normal changes of pregnancy.

Hepatic diseases of various etiologies and varying severity can occur in pregnancy. They have a differential impact on pregnancy. Maternal, and subsequently the perinatal outcome are affected by the etiology, severity and gestational age of occurrence of the hepatic dysfunction. There are a number of disorders specific for the pregnant woman, which are not seen at any other time in life and they command the attention of the obstetrician. The spectrum of liver diseases can be divided into pregnancy-specific and pregnancy-associated. Some examples of these conditions are presented in Table 2. Diseases from both groups can be severe enough to cause hepatic failure (Flow chart 1).

VIRAL HEPATITIS
Hepatitis is the most common serious liver disease encountered in pregnant women. The mode of transmission, etiopathology and clinical picture is not altered in pregnancy in most women. Most cases of viral hepatitis are self-limiting. About 10% of women infected with hepatitis B virus will become carriers. There is a high-risk of vertical transmission of the hepatitis B virus to the neonate to the tune of 95% when the mother is HBsAg and HBeAg positive. About 1% of cases with viral hepatitis develop fulminant hepatic necrosis. The usual presentation in this case is hepatic encephalopathy and mortality is as high as 80% in these patients. The course of hepatitis E virus infection is altered by the pregnant state. The case fatality rate amongst pregnant women was up to 12 times that for nonpregnant females and males. The risk of fulminant hepatic failure is about 15% and mortality is 5%.3 This infection is also more common than what it was thought to be earlier.

ACUTE FATTY LIVER OF PREGNANCY
Acute fatty liver of pregnancy (AFLP) is a rare disorder characterized pathologically by microvesicular steatosis on liver histology. The pathology resembles that seen in Reye’s syndrome. It usually appears in the third trimester. The reported incidence is 1 in 10,000 pregnancies. However, modern reports suggest that milder varieties of the syndrome may be more common and not universally fatal.4 The etiology
13
CHAPTER
Liver Disease in Pregnancy

Table 1: Liver function tests in pregnancy

<table>
<thead>
<tr>
<th>Serum test</th>
<th>Nonpregnant</th>
<th>Change in pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin</td>
<td>0.5–1.0 mg/dL</td>
<td>No change</td>
</tr>
<tr>
<td>Transaminase (SGOT, SGPT)</td>
<td>7–40 IU/L</td>
<td>No change</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>30–130 IU/L</td>
<td>Total alkaline phosphatase levels double at term</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Much of the increase is attributable to heat-stable placental isoenzyme</td>
</tr>
<tr>
<td>Gamma-glutamyl transferase</td>
<td>&lt; 30 IU/L</td>
<td>No change</td>
</tr>
<tr>
<td>S-nucleotidase</td>
<td>2–17 IU/L</td>
<td>No change</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>12–14 seconds</td>
<td>No change</td>
</tr>
<tr>
<td><strong>Proteins</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total protein</td>
<td>6.5–8 mg/dL</td>
<td>Fall by 1 mg/dL by 16 to 20 weeks</td>
</tr>
<tr>
<td>Albumin</td>
<td>3.5–5.5 mg/dL</td>
<td>Fall by 1 mg/dL in first trimester</td>
</tr>
<tr>
<td>Globulin</td>
<td>3.0–5.0 mg/dL</td>
<td>Small progressive rise till term</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>200–400 mg/dL</td>
<td>Progressive rise till term. Normal levels are above 300 mg/dL</td>
</tr>
<tr>
<td><strong>Lipids</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol</td>
<td>4.0–6.5 mmol/L</td>
<td>Progressive rise to term</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>&lt; 1.5 mmol/L</td>
<td>Progressive rise to term</td>
</tr>
</tbody>
</table>

Table 2: Liver diseases in pregnancy

<table>
<thead>
<tr>
<th>Pregnancy-specific</th>
<th>Pregnancy-associated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperemesis gravidarum</td>
<td>Hepatitis (viral and nonviral)</td>
</tr>
<tr>
<td>Intrahepatic cholestasis of pregnancy</td>
<td>Cirrhosis</td>
</tr>
<tr>
<td>HELLP syndrome</td>
<td>Cholelithiasis and cholecystitis</td>
</tr>
<tr>
<td>Acute fatty liver of pregnancy</td>
<td>Neoplasms Drug-induced hepatic failure Familial syndromes, viz Wilson’s disease, Dubin-Johnson syndrome, etc.</td>
</tr>
</tbody>
</table>

Flow chart 1: Evaluation of cholestasis during pregnancy

Abbreviation: RUQ, right upper quadrant

The syndrome of hemolysis, elevated liver enzymes, and low platelets (HELLP) is considered to be a complication or a variant of severe preeclampsia-eclampsia. There is considerable debate regarding the definition, diagnosis, incidence, etiopathology and management of this syndrome. The name was coined by Weinstein in 1982. The criteria for diagnosis have varied with different reports. A standard definition utilized by most studies, however, is given by Sibai as follows:

- Hemolysis—microangiopathic hemolytic anemia characterized by burr cells, increased bilirubin (> 1.2 mg/dL), and increased lactic dehydrogenase (> 600 IU/L).
• Elevated liver enzymes—increased SGOT (> 72 IU/L), and increased lactic dehydrogenase as above.
• Low platelets—platelet count less than 100,000 per mm³.

**CLINICAL PRESENTATION,**
**INVESTIGATION AND DIFFERENTIAL DIAGNOSIS**

Jaundice may be of varying severity and presentation. The timing of the onset may be a clue to the etiology. Viral hepatitis may occur in any trimester or the puerperium. Hyperemesis is generally seen in the first trimester, whereas HELLP syndrome and AFLP occur in the late second or third trimester. The highlights of the differential diagnosis of these three important conditions are presented in Table 3 and Flow chart 2.®

With reference to hepatitis B, screening should be offered as a routine to all pregnant women. If they are found to be carriers, the infectivity should be evaluated by assessing the antigen status.

**Table 3: Differential diagnosis of severe liver disease in pregnancy**

<table>
<thead>
<tr>
<th>Clinical picture</th>
<th>Serum bilirubin (mg/dL)</th>
<th>SGOT (IU/L)</th>
<th>DIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>HELLP syndrome</td>
<td>Preeclampsia, upper abdominal pain</td>
<td>&lt; 5</td>
<td>&gt; 500</td>
</tr>
<tr>
<td>Acute fulminant hepatitis</td>
<td>Fever, malaise, jaundice</td>
<td>&gt; 5</td>
<td>&gt; 5000</td>
</tr>
<tr>
<td>Acute fatty liver of pregnancy</td>
<td>Malaise, upper abdominal pain, jaundice, rapid deterioration</td>
<td>&lt; 5</td>
<td>&lt; 500</td>
</tr>
</tbody>
</table>

**Abbreviations:** HELLP, hemolysis, elevated liver enzymes, and low platelets; SGOT, serum glutamic oxaloacetic transaminase; DIC, disseminated intravascular coagulopathy
Recommended serologic tests are: hepatitis A IgM, hepatitis B surface antigen and hepatitis B core antibody, hepatitis C antibodies, cytomegalovirus IgM, herpes simplex virus IgM and Epstein-Barr virus IgM.

**MANAGEMENT**

Jaundice is usually managed supportively and conservatively in pregnancy as in the nonpregnant state. The mainstay of therapy is hydration, avoidance of fatty and high protein diets, maintaining normoglycemia and vitamin supplementation. When there is hepatic failure, measures to minimize the mortality from encephalopathy are initiated such as low protein diet, high bowel enemas and lactobacillus supplementation. The management points of special interest in pregnancy are discussed with the specific condition.

**Viral Hepatitis**

Human serum immunoglobulins against the hepatitis A and B virus are available. If administered early in the disease process, they may reduce morbidity. This may be relevant for women who already have compromised liver or immune function.

In the carrier state, hepatitis B does not seem to have any additional risks for pregnancy. Delivery should be as atraumatic as possible to minimize vertical transmission risk. Fetal scalp blood sampling, scalp electrodes and ventouse delivery may be avoided in these cases. There is no indication for an elective cesarean section to prevent vertical transmission of hepatitis B. Risk of transmission to the neonate is minimized by administration of hepatitis B immunoglobulin in the first 24 hours of life. Active immunization with hepatitis B vaccine should be initiated simultaneously. Breastfeeding is not contraindicated provided the babies are immunized.

**Acute Fatty Liver of Pregnancy**

The pathophysiological derangements should be corrected as rapidly as possible while embarking on the chosen plan for delivery. There is no role for conservative management for this condition. Intensive care support is required. Correction of coagulopathy and preventing hypoglycemia are established modalities of treatment. Cesarean delivery does not seem to improve the outcome and vaginal birth would be in the best interests of the mother, keeping in view the high-risk of anesthesia and surgery in these patients.

**HELLP Syndrome**

Management of patients with HELLP syndrome includes the same principles as that of severe preeclampsia-eclampsia. A rapid assessment and liberal use of blood products to correct coagulation abnormalities is central to the management. Fetal status should be evaluated. The combination of maternal and fetal status should be considered in order to decide the timing and mode of delivery. Newer developments include the use of high dose steroid therapy. Magann et al. have showed significant improvement in the laboratory and clinical parameters associated with HELLP syndrome in women who received high-dose antenatal corticosteroids. This is one of the therapeutic modalities, which is feasible as compared to the use of the other proposed therapies such as use of antithrombin and plasmapheresis. Further work needs to be done in this area to clarify the precise role, dose and results with high-dose steroid therapy. The reversal of the pathological features and improvement in maternal condition is ultimately achieved only by delivery. Recovery of laboratory abnormalities usually is within 60 hours from delivery. However, these patients need to be followed up after delivery with serial laboratory assessment to rule out deteriorating maternal parameters. An important aspect to be considered is the risk of recurrence. An extensive study by Sullivan et al. found the risk of recurrence of the HELLP syndrome to be 19–27%. A large number of patients in a developing country being illiterate, may fail to grasp the magnitude of the disease they have survived. Educating the patient to be especially cautious with all future obstetric events and inform the next caregiver about earlier complications is a vital part of the management.

**REFERENCES**

INTRODUCTION

Malaria is an endemic disease in many parts of Asia, Africa, Oceania, Central and South America. Worldwide it is a major health concern. About 300–500 million infections and approximately 1.1–2.7 million deaths in each year are caused by malaria. World Health Organization (WHO) (Table 1). Malaria has been eradicated from North America, Europe and Russia. Though resurgence is observed predominantly in the tropical countries, it is a persistent threat to the non-malarious countries, because of transmission across the international borders and travelers.

Malaria is a protozoal disease caused by the bite of an infected female Anopheles mosquito (Figs 1A and B), four species of plasmodium (P. vivax, P. falciparum, P. malariae and P. ovale) are the infective agents. Malaria through blood transfusion is not uncommon. Incubation period is usually short in that case.

EPIDEMIOLOGY OF MALARIA COMPLEX

Plasmodium vivax and P. falciparum are the causative agents in South-East Asian Region (SEAR). Deaths from malaria are mainly due to P. falciparum. P. falciparum infection predominates in Africa, New Guinea and Haiti. P. vivax is more common in central America and Indian subcontinents. Infection with P. malariae is observed in sub-Saharan Africa.
Infection with *P. ovale* is rare (<1%). *P. falciparum* infection is on the rise. Transmission of malaria is mainly by female *Anopheles* mosquitoes. However, infection may sometimes occur through blood transfusion (vertical transmission) which is rare. Transmission by needlestick injury has been recorded in a few cases. In India during the year 2000-01, there is resurgence of malaria in the states like Orissa, Meghalaya, Mizoram, Assam, Tripura, Andhra Pradesh and Chhattisgarh. Increase in the proportion of *P. falciparum* infection (80–85%) has been observed in the SEAR. During the year 2000-01, slide positivity rate (SPR), in India ranged from 0% to 17% (Fig. 2) depending upon the region. State-wise infection percentage rate with *P. falciparum* in the year 2000 and 2001 revealed significant rise in the Eastern States (Orissa, Bihar), North-Eastern States (Meghalaya, Tripura, Assam, Mizoram, Manipur, Sikkim), Western State (Maharashtra), Southern State (Andhra Pradesh) and Central States (Madhya Pradesh, Chhattisgarh) compared to the others (Fig. 3).

Percentage distribution of death from malaria during the years 1997, 2000 and 2001 revealed significant fall in the majority of the states except the North-Eastern States (Fig. 4).

The development of drug resistance has further intensified the problem. Vector resistance, inadequate control programs are the other factors for the resurgence.

Endemicity of malarial infection depends on parasite density. Areas may be defined as hypoendemic, meso-endemic, hyperendemic or holoendemic when the parasitemia rate is 10%, 11–50%, 51–75% or more than 75%, respectively.

### PATHOLOGY

The infected erythrocytes become irregular, rigid and antigenic. The hemoglobin (Hb) is consumed and degraded by the growing parasite. The red cell membrane becomes sticky due to an adhesive protein. This phenomenon of cytoadherence and resetting is significant in *P. falciparum* infection. This results in sequestration of red cells in vital organs where this interferes the microcirculation and metabolism. Immunity is impaired during the second and third trimesters of pregnancy. This results in high infection rate. Due to the same reason severity of infections and complications are more.

Spleen removes both the parasitized and uninfected red cells by immunologic and filtrative function.

### Immunology

The mechanism of complex cellular and humoral immunity is not clearly understood. Immunoglobulin G (IgG) antibody is protective. Both humoral and cell-mediated immunities are developed with plasmodial infection. Unfortunately such
**Fig. 3:** Statewise *Plasmodium falciparum* percentage (PF%) in 2000 and 2001

**Fig. 4:** Percentage distribution of death from malaria during 1997, 2000 and 2001
immunity lasts for only a short period. Passively transferred IgG from mother to neonate confers relative protection against malaria in the first few months of life. Primiparous women are more susceptible to infections than the multiparous, especially with *P. falciparum* malaria. Placental parasitemia is common (20–60%). But congenital malaria occurs which is less than 5% of newborns.

Maternal intravenous (IV) infection and/or tuberculosis, cause intense parasitization of the placenta with sequestration of parasitized erythrocytes in the placental circulation. High parasite density increases the risk of congenital malaria.

**Diagnosis**

The typical paroxysms of fever occur every 48 hours for *P. vivax* and *P. ovale*, every 36–48 hours for *P. falciparum* and every 72 hours for *P. malariae*. Fever is due to release of Hb, merozoites, malaria pigments, toxic cellular debris and various cytokines. Demonstration of asexual forms of the parasite in the peripheral blood smears (thick and thin film) by Romanovsky staining is diagnostic. Both the parasites and a minimum of 200 white cells should be counted. Card tests for the detection of specific antibody have been introduced currently. Fluorescent microscopy, polymerase chain reaction (PCR)-based detection of *plasmodium* deoxyribonucleic acid (DNA) in the blood are also being used. Unfortunately negative blood film does not rule out malaria infection.

**Effects of Malaria on Pregnancy**

In hyperendemic (51–75%) and holoendemic (> 75%) areas, pregnancy complications are increased specially with *P. falciparum* malaria. Complications involve both the mother and the fetus. *Maternal complications* are high due to increased severity of the disease as compared to a nonpregnant state. *Maternal morbidity and mortality* are directly related to the degree of vital organ dysfunction and the proportion of infected erythrocytes. Mortality rises significantly when 3% or more erythrocytes are infected.

**IMPORTANT MATERNAL AND FETAL COMPLICATIONS**

Pregnancy complications are directly related to the type and degree of parasitemia. Infection in early months often ends in miscarriage. Preterm labor and prematurity are well-known complications.

Low birthweight baby is seen more specially when mother suffers from anemia and other complications. Severe parasitization may even cause fetal death. Maternal human immunodeficiency virus (HIV) and/or tuberculosis predisposes to higher rate of fetal complications. At times mother may remain asymptomatic due to sequestration of parasitized erythrocytes in the placental microcirculation. Fetal growth restriction is more with falciparum infection as compared to vivax. During labor, fetal distress is often observed.

Diagnosis of congenital and neonatal malaria is often difficult. Clinical manifestations are rare before 3 weeks. Maternal antibodies offer protection to the neonate, and may delay the onset of clinical manifestations and diagnosis. The major maternal complications are:

- **Anemia and other hematological changes:** Anemia is the major maternal complication in pregnancy. Anemia is usually normochromic and normocytic type. It is due to accelerated red cell destruction, and also removal by spleen. There is associated ineffective erythropoiesis due to bone marrow suppression. Drug resistant cases develop severe anemia due to repeated or continued infection. There is thrombocytopenia and reduced antithrombin III level. Blood coagulation parameters are altered specially in severe cases.

- **Hypoglycemia:** It is a significant problem in pregnant women. It is due to increased glucose consumption both by the host and the parasite. There is also decreased hepatic gluconeogenesis and increased pancreatic insulin secretion by the drugs used (quinine). Hypoglycemia (plasma glucose < 40 mg/dL) is a poor prognostic indicator.

- **Metabolic acidosis (lactic acidemia):** It is due to anaerobic glycolysis. It is often associated with hypoglycemia. Arterial pH less than 7.25 with venous lactate level greater than 15 mmol/L indicates severe metabolic abnormality.

- **Convulsions and/or coma:** They are commonly observed in cerebral malaria. Falciparum malaria carries a high mortality rate (20%), unless promptly detected and treated. Associated complications like hypoglycemia, severe anemia, encephalopathy worsen the outcome.

- **Pulmonary edema and acute respiratory distress syndrome:** They are observed specially with falciparum malaria. However, it may be observed in cases with vivax malaria also. Ethiopathogenesis of such noncardiogenic pulmonary edema is not well-understood. Decreased pulmonary compliance, severe hypoxemia is associated with diffuse pulmonary infiltrates on chest radiograph. Reduction in surfactant synthesis due to damage of type II pneumocytes and alveolar protein exudates are the important patholoogy. The patient needs mechanical ventilatory support besides the treatment of malaria.

- **Renal failure:** It is due to block of renal microcirculation by sequestrated erythrocytes. This is common with severe falciparum infection. Acute tubular necrosis is the pathology. Cortical necrosis is not observed. Renal failure is associated with high maternal mortality. Early diagnosis and dialysis improves the outcome.

- **Jaundice (hepatic dysfunction):** Mild jaundice is common due to hemolysis. Jaundice may be severe with falciparum infection. Excessive hemolysis, hepatic cell damage and
choleretic agents. Choleretic agents increase the bile flow, thereby promoting the elimination of bilirubin and biliverdin. They are used to treat obstructive jaundice, where biliary flow is impaired due to obstruction of the biliary ducts.

- **Others**: Other types of choleretic agents include the bile acid sequestrants, which bind bile acids in the gastrointestinal tract and reduce their absorption, thereby increasing their excretion in the feces. Examples include cholestyramine and colestipol.

In the context of malaria, the treatment and prevention strategies are crucial.SECTION

**EFFECTS OF PREGNANCY ON MALARIA**

- Risk of infection is high due to immunocompromised state.
- Frequency of infection is high, especially in the second or third trimester.
- Severity of infection is high, especially in primigravida.
- Complications are high.

**MANAGEMENT**

**Prevention** is directed for improvement of sanitation and initiation of control programs with infrastructure. Personal protection is obtained with the use of repellants and bed nets. Strategies have been adopted by WHO, United Nations Children’s Fund (UNICEF), United Nations Development Programme (UNDP), World Bank, Government of India (1998) against malarial infection. These include:

- Intensity of malaria control activities in “high-risk areas”
- Early case detection and treatment
- Personal protection and community participation
- Vector control.
- High-risk area is defined where:
  - Slide positivity
  - Slide falciparum rate is 30% with SPR of 3%
  - Area with chloroquine-resistant falciparum infection.

Revised strategy subsequently has been recommended by WHO (2000). These include:

- Presumptive diagnosis of malaria and to institute treatment
- Radical treatment of malaria
- Mass chemoprophylaxis where annual parasite index (API) is more than 5
- To institute antenatal chemoprophylaxis
- Consideration of multidrug therapy for patients with HIV/acquired immunodeficiency syndrome (AIDS) and/or tuberculosis to minimize drug resistance.

Mass chemoprophylaxis in children and in pregnant women is not recommended universally. There are several reasons from this. It is not possible to achieve complete suppression of infection. Secondly, it interferes with the development of immunological defense of the individual. Lastly, it causes development of drug resistance. Drug hazards are not uncommon when used on a long-term basis, especially during pregnancy. These strengthen the importance of personal protection.

**Chemoprophylaxis**: Pregnant women residing or traveling in endemic (malarious) areas should receive prophylaxis with chloroquine or proguanil. Chloroquine (300 mg base) is given orally once a week. This is considered safe and is well-tolerated in pregnancy. Proguanil 200 mg/day is also used as an alternative. Folic acid 5 mg/day should be given when proguanil is used.

Mefloquine (15 mg/kg as single dose) is being used in many countries as it is found effective against multidrug-resistant falciparum malaria. It is reasonably well-tolerated. But its safety in pregnancy is yet to be determined. Studies in Africa mefloquine prophylaxis found effective and safe during pregnancy. One study from Thailand revealed its use was associated with an increased risk of stillbirth. The manufacturer advises that prophylaxis with mefloquine should be avoided. Though most of the studies in pregnancy including its use in the first trimester revealed no evidence of harm.

Travelers should start antimalarial drug at least 1 week before departure to achieve the desired therapeutic antimalarial blood concentration. The chemoprophylaxis should continue for another 4 weeks after leaving the endemic area.

In sub-Saharan Africa, severe anemia in pregnancy due to malaria is common. A trial in Kenya showed intermittent treatment with sulfadoxine-pyrimethamine during pregnancy reduced the severe anemia by nearly 40% and halved the incidence of low birthweight.

**TREATMENT**

Not all the antimalarial drugs are safe in pregnancy. Drug selection depends upon the severity of infection (parasite density) and the drug sensitivity of the parasite. Parenteral antimalarial therapy is needed in a case with severe and/or complicated malaria. Because of resistance, chloroquine may not be effective. Drugs and dosage of commonly used antimalarials in pregnancy are given in Table 2.

Drugs not used (contraindicated) or used with limited experience in pregnancy are: doxycycline, artemisinin (artemether, artesunate), pyrimethamine, halofantrine, atovaquone, maloprim and mefloquine. Proguanil with atovaquone: Proguanil with atovaquone are recommended for treatment of falciparum malaria when other antimalarial drugs are found resistant. For the use in pregnancy, no information is available. Manufacturer’s advice is to avoid unless potential benefits outweigh the risks.

For eradication therapy, primaquine is the recommended drug. But it is contraindicated in pregnancy and in glucose-6-phosphate dehydrogenase deficiency.

Patients with severe anemia in pregnancy need blood transfusion. Those with hematocrit less than 20 should be given packed cell transfusion or exchange transfusion. Folic acid supplementation should be continued. Associated complications should be managed appropriately with careful monitoring of the patient. Intensive care monitoring is needed for patients with acute respiratory distress syndrome.
Malaria in Pregnancy

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(ARDS), renal failure, metabolic acidosis of hepatic dysfunction.

Hyperpyrexia needs immediate care with ice sponging, antipyretic (paracetamol), specific drug therapy and maintenance of fluid balance. Fluid balance and blood glucose should be monitored at a regular interval. Convulsions should be aggressively treated. Lumbar puncture and examination of the cerebrospinal fluid should be done when the patient remain unconscious for a prolonged period.

Poor Prognostic Indicators

Clinical Features

Features of severe falciparum malaria

Laboratory Findings

- Hyperparasitemia level (> 5%)
- Severe anemia (Hb < 7 gm/dL)
- Hypoglycemia (< 40 mg/dL)
- Acute respiratory distress
- Elevated total bilirubin (> 50 mmol/L)
- Acidosis (arterial pH < 7.3)
- Raised serum creatinine (> 265 mmol/L)

Immunology, host response and vaccines: Pregnancy is not a state of immunodeficiency, but is a state of altered immune function. The major changes observed are a modulation away from cell-mediated immunity to humoral or antibody-mediated immunity. T helper 1 cells and natural killer cells decline whereas T helper 2 cells increase. Clinically the decrease in cellular immunity leads to the increased susceptibility to intracellular pathogens like malaria.

Both humoral (IgG, IgM and IgA) and cellular immunity can protect malarial infection. But mechanism is not well-understood. Genetic disorders (Hb A/S) confer protection because of low oxygen tension. Antibodies to parasitic antigens prevent parasitic multiplication. The protein PEMPI is an important antigen of falciparum malaria. Unfortunately parasite-strain diversity, lack of correlation between level of antibodies and clinical response made the progress of vaccine development slow.

ACKNOWLEDGMENTS

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Thrombophilia in Pregnancy

INTRODUCTION

Hemostatic Changes in Pregnancy (Table 1)

During pregnancy, there is a marked increase in the procoagulant activity and concomitant decrease in anticoagulant activity.

Pregnancy itself can be considered as an acquired thrombophilic state. Even though procoagulant activity is increased during pregnancy, very efficient balance is maintained between clot formation and clot breakdown. Pregnant woman is 4–10 times more prone to develop intravascular thrombosis as compared to nonpregnant, in presence of some triggering factors such as:

- Immobilization after a major surgery
- Obesity
- Presence of congenital or acquired thrombophilias.

THROMBOPHILIA

Thrombophilias refers to disorders which are associated with persistent hypercoagulable state and a tendency towards thrombosis. Thrombophilia is of two types:

1. Inherited thrombophilia
2. Acquired thrombophilia

Most thrombophilias are inherited, though some can develop later in life.

Risk Factors for Thrombosis

They can be acquired or inherited.

Inherited Risk Factors

The inherited causes for thrombosis are enumerated in Table 2.

Acquired Risk Factors

- Antiphospholipid syndrome
- Hyperhomocysteinemia due to B₁₂, B₆, or folate deficiency.

Etiopathogenesis

Of the different risk factors, in the inherited group the most common are:

- Factor V Leiden: Incidence of 5.9%
- Prothrombin mutation: Incidence of 2.3%

Both are inherited in an autosomal dominant pattern, meaning that an affected person needs to inherit the gene

Table 1: Hemostatic changes in pregnancy

<table>
<thead>
<tr>
<th>Procoagulant factors are increased</th>
<th>Anticoagulant factors are decreased</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factors VII, X, VIII, von- Willebrand factor, fibrinogen prothrombin fragment (PF1+2)</td>
<td>Protein S, acquired activated protein C resistance (APCR), placental production of plasminogen activator inhibitor type 2 (PAI-2)</td>
</tr>
</tbody>
</table>

Table 2: Inherited causes for thrombosis

- Factor V Leiden
- Protein C deficiency
- Protein S deficiency
- Activated protein C resistance (APCR)
- Antithrombin deficiency
- Prothrombin 20210 mutation (elevated prothrombin level)
- Hyperhomocysteinemia [cytosine 677 thiamine (C-677T) methyl-ene tetrahydrofolate reductase (MTHFR) mutation]
from only one parent. Each child of an affected parent has a 50% chance of inheriting the thrombophilia.

Factor V Leiden: Heterozygosity for factor V Leiden mutation is responsible for venous thromboembolism in about 20–30% of women. When guanine is substituted for adenine at position 506 in factor V polypeptide then it is called as factor V Leiden. Resistance to activated protein C (APC) caused by factor V Leiden is responsible for increased risk of venous thrombosis.1,2

Prothrombin mutation: Recently described guanine 20210 adenine (G20210A) mutation in prothrombin is associated with higher plasma prothrombin concentrations and increased risk for venous thromboembolism.3

Hyperhomocysteinemia: It could be inherited or acquired. Mutation in MTHFR (C-677T) results in decreased synthesis of 5-methyltetrahydrofolate, which is primary methyl (CH₃) donor in conversion of homocysteine to methionine. On account of this homocysteine concentration is increased, which is a risk factor for thrombosis.4 About 3% of patients with intravascular thrombosis may have deficiency of protein S, protein C and antithrombin.5

MECHANISM OF CLOTTING DISORDERS DUE TO INHERITED DEFECTS

Antithrombin Deficiency

Antithrombin III deficiency is a heterogeneous disorder inherited in an autosomal dominant mode.

Antithrombin III is a naturally occurring anticoagulant. It is a serine protease inhibitor. It is a major physiological inhibitor of thrombin and factor IXa, Xa, Xla and XIIa. Its deficiency is responsible for increase in fibrin formation. In 70% of women, it causes vascular thrombosis during pregnancy or puerperium.

The frequency of symptomatic antithrombin deficiency in general population has been estimated to be 1:600 to 1:5,000. In all women with vascular thromboembolism (VTE), antithrombin III deficiency is detected in about 1%.6

Preston et al. in 1996 reported the highest risk of miscarriage and 5.2-fold increase in stillbirth rate in cases with antithrombin III deficiency.

Protein C Deficiency

Protein C is naturally occurring anticoagulant which gets activated by conversion to an active serine protease called APC.

In presence of protein S, it can inactivate factors V and VIII.

Prevalence of protein C deficiency in general population is 1 : 200 to 1 : 300 (Flow chart 1).

Data from European Prospective Cohort on Thrombophilia (EPCOT) study showed the modest increase in the risk of stillbirth among women with protein C and protein S deficiencies. There is not much difference in the risk of abortions as compared to control group.

Activated Protein C Resistance (Factor V Leiden)

Activated protein C deficiency was described in year 1993. In some cases production of APC is adequate, but due to presence of factor V Leiden, there is resistance to its anticoagulant effect.

Factor V Leiden mutation is frequent in 3–7% of healthy white population but it appears to be far less prevalent or even nonexistent in Asian population. In various studies, APCR was found in a wide range (10–64%) of patients with venous thromboembolism. There are controversial reports regarding the increased risk of recur rent fetal loss in pregnant women with factor V Leiden mutation. The EPCOT study revealed hardly any change in the risk of abortions and stillbirth. Study carried out by Rai et al. and Grandone et al.7,8 revealed significant increase in prevalence of recurrent pregnancy loss. In a nonpregnant population, 90–95% cases of APCR are associated with factor V Leiden mutation. Rest of the 5% can be attributed to more recently described mutation—factor V Cambridge mutation. This is the mutation occurring at 306 APC cleavage site. During pregnancy, resistance to APC increases as pregnancy advances.

Prothrombin Gene Mutation

The substitution of guanine for adenine at nucleotide 20210 of the prothrombin gene has been associated with elevated plasma levels of prothrombin and increased risk of venous thrombosis. Prothrombin gene mutation is found in 2% of the population worldwide. This risk is the second common genetic factor for venous thrombosis in certain white population. In 6–18% of patients with venous thromboembolism, prothrombin gene mutation is the causative factor.9

Protein S Deficiency

It goes hand in hand with APC deficiency causing loss of fibrin generation. Its prevalence among patients of venous thromboembolism is about 1–2%.
Hyperhomocysteinemia

Homocysteine is derived from dietary methionine and its plasma level during pregnancy is very low. In non-gravid stage, it is 5–15 µmol/L. Hyperhomocysteinemia causes:
- Increased production of reactive oxygen species (ROS) with increase lipid peroxidation.
- Glutathione peroxidase enzyme activity is suppressed; thus, detoxification of lipid peroxide cannot be adequate.
- It suppresses nitric oxide (NO) production by endothelial cells by stimulating increased production of asymmetric dimethyl arginine.
- It increases concentration of free oxygen radicals, thus decreasing the bioavailability of NO.
Due to these effects, there is vasoconstriction and intravascular thrombosis.10

Postimplantation Effect
- There is accumulation of lipid-laden macrophages in the intima of spiral and decidual arteries along with fibroblastic proliferation and fibrinoid necrosis of the media, causing uteroplacental insufficiency.
- Recent studies have suggested that APLA may reduce annexin V on the surface of placental villi which have antithrombotic factor.13 Reduction of annexin V promotes thrombosis in the intervillous space leading to placental insufficiency. Elevated levels of APLA are associated with recurrent abortions,14,15 as well as pregnancy-induced hypertension (PIH), intrauterine growth restriction (IUGR), intrauterine death (IUD) and abruptio placentae. However other investigators such as Simpson et al. recently challenged the role of APLA as main causative factor in abortion.16,17
The risk of thrombosis in otherwise healthy individuals with APLA appears to be very low. As per the APLA titer women are classified as:
- Negative: Less than 10 immunoglobulin G phospholipid units (GPL) units
- Low positive: 10–20 GPL units
- Moderate positive: 20–100 GPL units
- Strong positive: Greater than 100 GPL units.

Hyperhomocysteinemia

This could be acquired due to dietary deficiency of B₁₂, B₆, folic acid which act as cofactors in the conversion of homocysteine to methionine.
There are clinical and experimental evidences suggestive of an association between hyperhomocysteinemia and arterial thrombosis.

Placental Pathology Associated with Thrombophilias and Pregnancy Complications

In normal pregnancy, there is high volume and low pressure intervillous blood flow. This is because of trophoblastic invasion in spiral and radial arteries replacing intima and media. This is regulated to some extent by the balance between plasminogen activators and inactivators.
Even though pregnancy is a hypercoagulable state, thrombosis in the intervillous space is prevented by anticoagulants such as protein S, protein C and surface annexin V due to which placental perfusion is maintained.
Due to activation of coagulation cascade (Flow chart 2), fibrin deposition has been seen on the chorionic villi. Endothelial cells in these areas appear to be deficient in the production of anticoagulant factor such as plasminogen activator inhibitor type 1 (PAI-1), causing intravascular microthrombi and placental infarcts.

ACQUIRED THROMBOPHILIA

The most common causes of acquired thrombophilia, which have adverse effect on pregnancy, are:
- Antiphospholipid antibody (APLA) syndrome
- Acquired hyperhomocysteinemia

Antiphospholipid Antibody Syndrome

Antiphospholipid antibodies are heterogeneous group of antibodies directed against negatively charged phospholipids. The most common antibodies are anticardiolipin antibodies, lupus anticoagulant, antibodies to phosphatidylserine, etc. Relation between APLA and recurrent pregnancy loss has been recognized for the past 2 decades. It is the most acceptable and treatable cause of recurrent pregnancy loss.

Action on Endothelium

Antiphospholipid antibodies generate hypercoagulable state by activating endothelial cells for production of endothelial cell adhesion molecule 1 (ECAM-1)/vascular cell adhesion molecule 1 (VCAM-1). Due to its glue-like action, aggregations of the platelets occur. So the production of thromboxane A₂ (TXA₂) is increased thus leading to vasoconstriction and intravascular thrombosis. It also inhibits the production and impairs fibrinolytic response of protein C, protein S and antithrombin III.

Implantation Loss

Cytotrophoblastic cells express phosphatidylserine on their surface. Antibodies against it prevent differentiation of syncytiotrophoblast and cytrophoblast along with cell injury and death of the embryo.
Many et al.\textsuperscript{18} carried out study on placental findings in women who had thrombophilia and severe pregnancy complications with a group of women having pregnancy complications without thrombophilia. In the first group, large number of placentae showed villous infarcts, fibrinoid necrosis as compared to second group. However, reports of Mousa et al.\textsuperscript{19} quoted no such difference in very similar designed study.

Arias et al.\textsuperscript{20} evaluated 13 women with obstetric complications having thrombotic lesions of the placenta. In 10 out of 13 women (77\%) inherited thrombophilias was detected.

**CLINICAL PRESENTATION**

**Thrombophilia Associated Pregnancy Wastage**

Successful outcome of pregnancy is dependent on the development of adequate placental circulation. Intervillous or spiral artery thrombosis and inadequate placental perfusion due to inherited or acquired thrombophilia may result in various gestational pathologies (Table 3) such as:

- Implantation failure
- Abortions
- Preeclampsia with early onset

- Intrauterine growth restriction
- Intrauterine death
- Abruptio placentae
- Vascular thromboembolism
- Deep vein thrombosis (DVT)

The frequent pathological findings of infarction and utero placenta thrombosis in placentae from pregnancy complicated by fetal growth restriction (FGR), fetal loss, abruptio placentae, preeclampsia suggest strong relationship between inherited thrombophilia and pregnancy complications. Majority of the complications are because of abnormal placental vasculature.\textsuperscript{21-23}

Dekker et al.\textsuperscript{24} tested women with severe preeclampsia for presence of inherited and acquired thrombophilias. A high
rate of protein S deficiency, APC, hyperhomocysteinemia and antiodioplin antibodies was found.

Dizon-Townson et al.25 and Nagy et al.26 described higher prevalence of factor V Leiden mutation in women with severe preecclampsia as compared to the control. Rajkovic et al.27 reported that homocysteine levels were doubled in 20 women with preecclampsia as compared to normotensive women (n=19).

Recent meta-analysis28 suggested association of factor V Leiden mutation, hyperhomocysteinemia, deficiency of protein S, protein C and antithrombin III only with severe preecclampsia. The association between placental abruption and thrombophilia has been demonstrated in several studies. Alfrevic et al.29 found that there was significant relationship between placental abruption and factor V Leiden mutation.

European prospective cohort on thrombophilia study report revealed that the risk of fetal loss was 1.3 times greater in women with thrombophilia than in a woman without thrombophilia.

De Vries et al.30 studied 62 women with thrombophilia. Of them 31 women had abruptio placentae, 18 had intrauterine growth restriction and fetal demise (IUFD), 13 had IUFD. Of the 13 cases of IUFD, hyperhomocysteinemia was present in 38%, protein S deficiency in 23% and factor V Leiden mutation in 12.5%.

Several studies have reported that early fetal loss in women with APL syndrome is in the range of 50–70%. Of all inherited thrombophilias, many reports find high prevalence of factor V Leiden mutations and recurrent fetal loss.

Methylenetetrahydrofolate reductase or prothrombin mutations were not very common in women with fetal loss.

**Congenital Thrombophilia and Maternal Venous Thromboembolism**

Risk of VTE in pregnancy is approximately 6 times greater than in nonpregnant women. It is a major cause of death among women during pregnancy and puerperium.

Recently, Gerhardt et al.31 described the prevalence of congenital thrombophilia in 352 women, 119 of them had VTE during or immediately after delivery. In the prevalence of factor V Leiden mutation was 43.7% compared to only 7.7% in control group. Prevalence of prothrombin gene mutation was seen in 16.4% and mixed risk factors were in 9.3% of the cases.

There was no association seen in MTHFR mutation with venous thromboembolism.

**Which Pregnant Women Should be Tested for Thrombophilias?**

Thrombophilia, inherited or acquired is not an uncommon condition. At present, there is no evidence to support routine screening of all pregnant women for thrombophilias. Women with recurrent abortions, with history of stillbirths, early onset of severe preeclampsias, placental abruption, unexplained IUGR should to be tested. Testing should be done before pregnancy is planned or initiated.

All women with past history of DVT or VTE or family history of VTE, stroke, etc. should be tested. About 50% of such women will have thrombophilia.

**Laboratory Investigations**

- Antiphospholipid antibodies—immunoglobulin (Ig) M, IgG, IgA
- Lupus anticoagulant antibody
- Factor V Leiden mutation [deoxyribonucleic acid (DNA) test by polymerase chain reaction (PCR)]
- Hyperhomocysteinemia MTHFR mutation (DNA test by PCR)
- Prothrombin gene mutation G20210A (DNA test by PCR)
- Protein C levels
- Protein S levels
- Activated protein S activity
- Activated partial thromboplastin time (APTT)
- Prothrombin time (PT)
- Partial thromboplastin time (PTT)

**TREATMENT**

There are no clear cut control trials to guide us as to how to manage women with thrombophilia and thus prevent placental thrombosis and severe pregnancy complications. Generally, treatment is not recommended for most pregnant women who are of less severe thrombophilic group such as having factor V Leiden or prothrombin mutation. If there is no history of pregnancy complications or VTE in the past, the risk of development of complications in current pregnancy due to thrombophilia appears to be less than 1% in these women.

Before deciding line of treatment it is essential to know the severity of thrombophilia, as the risk of pregnancy complications are different with the different types. For example the risk of pregnancy associated VTE is higher in women with antithrombin III deficiencies than with the abnormalities of protein C and protein S systems. Previously, unfractionated heparin was used for the treatment of thrombophilia. But nowadays low-molecular-weight heparins (LMWHs) have proved to be more beneficial during pregnancy (Table 4). Before starting the treatment assessment of platele count is mandatory in all cases. Further measurement is done a week after commencing the treatment and thereafter at monthly intervals.

**Thromboprophylaxis**

Women with thrombophilia who have had DVT or VTE in the past should receive prophylactic anticoagulation therapy throughout pregnancy and 4–6 weeks postpartum (Table 4).
Thrombophilia and Preeclampsia

The association of preeclampsia and thrombophilia is also controversial. To date, there are no placebo-controlled trials on prevention of preeclampsia at subsequent gestation with LMWH.

Recently, the Cochrane collaboration35 reported a 15% reduction in the risk of preeclampsia and 14% reduction in the fetal and neonatal deaths with thromboprophylaxis.

Kupferminc et al.36 reported on the use of LMWH in women having thrombophilia with past history of severe preeclampsia, abruptio placentae, IUGR or IUFD (n = 33). They were treated with enoxaparin 40 mg/day and 100 mg aspirin starting from 8 weeks to 12 weeks of gestation. Majority of patients in the study group delivered at the end of 37.6 ± 2–3 weeks whereas patients in other group who had not received thromboprophylaxis delivered at 31 ± 2 weeks. Mean birth weight of the infants in study group was 2,719 ± 526 g whereas in control group it was 1,175 ± 590 g.

Of the 33 women from study group, only three women had preeclampsia in current pregnancy.

Riyazi et al.37 observed no much difference in treated and control group. Acute DVT and VTE in pregnancy with or without thrombophilia is usually treated with full dose of intravenous (IV) heparin for 5–10 days followed by maintenance with subcutaneous (SC) heparin given twice daily, adjusted to prolong the aPTT into the therapeutic range.

Therapeutic Regimens in Patient with APLA Syndrome

Current focus of therapeutic modalities deals with the relative role of heparin compared with aspirin.

A recent study demonstrated an increase in the success rate of pregnancy outcome from 19% to 70% with aspirin therapy.38

The reason as to why some women with APLA respond only to aspirin and others to anticoagulants is still unknown.

Rai et al. (1997)39 reported decrease in the rate of recurrent fetal death to 20.9% when women were treated with aspirin 75 mg plus LMWH enoxaparin 40 mg SC once daily.

During Labor

It is essential to omit the anticoagulant dose at the onset of labor. If the labor is to be induced, then the morning dose should be omitted. Prophylactic dose can be started 6 hours after delivery. In absence of any obstetric indication, vaginal birth is the preferred mode of delivery. There is increased risk of hematoma seen with epidural anesthesia.

During Puerperium

Thromboprophylaxis should be continued for 6 weeks after delivery. In some cases, we may have to continue for 3 months.

<table>
<thead>
<tr>
<th>Table 4: Dosage schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low-molecular-weight heparin (LMWH)</strong></td>
</tr>
<tr>
<td>• Dalteparin (fragmin)</td>
</tr>
<tr>
<td>• Enoxaparin (Clexane)</td>
</tr>
<tr>
<td>• Tinzaparin (innohep)</td>
</tr>
</tbody>
</table>

For women with protein C and protein S deficiencies or with factor V Leiden having history of VTE in previous pregnancies, anticoagulant prophylaxis with LMWH should be started 4–6 weeks prior to that period of gestation at which the previous incidence occurred. There are no guidelines for anticoagulant prophylaxis with hyperhomocysteinemia. Vitamin B<sub>12</sub>, B<sub>6</sub>, and folic acid supplementation can bring down the homocysteine level, but it is not sure whether it reduces the risk of thrombosis.32

**Thrombophilia and Recurrent Pregnancy Loss**

Data on treatment of women with inherited thrombophilia and pregnancy loss are predominantly uncontrolled and include small series of patients treated mostly with LMWH. A recent collaborative study demonstrated the safety of using LMWH during 486 gestations.33

A successful outcome was reported in 89% of 93 gestations in women with history of recurrent pregnancy loss and in 28 gestations in women who had preeclampsia in previous pregnancy.

Carp et al.34 reported a cohort study undertaken to assess the effect of enoxaparin on subsequent livebirth rates in women with three or more consecutive abortions and hereditary thrombophilia. Livebirth rate in treated group was 26/37 (70.2%) compared to 21/48 (43.8%) in untreated group.

According to different studies, patients with history of recurrent fetal loss should receive prophylactic dose of LMWH in subsequent pregnancy (enoxaparin 0.5 mg/kg or dalteparin 5,000 U) immediately once pregnancy is diagnosed and should continue throughout pregnancy and 6 weeks after delivery.

**Thrombophilia and IUGR**

The association of IUGR and thrombophilia is controversial. Association was demonstrated in women with severe IUGR and not with mild. Data on antithrombotic prophylaxis for IUGR at index pregnancy and on subsequent gestations is limited. However, in view of the risk of recurrence of IUGR with other gestational complications, prophylaxis can be considered.
Thrombophilia in Pregnancy

FUTURE PERSPECTIVES

There are number of issues in the field of thrombophilia which cannot be explained. Even though many tests are available for detection of thrombophilia, in 30–50% of cases the cause for intravascular thrombosis cannot be detected. Whether other genetic or acquired thrombophilia play a role remains to be determined. Complete thrombophilia work-up is costly. Pathogenetic mechanisms responsible for placental vascular pathologies in women with thrombophilia have not been elucidated and it is yet unknown as to why certain women with thrombophilia express vascular gestational pathologies while others do not.

Large prospective trails of antithrombotic modalities are essential to improve the results in women who experience poor pregnancy outcome.

SUMMARY

- Treatment is not recommended in pregnant women having less severe thrombophilia without pregnancy complications in the past.
- Severity of the thrombophilia must be decided.
- Pregnant women with factor V Leiden or prothrombin mutation with history of DVT or VTE must receive thromboprophylaxis.
- Low-molecular-weight heparin is recommended throughout pregnancy and in the postpartum period, in women with severe thrombophilia, (antithrombin III deficiency) or having more than one deficiency even if they had no pregnancy complications or VTE in the past.
- Women with thrombophilia with recurrent pregnancy complications should be treated. Women with APLA syndrome with pregnancy complications are best treated with LMWH plus low-dose aspirin which is more effective than either medication alone, in preventing pregnancy complications.
- Women with mild hyperhomocysteinemia usually respond well to vitamin B<sub>6</sub> and B<sub>12</sub> supplementation. It has been observed that these women may not have the risk of intravascular thrombosis but they may be at an increased risk of pregnancy complications.

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INTRODUCTION

Physiologic changes occurring in pregnancy involve nearly every organ system, and the kidneys are no exception. This chapter focuses not only on renal diseases that occur in pregnancy but also on how pregnancy affects chronic renal diseases. Patients with end-stage renal disease (ESRD) requiring renal replacement therapy and patients after renal transplantation pose additional interesting scenarios and possible complications. It is important to ask two questions in the setting of pregnancy and renal disease: How does pregnancy affect kidney disease? How does kidney disease affect pregnancy?

Anatomical Changes in Renal System during Pregnancy

A dilatation of the ureters and pelvis occurs and is presumed to be secondary to the smooth muscle-relaxing effect of progesterone. This dilatation is often more pronounced on the right secondary to dextrorotation of the uterus and dilatation of the right ovarian venous plexus. This can lead to urinary stasis and as discussed later, an increased risk of developing urinary tract infections (UTIs).

There is also an increase in overall kidney size by about 1–1.5 cm.

Physiological Changes in Renal System during Pregnancy

Renal plasma flow increases by 50–70% in pregnancy, and this change is most pronounced in the first two trimesters. This is one of the factors that lead to an increased glomerular filtration rate (GFR). The GFR peaks around the 13th week of pregnancy and can reach levels up to 150% of normal. Therefore, both blood urea nitrogen (BUN) and creatinine levels, the plasma markers of GFR, are decreased. This decrease has clinical significance in that a normal BUN or creatinine level in a pregnant female may actually indicate underlying renal disease.

Similarly, in the initial part of pregnancy, increased levels of progesterone enhance relaxation of the arterial smooth muscles and thus decrease peripheral vascular resistance. Therefore, a blood pressure fall of approximately 10 mm Hg occurs in the first 24 weeks of pregnancy. The blood pressure gradually returns to a prepregnancy level by term. Thus, a consistent normal or prepregnancy blood pressure may suggest the presence of a condition that predisposes patients to hypertension.

A change in tubular function with increased glucosuria also occurs. In addition, a reset in the osmostat occurs, resulting in increased thirst and decreased serum sodium levels (by approximately 5 mEq/L) compared with nonpregnant females.

Effects of progesterone also result in a state of mild respiratory alkalosis and a blood gas of 7.44/30 pCO₂/HCO₃ is representative.

RENAL DISEASE OCCURRING DURING PREGNANCY

Urinary Tract Infections

- Asymptomatic bacteriuria
- Cystitis
- Pyelonephritis

Urinary tract infections are the most common renal disease occurring during pregnancy and range from asymptomatic...
bacteriuria to pyelonephritis. UTIs have been associated with small for gestational age (SGA) babies, premature labor, and intrauterine fetal death.

Pregnant females are at increased risk for development of UTIs, primarily because of the anatomic and physiologic changes that occur in normal pregnancy. As mentioned previously, the collecting system is dilated during pregnancy, most likely secondary to the smooth muscle-relaxing properties of progesterone. This dilatation almost always resolves 2–4 days after delivery. In addition, increased vesicoureteral reflux occurs.

**ASYMPTOMATIC BACTERIURIA**

**Incidence**
- This affects 4–7% of pregnant women, of which up to 40% will develop symptomatic UTI in pregnancy of pregnant women, 2% develop pyelonephritis.
- Women who have a history of previous UTI and are found to have bacteriuria have a tenfold increased risk of developing cystitis or acute pyelonephritis in pregnancy.

**Pathogenesis**
- Seventy-five to ninety percent of bacteriuria in pregnancy is due to *Escherichia coli*, probably derived from the large bowel.
- Colonization of the urinary tract results from ascending infection from the perineum and is related to sexual intercourse.

**Diagnosis**
- Most women with asymptomatic bacteriuria are infected during early pregnancy. Very few subsequently acquire asymptomatic bacteriuria.
- Bacteriuria is only considered significant if the colony count exceeds 100,000/mL on a midstream urine (MSU) specimen.
- Urine culture resulting in a non-significant or mixed growth should be repeated on a fresh MSU specimen.
- Dipsticks for nitrites and leukocyte esterase may be used to help exclude UTI.

**Complications**
- Twenty-five percent develop symptomatic infection during pregnancy
- Increase risk of low birthweight infant
- Preterm delivery
- Pregnancy associated hypertension
- Anemia
- Pyelonephritis
- If bacteriuria that persists or recurs after delivery has been associated with pyelographic evidence of chronic infection, obstructive lesions and congenital abnormalities.

**Management**
- Because dilation of the upper renal tract during pregnancy increases the risk of pyelonephritis asymptomatic bacteriuria should be treated.
- Treating asymptomatic bacteriuria reduces the risk of preterm delivery and low birth weight babies.
- The choice of antibiotic depends on the sensitivities of the causative organism (Table 1).

**ACUTE CYSTITIS**

**Incidence**
Cystitis complicates about 1% of pregnancies.

**Clinical Features**
- These include urinary frequency, urgency, dysuria, hematuria, proteinuria and suprapubic pain.
- Urinary tract infection in pregnancy is more common in diabetics (both with pre-existing and gestational diabetes) and in those receiving systemic corticosteroids.

**Pathogenesis**
- Most infections are due to *E. coli*.
- Keep in mind that symptoms of cystitis and pyuria accompanied by a “sterile” urine culture finding may be the consequence of urethritis caused by *Chlamydia trachomatis*, a common pathogen of the genitourinary tract.
- Mucopurulent cervicitis usually coexists, and erythromycin therapy may be effective.

**Diagnosis**
- This is confirmed by the finding of significant bacteriuria (colony count exceeding 100,000/mL) following culture of a MSU specimen.
- Microscopy of the urine may reveal organisms, white cells and occasionally red cells, but the false-positive rate is very high, therefore it is no longer recommended for diagnosis of UTI.

**Management**
- Antibiotic therapy is guided by sensitivities of the organism. For organisms resistant to penicillins, cephalosporins, nitrofurantoin and trimethoprim; ciprofloxacin may be appropriate but this is not used as first-line therapy in pregnancy.
- Antibiotics should be continued for 5–7 days.
- Several non-pharmacological maneuvers may help prevent recurrent infection in those women troubled by UTIs in pregnancy. These include:
- Increasing fluid intake. This ensures frequent voiding and a high volume dilute urine, all of which reduce the risk of symptomatic infection.
- Emptying the bladder following sexual intercourse. This “washes away” organisms massaged up the urethra from the perineum into the bladder during coitus, before they have a chance to replicate in urine within the bladder.
- Double voiding (to ensure no residual urine is left in the bladder following micturition).
- The perineum should be cleaned from “front to back” following defecation to minimize the risk of bowel organisms colonizing the urethra.

**ACUTE PYELONEPHRITIS**

**Incidence**

- This complicates 1–2% of pregnancies.
- It is more common in pregnancy because of the physiological dilatation of the upper renal tract.

**Clinical Features**

- These include fever, loin and/or abdominal pain, vomiting, rigors as well as proteinuria, hematuria and concomitant features of cystitis.

**Table 1: Oral antimicrobial agents used for treatment of pregnant women with asymptomatic bacteriuria**

<table>
<thead>
<tr>
<th>1. Single dose treatment:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin 3 g</td>
</tr>
<tr>
<td>Ampicillin 2 g</td>
</tr>
<tr>
<td>Cephalosporin 2 g</td>
</tr>
<tr>
<td>Nitrofurantoin 200 mg</td>
</tr>
<tr>
<td>Trimethoprim sulfamethoxazole 320/1600 mg</td>
</tr>
<tr>
<td>2. Three-day course:</td>
</tr>
<tr>
<td>Amoxicillin 500 mg three times daily</td>
</tr>
<tr>
<td>Ampicillin 250 mg four times daily</td>
</tr>
<tr>
<td>Cephalosporin 250 mg four times daily</td>
</tr>
<tr>
<td>Ciprofloxacin 250 mg twice daily</td>
</tr>
<tr>
<td>Levofloxacin 250 mg daily</td>
</tr>
<tr>
<td>Nitrofurantoin 50–100 mg four times daily; 100 mg twice daily</td>
</tr>
<tr>
<td>Trimethoprim sulfamethoxazole 160/800 mg twice times daily</td>
</tr>
<tr>
<td>3. Others:</td>
</tr>
<tr>
<td>Nitrofurantoin 100 mg four times daily for 10 days</td>
</tr>
<tr>
<td>Nitrofurantoin 100 mg twice daily for 7 days</td>
</tr>
<tr>
<td>Nitrofurantoin 100 mg bed times for 10 days</td>
</tr>
<tr>
<td>4. Treatment failures: Nitrofurantoin 100 mg four times daily for 21 days</td>
</tr>
<tr>
<td>5. Suppression for bacterial persistence or recurrence: Nitrofurantoin 100 mg at bedtimes for remainder of pregnancy</td>
</tr>
</tbody>
</table>

**Risk Factors**

- Diabetes
- Steroid therapy
- Polycystic kidneys
- Congenital abnormalities of the renal tract e.g. duplex kidney or ureter
- Neuropathic bladder (e.g. in those with spina bifida or multiple sclerosis)
- Urinary tract calculi.

**Pathogenesis**

The most likely etiologic organisms include E. coli, Klebsiella, Enterobacter and Proteus species.

**Diagnosis**

- This is confirmed by the finding of significant bacteriuria following culture of a MSU specimen.
- Differential diagnosis includes pneumonia (especially right lower lobe), viral infections, cholecystitis and biliary colic, acute appendicitis, gastroenteritis, placental abruption and a degenerating uterine fibroid
- Investigation in women with fever should include blood cultures and a full blood count.

**Pregnancy**

- Acute pyelonephritis increases the risk of premature labor at least in part because of associated pyrexia.
- There is also evidence for an increased risk of low birthweight babies, but this is partly related to an increase in preterm delivery.

**Management**

- This should be undertaken in hospital.
- Once the diagnosis is suspected and a urine sample obtained, antibiotic treatment with appropriate intravenous (IV) antibiotics should begin immediately, before awaiting the results of urine culture or sensitivities.
- Intravenous penicillins or cephalosporins (e.g. Cefuroxime) are usually the first choice, although in the case of septicemia or resistant organisms or women who are allergic to both penicillins and cephalosporins, an aminoglycoside such as gentamicin may be used. There is a theoretical risk of fetal ototoxicity with the use of gentamicin in pregnancy, but provided drug levels are measured and kept within the therapeutic range, this should not be a problem encountered in clinical practice.
- Antibiotics should be given intravenously until the pyrexia settles when they may be changed to an appropriate oral formulation. Antibiotics should be continued for a period of at least 2 weeks.
- Renal function should be checked regularly since renal impairment may complicate acute pyelonephritis in pregnancy, especially, if there is associated sepsis.
Intravenous fluids may also be required, if the woman is volume depleted as a result of vomiting or sweating. An ultrasound examination of the kidneys should be undertaken to exclude hydronephrosis, congenital abnormalities and renal calculi.

**Prophylaxis**

- Women who usually take antibiotic prophylaxis against UTIs should continue this in pregnancy.
- Suitable regimes in pregnancy include low-dose amoxicillin or low-dose oral cephalosporins (cephalexin 250 mg), or nitrofurantoin 50 mg o.d. but depend on the sensitivities of the usual infecting organisms.

**ACUTE RENAL FAILURE**

Acute renal failure (ARF) in pregnancy follows a bimodal distribution. There are peaks in the first trimester (related to unregulated and/or septic abortion) and the late third trimester (related to obstetric complications). The incidence of ARF due to sepsis has fallen significantly in the last 30 years relative to the incidence secondary to obstetric complications (e.g. abruptio placentae, amniotic fluid embolism, postpartum hemorrhage).

Acute renal failure is conventionally and conveniently divided into three categories: (1) prerenal; (2) intrinsic (or “renal”); and (3) postrenal. Sepsis secondary to illegal abortion, while now less common in industrialized nations, is still a common cause of renal failure worldwide. Milder forms of ARF are observed in industrialized countries, and only about 1 case in 15,000 pregnancies requires dialysis.

**Prerenal**

Prerenal causes include the following hypovolemic states:
- Hemorrhage
- Volume depletion from gastrointestinal (GI) or renal losses, burns, fluid sequestration, or low cardiac output states (e.g. chronic heart failure and other diseases of myocardium, valvulopathy, arrhythmia, pericardial diseases, tamponade)
- Systemic vasodilation (e.g. sepsis, anaphylaxis)
- Disseminated intravascular coagulation.
- Sepsis from illegal abortions is often due to *Clostridium welchii*.

**Renal**

**Acute Tubular Necrosis**

- Acute tubular necrosis (ATN) is the most common pathologic finding for ARF in pregnancy.
- Acute tubular necrosis typically occurs after an acute ischemic or toxic event.
- Ischemic ATN is often considered to be a continuum of prerenal azotemia. Indeed, the causes of the two conditions are identical. In pregnancy, these causes are often related to hemorrhage, abruptio placentae, amniotic fluid embolism, and retained dead fetus.
- In addition, nephrotoxic medications are implicated. Remember that gentamicin is occasionally administered in pregnancy, especially in pyelonephritis.

**Cortical Necrosis**

- The presentation of cortical necrosis is similar to that of ATN and is differentiated only by arteriogram and/or biopsy. It was a common finding in ARF because of septic abortion.
- No specific treatment for cortical necrosis is available, so these tests may not be necessary other than for prognostic value.

**Thrombotic Microangiopathies**

- Both thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) can be seen in pregnancy. Incidence of HUS is actually increased in pregnancy, whereas TTP remains the same. Both of these microangiopathies need to be distinguished from hemolysis, elevated liver enzyme levels, and low platelet levels (HELLP) syndrome.
- Plasma exchange is required for both TTP and HUS.

**Postrenal**

- Postrenal causes, i.e. obstructions are rare but must be considered in all patients with ARF because of the ease of reversibility. Diagnosis, however, may be difficult.
- The collecting system undergoes a physiologic dilatation secondary to the smooth muscle-relaxing effects of progesterone. Therefore, ultrasound, which relies heavily on visualization of the dilated collecting system for the diagnosis of obstruction, may be difficult to interpret.
- Use of intravenous or retrograde pyelography may be necessary, realizing that this modality exposes the fetus to radiation.

**Dialysis Requiring Acute Renal Failure**

- Renal failure severe enough to warrant dialysis usually also warrants termination of pregnancy.
- If subacute and if the fetus is still viable, an early initiation (approximately BUN 50) is preferred to prevent uremic insult to the fetus.
- In an effort to prevent dialysis-related hypotension, frequent HD sessions (5–7 sessions/weeks) are scheduled.

**Pregnancy in Pre-existing Renal Disease**

Historically, pregnancy has been commonly regarded as very high-risk to the female with chronic renal disease. Attempts have been made to clarify these risks in the settings of chronic renal insufficiency, dialysis, and transplanted kidneys.
In general, patients receiving dialysis have a marked decrease in fertility, yet pregnancy occasionally occurs. Certainly, a return of fertility in transplant recipients is the rule. These transplant patients have other special considerations, including the use of immunosuppressive medications and the risk of opportunistic infections.

The following discussion addresses pregnancy as it affects patients with chronic renal insufficiency, those with ESRD requiring dialysis, and those who have received a renal transplant. Keep in mind the effects of pregnancy on kidneys and the effects of kidney disease on pregnancy.

CHRONIC RENAL INSUFFICIENCY

Effect of Pregnancy on Chronic Renal Disease

The risks include:
- Possible accelerated decline in renal function
- Escalating hypertension during pregnancy
- Worsening proteinuria during pregnancy.

Increased proteinuria is a physiological response to pregnancy and may not necessarily indicate superimposed preeclampsia or deteriorating renal disease.

Effect of Chronic Renal Disease on Pregnancy

The risks include:
- Miscarriage
- Preeclampsia
- Intrauterine growth restriction (IUGR)
- Preterm delivery
- Fetal death.

Factors Influencing Outcome

The outcome of pregnancy and any adverse effect on underlying renal disease are both influenced by:
- Presence and degree of renal impairment
- Presence and severity of hypertension
- Presence and degree of proteinuria
- Underlying type of chronic renal disease.

In general, women without hypertension or renal impairment prior to conception have successful pregnancies and pregnancy does not adversely influence the progression of the renal disease.

Specific Types of Renal Disease

Glomerulonephritis

- Most pregnancies are successful. Those with hypertension are at increased risk of superimposed preeclampsia.
- Fetal loss and preterm delivery rates are about 20%.
- Less than 10% have a reversible and 3% a progressive decrease in renal function related to pregnancy.
- Over 25% have a reversible and less than 10% have a permanent increase in blood pressure.
- In those with normal renal function at conception, pregnancy does not affect the course of renal disease or the occurrence of ESRD. Hypertension and proteinuria accelerate the rate of decline in renal function, whether or not a woman has been pregnant.

Table 2: Effect of pregnancy on renal impairment

<table>
<thead>
<tr>
<th>Degree of renal impairment</th>
<th>Mild (%)</th>
<th>Moderate (%)</th>
<th>Severe (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of function</td>
<td>2%</td>
<td>40–65%</td>
<td>75%</td>
</tr>
<tr>
<td>Postpartum deterioration</td>
<td>20–50%</td>
<td>60%</td>
<td></td>
</tr>
<tr>
<td>End-stage renal failure</td>
<td>2–33%</td>
<td>40%</td>
<td></td>
</tr>
</tbody>
</table>
Reflux Nephropathy
- This is one of the most common renal diseases in women of child-bearing age.
- About 25% of women develop preeclampsia and this risk is increased in cases of bilateral renal scarring.
- Even those with normal renal function and without hypertension prepregnancy are at increased risk of hypertension (33%) and preeclampsia (15%).
- Those with renal impairment may experience rapid worsening of renal function.
- There is a particular association between reflux nephropathy in the mother and severe IUGR.
- Reflux nephropathy may be inherited as an autosomal dominant condition, and therefore offspring of affected mothers should be screened with a micturating cystogram, as US may miss the diagnosis.

Diabetic Nephropathy
- Adverse pregnancy outcome and maternal complications are doubled compared to pregnant diabetics without nephropathy.
- The specific risks are UTI, preeclampsia, proteinuria and edema that may be severe but usually revert after delivery to prepregnancy levels.
- Nephrotic syndrome can be severe with marked hypoalbuminemia and the risk of pulmonary edema and thrombosis.
- Over 30% of affected women have preterm deliveries and over 50% have an increase in blood pressure.
- Most women with diabetic nephropathy show the normal increase in GFR and pregnancy does not increase the rate of deterioration in renal function.

Systemic Lupus Erythematosus Nephritis
- In women with lupus nephritis, pregnancy does not seem to jeopardize renal function in the long term, although systemic lupus erythematosus (SLE) nephropathy may manifest for the first time in pregnancy. The risk of deterioration is greater the higher the baseline serum creatinine, although women with moderate renal impairment (serum creatinine > 125 μmol/L) may have uncomplicated pregnancies.
- Pregnancy outcome is particularly affected by renal disease. Even quiescent lupus is associated with increased risk of fetal loss, preeclampsia and IUGR, particularly if there is hypertension or proteinuria.

Polycystic Kidney Disease
- This is an autosomal dominant disorder usually presenting in the fourth decade with hypertension, recurrent UTIs, hematuria or renal impairment. Some asymptomatic women are aware of their diagnosis because of affected family members and positive screening. Women may remain undiagnosed throughout pregnancy.
- The risks in pregnancy are of preeclampsia, which is more common in those with preexisting hypertension or renal impairment, and UTIs. Loin pain and hematuria may occur without UTI.
- Pregnancy has no adverse long-term effect on renal function.
- Polycystic kidney disease (PKD) may be associated with polycystic liver disease and subarachnoid hemorrhage from intracranial aneurysms. Liver cysts may enlarge during pregnancy and those with a family history of intracranial aneurysms should be screened for aneurysms prior to pregnancy.
- Since PKD is an autosomal dominant disorder, there is a 50% chance of transmission to the affected woman’s offspring.

Management of Pregnancies Complicated by Chronic Renal Disease
- Management should begin with prepregnancy counseling. Assessment of preconceptual renal function and blood pressure enables accurate counseling and provides a baseline with which to compare trends in pregnancy.
- Obstetricians and physicians who have expertise in the care of renal disease in pregnancy should manage jointly women with chronic renal disease.
- In view of the increased risk of preeclampsia, treatment with low-dose aspirin should be considered, especially in those with hypertension and renal impairment or a previous poor obstetric history.
- Careful monitoring and control of blood pressure both in prepregnancy and antenatally is important. Treatment for blood pressure problems is no different from the management of pregnant women without renal disease. However, the threshold for treatment may be lower, since good control of hypertension is important to preserve renal function.
- Regular assessment of renal function by creatinine clearance and 24-hour protein excretion, as well as serum creatinine and urea is essential. It may useful to give

| Table 3: Effect of degree of renal impairment on pregnancy outcome |
|-------------------|------------------|------------------|
|                   | Mild Cr < 125 | Moderate Cr = 125–249 | Severe Cr > 250 |
| Preeclampsia      | 25%            | 50%              | 85%             |
| IUGR              | 30%            | 60%              | 70%             |
| Preterm           | 55%            | 60–90%           | 20–30%          |
| Success           | 85–95%         | 60–90%           | 20–30%          |

Abbreviations: Cr, creatinine in μmol/L; IUGR, intrauterine growth restriction
the woman urine testing strips so she can monitor the presence and severity of any proteinuria or hematuria.

- The fetus should be monitored with regular US assessment of growth and Doppler assessment of uterine and umbilical circulation.
- Admission should be considered, if the woman develops worsening hypertension, deteriorating renal function or proteinuria, superimposed preeclampsia, or polyhydramnios.
- The differentiation between preeclampsia and deterioration of preexisting renal disease may be extremely difficult. However, the indications for renal biopsy during pregnancy are mostly limited to situations where a delay before delivery is desirable (i.e. before 32 weeks' gestation) and a diagnosis of a steroid or chemotherapy-sensitive lesion is suspected.

**PREGNANCY IN DIALYSIS PATIENTS**

- Fertility is reduced in women on hemodialysis or chronic ambulatory peritoneal dialysis (CAPD). The pregnancy rate is about 1 in 200 women per year.
- The chance of successful pregnancy outcome is low (30%) with both hemodialysis and CAPD.
- Poor prognostic features for pregnancy in dialysis patients include:
  - Age more than 35 years
  - More than 5 years on dialysis
  - Delayed diagnosis of pregnancy (leading to late increase in dialysis times).

**Effect of Pregnancy on Renal Replacement Therapy**

- Anemia is exacerbated by pregnancy. Transfusion requirements increase. Erythropoietin and iv iron may be safely used and increased in pregnancy.
- Pregnancy is associated with markedly increased requirements for dialysis.
- Doses of heparin may need to be increased to prevent clotting of dialysis lines.
- Pregnancy causes fluctuations in fluid balance and blood pressure.
- Doses of vitamin D and calcium may need to be reduced.

**Effect of Dialysis on Pregnancy**

The risks include:
- Miscarriage
- Intrauterine death
- Hypertension and preeclampsia
- Preterm labor
- Preterm rupture of membranes
- Polyhydramnios related to uremia
- Placental abruption.

Full heparinization requirements during hemodialysis increase the risk of bleeding. The specific problems with GAPD include peritonitis.

**Management**

In women on hemodialysis, the duration and/or the frequency of dialysis must be increased, to more than 20 hours/week. The aim should be to maintain the pre-dialysis urea at less than 15–20 µmol/L.

Dietary restrictions can usually be lifted, although continued adherence fluid restriction is important to avoid large fluid shifts during dialysis.

**Renal Transplant Recipients**

- Women receiving renal transplants should be warned that as renal function returns to normal, ovulation, menstruation and fertility also resume.
- Women desiring pregnancy are usually advised to wait about 1–2 years after transplantation, by which time graft function has stabilized and maintenance levels of immunosuppressive drugs will have been reached, thus minimizing any risk to the fetus.
- Survival is improved for recipients of living, related donors compared to cadaveric donors.
- Successful pregnancy outcome for those transplant recipients who become pregnant and do not miscarry before 12 weeks is now 95%.
- As with chronic renal impairment, pregnancy outcome and effects on the renal allograft are both dependent on the baseline serum creatinine level and the presence of hypertension; the poorer the graft function at conception, the higher the risk of complications and deterioration in graft function.

**Effect of Pregnancy on Renal Transplants**

- Pregnancy has no adverse long-term effect on renal allograft function or survival in women with baseline creatinine levels of less than 100 µmol/L.
- For women who enter pregnancy with a serum creatinine level more than 130 µmol/L renal graft survival is only 65% at 3 years.
- Renal allografts adapt to pregnancy in the same way as normal kidneys, and exhibit an increase in GFR and collecting-system dilatation. As with normal kidneys, the GFR may decrease again in the third trimester.
- About 15% of women develop significant impairment of renal function during pregnancy and this may persist after delivery.
- About 40% of women develop proteinuria towards term, but this usually regresses postpartum.
- More than 10% of women are likely to develop new long-term problems following pregnancy, although whether this
is as a direct result of pregnancy is difficult to ascertain. The risk of long-term problems is higher in women developing pregnancy complications prior to 28 weeks’ gestation.

- About 10% of women will die within 1–7 years after pregnancy, and about 50% within 15 years.

**Effect of Renal Transplants on Pregnancy**

- Outcome is optimal in those without hypertension, proteinuria, recent episodes of graft rejection, and in those with normal or near-normal renal function (serum creatinine level < 125 µmol/L).
- The chance of successful outcome beyond 12 weeks is 97% with a baseline creatinine level less than 125 µmol/L, but this is reduced to 75% if the baseline creatinine level is more than 125 µmol/L.
- The complication rate is higher for diabetics, and those with poor graft function.
- The incidence of problems in pregnancy is about 50% and includes:
  - Hypertension/preeclampsia (30%)
  - Graft rejection (10%)
  - IUGR (20–40%)
  - Preterm delivery (45–60%)
  - Infection, especially UTI.

**Antenatal Management**

- Women should be managed jointly by nephrologists and obstetricians with expertise in the care of pregnant renal transplant recipients.
- Careful monitoring and control of blood pressure is important.
- Regular assessment of renal function by creatinine clearance and 24-hour protein excretion, as well as serum creatinine and urea is essential.
- A full blood count and liver function tests should also be checked regularly. Anemia is common and hematinsics should be prescribed. Maternal hypocalcemia and hypercalcemia are both potential problems, and calcium status should be carefully monitored. Doses of calcium and vitamin D may need to be altered in pregnancy.
- An MSU specimen should be taken and sent at each visit and any infection treated promptly. Some women require prophylactic antibiotics.
- Cytomegalovirus (CMV) titers should be checked in each trimester if the woman is CMV negative at the onset of pregnancy.
- The fetus should be monitored with regular USG assessment of growth and Doppler assessment of uterine and umbilical circulation.
- Provided proteinuria is not accompanied by deteriorating renal function or hypertension, this is not an indication for delivery.

- The differential diagnosis of deteriorating renal function includes:
  - Reversible causes, e.g. infection (e.g. UTI), dehydration
  - Preeclampsia
  - Cyclosporin nephrotoxicity
  - Acute and/or chronic rejection.

- The features of acute rejection include:
  - Deteriorating renal function
  - Fever
  - Oliguria
  - Graft swelling and tenderness
  - Altered echogenicity of renal parenchyma and blurring of corticomedullary junction on ultrasound.

- Definitive diagnosis of rejection is only possible with renal biopsy.

**Immunosuppressive Therapy**

- The levels of immunosuppressive drugs are maintained at prepregnancy levels. Regimes vary but include treatment with:
  - Prednisolone
  - Azathioprine
  - Cyclosporin
  - Tacrolimus

- **Mycophenolate mofetil**: This is contraindicated in pregnancy and effective contraception is required during and for 6 weeks after discontinuation of treatment.
- Women require reassurance regarding the relative safety of their drugs, as reduction or cessation of immunosuppressive therapy may provoke rejection
- Azathioprine dose may be monitored via maternal white-cell count.
- Both cyclosporin and tacrolimus appear to be safe for use in pregnancy. Plasma levels should be measured regularly.
- Mycophenolate mofetil (MMF) is teratogenic and women desiring pregnancy should be converted to azathioprine prior to conception. They should be counseled regarding possible detrimental effects on graft function from a change in therapy. In some cases discontinuation of MMF, and therefore pregnancy, is contraindicated.
- Pregnancy success rates are similar in women taking azathioprine cyclosporin, but the incidence of IUGR is higher (30–40% versus 20%) in women taking cyclosporin.

**Delivery**

- Cesarean section is only required for obstetric indications, although overall section rate is increased (25%) compared to background rates, renal allograft does not obstruct vaginal delivery.
- Prophylactic antibiotics should be given to cover any surgical procedure including episiotomy.
- Parenteral steroids are necessary to cover labor, as with any woman on maintenance steroids.
Neonatal Problems

These are largely related to prematurity but also include the following:
- Thymic atrophy
- Transient leukopenia or thrombocytopenia
- Depressed hemopoiesis
- Adrenocortical insufficiency
- Septicemia
- Cytomegalovirus and hepatitis B infection.

Congenital abnormalities are no more common in the offspring of mothers taking antirejection doses of the earlier mentioned immunosuppressive drugs.

BIBLIOGRAPHY

HIV Infection in Pregnancy

The human immunodeficiency virus (HIV) continues to devastate populations throughout the world, and poses as one of the most vexing public health problems of the twentieth and twenty-first centuries.

According to the latest update on the worldwide acquired immunodeficiency syndrome (AIDS) epidemic from the Joint United Nations Program on HIV/AIDS, the global population of women living with HIV/AIDS grew by 1.2 million between 2004 and 2006 to a total of 17.7 million, or 48% of the total population of adults living with HIV.

This increasing prevalence among adult women has been observed in every region and country, including India. This is in contrast to earlier times in the epidemic when HIV and AIDS were seen much less frequently among women than among men.

According to the National AIDS Control Organisation, with 27 million pregnancies a year and an overall estimated 0.3% prevalence rate of HIV infection among pregnant women, it is estimated that about 100,000 HIV infected women deliver every year in India.

Moreover, the majority of these cases occur in women between 15 years and 39 years of age, the period during which childbearing potential is greatest.

The intervening period has seen significant advancement in the use of antiretroviral therapy that has extended life expectancy among HIV-infected patients and reduced the risk of mother-to-child HIV transmission to less than 1% especially in resource rich settings. As a result, HIV-infected women may not differ substantially from uninfected women regarding reproductive patterns or their intention to have children.

A survey of 118 HIV-positive women 18–46 years of age who were receiving care at a US-based HIV care center in 2004 found that one-third wished to have a child in the future.

It is recognized that mother-to-child transmission remains a significant driver of the global HIV/AIDS epidemic because of disparities in healthcare provision. This chapter describes strategies to manage conception, pregnancy, and reproductive health in HIV-infected women in India, both in well-resourced healthcare settings and resource constrained settings.

REPRODUCTIVE HEALTH ISSUES IN HIV-INFECTED WOMEN

Although no data is available on pregnancies that occur unplanned in India, but approximately one half of all pregnancies that occur in the United States are unplanned.

As a result, the US Department of Health and Human Services, guidelines on reducing perinatal HIV transmission includes new recommendations regarding the provision of preconception counseling to all HIV-infected women as a regular component of their ongoing care.

The aim of this intervention is to improve women’s health before conception and to provide education to reduce the risk of adverse maternal or infant outcomes.

METHODS OF CONCEPTION IN HIV-INFECTED PATIENTS

Ethically all doctors share responsibility with HIV-infected patients for the safety of uninfected partners and of potential offspring.

Patients who wish to bear their own genetically related children should be referred to specialist institutions for evaluation, treatment, and follow-up. Alternatively, patients may be advised to consider other options, such as the use of donor sperm, adoption, or not having children. If reproductive counseling and care are not provided, it must be anticipated
that some women will try to conceive through unprotected sex, presenting a potential risk of HIV transmission or superinfection. The risk of HIV transmission from male to female has been estimated to be about 1/1,000, approximately eight times more efficient than female-to-male transmission.11

Longitudinal studies that have evaluated the risk of HIV transmission between discordantly infected heterosexual couples who were counseled regarding condom use have reported seroconversion rates between 3% and 8% per 100 person-years of observation in couples who used condoms either inconsistently or not at all.12-15 In a European study, the estimated cumulative incidence of seroconversion at 24 months among 121 discordant couples who used condoms inconsistently was 12.7% [95% confidence interval (CI): 5.9-19.5], and the rate did not differ between male and female index partners.12 Investigators for the Ugandan Rakai Project Study Group have reported that the HIV-1 ribonucleic acid (RNA) level is an important predictor of risk of HIV transmission between discordant couples and that transmission appears to be rare among persons with HIV-1 RNA less than 1,500 copies/mL.16

Viral shedding in semen, however, is intermittent and correlates poorly with plasma HIV-1 RNA.17 Unprotected sex thus remains a potential mode of HIV transmission between discordant partners even when effective highly active antiretroviral therapy (HAART) has reduced plasma HIV-1 RNA to undetectable levels in the HIV-infected partner. To avoid this risk, alternative methods of conception can be presented to patients who are considering pregnancy, according to the HIV status of the respective partners.

**HIV-Positive Female with HIV-Negative Male**

In discordantly infected couples in which the female is HIV positive and the male is HIV negative, artificial insemination of husband semen is an appropriate conception method that protects the male from HIV infection.

**HIV-Negative Female with HIV-Positive Male**

In this scenario, where it is important to protect the female partner from HIV infection, methods of semen processing (sometimes known as “sperm washing”) may be considered, where such services are available. The aim of semen processing is to separate sperm, which lack HIV-1 receptors, from seminal plasma and nonsperm cells, which may harbor virus. The separated sperm fraction is then assayed to confirm absence of HIV-1 RNA using a polymerase chain reaction (PCR) method and to verify the quality of the sperm before either intrauterine insemination, in vitro fertilization, or intracytoplasmic sperm injection. There is no consensus on the optimal method of semen processing for use in HIV-infected men,17 although there is some evidence that techniques are more effective in removing virus from semen in men who are receiving HAART compared with untreated men.18 Where provided by specialist centers, however, semen processing and assisted reproduction techniques offer discordantly infected couples the chance to conceive with a greatly reduced risk of HIV transmission to the uninfected female. A recent report from Savasi and colleagues19 described outcomes in 741 couples (HIV-positive male with HIV-negative female) who received sperm washing plus either intrauterine insemination or in vitro fertilization/intracytoplasmic sperm injection. The overall pregnancy rate was 70.3%, and all female partners remained HIV negative during follow-up.

**HIV-Positive Female with HIV-Positive Male**

In cases where both partners are HIV-positive, semen processing and donor insemination may also be considered to avoid the risk of HIV superinfection.

**EFFECTS OF PREGNANCY ON HIV INFECTION**

CD4+ cell counts decline during pregnancy but typically return to baseline following delivery.20 Plasma HIV-1 RNA tends to remain stable in pregnancy but then increases in the postpartum period.21 However, there is little evidence that pregnancy adversely affects clinical disease outcomes. A systematic review of data from seven prospective cohorts on the impact of pregnancy on HIV disease progression and survival found no significant differences in risk of death, HIV disease progression, or decline of CD4+ cell count to less than 200 cells/mm³ among pregnant versus nonpregnant HIV-infected women, although there might have been some increase in the risk of progression to an AIDS-defining illness among pregnant women (odds ratio: 1.63; 95% CI: 1.00-2.67).22

A separate study investigating disease outcomes in HIV-infected women who had single or multiple pregnancies found that repeat pregnancies had no significant impact on disease progression.23

**EFFECTS OF HIV INFECTION ON PREGNANCY**

Without intervention, HIV infection is efficiently transmitted from mother to child. Before the use of antiretroviral prophylaxis, reported vertical transmission rates ranged from 13% to 32% in industrialized countries and from 25% to 48% in resource-poor settings.24 Transmission may occur at any time during gestation, although evidence suggests that in the absence of any preventive measures, most transmission events occur during the intrapartum period.25 Several factors are known to influence the likelihood of vertical HIV transmission. These can be divided into factors related to HIV disease, health and social factors related to the mother, factors related to the delivery, and infant factors.
Antiretroviral therapy and avoidance of breastfeeding are the primary interventions that reduce the risk of mother-to-child HIV transmission. In 1994, results from the pediatric AIDS clinical trials group (PACTG) 076 trial were published showing a multicomponent zidovudine regimen reduced mother-to-child HIV transmission by nearly 70% (Table 1).

Later that year, the US Public Health Service (USPHS) issued guidelines for the use of zidovudine to reduce perinatal HIV transmission. The PACTG 076 study and the subsequent USPHS recommendations spurred a dramatic decline in the number of perinatal AIDS cases in the late 1990s. Clinical trials and observational studies in developed countries, as well as clinical trials of shorter course regimens in low resource settings, have demonstrated that a variety of antiretroviral regimens reduce the risk of maternal-child HIV transmission, with the greatest risk reductions seen with longer duration and more complex regimens (Fig. 1). With the use of combination antiretroviral therapy during pregnancy (Table 2) and the achievement of very low or undetectable maternal HIV RNA levels (at the time of delivery or near delivery), perinatal transmission of HIV occurs in fewer than 1–2% of women, in contrast with the transmission rate of 20–25% in women who receive no antiretroviral therapy (Fig. 2 and Table 3). The use of antiretroviral therapy may provide significant benefit even if the pregnant woman does not achieve an undetectable HIV RNA level. Among women with comparable low-level detectable HIV RNA (less than 1,000 copies/mL) at the time of delivery, those who received antiretroviral therapy (during pregnancy, at the time of delivery, or both), had a significantly lower rate of HIV transmission compared with those who received no antiretroviral therapy. Thus, it appears that antiretroviral therapy decreases maternal-child HIV transmission via multiple mechanisms, including those dependent and independent of HIV RNA levels. Taken together, available data clearly show that antiretroviral therapy significantly reduces the risk of maternal to child HIV transmission, and these data justify recommendations to use antiretroviral therapy for all HIV-infected pregnant women during pregnancy.

### Table 1: Pediatric AIDS clinical trials group (PACTG) 076 zidovudine regimen

<table>
<thead>
<tr>
<th>Time of administration</th>
<th>Zidovudine regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antepartum</td>
<td>100 mg orally five times daily, initiated at 14–34 weeks and continued throughout pregnancy*</td>
</tr>
<tr>
<td>Intrapartum</td>
<td>During labor, intravenous zidovudine in a 1 hour initial dose of 2 mg/kg followed by a continuous infusion of 1 mg/kg/hr until delivery†</td>
</tr>
<tr>
<td>Neonate</td>
<td>Begin at 8–12 hours after birth, and give syrup at 2 mg/kg every 6 hours for week§</td>
</tr>
</tbody>
</table>

* Acceptable alternative regimens include 200 mg three times daily or 300 mg twice daily.
† For elective cesarean delivery, intravenous zidovudine is begun at least 3 hours prior to surgery. For premature rupture of membranes of labor with a planned operative delivery, the loading dose may be given over the half hour prior to surgery.
§ Intravenous dosage of infants who cannot tolerate oral intake is 1.5 mg/kg intravenously every 6 hours.

Abbreviation: AIDS, acquired immunodeficiency syndrome
Table 2: Recommendations for antiviral drug use during pregnancy

<table>
<thead>
<tr>
<th>HIV-infected woman on antiretroviral therapy who become pregnant</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Continue current medication if viral suppression adequate and patient tolerating</td>
<td></td>
</tr>
<tr>
<td>• If virus detectable, order HIV antiretroviral drug-resistance testing</td>
<td></td>
</tr>
<tr>
<td>• If first trimester, continue medications. If stopped, stop all medications and then</td>
<td></td>
</tr>
<tr>
<td>reinitiate in the second trimester</td>
<td></td>
</tr>
<tr>
<td>• If not receiving zidovudine (ZDV) antepartum, start IV ZDV in labor</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HIV-infected woman who is antiretroviral naive and has maternal indications for HAART</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Order HIV antiretroviral drug-resistance testing</td>
<td></td>
</tr>
<tr>
<td>• <strong>Initiate HAART:</strong></td>
<td></td>
</tr>
<tr>
<td>• Avoid efavirenz in the first trimester</td>
<td></td>
</tr>
<tr>
<td>• Use ZDV-containing regimen if feasible</td>
<td></td>
</tr>
<tr>
<td>• Avoid nevirapine (NVP) in women with CD4+ count &gt; 250 cells/mm³</td>
<td></td>
</tr>
<tr>
<td>• HAART should be initiated as early as possible for maternal indications</td>
<td></td>
</tr>
<tr>
<td>• If not receiving ZDV antepartum, start IV ZDV in labor</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HIV-infected woman who is antiretroviral naive with no maternal indication for HAART</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Order HIV antiretroviral drug-resistance testing</td>
<td></td>
</tr>
<tr>
<td>• <strong>Initiate HAART:</strong></td>
<td></td>
</tr>
<tr>
<td>• Consider delaying therapy until the start of the second trimester</td>
<td></td>
</tr>
<tr>
<td>• Use ZDV-containing regimen if feasible</td>
<td></td>
</tr>
<tr>
<td>• Avoid NVP in women with a CD4+ count &gt; 250 cells/mm³</td>
<td></td>
</tr>
<tr>
<td>• ZDV monotherapy is controversial:</td>
<td></td>
</tr>
<tr>
<td>• If used, use in women with HIV RNA levels, 1,000 copies/mL</td>
<td></td>
</tr>
<tr>
<td>• If not receiving ZDV antepartum, start IV ZDV in labor</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HIV-infected woman previously on antiretroviral medications but not on medications currently</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Order HIV antiretroviral drug-resistance testing</td>
<td></td>
</tr>
<tr>
<td>• <strong>Initiate HAART with regimen, based on prior therapy history and resistance testing</strong></td>
<td></td>
</tr>
<tr>
<td>• Avoid efavirenz in the first trimester</td>
<td></td>
</tr>
<tr>
<td>• Use ZDV-containing regimen, if feasible</td>
<td></td>
</tr>
<tr>
<td>• Avoid NVP in women with a CD4+ count &gt; 250 cells/mm³</td>
<td></td>
</tr>
<tr>
<td>• If not receiving ZDV antepartum, start IV ZDV in labor</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HIV-infected woman on no antiretroviral medication who presents in labor</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Order initial HIV laboratory assessment</td>
<td></td>
</tr>
<tr>
<td>• Start ZDV intravenous protocol (Table 1)</td>
<td></td>
</tr>
<tr>
<td>• Start intravenous ZDV plus a single dose of NVP. If NVP initiated, consider adding lamivudine for 7 days postpartum to decrease NVP resistance</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: HAART, highly active antiretroviral therapy; RNA, ribonucleic acid

Table 3: Effect of single and multiagent antiretroviral therapy (ART) with respect to maternal plasma viral loads on mother-to-child transmission of HIV infection

<table>
<thead>
<tr>
<th>Last HIV RNA (copies/mL)</th>
<th>Last ART</th>
<th>Transmission rate</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1,000</td>
<td>Single agent</td>
<td>5.7%</td>
<td>1.0</td>
</tr>
<tr>
<td>≥ 1,000</td>
<td>Multiagent</td>
<td>2.7%</td>
<td>0.05 (0.2 to 1.1)</td>
</tr>
<tr>
<td>&lt; 1,000</td>
<td>Single agent</td>
<td>2.2%</td>
<td>1.0</td>
</tr>
<tr>
<td>&lt; 1,000</td>
<td>Multiagent</td>
<td>0.6%</td>
<td>0.3 (0.1 to 1.5)</td>
</tr>
</tbody>
</table>

Fig. 2: Effect of no antiretroviral therapy (ART), mono, dual or multi-drug ART regimens on mother-to-child transmission of HIV infection
GUIDELINES FOR USE OF ANTIRETROVIRAL THERAPY IN PREGNANCY

Guidelines in this chapter will focus on four major clinical scenarios (Fig. 3) in which antiretroviral therapy can be used to reduce maternal to child transmission of HIV:

1. A woman who is newly diagnosed with HIV in pregnancy
2. HIV-infected woman is receiving antiretroviral therapy that was started before she became pregnant
3. HIV-infected woman is in labor and has not received prior antiretroviral therapy
4. An infant is born to an HIV-infected woman who has received no antiretroviral therapy during pregnancy or in the intrapartum period.

The following discussion will focus on management issues related to the above four major scenarios that involve the use of antiretroviral therapy during pregnancy. All HIV-infected pregnant women, regardless of what regimen they receive during pregnancy, should receive zidovudine during labor, and the newborn should receive zidovudine by oral suspension for the first 6 weeks of life.9

SCENARIO 1

Approach to Women Who is Newly Diagnosed with HIV in Pregnancy

When an antiretroviral therapy-naïve HIV-infected woman becomes pregnant or is newly diagnosed with HIV in pregnancy, she should promptly undergo clinical, immunologic, and virologic evaluation. In this scenario, many experts would recommend deferring initiation of antiretroviral therapy until after the first trimester to minimize fetal exposure at the most vulnerable period of development. If, however, the clinical or immunologic condition of the woman indicates the need for more immediate initiation of therapy, effective combination antiretroviral therapy should be started.9 When the pre-antiretroviral therapy HIV RNA level exceeds 1,000 copies/mL, combination antiretroviral therapy is recommended, regardless of the patient’s CD4 cell count or clinical status. In addition, the pregnant woman should receive combination antiretroviral therapy, if she has an indication for antiretroviral therapy based on her immunologic status. Although zidovudine monotherapy with the three-part regimen used in the PACTG 076 study would be considered acceptable in women who have a CD4 count greater than 350 cells/mm³ and HIV RNA less than 1,000 copies/mL, data from PACTG 367 suggest that combination therapy achieves an even lower rate of HIV transmission.34

In addition, the use of zidovudine monotherapy during pregnancy can result in the development of resistance to zidovudine and can thus negatively affect future antiretroviral therapy options.

SCENARIO 2

Approach to HIV-Infected Pregnant Women Receiving Antiretroviral Therapy that was Started before She Became Pregnant

In the second scenario involving an HIV-infected woman who becomes pregnant while taking antiretroviral therapy, most experts would recommend continuing therapy, especially if the woman has already entered the second or third trimester of pregnancy. If, however, the woman is still in the first trimester, the risks and benefits of continuing therapy should be discussed in detail with her. In some instances, antiretroviral therapy may need to be interrupted in the first trimester if the woman has significant nausea and vomiting, a situation that may create problems with adherence and proper absorption. If, for whatever reason, antiretroviral therapy is discontinued during the first trimester, all antiretroviral medications should be stopped in a pattern to avoid the development of resistance and then restarted at the onset of the second trimester. If the regimen includes efavirenz or nevirapine, most experts would recommend discontinuing these drugs several days prior to other medications in the regimen because of their very long half-life and low genetic barrier to developing resistance; in this situation, the clinician should ideally consult with an expert in antiretroviral therapy. If the decision is made to continue antiretroviral therapy during the first trimester, and the woman’s existing regimen contains efavirenz, another effective agent should replace efavirenz, because of the increased risk of neural tube defects associated with first trimester exposure to this drug.35,36 Some experts would consider the use of efavirenz in the second or third trimester acceptable, if no other effective antiretroviral option existed. In addition, if therapy is to be continued, but
the existing regimen does not include zidovudine, many experts would recommend substituting zidovudine for one of the nucleoside (or nucleotide) reverse transcriptase inhibitors (if this would be likely to maintain optimal effectiveness) or adding zidovudine to an existing regimen, mainly because of the extensive data with zidovudine in preventing maternal-child HIV transmission.

Specific Drug Recommendations for Use in Pregnancy

Most of the same general principles exist when choosing antiretroviral regimens for use during pregnancy as when choosing regimens for HIV-infected adults and adolescents who are not pregnant. Consensus guidelines all over world recommend antiretroviral therapy for HIV-infected pregnant women consisting of combination therapy with three or more antiretroviral medications, typically two nucleoside reverse transcriptase inhibitors (NRTIs) plus a protease inhibitor (PI). These guidelines categorize antiretroviral drugs in pregnancy as either recommended, alternative, those for which insufficient data exists, and those not recommended. These categorizations are based on experience (or lack of experience) and available data with these medications related to safety and effectiveness in reducing perinatal HIV transmission. Any decision regarding regimen selection should also include consideration of effectiveness for maternal treatment. The preferred dual NRTI backbone consists of zidovudine combined with lamivudine, most often given as the fixed-drug preparation. The preferred PIs include either nelfinavir or saquinavir boosted with ritonavir. As noted above, the use of efavirenz should be avoided during pregnancy. Although the use of single or dual NRTIs alone is not recommended for treatment of HIV infection, zidovudine monotherapy is considered acceptable for prophylaxis of perinatal transmission in pregnant women who have a baseline HIV RNA less than 1,000 copies/mL and who do not meet CD4 criteria for initiating antiretroviral treatment. The clinician should also be aware of several special considerations when using antiretroviral agents in pregnancy: (1) pharmacokinetics may be altered during pregnancy; (2) antiretroviral therapy toxicity and side effects may be altered in pregnancy, or may be more easily overlooked; and (3) potential fetal and newborn toxicity, such as birth defects, carcinogenicity, anemia and mitochondrial toxicity must be considered, since these could potentially occur with babies exposed to these drugs in utero, irrespective of their HIV status.

Special Risk with Antiretroviral Therapy during Pregnancy

Women initiating nevirapine with a CD4 greater than 250 cells/mm³ have a tenfold increased risk of developing symptomatic, often rash-associated hepatotoxicity and hepatic failure, usually within the first 18 weeks after starting nevirapine. These adverse reactions to nevirapine have included several deaths among pregnant patients. Although women who enter pregnancy on a well-tolerated nevirapine-containing regimen may continue on this regimen, initiating nevirapine-containing combination therapy in women with a CD4 count greater than 250 cells/mm³ should be avoided. Although it is recommended that whenever possible antenatal antiretroviral therapy should include zidovudine as part of the regimen, zidovudine is associated with bone marrow suppression and pregnant women are more likely to be anemic. Accordingly, severe anemia constitutes a relative contraindication for using zidovudine, unless a transfusion is given. Stavudine is considered an alternative NRTI in pregnancy and can substitute for zidovudine, as in the patient in this case. The combination of stavudine and didanosine has been associated with several cases of lactic acidosis, some fatal, in pregnancy and should not be used unless no other options are available. Sparse data exist regarding the use of tenofovir, abacavir, or emtricitabine during pregnancy. Tenofovir has become a very commonly used agent for nonpregnant HIV-infected persons, but its use in pregnancy remains limited because of concern regarding potential fetal bone effects. Among the protease inhibitors, there are some concerns with indinavir and atazanavir use late in pregnancy, mainly because these drugs can increase indirect bilirubin levels and thus theoretically exacerbate physiologic hyperbilirubinemia in the neonate. Although there are concerns with maternal toxicity resulting from antiretroviral therapy, the benefits of therapy in preventing perinatal transmission and improving maternal health when maternal treatment is indicated far outweigh the risks.

SCENARIO 3

Presentation in Labor with No Prior Antiretroviral Therapy (Applicable in Settings where Mothers do not Access Prenatal Care or where HIV Testing is not Offered)

Use of Rapid HIV Testing for Women in Labor

Unfortunately, some HIV-infected women present at the time of labor and delivery without having undergone prior HIV testing. For those women, who present at the time of labor without prior HIV testing, rapid HIV testing now provides a means to promptly identify previously undiagnosed HIV-infected women in whom antiretroviral therapy could provide substantial benefit in reducing maternal-to-child HIV transmission. In the mother-infant rapid intervention at delivery (MIRIAD) study, which involved women in labor with undocumented HIV status, rapid HIV testing was well received, feasible and performed with greater than 99% sensitivity and specificity. Based on these results, along with
strong evidence that antiretroviral interventions can reduce the risk of perinatal HIV transmission when initiated in labor, rapid HIV testing is recommended for all women in labor who have undocumented HIV status after consent.53,54 If a woman in labor has a positive rapid HIV test, the clinician should initiate antiretroviral prophylaxis using zidovudine without waiting for the confirmatory HIV antibody test result.

Antiretroviral Prophylactic Regimens with Presentation in Labor

Because most maternal-to-child HIV transmission occurs shortly before or during labor, HIV-infected women who present in labor with no prior antiretroviral therapy can still derive major benefit from receiving antiretroviral therapy. The decision regarding whether the mother should undergo cesarean delivery in this setting is discussed in detail separately in the last section. The 2006 Public Health Service Task Force Guidelines lists four possible intrapartum and postpartum antiretroviral regimens for use when started in labor.55 Epidemiologic data have established benefit for women presenting in labor with the use of zidovudine alone,47 and clinical trials in sub-Saharan Africa have established benefit in similar situations for the combination regimen of zidovudine plus lamivudine and with nevirapine monotherapy.7,9 In addition, zidovudine plus nevirapine is listed as a theoretically effective regimen. After the publication of these guidelines, results from a trial in Africa showed similar transmission rates when infants received single-dose nevirapine with or without 1 week of zidovudine;60 in both groups, the mothers received single-dose nevirapine prior to birth if they presented early in labor.49 In the western world, the most commonly used regimen for women presenting in labor consists of zidovudine by intravenous infusion during labor and delivery followed by 6 weeks of zidovudine oral suspension for the newborn. This regimen is the same as the second and third components of the PACTG 076 protocol.29 Although, it is difficult to compare results between clinical trials and observational studies and between those conducted in the western countries and those in low resource countries where HIV-infected mothers often breastfeed, zidovudine appears to be equal to or superior to other regimens that have been studied for use in this setting.

Nevirapine Monotherapy with Presentation in Labor

In resource constrained areas, there has been major interest and investigation in simple, cost-effective regimens that do not require the use of intravenous zidovudine or the prolonged administration of zidovudine to the infant. Nevirapine given as a single dose to the mother at the onset of labor and as a single dose to the infant within the first 48–72 hours of life reduced maternal-to-child transmission rates by approximately 50% in the HIV NET 012 clinical trial in Uganda.46 It is inexpensive, simple and has a good safety profile (hepatotoxicity has not been described with use of single-dose nevirapine). There are, however, increasing concerns with this regimen because of the high rates of non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance that have been documented in both mother and child after only one dose or two doses of nevirapine.50–52 The development of resistance is thought to result from the long half-life of nevirapine with significant blood levels detectable for up to 3 weeks after a single dose53,54 resulting essentially in prolonged monotherapy with an agent that has a low genetic barrier to resistance. Development of resistance may affect subsequent response to NNRTI-based regimens given for maternal therapy55 and secondary transmission of resistant strains to partner. The recent trial from Africa noted above clearly showed a lower rate of infant NNRTI resistance when the infants took a 1-week course of zidovudine in addition to the single dose of postpartum nevirapine.45 This study, however, did not address maternal NNRTI resistance, nor did it address the impact of adding other antiviral agents, such as zidovudine, to the single dose intrapartum nevirapine. Another recently published trial from Africa showed very low rates of maternal and infant NNRTI resistance with a prepartum regimen of zidovudine plus lamivudine (started at week 32 of gestation), an intrapartum regimen of single dose nevirapine, zidovudine and lamivudine given at the onset of labor, and a postpartum regimen of zidovudine plus lamivudine given to the infant for 3 days after birth combined with a single dose of nevirapine given on the second day.56 Taken together, the available data strongly suggest that nevirapine monotherapy should be used only if other intrapartum prophylactic regimens are not available.

SCENARIO 4

An Infant is Born to a HIV-infected Woman Who has Received no Antiretroviral Therapy

Impact of Neonatal Antiretroviral Therapy

Since the mid-1990s, maternal-child transmission of HIV has markedly declined. As a result, the number of perinatally-acquired AIDS cases has also dramatically declined.27 Most of this success can be attributed to universal HIV counseling and voluntary HIV screening during prenatal care, combined with the use of antiretroviral therapy during pregnancy and labor. In 1994, the PACTG protocol 076 demonstrated a nearly 70% decrease in the risk of vertical HIV transmission to newborn infants with the use of a three-part zidovudine regimen that consisted of oral zidovudine initiated at 14–34 weeks gestation (antepartum), intravenous zidovudine given during labor (intrapartum) and oral zidovudine administered for 6 weeks to the infant (postpartum).28 Although this study did not
delineate the relative importance of each of the components of the zidovudine regimen, subsequent work has established that most maternal-to-child HIV transmission occurs close to or during the time of labor and delivery.\textsuperscript{23}

Currently, it remains unclear whether the third component of PACTG 076—oral zidovudine given for 6 weeks to the newborn—plays a significantly role in reducing maternal-to-child HIV transmission. One epidemiologic study that involved infants whose mothers did not receive antepartum or intrapartum zidovudine failed to show benefit from neonatal zidovudine.\textsuperscript{57} In contrast, a retrospective study suggested a benefit in this setting if the neonate started receiving zidovudine shortly after birth (most within 12 hours).\textsuperscript{58} Data from Africa have demonstrated conflicting results regarding the benefit of short-course neonatal zidovudine when given in addition to single dose neonatal nevirapine.\textsuperscript{59,60} Thus, further study is required to better define the impact of neonatal antiretroviral therapy on maternal-to-child HIV transmission and the optimal regimen in this setting.

**Recommendations for Neonatal Antiretroviral Therapy**

Despite the limitations that exist in our understanding of the benefit of neonatal antiretroviral therapy, the current guidelines recommend that infants born to HIV-infected women should receive a 6-week course of zidovudine with the recommended dosing for infants born at 35 weeks gestation or later consisting of 2 mg/kg of zidovudine syrup given orally every 6 hours.\textsuperscript{7} The infant should receive the first zidovudine dose as soon as possible after birth, preferably within 6–12 hours. For those infants born at less than 35 weeks gestation (but after 30 weeks) at delivery, the zidovudine should initially be dosed every 12 hours; the zidovudine dose interval should then change to every 8 hours after 2 weeks of age.\textsuperscript{61} If the neonate was less than 30 weeks gestation at birth, the dosing interval should change after 4 weeks of age. For HIV-infected mothers with known or suspected zidovudine resistance, some experts would recommend using an alternative to zidovudine, either as monotherapy or combination therapy.\textsuperscript{61,62} Nevertheless, use of drugs other than zidovudine or combination therapy have not been shown to be more beneficial than zidovudine monotherapy in the setting of suspected or known zidovudine resistance. If combination therapy is used in this setting, expert consultation is recommended. Those infants who receive zidovudine should undergo hematologic monitoring consisting of a complete blood count with differential at baseline, at the end of the 6 weeks course, and, if an earlier value is abnormal, again at 12 weeks. Those infants with anemia at birth should undergo more intensive monitoring. Infants who receive combination antiretroviral therapy should have expanded monitoring that also includes serum chemistry, hepatic transaminase levels and serum bilirubin levels.

**PERINATAL HIV TRANSMISSION AND ROUTE OF DELIVERY**

**Background**

The last two decades has seen significant improvements in the therapeutic options for HIV-infected individuals, resulting in increased longevity and improved quality of life. Concomitant with these improvements in therapy, there has been an increase in the number of perinatally HIV-infected women anticipating the birth of their own children.\textsuperscript{63} Although reducing the risk of vertical transmission is a primary concern, it is important to keep in perspective the patient’s commitment to taking the medications, her likely adherence while taking antiretroviral medications, and the potential long-term implications of non-adherence. If effective HAART is taken during pregnancy, the risk of maternal-to-child HIV transmission is very low.\textsuperscript{30} Unfortunately, in some situations, pregnant HIV-infected mothers may go through pregnancy without taking antiretroviral therapy. In such scenarios, efforts to prevent HIV transmission at the time of delivery are of paramount importance. Indeed, it is estimated that among newborns with perinatally-acquired HIV, approximately 60% become infected during labor and delivery.\textsuperscript{64} The mother-to-child transmission of HIV that occurs during labor and delivery is believed to result from transplacental maternal-fetal microtransfusion of blood during uterine contractions and fetal exposure to maternal cervicovaginal secretions and blood during delivery.\textsuperscript{65} Investigators have identified a number of factors prior to and during delivery that may affect the risk of HIV transmission. The remaining discussion will focus on the impact, indications, timing, and complications of cesarean section delivery in HIV-infected mothers, as well as use of antiretroviral therapy administered during delivery.

**Impact of Cesarean Section on Perinatal HIV Transmission**

Prior to the widespread use of viral load testing and the use of combination antiretroviral therapy during pregnancy, several studies clearly established that cesarean section, if performed before the onset of labor and rupture of membranes, significantly reduces perinatal transmission of HIV when compared with other modes of delivery.\textsuperscript{3,66} In 1999, the international perinatal HIV group published the findings of a meta-analysis of 15 prospective cohort studies that addressed the impact of elective cesarean section versus vaginal delivery on the risk of mother-to-child HIV transmission.\textsuperscript{66} These studies involved a cumulative total of 8,533 mother-child pairs, and the data were adjusted for receipt of antiretroviral therapy, maternal stage of disease, and infant birth weight. The investigators found that elective cesarean section decreased the risk of transmission by approximately 50%, with a transmission rate of 8.4% for women who underwent elective cesarean section versus...
Indications for Cesarean Section

Consensus guidelines recommend that women with viral loads above 1,000 copies/mL near term should undergo scheduled cesarean section at 38 completed weeks of gestation, prior to the onset of labor or the rupture of membranes.\(^6\) In addition, intravenous zidovudine should be started 3 hours prior to delivery and continued throughout delivery.\(^6\) For women with a near-term HIV RNA level less than 1,000 copies/mL, cesarean section probably does not significantly reduce the risk of HIV transmission, and thus most experts would not recommend scheduled cesarean section in that situation.\(^9\) If a near-term viral load has not been performed, decisions regarding cesarean section should be made based on the most recent HIV RNA level. Women taking antiretroviral therapy should remain on therapy through delivery and continue therapy after delivery if indicated for maternal purposes.

Timing of Planned Cesarean Section

For women scheduled to undergo cesarean section, most of the guidelines recommend that it take place at 38 completed weeks of gestation (determined by best clinical estimate), prior to the onset of labor or the rupture of membranes.\(^9,65\) Majority of the guidelines recommend performing a scheduled cesarean section delivery at 38 completed weeks of gestation, as opposed to the 39 weeks recommended for persons not infected with HIV, because of the substantially higher risk of entering labor or rupturing membranes after 38 weeks of completed gestation. On the other hand, performing a cesarean delivery at 38 versus 39 completed weeks of gestation confers a small increased risk of infant respiratory distress possibly requiring mechanical ventilation. Although it would be ideal to know the status of the fetal lung maturity prior to cesarean section, it is recommended to avoid amniocentesis, primarily to avoid fetal exposure to maternal blood.\(^6\)

Scheduled Cesarean Section, but Woman Presents in Labor

When a woman is scheduled to undergo cesarean section, but presents early in labor (or shortly after rupture of membranes), the benefit of cesarean section is unknown and decisions regarding the approach to delivery should be individualized. If the woman has minimal cervical dilatation and is likely to have extended labor, one option is to immediately give the loading dose of intravenous zidovudine and then proceed to cesarean section.\(^9\) Alternatively, one could immediately give the loading dose of intravenous zidovudine and then start oxytocin to expedite delivery with vaginal delivery performed as long as rapid labor ensues.\(^9\) For any vaginal delivery, the duration of ruptured membranes should be as short as possible, given the increased risk of HIV transmission with longer duration of membrane rupture. Rupture of membranes for longer than 4 hours doubles the risk of HIV transmission.\(^6,66,68\) For any vaginal delivery, the clinician should, if possible, avoid using scalp electrodes or other invasive monitoring devices, forceps, or the vacuum extractor.

Complications of Cesarean Section

Although limited data exist regarding maternal morbidity following cesarean section in HIV-infected women, several studies have suggested that HIV-infected women who undergo cesarean section have higher complication rates than women who deliver vaginally.\(^7,71\) Post-delivery complications most frequently consist of hemorrhage, postpartum fever, cesarean wound infection, endometritis, urinary tract infection and sepsis.\(^6,67,70,72\) Among HIV-infected women who deliver via cesarean, those with CD4 counts less than 200 cells/mm\(^3\) have a greater rate of complications.\(^70\) Because of the increase in infectious complications, the consensus guidelines recommend that following cord clamping with a cesarean delivery, the mother should receive prophylactic antibiotics, which reduces the risk of postpartum maternal infection.\(^9\)

SUMMARY

- A woman with HIV can transmit the virus to her infant either during pregnancy, labor or after childbirth via breastfeeding. Several factors are associated with a higher risk of transmission, including the maternal viral load and CD4 cell count.
• Without treatment, the chance of transmitting HIV from a mother to a baby is somewhere between 12% and 25% in the developed world, and between 20% and 45% in resource-limited settings. It is greatly influenced by whether the child is breastfed.

• In 1994, a controlled clinical trial demonstrated that treatment with AZT or zidovudine during pregnancy, delivery and to the infant after birth can reduce the risk of mother-to-child transmission of HIV by two-thirds. Subsequent studies reported that other treatment courses with AZT and other antiretroviral drugs could also reduce the likelihood of infection of the infant.

• One trial in Uganda demonstrated significant reductions in HIV transmission simply by giving a single dose of nevirapine to the mother at the start of labor and to her infant within 72 hours of childbirth. This simple and inexpensive approach allowed resource-limited countries to design and implement programs for the prevention of mother-to-child transmission (PMTCT). However, there are concerns that this strategy could lead to the development of nevirapine resistance in mothers and infants who become infected. This could limit their future treatment options.

• In the developed world, widespread use of antiretroviral therapy during pregnancy has been associated with a dramatically reduced incidence of mother-to-child transmission among women with HIV who do not breastfeed.

• The long-term safety of exposure to antiretroviral drugs in the womb and early in life is not known and is a risk that must be balanced against the benefit of reduced HIV transmission. There is little evidence that antiretroviral drugs cause a significant risk of serious abnormalities.

• Planned caesarean delivery reduces mother-to-baby transmission in women who do not take any treatment, and in women who receive AZT in pregnancy. However, it is not clear whether this mode of delivery is advisable for pregnant women whose viral load is suppressed by antiretroviral therapy.

• The management of any HIV-positive pregnant woman requires a careful consideration of the balance between the mother’s health needs, locally available treatment options, the need to reduce transmission and the adverse effects of antiretroviral therapy. Recommended treatment options vary by country and local resources.

• After birth, breastfeeding poses an ongoing transmission risk, and additional effective measures are needed to reduce transmission through this route.

• Most women in the developed world choose to feed their child with infant formula. However, in resource-poor settings, replacement feeding is not always a viable option because of the lack of safe water or a reliable supply of infant formula. Even when formula is available, the choice is not a simple one in areas where malnutrition and childhood illness are common, because infants who are not breastfed are more likely to die from other causes.

• Two studies have shown that mixed breast and formula or solid feeding carries a higher risk of HIV transmission than exclusive breastfeeding. Exclusive breastfeeding and early weaning are recommended.

• Ongoing studies are evaluating the potential role for antiretroviral treatment to prevent HIV transmission to breastfed infants.

• Though PMTCT appears to have become more complicated, it continues to be the most effective approach in HIV infection in pregnancy.

REFERENCES


“I don’t have any solution, but I certainly admire the problem”
—Ashleigh Brilliant

INTRODUCTION
Approximately 10% of all human pregnancies end in spontaneous abortions. In the majority of such cases the etiology remains unknown, but anticardiolipin antibodies (aCL) are gaining recognition as potential causes of recurrent miscarriage. Repeated pregnancy loss and being childless is not only a gynecological problem but also a social stigma, in the Indian scenario. The price of motherhood is high and helpless couples seek to tide over this major crisis in their homes and society. Multiple studies have demonstrated the high incidence of psychological problems like low self-esteem, security and self-confidence among the childless couples. Women in particular suffer the deleterious consequences due to the common misconception that it is always the shortcoming of the female. This takes huge toll on the woman in terms of loss of self-esteem, grief, and feelings of failure. Recurrent abortion is a heterogeneous condition which is extremely traumatic emotionally as well as physically. Despite thorough investigation according to various clinical protocols, the underlying etiology remains obscure in the majority of patients, and obstetricians are facing a challenge to determine the cause of these unexplained abortions. Recently, the presence of IgG-aCL has been associated with approximately 40% of such cases. As the technology advances, physicians today have the ability to achieve successful outcome in many couples who would have been totally incapable doing so only a few years ago.

The aim of this chapter is to highlight the importance of different causes of recurrent spontaneous abortions (RSA) and the outcome of such treatment protocols and counseling the patients in case of adverse result. The ultimate aim is to improve the take home baby rate. The discussion can be exhaustive and hence for the purpose of this chapter we are discussing the causes and the management of recurrent first trimester abortions only. The management of second trimester losses is being handled in another part of this book. The literature review is by the Medline (1966 to November 2005), the Cochrane Library (2005, Issue 4), and the Cochrane Pregnancy and Childbirth Group (The Cochrane Library 2005, Issue 2) databases, and journal search, for the different options available for the same, and highlights the current modes of treatment.

INCIDENCE
Sixteen percent of all clinically recognized pregnancies result in a miscarriage; however, 80% of all conceptions are not even recognized as pregnancies due to early biochemical losses. The risk of abortion rises to 55% after three consecutive spontaneous abortions¹ (Box 1).

<table>
<thead>
<tr>
<th>Box 1: Incidence of spontaneous abortions¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 15–20% of all pregnancies</td>
</tr>
<tr>
<td>• 11–13% in first pregnancy</td>
</tr>
<tr>
<td>• 13–17% after first abortion</td>
</tr>
<tr>
<td>• 38% after two abortions</td>
</tr>
<tr>
<td>• 55% after three consecutive abortions</td>
</tr>
</tbody>
</table>
DEFINITION

Recurrent pregnancy losses can be divided as follows:
- Recurrent spontaneous abortions (before viability)
- First trimester and second trimester
- Recurrent bad obstetric outcomes (after viability)
- Late second trimester and third trimester

Classical definition: It is classically defined as three or more consecutive pregnancy losses at 20 weeks or less or with fetal weight less than 500 g. Most women with recurrent miscarriage have embryonic or early fetal loss, and the minority of losses are after 14 weeks. Although the definition includes three or more miscarriages, many agree that evaluation should at least be considered following two consecutive losses:
1. Primary recurrent miscarriage—no successful pregnancies
2. Secondary recurrent miscarriage—one prior livebirth as the latter group does not reach a risk of subsequent loss of 32% until after three miscarriages. Thus, it is reasonable to delay evaluation of secondary recurrent loss until three consecutive losses.

Most of us in clinical practice would start basic investigation after two losses and aggressive management after three losses. This is also due to the fact that, spontaneous chance of the third pregnancy succeeding after two losses is not unknown but risk of a third abortion is nearly 38%.\(^1,2\) Research in RSA is associated with numerous problems which are listed in Box 2.

ETIOLOGY OF RECURRENT SPONTANEOUS ABORTIONS

We can divide the causes of RSA into two main categories. Those which have known causes and the unknown (Table 1, Box 3). More than 50% of RSA patients fall into the latter group. With more understanding of the immune system and the role of antibodies in governing the pregnancy, antiphospholipids seem to have role to play in the etiology of RSA.\(^3\) They can also be divided into doubtful causes and possible causes. The important factor to understand is that it is necessary to prove the same cause in every pregnancy loss before we label a factor as the etiology behind the RSA. Having a positive test in one pregnancy is not to be included as the causes of RSA (Table 2).

### Box 2: Problems of research in recurrent spontaneous abortions
- The cause of individual abortion may be different
- More than one factor may exist
- Thorough investigation often fails to reveal a cause

### Table 1: Etiology of recurrent spontaneous abortions\(^1,2\)

**Doubtful causes of RSA**

- **Endocrine and metabolic disease:**
  - Untreated adrenal hyperplasia
  - Diabetes mellitus
- **Exogenous causes:**
  - Environmental factors, alcohol, street drugs, anesthesia, gases, etc.
- **TORCH infections**

**Possible causes of RSA**

- **Fetal abnormalities of genetic origin:**
  - Parental chromosomal rearrangement, aneuploidy, previous abnormality, chance, molecular mutations
- **Uterine anatomical defects:**
  - Body: Fibroids, septum, bicornuate uterus, etc.
  - Cervix: Incompetent internal orifice
- **Immunological:**
  - SLE, antiphospholipid antibodies, alloimmune factors, NK cells
- **Maternal age (Table 2)**
- **Hormonal:**
  - Corpus luteum deficiency (LPD), PCOS, Hypo/Hyperthyroidism
- **General disease:**
  - Wilson’s disease, renal dysfunction, chronic essential HT, etc.

**Abbreviations:** HT, hypertension; SLE, systemic lupus erythematosus; PCOS, polycystic ovary syndrome; LPD, luteal phase deficiencies; NK, natural killer

### Table 2: Maternal age and risk of abortions

<table>
<thead>
<tr>
<th>Maternal age/years</th>
<th>Risk of loss %</th>
</tr>
</thead>
<tbody>
<tr>
<td>15–19</td>
<td>9.9</td>
</tr>
<tr>
<td>20–24</td>
<td>9.5</td>
</tr>
<tr>
<td>25–29</td>
<td>10.0</td>
</tr>
<tr>
<td>30–34</td>
<td>11.7</td>
</tr>
<tr>
<td>35–39</td>
<td>17.7</td>
</tr>
<tr>
<td>40–44</td>
<td>33.8</td>
</tr>
<tr>
<td>44 and older</td>
<td>53.2</td>
</tr>
</tbody>
</table>

### Box 3: Causes of recurrent spontaneous abortions

- **Explainable:** 50–60%
  - Genetic
  - Infections
  - Endocrine
  - Autoimmune: SLE, anticardiolipin antibodies
- **Unexplainable:** 40–50%

**Abbreviation:** SLE, systemic lupus erythematosus
MANAGEMENT OF A PATIENT WITH RECURRENT SPONTANEOUS ABORTIONS

Recurrent abortion is a heterogeneous condition which is extremely traumatic emotionally as well as physically. Despite thorough investigation according to various clinical protocols (Box 4), the underlying etiology remains obscure in the majority of patients, and obstetricians are facing a challenge to determine the cause of these unexplained abortions.

Whenever the cause is found, the treatment remains treatment of the cause. Since more than 50% of the patients of RSA have no cause, the treatment remains empirical to a large extent. Recent evidence seems to suggest that the so called unknown etiologies may have an immunological basis (Figs 1A and B) and hence immune-modulation and prevention of thrombotic activity, forms the mainstay of management in known and unknown cases. Most often by default, the patients are advised bed rest in the hope of improving the uterine circulation. However, there is no obvious evidence that bed rest works, but is still commonly recommended. Some observational studies have suggested that TLC (Tender Loving Care) seems to be more effective as it instills confidence in the patient that there is someone who cares and is doing their utmost to help them. Once again, there is no evidence to support this. Tocolytic drugs have no role in the first trimester and should not be recommended for RSA.

Progesterone Support

It is a well-known fact, that luteal phase insufficiency can result or present as RSAs. The difficulty is in establishing the diagnosis. The gold standard is an endometrial biopsy, but with availability of serum markers, this invasive test is hardly resorted to. In the absence of any factor, the patients are given progesterone support till the placenta takes over luteal function. There are some early studies suggesting that there is no role for progesterone once the pregnancy test is positive and recommend stopping progesterone once beta-human chorionic gonadotropin is positive. Some studies suggest stopping progesterone once the fetal heart is demonstrated on ultrasound. However, most continue giving progesterone till the end of first trimester.

What is important to understand is that progesterone is the hormone which is responsible for the immune cascade of pregnancy and hence is called as an immunomodulator. How this precise mechanism works is unclear, but progesterone does help. It should be given in the dose of 600–800 mg per day either vaginally or orally. The vaginal route is preferred as it is locally administered and hence the bioavailability is
better. Injectable progesterone has good blood levels but local bioavailability is lesser than the local route. Progesterone can be given in the form of 8% vaginal gel also.8,9

POLYCYSTIC OVARY SYNDROME CAUSING RECURRENT PREGNANCY LOSSES

Rai et al.10 suggest that there is need to search for a specific endocrine abnormality that can divide women with polycystic ovary syndrome (PCOS) into those with good pregnancy outcomes and those with poorer pregnancy outcomes, irrespective of the type of conception. Of all clinical pregnancies, about 15% end in a first trimester loss or miscarriage.11 While the cause for recurrent miscarriage is impossible to identify in many cases, the incidence of PCOS amongst women with recurrent miscarriage is high,9 with one study suggesting the ultrasound incidence of polycystic ovaries (PCO) as high as 82%.12 Several studies have shown a clear relationship between the raised serum luteinizing hormone (LH) often found in association with PCOS and early pregnancy loss. In their study, Glueck et al.13 have demonstrated that, plasminogen activator inhibitor activity is an independent risk factor for the high miscarriage rate during pregnancy in women with PCOS. They concluded that “PAI-Fx is a predominant, independent, significant, positive and reversible risk factor for miscarriage in women with PCOS.” This may help us in reaching successful pregnancies in future of these women.

Hyperinsulinemia and Insulin Resistance

The association between increased insulin resistance and polycystic ovaries is now well-recognized. Insulin resistance is defined as a reduced glucose response to a given amount of insulin. The reason for hyperinsulinemia is increased peripheral target tissue resistance, and a decreased hepatic insulin clearance. There are three categories of peripheral target tissue insulin resistance: (1) decrease insulin receptor number, (2) decreased insulin binding and (3) postreceptor failure. The measurement of the ratio of fasting glucose to fasting insulin if less than 4.5, is consistent with insulin resistance. Women with PCO have android obesity which is seen as a waist-hip ratio (WHR) of greater than 0.85, and many of them have increased body mass index (BMI).14,15

There are various studies13,16-18 which were conducted to examine the effect of metformin therapy on ovarian response in clomiphene-resistant PCOS patients. In almost all of them, the total gonadotropin doses, duration of therapy, and plasma estradiol in the metformin-study group were significantly lower and there was a higher pregnancy outcome, along with a decrease in hyperstimulation risk, cycle cancellations, and multiple pregnancy rates. Glueck et al.13,18 concluded that “metformin therapy throughout pregnancy in women with PCOS reduces the otherwise high rate of first-trimester spontaneous abortion seen among women not receiving metformin and does not appear to be teratogenic.”

Hyperandrogenemia

Raised serum levels of free testosterone and androstenedione and reduced levels of sex-hormone-binding globulin are found in association will PCOS.15,20 However, these changes have also been reported in women with recurrent miscarriage without other features of PCOS (raised LH or PCO by ultrasonography) and hence are of doubtful significance.21,22

It is clear that there is an association between PCOS and early pregnancy loss, and more so in women with hypersecretion of LH and hyperinsulinemia. It would appear that presence of raised early follicular LH levels, ultrasound diagnosis of PCOS, obesity, hyperinsulinemia, and hyperandrogenemia either single or in combination are associated with an increased risk of miscarriage.

GENETIC ABNORMALITIES

Most common causes of chromosomal problems are seen in the form of parental chromosomal rearrangements and/or aneuploidy. These can be because of a previous abnormality or a chance molecular mutation. The fact is that the incidence of finding chromosomal abnormalities is 3.6–6.1% as against 1.2% in the general population. These abnormalities can be a balanced translocation (Reciprocal or Robertsonian) or an inversion which gives rise to unbalanced translocation.1,2,4

The management options are limited and are as follows:

• Genetic counseling against risks
• Preimplantation genetic diagnosis (in known cases of abnormality)
• Donor eggs or sperm
• Genetic evaluation of fetus by chorion villus biopsy or amniocentesis.

ANTIPHOSPHOLIPID ANTIBODY (APLA) SYNDROME

Antiphospholipid antibodies were first described in 1906 in a study by Wassermann et al.23 among patients with positive serologic test results for syphilis. Antiphospholipid antibodies are a heterogeneous group of autoantibodies directed against phospholipid-binding proteins. Antiphospholipid antibodies can be broadly categorized into those antibodies that prolong phospholipid-dependent coagulation assays, known as lupus anticoagulants (LA), or aCL, which target a molecular congener of cardiolipin (a bovine cardiac protein). The presence of these antibodies in patients with arterial or venous thrombosis or pregnancy morbidity comprises the antiphospholipid antibody syndrome (APLAS), when this occurs in association with other conditions, such as systemic
lupus erythematosus (SLE). Antiphospholipid antibodies are also found in patients with infections such as human immunodeficiency virus and may develop during therapy with medications such as chlorpromazine.24,25

The presence of antiphospholipid antibodies in serum has been associated with the antiphospholipid-antibody syndrome, which is characterized by arterial and venous thrombosis or recurrent pregnancy loss attributed to placental thrombosis.23,25 The pathogenic mechanisms of this disorder are unknown. Remarkably, "lupus anticoagulants"—antibodies against anionic phospholipids or associated proteins, which inhibit phospholipid-dependent blood coagulation—are frequently found in patients with this disorder. Yet, paradoxically, these anticoagulants are associated with thrombotic manifestations and not with bleeding disorders.

Treatment of antiphospholipid antibodies is problematic because of a lack of laboratory standardization, limited data on their natural history, and a lack of randomized treatment trials. Depending on the assay, antiphospholipid antibodies are reported in up to 10% of healthy individuals and in 30–50% of patients with SLE.26,27

**Laboratory Detection of Antiphospholipid Antibodies**

Laboratory testing for antiphospholipid antibodies is complicated because there is certainty about their antigen target. Both LA and aCL may demonstrate specificity for β₂-glycoprotein I,28 but many other antigenic targets have been described including prothrombin and annexin V.29,30

**Lupus Anticoagulants**

Lupus anticoagulants, also referred to as nonspecific inhibitors, are antibodies that block phospholipid surfaces important for coagulation. They reduce the coagulant potential of the plasma and prolong the clotting time in coagulation tests based on the activated partial thromboplastin time. Failure of the prolonged clotting time to correct after a 1:1 mix with normal platelet-free plasma and correction of the clotting time after addition of excess phospholipids confirms the presence of LA. Anticoagulant therapy may interfere with the detection of LA.28,31

**Anticardiolipin Antibodies**

Anticardiolipin antibodies share a common in vitro binding affinity for cardiolipin and can be detected using enzyme-linked immunosorbent assays. The immunoglobulin isotype may be IgG, IgM, or IgA. Enzyme-linked immunosorbent assay tests for aCL are poorly standardized and aCL testing has shown poor concordance between laboratories. aCL are reported as a titer specific to the isotype (IgG, IgM, or IgA phospholipid antibody titer), but because the accuracy and reliability of assays are limited, consensus guidelines recommend semiquantitative reporting of results (low, medium, or high titer).29,31

**Anti-β₂-Glycoprotein I Antibodies**

Anti-β₂-glycoprotein I antibodies32 are currently not included in the Sapporo criteria but may be incorporated in future updates. The laboratory assay for these antibodies is not standardized, making comparison between studies difficult.32,33 The clinical relevance of anti-β₂-glycoprotein I antibodies also is uncertain, although there is some evidence that these antibodies are more specific for APS.

**Diagnostic Criteria for Antiphospholipid Antibody Syndrome**

Consensus-derived diagnostic criteria formulated by the Sapporo international workshop require repeated measurement to establish a diagnosis of APS.34 APS is present in patients when there is at least one clinical and one laboratory criterion.

**Clinical Criteria**

- Confirmed arterial, venous, or small-vessel thrombosis
- Pregnancy morbidity consisting of recurrent fetal loss before the tenth week of gestation
- One or more unexplained fetal death at or beyond the tenth week of gestation
- Premature birth due to placental insufficiency, eclampsia, or pre-eclampsia

**Laboratory Criteria**

- Medium or high titer IgG or IgM aCL
- The presence of LA on two or more occasions at least 6 weeks apart

**Association of Antiphospholipid: Antibodies and Thrombosis**

In a general obstetric population, the prevalence of LA was 0.3% and the prevalence of aCL was 2.2–9.1%, which was similar to that observed among patients who are not pregnant (5.6%).29,30 Persistently positive antiphospholipid antibodies are unusual in healthy individuals (< 2% of healthy blood donors initially found to have aCL still had increased levels 9 months later).28 In comparison, the prevalence of antiphospholipid antibodies appears to be higher, in the range of 4–21%, among patients presenting with thrombosis or recurrent pregnancy.31,33 The increased prevalence of antiphospholipid antibodies among patients with thrombosis suggests an association between antiphospholipid antibodies and thrombosis, and the increasing risk of thrombosis...
among those patients with increasing antibody titers further strengthens the evidence that the association is causal. However, there remains controversy about the true nature of this relationship, which may also be confounded by the presence of unmeasured LA. The association between antiphospholipid antibodies and thrombosis is stronger with LA than with aCL. In a meta-analysis of 25 studies involving more than 7,000 patients, the mean odds ratio for thrombosis was 1.6 for aCL and 11.0 for LA.\textsuperscript{2,33,36}

Thrombosis is presumed to cause many of the pregnancy complications associated with APS. In women without SLE, a retrospective review of more than 13,000 patients found a prevalence of antiphospholipid antibodies of 20% among women with recurrent fetal loss compared with 5% in healthy women.\textsuperscript{36} The association between antiphospholipid antibodies and fetal loss is strongest for loss occurring after 10 weeks.\textsuperscript{37,38}

**Antithrombotic Treatment of Antiphospholipid Antibody Syndrome in Pregnancy**

The optimal treatment of pregnant women with antiphospholipid antibodies and one or more fetal losses after 10 weeks’ gestation without thrombosis is controversial. A systematic review\textsuperscript{38,39} of 13 randomized and quasi-randomized trials involving 849 pregnant women with a history of pregnancy loss and antiphospholipid antibodies found that combination therapy with unfractionated heparin (5,000 units subcutaneously twice daily) and aspirin (75–81 mg/day) significantly reduced pregnancy loss compared with aspirin alone [relative risk (RR), 0.46; 95% confidence interval (CI), 0.29–0.71]. However, this particular comparison was examined in only two trials involving 140 patients. The combination of low-molecular-weight heparin (5,000 units subcutaneously daily) and aspirin (75 mg/day) compared with aspirin alone did not significantly reduce pregnancy loss (RR, 0.78; 95% CI, 0.39–1.57), based on one trial of 98 patients.\textsuperscript{40,41} Aspirin (50–81 mg/day) compared with placebo or usual care did not reduce the rate of pregnancy loss in three trials (RR, 1.05; 95% CI, 0.66–1.68).\textsuperscript{42,43} Low doses of subcutaneous unfractionated heparin (5,000 units twice daily) appear to be as effective as high-dose heparin (10,000 units twice daily) (RR, 0.83; 95% CI, 0.29–2.38).\textsuperscript{44,45}

**Patients with Fetal Loss but No Prior Thrombosis**

The risk of thrombosis among women with antiphospholipid antibodies and fetal loss may be increased, based on the results of a retrospective study comparing aspirin with no prophylaxis in 65 nonpregnant women with antiphospholipid antibodies and a history of pregnancy loss. During a mean (standard deviation) duration of 8.1 (3.5) years, 20 (59%) of 34 patients who were not treated experienced venous or arterial thrombosis.\textsuperscript{46–49}

Consensus recommendations suggest that women with antiphospholipid antibodies and a history of two or more early pregnancy losses or one or more late pregnancy losses who have no prior history of thrombosis receive treatment with combination aspirin and heparin (unfractionated or low-molecular-weight) during pregnancy. Aspirin (81 mg/day) should be started with attempted conception and heparin (5,000–10,000 units every 12 hours) or low-molecular-weight heparin in prophylactic doses (enoxaparin, 1 mg/kg or 40–80 mg; dalteparin, 5,000 units; or nadroparin, 3,800 units, all administered once daily) should be started when a viable intrauterine pregnancy is documented and continued until late in the third trimester.\textsuperscript{40,44,46–53}

**Controversies in Antithrombotic: Prophylaxis in Antiphospholipid Antibody Syndrome**

The treatment of patients who are incidentally found to have an antiphospholipid antibody and have no prior thrombosis has not been adequately studied, except in patients with SLE. Consensus opinion suggests low-dose aspirin (81 mg/day) may be considered for asymptomatic patients who are not pregnant.\textsuperscript{53–55}

Researchers have suggested that the evidence of a potentially important prothrombotic effect of these antibodies—areduction in the quantity of the potent anticoagulant protein annexin V on the surface of placental trophoblasts and vascular endothelial cells. This is associated with an increase in the rate of coagulation at the cell surface. It stands in contrast to the “lupus anticoagulant” phenomenon observed with routine phospholipid-dependent coagulation assays. The 54-kd serum glycoprotein $\beta_2$-glycoprotein I ($\beta_2$-GPI, also known as apolipoprotein H) and other phospholipid-binding proteins appear to serve as cofactors in the recognition of their putative antigens by antiphospholipid antibodies.

**Obstetrical Considerations**

Women with antiphospholipid antibodies have an unusually high proportion of pregnancy losses within the fetal period (10 or more weeks of gestation). In contrast, in unselected women with sporadic or recurrent miscarriage, pregnancy losses occur more commonly in the pre-embryonic period (less than 6 weeks of gestation) or the embryonic period (6–9 weeks of gestation). Pregnancies in women who are positive for antiphospholipid antibodies can also be complicated by premature delivery due to pregnancy-associated hypertensive disease and uteroplacental insufficiency. Adverse pregnancy outcomes in women with the antiphospholipid syndrome may result from poor placental perfusion due to localized thrombosis, perhaps through interference with trophoblastic annexin V that is mediated by antiphospholipid antibodies. Antiphospholipid antibodies may also impair trophoblastic invasion and hormone production, thereby promoting not only
pre-embryonic and embryonic loss but also fetal loss and uteroplacental insufficiency.\textsuperscript{40,56-58}

Treatement has evolved considerably. Early enthusiasm for glucocorticoids waned when a small, randomized trial found heparin administered to pregnant women to be as effective as prednisone. Recently, two prospective trials showed that heparin plus low-dose aspirin is more effective than aspirin alone for achieving livebirths among women with antiphospholipid antibodies and predominantly pre-embryonic and embryonic pregnancy loss. A third prospective trial of women who were positive for antiphospholipid antibodies and had repeated pregnancy loss but no history of thrombosis or SLE found similar rates of livebirths (approximately 80%) with the use of either low-dose aspirin or placebo, suggesting that treatment may be unnecessary in some women. Although intravenous immune globulin has been used to treat some autoimmune conditions in pregnancy, a randomized, controlled study found no benefit of intravenous immune globulin as compared with heparin and aspirin in reducing adverse obstetrical outcomes in women with the antiphospholipid syndrome.\textsuperscript{54,57}

Concern about patient selection notwithstanding, most experts recognize the antiphospholipid syndrome as a proven, treatable cause of recurrent pregnancy loss. Currently, heparin administered to pregnant women after ultrasonographic demonstration of a live embryo is the treatment of choice, although the dose is debated. Women with recurrent pre-embryonic and embryonic pregnancy loss and no history of thromboembolism may be treated with 5,000 U of heparin twice daily, but experts recommend higher doses, sufficient to produce full anticoagulation, for women with prior thromboembolism. The optimal treatment for women with pregnancy loss during the fetal period but no history of thromboembolism is controversial because of the potential risk of maternal thromboembolism. Generous thromboprophylaxis (15,000–20,000 U of heparin per day) or adjusted thromboprophylaxis (15,000–20,000 U of heparin per day) is favored by some, but there are no properly designed studies for guidance. Experts agree that low-molecular-weight heparin may be substituted for standard heparin in the treatment of pregnant women with the antiphospholipid syndrome.\textsuperscript{56,58-62}

\section*{CONCLUSION}

Recurrent abortion is a heterogeneous condition which is extremely traumatic emotionally as well as physically. Despite thorough investigation according to various clinical protocols, the underlying etiology remains obscure in the majority of patients, and obstetricians are facing a challenge to determine the cause of these unexplained abortions.

Progesterone supplementation is the recommended therapy for luteal insufficiency. Metformin may have a role in PCOS-induced recurrent pregnancy loss. Majority of research now is directed toward immunological causes and a lot of questions still remain unanswered. Since initial reports of an association between aCL and thrombosis and fetal death, much of the research has focused on the pathogenesis and clinical features of APS. The results of these studies indicate that patients with antiphospholipid antibodies and venous thrombosis should be treated with long-term (potentially indefinite) anticoagulation administered to achieve an INR of 2.0–3.0, when not pregnant. But, during pregnancy the treatment of choice is low dose aspirin and low molecular weight heparin. Prospective studies addressing the issue of primary antithrombotic prophylaxis in asymptomatic patients with antiphospholipid antibodies are in progress. The role of immunoglobulins is not yet fully established. These and other well-designed prospective studies are required to complete the understanding of the optimal treatment of patients with antiphospholipid antibodies and APS and recurrent pregnancy loss.

\section*{REFERENCES}

Medical Disorders in Pregnancy


SECTION 3

Fetus as a Patient
INTRODUCTION

The objective of prenatal diagnostic techniques is to provide physical, genetic, physiological and biochemical information about the fetus for reassurance of normalcy and gauging the severity of abnormality.

Prenatal genetic diagnosis was introduced as a formal test in early seventies.¹

The availability of first trimester prenatal diagnosis and the advent of presymptomatic diagnosis by deoxyribonucleic acid (DNA) analysis have created further opportunities to avoid disorders characterized by early death, severe disease or irreparable brain damage.

COMMONLY USED GENETIC TESTS FOR PRENATAL DIAGNOSIS

Biochemical Testing

Direct analysis of proteins and other metabolites that are abnormal in certain genetic conditions. For example, tyrosinemia type 1 involves measurement of succinyl acetone in amniotic fluid.²

Deoxyribonucleic Acid Testing

The most commonly used DNA tests in the prenatal setting are β-thalassemia, hemophilia, Duchenne muscular dystrophy, etc. For monogenic disorders testing is often reserved for families at risk for the disorder. This usually requires prior diagnosis of an affected individual or carrier couple for autosomal recessive disorders. Molecular diagnosis should ideally be done before the pregnancy to define the precise mutation. In some cases, definitive testing may not be possible and linkage analysis may be required such as in a family of Duchenne muscular dystrophy in which no mutation has been identified. A linked marker is a sequence of DNA that lies near the gene of interest and shows individual variation in the DNA sequence, which allows the tracking of the chromosome carrying the affected gene. Using several markers as close to the gene site as possible, scope of error is minimized.³

Cytogenetic Testing

Cell culture: Cells are cultured and then harvested at the metaphase stage, at which time chromosomes are condensed and display their banded appearance. High-magnification light microscopy is used to look for abnormalities of chromosome number and structure.

Direct preparation: Direct preparation of genetic material, without culturing, is possible after chorionic villus sampling (CVS) because the cytotrophoblastic tissue has an extremely high mitotic rate. This permits a provisional interpretation to be provided in as little as 24–48 hours. This method also minimizes the risk of maternal cell contamination but suffers from poor quality banding.

Fluorescence in situ hybridization: The technique for fluorescent in situ hybridization (FISH) relies on the unique ability of a portion of single-stranded DNA, known as a probe, to hybridize (bond) with its complementary target DNA
sequence. The signal is directly visualized by fluorescent microscopy, and the presence or absence of specific DNA sequence is determined by observing whether a signal is present. Using commercially available probes and proper temperatures, the entire FISH process can be completed within 6–8 hours and as many as 5–7 probes may be used simultaneously. Trisomies and microdeletions like DiGeorge syndrome (22q11.2) can be diagnosed by FISH.4

## COMMON DIAGNOSTIC PROCEDURES DURING PREGNANCY (TABLE 1)
### NONINVASIVE SCREENINGS

#### First Trimester Aneuploidy Screen for Trisomy 21

Among the biochemical markers free beta-subunit of human chorionic gonadotropin (β-hCG) and pregnancy-associated plasma protein A (PAPP-A) have been shown to be effective with detection rates in the range of 55–68%.5,6 Combining maternal serum biochemistry and nuchal translucency (NT) measurements in the first trimester is an effective screening protocol because the two modalities are independent and 89% detection with a 5% false-positive rate may be achieved.7

First trimester risk screening must be combined with the second trimester biochemical screening or possibly additional ultrasound screening to produce accurate risk estimates. Wald et al. have integrated information from selected first and second trimester markers to achieve detection rate of 94% for trisomy 21 at a 5% false-positive rate.8

#### Second Trimester Biochemical Screen at 15–21 Weeks for Trisomy 21

Alpha-fetoprotein (AFP), hCG and estriol together are used as a triple-marker combination with a detection rate of 61% at a 5% false-positive rate.9 Inhibin A has been added to the triple-marker test to form a “quadruple test” with an additional gain of 5–7%.10,11

**Trisomy 18:** An association of trisomy 18 has been found with a tendency toward decreased levels of all analytes that is low AFP, estriol hCG, progesterone, inhibin and PAPP-A levels.12,13

**Trisomy 13:** Second trimester screening with AFP, estriol, and hCG is probably not useful in detecting trisomy 13 and ultrasound alone can detect abnormalities in up to 90% of fetuses with trisomy 13 during the second trimester.14,15

#### Fetal Ultrasound for Detection of Anomalies at 18–20 Weeks

Ultrasound can frequently detect many abnormalities in fetuses. These may include structural defects, nonstructural findings, or sonographic markers of fetal aneuploidy.

Incorporation of ultrasound data improves the performance of second trimester serum screening, with aneuploidy (Table 2).16,17

#### Fetal Echocardiography: Optimum Time 20–24 Weeks

A fetal echocardiography should be offered to patients at risk for congenital heart disease such as history of a cardiac

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**Table 1: Common diagnostic procedures during pregnancy**

<table>
<thead>
<tr>
<th>Procedure</th>
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<tbody>
<tr>
<td><strong>Noninvasive screenings</strong></td>
</tr>
<tr>
<td>• First trimester screen biochemical combined with nuchal scan: 11–13 weeks and 6 days</td>
</tr>
<tr>
<td>• Second trimester biochemical screen: 15–21 weeks</td>
</tr>
<tr>
<td>• Fetal ultrasound for detection of anomalies: 18–20 weeks</td>
</tr>
<tr>
<td>• Fetal echocardiography: Optimum time 20–24 weeks</td>
</tr>
<tr>
<td>• Fetal magnetic resonance imaging (MRI): 12 weeks to term</td>
</tr>
<tr>
<td><strong>Invasive techniques for obtaining fetal sample</strong></td>
</tr>
<tr>
<td>• Amniocentesis</td>
</tr>
<tr>
<td>• Chorionic villus sampling</td>
</tr>
<tr>
<td>• Placental biopsy</td>
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<tr>
<td>• Umbilical vein sampling</td>
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<tr>
<td>• Fetoscopy, fetal skin biopsy, fetal muscle biopsy</td>
</tr>
<tr>
<td><strong>Noninvasive techniques for obtaining fetal sample</strong></td>
</tr>
<tr>
<td>• Cervical washing</td>
</tr>
<tr>
<td>• Preimplantation diagnosis</td>
</tr>
<tr>
<td>• Maternal blood sampling for fetal cells or deoxyribonucleic acid (DNA)</td>
</tr>
</tbody>
</table>

**Table 2: Hard and soft markers of major trisomies**

<table>
<thead>
<tr>
<th>Trisomy 21</th>
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</thead>
<tbody>
<tr>
<td>Cardiac defects, duodenal atresia, cystic hygroma, hydrops</td>
</tr>
<tr>
<td>Nuchal thickening, hyperechoic bowel, echogenic intracardiac foci (EIF), shortened limbs, pyelectasis, mild ventriculomegaly, widened pelvic angle, shortened frontal lobe, clinodactyly, widened sandal gap, hypoplastic or absent nasal bone.</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Trisomy 18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac defects, spina bifida, cerebellar dysgenesis, micrognathia, diaphragmatic hernia, omphalocele, clenched hands/wrists, radial aplasia, clubfeet, cystic hygroma, choroid plexus cysts, brachycaphaly, shortened limbs, intrauterine growth restriction (IUGR), single umbilical artery.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Trisomy 13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac defects, central nervous system abnormalities, facial anomalies cleft lip/palate, urogenital anomalies/echogenic kidneys, omphalocele, polydactyly, rocker-bottom feet, cystic hygroma, EIF, mild ventriculomegaly, pyelectasis, IUGR, single umbilical artery.</td>
</tr>
</tbody>
</table>
defect, insulin dependent diabetes mellitus, connective tissue disease, ingestion of cardiac teratogenic drugs, fetal cardiac arrhythmias, fetal hydrops, and extracardiac malformation. Detection of cardiac anomaly will facilitate medical and surgical management after birth or termination before viability.18

Fetal Magnetic Resonance Imaging: 12 Weeks to Term

The greatest utility of fetal magnetic resonance imaging (MRI) is to clarify brain anomalies or injury when the ultrasonography (USG) has raised questions or has been inconclusive. Magnetic resonance findings not visualized by ultrasound include porencephaly, hemorrhage, partial or complete agenesis of the corpus callosum, cortical gyral abnormality, tethered cord, cortical clefts, midbrain abnormalities, partial or complete agenesis of the septi pellucidi, holoprosencephaly, cerebellar hypoplasia, subependymal and cortical tubers, vascular malformation, and vermian cysts. Abnormalities better defined by MRI than ultrasound include encephaloceles, arteriovenous malformations, distal neural tube defects and the mass effect of arachnoid cysts.19

Fetal magnetic resonance has been shown to be helpful in evaluation of neck and chest masses that potentially obstruct the airway.20

INVASIVE TECHNIQUES FOR OBTAINING FETAL SAMPLE

All patients should receive appropriate genetic counseling and should give informed consent before any prenatal invasive technique. Ultrasound examination should be performed to identify the number of fetuses, gestational ages, fetal positions, placental location(s) and presence of any fetal abnormalities. After any procedure, Rhesus (Rh) immunoglobulin (RhoGAM) should be given for patients who are Rh negative.

AMNIOCENTESIS

Genetic amniocentesis is most commonly performed during the second trimester but can be performed at any time up to delivery. It accounts for approximately 90% of prenatal tests. A needle is inserted through the woman’s abdominal wall into the amniotic sac around the fetus, under ultrasound guidance, and a sample is collected (Fig. 1). The cells in the amniotic fluid have been shed from the surface of the fetus and membranes. When performed during the second trimester, fetal karyotyping is usually performed with traditional cell culture. The main limitation of amniocentesis is the relatively advanced gestational age at which it is performed and the time delay due to the need to culture cells in the laboratory.

Indications

- Increased risk of fetal aneuploidy based on maternal age.
- Abnormal serum screen results.
- Prior medical history.
- Abnormal prenatal sonographic findings.
- Monitoring pregnancies at risk for Rh immunization.
- Evaluation of intrauterine infection in premature rupture of membranes (PPROM) or congenital infections.

Complications

- Amniocentesis failure: With the universal use of real-time sonographic guidance and the centralization of amniocentesis procedures at expert centers, the success rates of obtaining an adequate fluid sample are maximized.
- Pregnancy loss rate: We currently counsel all patients with singleton or multiple gestations of a 0.5–1.0% procedure-related loss rate.21–24
- Direct fetal injury: Direct fetal injury to the fetus from amniocentesis needle is an extremely uncommon event in the hands of an experienced operator using continuous sonographic visualization of the needle tip.
- Transient amniotic fluid leakage: The incidence of postamniocentesis fluid leakage was 1.7% for second trimester procedures. The postamniocentesis amniotic fluid leakage is associated with a significantly better overall prognosis from cases of spontaneous membrane rupture.25
- Mosaicism: Chromosomal mosaicism occurs in approximately 0.3% of amniocentesis cases. A diagnosis of true mosaicism is made when two cell populations with different karyotypes are found in at least two independent culture vessels. Pseudomosaicism is diagnosed when there
is only one cell or one region in a colony with abnormal karyotype, or when only one entire colony has an identical abnormal karyotype, or when multiple colonies within only one culture vessel show an identical abnormal karyotype. Depending on which definition is used; between 0.7% and 2.5% of all amniocentesis specimens will show pseudomosaicism. Excluding true mosaicism requires fetal blood sampling, with karyotype of cultured fetal lymphocytes. All fetuses with apparent mosaicism should also have a targeted fetal sonographic anatomy survey to aid in counseling. In cases of true mosaicism, the actual phenotype of the child is difficult to predict. After birth, the placenta should be sent for careful cytogenetic analysis.

Amniocentesis performed before 13 weeks or at 6 or 7 weeks is commonly referred to as early amniocentesis (EA). There is increased technical difficulty and complications associated with EA and so is no longer recommended.25

**CHORIONIC VILLOUS SAMPLING**

Chorionic villous sampling is a reasonable alternative to amniocentesis for first trimester diagnosis.26

**Indications**

Indications for doing CVS include cytogenetics testing, biochemical testing, polymerase chain reaction (PCR) for single gene disorder and fetal infection testing.

**Technique**

Chorionic villi can be obtained by the transcervical method or the transabdominal approach (Figs 2A and B). Transcervical sample is obtained with either a biopsy forceps or an aspiration catheter. Transabdominal CVS may be performed with either a needle-guide attachment or the free hand technique. The transabdominal approach generally uses a sterile single-use 20-guage spinal needle. The tip of the needle is then directed into the chorion frondosum parallel to the chorionic plate, slowly moving backward and forward four or five times while suctioning with the syringe.

After aspiration, the contents of the syringe and catheter or needle are flushed into a petri dish containing additional nutrient medium and the sample is carefully examined to confirm the presence of at least 10–30 mg of tissue. Patients should be advised that it is quite common to expect some light vaginal spotting especially after transcervical procedure, during the first 24 hours following the procedure.

**Complications**

**Chorionic villus sampling failure:** When performed by a skilled team, it is very unusual to fail to obtain adequate villus sample.

**Pregnancy loss:** Pregnancy loss for CVS compared with second trimester amniocentesis is between 0.5% and 1.0% but is unlikely to be any greater than 2.7%.27

Controversy exists on whether the two approaches to CVS (transabdominal vs. transcervical) are equally safe. No significant differences between the two procedures in pregnancy loss rates has been observed.28

**Limb reduction defects:** Procedures before 10 weeks may be associated with limb reduction defects of approximately 1–2%.29

Chorionic villous sampling is not recommended prior to 10 weeks to minimize the effect of transverse digital defects.
CHAPTER

Prenatal Diagnosis and Therapeutic Procedures

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Fig. 3: Fetal umbilical vein sampling

Confined placental mosaicism is seen in 1% of all CVS specimens.\(^{30}\)

**FETAL UMBILICAL VEIN SAMPLING**

Fetal umbilical vein sampling, also known as *percutaneous umbilical blood sampling* (PUBS), refers to the aspiration of fetal blood from the umbilical vein using continuous sonographic guidance (Fig. 3).

**Indications**

The indications for PUBS have decreased with advances in alternative methods of diagnosis. DNA technology increased the range of genetic diseases that can be diagnosed using chorionic villi or amniocytes, and the range of infectious diseases that can be diagnosed using amniotic fluid. Additionally, advances in sonographic technology have increased the options for noninvasive diagnosis of fetal anemia, a relatively common indication for PUBS.

The most common genetic indication for PUBS is *rapid fetal karyotyping*; fetal karyotype can generally be achieved from cultured fetal lymphocytes in 48 to 72 hours. PUBS may also be indicated when *chromosomal mosaicism* is diagnosed at CVS or amniocentesis.

Hematologic indications for PUBS include assessment of fetal hematocrit in pregnant women with *red cell isoimmunization* and assessment of fetal *platelet count* in pregnant women with platelet alloimmunization, being used less frequently in the contemporary management of immune thrombocytopenia (ITP) in pregnancy.

**Technique**

Local anesthesia and prophylactic antibodies may or may not be administered. Sonography should be performed to select the best target for sampling: the most commonly used site is the umbilical vein at its placental insertion, as the cord is relatively immobile in this area. If the placenta is posterior and the placental cord insertion site cannot be reached, it is reasonable to attempt PUBS from the place umbilical vein can be reached; occasionally a free loop of cord may be sampled, although this is technically more difficult as the mobility of the cord can make needle entry difficult. Rarely, it may be necessary to obtain fetal blood from the intrahepatic vein if no other site is accessible. Needle placement may be performed with either a free hand technique or a needle-guided attachment. A 22 gauge needle is used for a diagnostic procedure and a 20 gauge for intrauterine transfusion.

After sampling into a heparinized syringe, confirmation of fetal origin of the blood cells is done.

**Complications**

Complications of PUBS include failure to obtain fetal blood and fetal loss rates of 0.9–3.2%\(^{31,32}\). Other complications of the procedure noted included needle site bleeding, transient fetal bradycardia, chorioamnionitis and umbilical cord hematoma.

**EMBRYO-FETOSCOPY**

Embryoscopy and fetoscopy were developed in the 1970s. They were introduced as diagnostic tools to visualize external malformations of the fetuses in the first, second and third trimesters of pregnancy as well as to obtain fetal tissue for diagnostic purpose.\(^{33}\)

Diagnostic fetoscopy during the second and third trimester was abandoned in the late 1980s due to the invasive nature of the technique and the development of high-resolution ultrasound imaging. Recently, there has been renewed interest in embryo-fetoscopy due to the increasing use of ultrasound in the first trimester together with the development of new equipment, especially miniature fiberscopes,\(^{34}\) and the use of laser for treatment of twin-twin transfusion syndrome.\(^{35}\)

**REFERENCES**


INTRODUCTION

Congenital infections have been the subject of clinical and laboratory research since the great rubella pandemics of the 1940s. Maternal infection can lead to fetal infection by hematologic spread to the placenta and hence to the fetus. As a consequence of this route of infection (Table 1), the infection can be limited to the placenta or both placenta and fetus can be infected. The timing and extent of fetal infection following maternal infection can vary, depending on the type of infection, the gestational age at infection, and the immunologic status of the mother. Fetal infection results from viruses, bacteria and parasites such as *Toxoplasma gondii*. Up to 10% of pregnancies yearly are affected. The occurrence during pregnancy of rubella virus infection, once an important causative agent of congenital malformations, has substantially decreased, thanks to a general program of vaccination.

The spectrum of fetal involvement ranges from asymptomatic infection to long-term sequelae (depending on the gestational age at exposure, infecting agent, and infectious load), to intrauterine death.

Congenital infections can be the cause of diseases in the neonate and are sometimes responsible for severe handicaps.

Under specific circumstances, they can be prevented and treated. We intend to describe the presentation and diagnostic approach to these infections. We have selected eight of these for detailing: rubella, cytomegalovirus (CMV), varicella, toxoplasmosis, parvovirus, herpes simplex virus (HSV), hepatitis B, and human immunodeficiency virus (HIV) for their importance from a practical point of view. For many of the specific infections discussed, few data are available in the literature, and specific recommendations cannot be made.

PRESENTATION

Fetal infection may occur at any time during pregnancy. Infection may occur early in pregnancy causing an embryonic/fetal demise or obvious stigmata at birth, during the second or third trimester causing either intrauterine growth restriction (IUGR) or nonimmune hydrops (NIH) or during labor and delivery. In addition, the active immunological capacity of the fetus and newborn is compromised compared to that of older children or adults.

DIAGNOSTIC TECHNIQUES

Evidence of fetal infection relies on the identification of the organism or detection of its antigens or genome in fetal compartments (amniotic fluid, fetal blood, or ascitic fluid) or the detection of specific immunoglobulin (Ig) M antibodies targeted to the offending organism in the fetal blood or amniotic fluid. Identifying an infectious agent can sometimes take weeks, however. The production of specific IgM antibodies depends on the maturity of the fetal immune system and the immunogenicity of the specific infectious agent. Therefore, the detection of specific IgM antibodies is reliable evidence of fetal infection, but their absence
does not rule it out. Nonspecific evidence of fetal infection can also be obtained from fetal blood sampling—elevated total IgM antibodies, thrombocytopenia, eosinophilia, and elevated liver enzyme levels—and although not diagnostic, it increases the likelihood of fetal involvement in the presence of a documented recent maternal infection.

**Amniocentesis**

First performed by Bevis in 1952 to detect the presence of bilirubin derivatives in the amniotic fluid of fetuses at risk for immune hemolytic anemia, this technique is now routinely used to detect infections (culture, electron microscopy). The risk of fetal loss is low (< 0.5% with ultrasound guidance) and complications are rare.

**Cordocentesis**

This technique is now routined for the investigation of fetal infections since, in most cases, pure fetal blood is obtained (i.e. no cross-contamination by maternal blood). The blood obtained may be cultured for virus (or other infecting agents) or used for serologic studies to identify IgM-specific antibody. The risk to the fetus is low and fetal loss occurs in less than 2% of procedures.

**Culture Methods**

The gold standard of diagnosis of fetal infection relies on culture of blood or buffy coat, amniotic fluid or placenta. However, in most cases the culture results are either negative or equivocal. Further, concern over maternal contamination is common. Lastly, identification is generally slow and certain viruses (i.e. parvovirus) do not readily grow in standard culture systems.

**Serologic Methods**

These methods have traditionally been relied on for antenatal diagnosis since culture is often not helpful. IgM-specific antiviral antibodies are sought since IgM is not normally passed transplacentally. Its presence in umbilical cord blood is generally considered diagnostic.

Diagnostic sensitivity of both culture and serology is related to the viral or parasitic load. In practice, an infectious etiology is documented by viral culture or serologic methods in only 5–15% of fetuses with hydrops or isolated ascites, pleural or pericardial fluids, with no obvious cause identified by these methods in over 20% of affected fetuses. For these reasons, diagnostic methods other than serology and culture have been sought.

**Polymerase Chain Reaction**

Polymerase chain reaction (PCR) permits the rapid detection (in 1–3 days) of nucleic acid from viruses, parasites and bacteria. PCR is an automated in vitro repetitive reaction that uses a heat-stable deoxyribonucleic acid (DNA) polymerase to amplify a specified segment of DNA. The elegance of PCR lies in its simplicity and ability to amplify a single copy of the target fragment of DNA up to a million-fold in a matter of hours, thus allowing easy access to large quantities of DNA of interest for analysis. The greatest limitation of PCR is the need to know a short stretch of nucleotide (base) sequence flanking both ends of the desired segment of DNA to develop the primers necessary for the amplification.

**Diagnostic Approach**

Possible viral disease should be sought using a combination of methods concomitantly. These methods include culture, serology and PCR analysis. The specimens of choice include amniotic fluid, fetal blood or placenta. Other samples such as ascitic, pleural, or pericardial fluids are acceptable but appear to be slightly less sensitive. In cases of fetal demise, at risk fetal tissue (i.e. heart, lung, liver, brain) is a good source for study and may be evaluated whether the tissue is frozen (best), fixed in formalin (useful) or paraffin (least useful). PCR may also be used in cases where nonviral etiologies (i.e. toxoplasma, chlamydia, etc.) are under consideration.

**DETAILS OF INDIVIDUAL INFECTIONS**

**Rubella**

The syndrome of congenital rubella was first described in 1941 by an Australian ophthalmologist. The virus of rubella is among the most pathogenic agents that can affect an embryo or a fetus. The most frequently encountered injury is neurosensory deafness. Before vaccination became the rule, rubella was responsible for 16% of the cases of deafness of central origin. Many other injuries including cardiac malformations, (persistent ductus arteriosus, ventricular septal defect) as well as eye lesions (cataract, microphthalmia, glaucoma, retinopathy) can be associated with it. The lesions of the central nervous system (CNS), including microcephaly, encephalitis, or mental retardation, can be extremely serious. These malformations are generally associated with IUGR and a dysfunction of the hematopoietic system. Ten to fifteen percent of the rubella infections contracted during the first trimester result in spontaneous abortion.

**Risks to the Fetus**

The risk of fetal infections and malformations varies with the different stages of pregnancy. The incidence of vertical transmission (fetal infection rate) declines from 90% during the first trimester to 25% at the end of the second trimester, and then rises again to 95–100% during the last month of pregnancy.
It is more difficult to assess the risk of fetal malformation, but serious and multiple damage is the rule when the infection occurs before 11 weeks of gestation. During the early second trimester, the global percentage of malformations is about 35%. After the 17th week of pregnancy, no further severe damage is observed and the children only present with subclinical forms of congenital rubella. It is not possible, however, to evaluate the possible long-term effects on neuropsychiatric development.

**Prenatal Diagnosis and Subsequent Approach**

In utero, diagnosis includes fetal blood sampling by cordocentesis for measurement of fetal levels of rubella—specific IgM, reverse transcription PCR (RT-PCR) and virus isolation from maternal pharyngeal swabs and products conception. RT-PCR can detect presence of viral ribonucleic acid (RNA) even when the fetal rubella virus-specific IgM obtained by fetal blood sampling is negative.

The accuracy of amniotic fluid culture, assessment of fetal blood for specific IgM or use of PCR is low enough that counseling based on gestational age-related risk of congenital infection provides equally good information on the risk of severe disease.

No treatment other than abortion is available. Immunoglobulin therapy after exposure to rubella early in pregnancy does not prevent fetal infection or teratogenic effects. Its use can be considered only when a pregnant woman with exposure to rubella would not consider terminating the pregnancy under any circumstances. No antiviral treatment is yet available or tested. Prevention of maternal infection is the best therapy.

**Prevention**

*Prepregnancy*: Widespread vaccination of children and susceptible adults will prevent outbreaks of rubella, thus reducing the possibility of congenital rubella infection. All children should receive a single dose of live, attenuated rubella vaccine at around 15 months of age (in a trivalent preparation of measles, mumps and rubella strains). Antibody to rubella virus should be detectable for up to 16 years after vaccination. However, individuals with low levels of antibody after vaccination may be susceptible to viremia and clinical infection. Vaccination is also recommended for adults found susceptible by serological testing or who do not have documentation of vaccination after their first birthday.

The rubella vaccine is a live virus preparation and should not be administered to pregnant women for theoretic reasons. However, the Centers for Disease Control has monitored inadvertent rubella vaccinations during pregnancy between 1971 and 1989, collecting over 500 cases. No case of congenital rubella syndrome was documented due to vaccine, although virus was isolated from the conception in several cases. Thus, patients accidentally vaccinated during pregnancy or becoming pregnant shortly after vaccination should be counseled and reassured that fetal risks are negligible.

Passive immunization by injection of specific immunoglobulins can be performed in cases of exposure during pregnancy. It is obviously useless if it is administered once the rash has appeared. Patients treated in this way may sustain a subclinical infection, and their serological condition should, therefore, be checked regularly. However, there is no evidence that passive immunization prevents fetal infection or damage.

**Cytomegalovirus**

Cytomegalovirus is a DNA virus and a member of herpes family of viruses, with an incidence of varying congenital infection, from 0.2% to 2.2% of livebirth, depending on the populations studies. The contagiousness of CMV is relatively low and its transmission requires prolonged and close contact (sexual intercourse, oropharyngeal secretions or transfusion of blood products). The infection is most often asymptomatic during pregnancy, and in Europe, 45% of pregnant women are positive at the beginning of pregnancy in the higher income groups and 85% of those in lower income groups are seropositive.

Among women with immunity to CMV, about 0.5–1% have a recurrent infection during pregnancy. Pre-existing maternal antibodies to CMV seem to protect the fetus, however, and lessen the incidence and severity of the manifestations of congenital CMV infection.

**Risks to the Fetus**

The risk of primary infection during pregnancy for seronegative women ranges from 1% to 4%. In 40% of the cases, the virus will be transmitted to the fetus. Eighty-five to 90% of the infected infants of these are likely to develop sequelae, most commonly hearing loss. The other 10–15% of the infected infants have symptoms at birth14 including petechiae, thrombocytopenia, increased conjugated bilirubin, hepatosplenomegaly, chorioretinitis, microcephaly and intracerebral calcifications. Pass published the long-term follow-up of 34 children suffering from cytomegalic inclusions disease: 10 of them were dead at the age of 2 years (most had died at the age of 3 months), 16 had microcephaly and cerebral palsy was extremely frequent. Twelve of them had impaired hearing or vision and the intelligence quotient (IQ) of 10 of the 24 survivors was under 80.

The transplacental transmission of CMV does not depend on the time when the mother was infected. Fetal infection has been described after primary infection during the first, second and third trimesters of pregnancy but the risk of symptoms and sequelae seems to be notably higher when the infection occurs during the first 27 weeks. There may be recurrences and reinfections, and the risk of fetal infection, then is the same as with primary infections. In such cases,
however, the risk of fetal damage is very low, if one considers that in areas where all pregnant women are seropositive no handicaps caused by CMV are observed.18,19

Prenatal Diagnosis

Prenatal diagnosis is based on fetal blood sampling and amniocentesis at 20–23 weeks. The virus itself can be isolated in amniotic fluid or fetal blood with the former being more reliable. Amniotic fluid culture is superior to fetal IgM in diagnosing fetal infection. Other nonspecific signs of infection, such as thrombocytopenia, elevated gamma-glutamyl transpeptidase (γ-GTP) and total IgM may also be seen. On ultrasonographic examination, intrauterine CMV infection may present as ascites or generalized hydrops, ventriculomegaly, intracranial calcifications, increased bowel echodensity, and growth retardation. It can be assumed that infected fetuses with ultrasonographic signs or evidence of hematopoietic or hepatic disease have an extremely high probability of severe disease and sequelae, however, the absence of abnormal sonographic findings does not rule out infection in a fetus.

Prevention

Vaccination is not widely available and consists of a live-attenuated virus, which should not be administered during pregnancy. Passive immunization is not possible since exposure to the infection cannot be identified in most cases. Given the particularities of CMV infection and the lack of prophylaxis or treatment, routine screening of pregnant women does not seem to be justified. The only mode of transmission of the CMV that can be prevented by the obstetrician is infection resulting from transfusions. Any pregnant woman receiving blood transfusions during pregnancy should receive CMV-negative blood, whatever her serological status may be.

No effective fetal therapy is yet available. Ganciclovir has been administered into umbilical vein of the fetus at 27 weeks. Dosage of 10 mg/day for 5 days, 15 mg/day for 3 days and 20 mg/day for 4 days was found to decrease viral load in amniotic fluid. But, fetal bradycardia and demise remain serious threats. It may decrease viral shedding and reduce the risk of organ damage in cases of in utero infection. Before this is attempted larger trials evaluating, the clinical efficacy and safety in newborns will be necessary.

For all these reasons, CMV congenital infections will probably remain a major cause of handicap in years to come.

Varicella

Primary varicella is rarely an adult’s disease. Approximately 95% of pregnant women are immune. Its incidence can be estimated at one to five cases in 10,000 pregnancies. However, maternal morbidity and mortality is relatively high. Out of 118 cases described in the medical literature, 20% had pneumonia, 10% of which resulted in the mother’s death.15 But, it should be pointed out that only the most serious cases are described in the literature. Pregnant women with acute Varicella infection, requires close observation for evidence of severe illness and dissemination. The high-risk women may be given varicella zoster virus (VZV) immunoglobulin in the dose of 125 u/10 kg of body weight, IM. The use of varicella zoster immune globulin (VZIG) is not recommended in pregnancy. Acyclovir in the dose of 5–10 mg/kg IV 8 hourly for 7 days has no untoward maternal or fetal side effects.

Risks to the Fetus

The virus is seldom transmitted to the fetus (1–2% of the cases). The syndrome of congenital varicella consists of typical malformations, such as cutaneous scars, hypoplasia of the hands and feet, cerebral cortical atrophy, mental retardation with convulsions, eye lesions such as chorioretinitis or cataract and IUGR. The risk of congenital varicella syndrome seems to be limited to first and early second trimester infections. All the cases of congenital varicella syndrome described have followed infections occurring between the 7th and the 21st week of pregnancy.

The pathogenesis of the lesions observed in cases of congenital varicella is not clear. Higa20 hypothesized that these injuries are not caused by the direct action of the virus but could result from the occurrence of genuine intrauterine fetal shingles.

The immunity conferred by varicella is stable and further infections are practically nonexistent. The risk of maternal varicella zoster is probably negligible because viremia is less frequent and the fetus is protected by the presence of maternal antibodies.

Prenatal Diagnosis and Subsequent Approach

In view of the small risk observed, termination of pregnancy is not indicated in cases of maternal varicella. Prenatal diagnosis by fetal blood sampling may be justified considering the severe CNS lesions observed in cases of fetal infection. Maternal varicella near the time of delivery carries a risk of neonatal varicella. In such cases, the risk of fetal infection ranges from 25% to 30%. The severity of neonatal varicella depends on the time of maternal infection with respect to delivery and on the development of maternal IgG. Maternal varicella occurring from 5 days to 21 days before delivery and developing in the infant during the first 4 days of its life will have a variable outcome with a good prognosis. When it occurs 4 days before to 2 days after delivery, which means that the child will develop the disease 5–10 days after birth, the infection can be very severe, with a very high risk of morbidity or mortality. The difference between benign neonatal disease during the first 4 days of life and the more severe manifestations of neonatal varicella at 5–10 days of life can easily be accounted for. In the first case, the maternal
antibodies are present with a very high concentration in fetal blood and protect the infant, whereas in the second case, the concentration of maternal antibodies in fetal blood is too low to ensure adequate protection.

**Prevention**

Passive immunization is currently available and should be administered within 24–72 hours to seronegative pregnant patients who have been exposed to varicella.

Once the rash is present, immunoglobulins should only be used at term if delivery is anticipated within 4–5 days.

Acyclovir crosses placental barrier\(^1\) and has been proposed by some authors for varicella occurring near delivery.\(^2\) However, the fetal effects are unknown, thus it cannot be recommended early in pregnancy. There is no evidence, however, that VZIG, acyclovir, or interferon treatment can alter the course of intrauterine infection or prevent fetal infection.

**Toxoplasmosis**

Toxoplasmosis is a parasite disease caused by a protozoan, *Toxoplasma gondii*. The cat is the only natural host. However, the toxoplasma can infect many animals (including humans). Humans can be either directly infected from cat feces or indirectly by ingestion of undercooked meat from parasitized animals. Infection is frequent but most often asymptomatic, except in cases of immunodeficiency. For pregnant women, the consequences of infection may be serious if the parasite is transmitted to the fetus.

**Risks to the Fetus**

The risk of fetal infection is 7%,\(^3\) but it varies with the time of seroconversion and regularly increases from the beginning to the end of pregnancy. Transmission to the fetus results from placental infection and secondary passage into the fetal circulation. On the other hand, the earlier the fetus is infected, the more serious are the sequelae. Severe congenital toxoplasmosis is a rare but most dangerous form of the disease, especially when the fetus has been infected during the first trimester of pregnancy. It is characterized by multisystemic damage and causes, in particular, destruction of cerebral tissue often associated with cerebral ventricle dilatation. Later the gestational age at infection, less severe the fetal damage. Overall, 70% are born without obvious damage, 10% suffer only ocular manifestations, 20% have the classic appearance of the TORCH baby.

**Prenatal Diagnosis and Treatment**

Prenatal diagnosis is based on ultrasound examination, amniocentesis and fetal blood sampling.\(^4\) It can be performed as of 18–20 weeks of amenorrhea. The analysis of fetal blood allows the detection of indirect biological signs of infection, i.e. leukocytosis, eosinophilia, thrombocytopenia, elevated levels of total IgM and gamma-glutamyl transferase, and specific fetal IgM. Parasitological test includes inoculation of fetal blood and amniotic fluid into mice and fibroblast cultures. Hohlfeld et al. demonstrated that prenatal diagnosis of congenital infection based on a PCR test using amniotic fluid is the preferred diagnostic approach. A serologic diagnosis requires a careful interpretation of the results because some tests have different sensitivities at various stages of infection. It is important to rely on a reference laboratory where several tests can be done in parallel with evaluations of previous specimens. There is as yet no consensus on whether routine testing for toxoplasmosis in pregnancy is cost-effective.

According to the prenatal diagnosis, three different approaches may be proposed. If the fetus is not infected, the treatment with spiramycin should be continued in order to avoid later contamination from an infected placenta, and ultrasound examinations will suffice until delivery.

Spiramycin is an antibiotic whose activity in toxoplasmosis has been experimentally and clinically documented.\(^5\) Its tissue concentration in the placenta is excellent, and it passes through the fetoplacental barrier having been found in fetal blood sampled for prenatal diagnosis.\(^6\) When toxoplasmosis occurs during pregnancy, spiramycin reduces the risk of fetal infection by 60%.\(^7\) Its purpose is not to treat an already infected fetus but to prevent the parasite from passing into the fetal circulation. The lapse of time between maternal seroconversion and the onset of spiramycin therapy seems to be of importance, as a prolonged interval is more often associated with the presence of severe fetal lesions on prenatal diagnosis.\(^8\) A dose of 3 g/day is necessary to obtain adequate placental concentrations. This treatment involves no particular risk, with excellent tolerance even when it is administered over long periods of time. No hepatotoxicity has ever been reported nor any interference with other drugs.

If the fetus is infected following toxoplasmosis acquired during the first trimester or if the ultrasound reveals cerebral damage, termination of the pregnancy should be considered.

**Prevention**

It is most important to warn seronegative pregnant women about the precautions they should take (Table 2).\(^9\)

**Parvovirus**

Human parvovirus B19 is a DNA virus in the family *Paroviridae*.

The pathogenic effect of parvovirus, particularly B19, on the fetus has been recognized for less than 10 years. The classical maternal symptoms are the typical facial rash and arthralgias, which are not very specific and usually do not lead to prenatal diagnosis.

Most often, prenatal diagnosis is considered once fetal hydrops is diagnosed on ultrasound. This is a consequence...
of acute fetal anemia due to the direct effect of the virus on the red blood cell precursors. B19 develops only on erythroid precursors [burst forming unit-erythroid (BFU-E)] and results in acute anemia and fetal death in 10–30% of cases.\textsuperscript{30}

**Prenatal Diagnosis**

Prenatal diagnosis is easily performed on fetal blood, which demonstrates an aplastic anemia and the presence of the virus (electron microscopy or DNA analysis).

**Evolution of Pregnancy**

Most hydropic fetuses will die of cardiac failure if in utero treatment is not instituted. However, spontaneous in utero recoveries have been reported without any sequelae at birth. Correction of the anemia by fetal blood transfusion is the only available treatment.\textsuperscript{31} It is unclear whether in utero transfusion improves fetal outcome. Infants who survive the severe anemia with or without in utero transfusion appear to develop normally. There is no conclusive evidence that B19 infection is associated with anatomic abnormalities. The efficacy of maternal prophylactic immunoglobulin administration after exposure has not been determined yet, and its use is not recommended at this time. A vaccine is not available.

**Herpes Virus**

Prevalence of herpes in pregnancy is 1%. Most women have recurrent rather than primary infection. Women with genital HSV during the first half of pregnancy have a significantly increased incidence of spontaneous abortion and in the second half have an increased incidence of preterm delivery and direct transmission of HSV to the newborn. The direct contact of the neonate with the virus containing maternal secretions during passage through the birth canal is the main source of infection. This allows the virus to enter the infant via the eyes, upper respiratory tract, scalp and the umbilical cord thereby leading to systemic infections.

Brown and associates\textsuperscript{32} found the following vertical transmission rates at the time of vaginal delivery: 50% for women with primary disease at the time of delivery, 33% for those with nonprimary first-episode disease, and 0–3% for those with recurrent disease. Neonatal herpes is divided into three categories of disease: (1) localized disease involving the skin, eye, and/or mouth; (2) disease involving the CNS and (3) disseminated disease. Although most infected infants have localized disease, it may progress to encephalitis or disseminated disease. Morbidity and mortality of neonatal disease are directly related to the severity of the disease. Whitley and colleagues\textsuperscript{33} reported no mortality with localized disease, 15% mortality with CNS involvement and 57% mortality with disseminated disease.

**Diagnosis**

The diagnosis of herpes infection is generally made clinically based on the appearance of painful vesicular lesions and ulcers in various stages of progression. However, one-third of women do not have typically appearing lesions. Herpes can also be diagnosed from changes noted in Papanicolaou smears (multinucleated giant cells and intranuclear inclusion bodies), although the sensitivity is poor. Viral culture of open lesions remains one of the best methods of detecting infection, but it too has a significant false-negative rate. When performing a viral culture for HSV from lesions that are not ulcerated, the lesion should be unroofed and the fluid sampled. Culture results are usually available within 48–72 hours. Other techniques, such as PCR and hybridization methods, are increasingly available. Commercially, available serologic tests have little utility. These tests cannot reliably distinguish between HSV-1 and HSV-2. Serologic diagnosis of primary infection can only be made by documenting seroconversion from a negative to a positive IgM antibody titer. The presence of antibody titer in an initial specimen or the presence of a typical lesion is suggestive of nonprimary first-episode or recurrent disease.

**Prevention**

Women who at the time of admission in labor have overt vesicular lesions from primary or recurrent infections should undergo cesarean section regardless of time since rupture of membranes. Asymptomatic women should be examined for prodromal symptoms and vesicular lesions and if absent, then vaginal delivery may be conducted.\textsuperscript{34} Scott\textsuperscript{35} has answered various questions related to the use of acyclovir. The first issue, about fetal and neonatal safety, appears to be answered positively. With more than 1,812 infants reported to have been exposed to varying amounts and duration of maternal acyclovir suppression, there has not been any apparent, short-term adverse fetal or neonatal effect. Use of acyclovir in infants, even in those that are premature, is very well-tolerated, with a wide margin of safety. Acyclovir suppression actually decreases asymptomatic shedding.
along with decreasing clinical recurrences. Women who experience their first genital herpes outbreak while they are pregnant seem to benefit from acyclovir suppression, with both a decrease in the risk of clinical recurrences at delivery and a decreased need for cesarean delivery. Acyclovir’s efficacy in patients who have a history of genital herpes infections antedating their pregnancy is less clear. Acyclovir appears to be effective, at least in some cohorts, and is probably safe for the fetus.

Currently, there is no vaccine for the prevention of herpes infection. Valacyclovir and famciclovir are two newer antiviral agents that are effective and safe for the treatment of genital herpes.\textsuperscript{36}

**Hepatitis B and Others**

Hepatitis B virus is a member of the *Hepadnaviridae* family of DNA virus, first discovered in the 1960s. The main mode of transmission of hepatitis virus is blood and blood products. However, body fluids like saliva, vaginal secretions are also infective. Transplacental infection occurs in 5–8% of infants born to hepatitis B surface antigen (HbsAg) positive carriers. Newborns may be infected by swallowing-infected material during parturition. Mothers who are positive for hepatitis B “e” antigen (HbeAg) but negative for hepatitis B “e” antibody (HbeAb) carry a high risk of vertical transmission to her newborn.

**Fetal Risks**

If the fetus survives the acute maternal illness, without delivering prematurely, patient can be reassured that there are no teratogenic or congenital anomalies likely.

**Prevention**

A comprehensive prevention and treatment strategy\textsuperscript{37,38} has been developed by the Centers for Disease Control and Prevention, which includes screening of all pregnant women for the presence of HBV, the administration of hepatitis B immunoglobulin (HB Ig) at birth, and the administration of hepatitis B vaccine at birth, at 1 month of age, and at 6 months of age.

In case of exposure to hepatitis A, pregnant women should be given gamma globulin 0.02 mL/kg as early as possible. In case of exposure to hepatitis B, HB Ig and full course of hepatitis vaccination should be given. Universal vaccination of all neonates with hepatitis B vaccine is now recommended. Infants delivered to HbsAg seropositive mothers also should receive HB Ig and vaccination immediately after birth.

Hepatitis E is extremely rare in the United States and is quite similar to hepatitis A, although perinatal transmission does occur with hepatitis E. Hepatitis C and D, which are transmitted parenterally and by sexual contact, have been associated with vertical transmission. No immunoprophylaxis currently is available for neonates of mothers with hepatitis C or E virus. Immunization against hepatitis B is protective against vertical transmission of hepatitis D.

**Human Immunodeficiency Virus**

Pregnancy does not have an impact on the course of the HIV infection and nor does the infection adversely affect the course of the pregnancy, labor, puerperium and lactation. It is recommended that all pregnant women should be counseled and encouraged to be tested for HIV infection in order to know their infection status, both for their own health and to reduce the risk of perinatal HIV transmission. Prenatal diagnosis is not recommended as invasive procedures like fetal blood sampling may theoretically introduce the virus into a previously uninfected fetus. The magnitude of this risk is unknown. Furthermore, a fetus may become infected anytime after prenatal diagnosis because maternal viremia persists. Fetal HIV-1 infection does not seem to be associated with a substantially increased incidence of IUGR, prematurity, microcephaly, or dysmorphism.

**Prevention of Perinatal Human Immunodeficiency Virus Transmission**

The mainstay of the treatment of nonpregnant women with acquired immunodeficiency syndrome (AIDS), AIDS-related complex, or CD4+ cell counts of less than 200 × 10\textsuperscript{6} per liter rests on antiretroviral therapy with zidovudine and pneumocystis carinii pneumonia prophylaxis with the combination drug trimethoprim and sulfamethoxazole. Because of the lack of solid data on the fetal side effects and toxicities, the Public Health Service has avoided recommending therapies in pregnancy, but as there are no adverse fetal effects known to outweigh the maternal benefits of these therapies, they should not be withheld during pregnancy. Most obstetricians offer zidovudine treatment to pregnant women in advanced stages of disease, avoiding its use during the first trimester because of possible teratogenic risks.

Prevention of perinatal HIV transmission is possible by drug regimes and as suggested on the basis of a review of the Cochrane database of systematic reviews.\textsuperscript{39,40}

**Human Immunodeficiency Virus Infection: Diagnosis in the Newborn**

In utero, diagnosis is not possible. Fetus could be infected in the antepartum, intrapartum or postpartum period.

Many advances have been made in the area of neonatal HIV diagnosis.\textsuperscript{41} Commercially, available virologic assays are sensitive and specific for the early detection of HIV in perinatal infection.\textsuperscript{42,43} The timing of the transmission of HIV from mother to child (in utero, at the time of birth, or postnatally by breastfeeding) is a critical consideration in the appropriate diagnosis of infants. Several algorithms can
be used to define early infection and the potential timing of acquisition of infection that combine different assays and timing of specimens. The use of virologic assays, including HIV DNA PCR and HIV RNA detection methods and culture, can define and rule out infection in infants less than 6 weeks of age. A dried blood spot specimen is all that is needed for PCR, but these methods are expensive. Serologic diagnostic methods, including HIV enzyme-linked immunosorbent assay, immunofluorescence, and western blot assays, can be used to diagnose infants more than 18 months of age, when transplacental antibody has disappeared in uninfected HIV-exposed infants. The challenge of the early and accurate diagnosis of perinatally HIV-exposed infants is the use of new assays to detect different HIV subtype infections that are prevalent in developing countries. Rapid, simple, and inexpensive serologic and virologic assays are being developed for worldwide use.

REFERENCES

Recent Trends in the Management of Recurrent Pregnancy Wastage

INTRODUCTION

Recurrent miscarriage is traditionally defined as three or more consecutive losses of pregnancy. This distressing problem affects approximately 1% of all women. By contrast, sporadic miscarriage affects 25% of all women who conceive a pregnancy. As such, sporadic pregnancy loss is the most common complication of pregnancy and it is important to recognize that the causes of sporadic and recurrent miscarriage are diverse.

Agreed that the spontaneous resolution rate of this condition is high, but the distress caused by repeated pregnancy failure and the ability of modern science to document an etiological factor in many cases justify the investigation of affected couples. Since women with recurrent pregnancy failure can experience miscarriages both early and late in pregnancy with a variety of clinical manifestations, there is unlikely to be a single etiology.

When to label as recurrent spontaneous abortion (RSA): after two or three pregnancy losses? Five percent of all couples trying to conceive have two consecutive miscarriages and 1% has three or more consecutive losses. Older the woman higher the risk for pregnancy loss. Outcome of the previous pregnancy is very vital in deciding when to start investigating. If there is a history of oligomenorrhea then it predicts a higher subsequent risk for miscarriage. However, a study carried out by us revealed that it is wise to start investigating a couple even after two losses if immunological cause is suspected.1

CHANCES OF CONTINUING THE PREGNANCY

When a subject presents with history of pregnancy losses this time early in pregnancy, her apprehension is rightfully expressed in knowing the chances of continuing this pregnancy. In a study carried out by us it was found that the maximum chances of missing this pregnancy again was in subjects in whom there were only recurrent pregnancy losses in the past.2 This is shown in Figure 1.

This data emphasizes the importance of research directed toward establishing the factor(s) that determine the outcome of a women’s previous pregnancy(s), which have a significant effect on the outcome of future pregnancies. However, in spite of our increasing knowledge about the details of implantation and early pregnancy, a clear etiology could not be identified in about 50% of the cases.3 This chapter reviews the work-up and management of factors that can lead to recurrent pregnancy loss.

GENETIC FACTORS AND RECURRENT MISCARRIAGES

Chromosomal abnormalities of the embryo are the most common cause of sporadic miscarriage, causing more than half of the early losses. A genetic etiology is less likely with late first-trimester or second-trimester losses. In women with a history of recurrent miscarriage, chromosomal
abnormalities of the embryo occur much less frequently. There is a tendency for successive abortuses to be karyotypically normal or karyotypically abnormal suggesting that some couples are at risk of recurrent aneuploidy. However, the risk of a subsequent miscarriage is higher when the index loss has a normal karyotype. The finding of an abnormal karyotype is invariably comforting to the affected couple who will readily be able to understand this cause of pregnancy failure.

Couples in which one or other partner carries a chromosome rearrangement are at risk of recurrent miscarriages with the loss of conceptuses with an abnormal karyotype. Chromosomal abnormalities are more common among men with an abnormal semen analysis. If three or more pregnancies are lost, it is important to evaluate with a karyotype from both partners.

The most common type of parental chromosomal abnormality is a balanced translocation (either reciprocal—65% or Robertsonian—35%) with a reported prevalence of 3–5% in couples with recurrent pregnancy failure, in contrast to a prevalence of 0.2% in an unselected population.

**Structural Chromosomal Anomalies and Recurrent Pregnancy Loss**

Structural chromosomal anomalies are higher in couples with history of RSA as well as past history of birth of anomalous or stillborn infants. When chromosomal anomalies are found in a conceptus aborted of RSA, over 50% are autosomal trisomies, 20% chromosomal monosomies, 19% polyplody, 3.8% structural anomalies and rest are mixoploidy. Most chromosomal abnormalities in RSA arise from errors in meiosis.

**Recurrent Aneuploidy and Recurrent Pregnancy Loss**

Chromosomal anomalies of the embryo are the most common cause of early pregnancy loss. Most chromosomal abnormalities result in disordered development, incompatible with prolonged intrauterine survival and livebirth. Couples in whom one or other partner carries a chromosomal rearrangement are at risk of recurrent pregnancy loss (RPL) with loss of conceptus with an abnormal karyotype.

An increased number of chromosome breaks and pericentric inversions are seen in recurrent abortion group. This presumably would lead to both, the loss of mitotically unstable elements during cell division and an increased rate of aneuploidy potentially contributing to early embryonic loss.

**Relevant Genetic Counseling**

Evidence is mixed as to whether chromosomal abnormalities tend to recur in subsequent pregnancies. Hassold studied 40 couples and found a 70% recurrence risk with a prior aneuploid pregnancy vs. 20% with a prior euploid pregnancy. Warburton et al. found no increased risk of chromosomal abnormalities in subsequent pregnancies after spontaneous abortions if the fetus carried an aneuploidy that is always lethal in utero or if the parents had normal chromosomes. Carriers of a translocation in chromosome 22 almost always miscarry; a woman with a translocation involving breaks in chromosome 13 or 14 has a 25% risk of spontaneous abortion. Empirically, the birth of a trisomic infant places a woman at an approximately 1% increased risk for a subsequent trisomic conceptus. There is a stronger tendency for ensuing abortion to be cytogenetically normal when index abortion has a normal karyotype. If atleast some of the antecedent abortions are trisomic, there probably is an increased risk for recurrence. Amniocentesis on chorionic villus (CV) biopsy should be encouraged in any pregnancy in couples with a previous abnormal karyotype because of the risk of an abnormal child. If aneuploidy is documented on a previous abortion, a centrally timed insemination is advocated based on animal studies relating aneuploidy to aging of ovum or sperm. The other choice is of donor insemination. If euploidy has been documented on a previous abortion, anatomic or endocrine factors should be corrected. Today, couples with serious high-risk abnormalities have the chance of pursuing a pregnancy by means of a donor sperm or in vitro fertilization (IVF) with donor oocytes (or both). The blastocysts are examined, and they are implanted only if they are chromosomally normal. Preimplantation genetic diagnosis (PGD) allows genetic screening of the embryos before transfer during an IVF cycle. A small opening is made on the zona pellucida of a cleavage stage embryo and one or two blastomeres are removed for genetic analysis.
Fluorescent in situ hybridization (FISH) is used to detect numeric and structural chromosomal anomalies, and polymerase chain reaction (PCR) is used to detect monogenic disorders. FISH analysis can be performed for 5–11 chromosomes. Several research groups have assessed whether PGD is beneficial for women with recurrent pregnancy loss. The results are controversial. PGD may not offer hope to all women with recurrent pregnancy loss, but there may be subgroups (e.g., based on age, number of previous losses, number of available embryos for testing) for whom its use is justified.

**ANATOMICAL CAUSES AND RECURRENT SPONTANEOUS ABORTION**

Congenital anomalies of the uterus have been cited repeatedly as an important cause of recurrent miscarriage, both in the midtrimester and in early pregnancy (Table 1). However, not all congenital defects cause pregnancy loss. For example, an arcuate uterus is usually associated with normal progression of a pregnancy, whereas a septate uterus is a frequent cause for loss. In order to cause early pregnancy loss, the embryo supposedly implants in an avascular part of the endometrium, such as a uterine septum, leading to arrested development and early pregnancy failure. For pregnancies to fail repeatedly implantation must be occurring in areas of abnormal vasculature in successive pregnancies.

The prevalence of uterine anomalies in women with recurrent miscarriage has been reported to be in the region of 10%. However, the prevalence in the general population is unknown and the majority of women with uterine anomalies probably have normal reproductive outcomes.

**Unicornuate Uterus**

Fetal pregnancies are lost in the second trimester. Uterus with a rudimentary horn is a doubtful risk factor for abortions. The possible mechanisms of abortions in cases of unicornuate uterus include decreased uterine capacity that does not permit adequate gestational growth and development, relative cervical incompetence contributing to midtrimester abortion and vascular anomalies in the distribution of uterine arteries in these cases.

**Uterus Didelphys**

Without a surgical correction, fetal survival rate in this condition is about 64%. Amongst all Müllerian anomalies, this condition has the best prognosis as regards the pregnancy outcome is concerned. Surgical procedures for treatment of pregnancy losses in this condition are rarely indicated. Benefits of metroplasty are not certain in this condition.

**Bicornuate Uterus**

Incomplete paramesonephric duct fusion produces bicornuate uterus. Women with bicornuate uterus can expect reasonable success (about 50%) in delivering a live child. Surgical correction by metroplasty is recommended in bicornuate uterus. It has been found that the incidence of cervical incompetence is increased with bicornuate uterus. It is therefore necessary to carry out a timely cervical cerclage in this condition.

**Septate Uterus**

The fibromuscular septum may be partial, complete or segmental. Diminished septal blood supplies, distortion of uterine cavity and associated cervical or hormonal abnormalities may be the causes of pregnancy loss. Also, pregnancy loss may be related to impaired embryo growth associated with septal implantation. Some reports put a 28–75% livebirth rate in cases of septate uterus. The surgical treatment recommended is hysteroscopic-guided septum transection.

<table>
<thead>
<tr>
<th>Uterine defect</th>
<th>Pregnancy</th>
<th>Surgery</th>
<th>Postoperative reproductive performance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unicornuate uterus</td>
<td>40% fetal survival</td>
<td>Prophylactic cervical cerclage</td>
<td>Not well-studied</td>
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<tr>
<td>Uterus didelphys</td>
<td>64% fetal survival</td>
<td>Metroplasty</td>
<td>50–75% livebirth rate</td>
</tr>
<tr>
<td>Bicornuate uterus</td>
<td>55% fetal survival</td>
<td>Surgical unification of two endometrial cavities</td>
<td>85% viable infants</td>
</tr>
<tr>
<td>Septate uterus</td>
<td>28% livebirth rate</td>
<td>Abdominal metroplasty or hysteroscopic-guided septum transection</td>
<td>70% survival rate</td>
</tr>
<tr>
<td>Ashermann’s syndrome</td>
<td>30% fetal survival</td>
<td>Hysteroscopic adhesiolysis</td>
<td>87% fetal survival</td>
</tr>
</tbody>
</table>
UTERINE FIBROIDS

A common acquired anomaly of the uterus is fibroids. Submucous myomas deform the cavity, and the endometrium covering them is usually thin and inadequate for normal implantation. Fibroids in a submucous location can also be associated with pregnancy loss. The case is less clear with intramural and subserosal fibroids. In these locations, the size and the number of the fibroids will make a difference. Larger (> 4 cm) and multiple fibroids are usually associated with adverse pregnancy outcome, and their removal is recommended.16-17

CERVICAL INCOMPETENCE

Cervical incompetence is one acquired cause of RPL that is well-described. The phrase “cervical incompetence” was first used in the mid-19th century, and consideration of possible treatment began in the early part of this century, with surgical “repair” of the cervix being described in the 1930s and 1940s.18 However, it was the description of surgical cervical cerclage, and the subsequent successful outcomes, initially by Shirodkar in India,19 and then McDonald in Australia20 that provided the starting point for the present-day enthusiasm for cervical cerclage in cases of presumed cervical incompetence.

Incidence of cervical incompetence was put up to 0.5–1% of all pregnancies.21 It is known to cause second-trimester abortions. There are many causes that can produce cervical incompetence. These include congenital causes like diethylstilbestrol (DES) uterus and Müllerian anomalies. Acquired causes include a past history of D and C, D and E, conization, cautery and similar surgeries on the cervix.

Cervical incompetence as a cause of midtrimester miscarriage has been well-described. The diagnosis is usually made after a history of a painless midtrimester loss but our experience suggests that this condition is over diagnosed. Cervical cerclage is not associated with significant difference in the fetal survival rate between the cerclage and control groups. In addition, cerclage is associated with increased obstetrics intervention and an increased incidence of puerperal pyrexia.

Cervical incompetence is not a cause of early pregnancy loss and cervical cerclage is therefore not indicated in women with recurrent early pregnancy failure.

A diagnosis of cervical incompetence is usually made on the basis of the woman’s past obstetric history. Classically, this consists of one or more late second-trimester or early third-trimester losses, characterized by a rapid, often relatively pain-free delivery, commonly following the rupture of membranes prior to labor and in the absence of an obvious precipitating cause. This description of cervical incompetence is subjective (both on the part of woman and the obstetrician) and also retrospective.

Based on limited clinical information, elective cerclage for historical factors generally should be confined to patients with three or more otherwise unexplained second-trimester pregnancy losses or preterm deliveries. Cerclage should be performed at 13–16 weeks of gestation after ultrasound evaluation has demonstrated the presence of a live fetus with no apparent anomalies.

Shirodkar, in an effort to place the suture as near the internal os as possible, described opening the anterior fornix and dissecting away the adjacent bladder, before placing the suture submucosally, tied internally and the knot buried by suturing the anterior fornix mucosal opening. The McDonald technique requires no bladder dissection, and the cervix is closed using four or five bites with the needle to create a purse string around the cervix. The suture is then removed either electively or if labor ensues. Other methods of cervical suturing have been described (including the Wurm’s procedure, with two mattress sutures placed at right angles to each other), but present practice largely uses variants of McDonald or Shirodkar’s cerclage procedures.

One further development in the 1960s was the description of the transabdominal cerclage by Benson and Durfee in 1965,22 a technique now largely used after the failure of vaginal cerclage procedures or in the presence of congenital anomalies, particularly those produced by DES exposure. The original intention with the transabdominal approach was that the suture was inserted between pregnancies or in early pregnancy, and left in situ for the rest of the woman’s reproductive life, delivery being undertaken by cesarean section for each pregnancy.

The results of all these forms of treatment, however, are muddied by the same complication: The lack of a precise (and objective) diagnosis or definition of what constitutes cervical incompetence, a difficulty which is likely to blur the results of any study by not distinguishing effectively between cervical incompetence and other causes of recurrent second-trimester losses.

A cervical compliance score has been suggested whilst several years earlier a similar Cervical Resistance Index (CRI) was suggested by Anthony, Zlatnik and Burmeister23 who suggested the use of three scores to be measured at hysteroscopy: (1) the canal-cannula ratio (the upper cervical canal width compared to the hysteroscope width on an X-ray film taken during hysteroscopy); (2) the degree of difficulty of passing a No. 8 Hagar dilator and (3) the degree of traction required to pull a catheter out through the cervical canal with the balloon filled with 2 mL of saline (Table 2).

The measurement of cervical resistance, cervical compliance and cervical strength is logical in the face of a presumed diagnosis of cervical weakness. However, there is a significant disadvantage in the reliance on hysteroscopically based investigation, in that no investigation or diagnosis can be done during pregnancy due to the invasive nature of the testing. Transvaginal ultrasonography (USG) has been
used for diagnosis of cervical incompetence. Urgent, or therapeutic, cerclage often is recommended for women who have ultrasonographic changes consistent with a short cervix or evidence of funneling. Management of this group remains speculative because of the limited number of well-designed randomized trials. Evidence suggests that the use of a cervical stitch should not be offered to women at low or medium risk of midtrimester loss, regardless of cervical length by ultrasound. The role of cervical cerclage for women who have short cervix on ultrasound remains uncertain as the numbers of randomized women are too few to draw firm conclusions.\(^7\)\(^4\)

**INFECTIONS AND RECURRENT SPONTANEOUS ABORTION**

Many infections of the genital tract have been reported to be associated with sporadic pregnancy loss. Bacterial vaginosis, a polymicrobial anaerobic infection, has been implicated in the etiology of preterm labor,\(^25\)\(^26\) but its role in RPL is doubtful. *Treponema palladium* has been implicated in causing stillbirths and second-trimester abortions. The postulated mechanism of spontaneous abortions is fetal infection causing fetal death or severe malformations incompatible with fetal viability. However, *Treponema palladium* infection is not a cause leading to RSAs. 

Maternal infection with *Toxoplasma gondii*, cytomegalovirus, rubella and herpes (TORCH) can cause sporadic pregnancy loss but evidence that these organisms are associated with recurrent miscarriage is lacking. It is also very difficult to prove that microorganisms lead to repetitive pregnancy losses. In order to lend sufficient scientific support to this explanation, one would need to culture out the same micro-organism with each pregnancy loss and show that antimicrobial therapy effectively reduces the subsequent risk.\(^27\)\(^28\)

**ENDOCRINE DYSFUNCTION AND RECURRENT SPONTANEOUS ABORTION**

There is now good evidence that well-controlled diabetes is not associated with an increased risk of early pregnancy loss.\(^29\)\(^30\) Poorly controlled diabetic patients, however, do have an increased incidence of early pregnancy failure\(^31\) and so prepregnancy counseling of established diabetic patients is important with the aim of obtaining good preconceptual glycogenic control. There is no value in performing glucose tolerance tests in symptomatic women presenting with recurrent miscarriage, as these are invariably uninformative.

Similarly, thyroid dysfunction is often cited as an etiological factor for recurrent pregnancy loss\(^31\)\(^32\) but no direct evidence exists. Recent studies using radioimmunological techniques to measure thyroid function have shown no role of thyroid function tests in patients of RSA. It has been reported that the presence of thyroid autoantibodies is associated with an increased risk of miscarriage\(^33\)\(^34\) but it is likely that this finding is secondary to a generalized autoimmune abnormality rather than a specific endocrine dysfunction, since thyroid function tests are usually normal.\(^35\) Although thyroid function assessments are simple and cheap, their utility in RSA is so small that justification in asymptomatic women (for thyroid) with RSA is difficult. There is little justification, therefore, in screening symptomatic women presenting with recurrent pregnancy failure with thyroid function tests.

### Hypersecretion of Luteinizing Hormone

Miscarriage rate has been found to be significantly higher in patients with high luteinizing hormone (LH) levels than in those with normal LH levels. There is now good evidence that the presence of polycystic ovaries (PCOs) is associated with both subfertility and early pregnancy failure. In contrast to the normal population, who have a reported prevalence of PCO of 22%,\(^36\) the prevalence of PCO in women with a history of recurrent early pregnancy loss was found to be 82%\(^37\) and in infertile women attending for IVF the prevalence of PCO is as high as 50%.\(^38\)

The link between PCO and early pregnancy failure would appear to be hypersecretion of LH (Table 3). Studies have shown that women with elevated LH levels undergoing IVF\(^39\)\(^40\) or ovulation induction are less likely to conceive and have an increased incidence of early pregnancy loss compared to women with normal LH secretion. In a prospective study of 193 women conceiving spontaneously\(^41\)\(^42\) hypersecretion of

<table>
<thead>
<tr>
<th>Score</th>
<th>No. 8 Hagar dilator</th>
<th>Catheter traction</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Will not pass</td>
<td>&gt; 700 g</td>
</tr>
<tr>
<td>1</td>
<td>Will pass with moderate force</td>
<td>&lt; 700 g</td>
</tr>
<tr>
<td>2</td>
<td>Will pass with a little or no force</td>
<td>&lt; 700 g</td>
</tr>
</tbody>
</table>

**Table 3:** Possible mechanism of action of the deleterious effect of hypersecretion of luteinizing hormone (LH) on the outcome of pregnancy

- Direct inhibition of oocyte maturation inhibitor (OMI) causing premature resumption of meiosis and the production of physiologically aged oocytes.
- Direct effect on endometrial function possibly via abnormal prostaglandin synthesis.
- Indirect effect on either the oocyte or endometrium via altered androgen production.
- Production of abnormal glycoforms of LH causing abnormal signal transudation.
LH was associated with a subsequent miscarriage rate of 65% compared to a rate of 12% in women with normal LH levels.

**Luteal Phase Defect and Recurrent Pregnancy Loss**

Luteal phase defect (LPD) has been characterized by inadequate, endometrial maturation resulting from insufficient progesterone production or shortened duration of the luteal phase. Progesterone plays an important role during implantation and pregnancy. Progesterone is required to induce secretory changes that prepare the endometrium for the arriving embryo. However, progesterone also has an immunomodulatory effect. It stimulates the production of progesterone-induced blocking factor that suppresses natural killer cell activity and increases the Th-2 response. This suppressive effect favors implantation and the progress of early development.

Luteal phase insufficiency used to be a common finding during the work-up of recurrent pregnancy loss. LPD is diagnosed on the basis of endometrial biopsies. When there is at least 2 days’ discrepancy between the histologic picture and the cycle day, LPD is diagnosed. Recently, however, it has been shown that many women with proven fertility have at least a 2-day discrepancy when evaluated. Another method for assessing the luteal phase is to measure progesterone levels (Day 21). Luteal phase progesterone is used to prove ovulation (value over 3 ng/mL), and values in excess of 10 ng/mL are considered adequate for the luteal phase. Other methods used to diagnose LPD include basal body temperature (BBT), USG of endometrium and others.

An association between the LPD and RPL is controversial. If a diagnosis of LPD is sought in a woman with recurrent pregnancy loss, it should be confirmed by endometrial biopsy. In addition to diagnosis, treatment of LPD is controversial.

**Ovarian Function**

Good quality oocytes are needed for a successful pregnancy. Pregnancy rates are lower and loss rates are higher with advanced reproductive age. Ovarian reserve testing serves the purpose of assessing the function of the ovaries. Among women 35 years and older, poor results for ovarian reserve testing have been shown to be associated with poorer quality oocytes. Also, women with elevated early cycle follicle-stimulating hormone (FSH) or elevated estradiol levels have been found to have higher rates of miscarriage.

**AUTOIMMUNE DISEASE AND RECURRENT SPONTANEOUS ABORTION**

Antiphospholipid antibody (APA) syndrome is an autoimmune condition that has profound bearing on obstetric conditions at times seemingly diverse. The association between raised circulating APAs and recurrent pregnancy failure is now well-established. The knowledge that some women with systemic lupus erythematosus have a poor reproductive outcome led to the discovery that the presence of circulating APAs is a marker for the poor outcome of pregnancy. Recurrent spontaneous missed abortions, intrauterine growth restriction (IUGR), recurrent stillbirths, accidental hemorrhage and thromboembolism are some diverse conditions that have this as its etiologic factor.

The primary APA syndrome, recurrent pregnancy loss, arterial and venous thrombosis or thrombocytopenia in the absence of overt autoimmune disease, are now well-documented.

Laboratory diagnosis of APA is currently done by enzyme-linked immunosorbent assay (ELISA) technique. Blood so collected is tested for APAs. Diagnosis is also helped by asking a history of allied complications of APA like RSA of missed type, recurrent stillbirths, recurrent IUGR, etc (Table 4).

Antiphospholipid antibodies or APA were identified to be of six types. Of these six, three are important for clinicians:

1. Anticardiolipin antibodies (ACAs)
2. Lupus anticoagulant (LAC)
3. Biologically false positive serological test for syphilis (BFPSTS).

Table 4: Features of the primary antiphospholipid syndrome

<table>
<thead>
<tr>
<th>Clinical features</th>
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<tbody>
<tr>
<td>Recurrent fetal loss</td>
</tr>
<tr>
<td>Arterial or venous thrombosis</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Early-onset/severe preeclampsia</td>
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<tr>
<td>Intrauterine growth retardation</td>
</tr>
<tr>
<td>Cardiovascular/cerebral thrombosis</td>
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<tr>
<td>Chorea gravidarum</td>
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<table>
<thead>
<tr>
<th>Serological findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lupus anticoagulant (LAC) (as detected by DRVVT, KCT or APTT)</td>
</tr>
<tr>
<td>Immunoglobulin G-anticardiolipin antibody (IgG-ACA) &gt; 5 GPL units</td>
</tr>
<tr>
<td>Immunoglobulin M-ACA (IgM-ACA) &gt; 3 MPL units</td>
</tr>
</tbody>
</table>

Abbreviations: DRVVT, dilute Russell’s viper venom time; KCT, kaolin clotting time; APTT, activated partial thromboplastin time; 1 MPL unit = mcg/mL 1 gm anticardiolipin affinity purified sera
Treatment

Nearly 18 different protocols have been tried over the period of years for the treatment of APA syndrome. But, the main stay is heparin and low dose aspirin. We use the following protocol:\(^\text{56}\)

- For low and moderate positive, aspirin in a dose of 1.2 mg/kg/day for 3 months—allow a conception—restart aspirin in the same dose from 12 weeks to 36 weeks.
- For high positive, aspirin in a dose of 1.2 mg/kg/day for 3 months. Allow conception—start aspirin from 12 weeks to 36 weeks (aspirin can be commenced as soon as the urine pregnancy test becomes positive).

As soon as pregnancy is diagnosed and fetal heart activity is seen on USG, we give 5,000 IU of heparin twice daily subcutaneously till 36 weeks of pregnancy. This combination of aspirin and heparin gives the best results.

Evidence indicates that combined unfractionated heparin and aspirin may reduce pregnancy loss by 54%. Large, randomized controlled trials with adequate allocation concealment are needed to explore potential differences between unfractionated heparin and low molecular weight heparin.\(^\text{57}\)

Currently, there is no reliable evidence to show that steroids improve the livebirth rate of women with recurrent miscarriage associated with APA when compared with other treatment modalities; their use may provoke significant maternal and fetal morbidity. In our study of more than 300 cases now subjects testing positive for APA were given the above treatment protocols. In the group where treatment could be given preconception as well as postconception, full-term delivery rates achieved were 88.3%. In the group where only postconception treatment could be given, the same rate was 72.3%. The incidence of pre eclampsia (PE) remote from term declined from 26.7% to 3.3%.\(^\text{56}\)

ALLOIMMUNE CAUSES AND RECURRENT SPONTANEOUS ABORTION

It has been suggested that a necessary prerequisite for successful pregnancy involves maternal recognition of the embryo, leading to a protective immune response. Further a failure to mount the appropriate maternal immune response will lead to recurrent pregnancy loss. Because immunological aberrations might be the cause of miscarriage in some women, several immunotherapies have been used to treat women with otherwise unexplained recurrent pregnancy loss. An increased degree of human leukocyte antigen (HLA) sharing between the parents could be responsible for the lack of maternal immune recognition is now strongly disputed.\(^\text{58,59}\)

Evidence suggests that immunotherapy including paternal cell immunization, third party donor leukocytes, trophoblast membranes and intravenous immune globulin provide no significant beneficial effect over placebo in improving the livebirth rate.\(^\text{60}\)

The use of immunotherapy should no longer be offered to women with unexplained recurrent miscarriage and routine tests for HLA type and antipaternal cytotoxic antibody should be abandoned.

UNEXPLAINED RECURRENT PREGNANCY LOSS

In about 50% of couples with recurrent pregnancy loss, an evaluation including parental karyotypes, hysterosalpingography or hysteroscopy and APA testing will be negative. Informative and sympathetic counseling appears to serve an important role in this situation. Livebirth rates between 35% and 85% are commonly reported in couples with unexplained RPL who undertake an untreated or placebo-treated subsequent pregnancy.\(^\text{61,62}\) Meta-analysis of randomized, prospective studies suggests that 60–70% of women with unexplained RPL will have a successful next pregnancy.\(^\text{63}\) Data suggest that the use of empirical treatment in women with unexplained recurrent miscarriage is unnecessary and should be resisted.

PSYCHOLOGICAL ASPECTS OF RECURRENT SPONTANEOUS ABORTION

Tender loving care: It consists of psychological support and weekly medical and USG examinations. Follow-up visits are advised after 2 weeks to share medical information and counseling about normal responses in the form of sadness, guilt and anger, depression, lack of concentration and difficulty at work. In case of considerable depression beyond 4–6 months, it is advisable to refer to an informed professional counselor and others with similar losses.

ENDOMETRIOSIS AND RECURRENT SPONTANEOUS ABORTION

A possible association between endometriosis and spontaneous abortion has been suggested in mostly uncontrolled and/or retrospective studies. Some controlled studies evaluating the association between endometriosis and spontaneous abortion showed important methodological shortcomings: Heterogeneity between cases and controls, analysis of the abortion rate before the diagnosis of endometriosis, and selection bias of study and control groups. On the basis of controlled prospective studies, there is no evidence that endometriosis is associated with (recurrent) pregnancy loss or that medical or surgical treatment of endometriosis reduces the spontaneous abortion rate.\(^\text{64}\) In programs of assisted reproduction, some studies have shown that the number and quality of oocytes, the fertilization rate, and the implantation rate per embryo may be reduced in women with endometriosis, but this observation has not been confirmed by other investigators.
TOXIC/ENVIRONMENTAL EFFECTS

Although a common concern of patients, environmental factors rarely have been linked to sporadic pregnancy loss, and no associations between environmental factors and RPL have been established. Likewise, occupational exposures to certain products, such as certain organic solvents, rarely have been linked to sporadic pregnancy loss. However, no associations between occupational exposure or working itself and RPL have been established. Study results are conflicting on the association of smoking, use of alcohol, and use of caffeine with sporadic pregnancy loss. They may act in a dose-dependent fashion or synergistically to increase the rate of sporadic pregnancy loss. However, none of these habits has been associated with recurrent pregnancy loss. Exercise does not appear to increase the rate of sporadic pregnancy loss, particularly in women in good physical condition, and there are no studies showing the effect of exercise in women with recurrent pregnancy loss.

Diagnosis

The diagnostic work-up has to be complete, as several factors could simultaneously be responsible for the recurrent reproductive failure. First, it is important to review the past obstetric history. Details about previous pregnancy losses may yield important clues. All prior pregnancies should be examined in detail, with attention to gestational age at time of loss, complications, USG findings, pathology reports, and chromosomal analyses. The etiology may differ if the loss occurred in the first vs the second trimester. The physical examination could also reveal important details. The body weight and height need to be measured, signs of hyperandrogenism should be looked for, and the breasts should be checked for the presence of galactorrhea. The pelvic examination may identify congenital and acquired genital tract lesions (e.g. vaginal septum, duplicated cervix, uterine enlargement, adnexal masses). Besides a complete history and a thorough physical examination, imaging studies and laboratory testing complete the evaluation.

Imaging Studies

Imaging studies play an important role in diagnosing uterine anomalies. A transvaginal ultrasound is usually the initial step. The size and position of the uterus can be evaluated, fibroids can be detected, and some other anomalies might be suggested by the ultrasound findings (e.g. duplicated cervix, uterus, uterine septum, unicorneuate uterus). A careful examination of the endometrial echo may lead to the detection of polyps and scarring. Saline infusion into the cavity improves the diagnostic accuracy of the ultrasound examination.

The routine use of HSG as a screening test for uterine anomalies is questionable. It is associated with patient discomfort, a risk of pelvic infection and radiation exposure and it is no more sensitive than the noninvasive pelvic ultrasound with (or without) sonohysterography.

Hysteroscopy offers a more precise evaluation of the cavity. During the procedure the intracavitary structures can be directly visualized and directed biopsies can be obtained when indicated. The intramyometrial extension of fibroids cannot be assessed, however, and therefore the size estimate remains imprecise. Hysteroscopy alone cannot differentiate between a septate uterus and a bicornuate uterus; laparoscopy is required to complete the evaluation.

Nowadays, hysteroscopy is the primary surgical method for the correction of the various intrauterine pathologies. Laparoscopy is also used for guidance during hysteroscopy, and for the removal of subserosal/intramural fibroids. Magnetic resonance imaging (MRI) is an accurate noninvasive technique for the evaluation of uterine anomalies. Its limited availability and the cost of the test, however, are drawbacks. Intravenous pyelogram is recommended during the work-up of congenital anomalies. Defects in the urinary tract are commonly seen when a uterine anomaly is diagnosed.

Laboratory Evaluation

Laboratory evaluation plays a very important role in the work-up of recurrent pregnancy loss.

- A karyotype should be obtained from both partners.
- Men with severe oligozoospermia (< 5 million/mL) should also be evaluated for Y-chromosome microdeletions.
- Antiphospholipid antibodies need to be measured on two separate occasions at least 6 weeks apart.
- Microbiological studies of vaginal secretions are unlikely to reveal any pathogens that are responsible for recurrent loss.
- Patients with recurrent vaginal infections, on the other hand, should be evaluated and treated as necessary.

TREATMENT

Surgical Treatment

Some of the anatomic defects require surgical correction, but others do not. Therefore, it is very important to know the exact anomaly. Endoscopic procedures are most commonly used to correct the defect. Intrauterine pathologies (e.g. septum, submucous fibroids, polyps) can be removed during hysteroscopy. A septum is most commonly excised with scissors, but laser or resection can also be used. Better hemostasis is achieved (bleeding is typically minimal) with the latter procedures, but thermal injury might lead to scar formation. Intramural and subserosal fibroids are removed via the laparoscopic approach. It is important to mention that uterine rupture during pregnancy has been reported following the laparoscopic procedure. Uterine artery embolization is
another intervention that has been used in the management of symptomatic myomas but it has a limited utility in these cases due to a possible risk of ovarian failure. Laparotomy has a very limited role in the management of congenital anomalies among women with recurrent abortion. As a bicornuate uterus is usually associated with problems during the third trimester of the pregnancy, the procedure should be limited to very few well-selected cases with recurrent second-trimester and third-trimester problems. When surgery is performed, the unification of the 2 horns with a bicornuate uterus is carried out via laparotomy (Strassman procedure). The procedure often leaves a small cavity with scarring, making implantation difficult.

**Medical Treatment**

Patients with pregestational diabetes should receive adequate insulin replacement. Ideally, the hemoglobin A\(_1c\) (HbA\(_1c\)) should be less than 7.5%. Thyroid dysfunction should also be treated to achieve euthyroidism before pregnancy. Most cases of hyperprolactinemia are managed medically. There are various treatment options to manage an inadequate luteal phase. Stimulation of follicle growth will typically result in a better quality secretory phase. The simultaneous growth of several follicles will result in the formation of many corpora lutea and, therefore, larger progesterone output. Ovulation induction also has an impact on endometrial development. Another option is to supplement progesterone to support the luteal phase. Typically, vaginal or intramuscular preparations are used and started in the luteal phase; when pregnancy follows, progesterone is continued up to 8–10 weeks of gestation.

There is no evidence to support the routine use of progesterone to prevent miscarriage in early to midpregnancy. However, further trials in women with a history of recurrent miscarriage may be warranted, given the trend for improved livebirth rates in these women and the finding of no statistically significant difference between treatment and control groups in rates of adverse effects suffered by either mother or baby in the available evidence. Insulin-sensitizing agents, most commonly metformin, have been widely used for the management of women with polycystic ovary syndrome (PCOS). Metformin is effective for ovulation induction. When continued during pregnancy, it has been associated with a lower rate of spontaneous abortion. Metformin is a category B drug. Its use during the first trimester should be considered in subjects with PCOS who have a history of adverse pregnancy outcome.

**REFERENCES**

Recent Trends in the Management of Recurrent Pregnancy Loss


Intrauterine Growth Restriction: Diagnosis and Management

INTRODUCTION

Intrauterine growth restriction (IUGR) remains a major obstetric and neonatal challenge. It is a condition which may take a while, before being diagnosed. Once diagnosed, it is difficult to treat with no specific cure or therapy available.

Perinatal asphyxia involving multiple organ systems is one of the most significant problems in growth-restricted low-birthweight infants. These cases have an increased risk of stillbirth, preterm labor, neonatal morbidity and mortality due to birth asphyxia, meconium aspiration, neonatal sepsis, hypoglycemia and hypothermia.

Long-term follow-up studies have demonstrated that babies who suffered intrauterine growth retardation are more likely to develop hypertension, coronary artery disease, and diabetes in adult life.

Thus, by identifying this condition early and instituting appropriate management—perinatal morbidity and mortality can be reduced and possibly long-term health problems in the individual avoided.

In India, according to the recent United Nations International Children’s Emergency Fund (UNICEF) survey, the incidence of IUGR is 25–30%.

DEFINITION OF INTRAUTERINE GROWTH RESTRICTION

Intrauterine growth restriction refers to a condition in which a fetus is unable to achieve its genetically determined potential size. This functional definition seeks to identify a population of fetuses at risk for modifiable but otherwise poor outcomes.

The most widely used definition of IUGR is a fetus whose estimated weight is below the 10th percentile for its gestational age and whose abdominal circumference (AC) is below the 2.5th percentile. At term, the cut-off birth weight for IUGR is 2,500 g (5 lb, 8 oz). This term is often erroneously used as synonymous of small for gestational age (SGA). Fetal growth is dependent on genetic, placental and maternal factors. The fetus is thought to have an inherent growth potential that, under normal circumstances, yields a healthy newborn of appropriate size. The terms “IUGR” and “SGA” are often used interchangeably. The IUGR fetus is a fetus that does not reach its potential of growth; whereas the SGA fetus does reach its potential of growth (Table 1).

In other words, a fetus who has a potential of growth at the 50th percentile but because of maternal, fetal, or placental disorders occurring alone or in combination, becomes growth restricted (birth weight < 10th percentile) is an IUGR fetus and he is at risk for adverse perinatal outcome. A fetus with a potential of growth at the 7th percentile who reaches Table 1: Comparison between intrauterine growth restriction (IUGR) and small for gestational age (SGA) fetuses

<table>
<thead>
<tr>
<th>Intrauterine growth restriction</th>
<th>Small for gestational age</th>
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<tbody>
<tr>
<td>Birth weight usually &lt; 10% but may be &lt; 25%</td>
<td>Birth weight &lt; 10%</td>
</tr>
<tr>
<td>Birth weight usually &lt; 2,500 g but may be larger</td>
<td>Birth weight &lt; 2,500 g</td>
</tr>
<tr>
<td>Low ponderal index</td>
<td>Normal ponderal index</td>
</tr>
<tr>
<td>Decreased subcutaneous fat</td>
<td>Normal subcutaneous fat</td>
</tr>
<tr>
<td>Frequently develops complications</td>
<td>Usually have an uneventful neonatal course</td>
</tr>
</tbody>
</table>
its potential of growth (7th percentile) is not an IUGR fetus but a SGA fetus. He is a normal small fetus and he is not at risk for adverse perinatal outcome.

The two components that are necessary to define an IUGR fetus are:
1. Birth weight < 10th percentile
2. Pathologic process that inhibits expression of the normal intrinsic growth potential.

The two components that are necessary to define a SGA fetus are:
1. Birth weight < 10th percentile
2. Absence of pathologic process.

**ANTEPARTUM RECOGNITION**

**Medical and Obstetric History**

A detailed medical history is mandatory to identify patients at high risk for IUGR. Mothers with significant medical or obstetric problems such as chronic hypertension, toxemia of pregnancy, chronic renal disease, twin gestation, diabetes are at high risk for IUGR fetuses. A patient with prior delivery of an IUGR baby is at high risk of having a similar problem in the present pregnancy.

**Uterine Fundal Height**

*Clinical evaluation of fetal and uterine size.* Clinical assessment of fetal growth includes estimating fetal size by traditional obstetrical manual examination and by measuring the uterine fundal height.3 It is an essential, inexpensive component of prenatal care and a simple screening tool for identifying mothers who would benefit from further, more definitive sonographic investigation.

Use the tape measure with the centimeters on the underside to reduce bias. Secure the tape measure at the fundus with one hand. Measure from the top of the fundus to the top of the symphysis pubis. The tape measure should stay in contact with the skin. Measure from the top of the fundus to the top of the symphysis pubis. The tape measure should stay in contact with the skin. Measure along longitudinal axis of uterus, note metric measurement. Record the metric measurement and plot it on the growth chart (Fig. 1).

![Customized antenatal growth chart](image-url)
Normal variability in measurement means that the slope will alter from one measurement to another. The line may cross centiles, but the overall slope of the curve should not be static (no growth over 2–3 weeks) and become abnormal if the slope falls away in subsequent measurements. In the case of normal fundal height growth, the measurements should reflect the curve on the customized charts. Using these charts in very small and very large women should reduce the number who would be referred for ultrasound assessment.

**Confirm Clinical Suspicion with Sonography**

Ultrasound biometry of the fetus is now the gold standard for assessing fetal growth, especially AC; estimated fetal weight derived from biparietal diameter (BPD) or head circumference (HC), AC and femur length (FL); and longitudinal progression of fetal growth.

Sonography is also capable of classifying the growth restriction on the basis of the presence or absence of symmetry among different anatomical structures.

*Type I IUGR*: The fetuses that are symmetrically small and have normal head-to-abdomen and femur-to-abdomen ratios.

*Type II IUGR*: The fetuses that have an AC smaller than the HC.

*Type III IUGR or intermediate IUGR*: The fetuses that are symmetric initially but become asymmetric later in pregnancy.

The most sensitive indicator of symmetric and asymmetric IUGR is the AC, which has a sensitivity of over 95% if the measurement is below the 2.5th percentile. Accurate dating of the pregnancy is essential in the use of any parameter. In the absence of reliable dating, serial scans at 2- or 3-weeks intervals must be performed to identify IUGR. It should always be remembered that each parameter measured, has an error potential of about one week up to 20 gestational weeks, about 2 weeks from 20 weeks to 36 weeks of gestation, and about 3 weeks thereafter.

Also useful is the ratio of the HC to the AC (HC/AC) (Figs 2A and B). Between 20 weeks and 36 weeks of gestation, the HC/AC ratio normally drops almost linearly from 1.2 to 1.0. The ratio is normal in the fetus with symmetric growth restriction and elevated in the infant with asymmetric growth restriction.

The difference between symmetric and asymmetric IUGR fetuses is shown in Table 2.

Another important use of ultrasound is estimating the amount of amniotic fluid. A decreased volume of amniotic fluid is closely associated with IUGR. Significant morbidity has been found to exist in pregnancies with an “amniotic fluid index (AFI)” value of less than 5 cm.

**Femur-to-Abdomen Ratio**

This compares the FL (Fig. 3) that is minimally affected by fetal growth impairment with the AC, which is most affected.

<table>
<thead>
<tr>
<th>Table 2: Comparison of symmetric and asymmetric intrauterine growth restriction (IUGR) fetuses</th>
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<tbody>
<tr>
<td><strong>Symmetric IUGR</strong></td>
</tr>
<tr>
<td>Symmetrically small</td>
</tr>
<tr>
<td>Normal ponderal index</td>
</tr>
<tr>
<td>Normal head/abdomen and femur/abdomen ratios</td>
</tr>
<tr>
<td>Genetic diseases, infection</td>
</tr>
<tr>
<td>Complicated neonatal course, poor prognosis</td>
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</tbody>
</table>

**Figs 2A and B:** Measurement of fetal circumferences. (A) Head circumference, (B) Abdominal circumference
Fetus as a Patient

Femur to abdomen (F/A) ratio remains constant after 20 weeks. A high F/A ratio indicates IUGR. When the F/A ratio is normal, the fetus may be small and healthy or may have symmetric IUGR.

**Fetal Ponderal Index**

Another ultrasound measurement useful for the diagnosis of fetal malnutrition is the fetal ponderal index (PI). The fetal PI is obtained by dividing the estimated fetal weight by the third power of the FL.

**ETIOLOGY (TABLE 3)**

Once diagnosed, one needs to find the cause of IUGR.

**INVESTIGATION**

A careful search for the causes of IUGR should be made, especially when IUGR presents early in pregnancy. Factors such as smoking, alcoholism, drug addiction, or proteinuric hypertension should be fully investigated.

Screening for evidence of recent maternal infection with toxoplasmosis, protozoa, rubella, chickenpox, and herpes viruses can be considered if fetuses are symmetrically small.

On ultrasonography (USG) anomalies should be ruled out, aneuploidy markers looked for carefully.

Karyotyping is usually not indicated in the isolated mild form of IUGR because the risk of aneuploidy remains remote. On the other hand, karyotyping should be considered when IUGR is severe but the Doppler scan is normal, or when IUGR is associated with the development of fetal anomalies.

In late second trimester the causes could be preeclampsia, diabetes or other medical disorders in the mother.

**Classification on the Basis of the Etiology**

**Intrinsic IUGR:** These fetuses are small because of fetal conditions as intrauterine infections or chromosomal abnormalities.

**Extrinsic IUGR:** These fetuses are affected due to an element outside of the fetus, like a placental condition or a maternal disease.

**Combined IUGR:** These fetuses are affected due to a combination of both the intrinsic and extrinsic factors.

**Idiopathic IUGR:** The cause of fetal growth failure is unknown.

**MANAGEMENT**

**Maternal Management**

**Bed Rest**

Bed rest has been the mainstay of IUGR therapy as it reduces the catecholamine release, improves central intravascular volume and improves uterine perfusion, resulting in better fetal nutrition. In practice “restricted bed rest” is what is
advised, i.e. an hour’s rest after breakfast, 2 hours after lunch and an 8 hour’s rest at night. Patients find it easier to comply with.

**Diet**

High protein diet has been advised with some improvement, provided it is started early in pregnancy. Evidence suggests that it does help the undernourished but may not be very useful for the well-nourished patients. However, we must remember that in our clinical setting, where a lot of ignorance and false beliefs are prevalent, the pregnant woman may not be eating right! Thus, the role of diet is important.

**Supplements**

Folic acid and zinc supplementation has been shown to be associated with some benefit in IUGR prone patients. Fish oil contains high levels of eicosapentaenoic acid which reduce synthesis of thromboxane and increase the prostacyclin levels, thus promoting vasodilatation. Hence, it is recommended as a therapeutic option by some workers. Some studies also suggest magnesium as a mode of treatment.

**Parental Nutrition**

Studies using parenteral solutions of 10% dextrose/fructose and 17% amino acids have shown an increase in the birth weight with some reduction in perinatal mortality in undernourished, but there is no evidence to suggest they would help the well-nourished patient.

**L-arginine**

This amino acid improves growth hormone-releasing hormone (GH-RH) secretion, with consequent increase of plasmatic GH influencing somatic growth. L-arginine moreover, is the obligatory precursor for nitric oxide (NO) enzymatic synthesis (endothelial-derived relaxing factor). Nitric oxide helps the prolapse of smooth musculature and, consequently, the improvement of placental blood circulation. Studies have shown that the total antioxidative activity in blood serum decreased in pregnancy connected with IUGR. L-arginine treatment decreased the oxidative stress risk. Carbonyl groups are the elements connecting protein structure; high concentration of carbonyl groups means high risk of protein destruction. L-arginine prevented protein damage in IUGR by decreasing the carbonyl groups in the process of treatment.

But, even though experimental studies have shown a positive aspect of treatment with L-arginine—no large study has yet conclusively confirmed it.

**Aspirin**

Low-dose aspirin therapy has been tried as antiplatelet agent, as it shifts the balance of thromboxane-prostacyclin in favor of the latter, but reports of its efficacy are quite contradictory. Wallenburg et al. studied a population of women at high risk for IUGR in a nonrandomized trial using historic controls. They noted a decline in the rate of IUGR from 61.5% in the historic controls to 13.3% in those treated with aspirin. But, the collaborative low-dose aspirin study in pregnancy (CLASP) trial failed to show any benefit in low risk mothers, but several other studies showed improvement in birth weights in the treated groups as compared to the controls, in high-risk population. To be effective, aspirin therapy should be started in first trimester itself. Intrauterine growth restriction treatment by low-dose aspirin had beneficial but nonsignificant impact on umbilical and middle cerebral artery (MCA) blood flow.

**Heparin**

The use of heparin is justified if antiphospholipid antibody (APLA) syndrome is proved.

**Amnioinfusion**

Reports of amnioinfusion helping are in general related to use in labor to decrease the incidence of meconium aspiration, or in a case of severe oligohydramnios—to do a targeted scan it may be helpful.

**Counseling the Patient**

The patient must understand the importance of her cooperation and involvement in the treatment for a good outcome.

**Monitoring the Fetus**

These patients need a surveillance plan that maximizes gestational age while minimizing the risks of neonatal morbidity and mortality.

**Fetal Biometry**

Serial measurements of “fetal biometry”—following the fetal growth by serial measurements—every 3 weeks give a fair idea of interval growth.

**Fetal Kick Count**

Patient is asked to maintain a kick count chart—and if there are less than 10 movements in 12 hours to report—when further testing would be necessary.
Amniotic Fluid Index

Measuring the amniotic fluid reflects the fetal health and a good amount of fluid can be reassuring. A fall below AFI 5 cm is considered dangerous and Doppler studies or nonstress test (NST) are indicated.

Nonstress Test

A satisfactory NST is reassuring—but a nonreactive pattern demands further evaluation of fetal status by Doppler studies.

Biophysical Profile

It is excellent for the identification of the nonhypoxic SGA fetus but can be a time-consuming exercise in diagnosing hypoxic IUGR and thus is not a very favored investigation. Cordocentesis is not recommended, as it has a procedure-related fetal mortality of about 1% and it represents merely a snap-shot of the fetal acid-base and biochemical states.

Doppler Studies

Currently, the two vessels yielding the best information in the fetus with IUGR appear to be the umbilical artery and MCA.

Use umbilical artery Doppler as the primary surveillance tool.

A systematic review with meta-analysis has provided compelling evidence that the use of umbilical artery Doppler to monitor high-risk fetuses reduces perinatal morbidity and mortality. In addition, there was a significant reduction in the number of antenatal admissions and inductions of labor associated with Doppler use. A study comparing fetal heart rate monitoring, biophysical profile and umbilical artery Doppler found that only umbilical artery Doppler had value in predicting poor perinatal outcomes in SGA fetuses. Use of Doppler does not lead to increased interventions as the rates of positive tests are low (2.7% of all umbilical artery tests in high-risk women). There is evidence that use of Doppler ultrasound to manage SGA fetuses reduces the use of resources compared with cardiotocography.

Ductus venosus Doppler: Severe Doppler changes in the ductus venosus occur late in the natural history of fetal growth restriction. There is strong empirical support for expeditious delivery of cases with significant changes in ductus waveforms. On this basis, it also seems that a good case could even be made for delivering fetuses before development of ductus venosus abnormalities.

How Often and When?

The frequency of fetal monitoring depends on the findings of various tests. Small for gestational age (SGA) fetuses with an otherwise normal fetal assessment can be monitored fortnightly, while those with abnormal Doppler results and/or oligohydramnios require more frequent monitoring, or delivery. If an elevation of the pulsatility index of the umbilical artery or oligohydramnios is found, twice-weekly cardiotocography, weekly Doppler studies, and measurement of the AFI are warranted. In pregnancies that are complicated by absent or reversed end-diastolic umbilical artery flow, daily fetal monitoring is needed if delivery is not considered.

Treatment of IUGR is largely limited to early delivery. The timing of delivery depends on the results of fetal monitoring tests and the gestational age (Flow chart 1).

Delivery is indicated when there are abnormal readings from cardiotocography or a low score on the biophysical profile. Doppler studies have shown that absent or reversed end-diastolic velocity waveforms in the umbilical artery are associated with high perinatal mortality and morbidity. Fetal hypoxia and acidosis have been found to be associated with pregnancies that are complicated by the loss of end-diastolic flow. Absent or reversed end diastolic umbilical artery flow merits delivery if the neonate of that gestational age or with that estimated birth weight can be handled by the local neonatal service.

There is also a current trend towards earlier delivery. Recent studies report that growth-retarded fetuses who are acidic during intrauterine life or exhibit antepartum abnormal heart rate tracings show poor neurological development at 2 years.

Growth-retarded fetuses with abnormal fetal Doppler studies of the descending thoracic aorta have a much higher neonatal mortality rate from necrotising enterocolitis and fetal hemorrhage.

While delivery of the term growth-retarded fetus is indicated when there are abnormal Doppler measurements, it is still controversial whether a preterm pregnancy should allow fetal maturity to be reached; the fetus may then become acidotic. Alternatively, the fetus could be delivered earlier to avoid damage from hypoxia and/or acidosis. It is not known whether the benefits of delivery at the stage of fetal hypoxia, but without acidosis, outweigh the risks of prematurity.

This issue will be addressed in the growth restriction intervention trial. The current recommendation is that results of fetal monitoring tests other than Doppler studies should also be taken into account. Both mother and obstetrician may find it difficult to face the situation of intrauterine death. In contrast, delivery by cesarean section may lead to early neonatal mortality or severe handicap, and could cloud the future obstetrical performance of the mother. Proper counseling is essential.

Harman and Baschat’s integrated fetal testing for IUGR, in increasing order of severity from one (least severe) to five (most severe), is described in Table 4.
Points to be Considered in Timing Delivery

- Administer steroids, if gestation is below 36 weeks.
- Deliver in a unit where optimal neonatal expertise and facilities are available.
- When end diastolic flow is present (PED), delay delivery until at least 37 weeks, provided other surveillance findings are normal.
- When end diastolic flow is absent or reversed, admission, close surveillance and administration of steroids are required. If other surveillance results (biophysical profile, venous Doppler) are abnormal, delivery is indicated.

CONCLUSION

Intrauterine growth restriction can occur in otherwise uncomplicated pregnancies. Because of the ill effects on the fetus its antenatal diagnosis and management is important. Because no effective treatments are known, the aim of every obstetrician is to deliver the most mature fetus in the best physiological condition possible while minimizing the risk to the mother.
### Table 4: Harman and Baschat’s integrated fetal testing for IUGR

<table>
<thead>
<tr>
<th>Test result</th>
<th>Situation 1</th>
<th>Situation 2</th>
<th>Situation 3</th>
<th>Situation 4</th>
<th>Situation 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>• AC less than fifth percentile</td>
<td>• IUGR criteria met</td>
<td>• IUGR with low MCA PI, oligohydramnios</td>
<td>• IUGR with brain sparing, oligohydramnios</td>
<td>• IUGR with accelerating compromise</td>
<td></td>
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<tr>
<td>• Low AC growth rate, high ratio of head circumference to AC</td>
<td>• BPS greater than or equal to 8</td>
<td>• BPS greater than or equal to 6</td>
<td>• BPS less than or equal to 6</td>
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<tr>
<td>• BPS greater than or equal to 8 and AFV normal</td>
<td>• AFV normal, UA with absent or reversed end-diastolic velocities</td>
<td>• Normal IVC, DV, and UV flow</td>
<td>• Increased IVC and DV indices, UV flow normal</td>
<td>• Abnormal IVC and DV indices, pulsatile UV flow</td>
<td></td>
</tr>
<tr>
<td>• Abnormal UV and/or cerebroplacental ratio; normal MCA</td>
<td>• Decreased MCA</td>
<td>• IUGR with low MCA PI, oligohydramnios</td>
<td>• IUGR with brain sparing, oligohydramnios</td>
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<td></td>
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<tr>
<td>Interpretation</td>
<td>IUGR diagnosed, asphyxia extremely rare, increased risk for intrapartum distress</td>
<td>IUGR with brain sparing hypoxemia possible and asphyxia rare, at risk for intrapartum distress</td>
<td>IUGR with significant brain sparing, onset of fetal compromise, hypoxemia common, acidemia/asphyxia possible</td>
<td>IUGR with decompen-sation, cardiovascular instability, hypoxemia certain, acidemia/asphyxia common, high perinatal mortality, death imminent</td>
<td></td>
</tr>
<tr>
<td>Recommended management</td>
<td>• Intervention for obstetric or maternal factors only</td>
<td>• Intervention for obstetric or maternal factors only.</td>
<td>• If at more than 34 weeks gestation, deliver (route determined by obstetric factors)</td>
<td>• If fetus is considered viable by size, deliver as soon as possible at tertiary center</td>
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</tr>
<tr>
<td></td>
<td>• Weekly BPS, multi-vessel Doppler every 2 weeks</td>
<td>• BPS 3 times a week, Weekly UA, MCA, and venous Doppler</td>
<td>• If at less than 34 weeks’ gestation, administer steroids to achieve lung maturity and repeat all testing in 24 hours</td>
<td>• Route determined by obstetric factors and OCT results. Fetus requires highest level of natal ICU care</td>
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</table>

**Abbreviations:** AC, abdominal circumference; IUGR, intrauterine growth restriction; MCA, middle cerebral artery; BPS, biophysical profile score; PI, ponderal index; IVC, inferior vena cava; DV, ductus venosus; UV, umbilical vein; AFV, amniotic fluid volume; UA, umbilical artery; ICU, intensive care unit

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INTRODUCTION
The number and rate of twin pregnancies has increased dramatically in the last two decades. Twin pregnancies are associated with an increased risk of perinatal morbidity and mortality. The bulk of these arise from preterm deliveries and low birth weights. They also face problems which are unique to twin pregnancies such as monoamnionicity, discordant growth, twin-to-twin transfusion syndrome (TTTS) and death of one twin. This chapter does not aim to cover all the aspects of care of twin pregnancies in pregnancy and labor. We have covered areas which are most relevant in improving perinatal outcome and do not have clear guidelines on care.

VANISHING TWIN
The incidence of twin pregnancies is greater in the first trimester than the incidence of twins at birth. A very wide range (21-70%) of incidence is quoted in the literature of the “vanishing twin” phenomenon. This phenomenon is often associated with bleeding, but the prognosis of the remaining fetus is good. The risk of spontaneous loss of the pregnancy with a vanishing twin is similar to the risk in other pregnancies that are complicated with first-trimester bleeding. However, pregnancies complicated with a vanishing twin are associated with an elevation of the maternal serum alpha-fetoprotein level and amniotic fluid alpha fetoprotein. This may lead to false results with the triple marker test.

PREVENTING PRETERM DELIVERY
A majority of twins are delivered before maturity. About half are delivered by 34 weeks and 90% by 37 weeks gestation. Preterm births are the leading cause of perinatal morbidity and mortality in twin pregnancies. Spontaneous labor or preterm prelabor rupture of membranes account for 54 and 22% of preterm twin births. These may be looked upon as avoidable or at least predictable. Current efforts are directed toward optimizing and predicting the time of delivery. Various efforts have been in the form of cervical assessment, cerclage, progesterone, hospitalization and bed rest, home uterine activity monitoring (HUAM), antibiotics, tocolysis and steroid use.

Routine Hospitalization for Bed Rest
Routine hospitalization with bed rest is not helpful in prolonging twin pregnancies. A study of 141 twin pregnancies randomized to outpatient care with normal activities or to hospitalization with restricted activities showed no differences in mean birth weight or mean gestational age at delivery between the two groups. Another study showed only a small increase in the birth weight with hospitalization but no appreciable improvement in the gestational age at delivery. Neonatal morbidity or mortality were not reduced in either study.

Cervical Assessment
Ultrasound assessment of the cervix is more accurate than digital examination. A 25-mm cut-off at 23 weeks gestation
has been used as a negative predictor for preterm and very preterm births. The false negative rate ranged from 1.2% at 28 weeks to 18.6% at 35 weeks. There are no studies evaluating the cervical length earlier in pregnancy. The clinical usefulness of ultrasound cervical assessment as a routine evaluation is questionable because of the lack of proven treatments affecting outcome.

**Cervical Encirclage**

There are no studies to assess the role of prophylactic cerclage in twin pregnancies. In twin pregnancies identified to have a short cervix (<25 mm) in the mid trimester, there was no significant prolongation of the gestational period with a cerclage. In fact, a meta-analysis of twins with short cervical length undergoing cerclage showed an increase in the rate of preterm delivery. These studies, however, pertain to patients who have undergone cervical assessment after 20 weeks of pregnancy. It would be interesting to know the impact of cerclage at earlier gestations.

**Tocolysis**

A double-blind, controlled study of the prophylactic use of oral salbutamol in 144 women with twins (74 on salbutamol and 70 placebo) showed no difference in the length of gestation, birth weight, or fetal outcome between the study and control groups. Complications occur more often with the use of tocolytic therapy in multiple gestations than in singletons. This is the result of a greater increase in plasma volume and cardiac output that occurs in twins compared with single gestations. Beta mimetic use gives similar delay in delivery of twins as compared to singletons.

**Steroids**

Meta-analysis does not show a reduction in the incidence of respiratory distress syndrome. It is likely that this may be due to small study group numbers. However, the use of corticosteroids to enhance fetal lung maturation in multiple gestations in preterm labor and impending delivery (<34 weeks gestation) is recommended by most professional bodies in their guidelines. There is no evidence to support the use of prophylactic corticosteroids. A study examined the use of prophylactic steroids every 2 weeks between 24 weeks and 32 weeks. There was no benefit in reducing respiratory distress syndrome. Term neonates in the study group weighed 129 g less as compared to the ones treated with placebo.

**ANTENATAL CARE**

Twins are a high-risk pregnancy. As per routine, such pregnancies are subjected to more frequent antenatal visits. Though it is not clear whether such an approach improves outcome, it could possibly lead to earlier recognition of the onset of hypertension.

**Genetic Testing**

With increasing maternal age, the incidence of both twin gestations and fetal aneuploidy increases. In monozygotic twin gestations, in which both fetuses have the same karyotype, the risk of fetal aneuploidy is the same as the age-related risk for a singleton. However, in dizygotic twin pregnancies, the risk of fetal aneuploidy is twice the maternal age risk for a singleton pregnancy. Scant information is available concerning maternal serum screening for aneuploidy in twin gestations. Currently, the reliability of the serum screening for Down syndrome in twins is unknown. In terms of invasive tests, chorion villus sampling and midtrimester amniocentesis under ultrasound guidance are as safe and effective for prenatal diagnosis as compared to singleton pregnancies. Careful ultrasound examination to map and label fetal positions relative to the maternal orientation, fetal membranes, and placental localizations is of paramount importance to sample the twins correctly. The use of dyes to identify the fetuses is avoidable.

**Antepartum Surveillance and Fetal Well-Being Tests**

Fetal growth in twin pregnancies after 30 weeks of gestation lags behind the growth of singleton pregnancies. Also, there can be unequal or intrapair discordant growth. Therefore, serial ultrasounds at 2-4 week intervals are done to monitor the interval growth of twin gestations in the third trimester. The estimated fetal weight provides the best discriminator for discordant growth. The estimation of “amniotic fluid volume” is problematic. Amongst the fetal well-being tests, nonstress test and Doppler velocimetry are more predictive of fetal well-being than amniotic fluid volume and biophysical profile. As in singleton pregnancies, “Doppler ultrasound” assessing the umbilical artery systolic/diastolic ratios is useful in diagnosing growth restriction. The positive predictive value of an abnormal Doppler outcome was 90%, and the negative predictive value was 95.6% in twin pregnancies.

**When is Term?**

The growth of twins begins to decline after 38 weeks of gestation. After 38 weeks gestation, the perinatal death rate and intrauterine growth restriction of twin pregnancies increase substantially. The data would therefore suggest that twins are “post-term” after 38 weeks. The ideal time of delivery for an uncomplicated twin pregnancy is still uncertain. However, the literature appears to support delivery by 38 weeks of gestation.
**Monoamniotic Twinning**

About 1% of all twin pairs are monoamniotic. The risk specific to this situation is cord entanglement. It appears that this event generally occurs before 32 weeks of pregnancy. This suggests that prophylactic preterm birth may not be indicated. The optimal route of delivery is not determined, but in general, cesarean section is recommended.

**Death of One Twin**

Death of one twin occurs in about 5% of all twin pregnancies. It is the second twin that is more likely to lose. In addition, the surviving twin is five times more likely to succumb in monochorionic pregnancies as compared to dichorionic twins. This likelihood is strongly related to birth weight discordance. Survivors of monochorionic twin pregnancies are more likely to suffer from anemia and intracranial pathology as compared to dichorionic twin survivors.

The decision to deliver/terminate the pregnancy immediately or after expectancy depends on weighing the risks of leaving the surviving fetus in an intrauterine environment that may have caused the death of its co-twin and the possibility of serious morbidity with the neonatal risks associated with preterm delivery of the surviving fetus. In “dichorionic twin pregnancies” with the death of one twin, the outcome of the surviving twin is usually benign. In “monochorionic twins”, the timing of injury is thought to be at the time of intrauterine fetal death and not at the time of diagnosis or thereafter. It seems the balance is in favor of expectant management until risks of fetal prematurity are diminished.

**Twin-to-Twin Transfusion Syndrome**

Twin-to-twin transfusion syndrome is usually a complication seen in monochorionic twin gestations. The imbalance in the vascular flows results in one of the twins being smaller and oligohydranmniotic while the other is plerohoric and polyhydramniotic. Central nervous system lesions may be seen in both twins. The criteria for the antenatal diagnosis of TTTS include the following: monochorionic twin gestation with placental vascular anastomoses, same-sex fetuses, intertwin birth weight difference greater than 20%, polyhydramnios of the larger twin, oligohydranmnios of the smaller twin, and hemoglobin difference of more than 5 g/dL. Factors that determine perinatal outcome include the gestational age at diagnosis, the gestational age at delivery, and the severity of the disease, i.e. presence of hydrops fetalis. The overall perinatal survival rate ranges from 21% to 65%. The watershed for survival appears to be 28 weeks gestation for delivery.

One of the treatments for TTTS is serial amnioreduction of the recipient, polyhydramnionic twin. In one study with 13 twins, the fetal survival rate for the serial amnioreduction group was significantly higher than the expectantly managed group (69% vs 20%, respectively). Amnioreduction may be less effective when there are fewer superficial anastomosis in the placenta. Fetoscopic neodymium: yttrium aluminium garnet (Nd: YAG) laser occlusion of the superficial vascular communications between the fetoplacental circulations has been used successfully at very early gestations. In a recent multicenter trial with 173 patients with TTTS before 27 weeks, laser-treated group had a significantly higher successful pregnancy outcome (at least one surviving infant) than the amnioreduction treated group (83.2% vs 66.7%, respectively). Also, neurologic morbidity was significantly lower in the laser-treated group. Other options for treating TTTS include septostomy and selective feticide in exceptional cases.

**ROUTE OF DELIVERY**

The two main factors which determine the route of delivery of twins are the “fetal presentations and lie” and the estimated weights of the fetuses. In general, when the first twin is nonvertex (breech or transverse lie), the recommended mode of delivery is cesarean section. When the first twin is vertex and second is nonvertex, decision-making is less clear. Though the Term Breech Trial favors planned cesarean delivery over vaginal presentation, its results in reducing perinatal morbidity may not be applicable to the second twin. When the estimated weight of the second twin is less than 1,500 g, there is benefit from avoiding a vaginal delivery. The benefit may be limited when birth weights are greater than 1,500 g. Though the vertex-vertex twin pair has traditionally thought to be suitable for vaginal delivery, there has been an interesting review of the subject by Smith et al. They retrospectively studied 8,037 twin births and found that in the intrapartum period, there were six deaths of the first twin and 30 deaths of the second twin. They concluded that a planned cesarean section in vertex-vertex twins may reduce the perinatal morbidity by 75%. This has raised the question of whether all twin pairs should be delivered by cesarean section.

Time restriction for interdelivery interval is thought to be less important if there is continuous fetal monitoring and the pattern is reassuring. Though there was no difference in Apgar scores or birth trauma in twins delivered more than 15 minutes apart, there was a higher incidence of cesarean section for the second twin with delayed delivery.

**POSTNATAL ISSUES**

Breastfeeding would be ideal for twins as for singletons. However, the rates of successful breastfeeding initiation and continuation depend on the degree of motivation of the mother and the support (family and support groups)
available. The rates may be 80–90% in optimal conditions. However, in less than ideal situations, rates are closer to 40%. The factors that can improve breastfeeding success include counseling before delivery, support and motivation after delivery and training in specific techniques (double football hold, double cradle position, etc.). The approach should be one of sensitivity and understanding. One must realize that partial breastfeeding may also be beneficial.

REFERENCES

Chapter 24

Preterm Premature Rupture of Membranes

**INTRODUCTION**
Preterm prelabor rupture of membranes (PPROM) is defined as rupture of membranes before onset of labor in a patient who has not completed 37 weeks of gestation.

**INCIDENCE**
Preterm prelabor rupture of membranes occurs in around 2% of all pregnancies and is associated with 30-40% of preterm deliveries.

**ETIOPATHOGENESIS**
An important etiological mechanism is infection; organisms implicated being *Chlamydia trachomatis,* group B *Streptococcus* and less pathogenic organisms, such as those involved in bacterial vaginosis.

Usually, rupture of fetal membrane is preceded by structural weakness associated with extracellular matrix degradation and cellular apoptosis, but a substantial proportion of cases are associated with chorioamnionitis.

Second-trimester elevated plasma thrombin, anti-thrombin complexes concentrations are predictive of subsequent PPROM which provides evidence that PPROM is also associated with decidual thrombin activation.

**RISK FACTORS**
Risk factors for prelabor rupture of membranes are previous preterm delivery (Odds ratio (OR) 2.8), early pregnancy bleeding (OR 2.4 for first trimester bleeding, OR 4.4 for second trimester bleeding) and cigarette smoking (OR 2.1).

Other clinical factors associated with PPROM include low socioeconomic status, low body mass index, tobacco use, urinary tract infection, cerclage and amniocentesis.

**MANAGEMENT**

**Diagnosis**
Prompt and accurate diagnosis is essential for optimal maternal and perinatal outcome. However, diagnosis may be difficult by any single method and is best made by an accurate history, careful examination and necessary investigations.

**History**
Most patients complain of a sudden gush of fluid from the vagina followed by persistent leakage. A detailed history regarding the time of membrane rupture, the color of the fluid (passage of meconium) and presence/absence of uterine contractions should be taken.

**Physical Examination**
A sterile speculum examination should be performed. If the fluid cannot be seen, the patients can be asked to cough or strain. If there is any doubt regarding diagnosis, the woman may be asked to wear a pad that can later be examined.

A digital examination is best avoided, if the patient is to be managed conservatively. Digital examination of the cervix with PPROM has been shown to shorten latency and increase...
risk of infections without providing any additional useful clinical information.

**Investigations**

The principle of investigations is to differentiate amniotic fluid from urine or cervical/vaginal secretions.

- **Nitrazine paper/Litmus test**: Amniotic fluid is alkaline with a pH of 7.5. Red litmus turns blue, and nitrazine paper, which is orange, also turns blue when it comes into contact with amniotic fluid. False positive reactions may occur due to vaginal infections.

- **Ferning**: Fluid from the vaginal pool is dried on a slide and examined under the microscope. Formation of a fern pattern suggests that the fluid is amniotic fluid.

- **Cytological methods for the detection of fetal cells in amniotic fluid**: When amniotic fluid is treated with Nile blue sulfate, fetal cells with a higher fat content take an orange color against a blue background. This test may not be reliable in very early PPROM as the percentage of fetal cells with fat is less.

- **Ultrasound** is valuable in assessing the amount of amniotic fluid, the gestational age and estimated birth weight.

- **Dye tests**: A dye like indigo carmine is introduced into the amniotic cavity. Leakage of the dye per vaginum confirms the diagnosis. This test is not commonly practiced as it may introduce infection and precipitate preterm labor.

**CONSEQUENCES OF PPROM**

The most common consequence of PPROM is preterm delivery. Irrespective of gestational age, a delay of more than one week will be achieved by less than half the women.

Infectious morbidity, mostly due to ascending intrauterine infection, is the second most important hazard for the baby.

Other consequences of PPROM include increased risks of pulmonary hypoplasia, especially with very preterm PROM, deformities associated with persistent oligohydramnios, placental abruption and cord prolapse.

**Prediction of Infection and Risk of Preterm Delivery in PPROM**

Chorioamnionitis is associated with maternal and neonatal sepsis and can become life-threatening. Presence of infection warrants immediate termination of pregnancy. Clinical features of infection are maternal or fetal tachycardia, maternal fever, uterine tenderness and foul smelling vaginal discharge. However, preclinical occult infection may be present, the detection of which is difficult.

Investigations, which should be performed, are complete blood count and C-reactive protein (CRP). Studies examining the use of CRP as a predictor of chorioamnionitis in PPROM report highly conflicting results. There is no clear evidence to support the use of CRP for the early diagnosis of chorioamnionitis.7

Lewis et al. performed a randomized clinical trial comparing daily non-stress testing with a biophysical profile in the prediction of infectious morbidity in patients of PPROM between 23 and 34 weeks of gestation. Their conclusion was that neither test had good sensitivity for predicting infectious complications.8

Interleukin-6 determinations in cervical fluid have diagnostic and prognostic value in PPROM.9 Amniotic fluid metalloproteinase levels are significantly elevated in women with intra-amniotic infection.10

Sonographic measurement of cervical length in pregnancies complicated by PPROM helps to distinguish between those women who deliver within 7 days and those who do not.11

According to a study done by Rizzo et al., the combined use of the amniotic fluid interleukin-6 assay and the cervical index in patients with PPROM provides a good prediction of the interval from admission to delivery, thus identifying a subgroup of patients at high-risk of imminent delivery.12

Cervical and/or regional fetal fibronectin levels can be done to predict the presence of upper genital tract infection. According to the preterm prediction study, women with a positive fetal fibronecin test who delivered before 32 weeks of gestation all had evidence of histologic chorioamnionitis. Women positive for fetal fibronectin had a 16-fold increase in clinical chorioamnionitis and a sixfold increase in neonatal sepsis.13

**MANAGEMENT OF PPROM**

There are many complex issues involved in the management. On the one hand, there is a fear of serious maternal morbidity and intrauterine infection and, on the other hand, there is apprehension about poor survival rates when delivery is necessary at early gestational age.

If a patient has evidence of intra-amniotic infection by clinical examination (maternal temperature greater than 38°C, fetal tachycardia, fundal tenderness, foul or purulent vaginal discharge, maternal tachycardia) or elevated CRP, amniocentesis shows positive Gram stain, glucose less than 20 mg/dL and amniotic fluid culture is positive for aerobic, anaerobic organisms or mycoplasma, then institution of broad spectrum antibiotics and delivery are necessary irrespective of gestational age.

If after initial evaluation of the mother and fetus, they are both determined to be clinically stable, expectant management of PPROM may be considered to improve fetal outcome.

**Antibiotics**

The initial step in management of PPROM is informed consent. The patient needs to be given risks and benefits information and must participate in decision making.
Two of the largest studies that have looked at the efficacy of antibiotic use in PPROM are the National Institute of Child Health and Human Development–Maternal Fetal Medicine Units (NICHD-MFMU) study of PPROM and the ORACLE trial. In the NICHD study, intravenous antibiotics were used for 48 hours—ampicillin 2 g q6h and erythromycin 250 mg q6h. The patients were then placed on oral amoxicillin 250 mg q8h and enteric-coated, erythromycin-base 333 mg every q8h to complete a 7-day course of antibiotic therapy. In this study, the control group, compared with the antibiotic group, had a significantly shorter duration of latency. The antibiotic group was twice as likely to remain undelivered after 7 days. The increased latency continued for up to 3 weeks after discontinuation of antibiotics. Composite and individual morbidities for the neonate were lower in the antibiotic group. The incidence of chorioamnionitis and neonatal sepsis, including group B streptococcal sepsis, was decreased.14

The ORACLE trial used erythromycin alone, amoxicillin with clavulanic acid alone or amoxicillin with clavulanic acid in combination with erythromycin. Their results were different in that no significant difference was noted in latency to delivery and neonatal morbidity was not decreased as defined in their primary outcome (death, chronic lung disease and major cerebral abnormality on ultrasonography). Decreased need for supplemental oxygen and positive blood culture results were apparent. When amoxicillin with clavulanic acid was used either alone or in combination with erythromycin, an increased risk of necrotizing enterocolitis (1.9% versus 0.5%, p = 0.001) was present.15

The authors of ORACLE also concluded that antibiotics should not be routinely prescribed to women in spontaneous preterm labor without clinical evidence of infection.16 Based on current evidence, 7 days of antibiotics, as proposed by the NICHD-MFMU study of PPROM, should be the antibiotic regimen used in patients with PPROM who are being managed expectantly. Therapy longer than 7 days should be avoided. It has not been shown to be more effective and may promote the emergence of resistant organisms.

Antenatal Corticosteroid Treatment

The use of corticosteroids to accelerate lung maturity should be considered in all patients with PPROM with a risk of infant prematurity from 24 to 34 weeks of gestation.17

The use of steroids has also been suggested to increase the risk of infection. However, the current evidence does not support this concern based on individual studies and meta-analyses; no difference (either higher or lower rates of infections) has been observed with corticosteroid use. In contrast to these concerns, data indicate that the use of corticosteroid reduces neonatal morbidity and mortality. The rates of respiratory distress syndrome (RDS), necrotizing enterocolitis and intraventricular hemorrhage were all lower when either 12 mg of betamethasone intramuscular was given twice in a 24-hour interval or dexamethasone 6 mg q12h was given for four doses.

The National Institutes of Health consensus panel also recommends the use of corticosteroids prior to 30–32 weeks in absence of chorioamnionitis.17

Role of Tocolytics

Tocolytics may be used to prolong gestation long enough to complete a course of steroids and for in utero transfer; chorioamnionitis being a strict contraindication. However, studies have failed to prove that tocolysis in patients with preterm premature rupture of membranes significantly improves the perinatal outcome.18

Antenatal Fetal Surveillance

A number of biophysical parameters have been used to predict infection. Fetal breathing activity is reduced after preterm PPROM and a number of groups have documented an association between subsequent sepsis and reduced breathing; however, some recent evidence seems to challenge this.8

Direct ultrasonographic measurement of fetal lung length in normal pregnancies and pregnancies complicated by prolonged rupture of membranes was found to be predictive of fetal pulmonary hypoplasia.20 However, recent studies have found that fetal lung length determined by ultrasound does not predict adverse neonatal respiratory outcome and that the prediction of pulmonary hypoplasia in livebirths after prolonged PPROM remains an elusive goal.21

Care must be taken during the expectant management of patients with nonvertex presentation. In a study by Lewis et al., patients with PPROM with non-vertex presentations appear to have a significantly higher risk for prolapsed umbilical cords, lower Apgar scores and/or lower umbilical cord blood pH values, when compared with their vertex counterparts. Additionally, there appears to be substantial risk of an unintended vaginal breech delivery.22

PPROM at Early Gestation

Loss rates are dependent on the gestational age at which PPROM occurs. Second trimester PPROM usually carries a dismal prognosis. In gestational ages less than 24 weeks, risk of chorioamnionitis is high (30–60%) and pulmonary hypoplasia exceeds 50%. In a study by Taylor, following PPROM at a gestational age of 23 weeks, only 10% of pregnancies produced a neurologically normal, long-term survivor.23

In these cases, maternal well-being should be the utmost concern and therapeutic termination of pregnancy is an option. Pulmonary hypoplasia is dependent on gestation at membrane rupture. Prediction is difficult but nomograms of chest circumference or lung length may help.
It is important to arrange for in utero transfer to institutions with a well-equipped neonatal intensive care unit at early gestation.

Management of Patients Who have a Cervical Cerclage Stitch and Subsequently Develop PPROM

The optimal management of PPROM in a patient with a cerclage is controversial. The issues are whether the latency period between rupture of membranes and delivery is decreased, if the cerclage is removed and whether there is an increased rate of maternal or neonatal infection if the cerclage is kept in place. Latency seems to be increased if the cerclage is kept in place, but maternal and neonatal infectious morbidity is also increased. In women at early gestational ages, keeping the cerclage in place may be warranted until labor ensues. In more advanced gestations, it seems preferable to immediately remove the cerclage upon diagnosis of PPROM.24

Role of Amnioinfusion

Although there have been several studies evaluating the value of amnioinfusion for PPROM, according to the recent Cochrane review, there is not enough evidence concerning the use of amnioinfusion for preterm rupture of membranes.25

SUMMARY AND KEY POINTS

- PPROM is a common complication of pregnancy occurring in about 3% of all pregnancies.
- Diagnosis needs to be confirmed.
- Digital vaginal examinations should be avoided.
- Ultrasonography should be performed to confirm gestational age, estimated fetal weight, presentation, amniotic fluid index and fetal anatomy if not already fully evaluated.
- Antibiotics should be given based on present evidence.
- Informed consent should be obtained for expectant management versus delivery with careful documentation in the chart.
- Maternal health is the primary indicator for the need to deliver. Any evidence of infection or maternal instability due to complications of PPROM, such as bleeding, requires careful evaluation and determination of the appropriateness of expectant management.
- Fetal monitoring should be performed at least daily until delivery, and fetal well-being and growth should be evaluated periodically with ultrasonography.
- After 32 weeks and certainly after 34 weeks of gestation, the appropriateness of expectant management of PPROM should be reevaluated individually for each case.
- The overall goal is to manage the patient expectantly until she has reached a gestational age beyond which neonatal morbidity and mortality is minimal and to deliver her before she and her fetus becomes infected.

REFERENCES

Current Trends in the Management of Preterm Labor

INTRODUCTION

Preterm birth continues to be one of the most important obstetric problems in the world, contributing to nonanomalous perinatal mortality ranging between 38% and 52%. The perinatal mortality among preterm Indian babies has been reported to be two to seven times higher than among babies born at term. Preterm birth complicates 5–10% of pregnancies, and is the leading cause of perinatal mortality and morbidity. The problem of neurological handicap in groups below 34 weeks has decreased considerably in the western countries. The same cannot be said of the developing countries; one has to think in terms of instituting more neonatal intensive care units, which at present are limited to a few tertiary centers. Therefore, the solution lies in improving antenatal care to prevent preterm labor (PTL) or refer such cases to institutions where expert care is available.

ETIOLOGY

Preterm labor is essentially multifactorial in origin. The pathophysiology of PTL is shown in Flow chart 1. Before instituting measures to prevent it, placental abnormalities, uterine anomalies, uterine overdistention and fetal mallformations should be ruled out. The philosophy of management of these cases is in a different direction, except for placenta previa. Other factors, which influence the occurrence of PTL, are as follows:

- **Infections:**
  - Intrauterine, both overt and subclinical (20–30%), caused by *Ureaplasma urealyticum*, *Bacterial vaginosis*, *group B Streptococcus* (GBS), *Escherichia coli*, *Bacteroides* sp., *Mycoplasma hominis*, *Fusobacterium* sp., *Listeria monocytogenes*, *Lactobacillus* sp., *Peptostreptococcus* sp. and *Chlamydia trachomatis*.
  - Extrauterine (5–10%), urinary tract infection (UTI), asymptomatic bacteriuria (ASB), GBS, trichomoniasis.

- **Inflammatory:** Mainly due to infection, redundancy in cytokine network, decreased production of interleukin-10 (IL-10).

- **Stress**

- **Inadequate expansion of plasma volume during pregnancy**

- **Withdrawal (suspension) of progesterone action**.

EPIDEMIOLOGY

The epidemiologic picture of women at risk for preterm delivery is influenced by infections, nutrition and sociodemographic factors like age, race, socioeconomic status and physical labor. The preterm delivery rate in blacks is approximately twice as that in whites, 16.3% as against 7.7%. The incidence of PTL is inversely related to the socioeconomic status. Other maternal characteristics, which influence the occurrence of PTL, are maternal prepregnant weight (< 51 kg), age, smoking, occupations requiring prolonged standing, long hours of work and physical labor. From an obstetrical point of view, factors which contribute significantly are: a weight gain of less than 11 kg or more than 13 kg during index pregnancy, and a previous history of abortions or PTL. Pregnant mothers who do heavy physical work are at an
increased risk (25% more) of developing PTL than those who do light work.11

The role of coitus in precipitating PTL has been debatable. Factors, which are believed to be responsible for PTL, are the prostaglandins present in seminal fluid, prostaglandin release during orgasm and ascending amniotic fluid infection.12

**IDENTIFYING WOMEN AT RISK OF PRETERM BIRTH**

Based on the epidemiologic factors mentioned above, various scoring systems have been developed to identify the women at risk of PTL. These scoring systems also take into account past and index pregnancies. Risk factors identify some women destined to go into PTL but they have been found to have a sensitivity of around 50%. Therefore, the usefulness of such scoring systems is limited. However, the risk of PTL in women with previous one and two preterm delivery is 17.2% and 28.4%, respectively.13 It should be remembered that the same level of surveillance is required for all pregnancies no matter how low the risk may be. Further the risk of recurrent PTL varies considerably by fibronectin status and cervical length, from less than 10% when the cervix is longer than 35 mm and the fibronectin is negative, to more than 60% when the cervix is shorter than 25 mm and the fibronectin is positive.14
DIAGNOSIS OF PTL

The importance of warning symptoms like dull low backache, abdominal cramping and mucous vaginal discharge prior to established PTL cannot be overemphasized.

According to Herron et al., the diagnostic criteria for PTL are as follows:15

- Gestational age between 20 weeks and 37 weeks
- Regular uterine contraction 5–8 minutes apart or less, accompanied by one or more of the following:
  - Progressive changes in the cervix
  - Cervical dilatation of 2 cm or more and cervical effacement of 80% or more.

Threatened PTL is the presence of uterine contractions with formation of the lower segment but with no definite cervical change.

EVALUATION OF PTL

The objectives of evaluation of a patient with threatened or established PTL are to:

- Confirm the diagnosis
- Identify the cause, if possible
- Estimate the period of gestation (in developing countries, the period of gestation should be at least 28 weeks)
- Plan intervention.

After obtaining a thorough obstetric and medical history and performing a complete physical examination, an ultrasonographic examination should be performed to assess the gestational age, the amniotic fluid volume and fetal weight to locate the placenta and to rule out fetal anomalies.

Transvaginal Sonography

It is useful in determining the cervical length and dilatation. At 24 weeks of gestation, the cervical length is about 35 mm and those with progressively shorter cervices experience increase in rate of preterm birth.16

The progressive changes in the cervix are shown in Figure 1.

INVESTIGATIONS

It is important to investigate a case thoroughly and detect the underlying etiology. The results of investigations also help one to evaluate the benefits of medical or surgical intervention. The following investigations are indicated:

- Hemogram including complete blood count and differential count
- Urinalysis and culture
- Serum C-reactive protein (chances of PTL if > 0.8)
- Glucose and creatinine levels
- Electrocardiogram if over 30 years old
- Cervicovaginal fluid for culture and sensitivity and fetal fibronectin levels18

Fig. 1: Representing the cervical changes seen on transvaginal sonography where T, Y, V, U denote the relationship between the lower uterine segment and the cervix17

- Amniocentesis for evidence of chorioamnionitis
- Amniocentesis should be performed in women with PTL whenever amnionitis is suspected, e.g. unexplained maternal fever, leukocytes, fetal tachycardia or uterine contractions which are difficult to arrest with standard doses of tocolytics
- Biochemical markers: Evaluation of activin, inhibin and relaxin may have a role in predicting PTL.19
- Cervical effacement of 80% or more, dilatation more than 2 cm, increase in dilatation of 1 cm or more, sonographic cervical length under 30 mm, or a positive fibronectin level should be documented before the diagnosis of PTL is accepted.14

TREATMENT OF PRETERM LABOR

Bed rest, especially in the left lateral position, is an accepted modality in the treatment of PTL. Administration of intravenous (IV) fluids further improve the outcome. Valenzuela et al. in their series, reported that 50% of patients responded to this therapy.20

The importance of tocolytic agents in threatened or established PTL cannot be overemphasized. Various tocolytics have been used with success rates varying from 40% to 90% (Table 1).

Tocolysis

It has been well established that tocolysis improves perinatal mortality and morbidity due to preterm birth. An ideal tocolytic drug would be one which produces tocolysis without any maternal or fetal side-effects. Such an agent is yet to be identified. Historically, various hormones, psycholeptics,
<table>
<thead>
<tr>
<th>Drugs</th>
<th>Administration</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoxsuprine</td>
<td>Parenteral</td>
<td>Beta sympathomimetics: 0.2–1 mg/min (individual titration) over 10 minutes; infusion rate maintained at 0.1–0.3 per minute for 24 hours followed by oral or intramuscular isoxsuprine 10–20 mg TID or QID</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Oral</td>
<td>30 mg orally followed by 20 mg orally TID</td>
</tr>
<tr>
<td>Magnesium salts</td>
<td>IV</td>
<td>4 g MgSO$_4$.7H$_2$O IV over 20 minutes followed by 2% maintenance infusion at 2 g/hour</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>Magnesium gluconate: 1 g q2-4h</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>Magnesium oxide: 200 mg q3-4h</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>Enteric coated Magnesium chloride: 535 mg q4h</td>
</tr>
<tr>
<td>Nitroglycerine</td>
<td>Dermal patch</td>
<td>5–10 mg patch over gluteal region. If uterine contractions persist after 1 hour patch can be repeated. Patch should be replaced after 24 hours; can be kept for 48 hours.</td>
</tr>
<tr>
<td>Terbutaline</td>
<td>IV</td>
<td>Start infusion at 5 µg/min increase q10m by 5 µg/min until a rate of 15 µg/min; if contractions have not ceased a double strength solution is prepared to avoid excessive IV fluids; can be increased until contractions disappear, toxicity appears, maternal pulse rate exceeds 1–0 bpm or a dose of 30 µg/min maintained for 12 hours. Do not taper before switching over to alternate mode.</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>5 mg q4h for 24 hours then adjust dosage to 2.5–5.0 mg q3-6h by 20 mg q6h orally</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>Oral/rectal</td>
<td>Initial dose 50 or 100 mg rectal suppository than 25–50 mg orally or as rectal suppository for 48 hours</td>
</tr>
</tbody>
</table>

**Side effects:**
- Maternal: Palpitations, tremors, anxiety, migraine, chest pain, pulmonary edema, hypoglycemia, paralytic ileus
- Fetal and neonatal: Inconsistent FHR changes, fetal acidosis, fetal hypoglycemia, sometimes neonatal relative hypoglycemia

**Contraindications:**
- Heart block, myocardial damage, compromised renal function, myasthenia gravis
- Hypothyroidism, sickle cell disease, patients on MAO inhibitors, asthmatics on beta-adrenergics

**Abbreviations:**
- TID, thrice a day; QID, four times a day; q20m, every 20 minute; q6h, every 6 hour; MgSO$_4$.7H$_2$O, magnesium sulfate; q10m, every 10 minute; q2-4h, every 2–4 hour; q3-4h, every 3–4 hour; q4h, every 4 hour; FHR, fetal heart rate; bpm, beats per minute; MAO, monoamine oxidase; q2h, every 2 hour; q3-6h, every 3–6 hour
sedatives, vasodilators and neuromuscular agents have been used to arrest PTL. Progesterone has not been proven to be an effective inhibitor of PTL. IV infusion of ethanol has fallen into disrepute because of the maternal side-effects like nausea, vomiting, headache, restlessness and also due to the fetal withdrawal syndrome. Tocolytic agents are generally contraindicated in the following situations:

- **Maternal**: Hypertension, cardiac disease, placental abruption, hypothyroidism, uncontrolled diabetes, chorioamnionitis, eclampsia, severe anemia and cervical dilatation more than 3 cm
- **Fetal**: Demise, severe intrauterine growth restriction, lethal anomalies and distress.

Tocolytic agents currently employed, their efficacy, dosage, administration and the mode of action is shown in Table 1 and Flow chart 2, respectively.

**Other Drugs which have been Used in the Management of Preterm Labor**

**Prostaglandin Synthetase Inhibitors**

Prostaglandins act by increasing the myometrial gap junctions and enhanced calcium release from intracellular stores, thus resulting in uterine contractions (Flow chart 1). Prostaglandin synthetase inhibitors act by inhibiting the action of cyclooxygenase enzyme which results in decreased prostaglandin synthesis. Indomethacin and more recently mefanemic acid, have been used as tocolytic agents. Prostaglandin synthetase inhibitors cause maternal gastrointestinal upset, drug rash and rarely bleeding disorders. In the fetus, indomethacin causes constriction of the fetal ductus arteriosus and decreased urine output leading to oligohydramnios. Therefore, indomethacin is advocated only before 32 weeks of gestation.

**Nitroglycerine**

Nitroglycerine is a donor of nitric acid, and can be applied in the treatment of PTL. Nitric oxide is an endogenous compound relaxing nonstriated muscles. In the uterine-placental unit, it acts synergistically with progesterone-inhibiting uterine contractility. It is a safe, well-tolerated, noninvasive method of tocolysis which is used as patches.

**Oxytocin Antagonists**

Oxytocin antagonists are peptides that block the action of endogenous oxytocin by effectively competing for the finite number of myometrial cell oxytocin receptors and by blocking the production of inositol triphosphate (IP3) receptors. An oxytocin antagonist, l-deamino-2-D-Tyr (Oet)-4-Thr-8-Orn oxytocin was used in a pilot study by Akerlund and associates. More recently, the use of atosiban at doses of 300 µg/min as an IV infusion for 2 hours has been reported.
Precautions

Tocolytic agents are potent drugs with abundant possibilities for serious complications and therefore, complaints of side-effects should never be ignored. Complications are more likely to occur in multiple gestation, maternal anemia, occult amnionitis or occult placental abruption, undiagnosed maternal heart disease, prolonged parenteral infusions of tocolytics for more than 24 hours, maternal age more than 30 years, combination therapy with multiple tocolytics and in those receiving steroids. A very careful attention to fluid balance is required, and a pretreatment electrocardiogram is a reasonable precaution. If amnionitis is ruled out, infusion can be continued for 12–24 hours. After 24 hours, it is prudent to start oral tocolytics with careful surveillance for another episode of PTL.

In order to avert the side-effects of the tocolytic drugs, acupuncture has been tried and found to be effective in the arrest of PTL.\textsuperscript{33}

Progesterones

Progesterone has been shown to prevent the formation of gap junctions and to have inhibitory effect on myometrial contractions. 17 alpha-hydroxyprogesterone caproate is injected in the dose of 250 mg intramuscularly on weekly basis till 36 weeks of gestation. Studies have shown that progestational agents did not increase the risk of spontaneous abortions, fetal congenital malformations, perinatal or neonatal morbidity or mortality.\textsuperscript{44}

Antibiotics

Earlier various studies showed that PTL was due to infection. Antibiotics were being used in many centers for treatment of PTL. In a randomized double-blind placebo-controlled trial, there was no statistically significant difference between clindamycin and placebo-treated groups.\textsuperscript{45} Norman et al. concluded from a multicentric, randomize controlled trial that a combination of ampicillin and metronidazole when given to women with PTL significantly prolongs pregnancy.\textsuperscript{36} However, it seems more logical to administer antibiotics to women at risk of PTL with infections proved by culture from a high vaginal swab or of amniotic fluid. The risk of PTL was successfully decreased from 40% to 25% in mothers treated with either metronidazole or erythromycin who had evidence of bacterial vaginosis.\textsuperscript{37}

Presently antibiotics for PTL with intact membranes are recommended when there is evidence:

\begin{itemize}
  \item Of chorioamnionitis
  \item Gestational age is less than or equal to 28 weeks
  \item Failure of tocolysis (before beginning a second tocolytic agent).\textsuperscript{48}
\end{itemize}

Steps to Reduce Neonatal RDS and IVH

Maternal administration of corticosteroids to promote fetal pulmonary maturity should be considered if the period of gestation is between 28 weeks and 32 weeks. The most extensively used regimens are two doses of betamethasone 12 mg given intramuscularly 24 hours apart, or four doses of dexamethasone given intramuscularly 12 hours apart. Because of insufficient scientific data from randomized control trials regarding safety and efficacy, repeated courses of steroids should be used.\textsuperscript{49} More recently, other strategies have been employed to reduce respiratory disease in premature infants. Maternal administration of thyrotropin-releasing hormone (TRH) elevates prolactin and thyroxin in the fetus, and has reduced the incidence of bronchopulmonary dysplasia. Preliminary reports are encouraging.\textsuperscript{50} The other agent, inositol, a component of membrane phospholipids has been supplemented to preterm infants with respiratory distress.\textsuperscript{51} Artificial surfactant therapy in the preterm neonate has been found to decrease the severity of RDS.

RISK TO THE NEONATE

Once the preterm baby is born, it is prone to a large number of complications which are as follows:\textsuperscript{13}

Immediate

\begin{itemize}
  \item Birth asphyxia
  \item Respiratory distress syndrome (RDS)
  \item Jaundice
  \item Hemorrhage
  \item Hypoglycemia
  \item Hypocalcemia
  \item Sepsis
  \item Feeding difficulties
  \item Necrotizing enterocolitis
  \item Patent ductus arteriosus
  \item Intraventricular hemorrhage (IVH)
  \item Iatrogenic-induced complications, e.g. retrolental fibroplasias
\end{itemize}

Late

\begin{itemize}
  \item Sensorineural deafness
  \item Developmental delay
  \item Reduced growth potential
  \item Recurrent respiratory infections
  \item Learning difficulties
  \item Social: Enforced separation of mother and baby
  \item Sudden infant death syndrome (SIDS)
  \item Blindness
  \item Child abuse
\end{itemize}

Antibiotics for PTL with intact membranes are recommended when there is evidence:

\begin{itemize}
  \item Of chorioamnionitis
  \item Gestational age is less than or equal to 28 weeks
  \item Failure of tocolysis (before beginning a second tocolytic agent).\textsuperscript{48}
Phenobarbital when given to mothers in established PTL at doses of 10 mg/kg IV over 30 minutes (500 mg minimum and 700 mg maximal dose), has been shown to prevent intraventricular bleeding in the newborn. Maternal administration of vitamin K reduces the incidence and severity of IVH in the neonate.

**IN UTERO TRANSFER**

One of the most important questions facing the obstetrician is whether or not to transfer the mother to a center where intensive neonatal care facilities are available. The survival of premature infants in neonatal intensive care units considerably exceeds those in institutions without such facilities. In developing countries where very few hospitals are equipped to take care of premature infants, it is advisable to refer the women at risk of PTL to tertiary care centers. Such referrals should be withheld if there is a strong likelihood of mother delivering in transit.

**INTRAPARTUM MANAGEMENT**

A close intrapartum surveillance is of paramount importance in PTL because intrapartum asphyxia increases the incidence of RDS and IVH. Electronic fetal heart rate (FHR) monitoring and fetal scalp pH measurement should be used liberally. Borderline pH values of 7.20–7.25 require prompt correction. These babies are likely to become asphyxiated early in labor. If cardiotocography is not available, auscultation of the fetal heart must be performed at 15-minute interval, especially during and soon after contractions. In delivering the preterm fetus, Cesarean section confers certain benefits like avoiding birth trauma, asphyxia and reduced incidence of IVH. If the lower uterine segment is thick and not well formed, it may be prudent to give a lower vertical incision. In developing countries, Cesarean section does not appear to be beneficial in the long run, especially when the gestational age is less than or equal to 32 weeks as expert neonatal care is always available.

In delivering the preterm baby vaginally, the routine use of forceps has become questionable since the work of Fairweather and Stewart. Elective liberal episiotomy has been advocated with a view to shorten the second stage of labor and to reduce the force compressing the soft fetal skull. It is now recognized that ventouse extraction of the preterm fetus may be harmful.

**PREPREGNANCY PREVENTION OF PRETERM BIRTH**

Proper counseling to discourage induced abortion, early detection and treatment of uterocervical anomalies and treatment of UTIs contribute to prevention of preterm birth. Social intervention with a view to eliminate risk factors like malnutrition, anemia, smoking and vaginal infections can to a great extent prevent preterm birth.

Developed countries like Singapore, Sweden and France have recorded a dramatic decline in the incidence of prematurity. This reduction of prematurity rate from 12% to 6.5% in Singapore was achieved by socioeconomic change, decreased fertility and improved health care.

**CONCLUSION**

In India, preterm births account for a sizeable number of perinatal deaths largely due to lack of neonatal intensive care units in most hospitals. Therefore, there is a need to identify the women at risk of PTL and institute intervention early in labor. A variety of potent tocolytic agents are now available, those with least maternal side-effects and those that do not cross over to the fetus must be selected. Efforts should be made to develop good referral networking for neonatal intensive care. The need to institute social intervention and improve reproductive health care cannot be overemphasized. A change in the attitude of the obstetrician toward the problem of preterm birth is necessary. Once the obstetrician is genuinely convinced, then many strategies to battle against prematurity become possible.

**REFERENCES**

INTRODUCTION

Perinatal deaths due to Rhesus (Rh)(D) alloimmunization have fallen 100-fold, since the introduction of anti-D immunoglobulin (IG) in 1969.\(^1\) Use of anti-D in Rh(D) negative women after sensitizing events during pregnancy and after birth of a Rh(D) positive infant has created a major impact on this disorder.

In India, a recent perinatal audit found the incidence of perinatal deaths due to Rh alloimmunization to be, between 1% and 2.5%.\(^2\) Postpartum administration of Rh(D) immunoglobulin (RhIG) was highly successful because most of the instances of alloimmunization are due to the exposure of the mother’s immune system to Rh antigen by the transplacental passage of fetal Rh(D) positive cells during labor and delivery. Unfortunately, in some cases sensitization can occur during pregnancy due to “silent bleeds”. In these cases, postpartum administration of RhIG is ineffective as Rh sensitization has already occurred. At a conference convened by the Royal College of Physicians of Edinburgh and Royal College of Obstetricians and Gynaecologists,\(^3\) the panel reached the conclusion that Rh(D) alloimmunization still occurs due to two main reasons:

1. Some women do not receive the benefit of the recent policy
2. Women are sensitized by small bleeds from the fetus, mainly in the last 12 weeks of pregnancy, which may go undetected.

Majority of the cases seen today are due to the under utilization of RhIG.

The following obstacles need to be addressed:

- Insufficient awareness of antenatal injection of Rho(D) immunoglobulin (RhIG)
- Controversies in certain situations like presence of vesicular mole or after surgical sterilization in women
- Uncertainty of dosage to be given after cesarean delivery
- Cost-effectiveness
- Widespread education on effective prevention
- Commitment to eradicate hemolytic disease of the newborn (HDN)
- Safety of prophylaxis
- Adequate supply
- Compliance with guidelines for treatment.

Effective elimination of Rh-isoimmunization will be a result of overcoming various problems with a combination of different options available to us.

Present day practice mandates a more aggressive utilization of antibody mediated immune suppression, in order to achieve a lower incidence of Rh disease.

Identifying Candidates for Immunization

On the first prenatal visit, ABO grouping, Rh typing and antibody screening should be performed to identify the requirement of RhIG. The mate of the Rh negative pregnant woman should also be tested, because if both partners are Rh negative, there is no need for Rh immunoprophylaxis. However, if there is any doubt about the identity of the father, the mother remains a candidate for anti-D prophylaxis. If the woman is found to be Rh negative and is not actively producing anti-D, she is a candidate for RhIG prophylaxis later in the pregnancy. She should be counseled at this time regarding
the need for prophylaxis and the possible dosage schedule and timing of administration of RhoIG. The laboratory should also perform a test for D<sup>o</sup> on all Rh(D) negative prenatal patients. D<sup>o</sup> positive individuals should be considered as Rh positive provided the D<sup>o</sup> control is negative. A positive D<sup>o</sup> test, indicates that the patient’s red cells possess a variant of the Rho(D) antigen and may be considered Rh positive. However, there is a potential for misinterpretation of positive D<sup>o</sup> test results in late pregnancy and at delivery due to the presence of fetal cells in the maternal circulation.

A noninvasive prenatal determination of the fetal Rh(D) status might be useful for the management of pregnancies in Rh(D) negative women whose partners are Rh(D) positive. Studies by Di Simone N et al. have found false positive results for Rh(D) in polymerase chain reaction (PCR) of deoxyribonucleic acid (DNA) obtained from maternal plasma. Based on these studies, flow cytometric analysis might be proposed as a clinical tool for the noninvasive prenatal determination of the fetal Rh(D) status independently of fetal gender.<sup>3</sup>

**ANTEPARTUM PROPHYLAXIS**

**Rationale for Antepartum Administration of Rh-immunoglobulin**

The most important cause of anti-D antibodies is now immunization during pregnancy where there has been no overt sensitizing event. Although most of the Rh sensitization occurs after delivery, the most common time Rh positive red cells from the baby enter the mother’s circulation about 15% are caused by small fetomaternal hemorrhages that occur between 20 weeks and 40 weeks. Until the present there has been a gap in the coverage and protection, because the protocols were outlined only for the postpartum period. By covering this group it is possible to reduce the immunization rate from 1.5% to 1.8%, following only postpartum prophylaxis to almost zero.

The risk of Rh(D) alloimmunization during or immediately after a first pregnancy is about 1.5%.<sup>4</sup> Administration of 100 μg [500 International units (IU)] anti-D at 28 weeks and 34 weeks of gestation to women in their first pregnancy can reduce this risk to about 0.2% without, to date, any adverse effects. Although, such a policy is unlikely to confer benefit or improve outcome in the present pregnancy, fewer women will have Rh(D) antibodies in their next pregnancy. Adoption of such a policy will need to consider the costs of prophylaxis against the costs of care for women who become sensitized and their affected infants, and local adequacy of supply of anti-D gammaglobulin. Two eligible trials, which involved over 4,500 women, compared anti-D prophylaxis with no treatment.<sup>4</sup> Although the data suggested, when women receive anti-D at 28 and 34 weeks of gestation, a reduced incidence of immunization during pregnancy [odds ratio (OR) = 0.44, 95% confidence interval (CI), 0.18–1.12], after the birth of a Rh positive infant (OR = 0.44, 95% CI, 0.18–1.12), and within 12 months after birth of a Rh positive infant “OR = 0.44, 95% CI, 0.19–1.01,” none of these differences were statistically significant. In the trial, which used the larger dose of anti-D (100 μg; 500 IU), there was a clear reduction in the incidence of immunization at 2–12 months following birth in women who had received Anti-D at 28 and 34 weeks (OR = 0.22, 95% CI, 0.05–0.88). No data were available for the risk of Rh(D) alloimmunization in a subsequent pregnancy. No differences were observed in the incidence of neonatal jaundice.

Late immunization during a first pregnancy is responsible for 18–27% of cases. Immunization during a second or subsequent pregnancy probably accounts for a similar proportion of cases, although in this situation it is impossible to distinguish late sensitization from failure of prophylaxis at the end of the preceding pregnancy.<sup>5</sup>

**Indications for Antepartum Use**

There was widespread acceptance of the principle of antibody mediated immune suppression, which was adopted into routine obstetric management of the mother “at-risk” of Rh(D) sensitization. It is now common practice to give passive immunization during the antepartum period in the following clinical situations:<sup>6,7</sup>

- Invasive prenatal diagnosis (chorion villus sampling, amniocentesis, fetal blood sampling)
- Other intrauterine procedures (insertion of shunts, embryo reduction)
- Antepartum hemorrhage, threatened, inevitable and induced abortion
- Ectopic pregnancy
- External cephalic version of the fetus
- Closed abdominal injury
- Intrauterine death.

**Dosage and Timing of RhoIG Injections**

To be successful, the proper amount of RhoIG must be administered prior to Rh sensitization. Thus, dosage and timing of injections are critical. The various indications and recommended doses for RhoIG administration to obstetric patients are summarized in Table 1.

**Uncomplicated Pregnancy (Routine Antenatal Prophylaxis)**

Pioneering studies from Canada by Bowman have suggested that antenatal administration of 300 mcg of RhoIG at 28–30 weeks of gestation to the pregnant unimmunized Rh negative woman is very effective in preventing Rh immunization. This is now the accepted standard of obstetric care in North America.<sup>9</sup>
Recommended dose (mcg)

- First trimester induced or spontaneous abortion: 50 mcg
- First trimester ectopic pregnancy: 50 mcg
- Second trimester induced or spontaneous abortion: 300 mcg
- Second trimester ectopic pregnancy: 300 mcg
- Second trimester amniocentesis: 300 mcg
- Prophylaxis at/about 28 weeks: 300 mcg
- Third trimester amniocentesis: 300 mcg
- Antepartum fetomaternal hemorrhage (accompanying abdominal trauma, abruptio placenta, unexplained fetal death, and placenta praevia, etc.): As determined by quantification of fetal red cells in aternal circulation (300 mcg will suppress the maternal response to 15 mL of packed red cells)

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommended dose (mcg)</th>
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<tbody>
<tr>
<td>First trimester induced or spontaneous abortion</td>
<td>50</td>
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<tr>
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</table>


A multicenter trial of antepartum low-dose anti-D (50 mcg) was undertaken in United Kingdom (UK) to test the efficacy of a lower dose of anti-D Ig than that used in earlier studies. It was concluded that, while two doses of 250 IU (50 mcg) anti-D may reduce alloimmunization, they are not as effective as two doses of 500 IU (100 mcg). On the basis of a theoretical calculation based on the half life of gammaglobulin, it is expected that a single injection of 300 mcg of RhIG at 28 weeks provided protection for 12 weeks or 84 days. Therefore, antepartum prophylaxis with a single injection at 28 weeks was implemented, as described by Bowman. This would cover most pregnancies until delivery.

Delayed Pregnancy

A second injection of RhIG should be administered, whenever a patient progresses in pregnancy more than 12 weeks beyond the date of initial RhIG administration. For instance, if a patient has received an injection of RhIG at 28 weeks and does not deliver by 40 weeks, she should receive a second 300 mcg injection as soon, after 40 weeks, as possible. In this case, if delivery occurs within 3 weeks of the second injection and if there is no fetometal hemorrhage (FMH) in excess of 15 mL of red cells, a third administration after delivery can be withheld.

First Trimester Pregnancy Wastage

A 50 mcg dose (micro-dose) is considered adequate to prevent sensitization in patients whose pregnancies are terminated prior to 13 weeks of gestation. This prophylaxis is important since Rh antigen expression has been demonstrated on erythrocytes of early embryos (0.5 cm and 7 g in weight). The rate of Rh-alloimmunization after abortion is 5–10%, without prophylaxis. The risk increases with the gestational age of the abortus from nil at 4 weeks to 2% at 8 weeks, to 9% at 12 weeks or more. The method of termination of pregnancy also affects the risk. Various studies have suggested that fetal cell leak is higher in induced abortions as compared to spontaneous abortions. However, a policy adopted by many physicians is—when in doubt, it is better to give, rather than withhold RhIG.

Antepartum Fetomaternal Hemorrhage

When significant antepartum FMH is suspected for any reason, such as abruptio placentae, abdominal trauma, unexplained fetal demise or placenta previa, the dosage of RhIG should be determined after estimating the FMH. One 300 mcg dose of RhIG should be administered for each 30 mL of fetal whole blood or 15 mL of packed red cells.

POSTPARTUM PROPHYLAXIS

The risk of postpartum immunization increases with the amount of FMH (Table 2). This is because the prevalence of primary alloimmunization is antigen dose-dependent. However, this does not hold true for a secondary immune response, where the mother was already exposed to the Rh antigen in the past. In such cases, after doses as little as 0.05 mL of Rh positive cells, the immune response is stimulated. As discussed above, the risk of alloimmunization at 6 months postpartum is about 85%. However, due to “sensitization”, i.e. undetectable antibody levels until a secondary immune response is mounted, another 8% show Rh alloimmunization subsequently. Hence, the risk is about 16% for the first Rh positive ABO compatible pregnancy.

Studies have found that 75% postpartum women have 0.1 mL of fetal cells in their circulation and only 3% have 15 mL of fetal cells in the circulation. Hence, 300 mcg of RhIG is adequate for 15 mL of fetal cells or 30 mL of whole blood, is sufficient to prevent immunization in a majority of patients. Mollison had reported that 99% of postpartum women have 3 mL of FMH. Hence, a dose of 100 mcg may be adequate for most women as it is sufficient to clear 4 mL of red blood cells (RBCs).

In Great Britain, a dose of 500 IU (100 mcg) Rh anti-D IG is given to all Rh negative mothers who deliver a Rh positive infant unless the mother has already made anti-D antibodies,
which has been stimulated either by a previous pregnancy or by transfusion. These dosage principles were reviewed by a consensus panel in the UK, and were recommended by them as the reference standard for good clinical practice.18

In Australia, the standard dosage of anti-D currently, given at all gestational ages is one ampoule containing 125 µg of anti-D. This dose is supplemented when needed on the basis of maternal Kleihauer testing. Certain workers19 have suggested that this protocol should be revised for early pregnancy, using only 30 mcg, which would remove the entire fetoplacental blood volume (3 mL) of a 12 weeks of pregnancy from the circulation.

In India, the usual dose recommended is 300 mcg postpartum, keeping in mind practical problems of assessing FMH and ensuring subsequent adequate dosing. A study at a large population based Rh clinic in Mumbai has shown that the incidence of Rh negativity was 5% in pregnancy.20 The rate of Rh alloimmunization in Rh negative pregnant women declined from 0.16% in 1981–83 to 0.09% during 1990–92. The overall rate in Rh negative women in the clinic, pregnant and nonpregnant also declined from 3.1% to 1.7%. In India, anti-D IG was mainly used postpartum. Hence, a more comprehensive Rh prophylaxis program, would be needed to eradicate Rh HDN. 1.5–1.8% of Rh negative women become immunized in spite of routine postpartum Rh immune prophylaxis, probably due to immunization occurring during pregnancy.

A retrospective audit has a recommended reduction in the recommended routine postpartum dose of anti-D from 625 IU to 250 IU when flow cytometric quantitation for FMH is available, should be considered. Adopting such a strategy would ensure the ongoing provision of a valuable human blood product currently in limited supply.21

**Apparent Failures of Prophylaxis**

Jennings showed that most of the so-called, failures of prophylaxis were the result of immunization during pregnancy.22 This was supported by immunological evidence of the clinical trials, where only 6.91% of controls (who did not receive prophylaxis) became immunized at 6 months as compared to 12.92% at the end of the second pregnancy. This illustrated the "booster" effect of the next pregnancy on the so-called "sensibilization" phenomenon first described by Nevalinna.23 This phenomenon describes how some women can become primed, but their immune response remains occult until revealed by a subsequent exposure to the Rh-antigen.

A very small percentage of failures of prophylaxis may be due to a large FMH. A single dose of Ig can reasonably be expected to suppress a certain amount of hemorrhage. If the hemorrhage is large, then some amount of sensitization can take place. However, use of anti-D globulin reduces the probability of immunization and; therefore, depending on the concentration of both antibody and antigen, the actual immunization frequency can be reduced to very small numbers but never to zero.

**MONOCLONAL VERSUS POLYCLONAL**

Immune suppression by passive antibodies in general is brought about by clearance of the antigen and immune deviation, i.e. nonexposure to antibody producing tissues. Clearance of the antigen could happen in Rh(D) negative mother by intravascular lysis as it happens in ABO incompatibility or by extravascular phagocytosis. Using an in vitro model, it has been shown that although both clearance and antibody-dependent cell-mediated cytotoxicity (ADCC) take place with both monoclonal antibodies and polyclonal antibodies, the ADCC activity is better with polyclonal antibodies than with monoclonal antibodies [(BRAD-3(IgG3) or BRAD-5(IgG1)]. This is because polyclonal antibodies interact better with the Fc receptors on the splenic cells. Further trials of antenatal and postnatal prophylaxis in Rh(D) women using monoclonals BRAD3 or BRAD5 are required to prove that they are suitable for the prevention of Rh(D) HDN.24

There is a report from Russia about the creation of a human-mouse heterohybridoma producing monoclonal IgG3 (cell-line HG-48/92).25 However, this preparation contains only IgG1 anti-D antibodies and not IgG3, which are important in removal of Rh(D) antigen through monocyte-mediated ADCC activity.

It would seem prudent to use a blend including both IgG1 and IgG3 antibodies.

In most instances, the current polyclonal anti-D consists of both IgG1 and IgG3. In a study of 21 polyclonal anti-D IgG preparations, the percentage of IgG3 was found to range between 1% and 18% with a mean of 8%.26

**LABORATORY TECHNIQUES IN EVALUATING A RHESUS ALLOIMMUNIZED PREGNANCY**

**Determination of Fetomaternal Leak**

A blood sample is obtained after delivery or any other event suspected to have caused a fetomaternal bleed. This post-event sample of maternal (Rh negative) blood is then tested for quantification of fetal leak into the maternal circulation.

**Rosetting Test**

This is an initial qualitative screening test. **Principle:** Rh positive fetal cells coated with anti-D form rosettes with Rh positive indicator cells, thus, making them distinguishable from the Rh negative maternal cell population. **Disadvantage:** It is not reliable when the infant/fetus or mother is weak D (D<sup>+</sup>) positive.
Kleihauer-Betke Test

The technique first reported by Kleihauer et al.\textsuperscript{27} has been modified by Nierhaus and Betke. A thin blood smear is prepared from maternal hemoglobin (Hb). The smear is then counter stained by erythrocyn to stain fetal red cells. Under the light microscope the number of fetal cells per 100,000 maternal ghost cells are counted. The amount of fetal blood in maternal circulation is calculated with the help of a graph,\textsuperscript{28} plotted by using the data obtained by counting smears prepared by mixing known amounts of adult and cord bloods. Table 3, illustrates the relationship between the number of fetal cells and amount of blood.\textsuperscript{29}

Quantitating the volume of fetal bleed can be done by various formula, e.g.

\[
\frac{\text{No. of fetal cells } \times 5,000}{1,000 \text{ adult cells}} = \text{mL of fetal bleed}
\]

Reasons for false positive results:

- **Faulty technique:** Hb F elutes if left too long in the eluting solution
- Some fetal cells containing HbA will be missed
- Some pregnant women (10–25%) may themselves produce elevated level of Hbf between 10 weeks and 32 weeks of gestation
- Genetic hemoglobinopathies.

New tests, advocated for detecting FMH include the microscopic Du test (micro Du) enhanced with polyethylene glycol (PEGD) and flow cytometry (FC). A study comparing five methods of detecting FMH\textsuperscript{30} assessed three qualitative methods:
1. Micro Du
2. Rosette test
3. PEGD

and two quantitative methods:
1. Acid elution, i.e. Kleihauer-Betke stain
2. FC.

Of the qualitative tests, the micro Du test was the least sensitive, with 20% false negative results occurring at 0.5% fetal cells. The PEGD test was only slightly more sensitive and offered no clinical advantage. The rosette test was the most sensitive, consistently detecting fetal cells at concentrations of 0.25% or greater. FC and Kleihauer Betke test showed similar results, with good correlation between measured and expected quantities of fetal cells. Although Kleihauer Betke (acid elution) test is a more commonly used method for quantitating FMH, FC offers an acceptable alternative which is capable of analyzing large number of cells with objectivity and reproducibility.

**Prenatal Investigations**

A blood sample must be collected from every woman at her first antenatal visit, for ABO and Rh typing. This policy should be universal and carried out irrespective of the parity or what tests are performed in the previous pregnancy. Rh(D) negative women and those having partial “D” or weak “D” antigens are screened for the presence of anti-D in their serum. In-depth investigations are carried out for Rh(D) alloimmunized mothers.

**Rhesus Genotype of the Husband**

When a woman has anti-D in her serum, it is desirable to know the Rh genotype of her husband.

**Rhesus Antibody Estimation**

Rhesus antibodies are immune (IgG) in nature having the molecular weight of 160,000 Daltons. They are able to cross the placental barrier and coat fetal Rh(D) positive red cells. After the D antigenic stimulus, IgM anti-D having the molecular weight of 900,000 Daltons, appears first, which later on gets converted to IgG. Women who respond to D antigen are likely to respond to “C” or “E” antigens of the Rh system. Hence, it is essential to screen all Rh(D) alloimmunized mothers for anti-C and anti-E response also.

Rhesus antibody titer and quantitation are the tests employed for estimation of Rh antibodies, in maternal serum.

**Rhesus Titer**

Manual Rh titration is a universally accepted test because it is simple, cheap and can be easily repeated frequently. A rise in Rh titer indicates a Rh(D) positive fetus. Several techniques are available to perform this test.

- Indirect antiglobulin test (IAT)\textsuperscript{31}
- Albumin method\textsuperscript{32}
- Enzyme method\textsuperscript{32}

**Quantitation of Anti-D Concentration**

Rhesus titer, being a semi-quantitative, visual test, results may vary from person to person. Therefore, autoanalyzer methods have been developed to quantitate Anti-D in \(\mu g\) amounts.

- Bromelin method

\[
\begin{array}{|c|c|}
\hline
\text{No. of fetal cells per} & \text{Amount of FCL} \\
100,000 \text{ adult cells} & (\text{mL}) \\
\hline
1–4 & 0.15 \\
5–8 & 0.25 \\
9–13 & 0.5 \\
14–24 & 0.75 \\
25–32 & 1.0 \\
33–64 & 2.0 \\
65–96 & 3.0 \\
97–157 & 5.0 \\
\hline
\end{array}
\]
Hemoglobin and hematocrit (Hb and HCT)

The normal values in the second trimester are 14 g/dL for Hb values for Rh HDN. Generally, a strongly positive (++) reaction indicates a severely affected fetus. Liley’s method, is considered reliable only for pregnancies from 27 weeks to term. Therefore, many workers have suggested modification in the Liley’s graph to evaluate the results of the amniotic fluid collected between 14 weeks and 26 weeks of gestation. It has been observed that considerable number of optical density values fall in Zone II (beginning or middle) even when the fetus is Rh(D) negative, hence an intrauterine transfusion (IUT) is recommended only if results indicate the end of zone II or zone III. Amniocentesis is recommended approximately 10 weeks prior to the occurrence of a previous adverse event such as the delivery of a hydropic, still born or a severely anemic infant.

INVESTIGATIONS OF THE FETUS

Rhesus Typing

Prenatal DNA based Rh typing of the fetus is possible as early as the 9th week of gestation, using trophoblasts recovered from the endocervical canal. DNA obtained from fetal cells in the maternal peripheral blood or amniotic fluid could also be used to determine the Rh status by PCR amplification.

Studies describing the second trimester screening test in reproductive health negative pregnancies conclude that either the connected value should be referred or double test result should be considered ignoring the unconjugated estriol result. Another option is the first trimester, Down’s syndrome screening test.

Fetal Blood Sampling

Specific indications of fetal blood sampling in Rh alloimmunization:

- All hydropic cases
- Optical density deviate (ODD) 450 result -> high zone II on Liley’s chart
- Rapid rise in ODD 450 value
- Risk of severe anemia in early to mid second trimester
- Fetal blood typing (e.g. heterozygous father)
- Unavoidable transplacental needle passage

Fetal blood for examination is obtained by cordocentesis.

Cordocentesis or Percutaneous Umbilical Sampling (PUBS)

Daffos and associates introduced PUBS in 1983, to diagnose fetal affection. In Rh-alloimmunization, PUBS is performed for immediate confirmation of the fetal antigenic status, obviating the need for further intervention in the Rh negative fetus. A detailed ultrasound examination should be performed before PUBS for evaluation of the gestational age and placental function. Fetal blood can be obtained by puncture of the fetal heart, intrahepatic portion of the umbilical vein or by puncture of the umbilical vessel close to its placental insertion, the latter being the most common and around 1-10 mL of blood can be withdrawn for diagnostic studies. Cordocentesis has also been used for repeated blood transfusion in utero for a hydropic fetus with hemolytic disease. In most of the centers now the fetal blood sample is obtained by a direct puncture of the umbilical vein under ultrasonography guidance.

Hematological parameters studied are:

- Purity of fetal blood sample: If there is a contamination with maternal blood or amniotic fluid, then one can get erroneous results. Coulter channelizer shows separate peaks of adult and fetal RBCs based on the diameter of the cells.
- ABO and Rh typing: The standard serological technique is used to determine the blood group of the fetus.
- Direct antiglobulin test (DAT): DAT reveals the presence of IgG anti-D molecules on fetal RBCs. The strength of agglutination is directly proportional to the severity of Rh HDN. Generally, a strongly positive (++++) reaction indicates a severely affected fetus.
- Hemoglobin and hematocrit (Hb and HCT): The normal Hb values during the DAT second trimester at different gestations range from 10 g/dL to 14 g/dL. During the third trimester the range is from 14 g/dL to 15 g/dL. The HCT ranges from 35% to 40% and 40% to 47% respectively. Nicolaides et al. label it as severe Rh HDN when fetal
Hb value is more than 7 g/dL below the normal mean at the same gestation and moderate when the Hb deficit is between 2 g/dL and 7 g/dL.

- **Platelet count**: Coagulation abnormalities could be associated with severe Rh HDN. A single parameter, that could be helpful in predicting hemorrhagic disorder, is the platelet count. A platelet count below 150 × 10⁹/L is considered low and an infusion of platelet concentrate is absolutely essential if the value is below 50 × 10⁹/L.

- **Immature erythrocytes**: Counting reticulocytes, erythroblasts and normoblasts could, indirectly assess the degree of destruction of sensitized fetal red cells.

### Ultrasound

Real-time ultrasound is used to detect the progression of disease from mild to severe. The findings include hepatosplenomegaly, increase in portal venous diameter and flow velocity, fluid in serous cavities, subcutaneous edema, liquor disturbances (poly- and oligohydramnios) and placentomegaly. Attempts to characterize or identify the exact sequence of the above sequelae have been inconclusive so far.

It is also seen that there is an increased flow through the umbilical vein in anemic fetuses, probably as a compensatory mechanism to maintain the oxygen saturation in the fetus with increasing hemolysis. This increased flow causes an increase in the diameter of the umbilical vein and intrahepatic portal vein. In alloimmunized fetuses the portal venous diameter can reach a maximum of 8 mm even at 25 weeks of gestation (normal < 5 mm). ⁴⁴

The presence of fluid in the serous cavities signifies severe fetal anemia in the presence of alloimmunization. De Vore and colleagues have proposed that the first site of fluid collection is in the pericardial space. They demonstrated presence of minimal amounts of pericardial fluid using M-mode echocardiography. ⁴⁵ Abnormal pericardial fluid effusion should be diagnosed only if the thickness of the fluid is more than 2 mm.

### Color Doppler

Demonstrates increased flow in the splenic vein, its branches and portal venous branches within the liver. The increased flow through the portal vein is also reflected in the ductus venosus, which appears prominent and shows a characteristic area of turbulence on color flow mapping. **The normal ductus venosus waveform has a characteristic “M” which reflects right atrial events. In anemic fetuses, the “M” pattern is maintained but with higher velocities.** In the presence of anemia, the portal venous waveform shows a “saw-toothed” appearance. Tricuspid regurgitation can be detected by color Doppler and has been used to identify fetuses, which might not be hemodynamically stable to tolerate a bolus intravascular transfusion. ⁴⁵

### Postnatal Diagnosis

Immediately after the birth of an infant to a Rh negative mother, blood from the umbilical cord or from the infant should be examined for Rh type, Hb, and reaction of the direct Coomb’s tests. Negative infant is falsely typed as Rh positive due to the locking of antigenic sites. A false negative direct Coomb’s test, is obtained if material antibody titers are low. Other essential investigations include indices of erythropoiesis (reticulocyte count, nucleated RBCs per 100 WBC) and RBC morphology. A cord Hb less than 14 g/dL is abnormal in term neonates. Reticulocyte count in Rh disease is more than 60% and may be as high as 30–40%.

### Additional Assessment

A number of studies, which are not routinely performed, may help assess the degree of hemolysis and risk of kernicterus. They are as follows:

- Serum albumin level
- Bilirubin to albumin ratio
- Serum free bilirubin
- Bilirubin reserve binding capacity (BRBC)
- Bilirubin saturation index
- Carboxy Hb level
- Exhaled carbon monoxide level
- Erthrocyte creatinine level

Tests that may suggest HDN are:

- **Rapid fall in Hb in the absence of hemorrhage and significant blood collection.**
- **Increased erythrocyte production**: Increased reticulocytes, nucleated RBCs, erythrocyte creatinine level, and stable or falling Hb level.
- **Hemoglobinuria.**

### CLINICIAN’S APPROACH TO RHESUS ALLOIMMUNIZATION

#### Fetal Transfusions

Recognition of fetal anemia is the first step in the management of an alloimmunized patient. Whereas severe anemia can be recognized, if obvious ultrasound features described above are present, early hemolysis may not produce any significant changes which may give a false impression of fetal well-being. The timing of the first intervention will therefore vary with each patient. The management of fetal anemia requires a team approach. Facilities must be available for obtaining “O” negative packed cells with a high HCT. Some centers advocate the use of washed and irradiated packed cells. In hydropic cases, a fetal blood sampling and a transfusion are done at the same sitting. In nonhydropic cases, the transfusion may be postponed to a later date if the fetal HCT is greater than 30. ⁴⁶

Several routes have been tried to infuse packed cells into the fetus. Intraperitoneal transfusion was the earliest method
tried even before the advent of ultrasound. The ability to access the fetal circulation percutaneously under real time ultrasound guidance has led to the use of the umbilical vein or portal vein as the common site for IUT. The basic objective in IUT is to correct the anemia at the optimal time with the appropriate quantity of RBCs.

**Intraperitoneal Transfusion**

The use of intraperitoneal route is on the decline after direct access to the fetal circulation was made possible. It is effective in non-hydropic cases and is resorted to only if vascular access is not available due to fetal position or there is a need to perform a transfusion prior to 20 weeks.

**Intravascular Transfusion**

Vascular access to the fetus can be achieved through the umbilical vein near the insertion into the placenta, in the free loop of the cord or near the fetal insertion of the cord. A more recent approach is through the intrahepatic portal vein, which is an ideal site for transfusion. The volume of blood to be transfused depends on the donor HCT, fetal HCT and the fetoplacental blood volume at this period of gestation. A chart gives the approximate volume to be transfused.

**Another Guideline**

Volume of packed cells [(desired HCT – Actual HCT) × estimated fetoplacental blood volume × estimated fetal weight (kg)]/donor HCT.

The cells are transfused at the rate of 1–2 mL per minute. Constant monitoring of the fetal heart is done to look for fetal bradycardia, which if noticed is an indicator to suspend the transfusion. The volume of blood to be transfused depends on the donor HCT, fetal HCT and the fetoplacental blood volume at this period of gestation. A chart gives the approximate volume to be transfused.

**Complications**

- The most dreaded complication during transfusion in the umbilical cord is cord hematoma, which occurs if the needle slips into the Wharton’s jelly. Immediate bradycardia is noticed and can lead to fetal demise, if not recognized.
- Fetal exsanguination is rare but can occur especially in cases where there is severe thrombocytopenia.
- Chorioamnionitis is another potential complication the risk of which can be minimized by adhering to strict aseptic principles and antibiotic cover.
- Preterm labor can occur especially in fetuses with polyhydramnios. Tocolytics prior to and after the procedure minimizes the risk of preterm labor.
- Placental abruption has been reported but is a relatively rare occurrence.

**Suppression of Rhesus Immunization/Alternative Therapies**

**Plasmapheresis**

This is a cumbersome procedure, which does not obviate the need for IUTs. Soon after the plasmapheresis is stopped, the anti-D titers increase in a “rebound” phenomenon. Moreover, it reduces the maternal levels of viral and bacterial antibodies with a resultant predisposition to infection.

**Promethazine Hydrochloride**

Studies with matched controls have shown no benefits with promethazine.

**Intravenous Immunglobulins**

Thought to act by either blockade of Fc receptor in the fetal reticuloendothelial system, thereby inhibiting the removal and destruction of fetal anti-D coated erythrocytes by the fetal spleen and liver. Also thought to act by blockade of the Fc-mediated antibody placental transport, thus limiting the trans-placental passage of anti-D to the fetus. This treatment has been used by a number of authors.46,47

In a study, it was found that intravenous immunoglobulins (IVIGs) is effective in decreasing the maximum bilirubin
levels and the need for repeated exchange transfusions in reproductive health hemolytic disease of newborn. There is however, an increased need for blood transfusions for late anemia in the babies treated with IVIG.\textsuperscript{50}

**Other Treatment Modalities**

Oral desensitization with erythrocyte membrane IG therapy and transfusion of marrow stem cells from the Rh negative mother to the Rh positive fetus has been tried. Oral administration of the Rh-antigen has also been tried in an effort to suppress the secondary immune response.

**Antenatal Monitoring of Fetal Heart**

It is of value but does not help to a great extent in the management. Abnormal fetal heart rate patterns have been described in severe Rh alloimmunization. Sinusoidal and decelerative patterns have been associated with very low cord Hb concentrations at delivery\textsuperscript{51} and high perinatal deaths.\textsuperscript{52}

**Delivery of the Fetus**

The time of delivery is determined by the clinician, taking into account a number of factors which would include:

- The gestation age of the fetus
- The severity of affection
- The survival rates of the neonatal intensive care unit of the concerned center.

Each case should be carefully considered on an individual basis, before arriving at a decision.

In pregnancies where the fetus is only mildly affected, the pregnancy is allowed to continue till term, provided the fetal well-being studies so permit. Labor is induced at 36–37 weeks of gestational age. An unfavorable cervix is initially ripened with the use of prostaglandin gel. Continuous intrapartum monitoring should be utilized to detect a distressed fetus and an operative delivery resorted to whenever indicated.

When the fetus is severely affected, the fetus is delivered earlier, and the timing of delivery would be determined by the survival figures of the concerned neonatal care unit. The fetus should be delivered as early as 32–34 weeks, provided pulmonary maturity is demonstrated by a prior amniocentesis. A lecithin: sphingomyelin ratio greater than two and the presence of glycerophospholipid indicate a mature pulmonary system. If the lungs are still immature, delivery can be performed after administering corticosteroids to the mother.\textsuperscript{48,53}

In conclusion, a small well-knit team comprising of obstetricians, sonologists, blood bank personnel, neonatologists and nursing personnel working in close coordination is required for successful management of alloimmunization. Early reference with assessment and judicious intervention as well as intensive neonatal care is essential to ensure satisfactory results.

**Management of the Erythroblastic Baby After Birth**

**Management at birth:** Therapy immediately prior to delivery should include drainage of large pleural effusions and ascites to facilitate postnatal gas exchange.\textsuperscript{54}

If the infant is very ill, (premature and/or hydropic), tracheal intubation and positive pressure ventilation may be necessary. Initially, a partial exchange transfusion and later a double volume exchange using blood with a normal HCT to normalize the Hb and HCT is advocated.

**Prevention of Bilirubin Encephalopathy**

Phototherapy followed by double volume exchange transfusion in the event of phototherapy “failure” remains the mainstay of treatment for hyperbilirubinemia due to disease.

**Phototherapy**

It should be started in term neonates if bilirubin rises 0.5 mg/dL/hr or greater, or if total bilirubin exceeds 10, 12 or 14 mg/dL at less than 12, less than 18 or less than 24 hours of life respectively. It should be initiated at lower levels for premature neonates in the first 24 hours. Blue light at 450 nm appears to be the light source absorbed best by infants.\textsuperscript{55}

Special care of the infant getting phototherapy includes the use of eye patches and diapers to prevent exposure to direct light. Babies are monitored for development of hyperthermia, diarrhea, dehydration, serum calcium levels and bronze baby syndrome.

**Exchange Transfusion**

It remains a major effective means of managing hyperbilirubinemia and of ameliorating neurotoxicity in the severely affected newborn.

The objectives of exchange transfusion are:

- To remove antibody coated red cells, which are potentially lethal sources of bilirubin, and to replace them with red cells compatible with the mother
- To remove the bilirubin
- To remove the antibody that would combine with any new red cells produced by the infant.

**Other Modalities of Treatment**

**Hemoygenase inhibitors:** Inhibition of bilirubin production may be a more effective therapy in patients with Rh disease. The enzyme hemoygenase catalyses the rate limiting step in bilirubin production, the conversion of haem to biliverdin. However, there is limited success with this mode of treatment.\textsuperscript{56}

**Intravenous immunoglobulin:** It has been used in the prenatal management of Rh sensitized women, in which case the possible mechanisms of action include:

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**SECTION**

**Fetus as a Patient**

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• Feedback inhibition of antibody synthesis through modulation of maternal T or B lymphocytes or both
• Blockade of F-mediated antibody transport across the placenta
• Blockade of Fc receptors on macrophages in the fetal reticuloendothelial system which is the site of red cells destruction. Postnatal treatment with IVIG may block neonatal Fc receptors and hemolysis.57

Studies document the possibility that, the frequency of transfusion therapy can be reduced by combining conventional phototherapy with high dose IVIG.58 The therapy is reported to be without adverse side effects.59

**Phenobarbital:** Prenatal and postnatal phenobarbital therapy has received considerable attention in the treatment of Rh disease, particularly in the era before improved phototherapy. It accelerates bilirubin clearance by increasing its uptake by the liver, increasing its conjugation by uridine diphosphate glucuronyl transferase, and increasing the excretion of conjugated bilirubin by increasing bile flow. Further studies and documentation of its safety are needed before phenobarbital therapy can be considered for routine use.

**Clofibrate:** In France, clofibrate, an inducer of glucuronyl transferase activity and of the two transport proteins, is reportedly more efficient than phenobarbital therapy.

### RHESUS ALLOIMMUNIZATION: THE FUTURE

Awareness needs to be created among medical staff and relevant health authorities. Educational information or information leaflets about the guidelines to prevent alloimmunization could be given to Rh(D)-negative women and their partners and relevant health professionals. Routine antenatal prophylaxis in all Rh(D)-negative women has the potential over time, to save more resources than if restricted only to primigravidae.

Attempts are on, to try various other methods of prevention of Rh alloimmunization. One of them is the use of Rh(D) antigen coated enteric tablets, as a desensitization procedure.60 Till the time, an effective method is found the use of Rh(D) IG in Rh(D)-negative mothers is the only effective solution for eradication of Rh alloimmunization.

### CONCLUSION

The conquest of Rh disease by a two-pronged approach has paid rich dividends. Administration of anti-D to Rh-negative mothers has greatly reduced the number of sensitized pregnancies. Combined with this, effective in utero treatment has helped to salvage about 80–85% of affected fetuses. However, in developing countries, the problem will persist due to various reasons like nonavailability of anti-D in remote areas and unaffordable cost for the lower socioeconomic group of patients.

### REFERENCES

Fetal Surveillance: Newer Developments

INTRODUCTION

During the last 30 years, antepartum fetal surveillance has evolved into complex methods of fetal testing the earliest and most widely used being electronic fetal heart rate (FHR) monitoring, e.g. contraction stress test (CST) and nonstress test (NST). Both of these tests are reliable indicators of fetal well-being with false negative rates of less than 1/1,000. NST is the most widely used primary test of antepartum fetal testing (AFT). With advent of real time ultrasound, biophysical profile (BPP) and amniotic fluid volume/index (AFV/AFI) were developed to reduce false positive rates of NST, estimated to be as high as 65% and to prevent unnecessary obstetrical interventions. Primary goals of any fetal testing program must be to prevent fetal demise or asphyxia and resulting long-term neurologic sequelae, and to guide further intervention of either pregnancy termination or continuation with reliable predictability of fetal health or compromise. With universal use of AFT in management of high-risk pregnancies, fetal deaths in United States of America have reduced from 18/1,000 in the 1950s to 7.5/1,000 in the 1990s. Validity of AFT in reduction of fetal deaths is demonstrated in Table 1. Fifty percent of fetal deaths appear to be preventable and occur predictably in maternal fetal conditions listed in Table 2.

Many newer concepts of AFT, e.g. condition specific testing, automated methods of assessment of NST, modified BPP using NST and AFV, individualization of activities during BPP, intrafetal cardiac and vascular flow measurements, etc. are available today to improve predictability of fetal health or compromise.

| Table 1: Validity of antepartum testing |
|-------------------------------|------------------|
| Condition                        | Death/1,000 births |
| Previous stillbirth              | 30 | 6.1 |
| Insulin-dependent diabetes mellitus (IDDM) | 50 | 16 |
| Hypertension                     | 26 | 7 |
| Untested                         | 10.8 | 53,027 |
| Tested                           | 0.8 | 15,842 |

Source: AJOG, 1996

<table>
<thead>
<tr>
<th>Table 2: Fetal deaths amenable to prevention</th>
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<tbody>
<tr>
<td>Yes (50% fetal deaths)</td>
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<tr>
<td>Antepartum asphyxia</td>
</tr>
<tr>
<td>Intrauterine growth restriction (IUGR)</td>
</tr>
<tr>
<td>Maternal diabetes</td>
</tr>
<tr>
<td>Toxemia</td>
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<tr>
<td>Hypertension (most)</td>
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<tr>
<td>Decreased F movements</td>
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<tr>
<td>Oligohydramnios</td>
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<tr>
<td>Previous fetal demise</td>
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<tr>
<td>No (50% fetal deaths)</td>
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<tr>
<td>Abruptio placenta</td>
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<tr>
<td>Congenital malformation</td>
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<tr>
<td>Perinatal infections</td>
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<tr>
<td>Intrapartum asphyxia</td>
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<td>Isoimmunization</td>
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NONSTRESS TEST

Nonstress test utilizes FHR accelerations in association with movements to be a sign of fetal well-being, indicating
integrity of fetal peripheral receptors, spinal cord, autonomic nervous system and myocardium. Beat to beat variability of FHR is produced as a result of balance between sympathetic and parasympathetic components of the autonomic system. A reactive NST is defined as presence of at least two FHR accelerations of 15 bpm lasting 15 seconds within a 20 minutes period in association with movements. The diagnostic value of NST is as reliable as its predecessor, CST; however, its false positivity remains up to 65–70%. A cumulative review of 50,000 cases revealed a perinatal mortality (PNM) of 6.2/1,000. Wide variations in false positives of NST are observed by many investigators, however, false negative rates remain low indicating it to be good predictor of fetal well-being (Table 1). AFT is indicated in maternal fetal conditions where fetal deaths are threatened (Table 1). Optimally fetal testing should begin at gestational age of 32 weeks in absence of severe complications in most high risk conditions. However, testing anytime after the viability age of 26 weeks in complicated diabetes, hypertension or severe intrauterine growth restriction (IUGR), etc. may be warranted. Most perinatal centers choose to perform NST twice weekly to ensure a lower false positive rate of 0.8/1,000 versus 1.9/1,000 when NST is done weekly.

**Table 3: Diagnostic values of the NST**

<table>
<thead>
<tr>
<th>Study</th>
<th>No of Patients</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>False positive</th>
<th>False negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rochard</td>
<td>125</td>
<td>83</td>
<td>37</td>
<td>20</td>
<td>11</td>
</tr>
<tr>
<td>Devoe</td>
<td>290</td>
<td>51</td>
<td>85</td>
<td>70</td>
<td>7</td>
</tr>
<tr>
<td>Devoe</td>
<td>281</td>
<td>50</td>
<td>100</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Lee</td>
<td>421</td>
<td>50</td>
<td>99</td>
<td>75</td>
<td>1</td>
</tr>
<tr>
<td>Mendenhall</td>
<td>367</td>
<td>55</td>
<td>85</td>
<td>81</td>
<td>3</td>
</tr>
<tr>
<td>Phelan</td>
<td>1,236</td>
<td>45</td>
<td>82</td>
<td>89</td>
<td>3</td>
</tr>
<tr>
<td>Brown</td>
<td>343</td>
<td>50</td>
<td>99</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>Nochimson</td>
<td>421</td>
<td>11</td>
<td>55</td>
<td>99</td>
<td>3</td>
</tr>
</tbody>
</table>

**Diabetes**

Poorly controlled diabetic pregnancy is at risk for fetal demise as a result of vasoconstriction associated with hyperglycemia. Additionally, large infant of a diabetic mother is more prone to hypoxia. AFT reduces the risk of fetal loss from 50/1,000 to 16/1,000 deliveries. Twice weekly testing is currently the norm in most perinatal centers. Some have advocated routine weekly BPP. Data presented here under fetal acid-base balance section does not support such an approach. NST appears to be the most sensitive detector of fetal acidemia. Minor variations in either FHR pattern or breathing does not appear to always indicate fetal acidosis, conversely acidotic fetuses will generally exhibit a nonreactive NST and/or late decelerations.

**Multiple Gestations**

Perinatal mortality in twins is known to be higher as a result of twin-twin transfusion, discordant growth, or IUGR of one or both twins and hence AFT is essential to allow for timely intervention to prevent death. A reactive NST appears to be of similar value in prediction of fetal well-being as in singletons. Knuppel demonstrated that late fetal deaths can be eliminated by routine testing of twins from 32 weeks. Blake et al. tested 94 pregnancies. Eighty-nine percent of reactive fetuses had uncomplicated outcomes while nonreactive fetuses had a sixfold PNM than reactive fetuses (12/1,000 versus 80/1,000). Simultaneous testing of both fetuses allows each twin to act as a control for its cotwin. Longitudinal studies of simultaneous NSTs in twins reveal synchronous accelerations of FHR to be more frequent in early third trimester and decrease to 46% at term. This synchronicity appears to be a proprioceptively originated by one or the other twin. Testing of twins poses a dilemma of management when a combination of reactive and nonreactive NSTs are encountered, particularly in a pregnancy remote from term. Age-related compromise of a normal twin has to be factored into the management schema.

**Post-term Pregnancy**

Testing for a postdate fetus should ideally begin at 41 weeks in well-dated patients. Special consideration must be given to accompanying amniotic fluid content. A general approach to delivery of all at 42 weeks can be justified to prevent compromise of 10–20% of fetuses. Miyazaki and Miyazaki have shown variable decelerations to be of particularly adverse significance in postdate fetuses mandating delivery.
Placental Insufficiency
Cases of hypertension, renal disease, IUGR or any other conditions exposing the fetus to hypoxic compromise should be tested at appropriate time and frequency. FHR amplitude, strength and frequency of movements decrease in IUGR babies. Amniotic fluid assessment by AFV or AFI remains of special significance as an important function of placental perfusion for these babies.

AMNIOTIC FLUID VOLUME/INDEX
It is recently recognized that AFV is an important component of fetal evaluation by virtue of it being the only indicator of placental perfusion and fetal urine output within any testing scheme of AFT, e.g. BPP. A threshold of a single maximum vertical pocket of greater than 1 cm of AFV (MVP) was considered reassuring within the original BPP described by Manning in 1980. Chamberlain et al. demonstrated that a single largest vertical fluid pocket (MVP) of 2–8 cm was the norm in third trimester and MVP of 1–2 cm was considered marginal. PNM with normal, marginal and decreased MVP was 4.5/1,000, 56.6/1,000, and 187.5/1,000 respectively. Phelan developed the concept of an AFV, a four quadrant quantitative measurement of largest vertical pockets. In a later study, a value of 8–18 cm was considered to be normal and less than 5 cm was associated with increased PNM in the third trimester. AFV may now be used as an alternate to the MVP in the schema of BPP as a measure of fluid content in utero. An only available study comparing AFV and maximum single pocket technique by Fisher found a 2 cm pocket to be of reassuring value similar to the AFI.

The chances for development of oligohydramnios within 4 days were 1/200 with a normal AFI of 8–18 cm and 5/100 for a marginal AFI of 5–8 cm. Hence, it is prudent to test a fetus for oligohydramnios every 4 days whereas an interval of 7 days appears sufficient in normal cases.

Biophysical Profile
Advent of real time ultrasound has heralded our sense of fetus as an individual having not only heart rate, but displaying physiologic behavior pattern. Biophysical profile (BPP), first described by Manning, uses reactivity of FHR at NST, fetal breathing movements (FBM), fetal movements (FM), fetal tone (FT) and AFV, the last four observed ultrasonically (Table 4). Presence of each factor is assigned a score of 2, 10 being a perfect score assuring fetal well-being and a score of 0 is indicative of severe fetal compromise threatening demise. Manning then demonstrated an increasing PNM, fetal acidemia and cerebral palsy with decreasing BPP score.

Biophysical Profile and Perinatal Mortality and Morbidity
Biophysical profile was first reported on by Manning et al. in 1980 using all five parameters of fetal activity individually and then in combination in 216 patients. The corrected PNM was 32.4/1,000. The positive prediction was highest with absent FBM and lowest with a nonreactive NST and the false negative was lowest with absence of FT and highest with a nonreactive NST. FBM appeared to be the most complex and sensitive function of well-being and FT was the least sensitive. The activities and their presence or absence reflect developmental order and the complexity of the neural center governing each activity. The most evolved centers lose function earlier with the advent of fetal hypoxia-acidemia.

Manning and coworkers used BPP in clinical management of 12,620 pregnancies, and reported a corrected PNM of 1.9/1,000 and a false positive rate of 0.6/1,000 within a week following a normal BPP. Corrected PNM has shown to vary between 0 and 26/1,000 in several other studies using BPP in a schema of AFT. Thereafter, PNM was reported to be reduced by 76% in Manitoba in 55,551 tested patients compared to 104,337 nontested fetuses. Similar reduction in immediate morbidity, e.g. operative delivery for fetal indications, intrapartum fetal distress, low Apgars and birth weight, and NICU admissions were observed in association with a normal BPP.

BPP and Acidemia
A significant inverse relationship exists between BPP and umbilical pH. A normal BPP of greater than 8/10 has not yet been found to associate with a fetal pH of less than 7.23 by cordocentesis. In a review of multiple studies including 572 patients, 14% cases had low BPP less than 6. Abnormal pH occurred in 48.19% in those with low BPP and in none with a normal BPP score of greater than 8/10. Manning correlated fetal acidosis with BPP and concluded that at a BPP of 4/10 or less:

- Fetal compensation ability is reduced, and metabolic acidosis begins. The risk of significant acidosis (pH < 2.0)

<table>
<thead>
<tr>
<th>Activity</th>
<th>Score</th>
<th>CNS</th>
</tr>
</thead>
<tbody>
<tr>
<td>FT</td>
<td>2</td>
<td>Cortex</td>
</tr>
<tr>
<td>FM</td>
<td>2</td>
<td>Cortex-Nuclei</td>
</tr>
<tr>
<td>FBM</td>
<td>2</td>
<td>4th ventricle</td>
</tr>
<tr>
<td>NST</td>
<td>2</td>
<td>Posthypotal medulla</td>
</tr>
<tr>
<td>AFV</td>
<td>2</td>
<td>Placental perfusion</td>
</tr>
<tr>
<td>Total score</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>
Manning reported 83% for NST, 22% for normal AFV, 13.6% for abnormal AFV, 2% for nil AFV, and 9.6% for AFT. A combination of a reactive NST and normal AFV rules out acidemia and no further testing need be done (modified BPP).

- Oligohydramnios is independently associated with acidemia.
- Acidemia is present when all activity parameters of BPP are abnormal regardless of AFV.
- BPP acute markers reflect fetal acid-status at the time.
- Loss of NST and FB are the earliest markers of compromise and loss of FM and FT indicate advanced stage acidemia.

Using a modified BPP program of testing with NST and AFI, in 17,211 cases, four fetal deaths were observed, with a false negative rate of only 0.02%.33 The incidence of CP rose sharply at BPP score of 2/10 or less.

### BPP and Cerebral Palsy

Cerebral palsy (CP), a neurologic disease involving muscular function occurs as a result of perinatal insult during the antepartum, intrapartum or neonatal periods. BPP contributes to prediction of CP by excluding or including the risk of fetal asphyxia during the antepartum period. When BPP results were used to guide intervention, 26,288 tested fetuses had a CP rate of 1.33/1,000 versus 4.72/1,000 untested fetuses.33 The need for NST was reduced to 5% of all patients during ultrasound.

The incidence of CP rose sharply at BPP score of 2/10 or less.

### Modified Methods of Biophysical Scoring

1. **Use of ultrasonic components only:** Manning reported similar benefits in reduction of PNM as with classic BPP. The need for NST was reduced to 5% of all patients requiring caregivers to perform ultrasonic testing only. Diagnosis of fetal anomalies was an additional benefit during ultrasound.

2. **Use of AFI to substitute for the largest vertical pocket measurement of AFV.** No significant differences in outcome are seen with both methods of AFV assessment. However with advent of the test described below, use of AFI can be justified as a routine test.

3. **Modified BPP using NST/AFI testing:** A reactive NST denotes FHR reactivity in association with FM abilities. Addition of AFI tests three of the five features of the classical BPP. NST and AFI, used in combination as a modified BPP test, appear to be physiologically sufficient as an AFT. Nagoatte34 showed a fetal death rate of 1 in 18,947 patients with a false positive rate of 0.05%. Vintzileos35 found a similar correlation with NST and AFV in the schema of management of 17,211 patients. Both of the above researchers correlated normal tests with normal fetal acid-base status with a false negative rate of 0.02%. In many perinatal centers in United States of America modified BPP is widely used now as a primary modality of AFT. It appears to be a reliable modality of primary AFT as a full BPP, reserving BPP and CST to a second line testing scheme for special cases.

### UMBILICAL ARTERY DOPPLER VELOCIMETRY IN ANTEPARTUM FETAL SURVEILLANCE35

Doppler flow assessment in the fetoplacental and intrafetal circulation is increasingly gaining importance in a comprehensive program of fetal surveillance to gain knowledge of fetal hemodynamics. Hemodynamic compromise is often at the root of abnormal fetal function assessed by surveillance measures described above. Umbilical arterial Doppler (UA) waveform is biphasic. A systolic component reflects forward flow while the diastolic component represents vascular resistance in the placental bed. Systolic/Diastolic velocity ratio (UA S/D) progressively declines with pregnancy due to decreasing resistance in the placental bed with advancing gestational age. It is less than 3 by 30 weeks of age when vasodilatory process in the placental villi is optimized. Absent diastolic flow (ADF) or worse, reverse diastolic flow (RDF) indicate severe resistance in the fetoplacental circulation and are often associated with fetal growth abnormalities, hypoxia-hypercarbia and acidosis.

Greater than 70% of placental obliteration is needed to result in ADF or RDF patterns (Table 5, Serra-Serra).36 Divon37 reported a meta-analysis which included 6,838 patients, showing impact of UA Doppler in clinical management to reduce PNM by 66%.

Compensatory redistribution of blood by way of vasodilatation favoring cerebral circulation can be represented by middle cerebral arteries (MCA). MCA can be easily accessed and sampled through a transverse scan of the fetal vertex depicting the circle of Willis. MCA is prominently displayed by color Doppler as biphasic wave commonly measured as pulsatility index (PI) or resistance index (RI) to predict hypoxia. UA to MCA RI less than unity may be indicative of neonatal morbidity Arias.38 In a study of blood gases by cordocentesis in 23 IUGR fetuses Hecher39 reported low resistance MCA Doppler to be associated with low pO2 and pH.

#### Table 5: Relationship between abnormal end diastolic flow pattern in the umbilical artery and perinatal outcome: Experience in 94 cases

<table>
<thead>
<tr>
<th></th>
<th>ADF</th>
<th>RDF</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>72</td>
<td>22</td>
<td>94</td>
</tr>
<tr>
<td>IUGR</td>
<td>94%</td>
<td>100%</td>
<td>94.5%</td>
</tr>
<tr>
<td>PNM</td>
<td>19%</td>
<td>27.3%</td>
<td>21.3%</td>
</tr>
<tr>
<td>PN morbidity</td>
<td>83%</td>
<td>13.6%</td>
<td>9.6%</td>
</tr>
<tr>
<td>ABN karyotype</td>
<td>—</td>
<td>—</td>
<td>6.4%</td>
</tr>
</tbody>
</table>

Source: Serra-Serra et al.36 1994
Venous Doppler pulsatility described later in this book occurred with further decrease in $P_O_2$ and $pH$.

Middle cerebral arteries maximum peak velocity is also used to predict anemia in cases of blood group incompatibility and other conditions (Mari). Blood flow patterns in the venous system, e.g. inferior vena cava (IVC) and ductus venosus (DV) [ductal flow is sampled in a transverse section of upper fetal abdomen at the level of its origin from the umbilical vein (UV)], reflect pressure gradient between right atrium and right ventricle indicating ventricular compliance. A marked increase in normally present small negative waveforms in the IVC and DV indicate reversal of flow and congestion in the venous system due to cardiac dysfunction and cardiac failure. Finally, appearance of pulsations in the normal monophasic waveform pattern of UV Doppler is the very last phase in deterioration of fetal hemodynamics prior to death.

In a program of fetal surveillance a stage of hypoxia progressing to acidosis is associated with occurrence of hypoxic ischemic encephalopathy (HIE) and resulting long-term sequelae of neurologic deficit in the infant or even fetal demise. Hence, it can be assumed that majority of these events can be preventable, by intensive scrutiny of hemodynamics in the fetus by peripheral vascular surveillance in the arterial as well as venous system if necessary and timely delivery prior to extreme fetal state.

Additionally, hypoxia may independently impair myocardial contractility. Despite both ventricles being exposed to different after loads, myocardial contractility is maintained until late stage hence cardiac function is seen to play an important role in IUGR fetal circulation. Cardiac failure may finally occur as direct hypoxic myocardial depression sets in.

CONCEPT OF A COMBINED TESTING PLAN

It has been suggested to use multiple parameters of AFT for best prediction of fetal state. BPP, modified BPP, etc. have been previously discussed in this report (Table 6).

Some have suggested using NST, AFV and umbilical Doppler velocimetry in combination with ultrasonic biometry for best prediction of overall fetal status. Devoe examined the reliability of NST, AFV and UAV in 100 high risk patients. AFV and UAV were less powerful than NST in prediction of fetal status.

In a study of multiple fetuses, Gandhi found UAV to be extremely useful in prediction of IUGR and discordant growth in 52 pairs of twins. IUGR could be predicted 80% of the time in combination with biometry compared to 45% of the time with biometry alone. Further, abnormal UAV was observed two weeks in advance of the biometric abnormality indicating IUGR.

- Newest developments in fetal surveillance
- Future of antenatal testing
- Automated methods of fetal development.

Meta-analysis of fetal testing has revealed many errors current system of perinatal practice. They range from unavailability of patient data, poor documentation, equipment and record abnormalities and individual physician bias in management without the benefit of evidence based schemes of practice. Automation, computer-based data availability, analytic algorithms, or dedicated software may improve outcome. Automated perinatal intelligent program combines computerized analysis of raw fetal signals, weighs them in context of the pregnancy, assesses fetal condition, renders probabilistic prognosis and advises safest management options to the clinician. Many such programs are available most in their early or research based phases. Some, e.g. Oxford Sonicaid System 8,000 from United Kingdom is available commercially and has been used at the Medical College of Georgia for FHR analysis. Fetal BPP can be automated. The system combines an electronic FHR monitor, a real time ultrasound scanner and a computer to collect online fetal FBM, FM, FHR, etc. data, analyzing it, and ultimately rendering management options to the clinician. Artificial neural network is an essential component of any system to be clinically useful. Devoe has used such system extensively. The advantages appear to be of accuracy, precision and ability to practice evidence-based medicine.

In conclusion, AFT saves lives and newer techniques and concepts continue to improve outcome in sicker and younger babies on an ongoing basis.

REFERENCES


Table 6: Progressive cardiovascular changes in hypoxic hypoxia hypercarbia and acidemia in IUGR fetus

<table>
<thead>
<tr>
<th>High resistant arterial flow and hypoxia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal umbilical arterial Doppler S/D ratio</td>
</tr>
<tr>
<td>Abnormal MCA PI</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IUGR + Hypoxia + Acidemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal umbilical arterial Doppler (ADF, RDF)</td>
</tr>
<tr>
<td>Abnormal MCA S/D (low)</td>
</tr>
<tr>
<td>Abnormal venous Doppler (I/C, DV)</td>
</tr>
<tr>
<td>Normal heart rate patterns, BPP</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IUGR + Hypoxia + Acidemia (late)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal umbilical arterial Doppler (ADF, RDF)</td>
</tr>
<tr>
<td>Abnormal MCA S/D (low)</td>
</tr>
<tr>
<td>Abnormal venous Doppler (I/C, DV)</td>
</tr>
<tr>
<td>Abnormal heart rate patterns, BPP</td>
</tr>
</tbody>
</table>

Source: Abuhamad 1999


INTRODUCTION
Cardiac anomalies are most common anomalies (1/3rd) found at birth. Its prevalence is 5 in 1,000 livebirths. Fifteen percent of neonatal deaths and 50% of infant deaths due to malformations are due to cardiac anomalies. Incidence of aneuploidy is 15–38% in fetuses with cardiac malformations and in livebirths. Also the incidence of aneuploidy is 11.8% in babies with congenital heart defects. Congenital cardiac diseases thus is taking a larger toll of the new born population than even the chromosomal anomalies. Therefore, diagnosis of cardiac diseases must not be missed in antenatal period. More so because many of these have good prognosis, if they are detected antenatally and can be treated immediately after birth, screening for cardiac diseases by fetal echocardiography must be included at least in the second trimester scan. Advancing technology and transvaginal approach now also allows fetal echocardiography with nuchal scan.

RISK FACTORS FOR CARDIAC ANOMALIES

Family History of Cardiac Disease (Holt-Oram Syndrome)
Mother having congenital heart disease (CHD), risk to fetus of CHD is 5–10%, though in fetuses who have fathers with CHD, the risk is lesser. Certain defects have higher (10–15%) recurrence rate, e.g. hypoplastic left heart, aortic stenosis, coarctation of aorta, 2–5% for septal and conotruncal anomalies and less than 5% for transposition of the great arteries (TGA) and single ventricle like abnormalities.

Maternal Diseases
- *Diabetes mellitus* [5% risk of CHD in fetus Ventricular septal defect (VSD), TGA, coarctation and conotruncal abnormalities]. phenyl ketonuria (VSD, coarctation of aorta, hypoplastic left heart and tetralogy of Fallot)
- Collagen disease (anti-Sjögren syndrome A or B antibodies) associated with myocarditis and heart blocks.

Teratogens: Drugs and Infections
- *Alcohol*: Patent ductus arteriosus (PDA) and septal defects: up to 25% risk of CHD,
- *Retinoic acid*: Conotruncal and great artery anomalies.
- *Anticonvulsants*: Valproic acid, phenytoin and trimethadione: PDA, Aortic stenosis, tetralogy of Fallot, TGA and coarctation of aorta
- *Lithium*: Ebstein’s anomaly
- *Daunorubicin*: Myocardial necrosis
- *Rubella*: PDA, Pulmonary stenosis, septal defects
- *Parvovirus*: Damage to myocardial cell itself.

Chromosomal Anomalies
Extracardiac anomalies are present in 25–45% of fetuses with CHD and so whenever an abnormality is found any where in the body, the heart must be evaluated with care.

Monozygotic Twins
Monozygotic twins have double incidence of CHD and risk is much higher in conjoined twins.

Arrhythmias
Septal defects.
Nonimmune Hydrops

The last two actually indicate that there is a possibility of CHD. But it is important to know that as for trisomy 21, only 30% of cardiac anomalies are detected in high-risk group, whereas 70% are detected in the low-risk group. Therefore, screening for cardiac anomalies must be included for each fetus.

Till now, by screening we meant looking at the four chambers of the heart and taking an M-mode to look for arrhythmias. But four chamber view diagnoses only 50–60% of cardiac anomalies and including outflow tracts will diagnose up to 75% of cardiac anomalies, if examined by trained experienced person.5

Approximately, 25% are still missed. A detailed fetal echocardiography is therefore essential. This must include gray scale, color Doppler, pulse Doppler and M-mode assessment all together.

**EQUIPMENT SETTINGS**

High resolution linear array, curved array or sector scanners can be used for this examination. 4–8 MHz is the preferred frequency range for this examination.

The setting for 2D imaging/gray scale is set at high contrast. The angle of the scanning field should be wide enough to include the transverse section of the thorax. The focal depth is kept sufficient so the area of interest is seen in the center of the screen, and the focal point is adjusted at the level of the heart. Orient region of interest (ROI) collinear to beam. Select smallest possible angle of insonation. Zoom the image so that the heart is seen large enough to identify all the structures but not too large that the sharpness of the image is lost. Maternal abdominal fat or scars, anterior fetal spine or limbs may make the visualization of fetal heart difficult. Using speckled reduction imaging (SRI) and compound resolution imaging (CRI) increases the sharpness of the image.

As heart has an anatomy to study and also the blood flows are to be understood, thus cardiac examination cannot be complete without color Doppler. For color Doppler high wall filter, high pulse repetition frequency (PRF), zero persistence and low color sensitivity settings are done. The color box should be big enough only to include the heart. The gains and PRF are so set that chambers of the heart are adequately filled with color but there is no aliasing. The color balance is adjusted so that both the gray scale and color can be defined adequately at a time. Using B-mode and color dual display can be helpful to correlate the anatomy and the blood flows better.

Using Zoom and Cine loop examination can be very helpful with both gray scale and color Doppler.

For pulse Doppler select small spectral sample volume to include the area of interest only with angle not more than 60°. PRF and wall filters should be high as for color Doppler. Sweep speed is set high. Remember angle corrections are required only for absolute values and not for study of waveform pattern or ratios. Spectral sample volume is placed just downstream of valve to study the flow through the valve. It is placed upstream to demonstrate regurgitation in outflow tracts. For tricuspid regurgitation (TR) the sample volume is placed across the valve. It may be placed by the help of color Doppler.

**M-MODE STUDY**

Fetal echocardiography cannot be considered complete without M-mode evaluation. The M-mode cursor is aligned perpendicular to the interventricular septum at the level of atrioventricular (AV) valves (Figs 1A and B).

Interpreting M-mode correctly is based on identifying and correlating each line of M-mode with the anatomical structure on gray scale. Ventricular chamber size is measured at the end diastole when ventricular size is the largest. Outer biventricular diameter is measured and right and left ventricular inner diameter is measured. Ventricular wall thickness and thickness of the interventricular septum are...
measured. Ventricular contractility is measured by measuring the systolic and diastolic outer dimensions and then subtracting systolic from diastolic measurement and then dividing it with diastolic measurement. Rhythm disturbances are assessed by correlating ventricular and atrial cycles when cursor passes through one atrium and one ventricle at 30° to the interventricular septum on four chamber view. M-mode can also be used with color Doppler to understand the regurge better.

B-mode scanning is the most important and color should be employed only after B-mode diagnosis for demonstration and confirmation of a particular pathology. Color may be required sometimes for identification of anatomy only when evaluation of the heart is done at 11–14 weeks scan. Though with high resolution probes and improving technology, early fetal echocardiography can be done at 11–14 weeks with the nuchal scan with transvaginal probe with 6–9 MHz frequency range.

Cardiac evaluations have been made less time consuming and much easier with advancing technology. New 4D US technology with spatio-temporal imaging correlation (STIC) (Figs 2A to C) can be used for offline 4D cardiac evaluation. After optimizing the 2D image a single sweep is taken from the upper abdomen to the upper chest in 7.5–15 seconds. Multiple images of the heart during different phases of cardiac cycle are captured and stored as a volume. This can be seen in all three planes: X, Y, Z (sagittal, axial and coronal) and can be run as a continuous cardiac cycle.

Walking through these sections give all the planes required for complete cardiac evaluation. The image can also be seen as live 3D by various rendering modes. Inversion mode of rendering can be an excellent tool to demonstrate septal defects and outflow tracts and great vessels. This mode shows all cavities as solid structures. Rendering from different angles can give all those views of the heart, which were never possible by any other modalities, e.g. basic view of the heart, which shows relationship of all the four valves, which is very informative of outflow tract relationship, inflow tract abnormalities and important for surgeons. Using tomographic ultrasound (US) imaging may also help looking at the heart at different angles. Though standardization of stored images is necessary to understand and correctly interpret them.

The new GE machines (Voluson E8) have now come up with a still easier and more standardized techniques of storage and evaluation. This software is known VCAD. When working with this, the essential views of the heart are only a finger-touch away. No manual rotations or walking through are also necessary. This makes cardiac evaluation much quicker both online and offline. However, detailed study of these techniques are out of scope of this chapter.

**EVALUATION OF THE HEART**

- As a thoracic organ
  - Situs
  - Position
  - Axis
  - Size
    - Transverse diameter
    - Cardiothoracic ratio
  - Rate and rhythm
- Internal anatomy.

**Deciding the Cardiac Situs**

Situs indicates sidedness of the heart in the chest, or may be defined on which side the apex points. Do not depend on the stomach shadow to decide the situs.

- First identify the position of the fetus: Vertex or breech and the position of the spine. Depending on this decide the left side of the fetus. If imagining is difficult in the beginning one can use a doll model for the same. Once the left side of the fetus is decided, confirm the presence of heart and the stomach shadow on left side.

- Another method, which is practically easier, is to see the fetus in its long axis on the screen and set the image so that the fetal head is seen to your right side on the screen. Turn the probe anticlockwise by 90°. Consider transverse section of the thorax as a clock face and spine is at 12 O’clock and fetal left side is at 3 O’clock. Confirm stomach in abdominal section and heart in thoracic section on left side.

Situs solitus which is a normal situs means that stomach is on left side and heart on left with morphological right atrium (RA) on right side and morphological left atrium (LA) on left side. The apex of the heart points towards left and that is levocardia (Figs 3A and B).
Abnormal Cardiac Situs

- **Solitary dextrocardia:** With normal position of all other viscera, the heart is on right side (apex of the heart points towards right side).
- **Situs inversus:** All the viscera and the heart are on the opposite side like a mirror image.
- **Situs ambiguous:** Undetermined visceral situs, position of the stomach may be right or left, polysplenia (bilateral left) or asplenia (bilateral right), may be seen.

Situs abnormalities are commonly associated with structural cardiac anomalies (Table 1).

Cardiac Position

Lines intersecting at point P showing cardiac position (Fig. 4). This means actual location of the heart in the chest is decided by point P. This point is where interatrial septum touches the posterior wall of atria. Point P is almost at the center of the transverse section of the thorax. That means normally two-thirds in left and one-third in right chest. Any intrathoracic lesion, diaphragmatic hernia, lung hypoplasia etc. will lead to abnormal cardiac position. A heart which is displaced towards right side is still a levocardia, if the apex points towards left (Fig. 5) and a dextrocardia if the apex points towards right.

### Table 1: Cardiac situs abnormalities with associated congenital heart disease

<table>
<thead>
<tr>
<th>Cardiac situs</th>
<th>Incidence of CHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal situs with levocardia</td>
<td>1%</td>
</tr>
<tr>
<td>Normal situs with dextrocardia</td>
<td>95%</td>
</tr>
<tr>
<td>Situs inversus with dextrocardia</td>
<td>5%</td>
</tr>
<tr>
<td>Situs inversus with levocardia</td>
<td>95%</td>
</tr>
</tbody>
</table>

Abbreviation: CHD, congenital heart disease

Cardiac Axis

Draw one line passing through the interventricular septum on four chamber view of the heart and a second line passing from sternum to spine. The angle formed anteriorly between the two lines is cardiac axis. It is normally 25°-65°. 79.3% of fetuses with cardiac/intrathoracic defects had abnormal cardiac axis (Fig. 6).

According to Crane et al. when axis is more than 65° outflow tract abnormalities are more likely and when it is less than 25° inflow tract abnormalities are more likely.

Cardiac Size

Transverse diameter of the heart (Fig. 7) in mm on four chamber view is less than number of weeks of gestation, after 22 weeks. If this is more, cardiac area to thoracic area ratio is taken and up to 30% is considered as normal. Enlargement suggests failing heart.
Rate and Rhythm

Normally at 5th week, cardiac activity is slow like peristalsis with a rate of 60–80 beats/minute, at the end of 5th week it reaches 100 beats/minute, at the end of 6th week it is 105–130 beats/minute and at 9 weeks it is 160–170 beat/minute, and then settles down at 120–160 beats/minute. It is called bradycardia when the rate is less than 100 beats/minute, and most likely it is due to heart blocks. Fifty percent of fetuses with bradycardia have structural cardiac defects like AV septal defects, ventricular inversion, Heterotaxy syndromes and corrected TGA.

It is tachycardia, if heart rate is more than 200 beats/minute. Atrial or ventricular arrhythmias may lead to cardiac failure and hydrops.

STUDY OF INTERNAL CARDIAC ANATOMY

The heart has four chambers, two septae, two AV valves and two outflow tract valves and inflow tracts into atria. Systematic study requires several views, which would show anatomy and circulation of all these structures (Fig. 8).

These are as follows:
- Four chamber view
- Left ventricular outflow tract (LVOT)
- Right ventricular outflow tract (RVOT)
- Three vessel view
- Short axis view
- Arch views.

A transverse section of the thorax at the level of fourth rib, gives a four chamber view (Fig. 9). This can be done by...
rotating the probe transverse after seeing the thoracic spine or by moving the probe cephalad from the transverse section of the abdomen, which shows a stomach bubble. A correct four chamber view will have only one rib in the transverse section of the heart. If one can see multiple rib ends it means it is an oblique section and will give erroneous calculation of cardiac size and axis and also erroneous impression about the symmetry of the cardiac chambers. All the other views can be achieved by systematic rotational or sliding movement of the probe from this view.

After several trials by several people, these movements of the probe have been systematized.

- **Cephalad sweep**: When fetus is supine or left side of the fetus is near the transducer.
- **Rotation towards left shoulder**: When interventricular septum is transverse or tangential.
- **Five short axis views** by Yagel et al.

### Cephalad Sweep

Using four chamber view as reference point the US beam is directed—angulated cephalad in a transverse plane till the neck is imaged and includes five imaging planes.8

**Level 1**: Four chamber view.

**Level 2**: LVOT—ascending aorta.

**Level 3**: RVOT—pulmonary trunk with its bifurcation running perpendicular to ascending aorta.

**Level 4**: Ductus arteriosus originating from the pulmonary trunk bifurcation runs directly posterior and to the left of the spine to join the aorta on rotating the probe to 90°.

**Level 5**: Transverse aortic arch: going from right side of the chest to descending aorta. Rotating the probe to 90° at this level shows aortic arch with neck vessels.

### Rotational Sweep

This has two variations:

1. **When interventricular septum is perpendicular to the beam**: From four chamber view rotate transducer 45° towards left shoulder of the fetus, so that beam bisects a plane between the left hip and right shoulder of the fetus. This shows LVOT—aorta and its curve as transverse part of the arch. Rocking the probe cephalad from this position shows RVOT—pulmonary trunk coursing perpendicular to the aorta.

2. **When interventricular septum is tangential to the US beam**: the angle of rotation increases or decreases depending on the angle of the interventricular septum, before the cephalad angulation.

### Five Short Axis Views

These were first described by Yagel et al. and have been claimed to be simpler in few fetal positions.10 First upper abdominal section is taken through stomach, second traditional four chamber, third five chamber, when aorta root is seen in the center of the four chamber view of the heart, fourth transverse view showing bifurcation of pulmonary trunk with aorta in the center which confirms the crossing over of great vessels, as aorta is seen in short axis and pulmonary trunk in long axis (Figs 10 to 15) and fifth showing three vessels and trachea.

We have seen that for any heart position four chamber view is the baseline and only four chamber view diagnoses 50–60% of cardiac anomalies. So, we shall first discuss four chamber view in detail and then the outflow tracts, short axis views and arch views.

Now let us understand what all the different views show.
FOUR CHAMBER VIEW

As name suggests it shows all four chambers of the heart in its long axis. This may be apical, basal, lateral/oblique. The view is apical when the apex is towards the probe, basal when base of the heart is close to the probe, lateral when interventricular septum is perpendicular to the probe and tangential when interventricular septum forms an angle with the US beam. Structures to be identified on four chamber view:

- Cardiac size and axis
- Two ventricles
- Two atria
- Atrial and ventricular septae
- Atrioventricular valves
- Pulmonary veins draining to LA
- Atrioventricular concordance.

On this view the chamber closest to the spine should be the LA and the one closest to the anterior thoracic wall is right ventricle (RV). Left ventricle forms the left heart border.

Features of Normal Four Chambers

- Cardiac area is approximately 1/3rd of thoracic area
- Cardiac axis 25°–65°.
- Both ventricles approximately same in size, ratio 1: 1.1 to 1: 1: 2. Morphological RV is identified by thicker walls due to...
to chordae tendineae/moderator band and is close to the anterior thoracic wall.

- Both atria approximately same in size. Morphological LA is the one in which the flap of foramen ovale opens and is the chamber closest to the spine. RA may show Eustachian valve lateral to foramen ovale and must not be mistaken for a mass.

Asymmetry is seen in almost all cardiac defects except
- Tetralogy of Fallot
- Double outlet RV
- Transposition of the great arteries

- **Interventricular septum:** Shows foramen ovale in its mid part, the flap of which opens into morphological LA. The upper and lower third of the atrial septum is always seen as a thin line from posterior atrial wall and from the crux of the heart respectively. Normal diameter of foramen ovale is 75–100% of the aortic root diameter. On color Doppler it shows a peak systolic velocity (PSV) of 45 cm/sec and flow seen from RA to LA.

- **Interventricular septum:** It has three parts but only the muscular part is seen on four chamber view. Subpulmonary part is evaluated on short axis view and perimembranous part on long axis view. Interventricular septum is best seen when it is perpendicular or tangential to the US beam that is in lateral or oblique four chamber view. The septum must be seen in its full width from side to side by sweeping the beam to stamp it as normal.

- **Atrioventricular valves:** Mitral valve = 1:1.1 to 1:1.2. Tricuspid valve is attached slightly more towards the apex than mitral at the intravenous (IV) septum and the attachment of the septal cusps of both the valves with the septum makes a cross which is known as crux of the heart. Color and Doppler to detect stenosis or regurgite.

- **Pulmonary venous (PV) drainage:** At least two pulmonary veins should be seen entering the LA, which rules out total anomalous PV drainage.

- **Atrioventricular concordance:** Concordance means the morphological RV is connected to the morphological RA with the tricuspid AV valve and vice-versa for left side.

**Four Chamber Alone can Tell us About**

- Ventricular hypoplasias
- Inflow or outflow tract anomalies due to chamber asymmetry
- Atrioventricular valvular abnormalities
- Septal defects
- Myocardopathies—thickened walls and decreased contractility
- Arrhythmias—by visual impression though confirmation is always by M-mode.

Apical or basal four chamber view are good for inflow tracts and lateral four chamber view is required for evaluation of septae.

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**LEFT VENTRICULAR OUTFLOW TRACT**

Figure 10 demonstrates the ascending aorta coming out of the left ventricle running anteriorly and to right from the ventricle. The crux seen on four chamber view is obliterated in this section and instead two parallel lines, which is the aorta. The posterior wall of the aorta shows continuity with the anterior leaflet of mitral valve and superior wall is contiguous with interventricular septum. This is the membranous part of the interventricular septum and VSDs of tetralogy of Fallot can be seen on this section.

**RIGHT VENTRICULAR OUTFLOW TRACT**

Figure 11 shows pulmonary trunk coming out of the RV. Its direction is always perpendicular to the aorta and runs posteriorly and to right.

Both the vessels should be traced further to see the aorta curving round and pulmonary trunk bifurcating. It is necessary to confirm ventriculoarterial concordance where morphological RV gives out the pulmonary trunk and morphological left ventricle gives out the aorta. Confirming crossing over of two outflow tracts is very important.

**THREE VESSEL VIEW**

Three vessels are seen running posteriorly and to left. From forward left to rear right pulmonary trunk and aorta, which are in long axis and superior vena cava (SVC) which is seen in transverse/oblique section. The vessels show reducing caliber from pulmonary trunk to SVC. On color Doppler the direction of flow is same in aorta and pulmonary trunk in this view normally. Reversal of pulmonary trunk to aortic caliber ratio suggests pulmonary stenosis.

Three vessel trachea section (Fig. 12) shows aorta and pulmonary trunk getting close to join by ductus arteriosus, forming a “V”. Ductus arteriosus is seen as a vessel running posteriorly to the left of the spine from the bifurcation of the pulmonary trunk.

Slight higher level also shows trachea, just anterior to the spine. Slight sweep of the transducer shows the right and the left pulmonary artery (PA).

Sliding the probe transverse further upwards shows aortic arch in transverse section with trachea in the concavity of “c”. Slight caudal and left tilt from this shows aortic arch and duct together, with thymus anterior to the great vessels.

**SHORT AXIS VIEW**

As described in Yagel’s technique it shows aorta in the center in transverse section and pulmonary trunk with bifurcation surrounding it which is also known as circle and sausage view. A section taken little inferior to this will show aortic root in the center protected by a complete circle formed by the RV with its inflow and outflow tracts. This view may be used for detection of subpulmonary VSD (Fig. 13).
ARCH/LONGITUDINAL VIEWS

- Aortic arch view (Fig. 14) can be achieved by rotating the probe 90° from the transverse aortic arch view.
- Ductal arch (Fig. 15) can be seen by rotating the probe 90° from ductus arteriosus in transverse view.

On this section, heart is seen as a three chambered structure and aorta is seen arising from the middle chamber—Left ventricle and is cane/"U" shaped. It gives off three neck vessels from the transverse part of the arch. Ductus arch is seen arising from the anterior most chamber—RV of the heart and is hockey shaped/flat. Both the arches can be seen connecting to each other, forming a "Y" anterior to the spine.

Right atrium inflow tracts: Angulating the probe a little towards fetal right side from this view shows SVC and inferior vena cava (IVC) entering the RA.

Color Doppler is used for difficult to image patients when gray scale image quality is not very good and for diagnosis of flow abnormalities. It has also been used to potentiate the diagnosis made on gray scale. Color Doppler is especially useful for ventricular septal defects, stenosis, coarctation of aorta, ventricular hypoplasias and ductus dependent diseases. Power Doppler is used to evaluate the septal defects when four chamber view is transverse. It also gives better edge definition.

Pulse Doppler is used to find absolute velocities and to diagnose regurgitation or stenosis of the valves. Each vessel and each valve has a particular flow pattern. This can be seen as a particular shape of waveform on pulse Doppler. To diagnose abnormalities in flow we need to know the normal waveform/signature for that particular vessel and normal velocities.

Normal velocities:
Outflow tracts: 60–70 cm/sec
Ductus arteriosus: 90–135 cm/sec in systole and 15–25 cm/sec in diastole.

Normal waveform through the atrioventricular valve (Fig. 16) is double peaked forward flow where the first one E-wave represents filling of the ventricle by atrial contraction with no reverse flow through out the cardiac cycle.

Outflow tracts show systolic single peaked forward flow due to ventricular systole. Studying and understanding these waveforms can also inform us about cardiac function.

M-mode: It is used to demonstrate arrhythmias, measure atrial and ventricular size and size of the outflow tracts.

Study of four chamber view can be considered complete only when it is studied with gray scale, color and pulse Doppler and M-mode.

Before discussing the abnormalities of the heart it is essential to understand the normal fetal circulation. This will help us to analyze the findings seen on fetal echocardiography and to arrive to a diagnosis.

FETAL CIRCULATION

Inferior and SVC bring unsaturated blood from lower and upper part of the body to RA. Saturated blood from umbilical vein enters ductus venosus. This is a trumpet shaped branchless structure with the narrowest part only 2 mm in diameter and opens into the RA. The shape helps to create a high speed jet of blood, which is directed from the RA, through foramen ovale to LA, unmixed with the unsaturated blood. LA also receives blood from pulmonary veins. RV receives blood from RA and left ventricle from LA. RV gives out pulmonary trunk, which apart from right and left PA also gives out a third branch—ductus arteriosus. Left ventricle gives out aorta, which gives out coronaries and neck vessels in turn and then through ductus arteriosus it is connected to pulmonary trunk. This causes mixture of blood from pulmonary trunk and aorta which is ultimately supplied to the unprivileged lower half of the body. Because of any abnormalities in the heart the atrial changes precede the ventricular changes (Fig. 17).

Cardiac diseases are of multiple but classification according to the structure involved may make the understanding of these abnormalities easier.

![Fig. 16: Normal atrioventricular valve waveform](image)
CLASSIFICATION OF CARDIAC DISEASES
- Septal defects
- Right heart abnormalities
- Left heart abnormalities
- Conotruncal defects
- Single ventricle defects
- Other cardiac abnormalities
- Arrhythmias

SEPTAL DEFECTS

Interventricular Septal Defects
Interventricular septal defects are most common and consists of 30% of cardiac defects. They cause no hemodynamic disturbances in utero if not too large as in utero, pressures in both ventricles are similar and there is no significant shunting of blood. VSDs can be further classified according to their location on the ventricular septum (Figs 18A to C).

Muscular Defects
In muscular part of the septum (Figs 19A and B), lateral four chamber view is the best to diagnose these defects and shows drop out in septal shadow. But small defects are difficult to diagnose without color Doppler. On apical and basal four chamber view, the part of the septum close to the crux is often not seen. This must not be misinterpreted as septal defect. It is a defect only if the end of the septal line shows a thickened end.

Color Doppler may be used to define these defects. Even on color Doppler no turbulence will be seen as there is no pressure gradient between both chambers. The flow may be left to right, or right to left. 3D US image rendered in inversion mode has been successfully used to demonstrate even small VSDs.

Perimembranous Defects
This defect is in membranous septum, below aortic valve and may extend into the muscular part. It is seen only in long axis view below the aortic valve. LVOT view may demonstrate this defect (Fig. 20). They are most commonly malaligned and associated with conotruncal defects.

Inlet Defects
This defect is in the inlet part of the septum, close to AV valves’ septal insertion.

Subpulmonary Defects
This is seen at inflow part of the RV and affects implantation of septal chordae of tricuspid valve. It can be demonstrated only on short axis view below the pulmonary valve.

Small defects (< 3 mm) may close spontaneously. Forty-six percent of nonmaligned VSDs close in antenatal life and 23% during the first year of life. Only 31% remain patent. Malaligned defects are less likely to be corrected without surgery. Large muscular and large perimembranous defects and inlet and subpulmonary defects usually require surgery.

Atrial Septum Defects
It consists of 8% of congenital cardiac defects. Defects can be at three locations: (1) secundum; (2) sinus venosus; and (3) primum.
- Secundum defects are commonest but can not be diagnosed antenataly as are located at fossa ovalis. These may be isolated or with VSD/pulmonary valve stenosis. It is to be differentiated from foramen ovale thickening. Small defects may close spontaneously.
- Redundancy of the foramen ovale flap is known as aneurysm of foramen ovale commonly associated with atrial arrhythmias.
- Sinus venosus defects are difficult to diagnose. Five to ten percent of Atrial septal defects (ASDs) are sinus venosus defects, situated posterior to foramen ovale and inferior to superior vena cava.
- Primum defects are mostly a part of AV defect. ASDs do not require alteration in obstetric care.
Figs 18A to C: Ventricular septum anatomy
Abbreviations: Ao, aorta; CS, coronary sinus; DAO, descending aorta; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle

Figs 19A and B: Muscular ventricular septum
Abbreviations: LV, left ventricle; RV, right ventricle
Atrioventricular Septal Defects

These are the defects of endocardial cushion causing primum ASD with VSD (Figs 21A to C). It may be associated with tetralogy of Fallot, double outlet RV, coarctation of aorta, ventricular hypoplasia subaortic or pulmonary valve stenosis. These defects are common with chromosomal abnormalities both aneuploidies and trisomies. The risk of recurrence is 7–17% in families with normal karyotype.11 Isolated defects have 85–90% survival rates after surgical repair.

On US complete AV septal defect will show single AV valve on four chamber view which is better demonstrated in diastole. In partial atrioventricular septal defects, both valves are attached at the same level to the septum instead of slight apical attachment of tricuspid valve normally. Color Doppler shows mixture of flow to ventricles. It is often associated with increased nuchal translucency. This anomaly can be diagnosed in late first trimester.

RIGHT HEART ANOMALIES

Tricuspid Valve Defects

Ebstein’s Anomaly

It is characterized by low placed tricuspid valve—septal and posterior cusps (Figs 22A and B). Due to this, RA appears enlarged but actually it is atrialization of RV, which is progressive in antenatal life. Color Doppler shows regurgitation into RA. Pulmonary trunk may be small/normal depending on the functional size of the RV. Severe right ventricular dysfunction may lead to severe pulmonary stenosis/ataresia, which is ductus dependent. Three vessel view shows reversal of pulmonary trunk to aortic ratio. It may often be associated with severe cardiac enlargement and lung hypoplasia. ASD may be associated with Ebstein’s anomaly. Other tricuspid valve abnormalities are:

- Thick, dysplastic tricuspid valve
- Unguarded tricuspid valve with almost no valvular tissue.12

Hypoplastic Right Heart/Pulmonary Valve Atresia with Intact Septum

Usually, the RV is small and hypoplastic with decreased contractility even in early gestation but may be progressive and may appear normal till 20 weeks. Interventricular septum is intact (Figs 23A and B).

Occasionally, RV may be enlarged and dysfunctional with dilated severely incompetent tricuspid valve. RA may be normal.

On color Doppler no forward flow is seen through tricuspid and pulmonary valve as both are atretic. On three vessel view aorta and pulmonary trunk show flow in opposite directions with turbulence at ductus as pulmonary trunk is filled through ductus arteriosus.13
Fetuses may develop cardiomegaly and hydrops due to cardiac decompensation. Termination should be offered for these fetuses.

**Pulmonary Stenosis**

There is thickening and doming of pulmonary valve. PA is small with increased Doppler velocities than in aorta causing turbulence. Septal defects are common. Reversed flow in ductus arteriosus is seen in ductus dependent disease, i.e. when pulmonary stenosis is critical.14

**Abbreviations:** LV, left ventricle; RA, right atrium; RV, right ventricle; TV, tricuspid valve

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**Aortic Stenosis**

Aortic stenosis may be progressive in utero. Aortic valve is thickened and shows doming. Left ventricle may be hypertrophied and there also may be asymmetric septal hypertrophy usually. Thickening of the ventricular septum may obstruct the LVOT and cause subvalvular stenosis where valve may appear normal. These are not diagnosed in utero. Sometimes left ventricle may be dilated with decreased...
systolic function. Association with endocardial fibroelastosis is known.

Color Doppler shows increased flow velocity through aortic valve with turbulence and reversed flow seen in aortic arch.

Decreased velocity in aorta in these cases is suggestive of left ventricular failure. Mitral regurgitation is often present. Critical aortic stenosis is ductus dependent.

Coarctation of Aorta

Localized narrowing of the juxta ductal arch is known as coarctation of aorta (Figs 24 and 25). Most commonly this narrowing is between left subclavian artery and ductus arteriosus. Transverse arch and aortic isthmus appear small. Aorta appears smaller than pulmonary trunk on three vessel view. Because of this there is relative right ventricular and pulmonary trunk enlargement without right heart disease. On color Doppler, there is high velocity flow in proximal descending aorta.

Interrupted Aortic Arch

Aorta is not at all formed beyond the arch. The descending aorta is a continuation of ductal arch. This is a difficult diagnosis but the clue is straight ascending aorta on aortic arch view. Branches may or may not be present depending on the type of interruption (Figs 26A to C).

Hypoplastic Left Heart Syndrome

Left ventricle is small on four chamber view with poor contractility. LA may be small or normal in size. There is no forward flow through mitral or aortic valve. Aortic size and origin site are important for postnatal prognosis. Heart may appear normal at 16–18 weeks and disease may be progressive in utero. It is important to differentiate it from single ventricle (Figs 27A and B).

Mitral Valve Defects

Mitral valve defects are rare as isolated abnormalities. Blood flow turbulences on color Doppler are diagnostic.

CONOTRUNCAL DEFECTS

These are commonly associated with deletion of chromosome 22q11.2, which can be diagnosed by fluorescence in situ hybridization (FISH). This anomaly is associated with short stature, psychiatric problems and mild to moderate learning difficulties are common with cardiac defects.
Tetralogy of Fallot

It is the most common cyanotic heart defect and almost always missed if only four chamber view is obtained as cardiac screening. It has four components: (1) perimembranous VSD; (2) overriding of aorta; (3) pulmonary stenosis; and (4) hypertrophic RV. But the last component always becomes manifest only after birth. Obstetric management needs no change with isolated Fallot’s tetralogy (Figs 28A and B).

On US increased angle of cardiac axis is seen on four chamber view, which is otherwise normal. Long axis view shows VSD in the membranous part, with large aortic root. RVOT view shows small PA. Three vessel view shows inverse PA/Aorta ratio. Color Doppler shows increased velocity in PA due to RVOT obstruction and aorta is fed by two ventricles. Many a time only membranous VSD may be evident in early gestation.17

Double Outlet Right Ventricle

Both TGA arise from RV and depending on the site of origin; one of the two may show variable degree of stenosis. When both arteries are arising side by side, it is named as Taussig-Bing syndrome. Its differentiation from other outflow tract anomalies with large VSD may be difficult (Figs 29A to C).

On US deviation of cardiac axis may be present but four chamber view is otherwise normal. Anterior angulation from four chamber view shows parallel great vessels instead of crossing over of great vessels and is known as Taussig-Bing heart. VSD may or may not be present but color Doppler is confirmatory.

Truncus Arteriosus

Both the arteries arise as a single trunk from the ventricles. It is usually associated with a large VSD with the trunk overriding the septum. Types of truncus (Figs 30A and B):

On US increased cardiac axis is seen on otherwise normal four chamber view. Malalignment type large VSD is seen in outlet. Truncal root is seen arising from RV or overriding the septum. Abnormal truncal valve may or may not be present. The origin of PA must be confirmed to exclude pulmonary stenosis.

On color Doppler VSD is seen with origin of truncus overriding the septum. Origin of PA from the main trunk must be diagnosed. If dysplastic valve is present, it shows holodiastolic regurgitation on pulse Doppler.

Complete Transposition of Great Vessels

Aorta arises from RV and lies anteriorly and to left of pulmo- nary trunk and pulmonary trunk from left ventricle. This means two great arteries arise side by side at the base of the heart instead of crossing over of the great vessels (Figs 31A to C).
Figs 29A to C: Double outlet right ventricle
Abbreviations: Ao, aorta; RV, right ventricle

Figs 30A and B: Types of truncus arteriosus

Figs 31A to C: Complete transposition of great vessels
Abbreviations: Ao, aorta; LV, left ventricle; PA, pulmonary artery; RV, right ventricle
On US normal four chamber view is seen. Outflow tracts show parallel great vessels at the roots. There is no crossing over of vessels. Vessel arising out of LV takes posterior course and bifurcates so is PA. Vessel arising out of RV takes long upward course and curves. This is aorta. If associated with VSD and overriding, the diagnosis is difficult.

**Corrected Transposition of Great Vessels**

This is a very rare abnormality. RA opens into morphological left ventricle which gives out pulmonary trunk and LA opens into morphological RV and gives out aorta. These patients may have dextrocardia.

On US four chamber view shows deviated cardiac axis. Evidently normal looking heart shows ventricular inversion. AV discordance is confirmed by looking at the morphology of the chambers. Flap of foramen ovale opens in LA, which opens in a ventricle which is morphologically right containing chordae tendinea and moderator band. Great vessels do not show crossing over, but are parallel. Ventriculoarterial discordance can be confirmed by tracing the outflow tracts. Atrioventricular complete heart block may be seen on M-mode.\(^\text{18}\)

**SINGLE VENTRICLE DEFECTS**

Single ventricle defects are tricuspid atresia, single ventricle and heterotaxy syndromes.

**Tricuspid Atresia**

This defect is commonly associated with transposition of great vessels but chromosomal defects are rare in such fetuses.

On US single AV valve is seen. Tricuspid valve is absent/thick. RV is hypoplastic. RA is normal/large with restrictive ASD. Septal defects are common.

**Heterotaxy Syndromes**

Heterotaxy syndromes are rare. These should be suspected when there is abnormal disposition of thoracic and abdominal organs also. Descending aorta and IVC are on same side. IVC is interrupted and large azygos vein may open into SVC. Complex cardiac lesions are associated. Viscero-cardiac heterotaxy may/may not be present. Fetal hydrops may develop and may have up to 100% in utero mortality with heart block.

**OTHER CARDIAC DEFECTS**

Other cardiac defects are anomalous PV drainage, ectopia cordis, cardiomyopathies, endocardial fibroelastosis, cardiac tumors, obstructed foramen ovale, premature constriction of ductus arteriosus and absent ductus venosus.

**Abnormal Pulmonary Venous Drainage**

Normally, two out of four pulmonary veins can be seen entering LA on four chamber view after 18 weeks. Anomalous PV drainage may affect one or more of these veins. If all the four are involved it is total anomalous PV drainage, otherwise it is partial. Only total anomalous drainage can be excluded antenatally. Pulmonary veins instead of emptying into LA, may empty in RA or any other systemic veins. These may be portal-hepatic veins, innominate vein, SVC or coronary sinus. Total anomalous PV drainage has obligatory right to left atrial shunt (Fig. 32).

On US no pulmonary veins seen on four chamber view entering the LA. PV confluence is seen behind the RA. RV is large, if total anomalous PV drainage is present, but enlargement is not seen if there is ASD or infradiaphragmatic drainage. Color Doppler may show the PV drainage precisely.

**Ectopia Cordis**

**Thoracic Type**

Heart protrudes from the chest cavity with cephalic orientation of the cardiac apex.

**Thoracoabdominal Type**

Pericardium and diaphragmatic defects are present and heart is displaced into the abdomen.
Myocardial Diseases

Hypertrophic Cardiomyopathy

Thickened less contractile heart, it is seen in diabetic mothers and may cause LVOT obstruction.

In dilated cardiomyopathy there are dilated ventricles with decrease systolic function and cardiac failure.

Fibroelastosis

Thickening of ventricular endocardium with bright echogenic shadows are seen on US with decreased systolic function (Fig. 33).

Both these conditions can lead to cardiac failure and hydrops.

Obstructed foramen ovale: Commonly associated with left heart obstructive defects. It may also be associated with mitral regurgitation, supraventricular tachycardia or fetal hydrops.

This can lead to prenatal right heart failure, hydrops and fetal death. Postnatally, it leads to persistent fetal circulation, right heart failure and death.

Cardiac Tumors

Rhabdomyomas are most common. They may be associated with tuberous sclerosis and may be multiple. It can be detected as early as 20 weeks of gestation and are progressive. They are seen as solid intracardiac tumors and show movements with cardiac cycle. Depending on size and position, they may cause obstructive defects, cardiac failure or arrhythmias. Others are fibromas, teratomas, myxomas and hemangiomas. Fibromas are usually solitary and commonly arise from left ventricular apex. Though usually homogenous may sometimes have cysts or calcifications.

Premature Constriction of Ductus Arteriosus

Use of indomethacin may lead to ductal obstruction between 28 weeks and 34 weeks. Evaluation for the same is to be done within 48–72 hours of starting indomethacin. Total ductal closure may be associated with fetal demise. Ductal arch patency must always be checked when doing a fetal echocardiography. Ductal obstruction will lead to RV enlargement, hypertrophy, RA enlargement and TR and ultimately may lead to right heart failure.

On pulse Doppler normal velocity in ductus arteriosus is 150 cm/s (Sys), 40 cm/s (Dias.). Its constriction causes higher systolic and diastolic velocities. Only high systolic velocity may be seen in last 4–6 weeks and in conditions with increased fetal cardiac output, but high diastolic velocity is diagnostic of ductal constriction.

Obstructed Foramen Ovale

It is commonly associated with left heart obstructive defects. It may also be associated with mitral regurgitation, supraventricular tachycardia or fetal hydrops. Prenatal death may occur due to right heart failure, hydrops and death.

Absence of ductus venosus: Umbilical vein is connected to either IVC or renal vein leading to significant dilatation of IVC since midgestation. Umbilical vein takes an inferior course. A long aberrant vessel is seen from liver to right abdominal wall crossing the diaphragm.

ARRHYTHMIAS

Arrhythmias must be always confirmed by M-mode.

Tachycardia

It is twice common than bradycardias. Tachycardias due to maternal fever, drugs, thyrotoxicosis, fetal distress or infection range from 180 beats/minute to 200 beats/minute. Those due to supraventricular tachycardia heart rates are 220–260 beats/minute. Atrial flutter gives heart rate of more than 300 beats/minute. Ventricular tachycardia may occur due to perinatal stress and hypoxia, cardiomyopathy, drug intoxication, electrolyte imbalance and ventricular aneurysm.

Bradycardia

Bradycardias are most likely due to heart blocks, which are often regular, 2:1 or variable. It is commonly associated with major cardiac defects or maternal anti-SS-A and anti-SS-B antibodies.

Irregular Rhythm

Arrhythmias are commonly associated with obstructed foramen ovale, cardiac tumors, cardiomyopathy, Ebstein’s
anomaly and atrial septal aneurysm. It can occur due to maternal ingestion of caffeine, Hydrazine, Nifedipine and are reversible after stopping drugs.

Fetal echocardiography must be included in the detailed structural scan in second trimester routinely and must be offered with nuchal scan or at least at 16–18 weeks for all the high-risk fetuses.

REFERENCES

DEFINITION AND BACKGROUND

The genetic sonogram is an ultrasound examination done on second trimester fetuses that not only evaluates the fetus for structural malformations, but also searches for the sonographic markers of fetal Down’s syndrome.1 Most workers have extended the definition to the second trimester fetal anatomic survey targeted at identifying features associated with any aneuploidy.2-5 It has evolved as an adjunctive screening tool capable of further refining the individualized risk-calculation for trisomy that is based on maternal age or serum screening markers.6

The common aneuploidies include trisomy 21 (Down’s syndrome), 13 (Patau syndrome) and 18 (Edwards syndrome), Turner’s syndrome (XO) and triploidy. Other aneuploidies are rarer and are encountered most frequently in abortus karyotypes. Trisomy 21 is associated with potential long-term morbidity and has an estimated prevalence of 1.21 per 1,000 live births.7 Trisomy 13 and 18 usually abort spontaneously or result in intrauterine demise, and, if born alive, rarely survive beyond the neonatal period. The greatest emphasis in the genetic sonogram, therefore, is to screen the population and then follow-up with an appropriate definitive diagnostic procedure for Down’s syndrome.

Screening procedures refer to tests that define an at-risk population and diagnostic tests refer to an actual demonstration of fetal karyotype. Screening tests for aneuploidies include maternal age, serum markers and ultrasound markers. The chromosomes themselves can be demonstrated by karyotyping of cells from amniotic fluid, chorionic villi or fetal cord blood or by identifying an abnormal karyotype by fluorescent in situ hybridization (FISH) or quantitative fluorescent polymerase chain reaction (QF-PCR) studies.

Although, the incidence of Down’s syndrome increases with increasing maternal age particularly beyond 35 years, 80% of Down’s syndrome babies are born to women younger than 35 years.1 The prevalence of trisomy 21 decreases with increasing gestational age, being about 30% higher at 16–20 weeks’ gestation compared with term8 and about 48–50% higher at 9–14 weeks compared with term.9

Soon after the finding of an association between low maternal serum alpha-fetoprotein (MSAFP) and Down’s syndrome, it was discovered that the addition of an assessment of maternal serum unconjugated estriol (E3) and beta human chorionic gonadotropin (β-hCG) in the form of the “triple test” was an effective screening test in women under 35 years of age with a sensitivity of 57% and a false positive rate of 3.25%.10

In recent years, improved resolution of ultrasound and its consequent ability to demonstrate abnormal morphology, have placed the sonographic examination in a more sensitive and specific position than maternal age and maternal serum screening. This is very significant in the perspective of the observation that amniocentesis for prenatal detection of chromosomal aneuploidy, a diagnostic tool offered at one time arbitrarily to all pregnant women aged 35 years or over, has in recent years lost favor as a first-line investigation.6 This shift in practice stems from a recognition that selection of candidates for amniocentesis for prenatal detection of chromosomal aneuploidy, a diagnostic tool offered at one time arbitrarily to all pregnant women aged 35 years or over, has in recent years lost favor as a first-line investigation.6 Furthermore, the well-established iatrogenic fetal loss rate associated with amniocentesis, although low (less than 1%), is increasingly being regarded by patients as unacceptable, particularly when the vast majority of apparently at-risk pregnancies are chromosomally normal.6 Patient access to information from professional medical counseling, the internet, and guide-
books, has put forth a demand for combining maternal age, maternal serum screening and sonographic findings in order to provide individualized patient-specific risk estimates and refine selection criteria for amniocentesis.\textsuperscript{12,13} The manner in which ultrasound information can be utilized to optimize obstetric decision-making in clinical practice is presented here.

\begin{center}
\textbf{SONOGRAPHIC MARKERS FOR DOWN’S SYNDROME (TRISOMY 21)}
\end{center}

Neonatologists have for many years used morphological features to identify Down’s syndrome. These include a flat facial profile, epicanthal folds, short stature, a mongoloid eye slant, muscle hypotonia, a single palmar crease, and excess skin over the back of the neck, hypoplastic middle digit of the fifth phalanx, sandal gap foot deformity, flat iliac wings, duodenal atresia and heart defects. Sonologists have extended morphological feature recognition to identify those fetuses at high risk for trisomy 21 using a combination of major anomalies, major markers and minor markers.

\section*{Overview of Markers}

Major anomalies are seen in about one-third of affected fetuses and include heart defects particularly ventricular septal defects and atrioventricular septal defects, ventriculomegaly, cystic hygromas, omphalocele and hydrops. Major markers include a thickened nuchal skin fold, short femur, short humerus, echogenic intracardiac focus, echogenic bowel and renal pyelectasis. Minor markers include flat iliac wings, brachycephaly and frontal lobe shortening, clinodactyly, sandal gap great toe deformity, short ear length, cerebellar hypoplasia and a single palmar crease.

A few of these features represent actual structural abnormalities that have clinical consequences regardless of karyotype. Most, however, are considered traits or markers that often have no serious clinical importance with the exception of their relationship with aneuploidy. To make matters more complicated, these features may be transient, resolving by the third trimester of gestation.\textsuperscript{14-16}

\section*{Major Markers}

A thickened nuchal skin fold was the first major marker identified for trisomy 21.\textsuperscript{17} This remains the most useful marker to date. This is measured in an axial plane through the posterior cranial fossa and calipers are placed corresponding to the outer surface of the occipital bone and the outer surface of the skin. A thickness of more than 5 mm is significant before 18 weeks of gestational age and a thickness exceeding 6 mm beyond 18 weeks.\textsuperscript{18-20}

\textit{Although echogenic bowel is often a normal variant in the second trimester, one in eight fetuses with Down’s syndrome show this feature.}\textsuperscript{21-23} Bowel should be labeled echogenic only if it is brighter than adjacent bone. It also needs to be remembered that high frequency transducers and equipment with real time enhanced contrast resolution and speckle reduction software options accentuate brightness of bowel. Bowel may also be echogenic in fetuses with cystic fibrosis, mesenteric ischemia and cytomegalovirus infections. Fetuses that swallow blood from a placental bleed also show increased bowel echogenicity consequent to ingested heme pigments.

\textit{The echogenic intracardiac focus (EIF) refers to calcified papillary muscle that is seen as a bright dot on ultrasound. This is usually in the left ventricle but occasionally in the right ventricle or both ventricles. It should be as bright as bone. 16\% of fetuses with trisomy 21 and 395 of fetuses with trisomy 13 demonstrate this feature.}\textsuperscript{16,24,25} The risk for trisomy is higher if the echogenic focus is in the right ventricle or both ventricles. The prevalence of this marker in normal fetuses is as high as 30\% in normal fetuses of Asian ethnic origin.\textsuperscript{36} As an isolated marker, therefore, it does not warrant further investigation. An EIF is not associated with cardiac anomalies in low-risk patients.\textsuperscript{15}

\textit{Pyelectasis} refers to an increase in the anteroposterior diameter of the renal pelvis beyond 4 mm at 15–20 weeks of gestation. Twenty to twenty-five percent of fetuses with Down syndrome demonstrate this feature.\textsuperscript{57-25} In isolation, this marker is not an indicator for amniocentesis. It should be used in conjunction with other markers.

Short humerus and short femur are defined as an observed-to-expected length of less than 0.9.\textsuperscript{34,38} The expected bone length is based on a biparietal diameter measurement. Expected femur length = – 9.3105 + 0.9028 × BPD. These have been identified as markers for trisomy 21 and are useful when combined with other markers.\textsuperscript{21} A short humerus is more sensitive as a marker than a short femur.\textsuperscript{32} Both these markers are limited by the requirement of data specific to the population being studied and by ethnic diversity. Femur/foot length ratio, although useful in assessing skeletal dysplasias are not useful in assessing for Down’s syndrome.\textsuperscript{31}

\section*{Minor Markers}

A widened iliac angle has been observed in children with Down’s syndrome and this has been extended to assessing the iliac angle in the fetuses.\textsuperscript{33,34} The increase in angle represents an increased distance between the iliac crests and should be measured in a transverse view of the spine. The mean iliac angle is 80 ± 19.7° in normal fetuses of 21 and 63.1 ± 20.3° in normal fetuses. The technique of measurement is cumbersome and limits routine use of this marker.\textsuperscript{63.1 ± 20.3°} Clinodactyly refers to hypoplasia of the middle phalanx of the fifth digit and is a morphological feature of children with trisomy 21 and can be seen in the fetus as well.\textsuperscript{3} Although initially regarded with skepticism, this marker has performed well and shows a sensitivity of 17.1\% and a false positive rate of 3\%.\textsuperscript{25} A wide space between the first and second toes is seen more frequently in trisomy 21 fetuses and is called a
sandal gap toe deformity. The reliability in various studies is variable. Nasal bone hypoplasia is a high sensitive and specific marker for trisomy 21. It is a feature of 62% of trisomy 21 fetuses and approximately 1% of chromosomally normal fetuses. The nasal bone was initially considered to be hypoplastic if it was either absent or strikingly small (less than 2.5 mm). Later data has described the nasal bone length increasing with gestation from a mean of 4.7 mm at 15 weeks to 8.2 mm at 22 weeks and such normative data is likely to be more specific in assessing this marker. The efficiency of using various nasal bone criteria for the detection of aneuploidy has been studied further and it has been observed that the optimal nasal bone threshold associated with trisomy 21 was a biparietal diameter/nasal bone length ratio of 11 or greater. An important prerequisite to consider when using this marker is the angle of insonation of the fetal nose, which should be between 45° and 135° to avoid false shortening. Brachycephaly in fetuses with trisomy 21 reflects a frontal lobe shortening and has been assessed in several studies. The frontothalamic distance was less than the 10th centile in 52% of fetuses with trisomy 21. Short ear length, cerebellar hypoplasia and amniodecidual separation have been described in literature but their reliability is questionable.

**Sensitivity of Marker Detection**

There is a wide variation in the detection rates of sonographic markers of trisomy 21. Strict standardization of definitions, operator experience and dedication can largely overcome this.

Other variables that influence detection rates include gestational age and maternal body habitus. The detection rate rises from 1 in 8 at 15 weeks of gestation to greater than 60% after 18 weeks. Serial reviews are, therefore, to be considered if the maternal abdomen is fat and hirsute and if the genetic sonogram is performed prior to 18 weeks of gestation. Pelviectasis is more frequently picked up in male fetuses.

**Significance of Individual Markers**

The accuracy of the genetic sonogram and the significance of each marker has been evaluated in several studies. All studies refer to the presence of major structural anomaly, soft markers or both. Identification of at least one marker conferred an overall sensitivity of 72–77% with a false positive rate of about 13%.

Significantly, about half of all fetuses had a nuchal fold thickness of 5 mm or more rendering this the most sensitive individual marker. The risk of trisomy 21 increases with the number of markers detected. The prevalence of isolated and multiple markers has been evaluated. In this analysis of 186 fetuses with trisomy 21, an isolated soft marker was identified in 22.6% of cases and 11.3% of euploid controls, while two or more markers were observed in 15.1% of cases and just 1.6% of normal controls.

The greatest challenge in risk assignment is where a marker is identified in isolation. If isolated soft markers are used as a basis for deciding to offer invasive testing, the resultant fetal loss rate would exceed the number of cases of trisomy 21 detected and indeed, that detection rates would fall. This assertion has been challenged by others who argue that while this may confirm the poor contribution that isolated soft markers make to risk assignment for aneuploidy, the performance of combined markers has been well validated in screening paradigms and furthermore, that dismissal of the role of soft markers in screening ignores the pivotal role their absence plays in providing patient-reassurance and avoiding invasive testing. The unacceptably high false-positive rate associated with identification of isolated soft markers in low-risk women presents a challenge insofar as there will always be a group of low-risk women undergoing “routine” mid-trimester sonography, in whom soft markers for aneuploidy may not be actively sought but may be incidentally noted. For this several scoring systems have been devised which correlate maternal age, serum biochemistry and sonographic markers.

A simple sonographic scoring index for the detection of chromosomal aneuploidy was devised by Benacerraf et al. Major structural anomalies and a thickened nuchal fold were each given a score of 2, as these are sufficiently strong even when detected in isolation. Soft markers were each allocated a score of 1. The panel of soft markers included: Short femur, short humerus, pylecasis, echogenic intracardiac focus (EICF), echogenic bowel, and choroid plexus cysts. The authors demonstrated that, where amniocentesis was reserved for fetuses scoring greater than or equal to 2, 73% of fetuses with trisomy 21 and 85% of fetuses with trisomy 18 could be identified with a false positive rate of 4%. Using likelihood ratios, two approaches have been proposed by Nyberg and Nicolaides to calculate a revised risk. The Nyberg method involves multiplication of the a prior risk by the likelihood ratio (LR) associated with any identified marker or markers. The latter calculation, proposed by Nicolaides, further takes into account the negative likelihood ratios associated with absent markers. The practical application of these two approaches in fact yields similar results. For example, a 39-year-old woman has an a priori age-related trisomy 21 risk of 1 in 100. The genetic sonogram identifies an isolated thickened nuchal fold. Applying the Nyberg method, the LR associated with this marker is multiplied by her a priori risk (0.01) to give a revised risk of 0.01 × 11 = 0.11, or 1 in 9. Applying the Nicolaides method in the same scenario requires multiplication of her a priori risk by a positive LR of 53.1 associated with nuchal fold thickening and also by the negative LRs associated with absent markers (i.e. combined negative LRs 0.7 × 0.9 × 0.6 × 0.9 × 0.8 = 0.272) associated with the absence of short humerus, echogenic bowel, short femur, pylecasis, and EICF, respectively). The same woman’s revised risk is computed by multiplying these risks (0.01 × 53.1 × 0.272) to arrive at a risk of 0.14 or one in seven. It is worth noting the consistently wide confidence intervals...
surrounding the point estimates of these likelihood ratios, inferring that while the identification of one or more markers is an effective screening tool, the actual computed risk is only an approximation.

**TRISOMY 18 (EDWARDS SYNDROME)**

Ninety percent of fetuses with trisomy 18 have an abnormal early second trimester morphology and up to 100% have an abnormal third trimester morphology. 

*Common stigmata include:* Choroid plexus cysts, ventriculomegaly, strawberry shaped skull, a large cisterna magna, agenesis of the corpus callosum, meningomyeloceles, microphthalmos, hypertelorism, low set ears, cystic hygromas, thickened nuchal skin fold, cardiac defects, diaphragmatic hernia, renal anomalies, omphalocele, short radial ray, clenched hand with overlapping fingers, rocker bottom foot, club foot, polyhydramnios, intrauterine growth restriction (IUGR) and a single umbilical artery, umbilical cord cysts and absent end diastolic umbilical artery flow velocity waveforms.

Ultrasound is often used to detect trisomy 18 when the triple screen shows a low alpha fetoprotein, low β-hCG and low free estriol. In addition, when choroid plexus cysts are present the search for other stigmata should be intensified. Isolated choroid plexus cysts do not warrant an amniocentesis for karyotyping.

**TRISOMY 13 (PATAU SYNDROME)**

Morphologic abnormalities are evident from 10 weeks onward and the sensitivity is 90–100%. It is very unusual for an affected fetus not to have a morphological stigma. Features include holoprosencephaly, agenesis of the corpus callosum, ventriculomegaly, enlarged cisterna magna, microcephaly, microphthalmia, hypertelorism, cyclopia, proboscis, cleft lip and palate, midline facial hypoplasia, nuchal thickening, cystic hygroma, cardiac defects, neural tube defects, echogenic enlarged kidneys, echogenic bowel, echogenic intracardiac focus, omphalocele, cystic kidneys, radial ray aplasia, polydactyly and a single umbilical artery.

**TURNER’S SYNDROME (XO)**

This is a syndrome consequent to the loss of an X chromosome, usually paternal. Most fetuses are spontaneously aborted. Ongoing pregnancies are characterized by extensive, often whole body, septated cystic hygromas which may regress over time and persist as only a webbing of the neck in an adult. Long-term survival is associated with a short stature, ovarian dysgenesis and occasionally mental retardation. It is also associated with left heart defects especially coarctation of the aorta and aortic valvular defects, horseshoe kidney and a short femur. There may be evidence of hydrops consequence to a high output cardiac failure. Mosaicism is common, often resulting in delayed menarche.

**TRIPOLOGY**

This occurs as a result of a complete extra set of chromosomes. Survival beyond 20 weeks of gestation is rare.

Features include severe early onset asymmetric IUGR, microphthalmia, hypertelorism, micrognathia, ventriculomegaly, midline brain defects, cystic hygromas, omphaloceles, renal anomalies, an enlarged placenta, oligoamnios, and abnormal umbilical artery flow velocity waveforms.

**GENETIC SONOGRAPHY AFTER FIRST TRIMESTER SCREENING**

First trimester genetic screening is now widely available and involves assessing maternal serum biochemistry and sonographic markers in order to identify patients who should undergo invasive testing. This is carried out between 11 and 13 weeks 6 days of pregnancy and has the advantage of an easier and safer termination of pregnancy and less parental psychological trauma. The combination of maternal serum pregnancy-associated plasma protein A (PAPP-A) and free hCG along with fetal crown-rump length to assess fetal size and a group of ultrasound markers allows detection of 88–90% of fetuses with Down’s syndrome. The ultrasound markers include nuchal translucency thickness, nasal bone delineation, fetal ductus venosus studies and fetal tricuspid regurgitation. Additional ultrasound markers include frontomaxillary facial angle, fetal growth, fetal heart rate, megacystis, cardiac anomalies and micrognathia.

In this group of patients sequential screening with a second trimester genetic sonogram enhances the detection rate for Down’s syndrome to 94–96%.

**REFERENCES**

SECTION


INTRODUCTION
The ultimate goal of prenatal diagnosis (PND) has always been to find a “cure”, not just the termination of pregnancy (TOP), or sometimes the birth of a sick diseased child to be salvaged by often futile postnatal treatments. Fetal treatment (or fetal therapy) is the “operative branch” of fetal medicine. It includes a series of interventions performed on the “sick” fetus with the aim of achieving optimal fetal well-being. These interventions include medical and surgical procedures. As more sophisticated tests of PND are becoming available, the desire and demand for fetal therapy is getting more and more precious and necessary.

Some of the conditions affecting various organ systems amenable today to in utero treatment are listed. There are, however, several ethical and social factors that should be considered while recommending the options. The fetal status has to be assessed accurately, in consultation with geneticist, radiologist, neonatologist, pediatric surgeon, cardiologist, microbiologist the Fetal Medicine Team. Parents have to be counselled on maternal/fetal risk, type of interventions, cost, hospital stay, etc. Cases are best referred to few super specialized centers with the necessary expertise, early.

MEDICAL FETAL THERAPY
In general, a medical intervention is performed by administering medication to the mother where in the drug crosses through the placenta and reaches the blood circulation of the fetus, or, the medication is given directly to the fetus usually through an ultrasound (US)-guided approach.

THYROID

Hypothyroidism
In the absence of maternal thyroid disease, or iodide-induced hypothyroidism, fetal goiter is extremely rare. Ultrasonographic features are presence of echogenic masses in the fetal neck (goiter), polyhydramnios and hypothyroidism diagnosed based on raised fetal serum thyroid-stimulating hormone (TSH) levels obtained by percutaneous umbilical blood sampling (PUBS).

Treatment
It involves series of intra-amniotic injections with triiodothyronine (T₃) or with levothyroxine (250–500 µg weekly). Shrinkage of the fetal goiter, increasing neck flexion and resolution of the polyhydramnios assures improvement. Following birth, neonatal serum TSH levels indicate dose of thyroxine (T₄).¹ In utero, therapy may not only reduce the obstetric complications associated with large goiters, but possibly improve the prognosis for normal growth and mental development of affected fetuses.²

Hyperthyroidism
This is usually secondary to maternal Graves’ disease or Hashimoto’s thyroiditis. Congenital hyperthyroidism is less frequent than hypothyroidism. During fetal life tachycardia, cardiac arrhythmia, growth restriction and prematurity are the consequences. Postnatal signs of hyperthyroidism are
irritability, tachycardia, hypertension, poor weight gain and thyroid enlargement. Even cardiac failure may occur if hyperthyroidism is severe and treatment not adequate which explains the high early mortality rate of 16%. The main complication of persistent hyperthyroidism in the neonatal period and during infancy is craniosynostosis. Severe developmental delay or even mental retardation can be the consequence of inadequate high T₄-levels during fetal and neonatal life.

It is of utmost importance to scrutinize fetal thyroid by ultrasonography and to have a team work with obstetricians and pediatric endocrinologists in pregnant women with Graves’ disease. Cord blood sampling allows confirmation of fetal status.

**Treatment**

Treatment is maternal propylthiouracil (PTU) 50–100 mg orally three times a day, or with methimazole.³,⁴

**CONGENITAL ADRENAL HYPERPLASIA**

Congenital adrenal hyperplasia due to enzyme deficiency in steroid biosynthesis most commonly 21-hydroxylase triggers excessive androgen production before birth. Affected females may have genital ambiguity, experience virilization both physically and psychologically. PND and treatment of congenital adrenal hyperplasia has been implemented for more than 20 years, through biochemical or molecular genetic analysis of fetal deoxyribonucleic acid (DNA) by amniocentesis or using chorionic villus sampling.

**Treatment**

In families at risk, prenatal maternal dexamethasone therapy is started at a gestational age of 6 weeks in a median dose of 20 mg/kg/day. PND by chorionic villus sampling at 10–12 weeks or amniocentesis at 16–18 weeks should be performed. In the female affected fetus, continued appropriate dexamethasone administration to the pregnant mother is necessary to reduce genital virilization in the fetus. This spares the newborn female the consequences of genital ambiguity, genital surgery, sex misassignment and gender confusion.

Current data from large human studies show the benefit and safety of prenatal treatment.⁵-⁸ Long-term follow-up of the safety of prenatal treatment is currently underway. This practice is a rare example of effective prenatal treatment to prevent a malformation caused by an inborn error of metabolism. In one series, 53% reported maternal adverse events, 8% observed adverse fetal events.⁵ There is need for further improvement in PND and treatment, compliance during puberty, screening programs, psychological aspect and corrective surgery.

**NONIMMUNE HYDROPS**

Nonimmune hydrops fetalis (NIHF) is used to describe fetuses and newborns with generalized edema or at least two cavity effusions. The prognosis of hydrops fetalis differs markedly between different etiological groups. Etiologies range from treatable causes with a good outcome and probably no long-term side effects [as in case of parvovirus B19 (PVB19)] to others which are incompatible with life or associated with considerable perinatal morbidity and mortality. A thorough maternal-fetal work-up will dictate treatment of the cause.

The rate of PVB19 infection in cases of “idiopathic” NIHF is reported to be approximately 16% with polymerase chain reaction (PCR)-based methods.³ Late (third-trimester) cases of “idiopathic” NIHF are likely to be negative by all methods, either because they are not attributable to PV infection or because PV protein and DNA are below detectable levels or are no longer present. Maternal serology for PV and TORCH (Toxoplasmosis, Rubella, Cytomegalovirus, Herpes simplex, Syphilis) agents may be the best method for investigating third-trimester losses to otherwise unexplained NIHF.

In one study, of 55 cases of NIHF,²⁸ eight (14.5%) were due to human PVB19 infection, 14 cases (25.5%) were associated with aneuploidy and four (7.3%) had primary hydrothorax. A cardiac cause was found in five (9.1%) cases: three had supraventricular tachycardia (SVT), one had congenital complete heart block. Cystic hygroma was associated with hydrops fetalis in six cases. Twin-twin transfusion syndrome (TTTS) was the cause for hydrops in two cases. Massive transplacental hemorrhage was identified in one case. Fetal akinesia and muscular dystrophy caused hydrops in one case each. In 14.5% (8/55) of cases, no obvious cause was identified and these were classified as “idiopathic.” Three other cases could not be classified because parents declined investigations (unclassified). The outcome was favorable in only 27.3% (15/55) of cases.

Fetal hydrops following massive fetomaternal hemorrhage can be successfully managed by serial fetal intravascular transfusions (IVT).¹¹,¹²

Autopsy in conjunction with placental examination and fetal US represent the best combination to determine the etiology of NIHF among stillborn fetuses. In a study of 51 cases of NIHF,¹³ pertinent diagnoses were maternal diabetes mellitus,⁴ congenital heart disease,³ and cystic hygroma,³ one instance each of cardiac tumor, twin transfusion syndrome, congenital adenomatoïd malformation, syphilis, Turner’s syndrome and cerebral arteriovenous malformation.

Postmortem and placental examination confirmed the following etiologies: congenital infections;¹⁴ placcental pathology significant enough to explain NIHF:¹⁰ cardiovascular diseases⁸ (further classified as congenital heart disease,³ rhabdomyoma¹ and vascular malformations⁸); chromosomal abnormalities⁶ uncontrolled maternal
diabetes;\textsuperscript{4} intrathoracic lesions\textsuperscript{2} prune-belly syndrome;\textsuperscript{2} and idiopathic NIHF.\textsuperscript{2} Only 3.9\% of the cases studied had no identifiable etiology. The cause of hydrops was confirmed by autopsy in 47 fetuses (92\%), which further supports the importance of performing an autopsy. Thirty-two cases (62.74\%) had placental abnormalities helpful to the etiology (PV, syphilis, Turner’s syndrome, etc.).

**INBORN ERRORS OF METABOLISM**

Inborn errors of metabolism are rarely amenable to fetal therapy.

**Maternal Phenylketonuria**

Maternal phenylketonuria (PKU) can result in multiple congenital anomalies. As the cohort of young women with treated PKU is growing steadily, maternal PKU is going to become an even greater cause for concern.

**Treatment**

Maternal dietary control should be established before conception. Most problems occur when dietary control is not established until after the second trimester. Women with PKU must follow a strict low-phenylalanine diet aimed at controlling blood phenylalanine to 120–360 µmol/L, during pregnancy in order to protect the fetus from the deleterious effects of high maternal blood phenylalanine.\textsuperscript{15}

Dietary control was established before conception in 17 pregnancies (44\%). Five mothers with hyperphenylalaninemia had 11 pregnancies.\textsuperscript{16} There were no congenital anomalies in this group, and all appeared to be developing normally. Fifteen women with classical PKU had 28 pregnancies. One pregnancy ended in a first-trimester miscarriage. Twelve out of twenty-seven (44\%) completed pregnancies produced babies with a congenital anomaly and/or developmental delay.

**3-Phosphoglycerate-dehydrogenase Deficiency**

3-phosphoglycerate-dehydrogenase (3-PGDH) deficiency is an L-serine biosynthesis disorder, characterized by congenital microcephaly, severe psychomotor retardation and intractable seizures. PND of an at-risk pregnancy is by DNA mutation analysis. 3-PGDH deficiency is an inborn metabolic error that can be successfully treated antenatally.

**Treatment**

*L-serine therapy*: In one case report, US assessment showed a reduction in fetal head circumference from the 75th percentile at 20 weeks gestation to the 29th percentile at 26 weeks.\textsuperscript{17} L-serine was given to the mother, which resulted in an enlarged fetal head circumference to the 76th percentile at 31 weeks. At birth, the girl’s head circumference was normal, and at 48-month follow-up, her psychomotor development has been unremarkable.

**ALLOIMMUNE THROMBOCYTOPENIA**

Fetomaternal alloimmune thrombocytopenia (FMAIT) is the most common cause of severe thrombocytopenia in term neonates but its management remains controversial. Human platelet antigen 1a (HPA-1a) antibodies are most commonly implicated in severe thrombocytopenia but HPA-5b and HPA-15b antibodies can also result in poor outcome.

**Therapy**

Use of *maternal therapy* as first-line treatment is recommended. It can be stratified on the basis of the sibling history of FMAIT—antenatal intracranial hemorrhage (ICH) or severe thrombocytopenia (platelet counts of < 20 × 10\(^9\)/L) have significantly lower pretreatment platelet counts than cases whose siblings had less severe thrombocytopenia or postnatal ICH.

**Serial Platelet Intrauterine Transfusions**

In one series, cases with maternal therapy resulted in a platelet count exceeding 50 × 10\(^9\)/L in 67\% of cases.\textsuperscript{14} None of the fetuses managed by serial platelet intrauterine transfusions (IUTs) suffered ICH following treatment. However, several serious complications arose with fetal blood sampling (FBS).

**Postnatal Transfusion**

Postnatal transfusion management is extremely variable and fetal transfusions are associated with significant morbidity. Of 123/200 (62\%) cases (two sets of twins) with no previous history of FMAIT, intrauterine deaths occurred in five: anti-HPA-1a alone, three; in combination with anti-HPA-5b, and one; with anti-HPA-15b.\textsuperscript{18} Of the 120 live neonates, 103 had severe thrombocytopenia and 17 (14\%) developed ICH (anti-HPA-1a, 13; anti-HPA-5b, three; anti-HPA-15b, one). Postnatal care varied widely with 37\% of neonates receiving random rather than HPA-1a and HPA-5b-negative platelets. Of the remaining 77 cases with a history of FMAIT, 40 received IUTs. Six (15\%) of these fetuses died in utero and an additional two developed ICH postnatally. Of the 19 children with ICH, one (anti-HPA-15b) died on Day +1, and neurologic sequelae persist in 13 (mean follow-up, 2.5 years).

**FETAL INFECTIONS**

**Parvovirus B19**

Most maternal infections with PVB19 occur through contact with infected children at home, and can cause several serious complications in the fetus such as fetal anemia, neurological
anomalies, hydrops fetalis and fetal death. Testing maternal serum for immunoglobulin M (IgM) antibodies against PVB19 and DNA detection by PCR can confirm maternal infection. If maternal infection has occurred, US investigation of the fetus and measurement of the peak systolic flow velocity of the middle cerebral artery are sensitive noninvasive procedures to diagnose fetal anemia and hydrops.

**Therapy**

Intrauterine transfusion is currently the only effective treatment to alleviate fetal anemia, but if the fetus is (near) term, induction of delivery should be considered. Fetal PVB19 infection may, however, induce central nervous system damage, and may, not, be related to the severity of fetal anemia and acidemia. A total of 25 IUTs were performed in 24 hydropic fetuses. Median fetal hemoglobin (Hb) concentration, platelet count and blood pH before IUTs were 4.5 g/dL (range: 2.4-11.4 g/dL), 79 x 10^9/L (range: 37-238 x 10^9/L) and 7.36 (range: 7.31-7.51), respectively. Of 16 survivors aged 6 months to 8 years, 11 children (68%) were normal, and five children (32%) demonstrated a delayed psychomotor development with suboptimal neurological examination (mild delay n = 3, severe delay n = 2). Neurodevelopmental status did not correlate with pre-IUT Hb, platelet, or blood pH values. Growth and general health status were normal in all. Two children had minor congenital defects. Neurodevelopmental status was abnormal in 5 of 16 survivors.

**TOXOPLASMOSIS**

Infections with *Toxoplasma gondii* occur worldwide, but are especially prevalent in Europe, South America and Africa. The primary problem for the diagnosis of *T. gondii* infection is longstanding IgM-antibodies, thus the presence of *T. gondii*-specific IgM-antibodies do not necessarily indicate an acute infection. The use of a Toxoplasma-specific IgG-avidity ratio, differentiated Western blots and two-dimensional immunoblots usually resolves diagnostic problems. There is no consensus on the best strategy to control congenital toxoplasmosis. Despite 3 decades of prenatal screening for congenital toxoplasmosis in some European countries, uncertainty remains about the effectiveness of prenatal treatment. Without treatment, congenital toxoplasmosis has recurrent, recrudescence and adverse outcomes. TOP is usually recommended to pregnant women who have infection with *T. gondii* before 26 weeks of pregnancy, especially if there are US features suggestive of fetal affection such as intracranial calcifications and hydrocephalus, hydrops fetalis.

**Treatment**

No randomized studies exist on the treatment of *T. gondii* infection in pregnant women and newborn children with congenital toxoplasmosis.

Maternal therapy recommended is spiramycin (3 million units/day). PND is performed by amniocentesis and serial US. If fetal infection is confirmed by PCR, IgM—pyrimethamine (50 mg/day) plus sulfadiazine (2-3 g/day) for 3 weeks alternating with spiramycin (3 million units/day) till delivery are started after parental counseling. Monitoring of mother for potential hematological toxicity of high-dose pyrimethamine should be done, of 35 infants born to mothers with toxoplasmosis acquired during pregnancy, who received spiramycin from diagnosis through labor and two received pyrimethamine and sulfadiazine at birth, infants had IgG antibody titers ranging from 1/1,350 to 1/109,350. All infants initially received pyrimethamine, sulfadiazine and folic acid but in only four cases treatment was continued beyond the 2nd month of life. Transient neutropenia was commonly observed. A follow-up period of 1.2-8.2 years did not reveal any remarkable sequelae. Treatment of infants without substantial neurologic disease at birth with pyrimethamine and sulfadiazine for 1 year results in normal cognitive, neurologic and auditory outcomes for all patients. Treatment of infants who had moderate or severe neurologic at birth resulted in normal neurologic and/or cognitive outcomes for greater than 72% of the patients and none had sensorineural hearing loss. Ninety-one percent of children without substantial neurologic disease and 64% of those with moderate or severe neurologic disease at birth did not develop new eye lesions. Almost all of these outcomes were markedly better than outcomes reported for children who were untreated or treated for 1 month in earlier decades (p < 0.01-0.001).

Review of 26 cohorts—1,438 treated mothers identified by prenatal screening, found weak evidence that treatment started within 3 weeks of seroconversion reduced mother–to–child transmission compared with treatment started after 8 or more weeks [adjusted odds ratio (OR) = 0.48, 95% confidence interval (CI) = 0.28–0.80; (p = 0.05); Systematic Review on Congenital Toxoplasmosis (SYROCOT) Study Group]. In 550 infected live born infants identified by prenatal or neonatal screening, there was no evidence that prenatal treatment significantly reduced the risk of clinical manifestations (adjusted OR for treated vs untreated = 1.11, 95% CI = 0.61–2.02). Increasing gestational age at seroconversion was strongly associated with increased risk of mother–to–child transmission (OR = 1.15, 95% CI = 1.12–1.17) and decreased risk of intracranial lesions (0.91, 0.87–0.95), but not with eye lesions (0.97, 0.93–1.00).

Prospective study of 163 mothers with acute toxoplasma infection before 28 weeks of amenorrhea received antiparasitic treatment with 9 million IU spiramycin orally, 23 also received pyrimethamine and sulfadiazine. All had cordocentesis and regular obstetric US examinations. The 162 live born infants were followed up for 15–71 months. Three fetuses died in utero. 27 of 162 live born infants had proven congenital toxoplasmosis: 10 had one or more clinical signs of congenital toxoplasmosis; five had isolated or multiple intracranial calcifications; seven had peripheral
Fetal tachyarrhythmia may cause fetal hydrops, and lead to fetal morbidity and mortality.

Supraventricular Tachycardia and Atrial Flutter

Supraventricular tachycardia and atrial flutter (AF) have been the most diagnosed.

Treatment

Various treatment modalities have been reported, with no consistent success. The efficacy of antiarrhythmic drug therapy for fetal AF has not been well established. Ectopic (premature atrial/ventricular) beats: Caffeine, sympathomimetic drugs should be avoided. Cases should be followed up weekly for SVT.

Digoxin and sotalol: They may be considered as the drugs of choice for fetal AF. If the fetal AF is resistant to these therapies, a combination of other congenital cardiac diseases or organic abnormalities should be considered. If maternally administered oral digoxin for the treatment of fetal SVT complicated by hydrops fetalis is ineffective secondary to poor transplacental drug transfer, maternal intravenous (MIV) administration of digoxin may be needed, using standard loading and maintenance protocols. MIV digitalis can be converted to oral after fetal stabilization. A case of fetal AF at the gestational age of 25 weeks with atrial rates of 480–520 beats per minute (bpm) and ventricular rates of 200–250 bpm was treated with digoxin then with a combination of digoxin and sotalol. The fetal heartbeat slowed after sotalol treatment but did not return to sinus rhythm. The fetus was delivered vaginally. Neonatal echocardiography showed a small apical ventricular septal defect and small patent ductus arteriosus.

Combination of fetal intramuscular (FIM) digoxin and MIV is described in refractory cases. FIM is administered at a dose of 88 µg/kg q12–24 hours, to a maximum of three injections in the fetal buttock. Direct FIM injection of digoxin combined with transplacental therapy appears to shorten the time to initial conversion of SVT and to sustain sinus rhythm in the fetus with SVT complicated by hydrops fetalis, conversion occurs by 1 week or so.

Amiodarone with digoxin or flecainide: It has been used successfully to convert SVT to sinus rhythm with resolution of hydrops, postnatal electrical cardioversion may be required, with no recurrences in AF after neonatal period.

One large study on management of fetal arrhythmia on the basis of superior vena cava (SVC)/ascending aorta (AA) Doppler flow velocity recordings of irregular rhythms in 307 cases showed that premature atrial and ventricular contractions were easily identified and generally self-limited in time. There was sustained bradycardia (n = 19), four had sinus bradycardia, six presented with blocked atrial bigemism, three showed 2:1 and five had a complete atrioventricular (AV) block. Another fetus that presented with first-degree AV block developed a Luciani-Wenckebach phenomenon 1 week later. Tachyarrhythmia developed in (n = 30). Five types of tachyarrhythmia were observed:

1. **Type I**: Short ventriculoatrial (VA) tachycardia (VA < AV; n = 11). Ten fetuses of this group were considered to have reentrant tachycardia through a fast-conducting AV accessory pathway; all 10 responded to digoxin therapy. The eleventh fetus with short VA tachycardia had atrial ectopic tachycardia with AV node dysfunction was treated successfully with sotalol.

2. **Type II**: Long VA tachycardia (VA > AV; n = 8). The drug of first choice in this group was sotalol.

3. **Type III**: Simultaneous onset of atrial and ventricular contractions: (n = 3). Two responded to amiodarone. The other fetus converted spontaneously to sinus rhythm.

4. **Type IV**: Flutter; (n = 7). Digoxin was prescribed as a first choice associated with sotalol in three cases. Conversion to sinus rhythm was documented in all; however, one hydropic fetus with advanced cardiomyopathy died 1 day after birth.

5. **Type V**: Ventricular tachycardia; (n = 1). The arrhythmia responded well to propranolol and no recurrence was recorded after birth.

Precise prenatal identification of arrhythmia type can be achieved with the SVC/AA Doppler approach. Such information allows for a better management and a rational choice of appropriate antiarrhythmic drug.

Congenital Complete Heart Block

Congenital complete heart block is an uncommon fetal arrhythmia characterized by complete dissociation of the atrial and ventricular contractions, the result of an anatomical anomaly of the conduction pathways, or even the transplacental passage of maternal antibodies causing fetal myocarditis with fibrosis of the conduction tissue, cardiac defects seen in 50% with a mortality rate of 20–30%.

Treatment

Cardiac pacing after premature delivery is associated with high morbidity and mortality, but it may be required in
case of distress and/or deteriorating cardiac function with development of hydrops due to cardiac failure. Vaginal delivery can be safely accomplished in patients with isolated congenital complete heart block, with the use of US and fetal scalp blood sampling to assess fetal well-being during labor and delivery, with postnatal pacemaker implantation if heart rate is still below 50 bpm.30

Prenatal treatment with oral sympathomimetic medication may allow delivery to be delayed until term. In presence of maternal anti-SS-A/Ro Bl Ab, maternal Betamethasone or dexamethasone, 4 mg daily can be useful.

In hydropic fetuses, MIV salbutamol/oral terbutaline raises ventricular rate by 20%. An increase in the fetal ventricular rate and complete resolution of hydrops fetalis occurred in a case of fetal complete heart block diagnosed in a 30-year-old woman when cardiac decompensation was detected at 32 weeks, and she was treated with oral terbutaline after a trial of IV isoproterenol.31 A male infant was delivered by Cesarean section at term, and underwent cardiac pacemaker implantation at 4 days of age with a successful outcome.

**CARDIAC MALFORMATIONS**

Cardiac malformations are common, with major lesions affecting about 3.5 per 1,000 pregnancies; however, only a small proportion of these is likely to benefit from an intrauterine medical intervention. Recent research and clinical developments have included percutaneous valvuloplasty for severe aortic and pulmonary stenosis, perforation of the closed or restrictive interatrial septum and pacing for complete heart block.32 Progress in these endeavors has been variable but overall shows promise for treatment of the human fetus.

**RHEUS ISOIMMUNIZATION**

Fetal death due to anemia (hydrops fetalis) and hemolytic disease of the newborn, secondary to Rhesus (Rh) alloimmunization, is still a major contributor to perinatal morbidity and mortality in India. Preterm delivery and neonatal exchange transfusion are commonly practiced in general, and plasmapheresis has outgrown its usefulness.

**Treatment**

**High-dose maternal intravenous immunoglobulin (IVIg) therapy** blocks Fc (fragment, crystallizable)-mediated antibody transfer across the placenta, blocks Fc receptor-mediated phagocytic function in reticuloendothelial system of mother and fetus, thereby reducing fetal red cell hemolysis. IVIg thus prevents or delays onset of fetal anemia, decreases need for IUT.33

**Fluoroscopic-guided intraperitoneal (IPT) IUT** was the first method of fetal blood transfusion to correct fetal anemia, by the pioneer in fetal therapy—Sir William Liley in 1963. The invention of US and subsequently cord blood sampling has made US-guided fetal blood transfusion a revolution in the management of Rh-isoimmunization, and replaced the more invasive fetoscopic-guided IUT. Planned delivery is done at a center where neonatal exchange transfusion can be performed after pregnancy is carried up to near term with IUTs for the anemic fetus.

**Ultrasound-guided fetal blood transfusion IUT (IVT, IPT):** Intensive monitoring by serial US for fetal anemia, serial middle cerebral artery peak systolic velocities using Doppler US, when necessary invasive testing with techniques such as serial amniocenteses to detect fetal bilirubin by delta-OD (450), and cordocentesis for Hb. If packed cell volume (PCV) is less than 30, or there is fetal hydrops, IUT is carried out through US-directed direct IVT or IPT injection of red cells. Fetal hydrops, mostly associated with late referrals, decreases the chance of survival. To improve the outcome of red cell alloimmunized pregnancies, early diagnosis of fetal anemia and referral to a specialized center are important, enabling the start of treatment IUT before hydrops develops.

Of 18 Rh-negative pregnant women presenting during a 7-year period, managed with serial intrauterine IVTs with the goal of delivery by Cesarean section beyond 33 weeks of gestation, 11 were mildly and seven severely hydropic fetuses.34 All fetuses with mild hydrops and five of the seven with severe hydrops were delivered alive after 32 weeks of gestation in a good condition. Two fetuses both with severe hydrops died in utero, at 28 weeks of gestation. Intrauterine reversal of hydrops occurred in 90.9% of fetuses with mild hydrops and in 57.1% of severely hydropic fetuses. The survival rate for the hydropic fetuses was 89.9% and prognosis was associated with the severity of fetal hydrops.

In prospective cohort study of 99 Rh-isoimmunized pregnancies referred to All India Institute of Medical Sciences (AIIMS) conducted over the last 5 years, 43 (25 hydrops fetalis and 18 non-hydropic fetuses) required 135 intrauterine blood transfusions, while the rest 56 pregnancies were managed conservatively.35 In the 43 cases who required transfusion, IUT was done starting from 16 weeks (IPT), 21 weeks (IVT) of gestation by the IPT/IVT routes. Pre-transfusion Hb ranged from 3 g% to 8 g%. Amount of blood transfused varied from 10 mL to greater than 110 mL depending on the period of gestation and degree of fetal anemia. Number of transfusions per pregnancy was 1–7, at intervals of 1–4 weeks, till delivery at 28–36 weeks of gestation. Overall survival rate was 86%. Survival of hydropic fetuses (72%) was significantly different from those without hydrops (89%); and in those receiving IUT (83.3%) versus without IUT (94%). Low survival rates were especially found in hydropic fetuses with the first transfusion at gestational ages of 20 weeks or less and in those with severe hydrops.

Over an 8-year period, 221 in utero transfusions were performed for Rh disease in 66 pregnancies. 86% had severe fetal anemia caused by anti-D, 10.6% by anti-Kell and 3.4% by anti-c.36 The median gestation at initial IUT was
25 weeks [interquartile range (IQR): 23–29 weeks]. A median number of three IUTs were performed in each fetus, with a median Hb at first fasting blood sugar (FBS) of 7.3 g% (IQR 4.6–8.8 g%) [73% ≤ 5 standard deviation (SD) and 27% ≤ 2 SD].

Of the total IVTs, 170 were performed via the intrahepatic vein (IHV) route (71.7%), 33 via cordocentesis (13.9%) and one by intracardiac puncture (0.5%). There were “transient” bradycardias complicating 4.1% of all transfusions and amniorrhexis following 1.4%. 92% of babies were live born at a median gestation of 34 weeks (range: 21–38). There was no significant difference in IVT complication rate when the procedure was performed via the IHV (7.6%) as compared to cord root puncture (3.0%).

FETAL SURGICAL THERAPY

Fetal structural abnormalities have a wide spectrum of clinical severity and prognosis. Detailed US should be done for other associated abnormalities or syndromes. Fetal status, prognosis has to be assessed in consultation with pediatric surgeon, neonatologist and geneticist. Parents have to be counseled on risk, prognosis, interventions during pregnancy or after birth (infancy and childhood, e.g. renal transplant), cost, hospital stay. If the structural defect is suggestive of a chromosomal abnormality, a fetal karyotype is performed by amniotic fluid or cord blood sampling. A lethal anomaly such as bilateral renal agenesis, anencephaly is best managed by TOP. An anomaly detected late, with mild organ damage such as mild ventriculomegaly, hydronephrosis may be left alone and the newborn managed after birth. If continuation of the pregnancy is desired in a case with fetal structural defect which could cause grave organ damage, morbidity or mortality if left alone in the expectation of treatment after birth, the option of therapeutic intervention during fetal life in utero fetal surgery is now possible for some conditions. In the 1990s, the merger of fetoscopy and advanced videoendoscopic surgery formed the basis for endoscopic fetal surgery. In India, very few centers such as the AIIMS, New Delhi, are involved in research and patient care in this exciting, rapidly advancing field.

Pertinent aspect of some defects and corrective fetal surgical procedures are described in Table 1.

TABLE 1: Fetal surgical procedures

<table>
<thead>
<tr>
<th>Fetal structural defect</th>
<th>Natural fetal outcome</th>
<th>Recommended treatment</th>
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<tbody>
<tr>
<td><strong>Urinary tract obstructive defects:</strong></td>
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<tr>
<td>- Urethral obstruction</td>
<td>Renal failure</td>
<td>Vesicocentesis</td>
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<td></td>
<td>Pulmonary hypoplasia</td>
<td>Vesicoamniotic shunt</td>
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<td></td>
<td>Oligohydramnios</td>
<td>Fetaloscopic vesicostomy</td>
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<td>Laser ablation</td>
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<td><strong>Lung defects:</strong></td>
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<tr>
<td>- Cystic adenomatoid malformation</td>
<td>Pulmonary hypoplasia</td>
<td>Pleuro-amniotic shunt</td>
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<tr>
<td>- Pleural effusion (PE)</td>
<td>Respiratory failure</td>
<td>Thoracoamniotic shunt</td>
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<td>- Pulmonary sequestration</td>
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<td>Open pulmonary lobectomy</td>
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<tr>
<td><strong>Multiple pregnancy:</strong></td>
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<tr>
<td>- Twin-twin transfusion syndrome (TTTS)</td>
<td>Hydrops fetalis</td>
<td>Laser ablation</td>
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<tr>
<td>- Acardiac twins [twin reversed arterial perfusion (TRAP)]</td>
<td>Intrauterine death</td>
<td>Cord occlusion</td>
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<tr>
<td><strong>Diaphragmatic hernia:</strong></td>
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<tr>
<td></td>
<td>Pulmonary hypoplasia</td>
<td>Open complete repair</td>
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<td></td>
<td>Temporary tracheal occlusion (TO)</td>
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<tr>
<td><strong>Fetal tumors:</strong></td>
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<tr>
<td>- Giant neck masses</td>
<td>Polyhydramnios</td>
<td>Resection of tumor</td>
</tr>
<tr>
<td>- Sacrococcygeal teratoma (SCT)</td>
<td>Hydrops fetalis</td>
<td>Radiofrequency ablation</td>
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<tr>
<td></td>
<td></td>
<td>Fetoscopic vascular occlusion</td>
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</tbody>
</table>

URINARY TRACT OBSTRUCTIVE DEFECTS

Lower urinary tract obstruction (LUTO) is commonly meant when discussing obstructive uropathy. Three serial bladder taps—“vesicocentesis” performed over the course of 3–4 days is most predictive of identifying underlying renal injury.

Fetal Vesicocentesis

Under continuous US guidance with color Doppler visualization to prevent inadvertent umbilical vessel injury, a 22/23 gauge needle is inserted into the fetal bladder. The bladder is completely emptied of urine by aspiration with 20-mL syringe or continuous rapid suction, while constantly maintaining the needle tip placement within the cavity of the shrinking bladder. The urine is sent for required analysis. Urine obtained at the initial bladder drainage represents old urine from within the fetal bladder. Urine from the second drainage represents urine that has collected in the bladder from the upper collecting systems. The third tap is fresh urine and is the most predictive of underlying renal function. In some cases,
however, a fourth or fifth tap is needed to determine renal status. The urine is analyzed for electrolyte and protein values as a reflection of the level and severity of damage to the fetal kidneys. Fetuses that demonstrate progressive hypotonicity on sequential urine samples and have final values which fall below recommended thresholds have been shown to benefit from in utero intervention. Fetal urine evaluation parameters showing good prognosis are:41

- Sodium ≤ 100 mg/dL
- Osmolality ≤ 200 mOsm/L
- Chloride ≤ 90 mg/dL
- Calcium ≤ 8 mg/dL
- Total protein ≤ 20 mg/dL
- β-2 microglobulin ≤ 6 mg/L

A fetal echocardiogram should also be performed to rule out congenital heart defects that occur in increased frequency in these cases. An ultrafast fetal magnetic resonance imaging (MRI) can be useful in evaluating the kidneys, collecting system and bladder in complex cases.

**Percutaneous Vesicoamniotic Shunt**

This is performed if kidney functions are normal, the karyotype is normal and there are no major malformations. It can be performed under local, regional or general anesthesia, usually local.42

The location and position of the placenta and fetus are identified on US to avoid passing through the placenta. Since most of these fetuses have oligohydramnios, amnioinfusion may be carried out if there is severe oligoamnios to facilitate catheter placement using warmed Ringer’s lactate solution; it is helpful in the placement of proximal part of shunt into the uterine cavity and not in the myometrium. The ideal fetal site of entry is below the umbilicus, avoiding vessels as seen by color Doppler. Fetus is first given analgesia (0.2 µg/kg pancuronium, 10 µg/kg/fentanyl). The maternal skin is anesthetized with 1% lignocaine, a small 3–5 mm stab wound made and shunt trocar carefully introduced into the amniotic space and then into the fetal bladder using sharp, shift movement and positioned centrally. Urine sample is aspirated, sent for culture and renal function. The double pigtail “Rodeck” or “Harrison” shunt catheter is now threaded into the trocar sheath prior to insertion of internal stylet wire. Using push rods, the proximal segment of the catheter is pushed into the fetal bladder while the distal end positioned in the amniotic space drains out the urine. US at 24–48 hours and then weekly for 4–6 weeks needs to be done to confirm proper catheter placement and function, amniotic fluid volume and progressive resolution of bilateral hydronephrosis. With shunt therapy, as the bladder shrinks, dislocation and malfunction of the shunt may occur in 60% cases due to pull from skin into the fetal abdomen or shunt being pulled out of the fetus into the amniotic cavity.

**Percutaneous Fetal Cystoscopy**

Techniques to evaluate the inside of the fetal bladder and proximal urethra (in utero microcystourethroscopy), identify the source of obstruction and surgically destroy it prenatally are being developed.44 This would eliminate need for temporary shunts with their inherent physical limitations, and it would allow more normal bladder and urinary tract development during fetal life.44

**Fetal Endoscopic Ablation of Ureteral Valve**

A 3 mm/3.9 mm trocar with 2.7 mm/3.3 mm operating endoscope is used. The fetal bladder is entered as in shunt procedure, and ablation of ureteral valve or ureterocele wall lysis is done using contact yttrium-aluminum-garnet (YAG) laser.

**Endoscopic Fetal Cystotomy (EFC): Fetal Hydrolaparoscopy (FHL) Ablation of PUV**

Similar to adult laparoscopy, access into the fetal peritoneal cavity by the endoscope is achieved, the bladder identified, dome incised using 20 W laser, and a 3.3 mm endoscope inserted inside the bladder and posterior urethral valves (PUV) ablated.

**Retrograde Urethral Catheterization (RUC)**

Fetal endoscope is inserted into the amniotic cavity near fetal penis. Foreskin is grasped with 1 mm forceps. A 2 mm monopolar electrode is passed into the urethra under laser.

**Prognosis**

Antenatal treatment of obstructive uropathy, although widely performed, remains controversial. In one large study, 58 patients were followed up from 6 months to 6 years and 6 months (mean 3.9 years).45 Group I included 12 patients who had vesicoamniotic shunt placement, and were confirmed postnatally to have PUV. Four fetuses died (33.3%); three out of the eight living had perinatal complications. Of the eight living neonates, three (37.5%) underwent valve ablation and five (62.5%) underwent urinary diversion (three vesicostomies and two cutaneous ureterostomies). Renal function returned to normal in only four (50%). Radiological abnormalities (hydronephrosis and/or reflux) resolved in three (37.5%), was downgraded in one (12.5%) and persisted in four cases (50%). Group II included 46 patients who were treated postnatally. Thirty-five (76%) underwent primary valve ablation, while 11 (24%) underwent urinary diversion (seven vesicostomies, four cutaneous ureterostomy and one
pyelostomy). Renal function returned to normal in all babies who underwent valve ablation, except in three, while renal function returned to normal in only three of 11 patients who underwent urinary diversion. Radiological hydronephrosis and/or reflux resolved in 28 patients (60.9%), was downgraded in six patients (13%) and persisted in 12 patients (26.1%).

Clinical outcomes in 20 pregnancies with a singleton male fetus, oligo/anhydramnios and LUTO studied, 1-year survival was 91%. Two neonatal deaths occurred from pulmonary hypoplasia. Mean days from shunting to delivery were 84.4, and mean birthweight was 2,574 g. Prenatal urinary prognosis was good in 13, borderline in two and poor in three of the survivors. Mean age at follow-up was 5.83 years. PUVs were confirmed in seven males, urethral atresia in four and prune belly syndrome in seven. Eight children had acceptable renal function, four had mild insufficiency, and six required dialysis and eventual renal transplant. Eleven children had normal bladder function with spontaneous voiding, six required catheterization and one child still had a vesicostomy. Although one-third of the surviving babies required dialysis and transplantation, the majority have acceptable renal and bladder function, and reported satisfactory quality of life. Thirty-three percent developed renal failure but did well after renal transplant.

Thus, antenatal vesicoamniotic shunt placement appears to make no difference to the outcome and long-term results of patients with PUV and debate about its efficacy on renal outcome remains. Primary valve ablation is emerging as the keystone of treatment for patients with PUV that might achieve the primary goal of nephron preservation. The lowest creatinine concentration in the 1st year of life is the most appropriate predictor of future renal function.

### LUNG DEFECTS

#### Congenital Cystic Adenomatoid Malformations

Congenital cystic adenomatoid malformation (CCAM) of the lung is a nonfunctioning benign lung tumor, hamartomatous or dysplastic in origin. They may be: macrocystic—usually a single, 2–10 cm cyst within lungs, and microcystic—appearing as solid, echogenic mass. Hydrops fetalis and polyhydramnios warrant fetal intervention. Treatment by means of decompression can improve substantially the clinical results in these patients. Antenatal evaluation using US, amniocentesis, PUBS and cardiac echo should be carried out to look for the presence of other fetal anomalies and fetal prognostic markers. If fetal hydrops is not present, the mother should be followed by serial US scans and arrangements made for appropriate postnatal care. An elective postnatal resection of lung mass at 4 weeks of age can be carried out. If the fetus has hydrops, or hydrops develops during follow-up, then management depends on the gestational age. For fetuses more than 32 weeks, delivery of the fetus and resection of the lesion ex utero in a center with extracorporeal membrane oxygenation (ECMO) facilities is appropriate.

#### Fetal Surgery

For fetuses that develop hydrops before 32 weeks of gestation, treatment options are:

- **Microcystic CCAM**
  - Posterolateral thoracotomy with resection of involved lobe
  - Percutaneous intrauterine laser therapy

- **Macroscopic CCAM**: Thoracoamniotic shunt placement: It carries a 70% success rate. Effect of prenatal pulmonary drainage (shunt, surgery or drainage) on perinatal survival was compared with no treatment, in fetuses with ultrasonic evidence of lung pathology, in 16 controlled observational studies involving 608 fetuses which showed that pulmonary drainage did not improve perinatal survival in cystic lung lesions compared with no drainage (OR = 0.56, 95% CI = 0.32–0.97, p = 0.04) overall. However, there was a marked improvement with this therapy in a subgroup of fetuses with fetal hydrops fetalis (OR = 19.28, 95% CI = 3.67–101.27, p = 0.0005) but not in the subgroup uncomplicated by fetal hydrops fetalis (OR = 0.04, 95% CI = 0.01–0.32, p = 0.002).

#### Bronchopulmonary Sequestration

Bronchopulmonary sequestrations (BPS) are intralobar and extralobar lung masses of benign pulmonary tissue without tracheobronchial communication. Prenatal identification of feeding vessel establishes the diagnosis of pulmonary sequestration allowing its differentiation from CCAM. Fetal extralobar pulmonary sequestration (EPS) is sometimes complicated by massive pleural effusion (PE) leading to fetal hydrops.

#### Fetal Surgery

Pleuro-amniotic shunting should be considered as a treatment option for fetal hydrothorax and hydrops associated with BPS. Procedure is same as vesicoamniotic shunt. Antenatally diagnosed “cystic lung disease” have an excellent prognosis in the absence of signs of hydrops.

#### Pleural Effusion

Fetal PEs may lead to lung compression and hypoplasia, and could be due to chylothorax.

#### Fetal Surgery

*Thoracoamniotic shunt* PE and skin edema on the thorax decreased significantly after shunt placement compared to
Twin-Twin Transfusion Syndrome

Twin-twin transfusion syndrome complicates approximately one in five of all monochorionic, diamniotic twin pregnancies. If of early onset and untreated, severe TTTS is associated with a dismal prognosis with perinatal mortality rates exceeding 90%. Left untreated, severe TTTS presenting in the early second trimester of pregnancy is often associated with significant maternal morbidity and almost universal perinatal loss.

Fetal Surgery

Selective Fetoscopic Laser Coagulation

Selective fetoscopic laser coagulation of vascular anastomoses on the placental surface in severe midtrimester twin-twin transfusion is a potentially corrective and effective, minimally invasive procedure. Endoscopic coagulation of the vascular anastomoses responsible for fetofetal transfusion is done with a neodymium:yttrium-aluminum-garnet (Nd:YAG) laser.54 With the use of local anesthesia and continuous US visualization, a rigid fetoscope 2 mm in diameter, housed in a 2.7 mm cannula, is introduced transabdominally into the amniotic cavity of the recipient twin. A systematic search is made for all vessels approaching or crossing the membrane between the twins, and these are coagulated with an Nd:YAG laser by means of a fiber in the side arm of the cannula.

Perinatal survival is significantly higher when treatment is performed in the early Quintero stages (95% in stage I, 76% in stage II, 70% in stage III, 50% in stage IV) (p = 0.02). Treatment with laser coagulation in 100 consecutive pregnancies with severe second trimester TTTS at median gestational age of 20 weeks (range: 16–26) resulted in mean gestational age of 33 weeks at delivery (range: 18–40). Perinatal survival rate of 70% (139/200), with at least one survivor at the age of 4 weeks in 81% of pregnancies was successfully prevented by OK-432.53

Multiple Pregnancies

Serial Amnioreduction

Removal of excessive amounts of amniotic fluid through serial amniocenteses [amnioreduction (AR)] has been the mainstay of therapy. Under US guidance, a needle is inserted into the amniotic cavity and amniotic fluid drained using suction drainage. A 5 year multicenter, prospective, randomized controlled trial of AR versus selective fetoscopic laser photocoagulation (SFLP) for the treatment of severe TTTS showed that there was no statistically significant difference in 30-day postnatal survival between SFLP or AR treatment for donors at 55% (11 of 20) versus 55% (11 of 20).57 Overall survival (newborns divided by the number of fetuses treated) was not statistically significant for AR at 60% (24 of 40) versus SFLP 45% (18 of 40). The outcome of the trial did not conclusively determine whether AR or SFLP is a superior treatment modality. TTTS cardiomyopathy appears to be an important factor in recipient survival in TTTS.

Septostomy

A single puncture under US guidance is used for the intentional perforation of the intervening twin membrane (septostomy). Of 73 women with TTTS before 24 weeks gestation randomly assigned to serial AR or septostomy, the rate of survival of at least one infant was similar in the AR group compared to the septostomy group [78% vs 80% of pregnancies, respectively; relative risk (RR) = 0.94, 95% CI = 0.55–1.61; p = 0.82]. Patient undergoing septostomy were more likely to require a single procedure for treatment (64% vs 46%; p = 0.04), and offers the advantage of often requiring a single procedure compared to serial AR in the treatment of severe TTTS.58

Umbilical Cord Ligation/Occlusion

Twin Reversed Arterial Perfusion

Twin reversed arterial perfusion (TRAP) occurs only in the setting of a monochorionic pregnancy, and complicates approximately 1% of monochorionic twin gestations, with an incidence of 1 in 35,000 births. Due to the abnormal circulation and the increased demand that the abnormal twin places on the heart of the pump twin, cardiac failure is of primary concern in TRAP sequence. If heart failure is left untreated, the pump twin dies in 50–75% of cases. This is especially true when the acardiac/acephalic twin is greater than 50% of the size of the pump twin by calculated estimated weight.
**Fetal Surgery**

**Fetoscopic Laser Coagulation**

Fetoscopic laser coagulation of placental vascular anastomoses or the umbilical cord of the acardiac twin is an effective treatment of TRAP sequence. This procedure is performed under continuous US guidance and involves the placement of a 3 mm diameter trocar needle into the amniotic space of the pregnant uterus. A 2-mm fetoscope (operative telescope) is then passed into the amniotic space in the umbilical cord and the abnormal fetus examined. Once an adequate site for cauterization is identified, the fetoscope is removed and a 2.7 mm bipolar instrument is introduced into the amniotic space. With US assistance it is guided to the chosen segment of umbilical cord. The umbilical cord is grasped by the bipolar instrument and cauterized, which closes off the blood vessels and blood flow to the abnormal fetus. The umbilical cord is released and again grasped 2–3 cm from the original site and cauterized again as a safety precaution measure. The bipolar instrument is removed and the fetoscope is again placed into the amniotic space and the two surgical sites are carefully examined.

In a prospective multicenter study, percutaneous fetoscopic laser coagulation of placental anastomoses (n = 18) or the umbilical cord of the acardiac twin (n = 42) was performed in 60 consecutive pregnancies at a median gestational age of 18.3 years (range: 14.3–24.7) weeks under local or locoregional anesthesia. Vascular coagulation with arrest of blood flow was achieved in 82% (49/60) of cases by laser alone and in a further 15% (9/60) by laser coagulation in combination with bipolar forceps, survival rate of 80%, and 67% of pregnancies with surviving pump twins going beyond 36 weeks gestation without further complications. Median interval between the procedure and delivery was 18.2 (range: 1.1–25.7) weeks. Median birthweight was 2,720 g (range: 540–3,840 g). Preterm premature rupture of membranes before 34 weeks gestation occurred in 18% (11/60) at a median of 62 (range: 1–102) days after the procedure, only two (3%) women delivered within 28 days of the procedure.

**CONGENITAL DIAPHRAGMATIC HERNIA**

This condition occurs in about one in every 2,500 livebirths. Absence of the diaphragm may occur on the left side or both sides, but the absence on the left side is most common. Correction of congenital diaphragmatic hernia (CDH) in utero has been very dramatic and many lessons in fetal therapy have been learnt.

**Fetal Surgery**

**Fetal Endoscopic Tracheal Occlusion (Clip/Balloon)**

Fetal tracheal occlusion (TO) was developed in an attempt to enhance prenatal lung growth and improve survival in fetuses with severe CDH. This procedure is performed at 23–27 weeks of gestation. Preoperative betamethasone is given to mother for fetal lung compliance. Under general anesthesia through low transverse maternal laparotomy, a 5-mm trocar is inserted into the uterus, and a 4-mm perfusion hysteroscope is guided through the fetal vocal cords under fetoscopic and US guidance. A detachable silicone balloon (target therapeutics) is placed in the fetal trachea midway between the carina and vocal cords, and inflated with iso-osmotic contrast material so as to fill the fetal trachea (0.5 mm diameter) and for at least 2 cm length. Pregnancy is continued.

**Ex Utero Intrapartum Therapy**

At delivery, ex utero intrapartum therapy (EXIT) procedure to ECMO is done. ECMO is a temporary heart/lung bypass machine that some babies with CDH need to help them survive the first a few days or weeks following birth. The EXIT procedure has been designed to provide time to secure an airway while the baby is still attached to the umbilical cord and to preserve uteroplacental gas exchange. The procedure was originally described for delivery of fetuses with diaphragmatic hernia who had undergone in utero tracheal clip application to induce prenatal lung growth. At Cesarean section, a special uterine stapling device is used to open the uterus to prevent bleeding. General anesthesia is used to preserve uteroplacental blood flow, which allows time to perform procedures such as direct laryngoscopy, bronchoscopy, tracheostomy, surfactant administration, cyst decompression and tumor resection, some or all of which may be required to secure the airway and provide adequate ventilation.

The largest reported experience using EXIT to ECMO in the management of severe CDH showed that the procedure is associated with favorable survival rates and acceptable pulmonary morbidity in fetuses expected to have a poor prognosis under conventional management. Of 14 fetuses with severe CDH (liver herniation and a lung/head ratio less than 1.4, percentage of predicted lung volume less than 15, and/or congenital heart disease) that underwent EXIT with a trial of ventilation, fetuses with poor preductal oxygen saturations despite mechanical ventilation received ECMO before their delivery. Three babies passed the ventilation trial and survived, but two of them required ECMO within 48 hours. The remaining 11 fetuses received ECMO before their delivery. Overall survival after EXIT-to-ECMO was 64%. At 1-year follow-up, all survivors had weaned off supplemental oxygen, but 57% required diuretics and/or bronchodilators.

**Potential Risks to the EXIT Procedure**

Bleeding from uterine atony—with expert management and stapling device, the average intraoperative maternal blood loss of around 930 mL, is well within the accepted range for traditional Cesarean section.
Fetal Therapy: Medical and Surgical

A randomized, controlled clinical trial in 24 fetuses with severe left CDH (liver herniated into the thorax and low lung-to-head ratio) to compare survival after endoscopic fetal TO versus standard perinatal care (control) and follow-up of the 16 survivors (9 control, 7 TO) to compare neurodevelopmental, respiratory, surgical, growth, and nutritional outcomes, showed that 1-year and 2-year old, infants with TO were significantly more premature at birth (control vs TO, 37.4 ± 1.0 vs 31.1 ± 1.7 weeks; p < 0.01). There was considerable catch-up growth by age 2 years (growth failure: control vs TO, 22% vs 33%; p = 0.19). There were no differences in other growth parameters. There were also no differences in neurodevelopmental outcome at 1 year and 2 years. Supplemental oxygen at hospital discharge was a significant predictor of worse neurodevelopmental outcome at 1-year and 2-year old (p = 0.05 and p = 0.02, respectively). Fetuses with severe CDH, carries significant risk of chronic morbidity. Factors found to predict death of live-born infants include right-sided hernia, major air leak, earlier gestational age at birth, lower birthweight and lower APGAR scores at 1 minute and 5 minutes.

Wide variations in survival rates are reported throughout literature, reflecting the influence of case selection bias, as well as variable referral policies and management practices. Overall mortality rate for this condition remains high, despite increased prenatal detection, transfer to tertiary institutions for delivery, and advances in neonatal care.

**FETAL TUMORS**

Giant neck masses, such as *cervical teratoma* and *lymphangioma*, can grow to such large proportions that the fetal airway becomes distorted and obstructed. In a small number of patients with cervical teratomas, the mass effect pulls the lungs into the apex of the chest and results in pulmonary hypoplasia.

In addition to obstructing the airway, these giant neck masses can compress the esophagus, resulting in polyhydramnios, which can lead to uterine irritability and preterm labor. Unsuspected obstructive fetal neck masses often prove fatal because of an inability to secure an airway and ventilate the neonate, which results in hypoxia and acidosis. If the delay is longer than 5 minutes, anoxic brain injury may occur. This complication is all the more tragic because most of these children have an isolated anomaly and do well after postnatal resection.

**Treatment**

If the neck mass is small and does not compromise the airway, close US surveillance is warranted to follow the growth of the mass. Polyhydramnios may necessitate amniotic fluid removal in some instance. If polyhydramnios persists and the mass continues to grow, the EXIT procedure is the treatment option of choice.

**SACROCOCCYGEAL TERATOMA**

Sacrococcygeal teratoma (SCT) is the most common tumor of the newborn, occurs in 1 out of every 35,000–40,000 livebirths. They may be cystic, solid or mixed in its sonographic appearance. The heterogeneous appearance of the mass may be due to mixed areas of tumor necrosis, cystic degeneration, hemorrhage or calcification. Most SCTs diagnosed in neonates are not likely to be malignant and the prognosis tends to be good after resection. SCT associated with fetal hydrops can be rapidly progressive and fatal in utero or can lead to polyhydramnios and premature delivery. The high-output cardiac failure is related to “vascular steal” from the high blood flow through the tumor. Fetuses that develop hydrops before 32 weeks, need to be referred to tertiary care center for fetal surgery factor, for either resection, laser vessel ablation, alcohol sclerosis, or cyst drainage.

**Open Fetal Surgery**

Open fetal surgery has been performed in hydropic fetuses or even before hydrops develops. One study of 27/41 SCTs managed antenatally, six underwent TOP, 12 underwent fetal intervention (laser vessel ablation: 4, alcohol sclerosis: 3, cyst drainage: 2, amniodrainage: 2, vesicoamniotic shunt: 1) for fetal hydrops. Of these, three died in utero, nine born alive, median gestational age, 33 weeks (27–37 weeks) but three more died in the neonatal period and six (50%) survived long-term.

Without intervention, 17 infants were born alive at median 38 weeks (26–40 weeks), 16 had excision surgery at median 2 days (1–16 days) with no recurrences on follow-up till median 39 months (8–86 months). Thus, overall survival was 77%, in utero intervention requirement being poor prognostic factor.

Fetal hydrops and placenomegaly may also jeopardize maternal health through the “maternal mirror” syndrome in which the mother’s condition mirrors that of the sick fetus.

**RECENT ADVANCES**

**Hydrocephalus: Neural Tube Defects**

*Hydrocephalus*: It is one of the most common congenital anomalies affecting the nervous system, occurring with an incidence of 0.3–2.5 per 1,000 livebirths. PND is a challenge for the team counseling parents regarding a prognosis for the fetus. True fetal hydrocephalus has a variety of causes: “aqueductal stenosis”,—blockage of cerebrospinal fluid (CSF) passage through the aqueduct of Sylvius; Chiari II malformation syndrome is characterized by myelomeningocele and posterior fossa abnormalities; Dandy-Walker malformation; X-linked recessive hydrocephalus (Bickers-Adam syndrome) characterized by aqueductal stenosis, severe mental retardation. Hydrocephalus may also
be present in a number of major and minor chromosomal aberrations affecting chromosome 8, 9, 13, 15, 18 or 21.

The fetus is followed with serial USs, and if the ventriculomegaly is mild and stable, the fetus is carried to term. Those with mild isolated ventriculomegaly of less than 12 mm have an excellent prognosis. Spontaneous resolution of mild-to-moderate hydrocephalus has been reported in some cases.

A small group of fetuses will undergo rapidly progressive ventricular enlargement, those cases before 28 weeks may have irreversible damage by 32 weeks, with significant adverse outcome. Hence, consideration should be given for early delivery and early shunting, but increased morbidity and mortality data related to prematurity and an increased risk of shunt infection argue against delivery and shunting before 32 weeks. The overall shunt infection rate is 3–10%, but may be as high as 20% in preterm infants. A Cesarean section is preferred, followed by immediate shunt insertion to eliminate vaginal and intensive care unit (ICU) flora exposure and colonization.

Progressive ventricular dilatation greater than 1.5 cm can be offered open surgery in utero, but (Denver) shunts have not been very useful as they got dislodged or obstructed, with poor outcome.67 The International Fetal Medicine and Surgery Society in 1985 agreed to a moratorium on the procedure, so shunting may be considered only in the context of a clinical trial and in a center with extensive experience in fetal surgery.

Open Spina Bifida

This remains a major source of disability despite an overall decrease in incidence. It is estimated that approximately 400 fetal operations have now been performed for myelomeningocele worldwide.68 Despite this large experience, the technique remains of unproven benefit. Preliminary results suggest that fetal surgery results in reversal of hindbrain herniation (the Chiari II malformation), a decrease in shunt-dependent hydrocephalus, and possibly improvement in leg function, but these findings might be explained by selection bias and changing management indications. A randomized prospective trial [the Management of Myelomeningocele Study (MOMS) trial] is currently being conducted by three centers in the United States, and is estimated to be completed in 2009.

FETAL GENE THERAPY

Gene therapy uses the intracellular delivery of genetic material for the treatment of disease. Fetal gene therapy would give another choice following PND of inherited disease, where TOP or acceptance of a treated/affected child is currently the only options. Application of this therapy in the fetus must be safe, reliable and cost-effective. Recent developments in the understanding of genetic disease, vector design and minimally invasive delivery techniques have brought fetal gene therapy closer to clinical practice.

Proof of principle for the hypothesis of fetal gene therapy has been provided during the last 2 years in Mouse Models for Crigler-Najjar disease, Leber’s congenital amaurosis, Pompe’s disease and hemophilia B showing long-term postnatal therapeutic effects and tolerance of the transgenic protein after in utero gene delivery. A wide range of diseases—including cancer, vascular and neurodegenerative disorders and inherited genetic diseases are being considered as targets for this therapy in adults.

Fetal application might prove better than application in the adult for treatment, or even prevention of early-onset genetic disorders such as cystic fibrosis and Duchenne’s muscular dystrophy, because gene transfer to the developing fetus targets rapidly expanding populations of stem cells, which are inaccessible after birth, and use of integrating vector systems results in permanent gene transfer.69

In animal models of congenital disease such as hemophilia, studies show that the functionally immature fetal immune system does not respond to the product of the introduced gene, and therefore immune tolerance can be induced, treatment could be repeated after birth, if that was necessary. However, recently it has also been observed that there is a high incidence of liver tumors after in utero application of an early form of third-generation equine infectious anemia virus vectors with SIN configuration.

In Utero Hematopoietic Cell Transplantation

Goal of in utero hematopoietic cell transplantation (IUHCT) is to achieve therapeutic levels of chimerism, but it typically achieves low-level mixed hematopoietic chimerism.

Prenatal adoptive immunotherapeutic strategies may achieve complete hematopoietic engraftment across full major histocompatibility complex (MHC) barriers when combined with IUHCT, as was seen in a study of 15 fetal mice that were transplanted with a mixture of C57BL/6 (B6) T-cell-depleted bone marrow (TCDBM) cells and splenocytes from B6 mice presensitized to BALB/C alloantigen.70

The splenocytes were preincubated in L-leucyl-L-leucine methyl ester (LLME), to minimize graft versus host disease (GVHD). Full donor hematopoietic chimerism following a single prenatal transplant was achieved in seven transplanted animals. Fully chimeric animals were healthy, without evidence of GVHD, and maintained their engraftment for the duration of the study (48 weeks). Strategies with greater hematopoietic specificity must be developed prior to consideration of clinical application.

CONCLUSION

Fetal Medical and Surgical Therapy is the exciting new field of expertise for limited but expanding indications, being practiced in few, select centers throughout the world. In India,
it is still in its infancy. Slowly, progress is being achieved and there is wide potential for further development and research, though many obstacles need to be overcome.

REFERENCES

SECTION 4

Intrapartum Management
INTRODUCTION
Induction of labor is the nonspontaneous initiation of uterine contraction that results in progressive dilatation and effacement of cervix with descent of the presenting part. It is the initiation of labor by artificial means.

Initiation of labor is usually carried out when continuation of pregnancy endangers the life or well-being of the mother or her unborn child. In current obstetrics practice, induction is usually performed for medical indications, however, sometimes it is performed for patient’s or care provider’s convenience. Despite the safety of induction, a liberal induction policy leads to an increase in operative deliveries creating potential risks for the mother and child.

INCIDENCE OF INDUCTION OF LABOR
Induction rates vary greatly between different countries, population groups and hospitals. National Center for Health Statistics reported that the rate of labor induction increased from 90 per 1000 live births in 1989 to 184 per 1000 live births in 1997.

In 1980, Pearson and Andrews reported induction rate of 4% whilst McNaughton reported it to be 40% in leading institutions of the UK.

Tipton and Lewis (1975) reported the figure to be as high as 55% in nonteaching institutions.

The incidence of induction has increased because of better antepartum and intrapartum surveillance, increased safety of induction, better pharmacological agents for induction and improved neonatal intensive care.

INDICATIONS FOR INDUCTION OF LABOR
The obstetrician who is conducting induction of labor must take into consideration one issue above all others—a detailed risk benefit analysis must indicate that the mother and her fetus are more likely to benefit from than be harmed by the artificial initiation of labor.

For maternal indication or interest, i.e. when continuation of pregnancy endangers mother’s life, induction may be carried out at any stage of pregnancy. However, if it is done for the fetal interests, it is carried out only when fetus is salvageable and safe outside the uterus than inside.

Maternal Indications
- Severe preeclampsia/hypertensive disorders
- Eclampsia
- Intrauterine fetal death
- Accidental hemorrhage
- Premature rupture of membranes (PROM)
- Chorioamnionitis.

Fetal Indications
- Prolonged pregnancy or postdatism
- Fetus with congenital malformations
- Gestational diabetes
- Unexplained intrauterine death in the previous pregnancy
- Maternal hypertensive disorders
- Previous bad obstetric history
• Intrauterine growth restriction
• Various tests for fetal well-being indicating fetal jeopardy, e.g. fetal kick count
  - Nonstress test (NST)
  - Visual acoustic stimulation test (VAST)
  - Color Doppler flow studies
  - Biophysical profile score (BPS)
• Rh-isoimmunization.

### ROLE OF CESAREAN SECTION

Whenever termination of pregnancy is indicated and if vaginal delivery is not possible or contraindicated it would be wiser to do cesarean section, e.g. in case of malpresentation, cephalopelvic disproportion, placenta previa, severe placental insufficiency, uninducible cervix where ripening may not be possible.

### FACTORS INFLUENCING THE OUTCOME OF INDUCED LABOR

The aim of induction of labor is to achieve a safe vaginal delivery for the fetus without causing any harm to the mother. Failed induction of labor may be associated with a poorer neonatal outcome and/or long labor with physical and emotional disturbances for the mother. Failed induction has been defined by Duff et al. (1984) as the failure to enter the active phase of labor after 12 hours of regular contractions.

Failed induction is diagnosed when a woman who was induced did not deliver vaginally in the absence of fetal distress, with acute events like abruption or prolapsed cord and/or failure to progress due to cephalopelvic disproportion and if the patient has not entered the active phase of labor despite adequate management for 12 hours.

The success of any method of induction depends largely on the parity and the state of the cervix at the beginning of induction. The process of prelabor cervical softening, shortening and eventual dilatation is a part of a continuum which culminates in spontaneous labor. The success of any method of induction in particular circumstances depends largely on the point in this continuum at which the efforts of induction start.

Cesarean section rate for failed induction of labor according to parity and cervical score is shown in Table 1.

### METHODS OF CESAREAN PRIMING

During last several years the use of different methods for cervical priming have become popular. During the process of cervical ripening, important structural and chemical changes take place and create a cervix that requires less uterine work to achieve cervical dilatation. A method used for cervical ripening might act as a method to induce labor.

#### Pharmacological Methods of Cervical Ripening

**Prostaglandins**

Prostaglandin E2 (PGE2) has been used through various routes: (a) oral, (b) intracervical and (c) vaginal.

- Oral PGE2 0.5 mg tablet 1 hourly for 4-8 tablets
- Intracervical instillation of PGE2 0.5 mg gel is done taking care that instillation is done below the level of internal os. Many a times besides ripening the cervix, uterine activity is also initiated. In case of poor response, repeat instillation may be done after 12–24 hours. During this period, fetal health surveillance (FHS) should be monitored.

Rafiqul Islam, Sritanu Bhattacharya and Bejoy Lakshmi Goswami (2001) in their prospective study to evaluate efficacy of intracervical PGE2 gel, showed that the mean initial Bishop score of 2.7 improved to 5.6 after 6 hours and to 9.6 after 12 hours in 84% cases. Only 16% cases required re-instillation of PGE2 gel. The success rate in terms of vaginal delivery was 75.6% with initial Bishop score of 1 to 2 and 88% in cases with a score of 3 to 4.

**Oxytocin**

Before introduction of prostaglandins, intravenous (IV)-infusion of oxytocin or buccal oxytocin was the usual method of ripening the cervix. However, IV-oxytocin is a laborious approach necessitating constant monitoring and was requiring 8–15 hours session, spaced over a number of days. Controlled studies have shown it to be a less satisfactory method than local PG application.

### METHODS OF INDUCTION OF LABOR

Historically, a wide variety of mechanical and chemical methods, some of them even bizarre have been used for inducing labor.

Modern obstetrics practice however uses only two broad approaches to induction of labor, namely amniotomy and the use of oxytocic agents. A third method which is widely used, but rarely a formal method of induction is sweeping or stripping of the membranes.

#### Sweeping or Stripping of Membranes

Sweeping or stripping of membranes from the lower uterine segment, which was apparently introduced by Hamilton...
in 1819, has been widely used to induce labor. Although it is rarely considered as method of induction of labor, it is frequently employed at term, especially where indications for induction are not strong enough. Uterine contractions are frequently established following the procedure resulting from the release of endogenous prostaglandins. Swann (1958) reported that when the cervix was favorable 69% of women would go into labor, if procedure was repeated daily for 3 days. It is a simple and useful method for women with a very good cervical score. If the procedure fails to induce labor within a few hours or a day, amniotomy can be performed.

**Amniotomy**

Hind water amniotomy with a Drew-Smythe catheter is hardly used in modern obstetrics. Amniotomy or artificial rupture of forewater, represents one of the most irrevocable interventions in pregnancy and calls for a firm commitment to delivery. Amniotomy alone would result in vaginal delivery in most women with a good cervical score. The main disadvantage being the occasional unpredictably long interval between the procedure and the onset of regular uterine activity. In current practice, amniotomy is usually combined immediately or after a variable interval, with intravenous oxytocin in order to reduce induction delivery interval.

**Use of Oxytocic Agents**

**Oxytocin**

Since the introduction of oxytocin as an intravenous infusion in the 1940s, it has come to be the most widely used method of induction of labor. The principles of current clinical usage of intravenous oxytocin are based on classic studies of Turnbull and Anderson (1968). These studies led to the concept of “titration” of oxytocin dosage in response to uterine contractions (Tables 2 and 3).

Customarily oxytocin dosage titration is based on the clinical feedback of labor ward staff on the characteristics of uterine contractions, their intensity, duration and frequency. There is still wide variation in the use of oxytocin, especially with regard to the initial starting dose, dose increment, rate of escalation and use of delivery system. Infusion solution varies from oxytocin 2.5–5 units per 500 mL of 5% glucose or Ringer’s lactate. The starting dose is usually 1–4 mU/minute and the dosage is subsequently increased every 30 minutes till effective contractions are established.

Throughout FHS are carefully monitored. Amniotomy is usually combined with oxytocin infusion during induction. Most obstetricians start with amniotomy followed immediately or within a few hours by oxytocin infusion. In cases with a high presenting part, it may be prudent to start the oxytocin infusion first and delay the amniotomy till effective contractions are established.

**Prostaglandins**

The most commonly used prostaglandins for cervical ripening and induction of labor are PGE2 preparations, which contain Dinoprostone. Two forms of PGE2 are available:

1. Dinoprostone tablets for oral use
2. Dinoprostone gel for intracervical instillations. Several randomized prospective studies have shown that PGE2 is more effective than oxytocin infusion for promoting vaginal birth. Oral PGE2 is started at a dose of 0.5 mg 1 hourly. The treatment is continued till labor is established or maximum of 8 tablets. Intracervical PGE2 may be repeated after 12–24 hours.

**Misoprostol**

Misoprostol (PGE1) is used for induction of abortion. In smaller doses, i.e. 25 µg it is also tried for induction of labor. However, the Cochrane Collaboration cites numerous reports if uterine rupture and fetal distress involving the drug use. The group concluded “It cannot be recommended for routine use at this stage.” The American College of Obstetricians and Gynecologists (ACOG) too issued guidelines in 2002 discouraging the use of misoprostol.

**Risks and Complications of Induction of Labor**

Induction of labor is a potentially hazardous obstetric intervention. There are three broad groups of risks associated with induction of labor:

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### Table 2: Calculation of the dose delivered in milliunits (mU) and correlation with drop rate per minute

| Units of oxytocin mixed in 500 mL Ringer’s solution (1 unit = 1000 milliunits) (mU) | Drops per minute (15 drops = 1 mL) |
|---|---|---|
| | 15 | 30 | 60 |
| 1 | 2 | 4 | 8 |
| 2 | 4 | 8 | 16 |
| 8 | 16 | 32 | 64 |

### Table 3: Convenient oxytocin regimen

<table>
<thead>
<tr>
<th>Dose of oxytocin</th>
<th>Solution used</th>
<th>Escalating drop rate at intervals of 20–30 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>To start with 1 unit</td>
<td>500 mL Ringer’s solution</td>
<td>15-30-60</td>
</tr>
<tr>
<td>If no response—2 units</td>
<td>-do-</td>
<td>-do-</td>
</tr>
<tr>
<td>If still no response—8 units</td>
<td>-do-</td>
<td>-do-</td>
</tr>
</tbody>
</table>
1. The risk associated with terminating pregnancy artificially before the spontaneous onset of labor. These are:
   a. Failed induction leading to cesarean section
   b. Inadvertent preterm delivery.
2. Risks associated with artificial stimulation of uterine contractions, hyperstimulation which could lead to fetal distress, fetal death, rupture of uterus, precipitate labor with injuries.
3. Risks associated with specific method of induction:
   a. Amniotomy leading to cord prolapse, infection, rarely abruption in case of hydramnios.
   b. Use of oxytocin has been associated with an increased incidence of neonatal jaundice; prolonged infusion of relatively high doses of oxytocin in dilute solution can lead to maternal water intoxication.
   c. Use of prostaglandins can lead to gastrointestinal (GI) upsets, bronchospasm, pyrexia.

The most important decision to be made when considering induction of labor is whether or not the induction is justified.

“The spontaneous onset of labor is a robust and effective mechanism......and should be given to operate on its own. We should only induce labor when we are sure that we can do better.”

—Turnbull (1976)

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INTRODUCTION

Management of labor continues to be an area of keen debate even in present day obstetric practice. Widely divergent views are held amongst specialists with regard to the philosophy of labor. This is reflected in the attitude of obstetricians toward the mother in labor under his/her care. The views held by obstetricians regarding the place for delivery-home/nursing home/institution resulted in the “risk approach” and the separation of cases into low risk and high risk cases. All high risk cases being encouraged to book for institutional confinement. However, there is always an ever lurking danger of a low risk patient showing an unexpected turn of events and assuming alarming features necessitating special care.

There has always been a strident call from the women’s lobby as to why such a natural and physiological phenomenon like childbirth has been so medicalized that human childbirth has assumed worrisome proportions. Women are also questioning the rising incidence of cesarean section in present day practice, and wondering whether all the monitoring systems in place in modern obstetric practice are truly justified.

Partographic Documentation

Partographic documentation has been accepted as a standard method of clinical monitoring of labor. It has promoted the concept of “active management of labor” and shown the benefits of this approach in improving obstetric outcome. However, this can be practiced only in an institutional set-up.

Opinions regarding pain relief during labor also excite divergent and widely polarized views. There are the protagonists of the “laissez-faire” policy of leaving things entirely to nature. Many mothers do not wish that there should be any attenuation of the peak emotional experience and reality at the time of childbirth; they look forward to the event of the baby emerging through the birth canal, listening to the first cry and early bonding. Others, less tolerant seek relief in analgesics and epidural analgesia. In modern practice, obstetricians are witnessing an ever increasing demand for pain relief amongst parturients.

“The delivery of an infant into the arms of a conscious and pain free mother, is the most exciting and rewarding moments of the medicine.”

Obstetricians have also changed their attitudes toward labor. There is less of rigidity and regimentation, this is evident by the fact that women are now allowed to have a companion present during her delivery. She is allowed ambulation until she has progressed well into labor, birthing postures and procedures also reveal a more tolerant approach by the profession; similarly the attitude toward a routine episiotomy in all primigravida has also undergone a change, so that obstetricians are resorting to it less frequently than before.

ADMISSION PROCEDURE

The admission procedure should be discussed with the patient during the antenatal visits. She should be asked to report for admission when she starts getting pains which seem to be increasing in frequency/intensity, if there is presence of show or any leaking of the amniotic fluid.

In the admission room: The attending doctor checks her antenatal chart and makes note of any high risk factors. Special orders for any high risk factors should be clearly outlined and communicated to all staff members on duty.

On interrogation and examination, the following points are documented:
**History**

The gestation maturity as calculated on the basis of her menstrual dates.
- Time of onset of labor pains, their frequency, and intensity
- Presence of show/leaking
- Time of consuming the last meal.

**General Examination**

- Document her total peripheral resistance and blood pressure on admission
- Auscultate the heart sounds and lungs
- Check for clinical pallor—tongue/conjunctivae.

**Obstetric Examination**

- Check the fundal height in centimeter
- Palpate the abdomen for fetal presentation and position
- Note the position of the anterior shoulder and auscultate the fetal heart rate (FHR)
- Observe the uterine contractions (palpation) for intensity, duration and frequency. Note alteration of FHR at height of pains and recovery time
- Perform a vaginal examination with full aseptic precautions and document the following:
  - The position of the cervix, its dilation in cm and extent of effacement (Table 1)
  - Presence or absence of the membranes, if leaking is present
  - Nature of amniotic fluid—clear/meconium present
  - The station of the presenting part, degree of flexion and how well it is applied to the fetal head
  - Assess fetopelvic relationship. Try to rule out any disproportion.

**Admission Orders**

The conventional enema and vulval shaving are often waived; however, it is advisable to clip the hair short, a dulcolax suppository ensures satisfactory bowel evacuation, this prevents soiling of the perineum during birth of the baby.
- A warm water bath, followed by a clean linen gown
- A sterile pad should be given and the patient admitted to the waiting ward. She should be encouraged to walk around, partake of easily digestible foods and clear fluid nourishment
- The FHR should be checked every hour. An admission documentation of the electronic FHR recording (Admission-test), if normal, is very reassuring of how the baby will fare during the course of labor. An abnormal tracing is often a harbinger of adverse events that are likely to arise, and alert the clinician to be very careful during the course of labor
- When the frequency of pains increases to 3/10 minutes lasting for 30–40 seconds, an internal examination to check the progress of labor is desirable. Should the patient have entered the “active phase” of labor, it is essential that the patient be transferred to the labor room for closer observation, and administration of any medication that may be necessary to procure pain relief.

**First Stage of Labor**

Clinical observations should be meticulous when the patient enters the active phase of labor. At this stage the patient complains of regular pains of good intensity every 3–4 minutes lasting for about 30–40 seconds. Often there is presence of show or passage of fluid discharge, the intensity of pain increases sufficiently, so that most patients generally ask for pain relief at this stage. The cervix is about 3–4 cm dilated and well-effaced.
- Commence a partogram and document all labor events, clinical observations and medications on this chart (Fig. 1)
- Clinical FHR monitoring is an ongoing observation of human fetal physiology, for years, obstetricians have depended on it for assessing fetal health during parturition, even in the present times, this method of monitoring the fetal status in low risk cases continues to provide satisfactory results; however, in high risk...

---

**Table 1: Bishop’s scoring**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervix Dilatation (cm)</td>
<td>Closed</td>
<td>1–2</td>
<td>3–4</td>
<td>5+</td>
</tr>
<tr>
<td>Effacement (%)</td>
<td>0–30</td>
<td>40–50</td>
<td>60–70</td>
<td>≥ 80</td>
</tr>
<tr>
<td>Consistency</td>
<td>Firm</td>
<td>Medium</td>
<td>Soft</td>
<td>-</td>
</tr>
<tr>
<td>Position</td>
<td>Posterior</td>
<td>Midline</td>
<td>Anterior</td>
<td>-</td>
</tr>
<tr>
<td>Head-Station</td>
<td>– 3</td>
<td>– 2</td>
<td>– 1, 0</td>
<td>+1, + 2</td>
</tr>
<tr>
<td>Cervical length (cm)*</td>
<td>&gt; 4</td>
<td>(2–4)</td>
<td>(1–2)</td>
<td>&lt; 1</td>
</tr>
</tbody>
</table>

Total score = 13; Favorable score = 6 to 13 and Unfavorable score = 0 to 5

*In modified Bishop’s scoring, cervical length replaces effacement (cm)
mothers—electronic FHR surveillance (cardiotocography) provides a superior means of assessing fetal oxygenation status

- Cardiotocography recordings should be commenced if desired (continuous or interrupted)
- Fetal heart rate recorded periodically (auscultation/cardiotocography) every 15–30 minutes until she reaches the second stage of labor
- An amniotomy is desirable. This accelerates labor, and clear amniotic fluid is reassuring to the obstetrician. However, if there is presence of meconium, it puts the attending staff on guard
- The choice of analgesia is left to the mutual decision of the patient and the attending obstetrician
- When the patient experiences strong repetitive contractions, and experiences bearing down pains, she is often in the second stage of labor.

**Second Stage of Labor**

The onset of the second stage of labor is recognized by the bearing down efforts of the patient, often the membranes rupture spontaneously at this time. Vaginal examination confirms full dilatation of the cervix. The membranes should be ruptured if as yet intact. Observe for passage of meconium, exclude cord prolapse/compound presentation. Note the position of the occiput in cephalic presentations and the degree of head flexion. Check for disproportion and document the station of the presenting part. The FHS is checked, the patient should be transferred to the labor ward for close monitoring.

The patient is encouraged to assume the lateral position, when she feels the urge to bear down and the perineum begins to stretch, the patient is encouraged to lie down on her back, she is encouraged to bear down with the pains, the FHS are checked after each pain and the perineum observed, the introitus progressively opens up, and the perineum is put on an increasing stretch. Obstetricians prefer to avoid the use of episiotomy; however, in case of impending tear, an episiotomy performed after local infiltration with 1% xylocaine for local anesthesia prevents bad perineal tears. After the head is born, the mouth is cleaned, a finger passed around the fetal neck to detect presence of nuchal cord loops, if present—the cord loop should be loosened or divided between clamps. With further pains the shoulders and the trunk follow. In modern times, women are encouraged to assume the positions of their choice at the time of child birth; these may require the obstetrician to adapt to the patient's needs.

**Third Stage of Labor**

Modern management of the third stage of labor involves "active management" of the third stage of labor. This method employs the use of oxytocic drugs to hasten placental separation and expulsion and to minimize the blood loss attending the third stage of labor. The drugs used include the following:

- Injection methergin (methyl ergometrine) 0.25 mg slowly intravenously (preferably diluted) at the time of crowning of the fetal head/delivery of the anterior shoulder.
- Injection oxytocin (pitocin) 10 units diluted in 10 mL of physiological saline/5% glucose into the umbilical vein, soon after the baby is born and the cord clamped and cut
- Injection PGE₂ 125 µg intramuscularly soon after birth.

The placenta usually separates within a few minutes, and is delivered by controlled cord traction. The blood loss is often minimized to about 50 mL. Details of commonly used uterotonic agents for the “Active Management of the Third Stage of Labor” are shown in Table 2.

**Active management of third stage of labor:**

**Principle:** To excite powerful uterine contractions within 1 minute of delivery of the baby (WHO) by giving parenteral oxytocics.

**Advantages:**

- Minimize blood loss in third stage approximately to one-fifth
- To shorten the duration of third stage of labor to half

![Figure 1: Partogram I](image-url)

<table>
<thead>
<tr>
<th>Time</th>
<th>2 pm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of labor</td>
<td>6 hrs</td>
</tr>
<tr>
<td>Frequency of contractions</td>
<td>2–3/10 min</td>
</tr>
<tr>
<td>Duration of contractions</td>
<td>30 sec</td>
</tr>
<tr>
<td>Intensity of contractions</td>
<td>Moderate</td>
</tr>
<tr>
<td>Station of Pr. Part</td>
<td>0</td>
</tr>
<tr>
<td>Amniotic membranes</td>
<td>Intact</td>
</tr>
<tr>
<td>Liquor on ARM</td>
<td>Clear</td>
</tr>
<tr>
<td>FHS</td>
<td>140 bpm</td>
</tr>
</tbody>
</table>

**Medications**

- 5% glucose infusion
- Inj. Tramadol 50 mg + Inj. Drotin 80 mg IM
- Inj. Pentazocine HCl 6 mg + Inj. Diazepam 2 mg slow IV—oral Primiprost Tab. 1 hourly
Disadvantage: Slight increased incidence of retained placenta and consequent increased (1–2%) incidence of manual removal.

Components:
- Use of oxytocics within 1 minute following the delivery of baby.
- Controlled CORD traction.
- Uterine massage.

**PARTOGRAPHY**

The concept of recording the progress of labor graphically introduced by Friedman (1955) resulted in the construction of the now famous “Sigmoid” curve known as the “cervical dilatation—time curve” (Fig. 2). Philpott and Castle (1972) demonstrated the importance of its clinical application in developing countries to identify “dystocic labors.” The partogram has now become an accepted mode of documenting the events in labor. In India, a partogram for primigravidae based on Indian data was created by Daftary and Mhatre (1977); this nomogram can be utilized for comparison with the patient’s partogram to detect early deviation from the normal expected progress in labor and to alert the attending clinician in good time about possible developing problems, to enable him to institute timely corrective measures.

Similar “nomograms” created by Studd JW (1973) has helped to identify problems early, to seek timely help/transfer the patient to a better facility in time. The incidence of maternal morbidity/mortality has thus been reduced considerably, and at the same time the perinatal outcome has been improved. This policy has not increased the rates of cesarean sections unduly (Fig. 3).

**ACTIVE MANAGEMENT OF LABOR**

The concept of “active management of labor” first advanced by O’Driscoll & the Irish master has received wide acceptance. This policy depends upon the vigilant observation of the progress of labor and timely intervention when delay is detected. It requires the cooperation of a well-trained nursing staff and experienced clinicians. It is well-established that prolonged labors predispose to infection, dehydration, ketosis, exhaustion and disillusionment in the mother, as well as fetal distress and increased morbidity in the unborn baby. The Irish workers have demonstrated that with the implementation of this policy, most primigravidae can be delivered within 12 hours of admission and multiparae within 6 hours. Obstetric
Fig. 3: Partogram (modified WHO) representing graphically the important observations in labor. The cervix dilatation and descent of head are shown in relation to alert and action lines. Intensity and duration of uterine contraction are shown with shades.
outcome is significantly improved, maternal morbidity reduced, perinatal outcome improved and the rates of cesarean sections reduced. The widespread use of amniotomy and oxytocics to optimize pains coupled with judicious use of analgesics help to ensure steady progress of labor, reduce the risks of dysfunctional labor and enable early identification of emerging obstetric problems.

**Obstetric Analgesia**

Women have suffered from the pangs of childbirth through centuries, enlightened physicians have been concerned with alleviating labor pain; however, the attitude toward providing pain relief has been conflicting. Many of the drugs used earlier have been known to cause respiratory depression in the newborn and require to be used with caution. Epidural anesthesia provides excellent relief without unduly jeopardizing the labor outcome. Pain relief is known to allay fear and anxiety and provide a more favorable environment for improved obstetric outcome. For the mother it provides relief from pain, controls alterations in circulation, ventilation and undue muscular efforts. It ensures better patient cooperation. For the fetus, labor analgesia means shorter and less traumatic labors, protection against hypoxia and fetal depression at birth, and protection against needless instrumental-assisted delivery necessitated by maternal distress. To the obstetrician, it provides a better control over events emerging during the course of labor, reduces the pressures from the patient and relatives to intervene, and ensures optimum conditions to prevail at the time of childbirth. Epidural anesthesia requires the services of a trained anesthesiologist; it can be employed in institutional deliveries, requires qualified staff for constant supervision and is expensive. Such facilities are available in a few institutions in metropolitan towns. For the vast majority of women in our country—this is still a distant dream. However, indigenous protocols to provide pain relief in labor have been developed in our country, which can be adopted by obstetricians in their own practices to provide pain relief in labor, ensure freedom from fear of childbirth and improve obstetric outcome. One such protocol developed at the Nowrosjee Wadia Maternity Hospital in Mumbai, and extensively evaluated in our country by the author and his colleagues aims at the use of drugs for pain relief programmed to be used in accordance with the progress already achieved, so that the excruciating pain of labor is mitigated, cervical dilatation is facilitated, and the incidence of dysfunctional labors is reduced. An improved obstetric outcome is obtained by adopting the principles of programmed labor, whilst at the same time reducing the need for obstetric interventions.

**PROGRAMMED LABOR**

This protocol developed by Daftary SN et al. (2001), rests on three pillars as outlined under.

- Ensure adequate pains—amniotomy, and/or use of prostaglandins/oxytocin infusion to ensure that the patient gets three sustained contractions/10 minutes intervals/lasting 35–45 seconds. The FHR pattern is satisfactory and the uterus relaxes well between pains.
- Ensure pain relief—epidural anesthesia may be used, if available. In absence of this facility, suitable combination of analgesic drugs can be gainfully employed to provide reasonable pain relief, freedom from anxiety and patient cooperation. When the patient is in established labor and reaches about 4.0 cm dilatation, the patient is closely observed in the labor ward, and partographic documentation implemented.
- Set-up an intravenous infusion line using ringer lactate solution. Administer a small dose of 2.0 mg diazepam + 6.0 mg pentazocine diluted in 10 mL of saline, slow intravenously as a bolus to initiate pain relief. This dose is so small that it does not affect the mother or the fetus adversely. Now administer injection tramadol 50.0 mg intramuscularly in thin patients. If the patient’s weight is over 60 kg, increase the dose to 1.0 mg/kg maternal body weight. Along with the tramadol, combine it with a smooth muscle relaxant (drozin, anafortan, buscopan epidosin as per clinician’s choice). The combined drug effect provides excellent pain relief and facilitates cervical dilatation. The labor progresses satisfactorily until the head comes down onto the pelvic floor. At this time the cervix is close to full dilatation and the station of the presenting part in the lower pelvic strait. Should the pains be strong and distressing, it is safe to administer ketamine in analgesic dose not exceeding 0.5 mg/kg maternal body weight after proper counseling. Generally in practice, an initial dose of 10 mg administered diluted and slowly often suffices. This medication provides marked analgesia and amnesia. The drug is short acting (effect wears off in about 20 minutes), in case further pain relief is required, a top-up-dose of half the initial loading dose may be repeated as required. Although, ketamine crosses over into the fetal circulation, it is rapidly metabolized and does not depress the respiratory center. After birth, if the baby does not cry lustily, ventilatory support with bag and mask is generally all that is required. Until the team of clinicians gets familiar with the use of ketamine, it is recommended to have an anesthesiologist stand by. During the third stage of labor, the practice of active management is recommended.
- After expulsion of the placenta, inspect the birth canal and perineum for any injuries and repair the same. A single dose of injection ketamine after delivery permits easy
examination of the birth canal and permits easy surgical repair of episiotomy/tears and lacerations.

Clinical Experiences with Programmed Labor

- **Programmed labor**: Daftary SN,11 Desai SV, Nanavati MS, Bhide AG, Patki AS, and Levi JM (Mumbai). They analyzed the experiences of their pooled data based on labor outcome of low risk patients, which included 800 primigravidae and 600 multigravidae.

  They reported normal vaginal deliveries in 90.4% of primiparas and 94.5% of multiparas, low forceps and ventouse assistance in 9.59% of primis and 3.5% of multiparas. The cesarean section rate in primigravidae was 9.6% and in multiparae it was 4.5%. The average duration of labors in primigravidae was 9.1 hours and in multiparae it was 5.8 hours. The mean rate of cervical dilatation during active labor was 2.2 cm/hour in primis and 2.8 cm/hour in multiparas.

  Partograms revealed the duration of the active phase of labor to be 3.5 hours in the primigravidae and 2.4 hours in multipaer. The third stage of labor lasted between 4 minutes and 6 minutes. The APGAR scores at the end of 5 minutes was less than 7 in 1.2% of primis and in less than 0.3 of multis. There was no perinatal loss.

- Hema Divakar12 and Anupama Patil of Bangalore analyzed their data on cases treated as per the programmed labor protocol and concluded that 85% of patients experienced substantial pain relief. The duration of labors was much curtailed, the obstetric interventions did not increase, they reported a cesarean section rate of 4.5% and a vaginal assistance rate of 6%, the neonatal outcome was satisfactory, and there was no perinatal loss. Maintenance of the partogram helped in early identification of emerging obstetric problems, alerting the clinician to adopt timely corrective measures.

- **A clinical study of programmed labor and its outcome**: Chauhan R, Gupta A13 from Jubbalpore, reported on their experience of 75 cases which included 25 primiparae and 50 multiparae. They reported the mean time for onset of analgesia to be around 16 minutes. Satisfactory pain relief was experienced by 88% of primiparae and 92% of multiparae. The mean duration of the first stage of labor was 3.4 +/- 1.55 hours in primis and in multiparae it was 2.50 +/- 1.25 hours which was significantly lower than in controls observed as 4.50 +/- 1.20 hours in primis and 3.58 +/- 1.47 hours in multis. In their study, 92% of primiparae and 98% of the multiparae had normal vaginal delivery. The duration of the third stage was 3–5 minutes. The total blood loss was much reduced. The APGAR scores were satisfactory in all patients in the treatment group.

- Priyanki Kadakia14 and Ragini Verma undertook a study of 90 parturients adopting the programmed labor protocol for labor analgesia at Government Medical College Surat. A summary of their experience is presented:
  - The study included 90 cases.
  - Sixty-two percent of the patients were aged between 17 years and 25 years.
  - Mean weight of the patients was 52.3 kg
  - Primiparas accounted for 49 cases and multiparae were 41.
  - 95.5% of cases delivered within 4 hours of commencing analgesia.
  - Mean time of onset of analgesia was 3.56 minutes.
  - 74.4% patients experienced substantial pain relief whilst in 10% pain relief was excellent.
  - 97.8% patients had normal deliveries.
  - The rate of cervical dilatation achieved was 1.9 cm/hour in primigravidae and 2.8 cm/hour in multiparae.
  - The FHRs and APGAR scores after birth remained unaffected.
  - Maternal vital parameters were unaffected.
  - Minor side effects like nausea, vomiting, drowsiness, and malaise were observed in 23 (25.5%) cases. None suffered any serious side-effects.

  The ease of administration, the need for minimal patient monitoring with systemic analgesia made programmed labor protocol highly acceptable. In the year 2005, FOGSI President Dr SV Desai propagated the theme of “Optimizing Labor outcome for safe motherhood” based on the above protocol using the Indian partogram. The illustrative cases shown below amply demonstrate the value of using the above management protocol.

**ILLUSTRATIVE CASES**

**Case 1**

Mrs D Khanna, aged 21 years, Primigravida—38 weeks pregnant, vertex (head down) position. No antenatal risk factors. On 12/5/03 at 10.00 am—labor induced with cerviprime gel. Admitted in labor at 2.00 pm. Patient given oral tablet of primiprost at 1 hourly interval to augment labor. At 4.00 pm, patient entered the “active phase” of labor. Further progress of labor recorded on the “partogram”. Figures 1, 2 and 4 show partograms at different stages in labor.

**Conclusion**

Short labor, pain relief—substantial; amnesia: fair; short third stage, reduced blood loss. Mother and baby well.

**Case 2**

Mrs M Pujari aged 25 years, Primigravida, 39 weeks pregnant, vertex (head down) position. No antenatal risk factors. On 22/11/02 at 5.00 am labor induced with cerviprime gel. Labor pains commenced at 8.00 am. Patient entered the “active phase” of labor at 9.30 am.

**Charting of Partogram Commenced**

All further events are shown on partograms (Figs 5 to 7).
Progress of labor

- **Time:** 4.30 pm
- **Duration of labor:** 8.5 hrs
- **Frequency of contractions:** 4/10 min
- **Duration of contractions:** 45 sec
- **Intensity of contractions:** Strong
- **Station of Pr. Part:** +3
- **Amniotic membranes:** Absent
- **Liquor:** Clear
- **FHS:** 136 bpm
- **Patient made to bear down**
- **Normal delivery at 4.45 pm**
- **Inj. Prostodin 125 mg IM**
- **Male baby, weight 3.2 kg, APGAR 8/10 at 1 min 10/10 at 5 min**
- **Placenta expelled at 4.48 pm**
- **Blood loss < 100 mL. Inj. Ketamine 15 mg IV**
- **Episiotomy sutured**

Fig. 4: Partogram III

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Progress of labor

- **Time:** 9.30 am
- **Duration of labor:** 4 hrs
- **Frequency of contractions:** 2–3/10 min
- **Duration of contractions:** 35 sec
- **Intensity of contractions:** Moderate
- **Station of Pr. Part:** +1
- **Amniotic membranes:** Present
- **Liquor ARM:** Clear
- **FHS:** 136 bpm
- **Medications—**
  - **IV 5% glucose infusion**
  - **Inj. Tramadol 50 mg**
  - **Inj. Anafortan 50 mg IM**
  - **Inj. Pentazocine 6 mg +**
  - **Inj. Diazepam 2 mg slow IV**

Fig. 5: Partogram IV

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Progress of labor

- **Time:** 11 am
- **Duration of labor:** 6 hrs
- **Frequency of contractions:** 3–4/10 min
- **Duration of contractions:** 40 sec
- **Intensity of contractions:** Strong
- **Station of Pr. Part:** +2
- **Amniotic membranes Absent, Liquor:** Clear
- **FHS:** 144 bpm
- **Medications—**
  - **Inj. ketamine 25 mg IV**

Fig. 6: Partogram V
CHAPTER 32
Modern Management of Labor

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Table 3: Diagnostic questions in cases of suspected dysfunctional labor

<table>
<thead>
<tr>
<th>Question</th>
<th>Possible pathology</th>
<th>Treatment options</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Is patient in true labor?</td>
<td>Prelabor or false labor</td>
<td>Serial observation, simple enema, sedation</td>
</tr>
<tr>
<td>2. Is the progress tardy?</td>
<td>Inefficient pains, disproportion</td>
<td>Partogram shows tardy progress in active phase</td>
</tr>
<tr>
<td></td>
<td>Occipito-posterior position and fetal macrosomia</td>
<td>Consider oxytocin drip, amniotomy, analgesia LSCS for disproportion</td>
</tr>
<tr>
<td>3. Are the membranes ruptured?</td>
<td>Chorioamnionitis, cord prolapse</td>
<td>Antibiotics, labor induction, LSCS</td>
</tr>
<tr>
<td>4. Is there an undiagnosed occipito-posterior position?</td>
<td>Android/anthropoid pelvis</td>
<td>Trial of labor, oxytocin stimulation, face to pubes delivery forceps/ventouse, LSCS</td>
</tr>
<tr>
<td>5. Is the fetus macrosomic generalized/locally?</td>
<td>Fetal weight &gt; 3,800 g</td>
<td>Trial labor/vaginal-assisted delivery/cesarean section</td>
</tr>
<tr>
<td></td>
<td>Diabetic mother, postdatism</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hydrocephalus, sacral tumor</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Distended fetal bladder</td>
<td></td>
</tr>
<tr>
<td>6. Is there an obstructed labor?</td>
<td>Contracted pelvis, cephalopelvic disproportion, fetal malpresentation/malposition, Mullerian anomaly, pelvic neoplasm, placenta previa</td>
<td>Avoid traumatic vaginal delivery/operatoric for cesarean section</td>
</tr>
<tr>
<td>7. Are the pains inefficient?</td>
<td>Hypotonic uterine activity</td>
<td>Consider use of PG/oxytocin infusion</td>
</tr>
</tbody>
</table>

Abbreviation: LSCS, lower (uterine) segment cesarean section

Conclusion

Patients partogram to the left of the nomogram indicates rapid progress and also helps in the following:
- Marked reduction in duration of labor
- Patient experienced considerable pain relief
- Patient able to bear down and deliver normally
- Marked reduction in third stage of labor
- Minimal blood loss in the third stage
- Condition of mother and baby satisfactory after delivery
- Minimal memory of labor events.

DYSFUNCTIONAL LABOR

This is diagnosed when the patient in active labor fails to accomplish cervical effacement and dilatation at an acceptable rate in the first stage of labor, or fails to accomplish descent of the presenting part at an acceptable rate in the second stage of labor. Before making any treatment plans, a series of diagnostic questions need to be answered as summarized in Table 3.

REFERENCES


INTRODUCTION

With the invention of the stethoscope (1810) physician could hear the fetal heart beat. However, the instrument could not detect subtle changes or provide continuous surveillance. These deficiencies were overcome in 1968 with the development of electronic fetal monitoring (EFM). The hope was that it would help physicians to diagnose fetal hypoxia, or lack of oxygen in time to prevent perinatal neurologic damage. By the early 1990s, more than 75% of the nation’s birth attendants had switched from intermittent auscultation (IA) to EFM.¹

Intrapartum fetal monitoring can be performed by:
1. Intermittent auscultation
2. Electronic fetal monitoring:
   • External (indirect) (Fig. 1)
   • Internal (direct) (Fig. 2)
3. Other intrapartum fetal monitoring techniques:
   • Fetal scalp blood sampling (FBS)
   • Scalp stimulation
   • Vibroacoustic stimulation
   • Fetal pulse oximetry
   • Fetal electrocardiography

Fig. 1: External monitoring uses two belts placed around the woman’s abdomen

Fig. 2: Internal monitoring uses two devices placed inside the uterus. One is attached to the fetus
consensus regarding the definition of “fetal distress” has not been established. Hypoxia with acidosis (often referred to as asphyxia although originally the term simply meant born without an evident pulse, from the Greek asphyxos) is widely perceived to be the most important cause but does not have a simple relationship with condition of baby at birth. According to ACOG (1991), birth asphyxia is defined as “intrapartum hypoxia sufficient to cause neurologic damage” as evidenced by:

- Umbilical artery pH less than 7.00
- Five-minute Apgar score less than or equal to 3
- Moderate or severe neonatal encephalopathy
- Multiorgan dysfunction [e.g. cardiovascular system (CVS), renal, pulmonary].

Birth asphyxia has also been implicated as a cause of cerebral palsy, although most cases of cerebral palsy occur in persons without evidence of birth asphyxia or other intrapartum events. The ACOG Task Force (2003) on neonatal encephalopathy and cerebral palsy stated the criteria to define an acute intrapartum event sufficient to cause cerebral palsy.

### Essential Criteria (Must Meet all Four)

- Evidence of metabolic acidosis in fetal umbilical cord arterial blood obtained at delivery (pH < 7 and base deficit ≥ 12 mmol/L)
- Early onset of severe or moderate neonatal encephalopathy in infants born at 34 or more weeks of gestation.
- Cerebral palsy of the spastic, quadriplegic or dyskinetic type.
- Exclusion of other identifiable etiologic disorders such as trauma, coagulation, infectious conditions or genetic causes.

Criteria that collectively suggest an intrapartum timing (within close proximity to labor and delivery, e.g. 0–48 hours) but are nonspecific to asphyxial insults:

- A sentinel (signal) hypoxic event occurring immediately before or during labor.
- A sudden and sustained fetal bradycardia or the absence of FHR variability in the presence of persistent, late or variable decelerations, usually after a hypoxic sentinel event when the pattern was previously normal.
- Apgar scores of 0–3 beyond 5 minutes.
- Onset of multisystem involvement within 72 hours of birth.
- Early imaging study showing evidence of acute nonfocal cerebral abnormality.

The fetus does not become acidotic as soon as the FHR becomes abnormal. Fleischer and associates showed that a well-grown fetus can cope with hypoxic stress for as long as 90 minutes before the pH of fetal blood starts to fall. Thus, a normal fetal scalp blood pH 60 minutes after the cardiotocography (CTG) has become abnormal does not indicate that the abnormality is a “false positive.”

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### Table 1: Guidelines for methods of intrapartum fetal rate monitoring

<table>
<thead>
<tr>
<th>Surveillance</th>
<th>Low-risk pregnancies</th>
<th>High-risk pregnancies</th>
</tr>
</thead>
</table>

**Acceptable methods**

- Intermittent auscultation: Yes
- Continuous electronic monitoring (internal or external): Yes

**Evaluation intervals**

- First-stage labor (active): 30 minutes
- Second-stage labor: 15 minutes

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#### LIMITATIONS

- Intrapartum Doppler velocimetry
- Cord blood gases (CBGs) for acid-base assessment (Table 1).

#### ELECTRONIC FETAL MONITORING

**External or Direct Monitoring**

Since its inception, the primary objective of EFM has been to identify the fetal distress so that measures might be taken to avert permanent fetal damage or death. However, the clear
Indications for Electronic Fetal Monitoring


- **Antenatal maternal conditions:**
  - Hypertension/hypertension with adverse condition
  - Diabetes
  - Antepartum hemorrhage
  - Other maternal medical disease
- **Antenatal fetal conditions:**
  - Growth-restricted fetus
  - Prematurity
  - Oligohydramnios
  - Abnormal umbilical artery Doppler velocimetry
  - Isoimmunization
  - Multiple pregnancy
  - Breech presentation
- **Intrapartum maternal conditions:**
  - Vaginal bleeding in labor
  - Intrauterine infection
- **Labor:**
  - Previous cesarean section
  - Prolonged membrane rupture
  - Induced labor
  - Augmented labor
  - Hypertonic uterus
- **Fetal conditions:**
  - Meconium-stained amniotic fluid
  - Post-term pregnancy
  - Suspicous (nonreassuring) FHR on auscultation.
- **Fetal health surveillance may not be warranted, if:**
  - Extreme prematurity (< 23 weeks)
  - Lethal fetal anomalies (e.g. anencephaly)

**Interpretation of Fetal Heart Rate Recording**

The key to reliable and consistent interpretation of FHR tracings from CTG machines is a systematic approach.

Four main aspects of the FHR should be assessed:

1. The base line rate
2. Baseline variability
3. The presence or absence of accelerations
4. The presence and classification of decelerations.

Many errors of interpretation occur because of an excessive concern with decelerations and a failure to appreciate the significance of the other three aspects of the FHR.

A detailed account of how the FHR can be assessed using CTG is given below in Tables 2 and 3.

**Current Recommendations of Electronic Fetal Monitoring**

The methods most commonly used for intrapartum FHR monitoring include IA or continuous electronic monitoring of the heart rate and uterine contraction.

- However, more recently, a number of systematic reviews, of randomized controlled trials (RCTs) have been published that do not support the routine use of EFM, especially in low-risk women. The data show that neurologic abnormalities are not caused by intermittent episodes of asphyxia that commonly occur during labor.

- The most recent meta-analysis by Cochrane Collaboration concluded that a statistically significant decrease in neonatal seizures was associated with routine continuous EFM. The authors, however, observed no significant difference in 1-minute Apgar scores below four, 1 minute Apgar score below seven, rate of admissions to neonatal intensive care units, or perinatal death. Women whose labors were monitored with EFM had an approximately 40% increased risks of cesarean delivery and 20% increased risk of operative vaginal delivery compared with women who received IAs.

- Despite the increase in neonatal seizures in children born after IA in the Dublin Randomized trial of intrapartum monitoring at follow-up at 4 years of age, there were no differences between the two groups with regard to the proportion of children who developed cerebral palsy.

- Meta-analysis of randomized clinical trials indicate that EFM changes indicating nonreassuring fetal status have poor predictive value i.e. there is high false positive rate which leads to increased operative deliveries (with or without FBS). Normal EFM tracing have a high predictive
Intrapartum Management

Table 3: Pathologic/ominous cardiotocography (CTG)

- Baseline fetal heart rate (FHR) more than 150 beats/minute and silent pattern and/or repetitive late or variable decelerations
- Silent pattern for more than 90 minutes
- Complicated variable decelerations (depth ≥ 60 beats/minute, duration ≥ 60 seconds) and changes in shape (over shoot decreased or increased baseline heart rate following the decelerations; absence of baseline variability, slow recovery)
- Combined or biphasic decelerations (variable followed by late)
- Prolonged bradycardia (FHR drops to < 80 beats/minute for > 2 minutes or < 100 beats/minute for > 3 minutes) more than 10 minutes
- Repetitive late decelerations
- Pronounced loss of baseline variability
- Sinusoidal pattern with no accelerations

Interpretation or action: Consider fetal scalp pH estimation (first stage expedite delivery if not imminent (second stage).

Internal or direct monitoring

- Indications:
  - External tracing inadequate for accurate interpretation
- Contraindications:
  - Placenta praevia
  - Face presentation
  - Unknown presentation
  - Human immunodeficiency virus (HIV) seropositive
  - Active genital herpes
  - Hepatitis B and C virus infection.

- The FHR is measured by attaching a bipolar spiral electrode directly to the fetus (Fig. 2). The wire electrode penetrates the fetal scalp and the second pole is a metal wing on the electrode. Vaginal body fluids create a saline electrical bridge that completes the circuit and permits measurements of the voltage differences between the two poles. The electrical fetal cardiac signals—P wave, QRS complex, and T wave—are amplified and fed into a cardiotachometer for heart rate circulation.

Disadvantages

If the fetus is dead, the weaker maternal signal will be amplified and displayed as the "FHR".

Other intrapartum fetal monitoring techniques

Fetal scalp blood sampling allows for determination of the fetal acid-base status during labor. According to the ACOG (1995b) measurements of the pH in capillary scalp blood may help to identify the fetus in serious distress.

Indications

- A confusing/nonreassuring FHR pattern is present with elements suggestive of fetal hypoxic acidemia, e.g. uncorrected late deceleration with average variability, or combined patterns of late or variable declarations with decreased variability.
- Variability less than or equal to 5 bpm with/without periodic changes.
Intrapartum Fetal Monitoring Controversies

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Intrapartum Fetal Monitoring Controversies

Fig. 3: Reassuring pattern. Baseline fetal heart rate is 130–140 beats per minute (bpm), preserved beat-to-beat and long-term variability. Accelerations last for 15 or more seconds above baseline and peak at 15 or more bpm. (Small square=10 seconds; large square=one minute)

Fig. 4: Saltatory pattern with wide variability. The oscillations of the fetal heart rate above and below the baseline exceed 25 bpm

Fig. 5: Early deceleration in a patient with an unremarkable course of labor. Notice that the onset and the return of the deceleration coincide with the start and the end of the contraction, giving the characteristic mirror image

Fig. 6: Nonreassuring pattern of late decelerations with preserved beat-to-beat variability. Note the onset at the peak of the uterine contractions and the return to baseline after the contraction has ended. The second uterine contraction is associated with a shallow and subtle late deceleration

- Sinusoidal pattern.
- Fetal cardiac arrhythmias.
- Mixed deceleration pattern which complicates interpretation.

Fetal Scalp Blood Sampling not Indicated When
- Electronic fetal monitoring is reassuring (Fig. 3).
- Nonreassuring EFM patterns suggest significant fetal decompensation requiring immediate delivery (Figs 4 to 11).

Contraindications
- Mother is a known carrier of hemophilia and fetus is either affected or of unknown status.
- Mother is HIV seropositive.
- Active maternal genital infection. (e.g. Herpes).

Classification of Fetal Scalp Blood Sampling Results
The classification of FBS results is shown in Table 4. During labor, a normal scalp pH is 7.25 to 7.35. Value of less than 7.25 indicates acidosis.

Disadvantages
- The method is time consuming and inconvenient to the obstetrician and patients.
- The procedure is difficult to perform if cervix is undilated, multiple sampling is required, maintenance of blood gas analyzer is not easy.
Advantages
The rising incidence of cesarean section with introduction of FHR monitoring was definitely reduced with the addition of scalp pH monitoring. 

Scalp Stimulation
Scalp stimulation is an alternative to FBS. This proposal was based on the observation that acceleration of the heart rate in response to pinching of scalp with an Allis clamp just prior to obtaining blood was invariably associated with a normal pH. Conversely, failure to provoke acceleration was not uniformly predictive of fetal acidemia. Fetal acceleration of 15 beats per minute for 15 seconds is seen in response to fetal scalp pH greater than or equal to 7.19. Among fetuses without an acceleratory response to scalp stimulation, 39% were considered acidotic (pH < 7.19).

Vibroacoustic Stimulation
Fetal heart rate acceleration in response to vibroacoustic stimulation has been recommended as a substitute for scalp sampling. This technique involves the use of an electronic artificial larynx placed a centimeter or so from, or directly onto, the maternal abdomen. FHR acceleration of at least 15 beats/minute for at least 15 seconds occurring within...
15 seconds after the stimulation and with prolonged fetal movements is considered normal. This technique is an effective predictor of fetal acidosis in the setting of variable decelerations. However, the predictability for fetal acidosis in the setting of late decelerations is limited. Vibroacoustic stimulation in second stage of labor is associated with FHR reactivity, but the quality of the response did not predict neonatal outcome or enhance labor management.

A meta-analysis of reports on intrapartum fetal stimulation tests published between 1996 and 2000 showed that results of all four types of tests like scalp puncture for pH testing, an Allis clamp to pinch the fetal scalp, vibroacoustic stimulation, and digital stroking of the scalp were similar. They concluded that intrapartum stimulation tests were useful to rule out fetal acidemia. However, they cautioned that these tests are “less than perfect”.

**Fetal Pulse Oximetry (Fetal Oxygenation)**

In 1994, fetal oximetry was marketed in countries outside the United States (US) including Europe and Canada. In January 2000, the Obstetrics and Gynecology Devices Panel of the Medical Devices Advisory Committee of the Food and Drug Administration (FDA) recommended approval of a fetal oximeter for use in Obstetrics (Oxifirst: N-400 Fetal Oxygen monitoring system Nellcor). The aim of fetal pulse oximetry is to provide a continuous assessment of fetal oxygen saturation. In this method, a sensor is placed transvaginally between the uterine wall and fetal face which measures oxyhemoglobin saturation (Fig. 12). The lower limit for normal fetal oxygen saturation is generally considered to be 30% by most investigators. In a US multicenter randomized, controlled trial of fetal oximetry showed that the rate of cesarean delivery for fetal distress was significantly lower in fetal pulse oximetry group 4.5% compared to 10.2% in the conventional fetal-monitoring group. However, the cesarean rate for dystocia was significantly higher in the oximetry group (18.5%) versus 8.6% in the control group. Thus, the overall cesarean rate were not different (29% oximetry plus EFM vs 26% EFM).

According to ACOG (2005), an ancillary test of fetal status, fetal pulse oximetry, is associated with a significantly lower rate of cesarean delivery. However, because of concerns about false reassurance of fetal oxygenation, use of fetal pulse oximetry is not recommended at this time.

**Fetal Electrocardiographic Wave Form Analysis**

Since the fetal electrocardiogram (ECG) was first demonstrated by Cremer in 1904, attempts have been made to assess fetal well-being by assessing changes in ECG waveform. One approach has been to analyze changes in the PR/RR interval ratio but this has not been found to be of value in a prospective RCT. Another approach used the T/QRS ratio as a measure of acidosis (based on hypothesis that it is altered by the production of lactate in the fetal heart secondary to hypoxia) and can reduces the need for FBS. Two prospective RCTs suggested that it can reduce the need for operative delivery for fetal distress, metabolic acidosis and neonatal encephalopathy. In ST segment changes monitoring, infants outcomes were not improved compared with those with use of conventional fetal monitoring alone, although there was a reduction in the cesarean delivery rates for fetal distress. ST analysis to conventional fetal monitoring significantly reduced cesarean delivery rates for fetal distress as well as metabolic acidemia in umbilical artery blood (Flow chart 1).

However, a recent study of its introduction into routine clinical practice did not show the expected benefits.31

**Flow chart 1: Intrapartum fetal monitoring**

![Flow chart 1: Intrapartum fetal monitoring](image-url)
Intrapartum Doppler Velocimetry

Doppler analysis of the umbilical artery has been scheduled as another potential adjunct to conventional fetal monitoring. But according to reviewed literature, this technique was a poor predictor of adverse perinatal outcomes.62

Cord Blood Gases for Acid-base Assessment

The Society of Obstetricians and Gynecologists of Canada (SOGC) suggests the CBGs for the acid-base assessment sample to be obtained at all births.11 This can be done by various method as transcutaneous gas measurements, percutaneous umbilical blood sampling and clamped segment of cord. Acid-base tests (pH, base excess pCO₂, pO₂, O₂ saturation) can be done to clarify if acidosis is metabolic or respiratory. However, pO₂ is not reliable on cord blood.63

Apart from these, fetal scalp lactate measurement tried. This can be done by various methods.64

Further investigation will be needed to address the role of intrapartum fetal surveillance in uncomplicated, low-risk pregnancies.

CONCLUSION

- Routine EFM is not recommended for low-risk women in labor when adequate clinical monitoring including IA by trained staff is available. There are insufficient evidences to recommend for or against EFM over IA for high-risk pregnancies.
- Electronic FHR monitoring in high-risk labors produces significant effect in short-term neonatal morbidity and a significant reduction in perinatal deaths due to hypoxia but a significant increase in cesarean section rates; but all studies were insufficiently robust to be able to demonstrate any effect on perinatal mortality or cerebral palsy rate.
- Human errors (especially delays in response time and interpretation) contribute to poor outcome in monitored labors.
- Further investigation will be needed to address the role of intrapartum fetal surveillance in uncomplicated, low-risk pregnancies.

REFERENCES


INTRODUCTION

Every year it is estimated that worldwide, more than 500,000 women die of complications of pregnancy and childbirth. At least 7 million women who survive childbirth suffer serious health problems and a further 50 million women suffer adverse health consequences after childbirth. The overwhelming majority of these deaths and complications occur in developing countries. Temptations to expedite delivery by the vaginal route may pose problems when the conditions are suboptimal and the case may be one of obstructed labor, a serious pregnancy-related complication. For each woman who dies, at least 30 and an estimated of 100 women survive childbearing but suffer serious disease, disability or physical damage if the case is of obstructed labor. Obstructed labor contributes 3–5% of hospital admissions. Eight percent of all maternal deaths in developing countries are due to obstructed labor. 

Obstructed labor means that, in spite of strong contractions of the uterus, the fetus cannot descend through the pelvis because there is an insurmountable barrier preventing its descent. Obstruction usually occurs at the pelvic brim, but occasionally it may occur in the cavity or at the outlet of the pelvis. Complications resulting from obstructed labor can be avoided by a woman if obstructed labor is identified early and appropriate action is taken.

ETIOLOGY

Obstructed labor is defined as an arrest of vaginal delivery of fetus due to mechanical obstruction and professional assistance is required for the further management. The causes can be classified as:

**Maternal Causes**

**Bony Contraction**
- Contracted pelvis
- Tumors of pelvis
- Bony deformities

**Soft Tissue Obstruction**
- Uterine-impacted fibroid
  - Constriction ring
  - Sacculation of uterus
• Cervical-stenosis, tumors
  – Vaginal-stenosis, septa, tumors
  – Ovarian-neoplasm

Others
• Pelvic kidney
• Tumors of urinary bladder and rectum
• Vesical calculus

Fetal Conditions
• Large size baby (macrosomia)
• Malpresentations and malpositions
• Locked twins
• Fetal anomalies in babies

What Happens in Obstructed Labor?
It is important for students and learning obstetricians to understand what happens when labor is obstructed. The various consequences of obstructed labor are as follows (Fig. 1).

• Premature rupture of membranes: When the head is arrested in the pelvic inlet, the entire force exerted by the uterus acts directly upon the portion of membranes in contact with the internal os. Consequently early rupture of membranes is likely.

• Abnormalities in dilatation: The cervix dilates slowly or not at all, because the fetal head cannot descend and put pressure on it. At the same time the cervix may become edematous. The first stage of labor is therefore prolonged. (However, the first stage may be normal or short if, for example, obstruction occurs only at the outlet. In this case only the second stage will be prolonged). Prolonged labor causes the mother to become ketoacidotic and dehydrated.

  An undilating cervix means that a cesarean will be necessary. On the other hand, if the cervix is dilating normally, this usually indicates that the obstruction has been overcome by labor and that vaginal delivery will be possible (provided there is no outlet obstruction).

• Danger of uterine rupture: When the membranes rupture and the amniotic fluid drains away, the fetus is forced into the lower segment of the uterus by contractions. If the contractions continue, the lower segment stretches, becomes dangerously thin and is likely to rupture (However, uterine exhaustion may occur before that point is reached, causing contractions to become weaker or cease altogether and making the occurrence of uterine rupture less likely) (Fig. 2).

  Rupture of the uterus is more likely to occur in multipara (it is very rare in nullipara), especially if the uterus is already weakened by the scar of a previous cesarean section. Rupture of the uterus causes hemorrhage and shock. Without treatment it is fatal.

Avoidable Factors
These are factors causing or contributing to maternal death where there is departure from generally accepted standards of care. They can also be defined as factors which make a condition more likely to happen or more dangerous.
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Risk Factors

These should not be used to predict complications. The system of risk categorization or “the risk approach”, previously used for selecting women for specialized management is not useful, because evidence shows that many women categorized as “high risk” do not actually experience a complication, while many women categorized as “low risk” do. All pregnant women should therefore be considered “at risk” of developing complication.

Relevant points to find out from the woman, her family or the healthcare worker are:

- Her age
- Height, gait and any disability affecting the pelvis or lower limbs
- Medical history, in particular rickets, osteomalacia or pelvic injury
- Whether this is her first pregnancy and/or labor commenced at term
- Reason for any previous operative deliveries
- Previous stillbirth or early neonatal death and cause; if known
- Any complications during pregnancy
- Length of time in labor so far
- If partograph has been used, does cervical dilatation cross the alert or action lines

- Pattern of uterine action so far, e.g. contractions increased in frequency and duration, or stopped, etc.
- If membranes have ruptured
- If membranes have ruptured, how long ago did they rupture and is there any meconium-staining or foul smell?

CLINICAL PICTURE OF THE OBSTRUCTED LABOR

General Condition

In cases of obstructed labor there will be signs of physical and mental exhaustion. Some or all of the following signs and symptoms may also be observed:

- Maternal and/or fetal distress
- Dehydration and ketoacidosis (sunken eyes, thirsty, dry mouth, dry skin identified by skin pinch going back slowly)
- Fever (raised temperature)
- Abdominal pain which may be continuous
- Shock, rapid, weak pulse (100 per minute or more), diminished urinary output, cold clammy skin, pallor, low blood pressure (systolic less than 90 mm Hg), rapid respiratory rate (30 per minute or more), anxiousness, confusion or unconsciousness. Shock may be due to a ruptured uterus or sepsis.
Diagnosis of unsatisfactory progress of labor, abnormal labor patterns, diagnostic criteria and methods of treatment are shown in Tables 1 and 2.

Figures 3A and B show formation of the birth canal at the end of pregnancy and during the second stage of labor.

Abdominal Examination

Signs of obstructed labor that may be revealed by an abdominal examination are:

- The widest diameter of the fetal head can be felt above the pelvic brim because it is unable to descend; a large caput succedaneum may be fixed in the pelvic brim and this can be misleading, but careful palpation should identify that the widest diameter of the head is still above the brim; if the uterus is tonic, it will be very difficult to palpate because it is continuously hard and very painful for the woman.
- Frequent, long and strong uterine contractions (although if a woman has been in labor for a long time, contractions may have stopped because of uterine exhaustion); they restart with renewed vigor.
- The uterus may have gone into tonic contraction (i.e. it is continuously hard) and sits tightly molded around the fetus.
- Bandl’s ring may be seen (Fig. 4).

- Bandl’s ring is the name given to the area between the upper and lower uterine segments when it becomes visible and/or palpable during labor. In the process of normal pregnancy and labor, this area is called a retraction ring. It should not normally be seen or felt on abdominal examination.

Table 1: Diagnosis of unsatisfactory progress of labor

<table>
<thead>
<tr>
<th>Findings</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervix not dilated</td>
<td>False labor</td>
</tr>
<tr>
<td>No palpable contractions/infrequent contractions</td>
<td>Prolonged latent phase</td>
</tr>
<tr>
<td>Cervix not dilated beyond 4 cm after 8 hours of regular contractions</td>
<td>Cephalopelvic disproportion</td>
</tr>
<tr>
<td>Cervical dilatation to the right of the alert line on the partograph</td>
<td>Obstruction</td>
</tr>
<tr>
<td>- Secondary arrest of cervical dilatation and descent of presenting part in presence of good contractions.</td>
<td></td>
</tr>
<tr>
<td>- Secondary arrest of cervical dilatation and descent of presenting part with large caput, third degree molding, cervix poorly applied to presenting part, edematous cervix, ballooning of lower uterine segment, formation of retraction band, maternal and fetal distress.</td>
<td>Inadequate uterine activity</td>
</tr>
<tr>
<td>- Less than 3 contractions in 10 minutes, each lasting less than 40 seconds</td>
<td>Malpresentation or malposition</td>
</tr>
<tr>
<td>- Presentation other than vertex with occiput anterior</td>
<td>Prolonged expulsive phase</td>
</tr>
<tr>
<td>Cervix fully dilated and woman has urge to push, but there is no descent</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Abnormal labor patterns, diagnostic criteria, and methods of treatment

<table>
<thead>
<tr>
<th>Labor pattern</th>
<th>Diagnostic criteria</th>
<th>Preferred treatment</th>
<th>Exceptional treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nulliparous</td>
<td>Multiparous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolongation disorder</td>
<td>Prolonged latent phase</td>
<td>&gt; 20 hour</td>
<td>Bed rest</td>
</tr>
<tr>
<td>Protraction disorders</td>
<td>Protracted active phase dilatation</td>
<td>&lt; 1.2 cm/hour</td>
<td>Expectant and support</td>
</tr>
<tr>
<td>Arrest disorders</td>
<td>Protected descent</td>
<td>&lt; 1 cm/hour</td>
<td>&lt; 1.5 cm/hour</td>
</tr>
<tr>
<td>- Prolonged deceleration phase</td>
<td>&gt; 3 hour</td>
<td>&gt; 1 hour</td>
<td>Evaluate for CPD: cesarean delivery No CPD: oxytocin</td>
</tr>
<tr>
<td>- Secondary arrest of dilatation</td>
<td>&gt; 2 hour</td>
<td>&gt; 2 hour</td>
<td></td>
</tr>
<tr>
<td>- Arrest of descent</td>
<td>&gt; 1 hour</td>
<td>&gt; 1 hour</td>
<td>Rest, if exhausted cesarean delivery</td>
</tr>
<tr>
<td>- Failure of descent</td>
<td>No descent in deceleration phase or second stage</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: CPD, cephalopelvic disproportion

Source: Modified from Cohen and Friedman (1983)
Intrapartum Management

Figs 3A and B: Diagrams of the birth canal (A) at the end of pregnancy and (B) during the second stage of labor, showing formation of the birth canal

Abbreviations: CR, contraction ring; Int, internal; Ext, external.

Source: Adapted from Williams, 1903

Fig. 4: Diagnosing obstructed labor

- Bandl’s ring is a late sign of obstructed labor. It can be seen as a depression across the abdomen at about the level of the umbilicus. Above this is the grossly thickened, retracted upper uterine segment. Below the Bandl’s ring is the distended, dangerously thinned lower uterine segment. The lower abdomen can be further distended by a full bladder and gas in the intestines.

- Fetal heart may not be heard in severe cases of obstructed labor because the fetus dies from anoxia.

Vaginal Examination

The signs of obstruction that must be looked for are as follows:

- Foul-smelling meconium draining
- Amniotic fluid already drained away
- Catheterization will produce concentrated urine which may contain meconium or blood
- Vaginal examination:
  - Edema of the vulva, especially if the woman has been pushing for a long time
  - Vagina hot and dry because of dehydration
  - Edema of the cervix
  - Incomplete dilatation of the cervix (may be fully dilated in case of outlet obstruction)
  - A large caput succedaneum can be felt
  - The cause of the obstruction, e.g. excessively molded head stuck in pelvis, shoulder, brow or posterior face presentation, prolapsed arm.

Partograph Recordings

Obstructed labor may also be revealed if the recordings on the partograph indicate:

Normal shape of the abdomen

Shape of the abdomen in obstructed labor

Bandl’s ring

Retracted upper uterine segment

Distended lower uterine segment

Fig. 4: Diagnosing obstructed labor
• A prolonged first or second stage of labor which is evident because cervical dilatation will cross first the alert line and then, if no action is taken, will cross the action line despite a history of strong uterine contractions.

**Symptoms and Signs of Ruptured Uterus**

Ruptured uterus is common in multiparas but rare in nulliparas.

*Warning signs:* Bandl’s ring and tenderness of the lower segment of the uterus

Suspect rupture of the uterus if the following signs and symptoms are present:

- Shock
- Abdominal distension/free fluid
- Abdominal uterine contour
- Tender abdomen
- Easily palpable fetal parts
- Absent fetal movements and fetal heart sounds
- Rapid maternal pulse

Diagnosis could be more difficult, if rupture is incomplete or the tear is small. In this case, the fetus will remain at least partially in the uterus and signs of shock in the mother are delayed until after delivery because the pressure of the fetus prevents bleeding to some extent. Symptoms in this case could be initially very slight, and labor may even continue. Suspect rupture if the fetus suddenly becomes distressed and the mother’s pulse starts rising.

**MANAGEMENT**

A good prenatal care, risk screening and early referral can minimize the problems of obstructed labor. But suboptimal healthcare infrastructure is responsible for the appealingly high maternal mortality and morbidity in managing obstructed labor at rural areas in India. The delay in getting the proper care to the pregnant females with obstructed labor can better be understood by the three delay model system (Flow charts 1 and 2).

The first two delays relate directly to issue of access to care, encompassing factors in the family and the community including transportation. The third delay relates to factors in the health facility. The management of obstructed labor can be strengthened in the community by promoting basic emergency obstetric care at primary health centers and district hospitals. Care of patients with obstructed labor patients can be discussed according to management at various health centers.

**Six Steps to Providing Effective Management**

1. Identify the problem
2. Decide on the aim of management
3. Select the best management
4. Provide management, determining priorities
5. Evaluate the outcome
6. Provide further management, if necessary. This may include referral.

Stress the importance of working quickly and according to priorities so that urgent things are done first.

**Rehydrate the Patient**

* Aim: To maintain normal plasma volume and prevent or treat dehydration and ketosis

- Put up an intravenous (IV) infusion. Use a large needle (No. 18) or cannula. The infusion rates for IV fluids are shown in Table 3.
- If the woman is shocked, give normal saline or Ringer’s lactate. Run in 1 liter as quickly as possible, then repeat 1 liter every 20 minutes until the pulse slows to less than 90 beats per minute, systolic blood pressure is 100 mm Hg or higher. However, if breathing problems develop, reduce to 1 liter in 4–6 hours.
- If the woman is not in a shock but is dehydrated and ketotic, give 1 liter rapidly and repeat if still dehydrated and ketotic. Then reduce to 1 liter in 4–6 hours.
- Keep an accurate record of all intravenous fluids infused, and urinary output.

**Give Antibiotics**

If there are signs of infection, or the membranes have been ruptured for 18 hours or more, or the period of gestation is 37 weeks or less, give antibiotics as follows:

- Ampicillin 2 g every 6 hours, and
- Gentamicin 5 mg/body weight IV every 24 hours

If the woman is delivered by cesarean section, continue antibiotics and give metronidazole 500 mg IV every 8 hours until the woman is fever-free for 48 hours.

**Give Supportive Care**

The woman’s birth companion should be encouraged to stay with her to provide comfort and support. Staff should explain all procedures to the woman, seek her permission, discuss results with her, listen and be sensitive to her feelings.

**Deliver the Baby**

The doctor will assess the woman and her progress in labor and decide on the mode of delivery.

**Cephalopelvic Disproportion**

- If cephalopelvic disproportion is confirmed and fetus is alive, delivery should be by cesarean section.

**Obstruction**

- If the fetus is alive, the cervix is fully dilated and the head is at 0 station or below, deliver by vacuum extraction.
Flow chart 1A: Management plan of obstructed labor

- **Is there an indication for referral?**
  - Yes: First stage → Yes: Transport available → Yes: Refer to hospital
  - No: Manage according to local policy and protocols

- **Signs of fetal distress, or cord prolapse, or breech**
  - Yes: Manage according to local policy and protocols
  - No: First stage: Not delivered after 12 hours in labor

  - **First stage: Not delivered after 12 hours in labor**
    - No: Not delivered after 12 hours in labor
    - Yes: Strong contractions, or signs of obstructed labor. Cervical dilatation crossed alert line and reached action line on partograph
      - No: Second stage: Prolonged over 2 hours
      - Yes: Transport available

  - **Second stage: Prolonged over 2 hours**
    - No: Ensure bladder is empty. If no fetal or maternal distress, encourage the woman to adopt an upright position
    - Yes: Monitor descent of the fetus and observe fetal and maternal conditions closely
      - No: If no progress within 1 hour, arrange urgent referral, unless vacuum extraction
      - Yes: IV fluids because may have general anesthesia

- **Vacuum extractor available and midwife knows how to use it**
  - No: IV fluids
  - Yes: Attempt vacuum extraction, if head low in pelvis and cervix fully dilated
    - No: Baby delivery
    - Yes: Normal aftercare

- **Transport available?**
  - Yes: IV fluids, Analgesia, Antibiotics, if fever or membranes ruptured for 18 hours
    - Refer to hospital with midwife and delivery package
  - No: IV fluids, Antibiotics in fever or ruptured membranes in case of 18 hours or more of labor
    - Refer to facility with cesarean section
Management of Obstructed Labor at a Referral Center

If the fetus is alive and the cervix is fully dilated and there is evidence of indication for symphysiotomy for relatively minor obstruction (if cesarean section is not possible) and the fetal head is at -2 station, then delivery should be by symphysiotomy and vacuum extraction. Symphysiotomy is rarely performed at clinical centers. If the fetus is alive but the cervix is not fully dilated or if the fetal head is too high for vacuum extraction, referral should be made immediately for delivery by cesarean section.

If the fetus is dead:
- Delivery should be by craniotomy or other destructive procedures
- If this is not possible, delivery should be by cesarean section.

Thus the ultimate aim of such a condition is to expedite the delivery either vaginally or by cesarean section. This depends on the viability of fetus (Flow chart 3) and pelvic conditions. Forceps or vacuum is applied in cephalic presentation when head is low down and there are borderline pelvic outlet contractions. Destructive surgeries should be promoted at higher centers by trained professionals. The incidence of destructive surgery in our country is 10–25%.

Cesarean section is the preferred method. Hyperthermia, dehydration, electrolyte imbalance, sepsis and anemia can pose problems for anesthesia. Surgical interventions by abdominal route may at times lead to morbid conditions. Trauma to the bladder is very common with inexperienced hands, when the abdomen is opened because the bladder is high up and distended. The lower uterine segment is severely stretched out and hematoma can be seen in lower segment or there can be rupture of lower uterine segment.
Intrapartum Management

If performing a cesarean, the lower uterine incision should be given slightly higher up as there are high chances of extension of incision line vertically down or laterally while extracting the baby as the presenting part is deeply impacted in obstetric labor.

Since the lower uterine segment is very vascular any extension of incision laterally or downward can cause torrential bleeding. Difficulties in extracting out fetus due to drained out liquor and over molded uterus can necessitate inverted T-shaped incision in lower uterine segment or obstetricians may need to do classical cesarean in multigravidas in badly impacted obstructed labor. Atonic PPH can be lethal and may require cesarean hysterectomy or iliac vessels ligation. In case of rupture of uterus, cesarean hysterectomy is to be performed. In severely infected patients, it is mandatory to put abdominal drainage tube to prevent collection of infected fluid in abdominal cavity following surgical procedure. Complications while conducting vaginal delivery are much more difficult to manage. Vacuum extraction is always a better option than forceps application. Application of forceps in edematous and vascular vaginal tissue can be very traumatic. During delivery of the fetus vaginally, there can be extension of episiotomy upward in fornices which can cause severe hemorrhage and is also difficult to repair. At times, it can extend up to broad ligament. Fetal injuries particularly intracranial hemorrhage to the fetus can be fatal. There can be traumatic injuries to fetus. The maternal mortality is 8–12% following cesarean section as compared to 0–2% after embryotomy and vaginal delivery.

Postpartum care of the patient is equally important in order to minimize puerperal complications. Strict watch on vitals and PPH in labor room for 48 hours, broad spectrum antibiotics, indwelling catheterization for 7–10 days, suppression of breast milk if fetal demise, blood transfusion, postpartum contraception and future pregnancy counseling are some of the essential components of peripheral care. Even with the management under expert hands, maternal and fetal complications cannot be ignored.

COMPLICATIONS

Maternal Complications

- Genital tract trauma and rupture of uterus
- Postpartum hemorrhage
- Pulmonary embolism
- Puerperal infection
- Septicemia and shock
- Subinvolution of uterus
- Delayed healing of wounds
- Urinary fistulae (0.5–1%)
- Obstetric palsies

Flow chart 3: Management of obstructed labor based on fetal condition

<table>
<thead>
<tr>
<th>Amount of fluid</th>
<th>Time period</th>
<th>Drops per cc (type of tubing)</th>
<th>Drops per minute</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 liter</td>
<td>20 minutes</td>
<td>10</td>
<td>Too fast to count</td>
</tr>
<tr>
<td>1 liter</td>
<td>20 minutes</td>
<td>10</td>
<td>Too fast to count</td>
</tr>
<tr>
<td>1 liter</td>
<td>4 hours</td>
<td>10</td>
<td>40</td>
</tr>
<tr>
<td>1 liter</td>
<td>4 hours</td>
<td>20</td>
<td>80</td>
</tr>
<tr>
<td>1 liter</td>
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<tr>
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<td>8 hours</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>1 liter</td>
<td>8 hours</td>
<td>20</td>
<td>40</td>
</tr>
</tbody>
</table>

In general, the formula to figure out any IV infusion rate is as follows:

Amount of fluid given (cc) _____________________________________________

Time for infusion to occur (minutes)

In order to convert the time period from hours to minutes, multiply the number of hours by 60. This will give the number of minutes over which the IV fluids are to be given.

Table 3: Intravenous fluid rates
• Postpartum psychosis
• Future obstetric complications

Fetal Complications
• Asphyxia
• Sepsis
• Fetal trauma
• Intracranial hemorrhage
• Death

In spite of the best management facilities at tertiary centers, maternal and fetal morbidity in obstructed labor is a challenge to the obstetricians. Worldwide norms of various health agencies promote training of dais, provision of emergency obstetric care at periphery, supply of delivery kits to and upgrading of PHCs and subcenters and transport facilities. Risks that women face in bringing life into the world are not mere misfortunes or unavoidable natural disadvantages but this injustice to the females health in the society must remedy through its political, health and legal system mainly by promoting adolescent education, community education, antenatal and interval care and genuine commitment by the community, professionals and the government. If all the recommended norms of various family welfare programs are fulfilled, perhaps we will not have an obstructed labor and even if we have one, we would be in a better position to manage such condition from a grass root level in future obstetric era.9

REFERENCES
INTRODUCTION

Instrumental vaginal delivery refers to a delivery in which the operator uses forceps or a vacuum device to assist the mother in transitioning the fetus to extraterine life. Either instrument is applied to the fetal head and then the operator uses traction to extract the fetus, typically during a contraction while the mother is pushing.

Initially instrumental deliveries were performed to extract fetuses from parturients who were at high risk of maternal mortality due to prolonged and/or obstructed labor. In these cases, saving the mother's life took precedence over possible harm to the fetus. The focus of these procedures has changed as a result of modern obstetrical practices that have drastically reduced the risk of intrapartum maternal mortality and major morbidity. Decisions regarding use of instrumental delivery are now based primarily upon the fetal/neonatal impact of these procedures and are weighed against the alternative options of cesarean birth, prolonging the second stage, and second stage augmentation of contractions with oxytocin.

HISTORICAL ASPECT

The historical aspect of forceps is quite fascinating. The development of obstetrics forceps dates from the innovation made by one of the members of the Chamberlen family around 1600 AD. It was kept as a family secret for more than 100 years. Introduction of pelvic curve of the forceps is attributed to Levret in Paris, during the first half of the eighteenth century. It was Smellie who first used the forceps in aftercoming head of the breech delivery.

In 1849, Sir James Young Simpson in Edinburgh was the first to produce an apparatus, which delivered a baby's head with the aid of suction. Malmstrom’s modern vacuum extractor differs only in detail and refinement from Simpson’s suction and traction mechanism.

INCIDENCE

Approximately 6% of all births in the United States are accomplished via an instrumental vaginal approach. Exact Indian data is not available but from various studies current prevalence rate is 10–20%. The overall rate of instrumental vaginal delivery has been diminishing, but the proportion of instrumental vaginal deliveries conducted by vacuum-assisted births has been increasing and is twice the rate of forceps-assisted births.

INDICATIONS

According to American Congress of Obstetricians and Gynecologists (ACOG) and Royal College of Obstetricians and Gynaecologists (RCOG) guidelines for instrumental vaginal delivery, no indication is absolute. The following indications are currently used:

- Prolonged second stage of labor. In nulliparous women, this is defined as lack of continuing progress for 3 hours with regional anesthesia or 2 hours without anesthesia. In multiparous women, it refers to lack of continuing progress for 2 hours with regional anesthesia or 1 hour without anesthesia.
- Suspicion of immediate or potential fetal compromise (e.g. non-reassuring fetal heart rate pattern, abruption) where expeditious vaginal delivery can be readily accomplished.
- Shortening the second stage of labor for maternal benefit (e.g. maternal cardiac disease, some neurologic conditions, exhaustion).
In the past, shortening the second stage was an acceptable option, independent of any specific maternal or fetal indications, because early studies suggested that the risks of fetal and maternal morbidity were higher when the second stage of labor exceeded two hours. The evidence does not support this practice.

The ability of fetal heart rate monitoring to identify the fetus not tolerating labor has made the arbitrary termination of labor because of any elapsed period of time unwarranted. Furthermore, maternal risks of a prolonged second stage (e.g. pelvic floor injury, postpartum hemorrhage) appear to be more related to instrumental intervention than the length of the second stage.

### PREREQUISITES

The operator should be an individual experienced in instrumental vaginal delivery. This individual should determine the following prerequisites prior to application of instruments.

- The cervix is fully dilated
- The membranes are ruptured
- The head is engaged.

Fetal presentation, position, lie and any asynclitism are known. The fetus must be in a vertex presentation (unless the purpose is to use forceps to assist in delivery of an aftercoming head). If fetal presentation or position is uncertain, use of ultrasound intrapartum can be helpful. In one study, digital examination incorrectly defined fetal head position in over 25% of cases about to undergo instrumental vaginal delivery. Large infants, extreme molding, extension of the fetal head, pelvic deformities and asynclitism may falsely suggest engagement of the vertex. In these cases, the leading bony part is at the ischial spines, although the biparietal diameter has not passed through the pelvic inlet. Ultrasound examination should be performed and is highly accurate.

- The fetal size has been estimated and clinical pelvimetry shows adequate mid and outlet pelvic dimensions, and no obstructions or contractures exist.
- Maternal anesthesia is satisfactory.
- The patient consents to the procedure. The risks of the procedure should be explained to the woman and documentation of the indication and maternal and fetal assessments should be made in the medical record.

The option of performing an immediate cesarean delivery should be possible if complications arise.

In addition, postdelivery, the pediatrician should be informed that the birth was attempted or assisted by vacuum or forceps.

### CONTRAINDICATIONS

Most contraindications to instrumental delivery are related to the potential for unacceptable fetal risks. Fetal prematurity is a relative contraindication. Other contraindications include known fetal demineralizing diseases (e.g. osteogenesis imperfecta), collagen disorders (e.g. Ehlers-Danlos syndrome), fetal bleeding diatheses (e.g. hemophilia, alloimmune thrombocytopenia), unengaged head, unknown fetal position and suspected fetal-pelvic disproportion. A nonreassuring fetal heart rate pattern is not a contraindication to instrumental vaginal delivery.

In addition, vacuum devices should not be used to assist delivery prior to 34 weeks of gestation because of the risk of fetal intraventricular hemorrhage. Prior scalp sampling or multiple attempts at fetal scalp electrode placement are also relative contraindications to vacuum extraction since these procedures may increase the risk of cephalohematoma or external bleeding from the scalp wound. Contraindications to the use of forceps are listed in Table 1. In some of these conditions, vacuum can be used safely.

### Table 1: Contraindications to the use of forceps

- Absence of a proper indications
- Incompletely dilated cervix
- Marked cephalopelvic disproportion
- Unengaged fetal head
- Lack of experience on the part of the operator

### Minimum and Maximum Estimated Fetal Weight

There is no consensus regarding the minimum and maximum estimated fetal weights that should preclude instrumental vaginal delivery.

**Upper threshold:** Instrumental delivery of the macrosomic infant may be associated with an increased risk of injury. A trial of labor and careful use of forceps or vacuum extraction are acceptable for most fetuses suspected to be macrosomic. Under these circumstances, the obstetrician should be aware of the risk of shoulder dystocia, especially when the second stage of labor is prolonged.

**Lower threshold:** As discussed above, vacuum devices should not be used to assist delivery prior to 34 weeks of gestation (mean birth weight 2,500 g because of increased risks of fetal intraventricular hemorrhage in premature infants. Premie sized forceps have been used on fetuses as small as 1,000 g.

There are no prospective randomized trials examining the impact of prophylactic low forceps delivery in low birth weight infants.

Immediate and later head ultrasound examinations of 230 infants with estimated fetal weights of less than 1,750 g observed that the overall incidence of cerebral hemorrhage was the same after vaginal and cesarean deliveries (41% and 44%, respectively). However, lower incidence of hemorrhage was noted after vaginal delivery with forceps (17%).

In contrast, several other studies have suggested an increased risk of intraventricular hemorrhage with prophylactic low forceps.
In summary, the evidence does not clearly identify a superior mode of delivery in cephalic presenting low birth weight infants. Reassuringly, larger trials do not demonstrate any increase in neurologic injury with the use of low forceps in low birth weight infants and a role for low forceps in clinically indicated situations would appear reasonable in this population. Two forceps are available which are smaller in dimension than standard forceps and are intended for use in the low birth weight or very low birth weight populations. “Baby” Elliot and “baby” Simpson forceps are among these instruments. Unfortunately, we were unable to identify any published studies or manufacturer guidelines regarding the estimated fetal weights or gestational ages at which these instruments might be most useful.

**TRIAL OF INSTRUMENTAL DELIVERY**

An instrumental vaginal delivery should only be considered when the likelihood of success is high because there may be a higher rate of birth trauma after failed attempts at instrumental delivery (although one can never be certain of a successful outcome). In one study, the rates of subdural or cerebral hemorrhage, facial nerve injury, convulsions, central nervous system depression and mechanical ventilation were higher in infants delivered by cesarean birth after a failed instrumental delivery than in those delivered by cesarean with no prior attempt at instrumental vaginal delivery. However, other studies have not shown adverse effects from failed instrumental vaginal delivery as long as cesarean delivery followed promptly.

**CHOICE OF ANESTHESIA**

Local anesthesia is preferred than general anesthesia as maternal voluntary bearing down efforts are present.
- Perineal infiltration
- Pudendal nerve block
- Epidural anesthesia
- Spinal anesthesia
- General anesthesia.

**CLASSIFICATION OF FORCEPS DELIVERIES**

The ACOG redefined the classification of forceps delivery in 1988 to better reflect the degree of difficulty and attendant risk (e.g. lower fetal station and smaller degrees of head rotation are associated with reduced maternal and fetal injury). The criteria for different types of forceps deliveries are as follows.

**Outlet forceps:** The application of forceps when the scalp is visible at the introitus without separating the labia, the fetal skull has reached the pelvic floor, the sagittal suture is in anteroposterior diameter or a right or left occiput anterior or posterior position, the fetal head is at or on the perineum, rotation does not exceed 45°.

**Low forceps:** The application of forceps when the leading point of the fetal skull is 2 cm or more beyond the ischial spines (at least +2 cm station), but not on the pelvic floor. Low forceps have two subdivisions: (1) rotation is 45° or less (left or right occiput anterior to occiput anterior, or left or right occiput posterior to occiput posterior) and (2) rotation more than 45°.

**Midforceps:** The application of forceps when the head is engaged, but the leading point of the skull is higher than +2 cm station.

**Rotational forceps (Kielland forceps) (Figs 1 and 2):** The pelvic curve is almost nonexistent, making the instrument ideal for rotating the fetal head. Rotation can be accomplished simply by twisting the closed handle instead of sweeping them through a wide arc, as is necessary when using forceps with a deep pelvic curve. The sliding lock makes the locking of blades easier. Delivery can be accomplished with the same instrument: no reapplication is needed.
Under very unusual circumstances, such as the sudden onset of severe fetal or maternal compromise, application of forceps above +2 cm station may be attempted while simultaneously initiating preparations for a cesarean delivery in the event the forceps maneuver is unsuccessful. Under no circumstances, however, forceps should be applied to an unengaged presenting part or when the cervix is not completely dilated.

**Choice of Instrument**

The choice of instrument is determined by level of training with the various forceps and vacuum equipment. Factors that might influence choice are the availability of the instrument, the degree of maternal anesthesia, and knowledge of the risks and benefits associated with each instrument. In general, vacuum devices are easier to apply, place less force on the fetal head, require less maternal anesthesia, and do not affect the diameter of the fetal head compared to forceps. By comparison, the advantages of forceps are that they are unlikely to detach from the head, can be sized to a premature cranium, may be used for a rotation, and do not aggravate bleeding from scalp lacerations.

**Vacuum (Figs 3 and 4):** Metal or rigid cups were more suitable for occiput posterior, transverse and difficult occiput anterior deliveries, whereas the soft cup was appropriate for uncomplicated deliveries.

**Obstetrics Forceps (Fig. 5)**

In general, the instrument selected should have cephalic and pelvic curves appropriate to the size and shape of the fetal head, maternal pelvis and planned procedure. Midpelvic deliveries are facilitated by an instrument that can be used with a traction handle (e.g. Bill’s axis-traction handle) and a sliding lock is helpful when there is asynclitism. Simpson type forceps tend to fit a long molded head, Elliot or Tucker-McLane type forceps are better suited to a round unmolded head and Kielland forceps are useful for rotations because of their minimal pelvic curve and sliding lock.

**APPLICATION (FIG. 6)**

**Forceps:** Appropriately, applied forceps grasp the occiput anterior fetal head such that:
- The long axis of the blades corresponds to the occipito-mental diameter
- The tips of the blades lie over the cheeks
- The blades are equidistant from the sagittal suture, which should bisect a horizontal plane through the shanks
- The posterior fontanelle should be one finger breadth anterior to this plane
- Fenestrated blades should admit no more than one finger breadth between the heel of the fenestration and the fetal head
- No maternal tissue has been grasped.

**Traction (Figs 4 and 7):** Traction with either forceps or vacuum should be steady (not rocking) and in the line of the birth canal. Traction should be exerted with each contraction and in conjunction with maternal expulsive efforts. In most cases, progress is noted with the first or second pull and delivery occurs by the third or fourth pull. The procedure should be abandoned if descent does not occur with appropriate application and traction. The negative pressure created in vacuum is 0.7–0.8 kg/cm². This takes 8–10 minutes. The total extraction time may be 15 minutes, or 5–10 tractions during uterine contraction. If the cervix is not fully dilated, it may take longer. The upper time limit is 30 minutes to prevent damage to the baby.

An observational study of 119 vacuum-assisted deliveries using a vacuum device with a traction force indicator found that 80% of extractions occurred with 11.5 kg (25 lbs) or less
traction and 20% with greater than 11.5 kg traction. Only two deliveries had greater than 13.5 kg (30 lbs). Neonatal scalp abrasion and cephalhematoma were more common in infants born with traction greater than 11.5 kg.

**Figs 4A to C:** Vacuum extractor. (A) Traction outward and posteriorly; (B) Traction outward and horizontally; (C) Traction outward and anteriorly

Multiple Trials of Instrumental Delivery

The ACOG has suggested that multiple attempts at instrumental vaginal delivery using different instruments (vacuum, different types of forceps) be avoided due to the greater potential for maternal and/or fetal injury. In one large study, the incidence of subdural or cerebral hemorrhage in infants delivered by vacuum and forceps, vacuum alone, or forceps alone was approximately 21, 10, and 8, per 10,000 births respectively.
All hematomas had resolved without clinical sequelae when reevaluated 4 weeks later.

RISKS

The risks associated with instrumental vaginal delivery need to be evaluated with respect to appropriate control groups and reasonable alternative procedures. This was illustrated by a study assessing the incidence of intracranial hemorrhage related to labor and mode of delivery in 583,340 singleton infants born to nulliparous women in California. The rate of subdural or cerebral hemorrhage associated with vacuum extraction was equivalent to that associated with forceps use or cesarean delivery during labor, but higher than after spontaneous delivery or a cesarean delivery performed prior to labor. This suggests that abnormal labor was the major risk factor for this complication, rather than mode of delivery.

Forceps versus Vacuum Extraction

Comparative data on the risks of instrumental delivery are illustrated by the following examples from large studies:

- A meta-analysis of 10 trials comparing vacuum to forceps delivery found vacuum deliveries were associated with less maternal soft tissue trauma (OR 0.41, 95% CI 0.33–0.50), required less general and regional anesthesia, and resulted in fewer cesarean deliveries. However, use of a vacuum device was less likely to result in successful vaginal delivery than forceps. The lower cesarean delivery rate after attempted vacuum extraction was likely due to follow-up trial of forceps, whereas failed forceps typically resulted in a cesarean delivery.

Neonates delivered by vacuum extraction had more neonatal cephalohematoma (OR 2.38) and retinal hemorrhages (OR 1.99) than those delivered by forceps. These problems generally are not associated with long-term complications.

Vacuum-assisted deliveries were associated with significantly lower rates of birth injury, seizures and assisted ventilation than forceps-assisted deliveries after adjustment for confounders; neonatal death rates were equivalent.

VENTOUSE

The term ventouse is derived from the French word meaning “soft cup”. Theoretical advantages of vacuum extractor compared with forceps includes:

- Avoidance of insertion of space occupying steel blades within the vagina
- No requirement for precise positioning over the fetal head
- Less maternal trauma
- Less intracranial pressure during traction

Technique

Proper cup placement is the most important determinant of success in vacuum extraction. The center of cup should be placed over the sagittal suture and about 3 cm in front of the posterior fontanel toward the face (Flow chart 1).

Complications

- Scalp lacerations and bruising
- Subgaleal hematoma
- Cephalohematoma
- Enhanced hemorrhage
- Neonatal jaundice
- Subconjunctival hemorrhage
- Clavicular fracture
- Shoulder dystocia
- Injury
Recomendations Regarding Vacuum Delivery

- The classification of vacuum deliveries should be the same as that used for forceps deliveries (including station).
- The same indications and contraindications used for forceps deliveries should be applied to vacuum-assisted deliveries.
- The vacuum should not be applied to an unengaged vertex, i.e. above 0 station.
- The individual performing or supervising the procedure should be an experienced operator.
- The operator should be willing to abandon the procedure if it does not proceed easier or if cup dislodges more than three times.

Risks Related to Instrumental Delivery

Maternal Short-term Risks

Maternal risks from instrumental delivery include pain at delivery, perineal pain at 24 hours, lower genital tract lacerations and hematomas, urinary retention, anemia and rehospitalization. These complications are higher with both vacuum and forceps compared to spontaneous delivery. The greater degree of perineal trauma associated with instrumental delivery was illustrated by a retrospective review of 50,210 vaginal deliveries. The rates of third and fourth degree lacerations for spontaneous vaginal delivery, vacuum extraction and forceps delivery is 1.7%, 9.3% and 19.2%, respectively.

Maternal morbidity related to different types of instrumental delivery was illustrated by a randomized study comparing deliveries by forceps and two different types of vacuum cup. There was at least one significant adverse maternal outcome (e.g. periurethral/labial laceration, vaginal laceration, third or fourth degree laceration, vulvar or vaginal hematomas, or cervical lacerations) in 48% of forceps, 36% of silastic vacuum extractor and 22% of Mityvac vacuum extractor deliveries.

Maternal trauma is greatest with rotational and midforceps operations. Direct bladder injury and ureteral lacerations/transsections have been reported in such cases.

It is customary to give episiotomy in instrumental deliveries. In multiparous patient, episiotomy can be safely avoided.

Fetal position also has an impact. For occiput posterior position, the rate of anal sphincter and rectal injury with forceps and vacuum is higher than the rate with occiput anterior position (54% for forceps and 27% for vacuum).

Although spontaneous vaginal delivery is less traumatic for the mother than instrumental vaginal delivery, the latter is associated with less short-term maternal morbidity than cesarean delivery.

Maternal Long-term Risks

Long-term maternal sequelae from instrumental delivery are primarily related to disturbances in urinary and anal function, such as urinary incontinence, fecal incontinence, pelvic organ prolapse and, occasionally, fistula formation. The range of these complications vary from center to center.

- In a new study, 4% developed new fecal incontinence postpartum. Forceps and vacuum delivery were the only independent risk factors identified for this complication.
- A prospective series of 159 women who underwent endosonography after spontaneous, forceps and cesarean delivery found sphincter injury in 8.7%, 83%, and 0% respectively.
- A study of 149 women before and 9 weeks after delivery reported stress urinary incontinence was more common after instrumental delivery compared to spontaneous delivery (34% versus 21%).
- Any increase in risk of long-term maternal morbidity from different types of instrumental vaginal delivery cannot be accurately quantitated and compared because of the lack of adequate randomized studies with appropriate control groups.

Recurrence Risk

Mode of delivery after a previous instrumental vaginal delivery has not been extensively evaluated. A 3-year follow-up study that surveyed women who had undergone a successful term instrumental vaginal delivery in the second stage reported 42 of 54 (78%) women achieved vaginal delivery in the subsequent pregnancy and 3 of the 54 (5.6%) women had another instrumental delivery.

Fetal Short-term Risks

The short-term risks to the fetus from instrumental vaginal delivery are usually caused by head compression and traction on the fetal intracranial structures, face and scalp.

- Vacuum-assisted deliveries: The incidence of serious complications with vacuum extraction is approximately 5%. Torsion and traction of the vacuum cup can cause fetal scalp abrasions and lacerations, separation of the scalp from underlying structures leading to cephalohematoma, subgaleal hematoma (26 to 45 per 1,000 vacuum deliveries; Figs 8A and B) intracranial hemorrhage, hyperbilirubinemia and retinal hemorrhage. These hemorrhages typically resolve without sequelae within 4 weeks of birth. A study of 913 term newborns who were successfully delivered using a vacuum device and who had a skull X-ray and head ultrasound reported skull fracture in 46 (5%). All of the fractures were linear (nondepressed) and no infant was symptomatic. The scalp is sucked into the cup and an artificial caput succedaneum (Chignon) is produced. The chignon usually disappears within few hours. Other injuries which can occur in fetal scalp are shown in Figures 8A and B.
Death from intracranial hemorrhage has been reported. Shoulder dystocia also appears to be more common with vacuum-assisted than forceps deliveries.

- **Forceps-assisted deliveries**: Short-term complications resulting from forceps deliveries include skin markings and lacerations, external ocular trauma, subgaleal hematomas, hyperbilirubinemia, retinal hemorrhage, lipoid necrosis, nerve injury, skull fractures and death. Facial palsies and depressed skull fractures, in particular, are more common with use of forceps than vacuum devices; both complications can also occur after a non-instrumental delivery.

**Fetal Long-term Risks**

Acute fetal injuries with potential long-term sequelae include intracranial hemorrhage (subdural, subarachnoid, intraventricular and/or intraparenchymal hemorrhage) and neuromuscular injury; however, these sequelae are rare.

Developmental outcome appears to be equivalent for both forceps-assisted and vacuum-assisted births. There was no difference in child development between the groups after 5 years of follow-up.

**Specific Points**

**Floating Forceps**

The whole fetal head is above the pelvic brim. This procedure is not performed today, having been superseded by cesarean section.

In the case of a brim or a high cavity application, the only alternative to axis-traction is the use of Pajot’s maneuver (Fig. 9), in which the same resultant effect is attempted by pressing downwards on the shanks of the blades at the same time as traction is exerted. This maneuver incidentally was introduced before the discovery of the principle of axis-traction and is far cruder. Nowadays the importance of axis-traction is dwindling, as the high forceps operation is rarely performed in sound obstetrics practice.

**Midpelvic Arrest: Forceps or Cesarean Section**

Current obstetrics practice is likely to discourage the use of midforceps for delivery of patients whose second stage of labor is prolonged. Some maintain that the danger of both obvious and hidden damage is too great, and that this procedure must be replaced by cesarean section.

Providing there is no cephalopelvic disproportion, midforceps when performed properly by competent hands and on correct indications need not be mutilating to the mother nor impose undue hazards on the fetus. When the head is engaged deeply with the biparietal diameter at the level of ischial spines and the station of +2, midforceps is the procedure of choice, as specially when uterine inertia or maternal fatigue results in arrest in the second stage. The midforceps operation is an important part of obstetrics.

**Failed Forceps or Catastrophic Success**

An attempt to deliver the baby by forceps may fail completely or it may produce a damage or dead baby and leave the mother with a lacerated pelvis. Pitfalls that contribute to making a wrong decision include:

- Misunderstanding the significance and the relationship of station and the level of the biparietal diameter
- Unrecognized disproportion
- Misdiagnosis of station
  - Rectal examination may be inaccurate and unreliable
  - Caput succedaneum
  -Molding
- Misdiagnosis of position, cervical dilatation, inefficient uterine action
- A constriction ring of myometrial spasm that grips the fetus tightly and prevents decent
- Premature interference
- Indecision and stubbornness.
Trial Forceps

The principle of trial forceps postulates that after successful application has been achieved, gentle traction is made. Should the head come down easily the operation is continued and the baby is delivered. If, on the other hand, the operator feels that an undue amount of force would be required to extract the head, the forceps are removed and cesarean section is carried out.

Forceps to Aftercoming Head (Figs 10A to C)

Piper forceps or divergent Laufe forceps may be applied electively or when the Mauriceau maneuver cannot be accomplished easily. The blades of the forceps should not be applied to the aftercoming head until it has been brought into the pelvic cavity by gentle traction, combined with suprapubic pressure and is engaged. Suspension of the body of the fetus in a towel effectively holds the fetus and helps keep the arms out of the way.

SUMMARY AND RECOMMENDATIONS

There is inadequate evidence upon which to base a recommendation for use of either vacuum or forceps for all circumstances when instrumental vaginal delivery is attempted. We believe current evidence supports use of vacuum to minimize maternal morbidity when the gestational age is greater than 34 weeks and the likelihood of success is very high. When success is uncertain, primary use of forceps may reduce the morbidity that has been
associated with combined sequential instrumental delivery. In addition:

- Non-medically indicated shortening of the second stage is not an indication for instrumental vaginal delivery
- Vacuum-assisted deliveries are associated with an increase in neonatal cephalohematomata and retinal hemorrhage. These complications generally resolve without sequelae
- Forceps-assisted deliveries cause significantly more acute maternal injury and fetal facial nerve injury than vacuum-assisted instrumental deliveries or spontaneous deliveries
- Vacuum devices should not be used prior to 34 weeks of gestation or longer than 20 minutes because of the increased risk of intraventricular hemorrhage
- There was no significant difference in results of cognitive testing when 5-year-old children delivered by instrumental vaginal delivery were compared to children delivered by spontaneous vaginal delivery.

An age-old dictum holds true even today! "By skill and not by force".

**BIBLIOGRAPHY**


CHAPTER 36

Modern Management of Breech Presentation

INTRODUCTION

Breech presentation accounts for 3–4% of term singleton pregnancies. At 28 weeks of gestation, 20% of fetuses present as breech and in the 29 to 32 weeks of gestation group, 14% of fetuses are in breech presentation. As term approaches, the incidence of breech presentation steadily decreases as in most cases, the fetus converts to cephalic presentation by 34 weeks of gestation (spontaneous version). Fifteen percent of babies presenting by breech at the onset of labor are preterm, three times the overall rate of preterm labor.

Any condition of the uterus, placenta, umbilical cord, amniotic fluid, fetus or pelvis which interferes with spontaneous version results in a persistent breech presentation. Any neuromuscular dysfunction in the fetus prevents the baby from kicking itself into the head-down position. Breech presentation, but not breech birth, has a predictive relationship to cerebral palsy, meaning thereby that central nervous system damage precedes labor and causes the malpresentation or persistent breech. Breech presentation may be caused by antecedent neurologic abnormalities that are not amenable to prevention by labor or delivery interventions.

Antepartum Risk Factors

The various antepartum factors associated with a persistent breech are:
- Prematurity
- Multiparity
- Multiple pregnancy
- Uterus—Müllerian anomalies, fibroids
- Contracted pelvis
- Placenta previa, placental implantation in cornual-fundal region
- Short umbilical cord
- Oligohydramnios, polyhydramnios
- Fetus—growth retardation
- Congenital anomalies like neural tube defects.

Incidence of anomalous fetus in breech is twice that seen in cephalic presentations, 6.3% versus 2.4%.

- Diabetes mellitus
- Smoking.

It is possible that smoking results in altered neuromuscular coordination and hence inability of the fetus to undergo spontaneous version.

In many cases, no reason or association for the breech presentation is found and, by exclusion, the cause is attributed to chance.

Intrapartum Factors in Breech

- The uneven fit of the breech to the pelvis predisposes to early rupture of membranes and cord prolapse. The incidence of cord prolapse in breech presentation is 4–5% and is higher in footling breech.
- Preterm, prelabor rupture of membranes.
- Dysfunctional labor—Breech is a poor dilator of the cervix compared to the fetal head, hence, labor, descent and cervical dilatation may take longer.
- Obstructed labor, entrapment of after-coming head of breech, nuchal arms are peculiar to breech births.
All the above antenatal risk factors, along with intrapartum events, place the breech fetus in a “high risk pregnancy and labor group”.

The various modalities of managing a term breech fetus are:
- External cephalic version and delivery as vertex
- Elective cesarean
- Trial of breech (selective cesarean).

**Modes to Promote Version**

- External cephalic version (ECV)
- Moxibustion is a procedure in Chinese traditional medicine wherein combustible herbal material is placed atop acupuncture needles at acupoints. Stimulation of acupoint BL67, located besides the outer corner of the fifth toenail, for 1–2 weeks, promotes correction of breech presentation by increasing fetal activity.
- Hypnosis
- Acupuncture
- Knee-chest position with buttocks higher than the trunk for 15 minutes, every 2 hours of waking for 5 days
- Abduction of thighs with elevation of pelvis with breathing techniques.

**EXTERNAL CEPHALIC VERSION**

External cephalic version (ECV) refers to external, per- abdomen maneuvers by which breech presentation is changed to cephalic. The use of sonography, electronic fetal heart rate monitoring along with tocolysis results in ECV being a safe and effective procedure for the management of the term breech. All women at term with an uncomplicated pregnancy and breech presentation should be offered ECV. Incorporating ECV in clinical practice would result in reduction in breech births from 78% to 44% and a reduction in cesarean section rate from 29% to 15%. Factors that may modify the success of external cephalic version are presented in Table 1.

<table>
<thead>
<tr>
<th>Pre-requisites for External Cephalic Version</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Written, informed consent.</td>
</tr>
<tr>
<td>2. <strong>Term breech:</strong> Traditionally, ECV was performed at 32 weeks though the present trend is to perform ECV after 36 weeks. In a preterm breech, ECV is technically easier to perform due to a relatively large amniotic fluid pool and a small fetus, but it is not recommended for the following reasons:</td>
</tr>
<tr>
<td>- The spontaneous cephalic version rate is 57% after 32 weeks and 25% after 36 weeks. This does not support the use of ECV with its attendant risks at lower gestational age. At term, the spontaneous version rate varies from 14% to 22% and there appears to exist a constant ratio of 3:1 between ECV success and spontaneous version rates.</td>
</tr>
<tr>
<td>- The risk of preterm labor and rupture of membranes exists with preterm ECV. Also, in the event of fetal distress during preterm version, one may be forced to deliver a baby before term resulting in iatrogenic prematurity, an avoidable complication.</td>
</tr>
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<td>- Spontaneous re-version to breech after ECV occurs in 1–4% cases at term and the incidence would be much higher if ECV is done in preterm fetuses.</td>
</tr>
<tr>
<td>- Contraindications to ECV like growth restriction, preeclampsia and oligohydramnios may not be apparent till term.</td>
</tr>
<tr>
<td>3. Ultrasonography to confirm presentation and to rule out contraindications for ECV.</td>
</tr>
<tr>
<td>4. Contraindications ruled out, namely:</td>
</tr>
<tr>
<td>- Compromised fetus—intrauterine growth restriction (IUGR), pregnancy-induced hypertension (PIH)</td>
</tr>
<tr>
<td>- Nonreactive nonstress test (NST)</td>
</tr>
<tr>
<td>- Oligohydramnios</td>
</tr>
<tr>
<td>- Placenta previa</td>
</tr>
<tr>
<td>- Multiple pregnancy</td>
</tr>
<tr>
<td>- Any contraindication to labor or vaginal delivery</td>
</tr>
<tr>
<td>- Any obstetric indication for cesarean</td>
</tr>
</tbody>
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   - Nonreactive nonstress test (NST)
   - Oligohydramnios
   - Placenta previa
   - Multiple pregnancy
   - Any contraindication to labor or vaginal delivery
   - Any obstetric indication for cesarean

External cephalic version in a case of previous transverse lower segment cesarean has been found to result in no serious maternal or neonatal complications.

5. Preprocedure NST.
6. Fetal heart rate monitoring during ECV and intra-procedure ultrasound surveillance.
7. Provisions made for immediate delivery in the event of fetal distress during ECV.
8. Postprocedure NST.
9. Administration of anti-D immunoglobulin to Rh-negative women, undergoing ECV.
10. **Tocolysis:** Terbutaline 0.25 mg subcutaneously is useful in cases wherein the tone of the uterus was a cause of an unsuccessful ECV. In other cases, use of tocolytics did not demonstrate an increased incidence of successful version. Use of nitroglycerine spray as a tocolytic
for ECV was not found to be useful and was associated with significant side-effects in the form of headaches and symptomatic hypotension.

Complications of External Cephalic Version

- Transient fetal bradycardia occurs in 3–4% cases
- Placental separation
- Rupture of membranes
- Cord prolapse, cord entanglements
- Fetomaternal hemorrhage in 1.8% cases
- Fetal distress, fetal death.

Successful External Cephalic Version Factors

Successful external cephalic version depends on the following factors:

- Multiparity (lax abdominal wall and lower resting tone of the uterus)
- Nonfrank breech—extended legs of a frank breech have a splinting effect and decrease the maneuverability of the fetus
- Unengaged breech
- Adequate amniotic fluid pool
- Posterior placental implantation
- Repeat ECV at a later date after an unsuccessful attempt
- Transabdominal amnioinfusion of saline in oligohydramnios
- Fetal acoustic stimulation to shift the fetal spine to a lateral position in cases of midline spines.

Success of ECV varies from 48% to 93% in various studies. A failed version is associated with an 83% cesarean rate while the cesarean rate in version cases drops to 37%.

Egge et al. state that the outcome of labor following ECV is no different from that of a cephalic presentation and that there is no dystocia or dysfunctional labor requiring cesarean in ECV successful patients. On the other hand, Lau et al. quoted a cesarean rate of 16.9% in the ECV successful group (cesarean rate 2–2.5 times higher than the control group of non-ECV cephalic presentations) due to fetal distress and dystocia labor. They concluded that pregnancy and labor after successful ECV should be considered as high risk in view of higher chances of fetal distress and dystocia. It is possible that the breech presentation by itself, with its association with atypical neuromuscular function and predilection to abnormal fetal heart rate patterns due to central nervous system dysfunction results in intrapartum fetal distress and dystocia which may be interpreted incorrectly as acquired fetal jeopardy in labor. The Westin scoring system for selecting mode of delivery in breech is presented in Table 2.

Vagaries of a Vaginal Breech Birth

An irregular presenting part, namely the breech (compared to vertex), is a slow dilator of the cervix with resultant tardy progress of labor.

The largest and the least compressible fetal part, the head delivers last in a breech delivery with the risk of entrapment of the aftercoming head.

Table 2: Westin scoring system for selecting mode of delivery in breech

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Score 0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inlet, anteroposterior diameter</td>
<td>&lt; 11.5</td>
<td>11.5–12.5</td>
<td>&gt; 12</td>
</tr>
<tr>
<td>Inlet, transverse diameter</td>
<td>&lt; 12.5</td>
<td>12.5–13.5</td>
<td>&gt; 13</td>
</tr>
<tr>
<td>Outlet, anteroposterior diameter</td>
<td>&lt; 10.5</td>
<td>10.5–1</td>
<td>&gt; 11</td>
</tr>
<tr>
<td>Outlet, interspinous diameter</td>
<td>&lt; 10</td>
<td>10–10.5</td>
<td>&gt; 10.5</td>
</tr>
<tr>
<td>Intertuberos diameter</td>
<td>&lt; 10</td>
<td>10–11</td>
<td>&gt; 11</td>
</tr>
<tr>
<td>Sum of outlet</td>
<td>&lt; 32.5</td>
<td>32.5–33.5</td>
<td>&gt; 33.5</td>
</tr>
<tr>
<td>Estimated weight of fetus in grams</td>
<td>&lt; 1500, &gt; 4000</td>
<td>1500–2000</td>
<td>2000–3500</td>
</tr>
<tr>
<td>Presentation</td>
<td>Double footling</td>
<td>Complete breech, single footling</td>
<td>Frank</td>
</tr>
<tr>
<td>Soft parts</td>
<td>Unripe cervix and rigid pelvic floor</td>
<td>Unripe cervix or rigid pelvic floor</td>
<td>Ripe cervix and relaxed pelvic floor</td>
</tr>
<tr>
<td>Previous deliveries</td>
<td>None</td>
<td>Uncomplicated breech &lt; 2000</td>
<td>Uncomplicated breech 2000–3000</td>
</tr>
<tr>
<td></td>
<td>Uncomplicated head &lt; 3000</td>
<td>Uncomplicated head &lt; 3000</td>
<td></td>
</tr>
</tbody>
</table>

If all the parameters of pelvis are included, a score of 12 is safe for vaginal delivery. However, if any single score lies within the outlined box, or any two entries within the interrupted lines, Westin considered that LSCS was indicated irrespective of the total score. However, a lot of parameters in this system are based on pelvimetry other than clinical, which is not routinely done.
An irregular ill-fitting presenting part, the breech, contributes to premature rupture of membranes along with the risk of cord prolapse.

Sudden excessive pressure on the after-coming head of breech results in tentorial tears and intracranial hemorrhage as opposed to the slow gradual head moulding in vertex deliveries.

Patients with failed ECV can be offered a choice of “elective cesarean” versus “selective cesarean (trial of breech)

**Recommendations for Delivery (Cesarean)**

Cesarean delivery is commonly, but not exclusively, used in the following circumstances:
- A large fetus
- Any degree of contraction or unfavorable shape of the pelvis determined clinically or with computed tomography (CT) pelvimetry
- A hyperextended head
- When delivery is indicated in the absence of spontaneous labor
- Uterine dysfunction—some would use oxytocin augmentation
- Incomplete or foaling breech presentation
- An apparently healthy and viable preterm fetus with the mother in either active labor or in whom delivery is indicated
- Severe fetal-growth restriction
- Previous perinatal death or children suffering from birth trauma
- A request for sterilization
- Lack of an experienced operator.

**ELECTIVE CESAREAN**

Proponents of this policy vouch that all breech births must be by the abdominal route because of the concern for birth trauma and birth asphyxia with vaginal birth and unexpected arrest of fetal parts at delivery. Lee et al. concluded that primary cesarean births as against vaginal birth for breech are associated with significantly lower neonatal mortality for all birth weight groups. Krebs et al. conducted a register-based study and concluded that elective cesarean for the term breech gives improved perinatal outcome with respect to intrapartum and early neonatal deaths and Apgar scores.

A landmark multicentric randomized controlled study—“The Term Breech Trial”, comparing planned cesarean versus planned vaginal birth was conducted by Hannah et al. of the University of Toronto, Canada from 1997 to year 2000. A total of 2088 women were recruited from 121 centers of 26 countries. Of the women assigned planned cesarean, 90.4% delivered by cesarean and of the women assigned planned vaginal birth, 56.7% delivered vaginally. Perinatal mortality, neonatal mortality and serious neonatal morbidity were significantly lower for the planned cesarean group. There was no difference between the two groups in terms of maternal mortality or serious maternal morbidity. The study concludes that planned cesarean is better than planned vaginal birth for the term breech, the benefits being greater in countries having lower perinatal mortality rates.

The authors (Dr Vandana Walvekar and Dr Pratima Anjaria of the Nowrosjee Wadia Maternity Hospital, Mumbai, Maharashtra, India) were part of the Term Breech Trial team. Wadia Hospital was one of the three centers from India to have participated in this international study. The authors’ experience with respect to maternal and fetal outcome was similar to the final result of the trial.

**TRIAL OF BREECH (VAGINAL BREECH DELIVERY)**

Patient selection is done by the following criteria:
- Thirty-seven completed weeks of gestation (term)
- Frank or complete breech (buttocks below the feet)
- Estimated fetal weight between 1.5 kg and 3.5 kg. For fetuses weighing less than 1.5 kg, it is justifiable to perform a cesarean if the baby can be received in an intensive care unit wherein it has at least a 40% chance of an unhandicapped survival
- Well-flexed head
- No fetopelvic disproportion
- No contraindication for labor or vaginal birth
- No obstetric indication for cesarean
- No growth retardation with head-sparing effect
- Informed consent. The patient is counseled about the 20% rate of failed trial of breech and resultant emergency cesarean.

**Pre-requisites and Requirements for Conduct of a Trial of Breech**
- Strict inclusion criteria and ruling out contraindications to a vaginal breech birth
- Informed consent
- Availability of a skilled and trained obstetrician along with a neonatologist and anesthetist
- Partogram to detect tardy labor
- Resorting to cesarean in cases of failure of descent of breech or failure of cervical dilatation (an indication of fetopelvic disproportion)
- Oxytocin to augment labor in the absence of fetopelvic disproportion
- Avoid ARM till the breech distends the perineum
- In cases of spontaneous rupture of membranes, an immediate per vaginal examination is mandatory to rule out cord prolapse
- Lumbar epidural analgesia relieves pain and prevents involuntary bearing-down efforts prior to full dilatation, thus preventing the occurrence of the breech slipping
through a partially dilated cervix with arrest of the aftercoming head
• Delivery in the operation theater by “assisted breech delivery” with an adequate and generous episiotomy and an anesthetist stand-by.

Dilemmas and Discussion

The fetus presenting by the breech at term, as compared to the cephalic presentation, is at greater risk of perinatal and neonatal morbidity and mortality, due principally to birth trauma birth asphyxia and congenital anomalies. There are two schools of thought regarding the management of a non-anomalous, term breech fetus.

Elective Cesarean

Proponents of this policy “elect” for an elective cesarean because of the concern for birth asphyxia and possibility of unexpected arrest of fetal parts at vaginal delivery. Most couples today, in this increasingly competitive world, opt for a small family but a “quality” family and hence any risk of compromised perinatal and neonatal outcome is not accepted. Also, ethical and medicolegal issues prevent many obstetricians from contemplating a vaginal trial for the term breech. Thus, the pendulum for the management of the term breech fetus has swung from routine vaginal breech delivery for all cases to the present trend of elective cesarean section for all.

The timing of the cesarean for breech seems important in decreasing neonatal morbidity. Cesarean before labor was better than a cesarean in early labor, which in turn was better than a cesarean in late labor. In this study by Su et al., of those patients who labored with a term breech, the risk of poor outcome was increased with labor augmentation, a longer second stage of labor and birth weight less than 2.8 kg.

Selective Cesarean or Trial of Breech

Obstetricians skilled in vaginal breech delivery argue that the above intrapartum risks with vaginal delivery are overstated due to improperly carried out research studies which involve selection bias, failure to comment on intrapartum management and no assurance that the accoucheur is skilled in the art of vaginal breech delivery. These proponents also point that the persistent breech is a result of poor fetal quality with respect to neuromuscular dysfunction and hence the mode of delivery is unlikely to change the perinatal outcome to that of vertex. Also, cesarean alone cannot guarantee a good neonatal outcome as maneuvers of delivering a breech fetus by cesarean are similar to that of a vaginal breech delivery.

All said and done, as more and more number of women undergo cesarean for breech, obstetrical trainee doctors have less opportunities to acquire the skills of conducting a vaginal breech delivery. A time would come when this art would be permanently lost. This would result in a greater neonatal adverse outcome in the event of an imminent breech delivery without adequate facilities of an experienced accoucheur. In the bargain, the prevailing enthusiasm for offspring of the highest quality in a one- or two-child family will continue to result in the frequent use of cesarean for the breech fetus.

Breech with Previous Cesarean Section: A Management Dilemma

Ophir et al. conducted a study of 71 breech births after previous cesarean and concluded that a trial of breech seems reasonable in carefully selected cases. Neonatal morbidity did not differ for women who delivered vaginally or by cesarean though maternal febrile morbidity was significantly higher in the cesarean group.

Preterm Breech

Cesarean was associated with a significant decrease in intraventricular hemorrhage and neonatal deaths in infants weighing less than 1.25 kg. Several studies suggest that nonfrank breech presentations are at greater risk for cord accidents and that fetuses of earlier gestations may be most likely to benefit from a cesarean because of the potential to avoid mechanical complications like head entrapment. Fetal mortality and morbidity associated with vaginal delivery of a term breech is three times that of cephalic presentations. The worst prognosis is in the preterm breech. In difficult vaginal breech delivery, the risk of fetal damage is 20%, in easy births it is 3.5%. Fifteen percent of fetal deaths occur during labor and intracranial hemorrhage associated with a preterm vaginal breech delivery is a major cause of fetal mortality.

References

13. RCOG view—The effective procedures in obstetrics suitable for audit, RCOG audit unit, Manchester, July 1993.
Changing Trends in Cesarean Section

HISTORY OF CESAREAN SECTION

Cesarean section is one of the oldest operations in surgery and probably derived its name after the births of Julius Caesar. The monograph of Trolle traces the history of cesarean section (CS) which was first performed on a dead patient. The case often cited as representing the first CS performed on a living woman is attributed to a German named Jacob Nufer, who performed the operation on his wife in 1500 AD. His wife survived and lived to give birth to two subsequent children by the vaginal route. The case was reported almost a hundred years later. CS on the living was first recommended by Francois Rousset in 1581 although he had never performed or witnessed the operation and his information was based on letter from friends. Authoritative statements by dependable obstetricians about early use of the operation, however, did not appear in literature until the middle of 17th century when it was employed in rare and desperate cases and was usually fatal. The appalling maternal mortality rate of CSs continued until the beginning of the 20th century and the rate reported in 1865 was 85%. A modification in technique was introduced by Porro of Italy in 1876 which consisted of amputation of the body of uterus and fixing the cervical stump to the lower angle of the abdominal wound. This reduced the maternal mortality to half. The turning point came in 1882 when Max Sanger introduced suturing of the uterine wall. The introduction of uterine sutures reduced the mortality rate of the operation from hemorrhage. However, generalized peritonitis remained the dominant cause of death and various operations were devised to combat this problem. The first extraperitoneal operation was described by Frank in 1907 and later modified by Latzko (1909) and Waters (1940). In 1912, Krong postulated that the main advantage of the extraperitoneal technique consisted of opening the uterus through its thin lower segment and then covering the incision with the peritoneum. The lower segment technique was introduced by Beck in 1919 and later popularized by Delee (1922). In these, however, the uterine cavity was opened by a vertical incision rather than a transverse one. An important modification recommended by Kerr in 1926 was to open the cavity by transverse rather than a longitudinal uterine incision.

INCIDENCE

The CS continues to be one of the most important surgical interventions performed in obstetrics practice. Its rate has increased dramatically over the past three decades. Taffel et al. reported the rate as 9.5% in 1965, 15% in 1978 and as high as 25% in 1988. The cesarean delivery rate decreased from 1987 to 1996, but has been on the increase since 1996. There is no single factor that can account for the dramatic increase in cesarean deliveries during the last 30 years. The distribution of maternal age and parity has changed over the course of the past four decades, with many women choosing to delay childbirth and limiting their number of pregnancies. CS rates have been shown to be related to the socioeconomic status of the patients, the proportion of patients purchasing private obstetric care, the risk of litigation, the increased availability of medical technology such as fetal monitoring and neonatal facilities, and patient demand for CS. The widespread use of repeat elective CS for women who have had a previous CS and maternity unit policies to deliver breech presentations and multiple pregnancies by CS have also made a significant contribution to its increasing rate. Teaching hospitals tend to have lower cesarean delivery rates than private institutions. This is mainly due to the role of residents and the use of clinical guidelines.
In the seventies dystocia accounted for 30% increase in CS rate. However, the vast majority of cesarean deliveries performed because of dystocia were often in pregnancies with normal sized infants, therefore, the increase in rate was difficult to understand. O’Driscoll and Foley in 1983 advocated the use of oxytocin and partogram and reduced the number of CSs due to dystocia. In 1993, Bhide in his study showed a decline in the rate of CSs due to dystocia, over the last five years. He attributed it to the active management of labor. A similar trend has been reported by other workers also.

Breech presentation at term is encountered in 3–4% of all pregnancies. Breech presentation is the primary indication for 10% of all CSs; overall 60–88% of pregnancies with breech presentation are delivered by CS. Williams reported breech presentation as the indication in 15% of all lower segment cesarean section. However, CS rates vary with gestational age, at term 91% women with a breech presentation had a CS, while at less than 28 weeks, the CS rate was less than 40% (evidence level 3). In the CEDS1 project 27/28 report, survival rates were significantly greater in those infants delivered by CS (86.5%) than those delivered vaginally (77.4%) (evidence level 3). In a retrospective study, conducted at UCMS and GTB Hospital, Delhi, the incidence of CS for breech was 40%. Apart from the parity, gestational age and the weight of the baby, other factors that determined the rate, in this study, included the socioeconomic status of the women and their reluctance for an operative delivery.

One-third of all sections performed each year in the United States are for women with previous cesarean delivery. Nine percent of women giving birth in England and Wales have had a previous CS. Repeat CS contributes about 14% to the overall CS rate. An increase in the percentage of women who have had a previous CS in a population will result in a disproportionate increase in the overall CS rate. Before 1978, trial of labor was virtually unknown. But now review of literature has documented the safety, acceptability and high rate of subsequent vaginal delivery in cases of previous CS. Overall, the chances of successful planned vaginal birth after cesarean (VBAC) are 72–76%. The single best predictor for successful VBAC is a previous vaginal birth, particularly previous VBAC which is associated with an approximately 87–90% planned VBAC success. The risk of uterine rupture in such cases is 22–74 per 10,000. Patients with induced labor, no previous vaginal birth, body mass index greater than 30, and previous CS for dystocia have more chances for unsuccessful VBAC (Table 1).

Table 1: Indication for cesarean delivery from the maternal-fetal medicine units network

<table>
<thead>
<tr>
<th>Case</th>
<th>Cesarean deliveries (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td></td>
</tr>
<tr>
<td>Dystocia</td>
<td>8,122 (37)</td>
</tr>
<tr>
<td>Nonreassuring fetal heart rate</td>
<td>5,404 (25)</td>
</tr>
<tr>
<td>Abnormal presentation</td>
<td>4,321 (20)</td>
</tr>
<tr>
<td>Other</td>
<td>3,323 (15)</td>
</tr>
<tr>
<td>Unsuccessful trial of forceps or vacuum</td>
<td>628 (3)</td>
</tr>
<tr>
<td><strong>Repeat</strong></td>
<td></td>
</tr>
<tr>
<td>No VBAC attempt</td>
<td>12,565 (82)</td>
</tr>
<tr>
<td>Failed VBAC</td>
<td>2,687 (17)</td>
</tr>
<tr>
<td>Unsuccessful trial of forceps or vacuum</td>
<td>60 (0.4)</td>
</tr>
</tbody>
</table>

Although according to Royal College of Obstetricians and Gynaecologists (RCOG) recommendations, women with a prior history of two uncomplicated low transverse CSs, in an otherwise uncomplicated pregnancy at term, with no contraindications for vaginal birth may be considered for planned VBAC (Grade B recommendation). Analysis of the NICHD study showed that there was no significant difference in the rates of uterine rupture in VBAC with two or more cesarean births (9/975, 92/10,000) compared with a single previous cesarean birth (115/16,915 and 68/10,000).

- **Induction and augmentation:** Patients with previous cesarean delivery have a two- to three-fold increased risk of uterine rupture and about 15-fold increased risk of CS in induced and/or augmented labor compared with spontaneous labor. Induction/augmentation in such patients should be preceded by careful obstetric assessment and maternal counseling, strict oxytocin dose titration and careful serial cervical assessments (Evidence level 3). Studies have shown a small but statistically significant higher uterine rupture risk (87/10,000 versus 29/10,000) with prostaglandin induction compared with nonprostaglandin induction.

- **Uterine exploration:** Though uterine exploration is not recommended after vaginal delivery but is still done by many. If a rent is found not communicating with the peritoneal cavity, there is no bleeding and the patient is stable, laparotomy is not required but trial of scar in a subsequent pregnancy is not recommended.

Fetal distress has accounted for 10–15% increase in the CS rate. Dalvi from Bombay reported that fetal distress was the indication in 26.5% of all CSs. Overall an abnormal cardiotocogram was noted in 69% of singleton pregnancies delivered by CS for presumed fetal distress. Systematic review
of 9 randomized controlled trial over 20 years (n = 18,561 women) have shown that the use of electronic fetal monitoring (EFM) during intrapartum care results in increased CS rates (RR, 1.4; 95% CI, 1.23–1.61). This increase is less marked if fetal blood sampling (FBS) is used (RR, 1.27; 95% CI, 1.08–1.51 for EFM with FBS, compared with RR, 1.41; 95% CI, 1.23–1.61 for EFM without FBS). It is now recommended that when CS is contemplated because of abnormal fetal heart pattern, in cases of suspected fetal acidosis, FBS should be offered if technically possible and there are no contraindications (Grade B recommendation). The distressed fetus often responds favorably to change in maternal position and use of oxygen, so that in a few cases cesarean delivery can be avoided. In cases complicated with thick meconium, Wennstroms and Parsons reported a significant reduction in the CS rate with the use of intrapartum saline infusion. In a study carried out at the author’s hospital, amnioinfusion was carried out in cases with thick meconium using 18 G suction catheter as a part of postgraduate thesis. It was found to be a safe and simple technique that resulted in decreased CS rate.

Maternal request for CS is an indication which is steadily increasing in today’s world. The rates of preference for CS expressed by the women surveyed during pregnancy in UK, Australia and Sweden range from 6% to 8%. Within these studies there was a consistent relationship between women’s preference for CS and either previous CS, negative birth experience, a complication in the current pregnancy or a fear of giving birth. RCOG recommends that maternal request is not on its own an indication for CS and specific reason for the request should be explored and discussed. If she requests a CS because she has a fear of childbirth, she should be offered counseling (such as cognitive behavioral therapy) to help her address her fears in a supportive manner (Grade A recommendation).

**CHANGING TRENDS IN OPERATIVE TECHNIQUE OF CESAREAN SECTION**

The endpoint of successful CS is a healthy mother and healthy child. In the recent years maternal risk from CS has declined significantly and major factors responsible for the reduced risk include improvement in surgical and anesthetic techniques, safe blood transfusion and the use of antibiotics. Durphy et al. in 1991 showed that the relative risk of neonatal asphyxia can be reduced to half if the decision to delivery interval is kept less than 20 minutes. The other factors that need in-depth discussion are the following:

**Abdominal Incision**

The skin incision is chosen to optimize access to the surgical field thereby minimizing maternal morbidity while producing a maximal cosmetic effect. Previously vertical incision was in vogue due to superior access to surgical field and potential for extending the incision. Nowadays, transverse incision is recommended as it is associated with better cosmetic effect, decreased postoperative pain and decreased inhibition of deep respiration (Grade B recommendation). The transverse incision of choice should be the Joel Cohen incision (straight skin incision 3 cm above symphysis pubis, subsequent tissue layers are opened bluntly) because it is associated with shorter operating time and reduced postoperative febrile morbidity (Grade A recommendation).

**Bladder Flap Formation**

This is dissection of bladder from lower segment. Hohlgenschwandtner et al. compared 102 women undergoing CS with “bladder flap” formation or “no bladder flap” formation. They found decreased operative time, blood loss and need for postoperative oral analgesics without an increase in infectious morbidity in the “no bladder flap formation” group. Eisenkop et al. in a retrospective study found rate of bladder injury to be 0.3%. These injuries most commonly occurred during formation of bladder flap, whereas only 2 out of 23 cases occurred during extension of uterine incision.

**Extension of Transverse Uterine Incision**

Extending the uterine incision either by blunt dissection or by scissors was studied by Rodriguez et al. They found no difference in operative time, blood loss, infectious complication or risk of extension between the two. When there is a well formed lower uterine segment, blunt rather than sharp extension of the uterine incision should be used as it reduces blood loss, incidence of PPH (Grade A recommendation). Under unusual circumstances variation in the uterine incision may be required.

- **Classical CS:** This is done in cases where the lower segment is not easily accessible; there is extreme kyphoscoliosis, dense bladder adhesions, myoma in the lower segment, carcinoma cervix, narrow lower segment and in some cases of renal transplantation where the kidney is close to or obscuring the lower segment.
- **Vertical lower segment:** In obstructed labor with the head deeply engaged and the lower segment thinned out, manipulations to dislodge the head may sometimes result in lateral extension and involvement of uterine arteries. In this circumstance, a low vertical incision is recommended. As the lower segment is wide here, extension to the upper segment is unlikely. However, in preterm delivery when the lower segment is not formed, extension to the upper segment may occur.
- **J-shaped incision:** This type of incision is preferred over the classical T-shaped in cases of transverse lie, hand prolapse and large baby to avoid extension. Table 2 shows the risk of uterine rupture in relation to scar location.
Delivery of Fetal Head

Use of ventouse or forceps, as compared to manual extraction of head provided no benefit in terms of uterine incision extension or blood loss. Forceps should only be used at CS if there is difficulty in delivering the baby’s head. The effect on neonatal morbidity of routine use of forceps is uncertain (Grade C recommendation).

Removal of Placenta

The Cochrane database meta-analysis of the topic demonstrated that there is a clinically and statistically significant decrease in maternal blood loss and postpartum endometritis associated with the traction method of placental removal as compared with manual removal. Sponge curettage of uterine cavity did not decrease the risk for endometritis.

Exteriorization of Uterus for Repair of Hysterotomy

The Cochrane database in a meta-analysis found no difference in blood loss or infectious complications between exteriorization and in situ repair of hysterotomy incisions. Exteriorization may facilitate repair but there is insufficient evidence to support its routine use. So, exteriorization of the uterus is not recommended because it is associated with more pain and does not improve operative outcome such as hemorrhage and infection (Grade A recommendation).

Closure of Uterine Incision

Both one layer and two layered closure of uterine incision have been practiced currently. One layered closure has shown to decrease operative time and blood loss in the short term. In long term, the risk of uterine rupture during subsequent labor is increased. Bujold et al. in an observational cohort study found a four-fold increased risk of uterine rupture among patients with previous one layered closure of uterine incision. The current recommendation is to close the uterus in two layers as the effectiveness and safety of single layer is uncertain (Grade B recommendation).

Closure of Visceral Peritoneum (Bladder Flap) and Parietal Peritoneum

Except for restoring the anatomy to preoperative state there is less data to support closure of peritoneum. In a study the peritoneal closure group was found to have increased incidence of cystitis, antibiotic use and analgesia, purportedly because of subperitoneal pocket formation which served as a nidus for infection.

The Cochrane database, in its meta-analysis concluded that nonclosure of parietal peritoneum reduces operative time without increasing infectious complications and may offer decreased analgesic requirement. The current recommendations are that neither the visceral nor parietal peritoneum should be sutured at CS as this reduces operative time and the need for postoperative analgesia (Grade A recommendation).

Closure of Subcutaneous Tissue

Routine closure of the subcutaneous tissue space should not be used, unless there is more than 2 cm subcutaneous fat, because it does not reduce the incidence of wound infection (Grade A recommendation).

Antibiotic Prophylaxis

A multitude of studies have consistently shown that parenteral antibiotic prophylaxis at the time of cesarean results in significant reduction in infectious complications. So, women having a CS should be offered prophylactic antibiotics, such as single dose of first generation cephalosporin or ampicillin to reduce risk of postoperative infections, which occurs in about 8% of women (Group A recommendation).

Modified Technique for Lower Segment Cesarean Section

Misgav Ladach Method

The Misgav Ladach method was based on the principle to minimize tissue trauma by reducing unnecessary dissection. The important steps of procedure are as follows:

- Joel-Cohen skin incision is given
- Uterovesical pouch is opened and the bladder is pushed down with blunt dissection
- Small transverse incision in the lower uterine segment is made to accommodate two fingers and the incision stretched manually
- Uterus is exteriorized after delivery of the fetus and placenta
- Single layer uterine closure; parietal and visceral peritoneum are left unsutured
- Abdominal closure is done in two layers (rectus sheath and skin)
A number of prospective studies have shown that CS performed by the Misgav Ladach technique compared to the conventional Pfannstiel method have a shorter operative time and less wound infection, postoperative pain and febrile morbidity.

**CONCLUSION**

Cesarean section is more traumatic than an easy vaginal delivery and an elective CS is preferred over a difficult vaginal delivery to avoid fetal and maternal trauma. Complaints and litigations are more frequent in obstetrics and gynecology than in other divisions or care groups of most hospitals. This is inevitable since the nature of work in reproduction generates high expectations from the family where everyone hopes for the best outcome for the mother and her baby.

**BIBLIOGRAPHY**

INTRODUCTION

Postpartum hemorrhage (PPH) is the single most important cause of maternal death in the developing countries which accounts for 130,000 deaths per year in India. About 88% occur within 4 hours of delivery and 70% are due to atonic PPH. This PPH can be prevented by active management of third stage of labor, identification of risk factors, and being on alert, should active management fail.

In 2003, the International Confederation of Midwives (ICM) and International Federation of Gynecologists and Obstetrics (FIGO) published a joint statement on the prevention of PPH. In addition to recommending that birth attendants have the knowledge, skills and judgment to carry out active management of third stage of labor and access to needed supplies and equipment. The statement also recommends that active management should be offered to all women in labor.

The ICM/FIGO definition of active management of third stage of labor includes:
- Delivery of oxytocin [10 international units (IU) intra-muscular (IM)] within 1 minute of birth of the baby
- Clamping of the cord once it stops pulsating
- Controlled cord traction
- Massage of the fundus of the uterus until it is contracted.

ACTIVE MANAGEMENT

A systematic review comparing active versus expectant (physiological) management of third stage identified five relevant randomized controlled trials, four of which the reviewers assessed to be of good quality. In these trials expectant management was defined as awaiting spontaneous delivery of the placenta with the aid of gravity or nipple stimulation. Cochrane reviewers advocate for active management of third stage as the routine management of choice for women planning a vaginal delivery in hospital, and suggest that additional research is needed to clarify the implications in other settings including home births. Active management is, however, associated with an increased risk of unpleasant side effects (e.g. nausea, vomiting) and hypertension where ergometrine is used (Cochrane review, 2006) (Table 1).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Control rate (%)</th>
<th>Relative risk</th>
<th>95% CI*</th>
<th>NNT†</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPH ≥ 500 mL</td>
<td>14</td>
<td>0.38</td>
<td>0.32–0.46</td>
<td>12</td>
<td>10–14</td>
</tr>
<tr>
<td>PPH ≥ 1,000 mL</td>
<td>2.6</td>
<td>0.33</td>
<td>0.21–0.51</td>
<td>55</td>
<td>42–91</td>
</tr>
<tr>
<td>Hemoglobin &lt; 9 g/dL</td>
<td>6.1</td>
<td>0.4</td>
<td>0.29–0.55</td>
<td>27</td>
<td>20–40</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>2.3</td>
<td>0.44</td>
<td>0.22–0.53</td>
<td>67</td>
<td>48–111</td>
</tr>
<tr>
<td>Therapeutic uterotonic</td>
<td>17</td>
<td>0.2</td>
<td>0.17–0.25</td>
<td>7</td>
<td>6–8</td>
</tr>
</tbody>
</table>

*95% confidence interval  
†Number needed to treat  
Abbreviation: PPH, Postpartum hemorrhage
The findings show a conclusive benefit for active management, with an approximately 60% reduction in the occurrence of PPH more than or equal to 500 mL and 1,000 mL, hemoglobin value of less than 9 g/dL at 24–48 hours after delivery and the need for blood transfusion. The need for therapeutic uterotonic agents was also reduced by 80%. These results were all highly significant, as indicated by the 95% (confidence interval) CI. A higher incidence of increased blood pressure (BP) following delivery (diastolic BP > 100 mm Hg), nausea and vomiting were observed. These appear to be a function of the chosen uterotonic, especially with ergot preparations and not with oxytocin.

There is a gap in the current research regarding what impact each of the individual components of active management has on preventing blood loss. It appears that the key element of active management is the administration of oxytocic drug.

**OXYTOCIC DRUGS FOR ACTIVE MANAGEMENT OF THIRD STAGE OF LABOR**

Commonly used drugs are:
- Oxytocin
- Ergot alkaloids (ergometrine/methyl ergometrine)
- Misoprostol
- Carbetocin (15-methyl PGF, alpha).

One debated aspect of active management is the ideal choice of prophylactic uterotonic. While some argue that currently there is little evidence that any route, dose or timing of oxytocin administration is superior, there has in fact, been a fair amount of research done which compares the effects of oxytocin, ergonovine or a combination of these drugs, administered intravenously (IV) or intramuscularly (IM).

**Oxytocin versus no Uterotonic**

In a study covering over 3,000 women there were clear benefits to women who received prophylactic oxytocin as a part of the third stage of labor when compared to women who did not receive any uterotonics. The benefits relate specifically to indicators of blood loss such as PPH, whether more than 500 mL or more than 1,000 mL and the need for therapeutic oxytocics. In this study, no differences were seen in the need for blood transfusion or manual removal of placenta. The results of these reviewers suggest that oxytocin appears to be the agent of choice of active management of third stage of labor (AMTSL) in low risk women. Prophylactic oxytocin may be given as 10 IU IM, 20–50 IU/L, IV drip run at 100–150 mL/min. or 5 IU IV push. Some authorities caution against the use of bolus of IV oxytocin, citing small studies which suggest that such practices could compromise women’s hemodynamic state. When caring for women who give birth without pain medication, care providers should remember that IM oxytocin is relatively painful.

**Oxytocin versus Ergot Alkaloids**

*Cochrane Review*

The drugs used in AMTSL are oxytocin and ergometrine, given alone or in combination. They may be given IM or IV and the injection may be administered with the crowning of the head, after delivery of the anterior shoulder, after delivery of the infant or after delivery of the placenta.

Oxytocin provides rhythmic contractions of the uterus augmenting retraction and its effect is noticeable in about 3 minutes after an IM injection.

Ergometrine by IM injection results in a more prolonged contraction with retraction and its effect is noticeable in about 7 minutes. When either drug is given IV, the uterine contraction commences in 30–40 seconds.

In a study covering over 2,800 women, overall there is little evidence of differential effects of these two oxytocics. The oxytocin is associated with fewer manual removals of the placenta, less raised BP than with ergot alkaloids. For all other outcomes definite conclusions can not be drawn.

**Oxytocin versus Oxytocin: Ergometrine**

*Cochrane Review*

A systematic review comparing oxytocin (syntocinon) versus oxytocin–ergometrine (syntometrine) for AMTSL, identified six relevant trials (involving 9,332 women). The combination was associated with a small but statistically significant reduction in the risk of blood loss more than 500 mL. However, there was no difference between groups for blood loss of more than 1,000 mL. The oxytocin–ergometrine was associated with statistically significant increase in the risks of nausea, vomiting and elevated diastolic BP. The advantage of a reduction in the risk of PPH, between 500 mL and 1,000 mL blood loss, needs to be weighed against the adverse side effects associated with the use of oxytocin–ergometrine combination.

The likely explanation for these differences is that ergot preparations act systemically on smooth muscles, whereas oxytocin is specific for uterine smooth muscle. Oxytocin causes increased contraction strength and frequency, but the uterus does not undergo tetanic contraction, as is the case with an ergot. Studies undertaken by the WHO also favor oxytocin because it is more stable when exposed to heat and light compared to ergot preparations. This makes oxytocin more useful in settings where storage capabilities, especially refrigeration, may be an issue. Trials have been performed using a synthetic oxytocin analog, carbetocin, which has a prolonged action (Dansereau, 1999). Results are favorable, but the drug is not easily available in the United States.
Misoprostol

Recent research focusing on AMTSL has examined alternatives to oxytocin and syntometrine. The majority of randomized controlled trials on the topic published in the last 8 years have investigated use of misoprostol, a prostaglandin E1 analog. Misoprostol is inexpensive, stable, easily stored and therefore, has potential to be particularly useful in developing countries. Three systematic reviews have been completed on misoprostol use since, 2002. This work concludes that misoprostol results in higher blood loss than conventional prophylactic uterotonics and is associated with significant increase in rates of shivering and fever (Gulmezoglu, 2001, 2004). Clearly, the presence of prostaglandin induced pyrexia and shivering in the postpartum period may lead to confusion in the diagnosis of sepsis.

Injectable Prostaglandins

Injectable prostaglandins are another alternative to conventional uterotonics. Mean blood loss appear to be reduced. Prostaglandin related side effects, especially shivering, pyrexia, nausea, vomiting and diarrhea were frequent and consistent across trials. The injectable prostaglandins appear to be more appropriate for the use in the treatment of PPH than its prevention.

Carboprost (15-methyl PGF2 Alpha)

The use of carboprost in the AMTSL, the clinical evidences suggest that carboprost in low dose IM (125 µg) is for AMTSL and the high dose IM (250 µg) is for high risk cases and management of PPH. This drug is mainly compared with methyl ergometrine.
Postpartum Conditions
INTRODUCTION

Postpartum hemorrhage (PPH) is a life-threatening emergency with possible grave maternal outcome. According to the World Health Organization (WHO) 5,29,000 women die annually due to complications of pregnancy and child birth, and 99% of deaths occur in developing countries. Incidence of PPH varies widely because of lack of uniformity in definition and deficient data collection. Estimated incidence is 4–6% of all deliveries and the recurrence risk is 20–25%. Postpartum hemorrhage contributes to about 25% of all maternal deaths in India. It is also an important cause of postpartum morbidity like chronic anemia, fatigue, failure of lactation, infections and associated risks of blood transfusions, postpartum depression and pituitary necrosis (Sheehan’s syndrome). All these factors would adversely affect the care of newborn and impose a financial and psychological burden on the entire family unit. Various causes of hemorrhage resulting in significant maternal mortality and morbidity have been illustrated in Figure 1. Predisposing factors and causes of immediate postpartum hemorrhage are presented in Table 1.

DEFINITION

Primary postpartum hemorrhage is defined by the WHO as blood loss from genital tract more than 500 mL in the first 24 hours of delivery. The American Congress of Obstetricians and Gynecologists (ACOG) has defined PPH as a decrease in hematocrit by 10% or a need for blood transfusion in 24 hours after delivery. Blood losses up to 500 mL are generally well tolerated by healthy women because of the volume expansion and relative hemodilution in pregnancy. Recent reports have stated that approximate blood loss at normal delivery is 500 mL, at lower segment cesarean section (LSCS) is 1,000 mL and at postpartum hysterectomy is 1,500 mL and not all women are compromised even in these situations. On the other hand, Indian women are small built with low blood volumes, prevalence of anemia during pregnancy is as high as 80% and it is not possible to perform regular hematocrit counts in busy hospitals with limited resources. Thus, clinical judgment along with amount of blood loss should define PPH.

Fig. 1: Incidences of some causes of obstetrical hemorrhage and their contribution to maternal death from hemorrhage. Percentages are approximations because of different classification schemata used. Source: Al-Zirqi (2008)\textsuperscript{a}, Zwart (2008)\textsuperscript{b}, Chichkali (1999)\textsuperscript{c}
ETIOPATHOLOGY

There are four primary causes of PPH, the four-Ts namely: Tone (atonic uterus), Tissue (retained placenta), Trauma and Thrombin (coagulation defects). The underlying risk factors for each is depicted in Table 2.

CLINICAL PRESENTATION (TABLE 3)

Clinical features depend on the antenatal hemoglobin levels and the amount of bleeding leading to hypovolemia and acute anemia.

It is important to note that in a malnourished or anemic patient the signs of shock can appear with mild bleeding (< 500 mL).

DIAGNOSIS

In majority of cases profuse bleeding at the time of cesarean or after vaginal delivery makes the diagnosis of PPH obvious. However, visual estimation of the amount of blood loss is always grossly inaccurate. Following methods have been proposed for estimation of blood loss at delivery but their usefulness is not yet substantiated:

- Collection of blood into bedpan or plastic bags as used in a study by WHO
- A plastic calibrated drape and receptacle has been used successfully to collect blood in a study in Karnataka

Table 1: Predisposing factors and causes of immediate postpartum hemorrhage

<table>
<thead>
<tr>
<th>Bleeding from placental implantation site</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Hypotonic myometrium—uterine atony</td>
</tr>
<tr>
<td>− Some general anesthetics—halogenated hydrocarbons</td>
</tr>
<tr>
<td>− Poorly perfused myometrium—hypotension</td>
</tr>
<tr>
<td>− Hemorrhage</td>
</tr>
<tr>
<td>− Conduction analgesia</td>
</tr>
<tr>
<td>− Overdistended uterus: large fetus, twins, hydramnios</td>
</tr>
<tr>
<td>− Prolonged labor</td>
</tr>
<tr>
<td>− Very rapid labor</td>
</tr>
<tr>
<td>− Induced or augmented labor</td>
</tr>
<tr>
<td>− High parity</td>
</tr>
<tr>
<td>− Uterine atony in previous pregnancy</td>
</tr>
<tr>
<td>− Chorioamnionitis</td>
</tr>
<tr>
<td>• Retained placental tissue</td>
</tr>
<tr>
<td>− Avulsed lobule, succenturiate lobe</td>
</tr>
<tr>
<td>− Abnormally adhered: accreta, increta, percreta</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Trauma to the genital tract</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Large episiotomy, including extensions</td>
</tr>
<tr>
<td>• Lacerations of perineum, vagina, or cervix</td>
</tr>
<tr>
<td>• Ruptured uterus</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Coagulation defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Intensify all of the above</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Causes of PPH</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Uterine atony—accounts for 90% of cases of PPH</td>
</tr>
<tr>
<td>a. Prolonged labor</td>
</tr>
<tr>
<td>b. Very rapid labor</td>
</tr>
<tr>
<td>c. Induced labor—use of high doses of oxytocin</td>
</tr>
<tr>
<td>d. Overdistended uterus</td>
</tr>
<tr>
<td>• Large baby</td>
</tr>
<tr>
<td>• Multiple pregnancies</td>
</tr>
<tr>
<td>• Hydramnios</td>
</tr>
<tr>
<td>e. Maternal factors</td>
</tr>
<tr>
<td>• Increased age &gt; 35 years</td>
</tr>
<tr>
<td>• Increased parity</td>
</tr>
<tr>
<td>• Obesity</td>
</tr>
<tr>
<td>• Jaundice, hypertension</td>
</tr>
<tr>
<td>• Fibroid uterus</td>
</tr>
<tr>
<td>f. Cesarean delivery</td>
</tr>
<tr>
<td>g. Chorioamnionitis</td>
</tr>
<tr>
<td>h. Previous H/O PPH</td>
</tr>
<tr>
<td>i. Uterine inversion</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Underlying risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Placenta related conditions</td>
</tr>
<tr>
<td>a. Mismanaged 3rd stage</td>
</tr>
<tr>
<td>b. Previous H/O LSCS or curettage</td>
</tr>
<tr>
<td>c. Grand multipara</td>
</tr>
<tr>
<td>d. H/O antepartum hemorrhage</td>
</tr>
</tbody>
</table>

| 3. Injury to genital tract             |
| It can be of various types:            |
| a. Extension of episiotomy            |
| b. Paraurethral, vulval and vaginal tears |
| c. Cervical tears                     |
| d. Uterine rupture                    |
| e. Vulval and vaginal hematoma        |
| f. Broad ligament hematoma            |
| g. Retroperitoneal hematoma            |
| a. Large baby                         |
| b. Occipitoposterior position         |
| c. Shoulder dystocia                  |
| d. Breech extraction                  |
| e. Previous H/O cesarean              |
| f. Previous H/O myomectomy/ metroplasty|

| 4. Coagulation defects                 |
| a. Abruptio placenta                   |
| b. Preeclampsia and HELLP syndrome     |
| c. Amniotic fluid embolism            |
| d. Sepsis                             |
| e. Intrauterine fetal death            |
| f. Massive blood transfusion           |
| g. Saline induced second trimester abortion |
| h. Anticoagulant therapy              |
| i. ITP                                |
| j. Liver disease                      |
| k. Hereditary disorders, e.g. Von Willebrand disease |

| 5. Anemia                              |
| a. Malnutrition/not taking iron supplements |
| b. Thalasemia                          |

Abbreviations: PPH, postpartum hemorrhage; H/O, history of; LSCS, lower segment cesarean section; ITP, idiopathic thrombocytopenic purpura
Weighing the sponges soaked in blood during cesarean and calculating the change in weight of the dry and soaked sponges.

**Acid/alkali hematin method**: The collected blood is converted to hematin and measurements of actual blood loss are calculated by colorimeter readings.

Monitoring of vitals and fundal height of uterus in each patient after delivery for early detection of abnormal bleeding or signs of hypovolemia is the best method to diagnose PPH because sometimes the blood loss is not severe but there is a constant trickle which may over a period of time assume significant proportions. Besides, bleeding may not be obvious in rare cases of broad ligament and retroperitoneal hematomas and uterine rupture. Diagnosis of the underlying cause of bleeding depends on the presence of antecedent risk factors as given in Table 2 and a careful examination of the patient. Ultrasound may be helpful in a few cases of uterine scar rupture, retained placenta, morbid adherent placenta and supraselevator hematomas. Calculation of maternal total blood volume is shown in Table 4.

**MANAGEMENT**

Principle of management is to ascertain the cause of bleeding and initiate prompt measures to control it. Interval between delivery, diagnosis of PPH and the start of resuscitation with appropriate medical or surgical measures is an important prognostic factor for subsequent maternal morbidity and mortality associated with PPH.

**Resuscitation**

- It is important to work as a team, call for help, summon senior obstetrician and anesthetist and enough junior staff. Alert blood bank and operation theater of the emergency.
- Perform a quick but thorough physical examination.
- Raise the foot end of patient.
- Administer oxygen by mask.
- Secure intravenous access with at least two large bore IV cannula.
- Collect adequate sample, about 20 mL, for blood grouping, cross matching and complete blood counts, if necessary for coagulation profile.
- Arrange for at least 4–6 units of blood in severe bleeding and also for fresh frozen plasma and cryoprecipitate if coagulopathy is suspected.
- Start fluid replacement with rapid infusion of crystalloids like normal saline 0.9% or Ringer’s lactated solution to restore blood pressure. 5% dextrose solution is hypotonic and is not helpful for acute volume expansion. Colloids like albumin or Hartman’s solutions may be used if only there is delay in obtaining blood. Blood or blood component therapy should be initiated as soon as available.
- Self-retaining catheter is to be inserted as full bladder interferes with contraction of uterus.
- Monitor vitals, urine output, bleeding p/v and fundal height. In severe bleeding, monitoring by electrocardiography (ECG), central venous pressure (CVP) line, pulse oxymetry is necessary.
- Nonpneumatic antishock garment has been shown to reduce blood loss by 50% and may be useful as a first aid measure in low-resource settings to obtain time to shift the patient to tertiary hospital. However, larger studies are required to demonstrate benefit on maternal mortality.
**Management According to Cause of Bleeding**

**Uterine Atony**

Presence of a soft and boggy uterus on per abdomen palpation suggests uterine atony. If the placenta is still attached post delivery, active management with oxytocin and controlled cord traction is attempted. Manual removal of placenta is done if required under general anesthesia. Bimanual compression of the uterus and massage with abdominal hand is carried out along side.

**Pharmacological Methods (Table 5)—Drugs Used to Aid Contraction of Uterus**

**Oxytocin:** It acts rapidly, latency period is less than 1 minute after intravenous injection. Higher concentration of oxytocin should be avoided as it does not improve the efficacy but can lead to side effects like water intoxication.

**Ergot alkaloids:** Methylergometrine, methyl ergonovine and syntometrine (5 IU oxytocin + 500 mg ergometrine maleate) have a prompt and sustained action. The latter two are not available in India.

**Prostaglandins:** Prostaglandins have potent uterotonic effects.

- **15-methyl prostaglandin F\textsubscript{2α}:** About 75% of the patients will respond to the first dose and the overall response is 95%. It is less effective in presence of chorioamnionitis.

- **Misoprostol:** It is rapidly absorbed following oral administration, plasma concentration increases rapidly to peak in 30 minutes while with vaginal administration the peak is reached in 1.5 hours. Its advantages are that it is a strong uterotonic, can be given orally, is inexpensive and does not need refrigeration for storage unlike oxytocin.

  Studies have found that neither intramuscular prostaglandins nor misoprostol (oral or rectal) given prophylactically was preferable to conventional oxytocin for third stage labor management, although prostaglandins are useful in treatment of intractable postpartum hemorrhage.

**Recombinant factor VIIa:** It has been used successfully in selected patients with coagulopathies and intractable hemorrhage. It is very expensive and more studies are required to assess its actual efficacy in PPH.

**Calcium gluconate:** It is not a uterotonic but may be useful in uterine atony secondary to use of antenatal magnesium sulfate or nifedipine.

**Nonpharmacological Methods**

These are intended to control hemorrhage until uterus itself can secure hemostasis by contraction, retraction and coagulation. They are reasonable alternatives to surgery in uncontrolled bleeding and may be helpful to avoid hysterectomy in patients keen to preserve fertility especially in cases of hemorrhage due to placenta previa and adherent placenta. Also, they can help to obtain time for transfer of the patient to a tertiary center.

**Uterine tamponade:** This method increases intrauterine pressure and stems the bleeding. It carries a potential risk of infection and trauma. Besides, it may conceal actual bleeding and give a false sense of security. Close monitoring with broad spectrum antibiotics and oxytocics should be given along side. The various methods are:

**Table 5: Drugs used to aid contraction of uterus**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosages</th>
<th>Side effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Oxytocin—Most effective drug to date</td>
<td>10–20 units in 500 mL crystalloid solution as IV infusion at 125 mL/ hour</td>
<td>Water intoxication and nausea at high doses</td>
<td>Nil</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Not recommended to use at dosages of &gt; 40 U/500 mL solution IV bolus injection can cause hypotension and arrhythmia</td>
</tr>
<tr>
<td>2. Methyl ergometrine (Methergin)</td>
<td>0.25 mg IM/IV injection</td>
<td>Nausea, vomiting hypertension retained placenta if given before separation</td>
<td>Hypertension, heart disease</td>
</tr>
<tr>
<td>3. 15-methyl prostaglandin F\textsubscript{2α} (carboprost)</td>
<td>250 µg given as IM injections every 15 minutes for a maximum of 8 doses</td>
<td>Diarrhea, nausea, vomiting, flushing, pyrexia and can also lead to hypertension, bronchoconstriction and intrapulmonary shunting</td>
<td>Significant pulmonary, cardiac, hepatic or renal diseases</td>
</tr>
<tr>
<td></td>
<td>Can be given intra-myometrial in exceptional cases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Misoprostol is a synthetic PGE\textsubscript{1} analog</td>
<td>600–1000 µg per rectal or oral have been evaluated with reasonable out come. Dose and frequency of administration is yet to be standardized</td>
<td>Diarrhea and pyrexia 40°C are characteristic</td>
<td>Same as above</td>
</tr>
</tbody>
</table>
• **Uterine packing**: Uterus is packed from the fundus with ribbon gauze soaked in povidone-iodine including the vagina. Self-retaining catheter is also inserted.

• **Balloon tamponade**: Tamponade of uterine cavity using a Sengstaken-Blakemore tube has been reported. The tube is left inflated for 24 hours and then deflated. Several studies have reported the use of large 30 mL Foley catheter placed into the uterine cavity. These are cheap, simple and effective methods in relevant situations.

• **Uterine artery embolization**: It is a safe alternative in centers with the radiological interventional facilities. Up to 95% success rates have been recorded with this method. This method is successful only if circulation in vessels is not compromised. Embolization gives better results in retroperitoneal hematomas as surgery is difficult due to distorted anatomy. The occlusion is carried out by injecting particles of gel foam or polyvinyl alcohol through the internal iliac artery. Side effects reported are hematoma at catheterization site, technical difficulty in accessing the uterine arteries and infection. Disadvantages are high cost of set-up and need of trained radiologists. Besides, further studies are required to prove its efficacy in PPH.

**Surgical Management**

Surgery involves laparotomy followed by either a conservative approach or the radical procedure of hysterectomy based on the general condition of patient, the facilities at the hospital, skill of the operating surgeon and the desire of the patient.

Conservative surgical methods are useful when conventional methods have failed and the patient is desirous of conserving fertility. They can be performed if the patient is hemodynamically stable. However, the surgeon needs to be skilled to perform the procedures.

**Uterine Artery Ligation**

The procedure is useful as 90% of blood supply to the gravid uterus comes from uterine artery. It is reported to be a satisfactory technique to control postcesarean hemorrhage and is easy to perform with minimal complications. It however may not be successful to control bleeding in cases of placenta previa or uterine rupture.

**Ovarian Artery Ligation**

It is usually performed with uterine artery ligation for better control of bleeding in some cases. Most patients are reported to resume normal menstruation and fertility despite an 80% decrease in the arterial pulse pressure with concomitant ligation of uterine and ovarian arteries.

**Internal Iliac Artery Ligation**

Bilateral artery ligation reduces pulse pressure by 85% but is seen to benefit only 48% cases. It requires great degree of surgical expertise and is reported to increase the total blood loss, operating time and operative morbidity. Hence, it is reserved for stable patients keen to preserve uterus for future childbearing.

AbdRabbo has reported 100% success with the judicious stepwise ligation of uterine vessels to control PPH.

**Hemostatic Compression Sutures**

These sutures when applied to the uterus have been reported to stop hemorrhage even in cases of placenta previa/accreta and disseminated intravascular coagulation (DIC). B-Lynch suture consists of application of a brace suture that compresses the fundus and lower segment of uterus. This method is simple, effective and safe. To test the potential efficacy of the suture it is recommended to check if bleeding stops by applying bimanual compression to uterus. Follow-up studies though limited have not shown any significant morbidity associated with the method. Hayman’s uterine compression suture and Cho multiple square suture are modifications of B-Lynch procedure with limited published data on their efficacy and safety.

**Hysterectomy** is the final life-saving measure in some cases of uncontrolled PPH.

**Genital Tract Trauma**

A well contracted uterus in the presence of hemorrhage warrants a thorough inspection of the genital tract. Adequate light and exposure with good assistance are necessary. It is best to start exploration from the highest point of genital tract and proceed downward as excess bleeding can obstruct the view of lower parts. Cervix should be explored with four ring forceps to inspect all quadrants. In large lacerations, suturing requires good anesthesia and an experienced surgeon. Laparotomy should be considered in extensive lacerations involving vaginal vault and in high cervical tears to help in the timely detection and management of broad ligament hematomas.

**Morbid Adhesions of Placenta**

It should be suspected in cases of PPH with retained placenta where no plane of cleavage is found between decidua and placenta and manual removal of placenta fails even under anesthesia. It may be detected antepartum by ultrasound in patients with previous cesarean and anterior placenta previa. The usual treatment is hysterectomy. In selected cases, conservative treatment to preserve fertility like uterine vessel ligation or embolization may help. A few case reports of leaving adherent placenta in situ with close follow-up of bleeding and sepsis with serial ultrasounds have shown success but the efficacy is yet to be proved.

**Coagulopathies**

Vigilant delivery in high-risk cases and prompt resuscitation with adequate fluids, blood constituents and coagulation...
factors is the most important factor in preventing maternal mortality in such cases. The underlying cause like sepsis, pre-eclamptic toxemia (PET), etc. need to be dealt vigorously.

**Uterine Inversion**

Inversion is suspected if the fundus of uterus cannot be felt per abdomen after delivery. The patient may suddenly develop acute pain in abdomen with neurogenic shock. Acute inversion can be managed by manual reposition (Johnson’s method) or hydrostatic replacement with warm saline (O’Sullivan method). Tocolysis or general anesthesia may be required to facilitate reposition. Use of uterotonic is stopped till the correction is performed after which bimanual massage and vigorous use of uterotonic will be required to contract the uterus. Laparotomy with surgical reposition or hysterectomy may be required in some cases.

**Secondary Postpartum Hemorrhage**

Excessive blood loss after 24 hours of delivery in postpartum period is termed secondary or “late” PPH. Retained placental tissue is the most common cause followed by infection causing subinvolution of placental site and sloughing of lacerations. Rare causes are chronic uterine inversion, placental polyp, choriocarcinoma. Replacing lost blood, use of broad-spectrum antibiotics, surgical evacuation of uterus if possible under ultrasound guidance are usually done. Occasionally, laparotomy and hysterectomy may be required. It is important to obtain histopathological diagnosis of tissue obtained to rule out choriocarcinoma.

**Preventive Management**

Active management of third stage of labor—this should be encouraged in all cases if possible. It includes administration of prophylactic uterotonic at birth of baby, early cord clamping and placental delivery with controlled cord traction. Uterotonic has a definitive role in preventing PPH, while the latter two have not been shown to prevent PPH. Oxytocin or ergometrine are the drugs of choice. Misoprostol 400–600 μg sublingual or per-rectal may be an alternative in low-resource settings.

**Long-term Interventions to Prevent PPH**

The etiology of PPH can be traced to as early as the birth of a girl child. A girl enters puberty and later pregnancy with chronic anemia, ill health and malnourishment. These problems are aggravated by early marriage, frequent pregnancies, unsupervised antenatal and intranatal period. The following measures are required:

- Care of the girl child by providing a healthy environment for the overall development and avoiding early marriage.
- Care during pregnancy and delivery: Iron and folic acid supplements in antenatal period, detection and treatment of anemia, identifying high-risk pregnancies and early referral to tertiary center. Supervised delivery of high-risk pregnancies by senior obstetrician with active management of third stage of labor. Continuous vigilance in immediate postdelivery period “the fourth stage of labor” is essential.
- Protocol for the management of PPH should be standardized in each hospital and the labor room staff should be fully trained for this obstetrical emergency. Regular “fire drills” should be conducted for the same. The hospital should also have regular internal audits to improve outcome in PPH.
- Contraceptive advice, treatment of anemia if present and health education in puerperal period.
- Social responsibility—Education to increase awareness of women’s health in society should be emphasized at all levels. It is important to sensitize each family about the importance of early decision and timely transport of all suspected cases of excess bleeding. Government and community-based programs, training of birth attendants, strengthening blood bank and transport facilities with involvement of mass media to reach out to all have an important role to play.

**Medicolegal Aspect**

It is important to realize that at times despite the best of medical expertise and resources available, death or serious morbidity cannot be averted. Hence an informed consent with time to time discussion of the status of the patient with her relatives is of paramount importance in all cases of PPH.

**CONCLUSION**

To conclude, early diagnosis, prompt intervention and management with availability of newer techniques has led to a reduction in maternal mortality due to PPH since our independence but further efforts are required to make each and every pregnancy safe. Preventive measures have a definitive role in management of PPH, the social aspect of which needs to be dealt with effectively.

**BIBLIOGRAPHY**

Management of Postpartum Hemorrhage

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INTRODUCTION

Puerperal pyrexia is defined as the rise of 1°F temperature on two occasions from day 2 to day 10 of delivery or abortion. The United States Joint Commission on Maternal Welfare and the World Health Organization (WHO) International Classification of Diseases (ICD-10) consider febrile morbidity when temperature is greater than or equal to 38°C (100.4°F). We do not take first 24 hours into account, as quite often there is transient pyrexia due to physical strain of labor.

Puerperal sepsis is defined as infection of genital tract which occurs as a complication of delivery. Although puerperium extends up to 42 days, it is the 1st week after delivery that is most critical. Puerperal sepsis is also known as puerperal infection or child bed fever. A WHO technical working group on “The Prevention and Management of Puerperal Infections” in 1992 defined following definition of puerperal sepsis:

- Pelvic pain
- Fever
- Abnormal vaginal discharge, i.e. pus
- Abnormal smell/foul odor of discharge
- Delay in involution of uterus (< 2 cm/day during the first 8 days).

At the same time, WHO technical working group considered that puerperal infections is a more general term than puerperal sepsis, and includes not only infections due to sepsis, but also all extragenital infections and incidental infections.

Maternal mortality is one of the major public health problems challenging the medical community, especially in the developing countries. WHO recently estimated that 585,000 maternal deaths occur annually, 99% of those are in the developing world.

The United Nations Population Fund (UNFPA) in its latest update (1998-99) reported 15% of the maternal mortality which was due to puerperal sepsis and that it was the second direct cause of maternal mortality. WHO also reported maternal mortality as 15% due to puerperal sepsis.

Fortunately, it is declining with modern obstetric care. Chhabra et al. 2005 from Rural Medical Institute, India, reported decline in maternal mortality due to puerperal sepsis to 10% in the last 5 years from 35% in earlier years. However, it is still a major health problem in the developing world, and has worsened with human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) infection. In rural India, maternal mortality continues to be high and it is different in different areas as shown in Table 1.

HISTORICAL ASPECT

Looking backward is always educative and it helps one to understand the condition better. In the 5th century BC, it was described by the Hippocrates as a serious complication of childbirth. By AD 200, Celsus and Galen had written in the support of the theories of Hippocrates. It was only in late 1,500s that lochial putrefaction or uterine inflammation was suspected as the cause of childbed fever. In 1659, Willis wrote on the subject of febrile puerperium, although the English term “puerperal fever” was probably first employed by Strother in 1716.
In the Modern Era, many individuals have contributed to its knowledge.

- In 1773, Charles White of Manchester suggested isolation of all cases. He postulated *Stagnation of Lochia* as a cause of fever.
- In 1843, Oliver Wendell Holmes presented to Boston Society, his study of puerperal fever. He blamed lack of precautions on the part of Doctors and Nurses as a cause of this condition.
- In 1861, Semmelweis of Vienna, linked it to Medical Students coming from postmortem room. He suggested washing hands before entering the labor room. He was ridiculed and later dismissed from his post (Fig. 1).
- Later in 1867, Lister’s Teaching of Antisepsis was known and Louis Pasteur’s development of Bacteriology was universally accepted and the whole concept of puerperal sepsis changed. Semmelweis by that time had suffered a nervous breakdown and died a miserable death on the streets of Vienna. But what he did not get in life, he got in death. He was now acclaimed to be a hero of all mothers and his contribution to midwifery was acknowledged. There is now a Museum in his home in Budapest and a monument to Mother and Child in his garden.

However, to practitioners of ancient Indian medicine, the art of asepsis was known even 2000 years ago. Charak, the famous Ayurvedic physician has reported about aseptic precautions in Labor Ward in his book “Charak-Samhita Sharirstan”, Chapter 8.3 and Shushrut in his book “Shushrut Samhita” has reported isolation of the parturient for 40 days to prevent infection.

### PREDISPOSING FACTORS FOR THE DEVELOPMENT OF PUERPERAL SEPSIS

It is generally considered that pelvic infections are common among women of poor socioeconomic status compared with upper or middle class women, but the precise reason is unclear. Factors responsible for predisposing puerperal sepsis are listed in Table 2.

In 1998, Dare et al.\(^1\)\(^3\) reported that predisposing factors associated with puerperal sepsis were anemia in pregnancy (69.2%), prolonged labor (65.7%), frequent vaginal examinations in labor (50.7%) and premature rupture of membranes (PROM) (31.5%).

During the last few years, a growing body of evidence suggests that the single most important risk factor for puerperal sepsis is cesarean section.\(^1\)\(^4\)\(^,\)\(^1\)\(^5\)

If one or more causes are present in a case, this forms a high-risk case. In such a case, prophylactic treatment to prevent major infection is justified. If possible, such cases should be transferred to suitable center at the earliest sign of infection.

Puerperal sepsis may be mild or severe. Severe sepsis may be in the form of:
- Pelvic cellulitis
- Adnexal masses

<table>
<thead>
<tr>
<th>Data</th>
<th>% of direct puerperal sepsis as a cause of MMR contributing factor</th>
<th>Hemorrhage</th>
<th>Sepsis</th>
<th>Toxemia</th>
<th>Ranking</th>
</tr>
</thead>
<tbody>
<tr>
<td>UNFPA (1998-99)(^4)</td>
<td>80%</td>
<td>25%</td>
<td>15%</td>
<td>12%</td>
<td>2nd</td>
</tr>
<tr>
<td>Bhattacharjee (Assam, 2001)(^7)</td>
<td>83.6%</td>
<td>19.6%</td>
<td>39.3%</td>
<td>19.6%</td>
<td>1st</td>
</tr>
<tr>
<td>Patel et al. (Gujarat, 2001)(^9)</td>
<td>65.5%</td>
<td>31.02%</td>
<td>20.69%</td>
<td>13.79%</td>
<td>2nd</td>
</tr>
<tr>
<td>Jayaram (AP, 2001)(^9)</td>
<td>66%</td>
<td>27.5%</td>
<td>13.5%</td>
<td>11.1%</td>
<td>2nd</td>
</tr>
<tr>
<td>Sharma (Kota, 2001)(^10)</td>
<td>59.3%</td>
<td>24.6%</td>
<td>14%</td>
<td>19.7%</td>
<td>3rd</td>
</tr>
<tr>
<td>Kulkarni et al. (Bangalore, 2001)(^11)</td>
<td>71.4%</td>
<td>24.4%</td>
<td>12.7%</td>
<td>25.8%</td>
<td>3rd</td>
</tr>
</tbody>
</table>

Abbreviations: MMR, maternal mortality rate; UNFPA, United Nations Population Fund
Pelvic abscess
Pelvic thrombophlebitis
Peritonitis
Necrotizing fasciitis.

**SEPTICEMIA AND SEPTIC SHOCK**

Septicemia and septic shock occur late and one must diagnose before this stage is reached. However, one still sees cases admitted in septic shock. The following investigations need to be done:

- Hemoglobin percentage (Hb%), white blood cell (WBC): total and differential, platelets, erythrocyte sedimentation rate (ESR)
- Serum HIV after pretest counseling
- Swab culture-antibiotic sensitivity
- Blood culture and sensitivity (C/S)
- Urine routine and C/S
- X-ray of chest and abdomen in erect posture
- Ultrasoundography (USG) scan of whole abdomen
  - Color Doppler, if indicated
- Computed tomography (CT) scan, magnetic resonance imaging (MRI) if indicated
- Exploration of uterus/curettage, if needed biopsy
- USG-guided aspiration of a mass

All facilities may not be available everywhere; hence, whatever possible should be done. Clinical judgment, close observation and consultation with other colleagues sometimes can be more valuable than mere laboratory data.

Eschenbach et al. studied the endometrial isolates from 51 patients of puerperal sepsis in 1986. The results are as follows in Table 3.

In 1998, American College of Obstetricians and Gynecologists reported the bacteria commonly responsible for female genital infections as follows in Table 4.

It is obvious that one has to deal with mixed bacterial flora. Aerobes and anaerobes are likely and one must anticipate polymicrobial disease whether cultures are possible or not.

In 1988, Purwar et al. reported 68 cases of sepsis, out of which 77% were due to obstetrical sepsis. From the cervical swab culture aerobes were isolated in 75% while anaerobes in 1.5% and both aerobes and anaerobes in 18%. *E. coli*...
Klebsiella, Pseudomonas, Peptostreptococcus and Bacteroides were the most commonly isolated organisms. They reported excellent results with clindamycin and metronidazole.

Sometimes the cause of fever in parturient is not easily found, one must entertain other causes which may be non-gynecological/obstetric causes.

DIFFERENTIAL DIAGNOSIS OF PERSISTENT FEVER

- Pelvic infections
- Breast lesions
- Urinary tract infections
- Resistant organisms
- Nongenital cause such as tooth abscess, malaria respiratory infection
- Tuberculosis, very common in India
- Drug reactions
- Inadequate treatment or noncompliance of a patient who is treated at home.

It is a great feat of nature that the products of conception are kept sterile. This is achieved by several means. One of the important means is amniotic fluid which has antibacterial activity. It prevents the growth of microorganisms in vitro and in vivo. Appelbaum et al. studied antibacterial activity in the third trimester and found that it was not uniform in all races. In Caucasians, 76% had antibacterial activity whereas:
  - Indians had only 52%
  - Africans had only 33%.

The amniotic fluid components causing antimicrobial activity are several enzymes like lysozyme, peroxidases, transferrins, B lysins, etc.

It was Kitzmiller who suggested that antibacterial activity was related to maternal nutrition. It is reported that transferrins, which increased in iron-deficiency anemia has significant antibacterial action.

Vaginitis in pregnancy is of great significance according to Krohn et al. 1999. It can cause preterm labor, PROM, chorioamnionitis, neonatal infection and postpartum endometritis. In 2000, Schrag et al. reported maternal mortality following vaginitis (1 in 345 cases). Proper screening for infection is advisable. It is necessary to institute proper antibiotic therapy and reduce the risks. Rarely, infection can occur in the intranatal period without the rupture of membranes and without the onset of labor. If it happens, then there will be premature onset of labor. Infection is more likely to occur after the onset of labor and more so after the rupture of membrane. One of the leading causes of intranatal sepsis is preterm PROM (PPROM). Mother’s health is more important than fetal outcome. However, conservative treatment is advised till adequate fetal maturity is reached. One has to watch carefully for signs and symptoms of infection. At the earliest sign of infection, one must intervene and conduct safe delivery.

**PUERPERAL SEPSIS**

**Signs and Symptoms (Table 5)**

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaise, headache, fever, rigor</td>
<td>Pyrexia, tachycardia</td>
</tr>
<tr>
<td>Abdominal discomfort/pain</td>
<td>Uterus boggy, tender, subinvolved</td>
</tr>
<tr>
<td>Vomiting/diarrhea</td>
<td>Infected wound-abdominal/perineal</td>
</tr>
<tr>
<td>Offensive lochia</td>
<td>Peritonism</td>
</tr>
<tr>
<td>Secondary postpartum hemorrhage</td>
<td>Paralytic ileus</td>
</tr>
<tr>
<td></td>
<td>Indurated fornices/adnexal masses and tenderness</td>
</tr>
<tr>
<td></td>
<td>Fluocant mass in Pouch of Douglas</td>
</tr>
</tbody>
</table>

**Investigations**

- Hb%, WBC total and differential, platelets, ESR
- Swab and culture: From the cervix and upper vagina for aerobic and anaerobic cultures
- Blood culture: Taken at peak of temperature in case of septicemia
- Urine analysis and culture: Midstream or catheter specimen

**Prevention of Puerperal Sepsis**

**Antenatal Prevention**

- Proper diet, vitamins and minerals
- Anemia and diabetes should be treated
- Avoid sexual intercourse late in pregnancy
- Prophylactic antibiotics in presence of predisposing factors

**Intranatal Prevention**

- Strict aseptic and antiseptic measures for the patient, attendants and instruments
- Minimize vaginal examinations
- Avoid bleeding and excessive blood loss should be replaced
- Lacerations should be properly sutured immediately
- Prophylactic antibiotics in presence of predisposing factors

Most antibiotics cross the placental barrier but cord blood levels are 50–70% of maternal levels. One has to balance the toxic reactions to the fetus. However, it is believed that chemoprophylaxis will prevent sepsis neonatorum.
Postnatal Prevention

- Maintenance of aseptic precautions
- Care of the perineal or abdominal wounds
- Minimize visitors and keep away who are infected
- Early isolation of cases of puerperal sepsis

Treatment of Puerperal Sepsis

General Treatment

- Isolation in a separate room or fever hospital
- Diet: Light diet rich in vitamins and minerals with plenty of fluids
- Supportive treatment: Restoration of fluid and electrolyte balance, correction of anemia
- Symptomatic treatment:
  - Analgesics
  - Antipyretics cold compression and hot fermentation
- Observations: Pulse, temperature, blood pressure, vaginal bleeding, lochia, manifestations of deep vein thrombosis (DVT)

In 1999, West et al. reported that vitamin A supplementation in women may have reduced maternal mortality by 40% in a Nepalese community and Nurdiati reported 50% reduction in puerperal fever in Indonesian community.

Antimicrobial Therapy

Antimicrobial therapy is the mainstay in the treatment of puerperal sepsis. Parenteral use is imperative and oral medication has no place. Treatment is aimed at polymicrobial mixed flora. The following are the options:

- Multiagent:
  - Penicillin and gentamycin
  - Clindamycin and gentamycin
  - Ampicillin, gentamicin and metronidazole
  - Clindamycin and aztreonam
  - Clindamycin and second-generation cephalosporins:
    - Preferred in renal insufficiency
  - Azithromycin
- Single agent:
  - Cephalosporins:
    - Cefoxitin
    - Cefoperazone
    - Cefotaxime

Any of these should be started immediately and later, one can review and revise the therapy:

- When C/S report is ready
- No response in 72 hours, antibiotic therapy may be changed
- If toxicity appears, change is necessary.

One must check daily:

- WBC, urine albumin and creatinine
- Adequate hydration and urine output should be ensured
- Hepatotoxicity and nephrotoxicity is a possibility with high dosage of medication.

Surgical Treatment

- In case of infected perineal wound, stitches have to be removed to facilitate drainage of pus
- Infected retained products should be removed under cover of antibiotics by exploration of uterine cavity
- Pelvic abscess should be drained by posterior colpotomy

It is very difficult to decide when surgical interference by exploratory laparotomy should be undertaken in puerperal sepsis. The following are the guidelines:

- If the diagnosis is in doubt
- Evidence of free fluid or masses in the abdomen
- Hemorrhage, recurrent, from a soft, flaccid uterus
- Ovarian vein thrombosis
- No response to medical treatment.

Sequelae of Puerperal Sepsis

In the absence of antibiotic treatment or in the more severe cases, puerperal sepsis may be complicated by chronic pelvic pain, pelvic inflammatory diseases and secondary infertility. The more severe cases are responsible for the high rates of maternal mortality, i.e. about 15%, especially in developing countries.

There are a few specific and interesting forms of puerperal infections. These are phlegmasia alba dolens or deep vein thrombosis (DVT), clostridial gas gangrene and necrotizing fasciitis (Fig. 2).
**Phlegmasia Alba Dolens**

Phlegmasia alba dolens is also known as milk leg. It is classical puerperal thrombophlebitis diagnosed when patient, who has delivered recently, complains of severe pain and edema of the leg and thigh. It is abrupt in onset and may be unilateral. Usually deep veins from foot to iliofemoral are involved. There is also reflex arterial spasm causing the limb to be pale and cold with diminished pulsation.

Predisposing causes include:

- Use of obstetric cholestasis (OC) in the pre-pregnancy stage
- Stasis, no ambulation
- Varicose veins.

It is diagnosed clinically. When facilities exists, color Doppler would be useful. DVT is to be managed by immediate hospitalization. Treatment includes:

- Heparin IV
- Rest
- Analgesics
- Antibiotics.

One must watch for pulmonary emboli, diagnosed by a triad of symptoms, namely hemoptysis, tachypnea, and chest pain. Thrombophlebitis and phlebothrombosis have to be differentiated. Williams\(^\text{27}\) reported that 10% of all maternal deaths were due to pulmonary emboli, following DVT.

**Clostridial Gas Gangrene**

Gas gangrene is a fulminant infection caused by *Clostridium perfringens* in 60–80% of cases. Clinically, it presents with a sudden onset of severe pain. On examination, there are bullae and a diagnostic crepitus. The tissue has a bronzed look. Patient is usually in septic shock. Treatment consists of giving 20 million units of penicillin-G in divided doses. Polyvalent antitoxin is to be given at the earliest. In difficult cases, the use of hyperbaric oxygen chambers is recommended.

When a case of gas gangrene occurs it is important to isolate the case, close down routine surgery and thoroughly fumigate the operation theater.

**Necrotizing Fasciitis**

Necrotizing fasciitis is an uncommon, rapidly progressive, severe infection involving perineal, vaginal tissues and abdominal incisions in Cesarean section. There is necrosis of fascial lining, but muscles are not affected (Figs 3A and B). It is associated with very high mortality. Usually, it is synergistic polymicrobial infection that occurs in patients with coexisting factors predisposing them to bacterial inoculation and the spread of infection. In 1996, McHenry et al.\(^\text{28}\) reported the possible role of increase in bacterial virulence and the immunological changes of pregnancy as potential predisposing factors in the development of necrotizing fasciitis. Owen and Andrews (1994) reported diabetes hypertension and obesity as risk factors for this condition. Clinically, it presents as severe edema, extending to thighs, buttocks and abdominal wall. Surgery in the form of debridement and drainage is necessary. In 1980, Gibbs\(^\text{4}\) described 19 cases when early intervention was carried out; only one patient was lost whereas in cases when intervention was delayed more than 6 days, 8 cases were lost. Hence, early diagnosis, surgical debridement, antibiotics and intensive care units (ICU) are necessary for successful treatment of this infection (Urschel, 1999).\(^\text{29}\)

It is best to involve a general surgeon and a physician with ICU facilities. Good teamwork is essential. Patient should be transferred by a flying squad to the nearest tertiary care center (Fig. 4).
CONCLUSION

Prevention is better than cure. It is of utmost significance in this condition.

- Health education programs must emphasize the early signs and symptoms of the common postpartum complications and stress the importance of seeking professional help timely.
- Continuing medical education programs on perinatal care for doctors and midwives; emphasis on the early signs and symptoms, correct management and the referral protocols for puerperal sepsis.
- Prophylactic antibiotics cover for all complicated deliveries and abortions are worth considering.
- Encourage hospital deliveries. Infection is most likely in domiciliary midwifery.
- Minimum 72 hours postnatal stay. This will eliminate the risk of thrombophlebitis and severe sepsis.
- Low dose of vitamin A given during second and third trimester of pregnancy substantially reduces the risk of postpartum infection in population of vitamin A deficient women.
- Special management of high-risk cases those with predisposing causes. The prevalence of puerperal sepsis is likely to rise in coming years, as the AIDS epidemic progresses further.
- More obstetric ICUs are needed, especially, at District level.
- Teamwork is necessary for successful outcome.
  Primary-secondary-tertiary care should have close links and good communication and transport facilities. This is an opportunity for obstetricians to work in close cooperation with surgeons and physicians.

REFERENCES


Breastfeeding Promotion

INTRODUCTION

Mothers’ milk is the ideal and complete food for the first 6 months of life. Breastfeeding saves more lives than immunization and oral rehydration solution (ORS) combined. More than 2.4 million child deaths occur in India each year; two-thirds of these are related to inappropriate infant feeding practices. Child-survival data, Lancet 2003 recommends promotion of exclusive breastfeeding in the first 6 months as the single most effective intervention to reduce under-5 mortality by 13–15%.

A nonbreastfed infant is 14 times more likely to die of diarrhea, three times more likely to die of respiratory infection, and twice as likely to die of other infections than an exclusively breastfed child. Death among newborns not suckled at the breast is at least five times higher than among those who receive colostrum and mother’s milk.

Does Breastfeeding Need to be Promoted?

Malnutrition has been responsible, directly or indirectly for 60% of 109 million deaths among children, two-thirds being associated with inappropriate feeding practices. Research continues to reveal evidence of the value of breastfeeding and breast milk.

There is a misconception in the minds of the majority that nearly every Indian baby is breastfed and hence the hesitation to accept promotion of breastfeeding as a major issue. However, a study from an under-5-clinic in a public hospital in Mumbai revealed that only 64% mothers exclusively breastfed their babies at birth, 17% near totally breastfed, while 19% partially breastfed their babies. This and other similar studies give lie to the myth that breastfeeding is widely prevalent in our country.

Advantages of Breastfeeding

There is strong evidence to show that breastfeeding decreases the incidence and/or severity of diarrhea, lower respiratory infection, otitis media, bacteremia, bacterial meningitis, botulism, urinary tract infection and necrotizing enterocolitis. A number of studies show a possible protective effect of human milk feeding against sudden infant death syndrome, insulin dependent diabetes mellitus (IDDM), Crohn’s disease, ulcerative colitis, lymphoma, allergic diseases and other chronic diseases.

Health benefits of breastfeeding can last a lifetime. Children and adults who were breastfed are less likely to develop asthma, IDDM and certain cancers (leukemia, lymphoma and Hodgkin’s disease). Babies who were breastfed may be less likely to become obese later in life.

A child’s first 3 years are the most critical in brain development. Optimal nutrition starts in utero and continues with breastfeeding, often called the “4th trimester.” A recent long-term study found breastfed children had statistically significant increases in intelligence quotient (IQ), reading, comprehension, mathematical ability and scholastic ability. Breastfeeding has also been related to possible enhancement of cognitive development, particularly in preterm babies.

Breastfeeding is the ideal way to begin, establish and nurture a close bond between mother and infant. The infant learns trust in early human closeness as well as cooperation with another human being. Mothers who breastfed successfully often have an increased sense of self worth and empowerment. Breastfed infants are rarely, if ever, victims of child abuse and neglect.

Exclusive breastfeeding reduces the chances of a next pregnancy for 6 months. As the fat accumulated during pregnancy is used in milk production, prolonged
breastfeeding can help mothers to return to their previous weight. Breastfeeding mothers have less risk of breast cancer and ovarian cancer, decreased insulin requirements in diabetics, stabilizing maternal endometriosis and less risk of postpartum hemorrhage, endometrial cancer and osteoporosis.

Breastfeeding not only saves lives but saves the family enormous finance, which is of particular importance in a country like ours.

**Who Should Promote Breastfeeding?**

Promoting breastfeeding is a subtle art with a blend of thoughtful suggestions and conveying accurate information over a period of time. There is perhaps no better time to do this than during the antenatal period where a breast examination should be made a routine. The 2nd trimester is considered to be a good time for breastfeeding advice as this is the time that the mother feels the baby move and is hence more receptive. Labor should be considered complete only if the mother feels the baby move and is hence more receptive. Labor should be considered complete only when breastfeeding has been successfully established.

**Different Compositions of Milk**

Breast milk has the unique property of being able to cater to the needs of the baby, depending on its maturity, be it a full term or preterm.

The various types of milk are:

- **Colostrum:** Colostrum is the thick, sticky, yellowish milk secreted in the first 72 hours after delivery. It is all that the baby needs for the first few days. It contains large quantities of protective substances.
- **Transition milk:** Transition milk is the milk seen after 72 hours of delivery and has lesser immunoglobulin and protein, but more fat and sugar content than colostrum. Exclusive breastfeeding of colostrum and transition milk minimizes infection related neonatal deaths in maternity care facilities.
- **Mature milk:** Mature milk is composed of fore-milk and hind-milk. Fore-milk comes at the start of the feed; is watery; has low fat, high lactose sugar, proteins, vitamins and minerals. It satisfies the babies’ thirst. Hind-milk comes later in the feed, is richer in fat and supplies energy. It has a satiety effect.
- **Preterm milk:** Preterm milk is the milk produced by a woman who delivers preterm and has more protein, minerals, immunoglobulins and lactoferrin.

**The First Feed—Early Initiation**

Early initiation of breastfeeding is the key to establishing a good milk supply. It is begun when rooming-in is practiced, i.e. the mother has the baby with her day and night.

Breastfeeding should begin as soon as possible after birth, usually within the 1st hour. The newborn infant should remain with the mother throughout the recovery period, except under special circumstances. Newborns should be nursed whenever they show signs of hunger, such as increased alertness or activity, mouthing or rooting; approximately 8–12 times every 24 hours until satiety, usually 10–15 minutes on each breast. No supplements should be given to breastfeeding newborns, unless a medical indication exists.

**How to Feed? Which Position?**

There are several positions in which a mother can breastfeed her baby. However, the best position is one in which both the mother and the baby are comfortable. The important principles of positioning are:

- The baby’s whole body should face the mother and be close to her, with the head and neck in a straight line facing the breast.
- The baby should be well attached to the breast, i.e. the baby’s mouth should be wide open with the chin touching the breast, the lower lip curled outward, the areola not being visualized and the mother not feeling pain in the nipple while feeding.

**Lactation Failure—Reality or Myth?**

Inadequate milk production is an important reason for resorting to top feeds. The reasons why a mother feels that she has insufficient milk are because the baby cries often, wakes up frequently, demands frequent feeds or is irritable. The common reasons for this so called lactation failure are giving prelacteal feeds, discarding colostrum and keeping mothers and babies separately.

The mother should be told that an exclusively breastfed baby showing a weight gain of 500–1,000 g/month and passing urine at least 6–8 times/day is definitely getting enough milk. The role of galactogogues is limited. The best galactagogue is a baby suckling at the breast in a correct position, frequently and for an adequate duration.

**SPECIAL ISSUES**

**Human Immunodeficiency Virus and Breastfeeding**

Human immunodeficiency virus (HIV) passes via breastfeeding to about one out of seven infants born to HIV-infected women. Analysis of available data shows that the maximum risk of transmission is during labor. However, in many situations where there is a high prevalence of HIV, the lack of breastfeeding is associated with a three- to fivefold increase in mortality. A research has highlighted a lower risk of HIV transmission with exclusive breastfeeding by HIV positive mothers (4% risk), compared to mixed feeding (10–40% risk). This is of particular importance in developing countries where infant formula is not widely available or safe to prepare.
Conditions that are not Contraindications to Breastfeeding\textsuperscript{17,18}

Certain conditions have been shown to be compatible with breastfeeding: such as infants born to mothers who are hepatitis B surface antigen–positive, or infected with hepatitis C virus, mothers who are febrile, have been exposed to low-level environmental chemical agents and mothers who are seropositive carriers of cytomegalovirus (CMV) (not recent converters if the infant is term).

*Tobacco smoking*\textsuperscript{19} by mothers is not a contraindication to breastfeeding, but tobacco-using mothers should avoid smoking within the home and to make every effort to wean themselves from tobacco. Breastfeeding mothers should avoid the use of *alcoholic beverages*, because alcohol is concentrated in breast milk and its use can inhibit milk production.

Women who have had breast surgery, such as breast enlargement or reduction, should discuss breastfeeding with their healthcare providers. Most will be able to breastfeed, though some may have problems, such as not being able to produce enough milk.

Contraindications to Breastfeeding\textsuperscript{12,17,18}

- Infants with classic galactosemia
- Mothers with untreated pulmonary tuberculosis
- If the mother is taking certain medications that suppress the immune system; uses potentially harmful substances such as cocaine, heroin and amphetamines; or has had unusually excessive exposure to heavy metals.

Medications and Breastfeeding\textsuperscript{14,20}

The vast majority of medicines are compatible with breastfeeding, but there are some that might be passed onto the child through the milk. While small amounts of many medications do enter breast milk, most do not harm the baby. However, a woman always should check with her and her baby’s healthcare provider before taking a medication (including over-the-counter and herbal preparations). The healthcare provider may switch a woman to a safer medication or may advise her to take her medication soon after breastfeeding, so most of the medication will be out of her system before the next feeding.

**The Role of Federation of Obstetric and Gynaecological Societies of India\textsuperscript{1}**

Besides declaring 1997 as the “Federation of Obstetric and Gynaecological Societies of India (FOGSI) Breastfeeding Promotion Year” the Federation:

- Printed slogans on all FOGSI envelopes and the letterhead of the Federation to propagate breastfeeding
- Released one issue of the Indian Journal of Obstetrics and Gynecology devoted to the many aspects of breastfeeding and its correct practice
- Released a booklet on “Breastfeeding Your Baby” at the World Congress on Labor and Delivery
- Developed a 3-hour program in the form of lectures and videotape which can be organized at all the societies
- Conducted workshops on safe motherhood which also emphasize breastfeeding
- Held training programs on lactation management.

Role of Employers\textsuperscript{14}

Employed mothers form an important group today as more women are joining the work force. Exclusive breastfeeding poses a special problem to women who work outside the home. An employer needs only to make minor accommodations to allow employees to breastfeed their babies. Working mothers should be given extended maternity leave for 6 months if possible. Crèche if available at the workplace should be used. Working mothers should also be taught and asked to express milk. This milk can be stored for 24 hours in a refrigerator. Once a mother returns from work she can continue to feed the baby when at home or during holidays. Expressed milk can be fed to the baby while she is at work.

The Role of the Judiciary\textsuperscript{14,21}

To protect infant health, India became one of the few countries in Asia to fully implement the International Code of Marketing of Breastmilk Substitutes with the enactment of the infant milk substitutes, feeding bottles and infant foods (Regulation of Production, Supply and Distribution) Act, 1992 (41 of 1992) (hereinafter referred to as “the IMS Act”). The objective of the IMS Act is to protect breastfeeding from commercial promotion, and thereby prevent malnutrition and deaths in infants and young children. The IMS Act controls marketing practices of baby food manufacturers.\textsuperscript{3}

Role of Voluntary Organizations

Various voluntary organizations like Breastfeeding Promotion Network of India (BPNI) and Association for Consumer Action on Safety and Health (ACASH) have already taken up the cause of fighting the menace of commercial foods by filing criminal cases against companies violating the IMS Act.

Role of Government/Media\textsuperscript{21}

The role of the government and policy makers does not end with the enactment of the law. They should take some bold steps to implement the policies and provisions of the act. The Health Ministry should start promoting and supporting breastfeeding through TV and radio channels. We see
National and International Action for Support of Breastfeeding\textsuperscript{14,22,23}

Alarmed by the harmful trends in infant feeding practice, international organizations stepped up their efforts to promote the breastfeeding culture. An important starting point is the joint WHO/UNICEF booklet—“Promoting, protecting and supporting breastfeeding”, in 1989.

This was followed by the Baby Friendly Hospital Initiative (BFHI) with its “10 steps to successful breastfeeding” in June 1991.

Baby Friendly Hospital Initiative was initiated in India in the Metropolitan cities and then spread to the whole country. The National Task Force comprises of representatives from Government of India (GOI), United Nations International Children’s Emergency Fund (UNICEF) and World Health Organization (WHO) along with professional bodies such as FOGSI, Indian Medical Association (IMA), Indian Academy of Pediatrics (IAP), Trained Nurses Association of India (TNAI), etc. with a secretariat located in the IMA headquarters in Delhi.

The Breastfeeding Promotion Network of India and the World Alliance for Breastfeeding Action (WABA) are national and global network of organizations and individuals who believe that breastfeeding is the right of all children and mothers and devote themselves to protect, promote and support that right. Since 1992, World Breastfeeding Week has been celebrated between 1st August and 7th August. The aims are protecting, promoting and supporting the mothers and babies by reinstating breastfeeding as an integral part of women’s reproductive cycle and health, creating awareness of women’s right to humane and noninvasive birthing practices and promoting a global initiative for support for breastfeeding as one way to strengthen the support for mothers.

CONCLUSION

Breastfeeding was the best, is the best and will remain the best as far as infant feeding is concerned. Extensive research shows that human milk and breastfeeding provide compelling advantages to infants, mothers, families and society, including nutritional, developmental, health, immunologic, psychologic, social, economic and environmental benefits. Hence, it deserves to be promoted through all possible means and avenues.

REFERENCES

A Few Observations

- During the postpartum period about 85% of women (10–15% to a severe extent) suffer from some kind of behavioral or mood disturbance.¹
- Puerperal psychosis is associated with 4% infanticide and high incidence of suicide.
- A majority of it were supposed to be suffering from schizophrenia whereas the modern look is that most of them are suffering from a type of mood disorder.
- The postpartum period has been identified as a time of increased risk for the development of psychiatric illness in women and this comes from observation that psychiatric admissions peak during the first 3 months after delivery. Hence a thorough understanding of this topic is must for a student of obstetrics.

Since 1858, when Marce² wrote a treatise on puerperal psychosis, the problems that some women experience in the postpartum period have been the subject of much confusion. These problems affect not only the woman but also her spouse, previously born children and new born baby. For 9 whole months preceding the baby’s birth, the mother to be prepared herself for the new arrival. And when the day finally comes, looking at her baby, holding him in her arms, she goes through a wide range of emotions, from relief to joy and exhilaration, to fear, uncertainty and anxiety. For many or most mothers, giving birth is one of the supreme moments of their lives.

Newly delivered mothers have to face a number of challenges, including the following:³
- **Physical exhaustion**: Due to prolonged labor pains
- **Multiple responsibilities of mother, housekeeper, and wife**
- **Breastfeeding**: Anxiety associated with its initiation
- **Insomnia**
- **Recovery of normal figure and attractiveness**
- **Loss of libido** and associated stress with spouse

With this background of rapid biological, social, and emotional transition, it is not surprising that a wide variety of psychiatric disorders occur; indeed the psychiatric complications of childbirth are more numerous and complex than in any other human situation.

The first description of postpartum disorder comes from Hippocrates who described mania related to lactation. There was virtually no mention of puerperal mental illness until the 1700s and 1800s, when case reports of “puerperal insanity” began to appear in the French and German medical literature.⁴ Since the first clear description by Osiander in 1797 and the authoritative accounts by Esquirol in 1818 and Marcé in 1858, there has been a long-standing controversy about their place in the nosology of the psychoses. In 1960 B Pitt described an atypical depression, later called as “Maternity Blues” that affected mothers soon after childbirth.⁵ It was relatively mild and short lived. The concept of a more severe form of nonpsychotic depressive illness (i.e. postpartum depression) emerged during the 1970s.

**ETIOPATHOLOGY**

It was Victor Louis Marce in 1858, who first suggested, long before the emergence of the modern field of endocrinology, that a physiological transition occurring after delivery may play an important role in the pathogenesis of puerperal illness. Other investigators have emphasized the importance of psychosocial factors and biological vulnerability to psychiatric illness during the puerperium. The factors which can be considered are:
- Demographic and psychosocial factors
- Biological factors
- Past psychiatric illness
Demographic and Psychosocial Factors

Experts are not exactly sure why postpartum psychosis happens. The possible reasons or contributing factors include a lack of social and emotional support; a low sense of self-esteem due to a woman’s postpartum appearance; feeling inadequate as a mother; feeling isolated and alone; having financial problems; and undergoing a major life change. One of the most consistent findings is that postpartum depressive illness is more common in women who report marital dissatisfaction or inadequate social supports.

There is little consistent evidence to suggest that any particular demographic factor including age, marital status, parity, education level, socioeconomic status or nutritional status, places a woman at increased risk for puerperal psychiatric illness. Some studies have found a relationship between adolescent mothers and risk for puerperal illness. Obstetrical complications (e.g. prolonged labor, cesarean section, stillbirths) may increase the likelihood of postpartum psychosis.

Biological Factors

During the postpartum period a rapid shift in the hormonal environment occurs in comparison to the pregnancy state. The blood levels of various hormones especially estrogen and progesterone and cortisol fall dramatically within the first 48 hours after delivery. Many investigators have proposed a role for these hormones in the emergence of a mood disorder during the postpartum period. It has been observed by some studies that postpartum estrogen deficiency and declining level of progesterone may result in postpartum mood disturbance. It has been suggested by a beneficial effect of progesterone and or estrogen hormone replacement in the treatment of postpartum psychiatric illness. Thyroid levels can drop rapidly and 10% of women will develop clinical hypothyroidism postpartum. Hypothyroidism may produce psychiatric symptoms nearly similar to depression.

Past Psychiatric Illness

There is a well-defined association between all types of postpartum psychiatric illness and a personal history of mood disorder. Women with a history of postpartum psychosis are at highest risk. The risk of experiencing an episode of postpartum psychiatric illness increased up to 70% in women who have had one episode of puerperal psychosis and as high as 30% in women who have had postpartum depression. A relapse rate of 20–50% has been noticed in women with history of bipolar disorders during the postpartum period. Women with histories of mild to moderate affective illness who remain euthymic during pregnancy are probably at lower risk for postpartum depression.

Reproductive Hormones

Reproductive hormonal fluctuations modulate central affective function. Estrogen modulated N-methyl-D-aspartate receptors induce the formation of new synapses. This observation suggests a pivotal role for estrogen in the plasticity of the nervous system.

Exposure to and withdrawal from the neurosteroidal metabolite of progesterone, allopregnanolone, influence a principal regulator of cognitive function and affect, the gamma-aminobutyric acid (GABA)-A receptor. Selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine and paroxetine, increased brain concentrations of allopregnanolone in rats, which may explain their antidepressant efficacy in depressed patients mediated via GABAergic receptor activity. Additionally, the SSRI sertraline prevents postpartum depression while the tricycle antidepressant nortriptyline does not. This phenomenon may be explained by the fact that SSRIs increase brain levels of neuroactive steroids, which may decrease the risk for depression in the postpartum milieu.

Thyroid Hormones

Postpartum thyroid dysfunction occurs in 5–10% of women within 1 year following delivery and may predispose a woman to affective dysregulation. Simultaneous treatment of both the thyroid dysfunction and the affective disorder is usually essential for optimum treatment results.

CLINICAL PRESENTATIONS

Postpartum psychiatric illness is typically divided into three categories: (1) postpartum blues, (2) nonpsychotic postpartum depression (also called as neurotic depression in past) and (3) puerperal psychosis. It is helpful to conceptualize these disorders as existing along a continuum, as there may be significant overlap between these three diagnostic subtypes.

Postpartum Blues

Postpartum blues also called as “baby blues” are the most common mood disturbance, affecting an estimated 50–85% of women. Given how common this type of mood disturbance is, it may be more accurate to consider the blues as a normal experience following childbirth rather than a psychiatric illness. Rather than feelings of sadness, women with the blues more commonly report mood liability, tearfulness, anxiety or irritability. These symptoms typically peak on the fourth or fifth day after delivery and may last for a few hours or a few days, remitting spontaneously within 1–2 weeks. Only support and reassurance is sufficient for most of the cases as postpartum blues are usually mild in severity and
Postpartum Pinks

While “the blues” refers to mood lability (or changes in mood from happy to sad), some women experience mild elation, or “the pinks,” following childbirth; again, this elation lasts for a few hours to days until a more normal level of happiness returns.

Nonpsychotic Postpartum Depression

Postpartum depression occurs in 10–15% of women in the general population. Women at highest risk are those with a personal history of depression, or previous episode of postpartum depression. Typically, postpartum depression develops insidiously over the first 3 postpartum months, though it may have a more acute onset. Symptoms may include depressed mood, tearfulness, anhedonia (lack of pleasurable feelings), insomnia, fatigue, appetite disturbance, suicidal thoughts, and recurrent thoughts of death. Anxiety is prominent, including worries or obsessions about the infant’s health and well-being. The mother may have ambivalent or negative feelings toward the infant. She may also have intrusive and unpleasant fears or thoughts about harming the infant. Postpartum depression often interferes with the mother’s ability to care for herself or her child. It is advisable to screen all women for depression during the postpartum period. Severity of illness should guide treatment.

Other Neurotic Disorders

Phobias, anxiety states and obsessive compulsive disorders may also occur and interfere markedly with child care. A mother with a germ phobia, for example, may have great difficulty in washing nappies and become upset if her baby does not develop a precise routine. For some women with postpartum anxiety, the fear or anxiety is general, but for others the symptoms may relate to something more specific (i.e. bathing the baby, taking the baby out in the car, coping with grocery shopping) or the symptoms may focus solely on the child (i.e. is the baby feeding properly and breathing properly, is the woman competent as a mother and able to look after the baby). Between 4% and 15% of women experience anxiety following childbirth. Many mothers feel anxious, overwhelmed and scared following the birth of their baby. This is understandable given the changes involved in becoming a new parent. However, for some women the level of anxiety is so severe that it interferes with their daily lives, and represents a change in normal character and functioning. The treatment strategy is similar to that of nonpuerperal anxiety disorders.

Puerperal Psychosis

Puerperal psychosis is a psychiatric emergency that typically requires inpatient treatment. Most patients with puerperal psychosis suffer from bipolar disorder. Postpartum (or puerperal) psychosis usually develops symptom within the first 2–3 weeks after delivery. Postpartum psychosis symptoms usually appear quite suddenly; in 80% of cases, the psychosis occurs 3–14 days after a symptomfree period. Postpartum psychosis is the most severe and rare form of postpartum mood disorder, with rates of 1–2 per 1,000 deliveries. Puerperal psychosis resembles a rapidly evolving affective psychosis with manic, depressive, or mixed features. The earliest signs are typically restlessness, irritability, insomnia and feelings of depression. Women with this disorder typically exhibit a rapidly shifting depressed or elated mood, disorientation or depersonalization, and disorganized behavior and excitement. Delusional beliefs often center on the infant and include delusions that the child may be defective or dying, that the infant has special powers. Auditory hallucinations that instruct the mother to harm or kill herself or her infant are sometimes reported. Cases of infanticide and suicide are rare but are a serious risk in women with postpartum psychosis. The symptoms of postpartum psychosis fluctuate rapidly, and a woman who was lucid and calm upon first interview can be suicidal and psychotic within a matter of hours.

INVESTIGATIONS AND DIAGNOSIS

The official classification of American Psychiatric Association [Diagnostic and Statistical Manual of Mental Disorders (DSM) IV] does not recognize postpartum psychiatric disorders as individual entity. According to DSM-IV, postpartum psychiatric disorders may be indicated with a postpartum onset specifier4 to the mood or schizophrenia disorder as the case may be. However, in WHO classification of International Classification of Diseases-10, these disorders are given a separate listing at code no. 099.3 and at F53. The British view postpartum psychiatric disorders as a distinct group whose etiology, clinical presentation and prognosis differ from those of nonpuerperal mental illnesses. In contrast, the American view is that the disorders are simply affective or schizophrenic episodes occurring postpartum.

Screening

Severe postpartum depression and psychosis are easily recognized; however, milder or more insidious forms of depressive illness are frequently missed. Even severe
depressive symptoms that arise during the puerperium may be dismissed by both patients and caregivers as normal or natural consequences of childbirth. Since it is difficult to reliably predict which women in the general population are likely to develop puerperal illness, it is advisable to screen all women for depression during the postpartum period. Screening for mood disorders during the postpartum period may, however, be more difficult than at other times. Many of the neurovegetative signs and symptoms characteristic of major depression (e.g., sleep and appetite disturbance, diminished libido, low energy) are also observed in nondepressed women during the acute puerperium. The Edinburgh Postnatal Depression Scale (EPDS) is a ten-item, self-rated questionnaire that has been used extensively for the detection of postpartum depression and has demonstrated satisfactory sensitivity and specificity in women during the postpartum period.\(^9\)

**DIFFERENTIAL DIAGNOSIS**

Various medical illnesses may mimic psychiatric illness during the postpartum period. Hypothyroidism is relatively common and may cause a constellation of symptoms resembling major depressive disorder. Women with a pre-existing psychiatric illness may experience exacerbation of symptoms during the puerperium. Furthermore, any psychiatric illnesses may emerge for the first time during the postpartum period. Schizophrenia or schizoaffective disorder, particularly when characterized by prominent positive symptomatology, may be difficult to distinguish from puerperal psychosis. A possibility of substance-induced mood disorder due to postanesthetic states, such as after cesarean section or meperidine-scopolamine analgesia should also be kept in mind.

**MANAGEMENT**

A clinician’s approach to the patient should be guided by the type and severity of the symptoms and the degree of functional impairment. However, before initiating psychiatric treatment, medical causes for mood disturbance (e.g., thyroid dysfunction, Sheehan’s syndrome) must be excluded. Initial evaluation should include a thorough history, physical examination, and routine laboratory tests.

**Postpartum Depression**

Milder forms of depression may respond to supportive psychotherapy. More severe depression may require pharmacological treatment. Non-pharmacological treatment strategies are useful for women with mild-to-moderate depressive symptoms. These modalities may be especially useful for mothers who are nursing and who wish to avoid taking medications.\(^9\) These may be used to address: role conflict, disturbed relationships with the husband and social supports, and interaction with the infant.

**Pharmacological Therapy**

Several studies have demonstrated the efficacy of antidepressant medications (e.g., fluoxetine, sertraline, venlafaxine) in the treatment of postpartum major depressive disorder. In all of these studies, standard antidepressant doses were effective and well-tolerated. The choice of an antidepressant drug should be guided by the patient’s prior response to antidepressant medication and a given medication’s adverse effect profile. The adjunctive use of a benzodiazepine may be very helpful. In women with severe postpartum illness, electroconvulsive therapy (ECT) should be considered early because it is safe and highly effective.

**Hormonal Therapy**

Some authors have suggested that progesterone is helpful in the management of postpartum depression. A study by Gregoire has suggested that estrogen alone (or possibly when used as an adjunct to an antidepressant agent) may be useful in the treatment of postpartum depression.\(^10\)

**Interpersonal Therapy**

Women with postpartum depression were 2–3 times more likely to recover when randomly assigned to 12 sessions of interpersonal therapy (IPT) compared to the wait list control. In a group intervention study based on IPT during pregnancy, Zlotnick et al. successfully prevented postpartum depression in at-risk women while 33% of the treatment as usual control group developed major depressive disorder.

**Electroconvulsive Therapy**

Electroconvulsive therapy administration is recommended as first-line treatment if psychotic symptoms are present and as an effective alternative to untreated depression in the peripartum period. However, uterine tocodynamometry and fetal cardiotocography monitoring to detect premature uterine activity and fetal arrhythmias are recommended precautions during ECT administration.

**Estrogen Therapy**

Endogenous estrogenic steroids exert both genomic and nongenomic activational effects on brain function. Gregoire et al. studied the antidepressive properties of transdermal estrogen (17β-estradiol) in 61 women with chronic treatment-resistant postpartum depression. The mean EPDS scores improved rapidly during the first month of treatment when compared with controls with an overall treatment effect of 4.38 points on the EPDS (95% CI, 1.89–6.87). Although sustained over 5 months, the estradiol antidepressant effect was confounded by the co-administration of antidepressant in half the population.


**Bright Light Therapy**

The effectiveness of bright light therapy for antepartum depression was provided in a small controlled trial. Ten pregnant women were randomized to 5 weeks of 7,000-lux box (active) or a 500-lux (placebo) box. At 10 weeks, there was significant treatment effect; phase advancement of melatonin circadian rhythm on measured salivary melatonin levels was correlated with the treatment effect.

**Essential Fatty Acids**

Hibbeln and Otto et al. demonstrated a significant association between low docosahexaenoic acid (DHA) levels, an ω-3 essential fatty acid, and the occurrence of postpartum depression. In an open-label trial of ω-3 essential fatty acid, seven depressed women at least 16-weeks-pregnant were prescribed between 0.93 g/day and 2.8 g/day of eicosapentaenoic and docosahexaenoic acid (EPA/DHA). Five of the seven patients experienced a decrease of greater than 40% on the EPDS scores which were more than 12 at the beginning of the study. This approach merits further studies because of its safety and tolerability.

**Acupuncture**

Manber et al. randomized 61 women to active acupuncture, valid control acupuncture that did not address depression symptoms and massage for 8 weeks. Responders were provided treatment until 10 weeks postpartum. The active acupuncture group achieved a 43.8% remission in symptoms compared with 21.1% in the control group and 31.6% in the massage group. This novel study provides preliminary efficacy data for acupuncture treatment in antepartum depression and warrants further trials.

**Prevention Trials in Postpartum Depression**

Women who have experienced postpartum depression have a 25% risk of recurrence with a subsequent pregnancy. Thus, women with a history of postpartum depression should be at a minimum closely monitored with established screening tools. Preventive pharmacotherapy should also be considered after delivery. Effective prophylaxis may require treatment for 6 months using the drug that previously provided a good response or from an SSRI. Following the treatment phase, a gradual taper of the antidepressant dose at a rate of 33% per week is recommended to prevent the onset of a discontinuation syndrome.

**Puerperal Psychosis**

There are no specific treatments. The first resource is sedation by neuroleptic agents, but these should be used with caution because of the risk of severe extrapyramidal side effects, including the neuroleptic malignant syndrome. It is usual to stop breastfeeding, although this may not be necessary because the infant receives only a minute dose of the neuroleptic and adverse effects have not been noted. Some have argued that postpartum psychosis is indistinguishable from a manic psychosis and should be treated similarly. Acute treatment includes a mood stabilizer in the form of lithium, valproic acid, carbamazepine in combination with antipsychotic medications and benzodiazepines. Short-term treatment with an antipsychotic medication as well as a mood stabilizer is appropriate. However, lithium may have adverse effects on breastfed infants. ECT is highly effective in all varieties of puerperal psychosis, including puerperal mania. Untreated puerperal psychosis is associated with increased risk of infanticide as high as 4% and extremely high risk for suicide. A maintenance treatment should be given to prevent relapses.

**Reproductive Toxicity of Antipsychotic Treatment**

The categorical format (A, B, C, D, X) of teratogenic risk as classified by the Food and Drug Administration is under revision. The sophistication of risk-benefit decision analysis has improved with the incorporation of multiple domains of reproductive toxicity. Intrauterine fetal death, morphological teratogenicity, growth impairment, neonatal toxicity and neurobehavioral teratogenicity represent these five domains.

**Intrauterine Death**

Intrauterine death is not associated with exposure to fluoxetine, sertraline, paroxetine, citalopram and fluvoxamine, venlafaxine, or tricyclic antidepressants.

**Morphological Teratogenicity**

Minor malformations (which by definition have no functional or cosmetic significance) have been reported after first trimester fluoxetine exposure. Major malformations have not been reported with tricyclics, the SSRIs, venlafaxine or the phenylpiperazine antidepressants, trazadone and nefazodone.

**Growth Impairment (Low-birth Weight, Small for Gestational Age Infants and Preterm Labor)**

In small cohort studies, comparable antenatal growth and birth weights occurred in infants exposed to tricyclics, newer SSRIs, venlafaxine, trazadone and nefazodone relative to nondepressed controls. In a study that involved 969 pregnant women, the mean birth weight in a specific pregnancy week was greater in infants of mothers who were on antidepressants compared with nondepressed controls. Chamber et al. reported significantly lower birth weights related to lower maternal weight gain after fluoxetine exposure in the third trimester.

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Women who have experienced postpartum depression have a 25% risk of recurrence with a subsequent pregnancy. Thus, women with a history of postpartum depression should be at a minimum closely monitored with established screening tools. Preventive pharmacotherapy should also be considered after delivery. Effective prophylaxis may require treatment for 6 months using the drug that previously provided a good response or from an SSRI. Following the treatment phase, a gradual taper of the antidepressant dose at a rate of 33% per week is recommended to prevent the onset of a discontinuation syndrome.

**Puerperal Psychosis**

There are no specific treatments. The first resource is sedation by neuroleptic agents, but these should be used with caution because of the risk of severe extrapyramidal side effects, including the neuroleptic malignant syndrome. It is usual to stop breastfeeding, although this may not be necessary because the infant receives only a minute dose of the neuroleptic and adverse effects have not been noted. Some have argued that postpartum psychosis is indistinguishable from a manic psychosis and should be treated similarly. Acute treatment includes a mood stabilizer in the form of lithium, valproic acid, carbamazepine in combination with antipsychotic medications and benzodiazepines. Short-term treatment with an antipsychotic medication as well as a mood stabilizer is appropriate. However, lithium may have adverse effects on breastfed infants. ECT is highly effective in all varieties of puerperal psychosis, including puerperal mania. Untreated puerperal psychosis is associated with increased risk of infanticide as high as 4% and extremely high risk for suicide. A maintenance treatment should be given to prevent relapses.

**Reproductive Toxicity of Antipsychotic Treatment**

The categorical format (A, B, C, D, X) of teratogenic risk as classified by the Food and Drug Administration is under revision. The sophistication of risk-benefit decision analysis has improved with the incorporation of multiple domains of reproductive toxicity. Intrauterine fetal death, morphological teratogenicity, growth impairment, neonatal toxicity and neurobehavioral teratogenicity represent these five domains.

**Intrauterine Death**

Intrauterine death is not associated with exposure to fluoxetine, sertraline, paroxetine, citalopram and fluvoxamine, venlafaxine, or tricyclic antidepressants.

**Morphological Teratogenicity**

Minor malformations (which by definition have no functional or cosmetic significance) have been reported after first trimester fluoxetine exposure. Major malformations have not been reported with tricyclics, the SSRIs, venlafaxine or the phenylpiperazine antidepressants, trazadone and nefazodone.

**Growth Impairment (Low-birth Weight, Small for Gestational Age Infants and Preterm Labor)**

In small cohort studies, comparable antenatal growth and birth weights occurred in infants exposed to tricyclics, newer SSRIs, venlafaxine, trazadone and nefazodone relative to nondepressed controls. In a study that involved 969 pregnant women, the mean birth weight in a specific pregnancy week was greater in infants of mothers who were on antidepressants compared with nondepressed controls. Chamber et al. reported significantly lower birth weights related to lower maternal weight gain after fluoxetine exposure in the third trimester.
Simon et al. reported a twofold increased in preterm labor after SSRI exposure that was not limited to infants exposed late in pregnancy. However, they did not report the specific dosing or timing of treatment during pregnancy to justify the negative attributions to the SSRI exposure. Obstetrical factors were not excluded and depressive symptoms were not assessed directly. The active (state) effects of depression and the residual (trait) effects (changes in maternal physiology which remain even when the mother is asymptomatic) could affect pregnancy outcome negatively. Thus, the negative outcomes attributed to the SSRI may well have been related to either unremitting depression or the interaction of depression with SSRI exposure.

Chambers et al. also reported an increased risk for preterm birth (14.3%) in infants whose mothers took fluoxetine in the third trimester compared to infants whose mothers discontinued fluoxetine before the third trimester (4.1%) as well as controls (5.6%). Compared to a combined group of infants whose mothers took paroxetine during the first and second trimesters as well as controls, increased preterm birth in infants whose mothers took paroxetine in the third trimester has been reported. Firm conclusions based on these early observations await further robust studies.

**Neonatal Toxicity**

Both withdrawal symptoms and direct pharmacological toxic effects can occur after prenatal exposure to any antidepressant. Simon et al. recently reported lower APGAR scores after third trimester SSRI exposure. Anticholinergic stimulation causing bladder distension and gastrointestinal stasis in newborns has been described. Serotonin over-stimulation (myoclonus, restlessness, tremor, shivering, hyper-reflexia, incoordination, rigidity) with fluoxetine, paroxetine, and sertraline has also been reported.

The risk of withdrawal reactions may be greater with short half-life drugs such as paroxetine and venlafaxine when compared with fluoxetine. The half-lives of paroxetine and venlafaxine when compared with fluoxetine. The half-lives of paroxetine and sertraline are similar at 24 hours but the largely inactive metabolite of sertraline, desmethylsertraline, is eliminated slowly, which prevents occurrence of frequent withdrawal reactions. It has been suggested that a dose taper before delivery will minimize the fetal drug load at birth. However, predicting labor is rarely accurate; therefore, this decision requires clinical judgment based on a risk-benefit analysis.

**Behavioral Teratogenicity**

Antepartum exposure to agents that affect the central nervous system can impact the neurology and behavior of the infant in the postpartum period. Oberlander et al. examined pain sensitivity in SSRI-exposed neonates relative to controls and found attenuated acute pain response in the SSRI-exposed group that persisted at 2 months of age. Increased tremulousness, increased sleep times and REM sleep in newborns exposed to SSRIs relative to unexposed newborns has been recently reported. The long-term significance of these findings remains to be established. In a 7-year follow-up study, Nulman et al. reported that global IQ, verbal comprehension, expressive language development, temperament and general behavior were similar in children exposed at any time in pregnancy to tricyclics or fluoxetine compared with controls. Similar studies on newer drugs are not available.

**Impact of Postpartum Illness on Infant Development**

A large body of literature suggests that a mother’s attitude and behavior toward her infant significantly affects mother-infant bonding and infant well-being and development. Depression not only hurts the mother, but also affects her family. Postpartum depression can affect a mother’s ability to parent. As a result, she may feel guilty and lose confidence in herself as a mother, which can worsen the depression. Mothers may harm their child during period of psychosis. Postpartum depression can affect the infant by causing delays in language development, problems with emotional bonding to others, behavioral problems, sleep problems, and distress. It helps if the father or another caregiver can assist in meeting the needs of the baby while mother is depressed. All children deserve the chance to have a healthy mother. All mothers deserve the chance to enjoy their life and their children. Do not suffer alone.

**Breastfeeding and Psychotropic Medications**

Women who plan to breastfeed must be informed that all psychotropic medications, including antidepressants, are secreted into breast milk. Concentrations in breast milk vary widely. Data on the use of tricyclic antidepressants, fluoxetine, sertraline, and paroxetine during breastfeeding are encouraging, and serum antidepressant levels in the nursing infant are either low or undetectable. Reports of toxicity in nursing infants are rare, although the long-term effects of exposure to trace amounts of medication are not known. Avoid breastfeeding in women treated with lithium. Avoid breastfeeding in premature infants or in those with hepatic insufficiency who may have difficulty metabolizing medications present in breast milk.¹³

**PREVENTION**

In most cases postpartum depression is preventable; early identification can lead to early treatment. A major part of prevention is being informed about the risk factors and education about identifying postpartum depression. Also, proper exercise, nutrition including proper hydration and
vitamin supplements, plays a role in preventing postpartum, and general, depression.

The high risk group of women who can develop postpartum psychosis is not clearly delineated but certain subgroups can be identified particularly those with a history of mood disorder, prior episode of psychosis. In such cases prophylactic interventions may be instituted near or at the time of delivery to decrease the risk of postpartum illness.14

**SUMMARY**

The puerperium is undoubtedly a time when a woman has an increased risk of developing a psychiatric disorder. Table 1 describes in short the various disorders and the treatment modalities. Childbirth is not a straightforward single life event and may best be considered as a cascade of life events; some, such as the birth itself, are initiated by physiological changes whilst others, such as the new social role of the mother, are determined by sociocultural variables. Much road has to be covered in our country to understand these disorders and to formulate long-term preventive goals.

**REFERENCES**

INTRODUCTION

Postpartum exercises and physiotherapy should be one of top priorities, because of the current trend towards briefer hospital stay and health awareness amongst the new mothers and her family. Also, it minimizes complications related to blood clotting. Its advantages have been tabulated in Table 1. Much innovative thinking is urgently required, because there will have to be substantial changes in the provision of immediate postnatal care and rehabilitation in hospital and its continuation in the community.

An average pregnant woman gains 10–12 kg during pregnancy. 5–6 kg weight is usually lost within a month of having baby. But this 3 or 4 kg can be hard to get rid of. With a little patience and consistent exercise program, one can get back to shape after delivery. However, before you do any exercise you should consult your doctor.

Simple exercises that one can do in the first few hours and week after birth are light exercises like walking and modified push-ups stretching especially if delivery is vaginal normal delivery.

Kegel’s exercises can also be started early since they involve small contractions of the muscle of the vaginal wall. Kegel’s exercise can help strengthen weak pelvis muscles, which could cause bladder control problems. Another easy one is walking! Short slow walks will help. A mother’s body gets ready for more vigorous exercises after the first few weeks. Walking at an easy pace is encouraged as it promotes healing and helps in preventing the complications related to blood clotting.

ASSESSMENT

Ideally, at a mutual convenient time within the first 24 hours, the obstetric physiotherapist should assess each new mother to determine her priority needs. Immediate advice and initial exercise instruction is best given individually, and specific therapies, where necessary, should be commenced as soon as possible.

However, after this it is more cost-efficient, more effective and much more pleasurable for the women to participate in postnatal classes. Most new mothers enjoy being in a group and benefit from the opportunity to exchange experiences, moan and laugh, discuss problems and work through ways of solving them together.

There is a wealth of information and advice, over and above simple exercise instruction, which is particularly important for those women who did not attend antenatal classes. The postnatal class can be taken in the parent craft from, if it is nearby, or the ward day-room. Most women are happy to participate, but only if their babies can come too. This should definitely be encouraged because it enables valuable teaching to be presented regarding the new activities, especially baby feeding and nappy changing, which if carried out incorrectly can lead to neck and back ache. Where women are cared for in single rooms and no common room exists, obstetric physiotherapists will be very restricted in what they can offer at this special time.

Table 1: Advantages of postnatal exercises

- It raises your metabolism
- It helps you shed those extra kilos
- It provides energy to deal with your chaotic life
- It gives you a little time for yourself
- It helps relieve stress and body tension.
Most women develop a gap in their abdominal muscles during pregnancy and labor. It takes 4-8 weeks after birth for this gap to close. Exercising before the gap closes can risk injury to muscles. If the diastases are less than two fingers in width, abdominal exercises like crunches or situps can be started. If the gap is greater, rotation and side flexion exercises should be delayed until the size of the gap has been reduced. Such movements may increase the gapping because of shearing forces. Static and gentle dynamic inner-range exercise may be performed with crossed hands.

One may like to perform her pelvic floor exercises at the one of labor or when you exhale lift your head and your shoulder off the floor and slide your right hand up your thigh towards your knee. This will make your abdomen muscles tighten and you should be able to feel the gap where muscles have separated. If the gap is more than 3-4 fingers you can gently begin to strengthen your abdominal muscles with pelvic tilts and leg slides.

The primary aims are to shorten stretched muscle fibers, close any diastases and strengthen weakened muscles. The first step in abdominal muscle re-education should be the initiation of a simple contraction, for example, drawing in the anterior abdominal wall in crook lying. It is most efficient when it is combined with expiration. However, many women cannot do this easily. The physiotherapist may find it helpful to suggest that women "breathe in breathe out, draw the tummy in-and then relax". A common fault is attempting to combine abdominal wall retraction with inspiration and breath holding. This has the effect of raising the rib cage with its abdominal wall attachments, thereby taking up the slack, possibly without any muscle contraction. For some women it will be much easier to initiate an abdominal muscle contraction side-lying. Because the abdomen protrudes and sags sideways the muscle fibers are in their outer to middle range—their pre-delivery state and this seems to make it easier to active a contraction. A similar situation exists in sitting women who can both see and feel their abdominal movement.

• One can perform these exercises lying down, sitting, standing or on your hands and knees
• Keep the lower back flat
• Breathe out, and draw your belly button back towards your spine. The lower back should not flex or move.
• Hold this position and breathe lightly. Count to 10.
• Relax, and repeat up to 10 times per set.
• One should do 10 sets, as many times per day as she can.
• One may like to perform her pelvic floor exercises at the same time.

Pelvic tilting can also be taught crook or side lying, again, it can be done slowly, holding the abdominal wall in while the mother counts to four, or it can be done quickly (tilt, relax,
Postpartum Exercises

Figs 1 to 4: Abdominal muscle exercises

Fig. 1

Fig. 2

Fig. 3

Fig. 4
tilt, relax). This second technique is often very helpful for the woman who has after pains or backache. The obstetric physiotherapist must be vigilant because it is possible to tilt the pelvis in crook lying without contracting the abdominal muscles; rhythmic gluteal contraction will help ease the pain from hemorrhoids.

**THE EARLY POSTNATAL CLASS**

All too often postnatal exercise are only taught to women who are lying down, this may well be one of the reasons why many of them fail to continue exercising, once they return home. If a woman does not realize that it is possible to strengthen her abdominal and pelvic floor muscles while she is standing or sitting, early exercises will not be done simply because she may never have time to lie down!

**Simple Postnatal Exercises**

**Walking (Figs 5A and B)**

After the 1st week, a slow to moderate walk of 30 minutes three times a week is fine. As one regains strength, you can increase the length or number of walks. If a mother had a cesarean section, then she should wait for 6–8 weeks before starting the exercises.

Walking at an easy pace is encouraged as it promotes healing and helps in preventing the complications related to blood clotting. It is important to remember that your joints and ligaments will remain loose for next 3–5 months, so vigorous exercises are better carried out under supervision of experts. Do not overdo exercises as your body needs time to heal and you need time to adjust to your new role as a mother.

**Sitting (Figs 6A and B)**

The early hospital class can begin with the women sitting comfortably and well supported on chairs which have been placed in a circle, pillows should be used where necessary for sore perineum and to support back. Women must realize that one of their first postnatal exercises is how they sit when feeding their babies. Once everyone is settled, attention should be drawn to the main areas of muscle weakness (abdomen and pelvic floor) and the problems that can follow misuse of their backs. Multiparous are often important sources of advice, and their previous exercise, can be very useful. The obstetric physiotherapist will find it helpful to have some simple, large diagrams that illustrate the pelvic floor and possible episiotomy sites, as well as the abdominal muscles and the diastases recite abdominals. The Birth Atlas can be used to demonstrate the extent to which their muscles have had to stretch. Women are fascinated by the changes experienced by their bodies during pregnancy and labor, and this realization is often the trigger that stimulates them to continue exercising in order to repair the weaknesses caused by child birth.

Back care advice for feeding, nappy changing, baby bathing, lifting and carrying should all be discussed. Correct heights for cots and pram or buggy handle should be mentioned. Crying babies can be usefully used to explain the value of slings and how they should be worn, with the baby high on the mother’s chest. The women should know that
simple abdominal retraction and pelvic floor work can be done while feeding (once they feel confident that both their babies and themselves are doing this correctly). Other easy exercises which may be done in sitting are side flexion and rotation (with the abdominal muscles well drawn in), elbow and head circling and foot exercises.

**Standing (Figs 7A and B)**

Similar movements can be carried out while standing: “hip hitching” and gentle trunk forward flexion for its relaxing effect are also useful exercises for the women who just cannot find the time or energy during the first few weeks to exercise lying down. While they are standing the women’s attention should be drawn to their posture, which in many cases will still reflect its adaption to pregnancy or to any postpartum pain they are experiencing. The dramatic differences between the measurements of the abdominal girth when women sags compared to that when “standing tall” (5–12 cm) is wonderfully motivating! Women spend a large part of their day standing if all they remember from this early postnatal class is the fact that post office and bank queues are ideal.
places to practice pelvic floor exercises, they will have learnt a valuable lesson!

**Lying (Figs 8A to C)**

Pillows and wedges should be available for the class to learn stronger abdominal work; mats (if there is no carpet) or rolls of disposable couch covering paper (if there is) will be necessary too. Every woman should be shown how to feel if her recti abdominals muscles have separated, and should understand that strong side flexions and trunk rotations, while lying, should be omitted until the anterior abdominal wall is strong enough to allow these movements without shearing.

In this class pelvic tilting can progress to include head raising and then head and shoulders rising. Prior to any postnatal abdominal exercise it is important to remind the mother to draw in the abdominal wall before the movement commences. If the abdomen bulges or ridges anteriorly it indicates extreme weakness of the recti abdominals muscles, and in such women head-raising should be delayed for at least another 24 hours. Where there is a diastasis of more than two finger-widths it has been suggested that crossed hands may be used to approximate and support the diverging recti muscles, although in fat women it may be difficult to find them! Alternate single leg sliding from crook lying with the abdominal wall retracted and head raised, is another excellent technique for strengthening the recti abdominals muscles if it is properly supervised and ridging does not occur.

Practically, every new mother will be having at least one bath each day, so the concept of exercising while bathing should be introduced. Pelvic tilting, pelvic floor contractions, head and shoulder raising and alternative single leg sliding, with the head raised and the chin tucked on to the chest, while holding the sides of the bath, are all good postnatal “aqua exercises”.

This early class should always be completed by a short relaxation session. Women need to be shown how to use pillows to enable them to lie prone comfortably again. Following a cesarean section, mothers can enjoy lying on their backs with a wedge under their knees. Simple relaxation suggestions linked with deep, calm, slow breathing will often result in one or two women falling asleep—this usefully demonstrates their intense fatigue and the importance of occasional catnaps once they return home.
SUMMARY

- By organizing the class in this manner the obstetric physiotherapist can give women valuable information and advice which can really lead to their full recovery and long-term body awareness, how much are useful and realistic than teaching three.
- Pelvic tilts are performed lying on your back, knees bent, feet flat. Lift your lower back and buttocks slightly off the floor, pushing your pelvis to the floor. Hold for 5 seconds and repeat for five reps. Kegel’s are performed by simply tightening your pelvic floor muscles. Pretend as if you are trying to stop a stream of urine. Do 10–12 Kegel’s every time you feed the baby.
- Try exercising in three 10-minute intervals throughout the day, in order to pace yourself.

- Choose exercises you enjoy.
- Try yoga. It is incredible for muscle flexibility and tone.
- Wear a sports bra over your nursing bra for added support and comfort.
- Eat right. Stay away from caffeine and sugar—they are quick energy-boosters that can leave you feeling empty or moody after they wear off.
- Some medical practitioners recommend waiting 6 weeks to exercise—until after your first postpartum check up.
- Be careful with high-impact leg and back exercises. Your joints and ligaments became relaxed during pregnancy, in order to carry and deliver your bundle. It will take your pelvis, back and legs time to realign and get back to normal.
- Make sure your baby is properly secured and dangerous items are out of harm’s reach before you start to exercise.
INTRODUCTION
Postpartum collapse is an acute emergency which we might face many times in our obstetric career. This dramatic event involves the brain, heart or lungs and may ultimately result in death.\(^1\) The exact incidence is difficult to quote.

Postpartum collapse is a consequence of several clinical conditions related to pregnancy and labor. The different pathologies leading to circulatory collapse are often unexpected and mostly not well understood. Moreover, this complex disorder is characterized by its abrupt onset and unfortunately often ends tragically. However, the major pathologies observed in the complex disorder are the trios of hypotension, hypoxia and disseminated intravascular coagulation (DIC). Immediate institution of resuscitative measures is recommended though may not be effective in all the cases. This means that unless the underlying pathology is diagnosed and the management is specific, only resuscitative measures may not improve the outcome. Clinicians’ experience of managing such rare pathologies is also limited. Because of all these reasons, this complex disorder adds to the significant proportion of maternal deaths. Fetal mortality is also high. Current research has provided more knowledge for the understanding of these clinical problems. These are expected to improve our diagnosis and management. No doubt that the involvement of multidisciplinary experts specially the obstetrician, anesthetist, intensivist and the hematologist is the key (to success) to save the life of the woman.

The causes of postpartum collapse can be classified into nonserious causes and serious causes and also on etiological basis (Table 1).

Nonserious Causes
Hyperventilation, hypoglycemia and vasovagal attacks are the nonserious causes of postpartum collapse. These are self-limiting and maternal observations will rapidly return to normal with simple measures, such as reassurance and changing maternal posture.

Serious Causes
- Massive postpartum hemorrhage (PPH)
  - Atonic
  - Traumatic
- Acute puerperal uterine inversion
- Eclampsia
- Embolism
  - Amniotic fluid embolism
  - Pulmonary embolism (PE)
  - Air embolism

Table 1: Etiological basis classification of postpartum collapse

<table>
<thead>
<tr>
<th>Hemorrhagic</th>
<th>Nonhemorrhagic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atonic</td>
<td>Causes related to obstetrics</td>
</tr>
<tr>
<td>Traumatic</td>
<td>- Amniotic fluid embolism</td>
</tr>
<tr>
<td>Mixed</td>
<td>- Acute uterine inversion</td>
</tr>
<tr>
<td></td>
<td>- Septic shock</td>
</tr>
<tr>
<td></td>
<td>- Pulmonary venous thromboembolism</td>
</tr>
<tr>
<td></td>
<td>- Cardiogenic shock—in a patient with pre-existing heart disease/cardiomyopathy</td>
</tr>
<tr>
<td></td>
<td>- Myocardial infarction</td>
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<tr>
<td></td>
<td>- Pneumothorax</td>
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<tr>
<td></td>
<td>- Mendelson’s syndrome</td>
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<tr>
<td></td>
<td>- Cerebrovascular accidents</td>
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<td></td>
<td>- Air embolism</td>
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<tr>
<td></td>
<td>- Anaphylaxis (drugs)</td>
</tr>
<tr>
<td></td>
<td>- Transfusion reaction</td>
</tr>
<tr>
<td></td>
<td>- Drug toxicity: Local anesthetic, magnesium sulfate.</td>
</tr>
</tbody>
</table>
- Cavernous sinus thrombosis
- Mesenteric vein thrombosis
- Hematological
  - Severe anemia
  - Bleeding disorders
  - Thalassemia
  - Sickle cell crises
- Cardiac causes
  - Heart failure (acute pulmonary edema)
  - Arrhythmias
  - Acute myocardial infarction
  - Cardiac arrest
  - Dissecting aortic aneurysm
- Intracranial hemorrhage
  - Spontaneous subarachnoid hemorrhage
  - Preeclampsia-associated intracerebral hemorrhage
- Endocrine
  - Diabetic ketoacidosis
  - Hypoglycemia
- Causes related to anesthesia
  - Anesthesia toxicity
  - Mendelson’s syndrome
- Miscellaneous
  - Septic shock
  - Anaphylactic shock—acute adrenocortical insufficiency
  - Adverse drug reaction.
- Proper intrapartum and postpartum monitoring of normal and instrumental deliveries
- Meticulous fourth stage monitoring
- Preoperative and postoperative care in patient undergoing cesarean deliveries.

**Advance Preparation of Health Care Providers**

It is always better to anticipate complications in high-risk patients and plan the line of management in advance; hence, it is important that health care providers should be prepared in advance to deal with emergency situations.

- Multiple factors will have to be considered during such a dramatic event, higher awareness of maternal risk factors together with active surveillance to identify causes of maternal compromise leading to early intervention and proper communication can minimize maternal morbidity and mortality.
- Meticulous planning for management during pregnancy, labor and puerperium will help to prepare and hopefully prevent poor outcome. This can be achieved by involving multidisciplinary team and clinical consultation with anesthetist and physician while assessing high-risk antenatal patients with coexisting medical conditions.
- Anticipation of any complication antenatally and postnatally.

As pregnancy has lot of physiological changes and patient is already in compensated state, so being vigilant and identifying changes in vitals of patient like pulse, respiration and BP helps in timely intervention.

- To inform seniors and to do documentation
- It is a team work of intensivist, gynecologist, physician and surgeon depending upon the cause of postpartum collapse.

**Training of Health Care Providers**

Resuscitation of newly delivered mother can be challenging, if health care provider is not prepared. Nowadays obstetrician and midwives are expected to be able to provide emergency critical care when required. To overcome these problems, obstetricians and the health care providers should practice emergency skills and drill sessions, including management of eclampsia, massive hemorrhages and cardiopulmonary resuscitation (CPR) by practicing on manikins and simulators and attending various courses of management of critically ill patients.

**Immediate Action to be taken by Clinician While Treating Postpartum Collapse**

- Ensure safe environment for patient and call for resuscitation team
- Obtain history from patient or companion
- To inform seniors and to do documentation
- Obtain consent from the patient or relatives
Resuscitation

As per advance life support group (ALSG), structured approach in the form of A, B, C, D and E.

A: Airway

Clearing airway of secretions or vomiting. Maintain airway by inserting oropharyngeal or nasopharyngeal airway. Whenever required experienced anesthetist should do endotracheal intubation as during pregnancy, there is laryngeal edema and increased risk of regurgitation and aspiration.

B: Breathing

Breathing is assessed by looking, listening and feeling, if no spontaneous respiration than mouth to face mask or ventilation by face mask and ambubag, if it does not resumes then tracheal intubation, if respiration assumes give left lateral position.

High flow supplementary oxygen at flow rate of 12 to 15 L/min is mandatory.

C: Circulation

Circulation is assessed by recording carotid pulse, if carotid pulse is not palpable than chest compression at the rate of 15 compression to two breaths is given until signs of circulation are established or defibrillation is advised. In hemorrhagic shock, two large caliber intravenous (IV) lines should be established, blood is sent for blood group and cross-matching along with rest of the investigation. Hypovolemia is corrected by warmed crystalloids, synthetic colloids and red cells followed by blood components.

D: Disability

Level of consciousness and papillary function reflects the neurological status and cerebral tissue perfusion. The Glasgow Coma Scale is used to assess neurological status. Score of 8 or less requires immediate intubation.

E: Exposure

Adequate exposure of patient to avoid missing of vital information to make definitive diagnosis including vaginal examination to exclude pathology is important. Hypothermia should be prevented during the exposure.

Definitive Care

Once the cause of postpartum collapse has been established, input from the relevant specialist is provided without delay and admission to intensive care unit is required for most of the patients.

Identify cause and following appropriate protocol. After identifying the causes, appropriate protocol should be implemented according to the cause.

After A, B, C, D and E

- Monitor—temperature, pulse and respiration (TPR)/BP/O./arterial blood gas (ABG)/I/O chart.
- Position—left lateral position, head low.
- Infusion—25% glucose 50 mL (IV), IV 500 mL Ringer’s lactate (RL)/blood/fresh frozen plasma (FFP) as required.
- Ventilation—endotracheal intubation/mechanical ventilation.
- For cardiac support—dopamine/dobutamine drip if required.
- If PPH—Follow guidelines for PPH-medical and surgical management
- If hemoperitoneum—exploration
- If eclampsia—follow guidelines for eclampsia
- If acute pulmonary edema, cardiac failure, embolism, septic shock—follow appropriate protocol
- If cardiac arrest—follow CPR protocol.

AMNIOTIC FLUID EMBOLISM

Pathogenesis

Disruption of the physiological barrier of the chorioamniotic membranes results in entry of amniotic fluid in the maternal systemic circulation. Steiner and Luschbaugh (1941) first observed the pathology. Subsequently several other workers, Adamsons et al. (1971), Stolte et al. (1967) observed that mere presence of amniotic fluid in systemic circulation is not pathognomonic. Fetal squames and trophoblasts are normally present in maternal circulation. Other workers (Clark et al. 1995) have suggested that individual human body response to amniotic fluid embolism is that of anaphylaxis. The different obstetric conditions that lead to amniotic fluid embolism are: tumultuous labor, high parity, uterine rupture, meconium stained liquor, cesarean delivery, placental abruption and even suction curettage. However, American College of Obstetricians and Gynecologists have ruled out any association between oxytocin use and amniotic fluid embolism. The pathophysiological changes of amniotic fluid embolism lead to the main issues, e.g. systemic hypotension, hypoxia and consumptive coagulopathy. Breach in the chorioamniotic membranes, placental separation—access of amniotic fluid in the maternal systemic circulation through the disrupted uterine vessels is the triggering factor. This leads to the onset of anaphylactic like reaction depending upon the individual human body response. There is activation of the complement pathway C5a. Chemical mediators that are released include prostaglandins, chemokines, cytokines, endothelin-1 and histamines. There is leukocyte migration and aggregation within the small vessels of the lung. Inflammatory mediators are released. There is transudation of intravascular fluid into the intra-alveolar and interstitial spaces. There is antithrombin effect and also thromboplastin effect of amniotic fluid. The coagulation system is activated, so also the fibrinolytic system. This is due to the effect of platelet
aggregation and release of plasminogen activator. Besides these biochemical changes, there is mechanical obstruction of pulmonary vessels causing pulmonary hypertension. The ultimate effects of all these pathological process are: severe hypoxia, left ventricular dysfunction or failure, imbalance of ventilation—perfusion, cardiopulmonary failure leading to shock. The majority of these patients develop hemorrhage due to coagulopathy.

Clinical Presentation and Diagnosis

Patient develops dyspnea, cough, pink frothy sputum and cyanosis. Very soon this phase passes into apnea, loss of consciousness and circulatory collapse. A few patients develop convulsions and majority develop coagulopathy.

Diagnosis is generally made by analyzing the clinical characteristics. Detection of squamous cells or fat, trophoblasts in the blood obtained from the central circulation via central venous pressure (CVP) measuring catheter, may be suggestive when the patient suffers with the clinical manifestation of amniotic fluid embolism. Hemodynamic measurements are obtained through the right heart catheterization. Immediately after the embolism, there is elevated pulmonary capillary wedge pressure (PCWP) and CVP. Electrocardiogram shows right axis deviation and there is evidence of acute right ventricular dysfunction. Cardiac output is decreased resulting in left ventricular failure.

Management

Principles of management are to initiate effective resuscitative measures immediately. Patient’s airway must be maintained to provide effective ventilation and oxygenation. Monitoring of the hemodynamic parameters is essential. Prevention of left ventricular dysfunction or failure and to start digitalization if needed. Infusion of dopamine L dobutamine may be needed to improve myocardial contractility and hemodynamic normalization. Maintenance of CVP and PCWP with crystalloid is continued. Prevention and or management of DIC is another important area. Deranged coagulation parameters should be treated by FFP, cryoprecipitate or fibrinogen. Heparin may also be needed in a few cases. Metabolic and electrolyte abnormalities should be corrected. Broad spectrum antibiotic coverage is needed to prevent any infection. All these supportive care measures are continued with monitoring till the cardiorespiratory functions are stabilized. Prognosis: unfortunately in spite of all the care, maternal mortality from amniotic fluid embolism is about 60–90%. The woman that survive often suffer from some neurological impairment.

Uterine artery embolization is a useful noninvasive technique which may be effective. Plasmapheresis and hemofiltration have been advocated and shown to be successful in arresting the progress of the disease, probably by clearing the plasma of cytokines.

PULMONARY THROMBOEMBOLISM

Overall incidence of pulmonary venous thromboembolism in pregnancy is about 1 in 2,500 pregnancies. Majority occur (75%) in immediate postpartum period. It is one of the significant causes of maternal deaths in many countries.

Pathogenesis

The risk of thromboembolism is increased in pregnancy or puerperium due to several physiological changes (Table 2). Increase in the level of coagulation factors (factors I, VII, VIII, IX, X) progressive rise in venous pressure in the leg veins, trauma of delivery either vaginal or cesarean section, and associated infection increase the risk of venous thrombosis and thromboembolism. There is decline in the level of proteins during pregnancy. Hypercoagulable state of blood and the vascular endothelial injury are the two main initiating factors. In some women, inherited deficiency of some regulatory proteins (thrombophilias) may be associated. Other high risk factors are elderly age of the woman (≥35 years) obesity, hypertension, high parity and operative delivery.

Clinical Presentation

In some women, clinical evidence of deep vein thrombosis in leg veins precedes PE. But in others, they remain asymptomatic until embolization occurs. The most common presenting symptoms are: dyspnea (80%), chest pain (50%), cough, syncope and hemoptysis. Clinical examination may reveal tachycardia and tachypnea, friction rub, cyanosis and circulatory collapse. ECG may reveal T-wave inversion and right axis deviation. Chest X-ray shows less vascular area of the lung field supplied by the obstructed artery. One should be careful that is normal blood gas report does not rule out PE.

Diagnosis

Diagnosis of PE is difficult. A high index of suspicion combined with the tests is helpful.

Ventilation perfusion lung scan: Segmental perfusion defects in association with normal ventilation and normal chest X-ray are seen. When ventilation-perfusion scan is equivocal, pulmonary angiography is performed. V/Q scan can detect large perfusion detects but a normal V/Q scan does not rule out PE.

Pulmonary angiography is done in selected cases only to detect the site and size of block. It has several complications like cardiac arrest, arrhythmia, allergic reactions due to the dye or even renal failure.

Spiral computed tomography (spiral CT) is helpful for imaging main pulmonary arteries and also the segmental branches. The four-channel multidetector spiral CT is
Magnetic resonance angiography has got the advantage of high resolution and without any risk of radiation. The sensitivity and specificity of magnetic resonance angiography are similar to that of spiral CT.

Management

Immediate resuscitative measures include maintenance of airway, ventilation and oxygenation. Hemodynamic circulatory status is maintained with isotonic crystalloids. Drug of choice for PE is intravenous heparin. An initial bolus dose of 5,000–10,000 units of heparin IV followed by a continuous infusion of 1,000 units/hour. The dose is adjusted to maintain the partial thromboplastin time at 1.5–2 times the control or the serum heparin concentration at 0.2–0.7 IU/mL. Heparin IV is continued for a minimum of 7–10 days, following which oral anticoagulants (Warfarin) are started. The major complication faced with the use of these drugs is hemorrhage. One should be careful when any surgical procedure is to be done in such a woman.

Thrombolysis is helpful to lyse the pulmonary clots. Risk of recurrence is lower when thrombolytic agents are compared to heparin. Recombinant tissue plasminogen activator is currently being used.

Surgery

Patient having massive PE may be treated with pulmonary embolectomy from the main pulmonary arteries. During pregnancy embolectomy is avoided in preference to vena cava filter. In cases with recurrent PE even with heparin therapy, vena cava filter (umbrella) may be indicated. Ligation of inferior vena cava has been done as an alternative in the management of recurrent PE.

**ACUTE INVERSION OF THE UTERUS**

This is an uncommon condition, the reported incidence is 1 in 2,500 deliveries. It may be complete or incomplete depending upon the descent of fundus through the cervical ring and vaginal introitus. It results in a varying degree of shock mostly of neurogenic origin due to traction of infundibulopelvic ligament. It can also result in PPH.

The most common cause of inversion is fundal placentation with excessive cord traction in third stage of labor when uterus is not well contracted. Uterine over distension and prolonged labor or morbid adherent placenta are some of the predisposing factors.

**Clinical Presentation, Diagnosis and Management**

Clinical presentation includes pain in the lower abdomen, vaginal bleeding and the sensation of vaginal fullness. Clinical features of shock are evident and often there is out of proportion to the amount of blood loss. Cupping of the fundus is felt on abdominal examination. On vaginal examination, the inverted uterus is felt as a soft purple mass. Diagnosis is made on clinical examination keeping in mind the differential diagnosis. A large uterine or cervical polyp occupying the vagina often needs to be excluded. Real time ultrasound scan may be helpful. Management needs immediate resuscitation to overcome the shock which is often expected to be the gold standard to replace the pulmonary angiography.³⁵

### Table 2: Acquired risk factors of thrombosis during pregnancy

<table>
<thead>
<tr>
<th>Risk Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical intervention (cesarean section, surgery on gravid uterus, application of forceps)</td>
</tr>
<tr>
<td>Complications during pregnancy accompanied by DIC:</td>
</tr>
<tr>
<td>- Rheumatic heart diseases, congestive heart failure, artificial cardiac valves</td>
</tr>
<tr>
<td>- Renal disease (acquired deficiency of antithrombin III due to nonselective proteinuria and nephrotic syndrome, arterial hypertension</td>
</tr>
<tr>
<td>- Gestosis</td>
</tr>
<tr>
<td>- Obstetrical bleeding</td>
</tr>
<tr>
<td>- Purulent-septic diseases</td>
</tr>
<tr>
<td>- Infectious and inflammatory diseases (inflammatory diseases of GIT, urinary infection)</td>
</tr>
<tr>
<td>- Age &gt; 35 years</td>
</tr>
<tr>
<td>- Pluriparas</td>
</tr>
<tr>
<td>- Obesity (BMI &gt; 29 kg/m² before pregnancy)</td>
</tr>
<tr>
<td>- History of DVT or thromboembolism</td>
</tr>
<tr>
<td>- Varicose veins</td>
</tr>
<tr>
<td>- Immobilization (e.g. during long-term tocolytic therapy, paralyses, air travel)</td>
</tr>
<tr>
<td>- Dehydration (vomiting of the pregnant)</td>
</tr>
<tr>
<td>- Ovarian hyperstimulation syndrome</td>
</tr>
<tr>
<td>- Trauma of pelvis</td>
</tr>
<tr>
<td>- Malignancy</td>
</tr>
</tbody>
</table>

Abbreviations: DIC, disseminated intravascular coagulation; GIT, gastrointestinal tract; BMI, body mass index; DVT, deep vein thrombosis
neurogenic. Volume replacement with crystalloids or blood is essential specially when it is accompanied by hemorrhage. Actual management involves immediate manual reposition of the uterus. Principle of manual reposition is to push the part of uterus first that came out last. Halothane anesthesia is recommended as it relaxes the cervical ring and helps in smooth reposition. Hydrostatic correction (O’Sullivan, 1945) is also done as an alternative procedure. In cases where the placenta is still attached, manual removal of placenta is done only after the reposition of the uterus. Oxytocics (oxytocin, ergometrine or PGF$_2$α are to be used following the correction to prevent reinversion of the uterus.

### REGIONAL ANESTHESIA/DRUG TOXICITY OR SELF POISONING (SUICIDE)

Toxicity with regional anesthesia is relatively less common. However, pregnant women are more susceptible to the toxic effects, compared to the nonpregnant ones. This is due to the effects of increased vascularity of the epidural and subarachnoid space. The patients on magnesium therapy are at risk and those having postnatal depression or alcohol and drug abuse history.

**Pathophysiology**

It results from inadvertent intravascular injection of the anesthetic agents. Any local anesthetic drug specially, if a long-acting (bupivacaine, etidocaine) one given in high doses, results in more systemic toxicity. High spinal blockage due to excessive dose results in hypotension, apnea and even cardiac arrest or myocardial depression.

**Diagnosis**

Common clinical features of systemic toxicity are metallic taste in the mouth, ringing in the ears, confusion or dyspnea. Sympathetic blockage results in hypotension, ptosis, miosis. Apnea may develop due to respiratory muscles paralysis. Cardiac arrest may develop due to hypoxia or due to the direct toxic effects of the drug. Convulsions though rare may be due to the effects of hypoxia. Magnesium toxicity is recognized by respiratory arrest and treated by administration of calcium gluconate.

**Management**

Resuscitative measures including maintenance of airway, ventilation and oxygenation has to be initiated immediately. To control convulsions, diazepam IV is to be administered. Resuscitative measures are to be continued till the effects of local anesthetic drugs have dissipated. Prognosis is usually satisfactory provided there is early recognition of complications and the effects of hypoxia and metabolic derangements do not develop.

### MYOCARDIAL INFARCTION

Acute myocardial infarction is not an uncommon complication. This is more common during the third trimester or in the immediate postpartum period. The maternal mortality is as high as 30–50%.

The high-risk factors for acute myocardial infarction are hypertension, pre-existing heart disease, hyperlipidemia, diabetes, obesity and elderly women.

**Clinical Presentation**

Signs and symptoms of this medical disorder are similar to that of nonpregnant state. The important features are substernal pain, nausea, vomiting, dyspnea. There may be radiation of pain into the neck and the left arm. When complications set up there may be arrhythmia pulmonary edema, or features of congestive cardiac failure or cardiogenic shock.

**Diagnosis**

It is similar to that of a nonpregnant condition. ECG changes and alternations in different cardiac enzyme levels are suggestive. Significant ECG changes in acute myocardial infarction include ST segment elevation, Q waves in leads II, III and AVF or poor R wave progression in the precordial leads. Cardiac enzyme estimation shows an elevation of creatinine phosphokinase, SGPT, SGOT and lactic acid dehydrogenase.

**Complications**

Several complications may develop in some of the cases. Cardiac arrhythmia, ectopic atrial or ventricular beats, ventricular tachycardia, fibrillation or heart block may develop.

In severe cases with large infarctions, congestive cardiac failure or cardiogenic shock may develop. Death is not uncommon from massive myocardiac infarction in the immediate postpartum period.

**Management**

Resuscitative measures for a woman with acute myocardial infarction in labor or in immediate postpartum period are the maintenance of patient’s airway, ventilation and oxygenation. Dopamine or dobutamine may be used when vasopressor drugs are needed. Arrhythmias, like ventricular fibrillation, tachycardia, may be treated with electric shock therapy. Heart block is treated with atropine or by a pacemaker. For definitive management, the patient needs to be transferred to a coronary care unit.
HEMORRHAGIC SHOCK

Pathogenesis

Massive PPH is still a major cause of maternal death and morbidity. Massive hemorrhage occurs in approximately 1,000 deliveries. Although PPH is classically defined as loss of 500 mL blood, blood loss exceeding 1,000 mL results in hemodynamic instability. Massive hemorrhage is defined as a blood loss of about 50% of blood volume in 3 hours or more than 150 mL/min blood loss. Hemorrhagic shock may be mild when 15–25% of blood volume is lost, whereas moderate shock is when 25–35% of blood volume is lost.

Atonicity of uterus is the most important cause of PPH. Over distended uterus due to twin, big baby or polyhydraminos, retained placental bits or membranes, prolonged labor, labor augmented by oxytocin, multiparity, uterus malformation are some of the predictable factors for atonic uterine bleeding in the postpartum period. Laceration and hematomas occur commonly following difficult, manipulative and operative deliveries. DIC often is the end result of various conditions as preeclampsia, intrauterine fetal demise (IUFN), abrupton placenta, amniotic fluid embolism, septicemia and hypovolemia.

Clinical Features, Diagnosis and Treatment

Tachycardia, hypotension, pallor, cold clammy extremities, low urinary output are the hallmarks of hemorrhagic/hypovolemic shock. Central nervous pressure and pulmonary wedge pressure monitoring helps in assessment of intravascular volume and helps in differentiating with non hemorrhagic shock. Evaluation of a patient with hemorrhagic shock includes estimation of hemoglobin, platelet count, measurement of prothrombin time and activated partial thromboplastin time, fibrinogen and fibrin degradation products.

Management

- Significant blood loss from any cause needs standard maternal resuscitation measures
- Appropriate intravenous access is critical
- One or two large bore IV catheters are introduced
- Estimation of blood loss and volume replacement begins with warm crystalloid solutions. Colloids and blood component replacement is needed according to the individual patients need and blood loss.

Drugs: Uterotonics are the mainstay in atonic PPH. Oxytocin, methylergometrine, PGF2α, and misoprostol are the different drugs used. In recent reviews, the promise of misoprostol is highlighting because of its low cost, ease of administration (per rectal) quick onset of action, mild side effect and lack of contraindications. 1,000 µg of misoprostol rectally is highly effective in controlling PPH due to atonic uterus.

Other Procedures

- Uterine massage: Bimanual uterine massage can effectively control PPH due to atonicity.
- Re-emergence of uterine packing: Tight intrauterine gauge pack, Foley’s catheter with 30 mL balloon or a Sengstaken-Blakemore tube have all been used for tamponade inside the uterine cavity of desperate situation. They need to be removed after 12–24 hours and found highly effective.
- Surgical: Compression sutures, B Lynch suture, has gained most popularity.
  - Stepwise devascularization of uterine, utero-ovarian and anterior division of internal iliac arteries is helpful in many cases where uterus has to be preserved.
  - Hysterectomy: Supracervical hysterectomy may be the final definitive management in an unstable patient with torrential bleeding not controlled with initial measures.

Management of Massive Hemorrhage

Management of massive hemorrhage has been summarized in Table 3.

Fluid Management

A 2006 guideline from the British Committee for Standards in Haematology summarizes the main therapeutic goals of management of massive blood loss is to maintain:

- Hemoglobin more than 8 g/dL
- Platelet count more than $75 \times 10^9$/L
- Prothrombin less than 1.5 x mean control
- Activated prothrombin times less than 1.5 x mean control
- Fibrinogen more than 1.0 g/L

By consensus, total volume of 3.5 L of clear fluids (up to 2 L of warmed Hartmann’s solution as rapidly as possible, followed by up to a further 1.5 L of warmed colloid if blood is still not available) comprises the maximum that should be infused while awaiting compatible blood. There is controversy as to the most appropriate fluids for volume resuscitation. The nature of fluid infused is of less importance than rapid administration and warming of the infusion. The woman needs to be kept warm using appropriate measures. This consensus advice must be viewed with a certain degree of caution, because there is evidence that infusion of such volumes promotes or exacerbates dilutional coagulopathy.

Medical Management

Medical management has been described in Table 3 and also in Chapter 39 in detail.
Mechanical Methods

Balloon Tamponade

In recent years, tamponade using various types of hydrostatic balloon catheters has superseded uterine packing for control of atonic PPH. Case series have used a Foley catheter, Bakri balloon, Sengstaken-Blakemore esophageal catheter and a condom catheter. The urological Rusch balloon has been described as preferable by virtue of large capacity, ease of use and low cost. A group from Sheffield has provided a detailed protocol for uterine tamponade using the Rusch balloon. The Scottish Confidential Audit of Severe Maternal Morbidity identified 64 cases where balloon tamponade was used for the management of major PPH; hysterectomy was averted in 50 (78%) women. This success rate is of the same order as that reported in other case series.

Some of the reports of balloon tamponade describe the intervention as the tamponade test. A positive test (control of PPH following inflation of the balloon) indicates that laparotomy is not required, whereas a negative test (continued PPH following inflation of the balloon) is an indication to proceed to laparotomy.

The concept of balloon tamponade as a “test”, serves to affirm its place as first-line “surgical” management. There is no clear evidence how long the balloon tamponade should be left in place. In most instances, 4–6 hours of tamponade should be adequate to achieve hemostasis; ideally, removal should take place during daytime hours and in the presence of appropriate senior staff if further intervention is necessary. Before its complete removal, however, the balloon can be deflated but left in place to ensure that bleeding does not recur.
Surgical Techniques

B-Lynch Suture

The B-Lynch suture, first described in print in 1997, has been used worldwide. More than 2,000 cases have been reported to the website http://www.cbl.uk.com with less than 10 requiring hysterectomy. Analysis of failures suggest that, in most cases, the operation was conducted late (often as late as 6 hours) when problems in clotting would be expected to be present. The sutures provide uterine compression so that hemostasis is maintained for prolonged times. It is, in effect, a continuous form of bimanual compression. The analogy offered by Professor Lynch is that the operation is the same as wearing a belt and braces (suspenders) at the same time in an effort to hold up one’s pants.

The operation requires minimal training, conserves the uterus, is less technically challenging and associated with less blood loss than hysterectomy. Further details are available in the Textbook of Postpartum Hemorrhage which also can be downloaded for free at http://www.sapienspublishing.com/medical-publications.php#1. The importance of this operation is such that many teaching programs make it an integral part of the instruction for cesarean delivery, stating that properly trained surgeons must know both techniques as PPH can occur at any time.

Hysterectomy

The decision to perform hysterectomy to control PPH is difficult. Death is the most likely outcome if one is incorrect in choosing to perform hysterectomy to save a life in the presence of intractable PPH. This is not to say that the surgery is technically simple, because the postpartum uterus does not present the same anatomic landmarks to aid the surgeon, and tissue planes do not always resemble their counterparts in the nonpregnant situation.

Regardless, hysterectomy (total or subtotal and with or without adnexectomy) remains a mainstay of the therapy of PPH, because it is likely that doctors will have had experience with this technique.

Emergency peripartum hysterectomy is an unequivocal marker of severe maternal morbidity and “near miss” mortality.

The indications for hysterectomy include abnormal placentation, persistent uterine atony, uterine trauma after variety of obstetric manipulations, lateral traumatic extension of the lower uterine segment incision into the uterine artery and sepsis. An equipment tray that is specially for PPH has been described.

Internal Iliac Artery Ligation

The importance of this operation cannot be underestimated. In fact, many teaching programs recognize that it is best to practice in the nonemergent situation or at the autopsy table. The physiology of the surgery is quite simple. The excellent collateral circulation of the pelvis protects the uterus from ischemic necrosis, because the hypogastric artery distal to the point of ligation is never truly emptied of blood, and the rich anastomotic network begins to function immediately after ligation. What happens is the virtual elimination of the arterial pulse pressure, associated with reduced mean BP and rate of blood flow in the collateral system. As a result, the trip hammer effect of arterial pulsations is abolished. Bilateral ligation is always more effective than a unilateral procedure and diminishes the chance of returning to the operating room for further surgery. Differentiation between prophylactic and therapeutic ligation is by no means absolute.

Adjunctive Measures

Nonpneumatic Antishock Garment

The comprehensive therapy of a patient with PPH often requires transfer of a desperately ill patient over long distances to a higher level facility. Under the best of circumstances, such transfers may be life threatening. A major advance in providing safe transfer has been the development and implementation of the nonpneumatic antishock garment (NASG). Unlike its predecessor garments, there are no pumps, tubes or gauges to add complexity or malfunction. Using the three way elasticity of neoprene and the tight grip of Velcro fasteners, the garment can apply 30-40 mm Hg of circumferential counter pressure to the lower body from the ankles to the diaphragm. This amount of pressure is effective in shunting blood from the lower extremities and the abdomen (5–1,500 mL) to the vital core organs. Widely tested in Egypt, Africa and Mexico, the garment is now used successfully in many areas of the world to provide additional safety during patient transport.

Aortic Compression

Occasionally during an operating to correct bleeding from PPH, blood loss is so massive and so rapid that death may ensue within a very short time. Such circumstances are not uncommon in the treatment of morbidly adherent placentas. A helpful measure is a temporary occlusion of the abdominal aorta (below the renal arteries) by manual pressure provided by a surgical assistant. This sounds easier than it actually is in real life, because the pressure required is equivalent to the pressure that one would have to make on a bathroom scale to reach the number 41 kg (90 lbs). Such pressure allows the surgeon to work with a much drier field and perhaps achieve better hemostasis and also facilitates clot formation at the traumatized vessels. External aortic compression device has been suggested as a simple and cost-effective approach in the management of PPH, especially in the developing countries.
SEPTIC SHOCK

Although rare in developed world, septicemia is one of the important causes of maternal mortality and morbidity in developing countries. Septic shock is the systemic inflammatory response to infection. It is manifested by hypotension, oliguria, lactic acidosis, perfusion abnormalities, acute respiratory distress and altered mental state. A variety of aerobic and anaerobic organisms are responsible for septic shock. There common organisms are: Escherichia coli, Klebsiella, Proteus mirabilis, Pseudomonas, Staphylococcus aureus and Bacteroides. Factors predisposing to such infection are PROM and chorioamnionitis, IUFD, surgical intervention, urinary tract infection and pyelonephritis, appendicitis and ovarian abscess.

Septic shock occurs when the offending organisms invade the maternal circulation and liberate endotoxins and exotoxins. All these interact with leukocytes and endothelial cells causing liberation of various mediators, such as cytokines, nitric oxide, prostaglandins, leukotrienes and tissue necrotic factor. These are responsible for all the clinical manifestation of septic shock.

The various biochemical and pathological abnormalities observed in septic shock are: (1) diffuse intravascular coagulation, (2) metabolic acidosis, (3) release of super oxide ($O_2^-$) and hydroxyl (OH$^-$) radicals, (4) failure of sodium pump operation, and (5) water and electrolyte imbalance. Organ changes are observed in the kidneys, liver, gastrointestinal tract, lungs and the myocardium also. Ultimately, multiple organ failure develops.

Management of Septic Shock

Investigations include complete hemogram, chest X-ray, septic work-up (including blood culture, vaginal swab), blood gas analysis, hepatic and renal function tests and coagulation profile.

The principles of management include control of infection, circulatory volume maintenance, adjustment of acid-base balance, maintenance of hemodynamic stability, ventilatory support and removal of the source of infection.

- Antibiotics are selected to cover the Gram-negative and Gram-positive aerobic organisms and the anaerobes. High dose parenteral regimen is initially started till the culture report is obtained for the specific organism and its sensitivity.
- Intravenous fluids (crystalloids, colloids, blood transfusion) to be administered and normal serum electrolytes levels are to be maintained. Maintenance of CVP, renal perfusion (urine output) and BP are to be continued.
- Correction, hypoxemia and metabolic acidosis are done simultaneously.
- Inotropic agents in a critically ill patient (dopamine/dobutamine) may be needed to improve myocardial contractility and perfusion pressure.

Corticosteroids are used in selected cases only. Disseminated intravascular coagulation is treated with FFP or whole blood transfusion. Heparin therapy may be considered in some cases.

Elimination of the source of infection should be done at the earliest whenever the patient is hemodynamically stable. Hysterectomy has been recommended in some septic cases.

ECLAMPSIA

Introduction

- Incidence: 2–3 per 100
- Risk factor: Preeclampsia
- Clinical symptoms/signs: Grand mal convulsion, postictal drowsiness, hypertension, hyperreflexia

Protocols for Management (Box 1)

Anticonvulsive Drugs

A key factor in anticonvulsive therapy is adequate administration of anticonvulsive drugs. Convulsions in hospitalized women are most frequently caused by undertreatment. Magnesium sulfate is the drug of choice for preventing and treating convulsions in severe preeclampsia and eclampsia. Administration is outlined in Table 4.

<table>
<thead>
<tr>
<th>Box 1: General management for eclampsia</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Start an IV infusion and infuse IV fluids</td>
</tr>
<tr>
<td>- After the convulsion:</td>
</tr>
<tr>
<td>- Give anticonvulsive drugs</td>
</tr>
<tr>
<td>- Position the women on her left side to reduce risk of aspiration of secretions, vomit and blood</td>
</tr>
<tr>
<td>- Aspirate the mouth and throat as necessary</td>
</tr>
<tr>
<td>- Monitor vital signs (pulse, BP, respiration), reflexes and fetal heart rate hourly.</td>
</tr>
<tr>
<td>- If diastolic BP remains above 110 mm Hg, give antihypertensive drugs. Reduce the diastolic BP to less than 100 mm Hg but not below 90 mm Hg.</td>
</tr>
<tr>
<td>- Catheterize the bladder to monitor urine output and proteinuria.</td>
</tr>
<tr>
<td>- Maintain a strict fluid balance chart (monitor the amount of fluids administered and urine output) to prevent fluid overload.</td>
</tr>
<tr>
<td>- If urine output is less than 30 mL per hour.</td>
</tr>
<tr>
<td>- Withhold magnesium sulfate and infuse IV fluids (normal saline or RL) at 1 L in 8 hours</td>
</tr>
<tr>
<td>- Monitor for the development of pulmonary edema</td>
</tr>
<tr>
<td>- Never leave the woman alone. A convulsion followed by aspiration of vomit may cause death of the women and fetus</td>
</tr>
<tr>
<td>- Auscultate the lung bases hourly for rales indicating pulmonary edema. If rales are heard, withhold fluids and give frusemide 40 mg IV once.</td>
</tr>
<tr>
<td>- Assess clotting status with a bedside clotting test. Failure of a clot to form after 7 minutes or a soft clot that breaks down easily suggests coagulopathy.</td>
</tr>
</tbody>
</table>
If magnesium sulfate is not available, diazepam may be used. Although a single dose of diazepam seldom causes neonatal respiratory depression, long-term continuous IV administration increases the risk of respiratory depression in babies who may already be suffering from the effects of uteroplacental ischemia and preterm birth. The effect may last several days. Administration of diazepam is outlined in Table 5.

**Antihypertensive Drugs**

If the diastolic BP is 110 mm Hg or more, give antihypertensive drugs. The goal is to keep the diastolic pressure between 90 mm Hg and 100 mm Hg to prevent cerebral hemorrhage. Hydralazine is the drug of choice.

- Give hydralazine 5 mg IV slowly every 5 minutes until BP is lowered. Repeat hourly as needed or give hydralazine 12.5 mg intramuscular every 2 hours as needed.

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**Table 4: Magnesium sulfate schedules for severe preeclampsia and eclampsia**

<table>
<thead>
<tr>
<th>Loading dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Give 4 g of 20% magnesium sulfate solution IV over 5 minutes</td>
</tr>
<tr>
<td>• Follow promptly with 10 g of 50% magnesium sulfate solution—give 5 g in each buttock as a deep intramuscular (IM) injection with 1 mL of 2% lignocaine in the same syringe. Ensure aseptic technique when giving magnesium sulfate deep IM injection. Warn the woman that a feeling of warmth will be felt when magnesium sulfate is given.</td>
</tr>
<tr>
<td>• If convulsions recur after 15 minutes, give 2 g of 50% magnesium sulfate solution IV over 5 minutes.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Maintenance dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Give 5 g of 50% magnesium sulfate solution with 1 mL of 2% lignocaine in the same syringe by deep IM injection into alternate buttocks every 4 hours. Continue treatment for 24 hours after delivery or the last convolution, whichever occurs last.</td>
</tr>
<tr>
<td>• If 50% solution is not available, give 1 g of 20% magnesium sulfate solution IV every hour by continuous infusion.</td>
</tr>
</tbody>
</table>

**Closely monitor the women for signs of toxicity**

Before repeat administration, ensure that:

- Respiratory rate is at least 16 per minute
- Patellar reflexes are present
- Urinary output is at least 30 mL/hour over 4 hours

Withhold or delay drug if:

- Respiratory rate falls below 16 per minute
- Patellar reflexes are absent
- Urinary output falls below 30 mL/hour over preceding 4 hours

Keep antidote ready:

- In case of respiratory arrest:
  - Assist ventilation (mask and bag, anesthesia apparatus, intubation)
  - Give calcium gluconate 1 g (10 mL of 10% solution) IV slowly until calcium gluconate begins to antagonize the effect of magnesium sulfate and respiration begins.

**Table 5: Diazepam schedules for severe preeclampsia and eclampsia**

**Note:** Use diazepam only if magnesium sulfate is not available.

<table>
<thead>
<tr>
<th>Intravenous administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Loading dose</strong></td>
</tr>
<tr>
<td>• Diazepam 10 mg IV slowly over 2 minutes</td>
</tr>
<tr>
<td>• If convulsions recur, repeat loading dose</td>
</tr>
<tr>
<td><strong>Maintenance dose</strong></td>
</tr>
<tr>
<td>• Diazepam 40 mg in 500 mL IV fluids (normal saline or Ringer’s lactate) titrated to keep the woman sedated but rousable.</td>
</tr>
<tr>
<td>• Maternal respiratory depression may occur when dose exceeds 30 mg in 1 hour:</td>
</tr>
<tr>
<td>- Assist ventilation (mask and bag, anesthesia apparatus, intubation), if necessary.</td>
</tr>
<tr>
<td>- Do not give more than 100 mg in 24 hours.</td>
</tr>
<tr>
<td><strong>Rectal administration</strong></td>
</tr>
<tr>
<td>• Give diazepam rectally when IV access is not possible. The loading dose is 20 mg in a 10 mL syringe. Remove the needle, lubricate the barrel and insert the syringe into the rectum to half its length. Discharge the contents and leave the syringe in place, holding the buttocks together for 10 minutes to prevent expulsion of the drug. Alternatively, the drug may be instilled in the rectum through a catheter.</td>
</tr>
<tr>
<td>• If convulsions are not controlled within 10 minutes, administer an additional 10 mg or more, depending on the size of the woman and her clinical response. Be prepared to assist ventilation.</td>
</tr>
</tbody>
</table>

Abbreviation: IV, intravenous
If hydralazine is not available, give labetalol or nifedipine:
- Labetalol—10 mg IV
  - If response to labetalol is inadequate (diastolic BP remains above 110 mm Hg) after 10 minutes, give labetalol 20 mg IV
  - Increase the dose to 40 mg and then 80 mg if satisfactory response is not obtained after 10 minutes of each dose
- Nifedipine—5 mg under the tongue
  - If response to nifedipine is inadequate (diastolic BP remains above 110 mm Hg) after 10 minutes, give an additional 5 mg under the tongue.

Note: There is concern regarding a possibility for an interaction with magnesium sulfate that can lead to hypotension.

Delivery

Delivery should take place as soon as the woman’s condition has stabilized. Delaying delivery to increase fetal maturity will risk the lives of both the woman and the fetus. Delivery should occur regardless of the gestational age.

In severe pre eclampsia, delivery should occur within 24 hours of the onset of symptoms. In eclampsia, delivery should occur within 12 hours of the onset of convulsions.

- Assess the cervix
- If the cervix is favorable (soft, thin, partly dilated), rupture the membranes with an amniotic hook or a Kocher clamp and induce labor using oxytocin.
- If vaginal delivery is not anticipated within 12 hours (for eclampsia) or 24 hours (for severe preeclampsia), deliver by cesarean section.
- If there are fetal heart rate abnormalities (less than 100 or more than 180 beats per minute), deliver by cesarean section.
- If the cervix is unfavorable (firm, thick, closed) and the fetus is alive, deliver by cesarean section.
- If safe anesthesia is not available for cesarean section or if the fetus is dead or too premature for survival:
  - Aim for vaginal delivery
  - If the cervix is unfavorable (firm, thick, closed), ripen the cervix using misoprostol, prostaglandins or a Foley catheter.

ANAPHYLAXIS

- Incidence: Very rare
- Risk factor: Asthmatic, history of atopy, drug administration, latex allergy
- Clinical symptoms and signs: Dyspnea, tachycardia, hypotension, wheezing
- Management: Crystalloid infusion, adrenaline and antihistamines, hydrocortisone.

CARDIOMYOPATHY

- Incidence: One in 3,500.
- Risk factor: Pregnancy induced hypertension, twins, advanced maternal age
- Clinical symptoms/signs: Severe left ventricular failure
- Management: Urgent cardiology review.

AORTIC DISSECTION

- Incidence: One in 5,000.
- Risk factor: Marfan’s syndrome.
- Clinical symptoms/signs: Back or chest pain, dyspnea.
- Management: Urgent specialist (cardiologist, cardiothoracic surgeon) review.

DETERIORATION OF CARDIAC DISEASE

- Incidence: Variable
- Risk factor: Pre-existing cardiac disease
- Clinical symptoms/signs: Back or chest pain, dyspnea.
- Management: Urgent specialist (cardiologist, cardiothoracic surgeon) review.

STROKE

- Incidence: One in 500
- Risk factor: Any hypertension
- Clinical symptoms/signs: Change in consciousness, headache, vomiting, photophobia, neurological deficit, cardiac arrest
- Management: Urgent CT/MRI scan, neurology review.
- Subarachnoid hemorrhage can also result
- Cerebral venous thrombosis
  - Incidence: One in 10,000
  - Risk factor: Any hypertension
  - Clinical symptoms/signs: Change in consciousness, headache, vomiting, photophobia, neurological deficit, cardiac arrest
  - Management: Urgent CT/MRI scan, neurology review.

INHALED VOMIT SYNDROME
(MENDELSON’S SYNDROME)

- Definition: Gastric contents which are highly irritant, may be inhaled during induction of anesthesia, especially during pregnancy, resulting in chemical pneumonitis.
- Risk factors: The risk is higher in late pregnancy which predisposes to regurgitation of gastric contents, and when there is difficulty in intubation as happens in obese patients.
Clinical signs and symptoms: Clinical features may appear between 2 hours and 5 hours after anesthesia and include cyanosis, tachycardia, dyspnea, wheeze, crepitant rales, and decreased arterial oxygen tension.

Management: Routine use of antacids and/or epidural anesthesia can help to reduce the risk.

CARDIAC ARREST

Incidence: One in 30,000 pregnancies
Risk factors: The most frequent reasons for cardiac arrest in pregnancy and postpartum are obstetric hemorrhage and complications of severe preeclampsia. A list of common causes is shown in Table 6.
Management: Prompt resuscitation of the mother provided on the spot can save both maternal and fetal life. However, resuscitation is difficult in pregnant patients due to the physiological changes of pregnancy. Individuals involved in resuscitation must be aware of these limitations so that they can provide effective resuscitation.

MORTALITY WHAT TO DO

Inspite of all critical evaluation and meticulous management, there can be a postpartum collapse and mortality.

Patient-oriented Problems
- Nonattendance of antenatal care
- Infrequent attendance
- Delay in seeking help
- Noncompliance.

Administrative Factors
- Delay in transport from home to institution
- Delay in transport between institution
- Delay in admissions area
- Insufficient intensive care unit (ICU) beds
- Lack of appropriately trained medical officers
- Lack of communication between health workers.

Medical Person-oriented Problem
- Initial assessment incomplete
- Delayed problem recognition
Management plan/protocol: Standard protocol may not be followed at each level
- Monitoring may be improper
- Resuscitation may not be trained
- Improper documentation.

Ethical Issues
Allowing relatives to be present during resuscitation, it has been reported that family members present during resuscitation may benefit from witness in the event. However, option may be given to the relatives. Sometimes, family members may panic and cause undue stress on the staff managing the patient.
Confidentiality should not be violated specially dealing with HIV positive women.
Consent from the patient or patient’s relative is obtained; however, in an emergency situation, a doctor may administer medical treatment without consent, provided the treatment is needed to save life or avoid significant deterioration in the patient’s health (seeking patient’s consent, the ethical consideration GMC 1998).

After the Event Debriefing of the Events
Accurate documentation of all the events, timing of all resuscitative process and treatment received must be done properly for retrospective review of management. It is a good practice to inform the patient’s relatives and treating physician regarding treatment given and outcome. If the outcome is good, careful counseling should be done by gynecologist regarding future obstetric outcome, underlying medical causes and contraception.

CONCLUSION
Sudden postpartum collapse is a rare but a serious obstetric complication. This is the manifestation of varied type of pathologies in the immediate postpartum phase. This needs an immediate attention and resuscitation to maintain the ventilation, oxygenation and hemodynamic stability.
Essential investigations, on the basis of clinical judgment, are needed to establish the diagnosis of the sudden circulatory collapse. Monitoring of the CVP, ECG, arterial blood gas analysis, spiral computed tomography are helpful. Subsequent managements are to be carried out by a specialist team according to the specific pathology. Management of complications may need anticoagulants, anti-arrhythmic drugs, blood transfusion with coagulation factor replacement, anticonvulsants or thrombolysis. In some cases, surgery may be needed in the form of embolectomy or in placement of inferior vena cava filter or hysterectomy. Because of its rarity, obstetric units lack the experience in dealing with nonhemorrhagic collapse cases. ICU is mandatory in each obstetric unit for managing such cases. Anticipation of risk factors, prompt diagnosis and intensive care with experts of multidisciplinary team holds the key to save the life in this critical condition.

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Emergency in Pregnancy
Antepartum Hemorrhage

INTRODUCTION

In addition to unacceptably high perinatal mortality, antepartum hemorrhage (APH) is an important contributory cause of maternal mortality and morbidity in the developing countries. Although it is not preventable, an early diagnosis and treatment can improve maternal and perinatal outcome to a large extent. Any bleeding to and from the genital tract, during pregnancy, between 20 weeks of pregnancy and delivery of fetus is known as APH. Similar bleeding prior to the age of viability is known as threatened miscarriage or threatened abortion. In the past, 28 weeks was considered the age of viability. But, currently with improved neonatal intensive care unit (NICU) facility, particularly in the industrialized world, fetal survival is possible as early as 22 weeks. Accordingly, a universal agreement is lacking regarding the age of viability. The gestational age, beyond which, the definition of APH should be considered is therefore variable from country to country. In Canada, 20 weeks and in United Kingdom (UK) 24 weeks was considered as the lower limit for defining APH. However, irrespective of the age of viability, any bleeding during the second half of pregnancy should be taken seriously and proper evaluation and treatment be given accordingly.

CAUSES

The causes of APH are diverse, varied and multifactorial (Table 1). The source of bleeding could be either fetoplacental or maternal. From the obstetric viewpoint, the two most important causes of APH are placenta previa and abruptio placenta. Together they constitute more than 50% cases of APH. However, in majority of the cases of APH, the cause remained unknown and classified under the category of indeterminate, unexplained, unclassified or idiopathic. The other rare but significant causes include vasa previa, rupture uterus and show prior to onset of labor. With a history of late trimester bleeding per vagina, it is necessary to exclude the causes of bleeding from local lesions of cervix, vagina, vulva, and also from the urinary or gastrointestinal (GI) tract.

One year study of 112 APH cases in a hospital revealed 52 cases (46.4%) of placenta previa, 28 cases of abruptio placenta (25%) and 32 cases of unclassified APH (28.6%).

Perinatal Outcome

Antepartum hemorrhage is an important cause for perinatal morbidity and mortality. In general, placental abruption

Table 1: Causes of antepartum hemorrhage

- Placenta previa
- Abruptio placenta
- Indeterminate: Marginal sinus rupture
- Cervicitis, cervical polyp, carcinoma
- Vulvovaginal varicosities
- Genital tumors
- Genital infections
- Rare causes: Vasa previa, show, rupture uterus
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MANAGEMENT

Principles

The management of APH should be planned as general management (applicable to all cases of APH) with appropriate modification, depending on the type and severity of bleeding and specific management depending on the cause of bleeding, gestational age and condition of the fetus.

It is preferable that the management should be undertaken in a set-up having facility of round the clock blood transfusion, immediate termination of pregnancy (if required) by cesarean section (CS), neonatal resuscitation and intensive care facilities for both the mother and the neonate. If the set-up lacks those necessary facilities, the patient needs to be transferred by an ambulance to a nearby appropriate center for management. If the patient is bleeding heavily and the transport facility is not readily available or the appropriate center is quite far off, resuscitation with intravenous (IV) fluids should be started without any delay. As the fetus is safer in uterus, it is better to continue the resuscitation and transfer of the patient simultaneously. Fetal hemoglobin oxygen-binding capacity maintains adequate oxygenation until maternal partial pressures are less than 60.

Many a times, the insignificant bleeding at presentation could herald a subsequent significant bleeding at a later date and those cases also demand equal attention.

Initial management includes eliciting a proper history, physical examination of the patient as regards to fetomaternal condition and initiation of immediate treatment and investigation.

History

On duty, doctor should take quick history with specific questions to identify the background of the patient to help planning immediate and subsequent management. A proper history should include following points shown in Table 2.

### Table 2: Evaluation of history in antepartum hemorrhage cases
- Initiating factors of bleeding, if any (trauma, coitus, etc.)
- Details of bleeding: amount, character, color
- Associated abdominal pains or uterine contraction
- History of previous bleeding in the current pregnancy
- History of ruptured membranes
- Gestational age estimation (by last menstrual period (LMP) and/or first-trimester ultrasonography (USG), if available)
- Information about placental site (by the latest USG)
- Perception of fetal movements

Physical Examination

This examination should evaluate both maternal and fetal conditions shown in Table 3.

Immediate Treatment and Investigations

Irrespective of the cause, significant vaginal bleeding during pregnancy needs to be managed with rapid assessment of maternal and fetal status, fluid resuscitation, replacement of blood products when necessary, and an appropriately timed delivery. Being unpredictable in nature and having the possibility of sudden deterioration in clinical condition, even a minor bleeding may have considerable significance in pregnancy and should receive appropriate attention by the on duty obstetrician.

For management of massive obstetric hemorrhage cases, each obstetric unit must have a protocol of their own. A good interdepartmental liaison between the labor ward and the blood bank is of paramount importance. Ideally, both should be nearby. A regularly organized “fire drills” amongst all the members of the labor ward staff including the blood bank personnel helps in keeping them aware of their individual role at the time of emergency.

Immediate treatment and investigation should include the following as shown in Table 4.

Subsequent Management

After initial assessment and institution of treatment, depending on persistence of bleeding and its quantum, gestational
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Types of Placenta Previa (Figs 1A to C)

Depending on the sites of implantation, placenta previa is typically divided into four grades:

- **Grade I—Low lying placenta**: Placenta is implanted into lower uterine segment, but the lower limit of it does not reach up to internal os.
- **Grade II—Marginal placenta previa**: Leading placental edge reaches but does not cover the internal os.
- **Grade III—Partial placenta previa**: Placenta partially or asymmetrically covers the internal os.
- **Grade IV—Total or central placenta previa**: Placenta covers the internal os completely.

Anatomical classifications based on endovaginal ultrasound:

- **Total**: Placenta completely covers internal os.
- **Partial**: Lower placental border does not cover but is within 30 mm of the internal cervical os.
- **Low lying**: Placental margin can be seen with endovaginal probe but is more than 30 mm away from internal os.

Summary: General

- Antepartum hemorrhage is an important cause of fetal and maternal mortality and morbidity
- Placenta previa and abruptio placenta are important causes. In majority, cause remains unknown
- The principles of management are:
  - Initial assessment of patient’s condition
  - Resuscitation of patient
  - Prolongation of pregnancy, if possible or indicated or immediate delivery for fetal or maternal indications
  - Subsequent management depends on specific cause.

**PLACENTA PREVIA**

Definition

Previa means “in front”. It is a type of placenta when at least a part of it is implanted in the lower uterine segment and in front of the internal cervical os. It is one of the leading causes of vaginal bleeding in second and third trimester of pregnancy and thereby responsible for both fetal and maternal morbidity and mortality.

Table 4: Immediate treatment and investigations

- Intravenous (IV) line is established preferably with a wide bore cannula to facilitate rapid volume replacement.
- Blood sample is obtained for hemoglobin or hematocrit estimation, and determination of grouping and typing.
- In presence of severe or continuous bleeding, at least four units of blood should be kept ready by cross-matching. Clinically, if abruptio is suspected, a coagulation profile and measurement of urea, creatinine and serum electrolytes are also performed.
- In Rh negative women, Kleihauer-Betke test is performed on maternal blood. If vasa previa is suspected, an alkali denaturation test (APT) is performed on vaginal blood to identify fetal source of bleeding.
- Pending arrival of blood, volume replacement should be started with IV fluids, initially with crystalloids and then, if necessary, by colloids.
- Soon after maternal and fetal condition is stable, an ultrasonography (USG) scan is arranged to localize placenta and to confirm or exclude placenta previa or to exclude a major placental abruption. It can also provide additional requisite information about the fetus.
- Cardiotocography may show evidences of fetal compromise, an indirect evidence of uterine irritability.

Table 5: Maternal condition following initial management

- Bleeding stopped and the pregnancy is at term
- Bleeding stopped and the pregnancy is preterm
- Mild to moderate bleeding continuing and pregnancy term or preterm
- Severe and life-threatening bleeding continuing
- Fetus distressed
- Fetus dead

Table 5: Maternal condition following initial management

- Figs 1A to C: Types of placenta previa. (A) Low placental implantation; (B) Low placental previa; (C) Complete placenta previa
Emergency in Pregnancy

Table 6: Risk factors for placenta previa

- Advanced age
- High parity
- Cigarette smoking—risk increased by 3- to 6-fold
- Cocaine use—risk increased by 2.4-fold
- Previous CS deliveries—risk increased more with number of previous CS
- Previous abortion or curettage—risk increased by 1.8-fold
- Previous manual removal of placenta
- Deficient endometrium due to presence or history of
  - Submucous fibroid
  - Endometritis
- Large placenta, e.g. multiple pregnancy

Incidence

At term, the incidence of placenta previa is 0.4–0.8% of all pregnancies. Placenta previa is a common incidental observation on second-trimester ultrasonography (USG) and found in approximately 4% cases at 20–24 weeks gestation. At term, the incidence is however reduced to only 0.4% of pregnancies. This is because of so called placental migration, resulting from differential growth of uterus and placenta.

Etiology

The exact reason for implantation of blastocyst into the lower uterine segment and subsequent development of placenta previa is unknown. Although a chance occurrence can not be ruled out, a number of well-recognized associations had been noted with placenta previa. Damage to the endometrium or myometrium due to previous uterine surgery or infection might be a contributory factor for such implantation. Significant association had been noticed between previous CS deliveries and placenta previa. A uterine scar also predisposes to morbid placenta and the risk of placenta accreta, increta and percreta increases with the number of cesarean deliveries. The incidence increases with age, parity, tobacco use and previous cesarean deliveries. Drug abuse (especially cocaine) and history of abortion (spontaneous or induced, particularly their number) are also recognized risk factors for placenta previa. Increase in number of cesarean deliveries increases the incidence of placenta previa so that it becomes almost 10% after four or more cesarean deliveries. Abruptio placenta in previous pregnancy increases the chance of placenta previa in present pregnancy. The risk of recurrence of placenta previa in subsequent pregnancy is increased by 8–10 times.

Maternal Complications

The complications are related to bleeding and its consequences. Globally, although maternal mortality had improved significantly over the years, in developing countries, wide spread pre-existing anemia, difficulties in transport and inadequacies of maternity care services are the important deterrents to improve maternal outcome comparably. In industrialized world, maternal mortality is improved to around 0.03–0.5%. The maternal risks could be summarized as follows:

- Although in up to 30% cases, there may not be any further bout of bleeding during the antenatal period, the relative risk of observed episode of bleeding is increased by 10%.
- The need for blood transfusion is increased by 10-fold.
- There is an increased likelihood ratio of retroplacental hemorrhage and placental abruption.
- Postpartum hemorrhage (PPH) is the major contributory factor of maternal mortality and is caused by inadequate occlusion of the placental venous sinuses in the lower segment in addition to bleeding from large surface area of the placental implantation site.
- Air may enter into the systemic circulation through low pressure open placental venous sinuses and lead to features of air embolism few hours after delivery.
- Increased association of morbidly adherent placenta further accentuates the bleeding and surgical complications and the need for hysterectomy.
- The probability of peripartum hysterectomy is increased by 33-fold.
- Emergency CS in a inadequately prepared patient increases the likelihood of anesthetic and surgical complications.
- Postpartum sepsis is caused by ascending infection of relatively nearby placental implantal site.
- The risk of recurrence of placenta previa in subsequent pregnancy is 4–8%.

Fetal Complications

Because of conservative management and improved neonatal care facility, perinatal mortality had improved significantly over the years, but compared to control population perinatal mortality associated with placenta previa is higher by a factor of 2.9–4.25. Perinatal mortality in industrialized world is 42–81 per 1,000 births. The causes of increased perinatal mortality and morbidity are shown in Table 7.

Presentation

The classic presentation is vaginal bleeding with the following characteristics (Table 8).

Second-trimester scan can identify asymptomatic low lying placenta. These cases need to be counseled properly mentioning the possible risk of bleeding and also the fact of so called placental migration during the course of pregnancy. In addition, 9–10% of cases of placenta previa are associated with placenta accreta, an abnormally firm attachment of the placenta to the wall of the uterus.
Table 7: Causes of increased perinatal mortality and morbidity

- Increased incidence of respiratory distress syndrome (RDS) (OR 4.94) because of increased frequency of preterm birth (almost 50%). More preterm births are associated with poor neonatal prognosis.
- Increase incidence of major congenital abnormalities (OR 2.48). The most common malformations are those of central nervous system (CNS), cardiovascular system (CVS), respiratory and gastrointestinal (GI) system.
- Perinatal mortality is also directly related to total amount of blood lost antepartum.
- Increased incidence of fetal anemia (OR 2.65)
- Increased incidence of intrauterine growth retardation (IUGR) (occurs in 16%). Although a recent data is contradictory, reduction in fetal growth velocity is a likely possibility and is due to repeated bouts of antepartum hemorrhage (APH).
- Additional fetal risks include cord prolapse and compression and sudden unexplained fetal death due to rupture of vasa previa and severe maternal hypovolemic shock.
- Fetal malpresentation.

Table 8: Presentation of vaginal bleeding

- Bleeding occurs suddenly and is usually unprovoked.
- Bleeding is usually bright red.
- Usually a painless condition and absence of pain is considered as a distinguishing point from abruptio placenta. However, some degree of uterine irritability is present in about 20% of the cases either because of associated abrasion or because of simultaneous onset of labor.
- Initial bleeding is not usually profuse. It spontaneously resolves on its own, only to recur later. First episode of bleeding is often referred to as “warning hemorrhage” or “sentinel bleed”.
- The first episode of bleeding is commonly noted at 27–32 weeks’ gestation.
- In more than 50% cases, bleeding occurs prior to 36 weeks.

**Diagnosis**

Many cases of placenta previa are diagnosed by routine ultrasound. In other cases, the initial diagnosis is made when the patient comes to the hospital with vaginal bleeding. Placenta previa is a common incidental finding on second-trimester USG and should be confirmed in the third trimester. A placenta previa is a common incidental observation on second-trimester USG and found in approximately 4% cases at 20–24 weeks gestation. At term, the incidence is however reduced to only 0.4% of pregnancies because of so-called placental migration, resulting from differential growth of upper and lower segments of uterus with the growth and development of pregnancy. Only 10% of low lying placetas identified at the 16–20 weeks USG will remain low at term. Ultrasonography is the mainstay of diagnosis of placenta previa. Transabdominal sonography (TAS) route is commonly employed. TAS is simple, safe and precise method to localize placenta with an accuracy of 93–98%. Because of focal uterine contraction or distension of bladder, false positive result is a distinct possibility. Errors in diagnosis are most likely in cases of posterior placenta previa, because of the difficulties in proper identification of lower uterine segment.

Transvaginal sonography (TVS) is considered as gold standard for localization of placenta and diagnosis of placenta previa. When the diagnosis of placenta previa is clinically suspected or remains uncertain or equivocal by TAS, TVS clarifies the situation and confirms the diagnosis (Fig. 2). TVS is safe, more accurate than TAS, does not increase the chance of bleeding and does not require full bladder and has better diagnostic accuracy with posterior placenta previa. In addition, TVS changes the diagnosis made by TAS in 26% of cases. The angle between the transvaginal probe and the cervical canal is such that the probe does not enter the cervical canal. Some advocate insertion of the probe no more than 3 cm for visualization of the placenta. Placenta previa is diagnosed on transvaginal scan when the leading placental edge is less than 3 cm away from the internal os. As an alternative to TVS, especially when instrumentation of the vaginal canal is a concern, experts in USG can utilize transperineal approach to diagnose placenta previa. This method could also be used as a complimentary to TAS. Magnetic resonance imaging (MRI) has been suggested as a safe, alternative and most accurate method to diagnose placenta previa. The high cost limits its availability. A large trial determining the efficacy and safety of the use of MRI during pregnancy has not been performed, and further investigation is required. MRI is not widely available or used and at the moment is relevant only in cases of inconclusive USG findings. It is suggested that MRI may help in confirming the diagnosis of invasive placenta and identify organ involvement associated with placenta percreta.

**Management**

The management of placenta previa is guided by the principle of expectancy; to allow the pregnancy to progress to as close to term as possible and then delivery is undertaken.

![Fig. 2: Transvaginal sonography of a complete posterior placenta previa: the placental edge covers the internal os](image)
Incidental Diagnosis of Placenta Previa

Because of the possibility of migration of placenta to upper uterine segment in more than 90% cases, expectant management is generally followed. The length by which the placenta overlaps the internal os at 18–23 weeks is highly predictive for the persistence of placenta previa. The likelihood of a previa persisting until term increases if the previa is complete, if it is present at a later gestational age or if there is a history of cesarean delivery. The length by which the placenta overlaps the internal os at 18–23 weeks is highly predictive for the persistence of placenta previa. If the overlap is less than 1.5 cm (0.6 inches) at 18–23 weeks, placenta previa typically resolves; if the overlap is 2.5 cm (1 inch) or greater at 20–23 weeks, persistence to term is likely. The likelihood of a previa persisting until term increases if the previa is complete, if it is present at a later gestational age or if there is a history of cesarean delivery.

Based on the aforesaid information, a conservative approach is logical and usually followed at home. During the interim period of expectancy, management is based on the following principles:

- Strenuous work is avoided
- Sexual intercourse is avoided
- Advised to attend hospital, if there is any bleeding
- Regular intake of hematinsics is ensured and maintained
- Placental location is again re-evaluated by USG.

If placenta previa is still present by repeat USG through transvaginal route, the same precautionary measures are followed. If placenta previa persists beyond 32–34 weeks, migration to upper segment by term is unlikely. Although, rescanning is usually followed in most of the centers, there is no evidence that rescanning “at risk” patients in the third trimester reduces adverse fetal or maternal outcome from placenta previa. Randomized trials addressing this issue are needed. Rescanning is definitely indicated in cases of persistent malpresentation and/or vaginal bleeding and TVS is preferred. Waiting beyond 37 weeks is not likely to benefit the fetus or mother. CS usually is scheduled at a gestational age that will maximize the likelihood of fetal maturity and minimize the risk of hemorrhage that may result from the normal onset of uterine contractions.

Because placenta previa may resolve to close to term, it is recommended that no decision on mode of delivery be made until after USG at 36 weeks. Women whose placental edge is 2 cm or more from the internal os at term can expect to deliver vaginally unless heavy bleeding ensues. The vaginal delivery should be attempted in a facility capable of moving the patient rapidly to cesarean delivery if necessary. Although not universally followed, documentation of pulmonary maturity by amniocentesis in women with a nonbleeding placenta previa at 36–37 weeks is performed in some centers prior to scheduled cesarean delivery.

If Presents with Bleeding

Initial management of APH (as discussed in the previous section) is instituted without delay. Depending on the severity or persistence of bleeding, gestational age, maternal and fetal condition, the options for subsequent management are: immediate delivery, expectant management and termination of pregnancy.

Following clinical situations shown in Table 9 demand immediate delivery by CS.

The mode of delivery depends on the grade of placenta previa and state of the cervix. The options are immediate CS and examination in the operation theater (OT), with or without anesthesia (“double set-up”). Cesarean route is the preferred method of delivery in most of the situations (fetal malposition or malpresentation, fetal heart rate (FHR) abnormality and major degree placenta previa) and the only option in presence of profuse bleeding. In case of a low-lying or marginal placenta previa, the descending fetal head may “ramponade” the bleeding placental edge (thereby reducing bleeding from the separated placental edge) and permit vaginal delivery.

The “double set-up” examination (Table 10) is indicated in cases of grade I or grade II anterior placenta previa or when the USG findings for localization of placenta are inconclusive.

Prerequisites for “double set-up” examination include:

- Intravenous (IV) lines started
- Cross-matched blood is available
- Examination is performed in the OT
- An experienced obstetrician should perform the examination
- Second obstetrician must be scrubbed and ready to operate

Table 9: Indications for immediate delivery

- Deteriorating condition of the mother
- Persistent heavy bleeding
- Gestational age more than 36 weeks
- Estimated fetal weight more than 2,500 g
- Fetal distress in a viable fetus
- Contractions that do not respond to medication

Table 10: “Double set-up” examination

- A sterile speculum examination is done to see the cervix. Cervix partly dilated and placental tissue is visible—placenta previa is confirmed and delivery is planned.
- If the cervical os is not dilated, vaginal fornices are palpated carefully
  - Spongy tissue felt—placenta previa confirmed
  - Fetal head felt—placenta previa excluded
- If the diagnosis is still in doubt, careful digital examination is done through the cervix
  - Soft tissue felt within cervix: Placenta previa confirmed
  - Fetal parts and membranes are felt both centrally and marginally, placenta previa is excluded.
Expectant Management

Provided the initial episode of bleeding resolves and the fetomaternal condition is stable, it is reasonable to delay delivery until fetal maturity is attained or any subsequent bouts of significant bleeding supervene. Although not universally followed, in some centers, expectant treatment is also considered even when the initial bleeding is severe and then the bleeding either stops or slows down. The goal of this expectant approach is to improve perinatal outcome by prolongation of pregnancy and several groups had reported that bed-rest is instituted with strict avoidance of any inciting factors of bleeding. Measures, including blood transfusion and administration of hematinsics, are taken to raise hemoglobin status to prepare the patient to withstand any further significant rebleeding. The aim is to maintain maternal hemoglobin at least 10 g% or hematocrit 30%. In addition to bed-rest, steroids are usually given to hasten fetal lung maturity. In Rh negative women, an injection of Rh immune globulin is also administered after performing Kleihauer-Betke test to determine the appropriate dose. In all cases of expectant management, two units of blood must be available at all times. During the expectancy period, some interventional measures were tried and/or adopted to improve maternal and fetal outcome.

Elective Cervical Cerclage

To prolong pregnancy and prevent iatrogenic prematurity due to bleeding, cervical cerclage has been proposed and tried. The Cochrane meta-analysis found that cerclage decreased the risk of premature birth before 34 weeks (relative risk = 0.45; 95% confidence interval, 0.23 to 0.87); however, it is recommended that additional studies of cerclage be performed before this clinical practice is introduced. In summary, cervical cerclage may reduce very premature births, although the evidence is not very strong.

Tocolytic Agents

Tocolytic agents may be used safely to prolong gestation if vaginal bleeding occurs with preterm contractions. Although studies using tocolytic agents show a trend toward increased frequency of bleeding episodes, neither is this bleeding significant nor does it increase the requirement of blood transfusion. Uterine contractions in presence of placental previa may be due to abruption (associated in 10% cases) and due consideration should be given to exclude abruption prior to administration of tocolytic agent.

At present, there is inadequate evidence to suggest that either in-patient or out-patient care leads to a superior outcome. On the contrary, outpatient management is appropriate for selected patients who do not have active bleeding and who can rapidly access a hospital with operative labor and delivery services. This approach is applicable to only Grade I to III placenta previa and asymptomatic Grade IV placenta previa. However, in clinical practice, frequently a combination of in-patient and out-patient management is undertaken. For a particular patient, the decision is taken by analyzing the following factors shown in Table 11.

### Table 11: Factors influencing the decision of in-patient vs out-patient management

- Each case is given due importance and individualized approach is adopted.
- History of bleeding—stopped/continuing
- Grade of placenta previa
- Patient’s social circumstances—distance of residence from the hospital, transport facility, manpower support
- Patient’s wishes
- Obstetrician’s preferred practice.
Termination of Pregnancy

Cesarean section is the recommended method of delivery in nearly all cases of placenta previa except those cases of Grade I placenta previa, where the distance between the leading placental edge and the cervix is at least 20 mm to allow vaginal delivery. CS, as an optional method of delivery, is also contributed by increased incidence of malpresentation and other obstetric factors. In cases of anterior placenta previa, it is often beneficial to perform a scan immediately prior to CS, to localize the placenta precisely and to look for any “placenta free window” so as to plan the incision at lower uterine segment during CS. In absence of such “placenta free window”, the options for access to the fetus are either transplacental approach or “classical” incision in the upper uterine segment. The former approach requires speed and may cause significant fetal blood loss. The latter approach may be associated with undue delay in delivery of the fetus, more troublesome bleeding from a partially separated placenta with resultant fetal blood loss and anoxia, along with the potential risk of scar rupture in subsequent pregnancy. However, a lower segment approach is preferred by most obstetricians. Because of inevitable fetal blood loss, cutting or tearing through placenta is avoided by many. Less retractile nature of the lower uterine segment provokes increased intraoperative bleeding through torn placental sinuses. To achieve hemostasis, following measures (Table 12) can be undertaken with variable degree of success:

- Recently, prothrombin complex and recombinant factor VII are being utilized to control massive hemorrhage with placenta previa.

Women with a history of previous cesarean delivery and placenta previa or a placenta located at the site of the previous incision are at a higher risk of morbidly adherent placenta and so, should be evaluated accordingly with color-flow Doppler imaging (Fig. 3). The method has a positive predictive value for detection of placenta accreta of 87.5%. MRI of the pelvis may help to confirm the diagnosis of an invasive placenta and delineate organ involvement in women with a placenta percreta. Nine to ten percent of cases of placenta previa are associated with placenta accreta, an abnormally firm attachment of the placenta to the wall of the uterus. Placenta accreta prevents separation of placenta from the uterine wall at the time of delivery and can induce severe bleeding thereby increasing the need for peripartum hysterectomy (>90%). This possibility needs to be discussed with the patient, prior to CS. More than 50% of patients with placenta accreta require blood transfusion. However, hysterectomy can be avoided by employing a conservative approach, wherein, the placenta is left in situ followed by either internal iliac artery ligation or uterine artery embolization or by adopting a medical approach with administration of systemic methotrexate.

When possible, the procedure should be performed electively with following preparations: adequate venous access, ready availability of blood and necessary medications and discussion about the possible need of hysterectomy in dire situations. An experienced surgeon, preferably a consultant should perform the operation or at least be readily available. Available data suggests that the risk of bleeding may be more with GA, which is contrary to the commonly held view. Accumulated evidence also indicates that regional anesthesia is a safe alternative to GA in both elective and emergency cesarean deliveries in cases of placenta previa.

Summary: Placenta Previa

- Transvaginal sonography is the most reliable diagnostic method and without any risk too.
- Postcesarean pregnancy increases the risk of placenta previa and also adherent placenta.
- Routine anomaly scan at 20–22 weeks has a high false positive and even 7% false negative rate for diagnosis, depending on whether abdominal or vaginal route of sonography is employed.

Table 12: Measures to reduce or stop excessive intraoperative blood loss

<table>
<thead>
<tr>
<th>Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Bleeding sinuses oversewn withatraumatic sutures</td>
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<tr>
<td>- Direct pressure with warm packs. But, if these packs are left in situ during closure of uterus, bleeding might continue and remain concealed.</td>
</tr>
<tr>
<td>- Administration of oxytocics with intramyometrial injection of prostaglandin $F_{2\alpha}$</td>
</tr>
<tr>
<td>- Horizontal and vertical compression sutures were tried with some success.</td>
</tr>
<tr>
<td>- Uncontrollable bleeding is tackled by ligation of uterine artery and internal iliac artery</td>
</tr>
<tr>
<td>- Hysterectomy may be required as a last resort to save woman’s life.</td>
</tr>
</tbody>
</table>

Fig. 3: Color flow Doppler ultrasonography demonstrating placenta percreta with bladder invasion
Abruptio Placenta

Definition
Premature separation of a normally situated placenta during the antenatal or intrapartum period of pregnancy is known as abruptio placentae. Approximately, 20% of all cases of APH are due to abruptio.

Incidence
Abruption has been estimated to occur in 6.5 pregnancies per 1,000 births,31,32 and up to 1.5% in all pregnancies. Many cases of abruptio remain unrecognized until delivery and in one study histological examination of placenta reveals that, the incidence is as high as 4.5%. Thus, the criteria used for diagnosis is responsible for reported wide variation in incidence (0.49–1.8%). Approximately, 50% of placental abruptions occur before 36 weeks’ gestation, resulting in adverse outcomes secondary to prematurity.33

Causative Associations
The cause of abruptio is unknown in most cases. Within few hours, however, the cause may become obvious. Various risk factors are associated with placental abruptio (Table 13).

Table 13: Risk factors of abruptio

<table>
<thead>
<tr>
<th>Risk Factors</th>
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<tbody>
<tr>
<td>Hypertension—the most common in 44% cases</td>
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<tr>
<td>Cigarette smoking</td>
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<tr>
<td>Trauma [road traffic accident (RTA), domestic violence]</td>
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<tr>
<td>Sudden decompression of the uterus</td>
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<tr>
<td>Short umbilical cord</td>
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<tr>
<td>Alcohol consumption</td>
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<tr>
<td>Cocaine abuse</td>
</tr>
<tr>
<td>Retrolental fibroid</td>
</tr>
<tr>
<td>Amniotomy or amniocentesis</td>
</tr>
<tr>
<td>Severe intrauterine growth retardation (IUGR)</td>
</tr>
<tr>
<td>Advanced maternal age</td>
</tr>
<tr>
<td>Prolonged preterm premature rupture of membranes (PROM)</td>
</tr>
<tr>
<td>Abruptio in previous pregnancy</td>
</tr>
<tr>
<td>Thrombophilia</td>
</tr>
<tr>
<td>Chorioamnionitis</td>
</tr>
<tr>
<td>External cephalic conversion</td>
</tr>
<tr>
<td>Hyperhomocysteinemia</td>
</tr>
<tr>
<td>Circumvallate placenta</td>
</tr>
<tr>
<td>Increased alpha fetoprotein level</td>
</tr>
</tbody>
</table>

The risk factors include chronic hypertension, preeclampsia, thrombophilies, abdominal trauma and abruptio in a previous pregnancy,34 tobacco or cocaine use.35 Chronic hypertension is associated with threefold increase in the risk of abruptio. Although maternal hypertension is considered a risk factor, there is no consensus as to whether hypertension precedes abruptio or vice versa. The other independent associations of placental abruptio include severe fetal growth restriction, prolonged rupture of the membranes, chorioamnionitis (infection of placenta and membranes), hypertension (including preeclampsia, nonproteinuric pregnancy-induced hypertension and pre-existing hypertension), cigarette smoking, advanced maternal age and unmarried status.36 Abruptio in cases of preterm premature rupture of membranes (PPROM) typically presents with bleeding followed by dribbling. Trauma, notably road traffic accidents and even domestic violence may also cause abruptio. Sudden uterine decompression after rupture of membranes or delivery of a first twin may precipitate placental abruptio.37 Placental abnormalities (especially circumvallate placenta) and increased level of alpha-fetoprotein are also associated with abruptio. Placental abruptio is twice as common in twin, than singleton pregnancies.38 The risk of placental abruptio in subsequent pregnancies is significant varying from 6% to 16.7% after one episode and increases to 25% after two such episodes. In one study, the incidence increased by at least 10-fold (incidence 4–5%).39

The association of folic acid deficiency with abruptio was not confirmed by any large prospective studies. On the other hand, the associations between abruptio and specific thrombophilias (such as factor V Leiden mutation, prothrombin gene mutation, hyperhomocysteinemia, activated protein C resistance, antithrombin III deficiency and anticardiolipin immunoglobulin G antibodies) have been reported in different literatures and this risk may be independent of the presence of preeclampsia. The presence of thrombophilias may also influence the severity of abruptio. The association between abruptio and thrombophilias, however, had not been uniformly documented in all the related studies.

Classification
Broadly, abruptio is classified into two groups: (1) revealed—where obvious bleeding is noted in the lower genital tract and (2) concealed—where entire blood is contained inside the gravid uterus without any manifestation of external bleeding. Abruptio is concealed in 20–35% and revealed in 60–65% cases.40 The concealed type is more dangerous and associated with more severe maternal and fetal complications. A more precise classification of abruptio based on the extent of separation (partial vs complete) and location of separation (marginal vs central) is as follows:
Emergency in Pregnancy

Class 0: is asymptomatic. Diagnosis is made retrospectively by finding an organized blood clot or a depressed area on a delivered placenta.

Class 1: is mild and represents approximately 48% of all cases. Characteristics include the following:
- No vaginal bleeding to mild vaginal bleeding
- Slightly tender uterus
- Normal maternal blood pressure (BP) and heart rate
- No maternal or fetal compromise

Class 2: is moderate and represents approximately 27% of all cases. Characteristics include the following:
- No vaginal bleeding to moderate vaginal bleeding
- Moderate-to-severe uterine tenderness with possible tetanic contractions
- Maternal tachycardia with orthostatic changes in BP and heart rate
- Fetal compromise or distress
- Hypofibrinogenemia (i.e. 50–250 mg/dL)

Class 3: is severe and represents approximately 24% of all cases (0.2% of all pregnancies). The characteristics are:
- No vaginal bleeding to heavy vaginal bleeding
- Very painful tetanic uterus with stony hard consistency
- Maternal shock
- Hypofibrinogenemia (i.e. <150 mg/dL) and coagulopathy
- Fetal death.

Maternal Risks

- Maternal mortality: Placental abruption is a recognized cause of maternal death, especially in resource poor settings and developing countries. The maternal mortality rate is approximately 1%.
- Hypovolemic shock: As a result of severe maternal blood loss, hypovolemic shock is the major immediate maternal risk. Because of concealed bleeding, blood loss is often underestimated.
- Coagulopathy/disseminated intravascular coagulation: There may also be clinical and hematological evidence of disordered blood clotting as thromboplastin are released by placental damage and coagulation factors are consumed in the enlarging retroplacental clot at a rate that is faster than the body’s ability to replace them.
- Postpartum hemorrhage: It can result from coagulation failure or from couvelaire uterus (a condition, where blood sips into the myometrium and impairs its ability to contract).
- Renal failure: Acute renal failure may result from either hypovolemia or disseminated intravascular coagulation (DIC) and may be seen later in the forms of either acute tubular or cortical necrosis.
- Ischemic necrosis of distal organs (e.g. hepatic, adrenal, pituitary) is the result of severe prolonged hypotension.

Fetal Risks

- Perinatal mortality rate of abruptio is 119 per 1,000. It varies from 4.4% to 67.3% depending on the severity of the condition and neonatal care facilities. More than 50% of perinatal deaths are stillbirths. Neonatal death occurs in 10–30% of cases. Approximately, 50% of placental abruptions occur before 36 weeks of gestation, resulting in adverse outcomes secondary to prematurity.
- The causes of perinatal deaths include prematurity, congenital malformation, intrauterine growth restriction (IUGR) and fetal hypoxia. DIC may result from the release of thromboplastin into the maternal circulation with placental separation. This occurs in about 10% of abruptions indicating severe abruption and is more common with fetal death.
- Fetal growth restriction is noted in 80% of infants born before 36 weeks of gestation.
- The rate of congenital malformation is increased by twofold to threefold.
- Significant fetal bleeding may cause neonatal anemia.
- The fetomaternal complications are dependent upon severity of hemorrhage, extent of placental separation, health status of mother and fetus, gestational age and effectiveness of interventions.

Clinical Presentation

Placental abruption may present with a variable combination of vaginal bleeding, abdominal pain, uterine contraction, shock or fetal distress depending on the degree of separation of placenta.
- Vaginal bleeding may or may not be obvious (“revealed” or “concealed” variety).
- Variable degree of pain over the uterus is a prominent feature and is continuous in nature.
- Uterine contractions may start and cause additional, intermittent, pain.
- Faintness and collapse with or without signs of shock may occur.
- Typically, the uterus is extremely hard and tender, without any relaxation.
- Fetal parts are difficult to palpate.
- Fetal heart may not be audible if death has occurred.
- Mild placental detachment: It may not be demonstrable on ultrasound as the blood clot is not easily distinguishable from the placenta.
- Moderate placental detachment and hemorrhage: At least one quarter of placenta has become detached and less than 1,000 mL of blood lost. There may be abdominal pain and tender uterus, mother may be in shock, fetus may be hypoxic and may show abnormal heart rate patterns.
Severe placental detachment and hemorrhage: At least 1,500 mL of blood lost, shock usual, uterus firm-to-hard and very tender. Fetus is almost always dead. Hypotension in one-third of cases, but may be normal in spite of shock. Coagulopathy is common. The presenting symptoms of abruption are as follows: vaginal bleeding—70–80% (characteristically dark and nonclotting), abdominal or back pain and uterine tenderness—70%, fetal distress—60% (in grade I and II cases), abnormal uterine contractions (e.g. hypertonic, high frequency)—35%. Uterine contractions are often difficult to differentiate from pain of abruption. Nearly 50% of the patients with abruption are in established labor. Fetal death (in grade III it is inevitable by definition) occurs in 15% cases.

Pathogenesis

It is thought that abruption is caused by degenerative changes in the spiral arterioles, leading to decidual necrosis. Following this, the vessels can rupture and bleeding ensue and ultimately forms a retroplacental clot. Placental abruption can be a self-extending process with the accumulating blood clot causing more separation and, thus more hemorrhage, until the edge of the placenta is reached. After this, blood can escape through the potential space between the chorion and the decidua until it reaches the cervix. Blood can also reach the amniotic cavity (by disrupting the placenta, producing blood stained amniotic fluid) and the myometrium (causing the bruised, so-called “couvelaire uterus”). There is usually severe fetal hypoxia associated with sizeable placental separation, and sudden fetal death is common.

Diagnosis

Placental abruption is essentially a clinical diagnosis. Features of moderate to severe abruption are suggestive. In mild cases, diagnosis is often suspected and confirmed after delivery by demonstration of a retroplacental clot indenting the maternal surface of placenta. Placental abruption can cause FMH. So, Kleihauer test could be diagnostic in mild and silent cases.

Ultrasound imaging has a much smaller role in the diagnosis. The sensitivity of USG for detection of abruption is only 24%. USG may not be helpful in diagnosing acute severe abruption, as the acoustic characteristics of a fresh retroplacental clot are similar to those of placenta and differentiation is difficult. In less severe cases where the pregnancy is allowed to continue, the clot becomes hyperechogenic within 1 week and sonolucent within 2 weeks and therefore more obvious by USG (Fig. 4).

Ultrasonography helps in excluding placenta previa and fetal congenital abnormality in addition to detecting fetal viability, number, presentation, estimated fetal weight and gestational age. The cases managed expectantly, can be monitored with USG by determining the size of hematoma, its location and change in size over time. This information may help to decide the time of delivery in mild cases managed expectantly.

Management (Flow Chart 1)

The management depends on:
- Severity of the condition
- Maternal condition
- Fetal condition
- Gestational age
- Associated complications.

The management can be divided into:
- General measures
- Specific measures.

The traditional, main principles of clinical care of a woman with placental abruption include:
- Adequate maternal resuscitation
- Assessment of fetal condition
- Adequate analgesia for pain relief
- Early delivery
- Adequate blood transfusion
- Monitoring of maternal condition.

Early Delivery

Early delivery is life saving for the fetus. In one case series, 30% of perinatal deaths occurred within 2 hours of admission. A decision-to-delivery interval of 20 minutes or less resulted in improved neonatal outcomes in a case-control study of severe abruption. Acute blood clots and the placenta are
hyperechoic on USG and is difficult to distinguish from one another. So, the definitive management should never be delayed for confirmation of diagnosis by USG.\(^{44}\)

If the fetus is already dead, as is often the case, vaginal delivery should be the goal.\(^{48}\) It has been suggested that in some cases of severe abruption, high levels of fibrin degradation products might inhibit uterine contractions and make vaginal delivery difficult to achieve.\(^{49}\) This might contribute to atonic PPH as well. Most women with abruption and DIC deliver vaginally. However, if surgical intervention is required at any point of time, measures to be taken to rapidly correct the coagulation defect by transfusion of fresh blood, fresh frozen plasma (FFP) and cryoprecipitate. To achieve vaginal delivery amniotomy is usually preferred. It not only accelerates labor, but is also believed to reduce the incidence of coagulopathy by reducing intra-amniotic pressure and thereby minimizing the entry of tissue thromboplastin into the maternal systemic circulation. Augmentation with oxytocin may be necessary in some cases. To identify fetal distress early, continuous fetal monitoring should be performed during vaginal delivery. A nonreassuring fetal heart tracing necessitates rapid, usually cesarean, delivery.\(^{57}\) As 15.4% of live born infants of abruptio do not survive,\(^{50}\) choosing a particular method of delivery in cases of live fetus may not always be very easy. The study that shows 52% perinatal mortality following vaginal delivery as compared to 16% following CS, favors CS as preferred option.\(^{51}\) A shearing force produced by uterine contraction, during vaginal delivery, may aggravate the chance of further placental separation. So, even an apparently normal fetus runs the risk of compromised oxygen supply during labor. In fact, it has been recommended that, if the baby is alive and the gestation not so preterm as to make fetal survival extremely unlikely, delivery should be by CS.\(^{52}\)

Initial management includes rapid stabilization of maternal cardiopulmonary status and assessment of fetal well-being. Prompt treatment and monitoring of the mother is essential. Maternal vital signs (pulse, BP, respiration rate) along with central venous pressure (CVP), urine output, vaginal bleeding, etc. are monitored continuously. Treatment of hypovolemic shock, if needed, should be initiated early and maintained vigorously with appropriate monitoring. In absence of fetal heart sound, it is anticipated that a massive-concealed bleeding had already taken place and traditional teaching advises transfusion of at least two units of blood. Coagulation parameters are also monitored in this situation and also when coagulopathy is suspected. As some degree of coagulopathy is expected in about 30% of severe cases of placental abruption, quick identification and treatment of

Abbreviation: EFM, electronic fetal monitoring
the condition are important. The best treatment for DIC, as a complication of placental abruption, is immediate delivery along with ancillary measures suggested by the hematologist. Maternal stabilization requires serial evaluation of the hematocrit and coagulation studies to determine whether DIC is present. Fetal condition is also monitored intermittently or continuously, as required. Because the unpredictable nature of abruption does not allow for controlled trials, the management remains empiric. Cochrane review found no randomized controlled trials assessing interventions for placental abruption that met inclusion criteria.

Expectant Treatment

In selected patients, with an aim to improve fetal maturity, expectant treatment is considered provided the following criteria are satisfied:

- Vaginal bleeding—slight
- Abdominal pain—mild and localized
- Uterus—relaxed and not irritable
- Fetal heart rate—normal
- Maternal condition—hemodynamically stable.

The treatment is continued with appropriate monitoring of fetal condition clinically and by investigations [cardiotocography (CTG), biophysical profile and Doppler velocimetry] as available. The timing of delivery was decided by:

- Any further episodes of vaginal bleeding
- Gestational age
- Fetal condition
- Neonatal care facilities.

Despite the lack of evidence, induction of labor is often advocated in patients at term because of the possible deterioration in placental function in patients even in absence of any acute or chronic fetal compromise being documented. For expectant treatment, routine admission of these patients lacks any concrete evidence. If any retroplacental clot is detected by USG, serial scan may help to monitor the size and change in echogenicity of the clot. Any deterioration of fetal condition demands immediate delivery. Some cases of mild abruption may be associated with labor. In such cases, it is difficult to determine what precedes the other. Although tocolysis is generally contraindicated, the only possible role of tocolysis is in cases of mild abruption before 34 weeks of gestation, is to allow administration of corticosteroids.

Prevention

Randomized controlled trials of sufficient power are required to assess interventions (diet, vitamin supplements and antithrombotic therapy) to prevent abruption. By reducing cigarette smoking, drug abuse and domestic violence, it is possible to reduce the incidence of abruption with intrapartum treatment of magnesium sulfate in cases of preeclampsia.

Summary: Abruptio Placenta

- A variety of associations are noted
- Diagnosis is essentially clinical
- Ultrasonography has small role in diagnosis. Sonography primarily is utilized for excluding placenta previa and monitoring retroplacental clot and fetal conditions during expectant treatment.
- Management depends on grade. Vaginal delivery in dead fetus and CS in live fetus is usually performed.
- Correction of coagulopathy is essential prior to embarking on delivery.
- Major risk factors include intrauterine device (IUD), maternal DIC and renal failure.
- Recurrence risk is 6–17% after one episode and almost 25% after two episodes.

UNCLASSIFIED (UNDETERMINED) ANTEPARTUM HEMORRHAGE

It is the most common cause of APH and the diagnosis is essentially made by exclusion of placenta previa and abruptio placentae and other obvious causes. The patient usually presents with painless bleeding which is usually mild in nature and settles spontaneously. Marginal sinus rupture appears to be the most common cause of bleeding in cases of undetermined APH. The bleeding is usually painless.

Causes

Although the cause remains unknown in majority of the situations, in a proportion of these cases, the cause may become evident later on and it includes circumvallate placenta, marginal sinus rupture, “show”, trauma, cervicitis, genital tract tumors, genital infections, vulval varicosities and vasia previa. Unrecognized cases of minor placenta previa or mild abruption, diagnosed only after delivery, are also included in the list of causes of undetermined APH.

Risks

The main concern about unclassified vaginal bleeding is their association with an increased risk of preterm delivery and a small increase in the risk of fetal congenital abnormality.

Management

Each case is managed with individualistic approach. Anti-D prophylaxis is offered to all Rh negative women. Once the diagnosis is reasonably established by exclusion of more important causes (not necessarily more common) the management depends on the following conditions:
Emergency in Pregnancy

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- **Nature of bleeding:** Persistent or recurrent
- **Severity of bleeding:** Mild or heavy
- **Gestational age of the fetus:** Term or preterm
- **Fetal condition:** Good or distressed
- **Fetal congenital abnormality:** Present or not
- **Presumed cause:** If possible to ascertain

The management options are either immediate delivery or expectant. The mode of delivery depends on the following conditions:
- State of the fetus
- Fetal lie and presentation
- Cervical condition
- Any other associated high-risk factor.

Once the significant causes of APH are excluded, there is no obvious advantage in managing such patients in the hospital. The patient can be monitored with appropriate advice and to attend hospital immediately, should any emergency arises. The general tendency is to discharge the patient from hospital once the bleeding stops for at least 24 hours.

**VASA PREVIA**

**Introduction**

Vasa previa is the velamentous insertion of the umbilical cord into the placental membranes overlying the lower uterine segment. As a result, the fetal vessels appear between cervix and the presenting part. Despite being very rare in incidence (0.03%), associated very high perinatal mortality made rapid intervention essential for fetal survival.

**Risk Factors**

Risk factors for vasa previa include in vitro fertilization, placenta previa, and bi-lobed and succenturiate-lobed placentas.

**Presentation**

Vasa previa typically manifests as unanticipated bleeding at the time of amniotomy or spontaneous rupture of membranes.

**Diagnosis**

The condition is considered when fetal vessels are seen or felt during vaginal examination. Rarely, vessels are palpated in the presenting membranes, prohibiting artificial rupture of the membranes and vaginal delivery. Antenatal diagnosis is possible by color Doppler visualization of fetal vessels by endocavity USG. CTG shows characteristic sinusoidal pattern or baseline fetal tachycardia or bradycardia.

The hemorrhage is fetal blood, and exsanguination can occur rapidly. Alkali denaturation test (APT) (based on the principle of fetal hemoglobin’s ability to withstand alkali denaturation) confirms the fetal source of bleeding. A blood sample from the vaginal vault may be obtained to check for fetal blood cells or fetal hemoglobin.

**Management**

Suspicion, diagnosis and immediate delivery are the crucial steps in the management of vasa previa. Delivery by immediate lower segment cesarean section (LSCS) is the only way to salvage the fetus. Delivery should not be deferred for confirmation of fetal blood in women with severe hemorrhage or when CTG is nonreassuring.

Management guidelines for vasa previa:
1. Emergency cesarean section in the presence of bleeding
2. Elective cesarean section prior to the onset of labor
3. Admission to hospital with appropriate neonatal facilities from 28 to 32 weeks of gestation
4. Corticosteroids for fetal lung maturity
5. Laser ablation in utero may be tried in well equipped centers.

**Prevention**

There are no strategies for primary prevention of vasa previa. Theoretically, the complications of vasa previa could be avoided by antenatal screening of high-risk women and by performing CS at 37–38 weeks when vasa previa is present. Screening can be carried out with transvaginal color-flow Doppler to identify the presence of vessels in the fetal membranes. Although it has been suggested for women at increased risk, there is no evidence that screening in a general population changes outcomes, and because the condition is rare (one diagnosis per 5,215 screenings), this approach is also cost prohibitive.

**Fetal Risks**

Studies demonstrate a 33–100% rate of perinatal mortality secondary to vasa previa.

**Summary: Unclassified Bleeding**

- Diagnosis is made by exclusion of other causes
- Vasa previa must be confirmed or excluded
- Increases the overall risk of adverse perinatal outcome.

**REFERENCES**


Tumors During Pregnancy: Management

**TUMORS ARISING FROM REPRODUCTIVE ORGANS**
The following tumors can arise from the reproductive organs:
- Ovarian tumor
- Fibroid tumor
- Carcinoma of cervix.

**TUMORS ARISING FROM NONREPRODUCTIVE ORGANS (INTRA-ABDOMINAL)**
The following tumors arise from nonreproductive organs (intra-abdominal):
- Omental cyst
- Broad ligament tumors
- Parovarian cyst
- Retroperitoneal tumor.

**TUMORS ARISING FROM EXTRA-ABDOMINAL ORGANS**
The following tumors can arise from extra-abdominal organs:
- Breast cancer
- Non-Hodgkin’s lymphoma
- Peripheral primitive neuroectodermal tumor.

**OVARIAN TUMORS DURING PREGNANCY**
Tumors which can arise from ovaries during pregnancy are as follows:
- Teratoma (90%) mature, immature and with malignant germ cell tumor components
- Dysgerminoma, embryonal carcinoma, endodermal sinus, yolk sac tumor, choriocarcinoma, gonadoblastoma, polyembryoma
- Epithelial origin—serous adenoma, mucinous cystadenoma.

**Diagnosis**

**Symptoms**
Patients may come with amenorrhea along with dyspnea, undue enlargement of abdomen, retention of urine, and occasionally acute abdomen. Lump abdomen, pain and fever may be associated after delivery.

**Signs**
During early pregnancy cystic mass is detected apart from pregnancy whereas in late pregnancy with tumor lying above the pelvic brim two separate masses, one being the tumor commonly lying at the loin and other containing the fetus having intermittent contractions were found.
Investigations
In addition to blood and hormonal profile, ultrasonography, computed tomography scan or magnetic resonance imaging (MRI) can be advocated to confirm diagnosis. Sonographic features help to differentiate the benign from the malignant lesions, i.e. septa more than 3 mm, solid areas, ascites and irregular inner wall.
- CA-125 and DNA ploidy test are also helpful to know malignant nature of tumors.

Effect of Ovarian Tumors on Pregnancy and Labor
- Abortion and preterm labor in large and complicated tumors
- Pressure symptoms to bladder and rectum
- Malpresentations and nonmanagement
- Obstructed labor: If a pedunculated tumor is impacted in the pelvis.

Effect of Pregnancy and Labor on Ovarian Tumors
- Torsion is the most common complication particularly in pedunculated tumors that lie above the pelvic brim. It is more common during puerperium than pregnancy due to:
  - Lax abdominal wall
  - Large intra-abdominal space after birth allows free mobility of the tumor
- Hemorrhage
- Rupture
- Infection
- Rapid growth.

Management
During Pregnancy
- Cyst less than 6 cm in diameter is left and followed up by periodic examination and ultrasound as it is usually a functional corpus luteum cyst
- Cyst of 6 cm or more in diameter:
  - Discovered in the first half of pregnancy: It is removed after the twelfth week when the placenta is formed so there is less liability for abortion
  - Discovered in the second half of pregnancy: It is left to be removed in the first week of puerperium
- Complicated or malignant tumors are removed immediately irrespective of the duration of pregnancy
- In case of twisted ovarian tumor—untwisting to be followed by one side ovariectomy/ovarian cystectomy. In borderline tumor, ovariectomy is the choice of treatment. In case of suspected malignancy, unilateral salpingo-oophorectomy along with ovarian biopsy in opposite ovary. Counseling regarding the potential risk is to be properly implemented.

During Labor
- If the tumor lies above the pelvic brim—causing no obstruction—vaginal delivery is allowed and tumor is removed in the first week in puerperium.
- If the tumor is impacted in the pelvis causing obstruction—cesarean section with immediate removal of the tumor is done.

During Puerperium
Tumors discovered for the first time should be removed immediately for fear of torsion. In case of bilateral salpingo-oophorectomy—in vitro fertilization with ovum donation it to be advised. In few cases, chemotherapy is advocated.

Effect of Pregnancy and Labor on Fibroid
- Abortion: Particularly in submucous myomas due to:
  - Distortion of the uterine cavity,
  - Affection of the decidual development,
  - Affection of the vascular supply to the implanted ovum
- Ectopic pregnancy: If it interferes with the passage of the ovum
- Incarceration of retroverted gravid uterus in case of posterior wall fibroid
- Placenta previa due to interference with implantation of the ovum in the upper uterine segment
- Malpresentations
- Abdominal discomfort if the tumor is large
- Torsion of the uterus is very rare in subserous fundal myoma
- Premature labor due to premature contraction of uterus
- Nonmanagement in case of cervical fibroid (both anterior and posterior)
- Prolonged labor: Inertia may be present due to interference with normal uterine contractions
- Obstructed labor: In cervical myoma or pedunculated subserous myoma impacted in the pelvis
- Postpartum hemorrhage due to:
  - Interference with uterine retraction
  - Increased vascularity
- Subinvolution of the uterus due to large sized uterus and delayed involution
- Inversion of the uterus—rare
- Puerperal sepsis due to subinvolution and ascending infection.

Effect of Pregnancy and Labor on Fibroid
- Increase in size due to:
  - Edema and increased vascularity
  - Hypertrophy of the uterine muscles
• Softening due to edema and increased vascularity
• Red degeneration
• Torsion of a pedunculated myoma
• Internal hemorrhage from rupture of a surface vein
• Infection supervenes due to bruising during labor
• Extrusion of submucous myoma may rarely occur in puerperium.

Management

During Pregnancy

• No treatment is indicated in the majority of cases
• Myomectomy carries the risk of abortion and severe hemorrhage so it is indicated in the following conditions only:
  - Red degeneration which is not responding to the conservative treatment in the form of:
  - Rest, analgesics, antibiotics to guard against secondary infection
  - Give progesterone before and after the operation, and remove the affected tumor only
  - Torsion of a pedunculated myoma
  - Internal hemorrhage from rupture of a surface vein.

During Labor

• If the myoma lies above the pelvic brim not causing obstruction, vaginal delivery is allowed and myomectomy is done after 3–6 months, if indicated.
• If the myoma lies in the pelvis causing obstruction cesarean section is indicated, but myomectomy is contraindicated.

Postpartum

• Give prophylactic antibiotics
• Observe for postpartum hemorrhage.

Management of Cancer Cervix with Pregnancy

Premalignant Lesions

In women with preinvasive lesions confirmed on histology, a close follow-up throughout the pregnancy must be maintained with cytology and colposcopy every 6–8 weeks, and biopsy performed if there is suspicion of progression of disease. When 62 women with high-grade squamous intraepithelial lesion (HSIL) were followed, the lesion regressed in 50% (complete regression in nearly half of these), persisted in 40.3% and progressed to microinvasive carcinoma in 9.7% (6 cases). Of the 82 women followed during pregnancy with a diagnosis of low-grade squamous intraepithelial lesion, complete regression occurred in 48.8%, persistence in 29.2% and progression to HSIL in 22%.

Microinvasive Carcinoma

Women with suspected invasion on cytology or colposcopy must be treated with conization. In 23 women, who underwent conization for suspect early invasion, there were six cases (26.1%) of microinvasive carcinoma and 17 cases (73.9%) of HSIL. One pregnancy aborted 2 days after the conization. Cone biopsies, as explained earlier, taken in pregnancy are shallower, therefore positive margins are common in pregnancy. Re-evaluation must be done 8 weeks postpartum and retreatment done if required.

Carcinoma of the Cervix

This involves one of the most difficult decisions in all obstetrics. The case for radical hysterectomy is a strong one in gravid carcinoma of the cervix. The operation is likely to cause considerable blood loss, but is facilitated technically by the great ease with which the tissue planes can be dissected. The chances of encountering an operable stage or early stage disease are high in pregnancy as nearly 75% are diagnosed with stage I disease.

The treatment plan would depend on a number of factors: the period of gestation, the stage of the disease, and the desire to continue pregnancy and preserve future fertility. Accurate staging is important keeping the pregnancy in view. Imaging involving the least radiation to the fetus should be employed. An ultrasound can be done to exclude liver and urinary tract involvement and an MRI may be helpful in detecting extension of disease in the pelvis and lymphadenopathy. An X-ray chest can be performed with abdominal shielding in advance disease.

When diagnosed in early pregnancy, (an arbitrary upper limit varying between 12 weeks and 16 weeks is taken), definitive treatment for the disease must be instituted disregarding the pregnancy. When the diagnosis is made in late second or third trimester, where fetal maturity can be obtained within 6–12 weeks, an informed decision to postpone treatment for cancer may be taken. This may be
supplemented with neoadjuvant chemotherapy antenatally, in advance cases, to reduce the risk of disease progression while waiting for fetal maturity.

*Early stage disease (Ia, Ib1, IIa):* The options available for treatment of stage Ia with positive cone margins or early invasive disease before 12–16 weeks are radical hysterectomy and pelvic lymphadenectomy with the fetus in situ, or radiotherapy. External beam radiotherapy can be started with fetus in situ followed by intracavitary brachytherapy following abortion. Abortion occurs spontaneously in most cases, otherwise surgical evacuation can be performed. Surgery is preferred as the treatment of choice in young women as it prevents radiation-associated morbidity, and ovarian function can be preserved. In advance pregnancy, treatment may be delayed after counseling the patient. A caesarean radical hysterectomy with pelvic lymphadenectomy can be performed as soon as the fetus can be salvaged. Antenatal steroids to the mother would help fetal lung maturation.

*Late stage disease (Ib2, IIb, IIIb):* Treatment of pregnant women with late stage disease should be planned with a multidisciplinary approach. The treatment of locally advance cervical cancer is radiotherapy with or without chemotherapy. In early pregnancy, radiotherapy can be started with fetus in situ, as described for early stage disease. In late pregnancy, where fetal maturity has been attained, the fetus should be delivered by cesarean section. Whole pelvic external radiation may be started immediately postpartum followed by intracavitary irradiation. If the mother does not wish to terminate pregnancy, and the fetus is immature, the option of neoadjuvant chemotherapy may be discussed with the mother to postpone definitive treatment, explaining the risks of teratogenesis and fetal growth restriction.

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**Cesarean Versus Vaginal Delivery**

Though there are no prospective trials to evaluate abdominal versus vaginal delivery, cesarean section is almost universally recommended for women with invasive carcinoma cervix for the fear of hemorrhage and dissemination of malignant cells as a result of cervical dilatation. Additionally, cases of recurrence at episiotomy site have been reported after vaginal delivery. Although metastasis may occur at the abdominal scar after abdominal delivery, the risk appears to be less than that of vaginal delivery. Women with premalignant lesions and very early invasive cancers with negative margins on a cone biopsy may consider vaginal delivery.

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**TUMORS ARISING FROM NONREPRODUCTIVE ORGANS (INTRA-ABDOMINAL)**

*They include:* Omental cyst, broad ligament cyst and paraovarian cyst retroperitoneal tumor.

These groups of tumors are occasionally found:
- During ultrasound scanning
- During cesarean section, or
- During laparotomy

*Treatment will depend on:*
- Type of tumors
- Complications (if any), during pregnancy, labor or after delivery. Each case deserves individual consideration on its own merit.
INTRODUCTION
Approximately, 0.2–2.2% of pregnant women requires surgery not related to the gestation itself. In addition, there are no reliable estimates of how often pregnancy is present during the treatment of various surgical conditions, and especially traumatic injuries, which remain the leading cause of maternal and fetal morbidity and mortality. For optimal care of these patients, both surgeons and obstetricians must be familiar with the effects of anesthesia, surgery and trauma on pregnancy, and conversely, how pregnancy may alter the course of surgical diseases.

MATERNAL PHYSIOLOGIC CHANGES RELEVANT TO SURGERY
Gestational changes of importance to surgeons occur in the cardiovascular, pulmonary, hematological, gastrointestinal (GI) and renal systems. Knowledge of these changes allows the physician to interpret findings and laboratory data and to respond appropriately, to alterations in maternal homeostasis.

Cardiovascular Changes
The most obvious cardiovascular changes during pregnancy are those in the traditional vital signs.

- The pulse rate gradually rises to a plateau of 90 beats per minute near the 32nd week of pregnancy. The heart rate depends upon the patient’s position, with the maximum occurring while standing. In contrast, the blood pressure decreases until the 16th–20th week when systolic and diastolic pressures are 5–10 mm Hg and 10–15 mm Hg lower, respectively, than in the nonpregnant state. In a pregnant patient presenting with a surgical illness, this relative tachycardia and hypotension compared to the non pregnant state must not be misinterpreted as early hypovolemic shock.
- Cardiac output rises progressively during early gestation. By the second trimester, it attains levels 30–50% above nonpregnant values. This increase is accompanied by a 15% increase in oxygen consumption above that seen in the nonpregnant state.
- The blood volume increases during pregnancy, with plasma volume increasing more than the red cell mass. The increment in plasma volume is approximately 1.0–1.5 L, and occurs mainly early in pregnancy so that it peaks by 32 weeks’ gestation. The red cell volume only increases by approximately, 300–500 mL, so that hematocrit and hemoglobin fall to a mean of 31% and 10.5 g/dL by the end of the gestation. Greater increases in both plasma volume and red cell mass occur with multiple gestations.
- In addition to receiving a great proportion of the cardiac output, the gravid uterus can exert profound mechanical effects on the circulation during late pregnancy. When patients are placed in the supine position, the uterus may compress the vena cava and cause decreased venous return of blood from the lower extremities. In addition, the uterus may compress the aorta and thus decrease iliac artery flow. Both the arterial and venous obstructions decrease uterine perfusion particularly when compensatory reflexes are blunted by narcotics or anesthesia, the supine position
may result in profound hypotension and markedly decreased uterine blood flow. This hypoperfusion can be disastrous to the fetus. Therefore, the pregnant patient should never be kept in the supine position. This can be avoided by rotating the patient to the left side with the right hip elevated approximately 15° and the uterus manually displaced to the left.

While the cardiovascular changes of normal pregnancy may mimic congestive failure, they may mask early hypovolemic shock. With blood volume increased, 40–50% above non-pregnant levels, clinical signs of hypovolemia such as tachycardia and hypotension may not develop until the patient has lost 30–35% of her blood volume. Thus, uterine blood flow and fetal oxygenation may decrease significantly, long before maternal blood pressure begins to fall. Early recognition of hypovolemia and prompt fluid resuscitation is essential to maintain uterine perfusion. In the presence of hypovolemia, vasoconstrictors may maintain maternal blood pressure while constricting the uterine arteries and further increasing fetal hypoxia. Vasopressors are beneficial only if the increase in cardiac output and perfusion pressure offsets the vasoconstriction in the uterine bed.

Respiratory Changes

Although the diaphragm is elevated during pregnancy, the ribs are displaced outwards.

- The net result is little change in either total lung volume or vital capacity
- However, functional residual capacity is lowered by 15–20% by the end of the fourth month
- Minute ventilation, increases by 40–50%, mainly through an increase in tidal volume. These changes in ventilatory pattern begin in the first trimester
- As a consequence of this hyperventilation, arterial oxygen tension rises slightly to near 105 mm Hg
- However, in one-quarter of all women it may decrease slightly upon assumption of the supine position
- Carbon dioxide tension falls to approximately, 30 mm Hg
- Although renal compensation reduces serum bicarbonate by about 4 mEq/L, arterial pH rises slightly to 7.44.
- Failure to appreciate these normal changes in arterial pH and carbon dioxide tension can lead one to miss an early acidosis or overlook impending respiratory failure.

Pregnancy also results in increased respiratory secretions, with the epithelial lining of the respiratory tract being congested and engorged. Thus, care must be taken during intubations to avoid both hypoxemia and airway trauma. To achieve this, one often must use a smaller-than-usual endotracheal tube. Because of these physiologic changes, problems with airway management are important contributors to maternal morbidity.

Gastrointestinal Changes

Particularly, in the third trimester, pregnant patients are at risk for aspiration during periods of sedation or induction of anesthesia.

- Gastric motility is decreased during pregnancy, and as a consequence, gastric emptying is delayed.
- Because of generalized muscular relaxation, the lower esophageal sphincter is less competent.
- Although the secretion of gastric acid is decreased, nasogastric tube decompression should be considered before the induction of anesthesia.

During pregnancy a history of abstinence from food and drink is not a reliable indicator of an empty stomach.

Changes in Coagulation

- Pregnancy is marked by hypercoagulable state, attributable to increases in coagulation factors V, VII, VIII, IX, X and XII.
- Fibrinogen increases the most, nearly doubling during pregnancy. Plasma fibrinolytic activity decreases because of placental inhibition.
- These coagulation changes, in combination with the increased venous pressure in the lower extremities, increase the risk of thromboembolic disease six times above that of nonpregnant women.

ANESTHESIA DURING PREGNANCY

The concerns related to the use of anesthetic agents, during pregnancy include teratogenicity or fetal toxicity of the anesthetics, and possible effects on the mother and fetus due to alterations in maternal physiology. Although these concerns are real, current evidence suggests that a much more serious threat to both mother and fetus is the severity of the surgical disease under treatment. In addition, there is great difficulty in distinguishing the effects of anesthetics or surgical manipulations from the effects of the illness.

Teratogenicity

Before implantation at 14 days, insults to the concepts generally, result either in death of the embryo or no ill effect. Organogenesis occurs in the 45 days after implantation. During this time, the embryo is vulnerable to non-lethal damage. After the period of organogenesis, the occurrence of structural anomalies is unlikely. However, any risk is unacceptable if it is unnecessary, so that elective surgery should be avoided if possible, during the period of fetal organogenesis (15–56 days gestation). Currently, most halogenated compounds and nitrous oxide are thought to be safe during human pregnancy.
Effects on Maternal Physiology

Given the physiologic changes of normal pregnancy it follows, that anesthetic techniques which cause vasodilatation may compromise uterine oxygen delivery, particularly in a volume depleted patient. Thus, the risks of sympathetic blockade from spinal and epidural anesthesia are increased during pregnancy.

Controlling ventilation and altering maternal blood gas tensions are not without risk. In humans, hypoxia induces vasoconstriction in most vascular beds and a fall in systemic vascular resistance. The exception is the uterine bed in the pregnant patient. Maternal hypoxia or a marked maternal respiratory acidosis induces uterine vasoconstriction. The fetal circulation responds with bradycardia, decreased blood flow, and a fall in oxygen content. The effects of maternal hypocapnia on uterine blood flow are variable. Alkalosis, either metabolic or respiratory, may compromise fetal oxygenation, presumably by causing umbilical artery vasoconstriction as well as shifting the maternal oxyhemoglobin dissociation curve. Finally, positive intrathoracic pressures produced by the ventilator may also depress uterine blood flow.

Another major concern is that surgery and anesthesia may provoke abortion or preterm labor. Duncan et al. reported that patients undergoing surgery during the first or second trimester had twice the usual number of spontaneous abortions.

SPECIFIC SURGICAL PROBLEMS IN PREGNANCY

Appendicitis

Appendicitis is one of the most common surgical complications of pregnancy. The incidence is between 1/1,000 and 1/2,000, which is roughly equivalent to that in the nonpregnant population. Thus, pregnancy does not appear to be a causative factor.

During pregnancy, the cecum is displaced upward. In late pregnancy, the appendix may at times lie as high as the right costal margin but usually is located up to 3 cm above the iliac crest. As the infection becomes more severe and involves the local peritoneum, the pain becomes more constant and localized to the site of inflammation. Thus, during late pregnancy, appendicitis commonly presents as right-flank or upper-quadrant pain. However, adhesions may limit appendiceal displacement by the enlarging uterus and may result in pain in the lower abdomen or even in the lower flank. The onset of crampy pain is typically followed by anorexia, nausea and vomiting. Many of these constitutional symptoms may be misinterpreted as complaints typical of the pregnant state.

Early in the course, the temperature and pulse rate may be normal. Later, low-grade temperature elevations or even a normal temperature may be present. Due to abdominal wall distention and thinning of the muscles, detection of local muscle spasm or rigidity becomes more difficult as pregnancy progresses. The pain may be increased by fetal movement.

Treatment with antibiotics is not indicated in uncomplicated appendicitis. Prompt surgical therapy will minimize maternal and fetal morbidity by preventing progression to rupture and peritonitis. The choice of incision is a matter of personal preference. The patient’s right side can be slightly elevated to improve operative exposure and relieve the pressure of the uterus on the major vessels. Manipulation of the uterus should be kept to a minimum, if there is doubt as to the diagnosis, a midline incision should be used for better access to other viscera.

The effects on the fetus depend upon the severity of the disease. Fetal mortality is 9% when acute appendicitis is diagnosed and promptly treated, but rises to 36% in the presence of peritonitis. Maternal demise may also occur in the presence of peritonitis and overwhelming intra-abdominal sepsis.

Biliary Tract Disease

The incidence of biliary tract disease is between 1/1,000 and 1/2,000 pregnancies. Pregnancy is thought to be contributory to biliary tract disease because of its effects in altering gallbladder function. The high progesterone levels inhibit smooth muscle contractility and the gallbladder volume is increased to twice the nonpregnant size after the first trimester. The rate and degree of emptying are reduced. The high residual volume may promote cholesterol precipitation.

Biliary tract disease during pregnancy may range from intermittent attacks of biliary colic, to acute cholecystitis, choledocholithiasis and biliary pancreatitis. These patients present with symptoms similar to those of the nonpregnant state (i.e. nausea, vomiting and right upper quadrant or epigastric pain with tenderness). Undoubtedly, many mild attacks are overlooked because the complaints may be indistinguishable from those of normal pregnancy. About one-half of women with history of mild gallbladder attacks before pregnancy will develop severe attacks during gestation which require surgery.

Acute cholecystitis may initially be treated with similar conservative measures and antibiotics. However, failure to suppress the infection with such therapy may lead to necrosis or perforation of the gallbladder, with significant risk of maternal death. Therefore, in the absence of immediate improvement, surgery is indicated.

Peptic Ulcer Disease

The most common causes of upper GI bleeding in pregnancy are esophagitis and gastritis. Medical therapy is almost always successful. Peptic ulcer disease generally becomes quiescent as gastric acid levels fall during pregnancy. Thus, complications are distinctly unusual. Bleeding has been
occasionally reported, but can almost always be controlled
with endoscopy or, in rare cases, with transcatheter occlusion.
Perforation of an ulcer is associated with high maternal and
fetal mortality rates unless prompt surgery is undertaken.
Perforations present with the sudden onset of excruciating
abdominal pain, which may be accompanied by nausea and
vomiting. On examination, the patient demonstrates diffuse
abdominal tenderness and involuntary guarding if there is
free perforation into the abdominal cavity.

Suspected perforation of a viscus is an indication for
radiographic evaluation. An erect chest film or plain films
of the abdomen will show free air, more than 95% of the
time. This study should be done in spite of the concern
about radiation exposure to the fetus. Simple repair of the
perforation is the standard surgical treatment.

**Bowel Obstruction**

Fortunately, this condition is rare, occurring only once in every
3,000–6,000 pregnancies. Adhesions after prior operations,
particularly after appendectomy and pelvic surgery are the
most frequent cause. Colonic volvulus, mainly cecal, is the
second most common cause and is responsible for 25% of the
obstructions. Intussusceptions may also cause obstruction,
but is extremely rare.

Obstruction due to adhesions usually occurs during the
first pregnancy after abdominal surgery. Pregnancy may play
a role in that the enlarging uterus displaces the bowel. Existing
adhesions may limit motion and thus lead to obstruction.
Postpartum obstruction may result when the uterus rapidly
decreases in size and returns to the pelvis.

Patients with bowel obstruction present with an abrupt
onset of crampy abdominal pain associated with hyperactive
peristaltic rushes heard on auscultation. Since, the small
bowel and cecum are midgut structures, the pain is generally
perceived as periumbilical. The pain is accompanied by
nausea, vomiting and constipation. As time passes, the
peristalsis decreases and the abdomen finally become
silent. Abdominal distension may be marked, although this
can be difficult to appreciate in late pregnancy. The patient
may continue to pass flatus or stool which is distal to the
obstruction. This should not mislead the physician into
discarding the diagnosis of bowel obstruction. Intestinal
infarction may not be ascertainable until shock supervenes.
At this point, more than one-half of all patients go into pre
term labor. Suspected obstruction is one of the few abdominal
conditions in which X-rays are clearly indicated. With small-
bowel obstruction, the supine film classically shows dilated
small-bowel loops containing air which produce the familiar
“ladder” pattern of air/fluid levels on the upright film.

Prompt and adequate fluid resuscitation is essential.
Nasogastric tube decompression should be performed and
the patient prepared for surgery. Hill et al. reported an overall
mortality rate of 10%, primarily due to sepsis and shock, with
a 3.3–50% incidence of fetal demise.

**Intra-abdominal Hemorrhage**

There are many possible sources of intra-abdominal bleeding
during pregnancy. Pre-existing aneurysms may rupture
during pregnancy. In some cases, the bleeding seems to have
arisen spontaneously from normal vessels. In other cases,
there may be no history of antecedent injury, but the bleeding
may be related to the occurrence of a minor, unremembered
trauma. In cases of massive bleeding, diagnostic studies
are foregone and the source of bleeding is established
intraoperatively.

Toxemia of pregnancy or maternal hypertension are
frequent, underlying causes of rupture of the liver during
pregnancy. Toxemia results in necrosis at the periphery of
the hepatic lobules. The necrotic areas become confluent,
resulting in a subcapsular hematoma which proceeds to
rupture. Bleeding occurs late in pregnancy, particularly in
preeclamptic patients. These women may have complained
of chronic epigastric or right hypochondral pain. In addition
to surgical control of bleeding, termination of the pregnancy
often is needed to reverse the underlying pathologic changes.

The surgical treatment of hepatic hemorrhage must be
individualized. In some cases, ligation of bleeding vessels
or mattress suturing of the bleeding area may suffice. In
others, partial lobectomy may be required. External drainage
of the hepatic bed is generally indicated because of the risk
of continued oozing. Replacement of clotting factors and
platelets correct the consumptive coagulopathy associated
with massive hemorrhage.

Splenic artery aneurysms are another source of intra-
abdominal hemorrhage, generally during the third trimester
of pregnancy possibly, the mechanical stresses associated
with displacement or increased intra-abdominal pressure
lead to rupture of a pre-existent aneurysm already weakened
by the medial changes associated with pregnancy. Splenic
aneurysms are often multiple or accompanied by aneurysms
elsewhere in the visceral arteries.

Rupture of the spleen itself is a rare complication of
pregnancy and may appear to be spontaneous or result
from prior trauma, either recent or remote in time. Prompt
splenectomy is required to control the bleeding.

Uterine and ovarian vessels may also rupture, particularly
during labor. Suture ligation, hypogastric artery ligation or
even hysterectomy may be needed to control hemorrhage.

Unfortunately, the sources of hemorrhage described
above are associated with rapid egress of blood from the
maternal circulation. Maternal mortality is about 15%, while
fetal loss is up to 70% in these cases. In late pregnancy,
emergency cesarean section may be employed to save the life
of the fetus. Other complications of emergency surgery, such
as infection or consumptive coagulopathy, are common after these operations.

**Anal Pathology**

Pregnancy tends to exacerbate problematic hemorrhoids. Sitz baths often relieve the pain of sphincter spasm. Dietary fiber supplementation may aid in controlling constipation. Prolapsed hemorrhoids should be manually replaced after each bowel movement. Clots should be removed from thrombosed hemorrhoids if the patient is in severe pain. Intractable bleeding is rare. Thus, conservative management generally suffices until after delivery.

Anal fissures may occur during pregnancy and are characterized by pain exacerbated by bowel movements. They generally respond to conservative therapy directed against constipation. If anorectal abscesses occur they should be drained promptly. If the infection penetrates beyond the external sphincter, an ischiorectal abscess may develop with systemic sepsis. If drainage of the abscess leads to development of a chronically draining fistula, definitive surgery can be postponed until the postpartum period.

**Hernias**

The displacement of intestine caused by the gravid uterus tends to empty lower abdominal hernias of their contents. As pregnancy progresses, even umbilical and suprapubic hernias are found devoid of bowel contents because of the enlarging uterus. If a hernia is reducible, it may be observed and repaired after delivery. If a hernia is not reducible, one must consider the possibility that adhesions have fixed the contents to the sack. As pregnancy progresses, obstruction or strangulation may occur. Accordingly, repair should be considered early in pregnancy for irreducible hernias.

**Cervical Cancer**

The most frequently diagnosed neoplasm of pregnancy is cervical cancer, with an incidence of 1/1,200 pregnancies. The great majority occur in multiparous women and are squamous in cell type. If diagnosed in the first trimester, termination of the pregnancy should be strongly considered if invasive disease is to be cured. The fetus may be delivered in utero, if radical hysterectomy is indicated. Later in pregnancy, hysterectomy may be required before radiation therapy. If the pregnancy is advanced, consideration should be given to waiting for fetal viability, particularly if microinvasive carcinoma is found at biopsy. However, there are no guidelines, defining a safe waiting period. These cancers, regardless of cell type, are not hormonally responsive. Therefore, pregnancy seems to have no effect on the prognosis of cervical cancer.

**Breast Cancer**

Breast cancer is discovered in 1/3,000 pregnant women. Examination of the breasts, and therefore, early detection, is more difficult than in nonpregnant patients. In the post-partum period, continued engorgement due to lactation also makes detection difficult. Cytologic specimens may be difficult to interpret due to the pregnancy related cellular hyperplasia. Unfortunately, about 41% of the patients present with advanced disease and in very rare cases the fetoplacental unit may be involved. Even with the recent evidence in favor of limited resection and radiation, modified radical mastectomy and axillary node dissection should be considered to avoid fetal irradiation.

**Melanoma**

Melanomas account for 8% of the cancers associated with pregnancy. This is the most frequent cancer to metastasize to the placenta and then to the fetus. Yet this is an extremely rare event. Although melanocyte-stimulating hormone (MSH) is increased in pregnancy, the influence of pregnancy on malignant melanomas is uncertain, with some authors reporting progression and others no effect on the lesions. It is clear that some melanomas do have estrogen receptors. However, there are no documented survival differences between pregnant and nonpregnant patients with melanoma.

**Ovarian Cancer**

Ovarian cancer is a rare tumor, with an incidence of 1/20,000 pregnancies. Epithelial cell and germ cell tumors predominate. Detection relies upon physical examination in early pregnancy or upon ultrasound examination, later on. Fortunately, only 2–5% of ovarian masses in pregnant patients are malignant. Any mass greater than 5 cm in size, which is solid on ultrasound examination should be an indication for exploration, if it persists into the second trimester. Complications such as torsion, rupture, bowel obstruction, or development of ascites mandate intervention. If a neoplasm is found, exploration of the contralateral ovary and staging by omentectomy, examination of the retro-peritoneum, and sampling of enlarged lymph nodes is necessary. Alkylating agents are often used for chemotherapy because of their lesser effect on the fetus.

**Hematologic Malignancies**

Although, leukemia is very rare in pregnancy, lymphoma is not. The incidence of lymphoma is 1/1,000–1/6,000 pregnancies, and after melanoma it is the most common neoplasm to involve the fetoplacental unit. Roughly, one-third of cases are Hodgkin’s disease. Staging laparotomy is generally...
Emergency in Pregnancy

not required for non-Hodgkin’s lymphomas, and in fact is not usually required even for Hodgkin’s disease. Therapy must be individualized. Early in pregnancy, particularly in advanced disease, termination of the pregnancy may be considered to allow effective therapy. Combination chemotherapy is generally required for non-Hodgkin’s lymphoma and poses significant risks to the fetus. For Hodgkin’s disease, radiation may be the treatment of choice for disease above the diaphragm. However, mantle-field radiation, even with shielding, may pose unacceptable risks to the fetus. Otherwise, chemotherapy is indicated. Occasionally, vinblastine, which seems to have minimal fetal effects, is used as a temporary measure while awaiting fetal maturity.

The diagnosis of cancer during pregnancy is an extremely traumatic event. Each patient deserves an individualized treatment plan after assessing the likely effects of therapy or its delay on the fetus and the mother. Many recent reviews of cancer during pregnancy, provide data upon which suitable recommendations can be made.

Neurosurgical Conditions

Spontaneous subarachnoid hemorrhage, is the most common cerebrovascular catastrophe associated with pregnancy. The initial symptoms are sudden headache, nausea, vomiting and nuchal rigidity, which can be followed by seizures or local neurologic deficits. Aneurysmal rupture occurs in approximately, 1/2,000–1/10,000 pregnancies and carries a mortality of more than 25%. Cerebral bleeding is frequent enough to account for 5–25% of all maternal deaths. About 5% of the population have unruptured intracranial aneurysms. Most authors feel that pregnancy appears to have little or no effect on the incidence of rupture. Aneurysms are more frequent in the anterior portion of the circle of Willis, and are multiple in 20% of patients. They are congenital, and rupture may be precipitated by hemodynamic changes. In pregnancy, ruptures cluster in the 3rd trimester. Arteriovenous malformations account for an equal number of subarachnoid hemorrhages. Bleeding occurs in a random fashion throughout pregnancy. They occasionally may occur in the spinal cord rather than the brain.

Angiography, usually demonstrates the structural abnormality causing the bleeding. Treatment must be individualized. Some patients may require surgery before delivery. Therapeutic embolization may be successful in preventing further bleeding. In patients with known, un-corrected aneurysm, labor does not appear to increase the incidence of rupture. Yet cesarean section, may be appropriate if the patient recently bled and there was no surgical correction. Even then, successful spontaneous vaginal delivery has been reported.

Pregnancy seems to increase cerebral edema in patients with neoplasms of the brain. Decisions about therapy and continuation of the pregnancy must be individualized depending upon the length of pregnancy, the symptoms, the type of tumor, and the expected prognosis. Pituitary adenomas often enlarge and sometimes cause neurological symptoms. Magyar and Marshall reported that 25% of their patients complained of headaches or developed visual disturbances during pregnancy. Thirty percent of these patients required surgical intervention or radiotherapy during pregnancy. If the tumor size remains stable throughout pregnancy or causes minimal symptoms, it will frequently regress in the postpartum period.

Cardiac Surgery

There is an increased incidence of prematurity and intrauterine growth retardation with uncorrected cyanotic congenital heart disease. Almost all types of cardiac surgery have been carried out during pregnancy, often using cardiopulmonary bypass. Two of the most common surgical problems are the existence of abnormal or prosthetic valves, and pregnancy in a patient at risk of aortic rupture.

Among the many hemodynamic derangements associated with maternal heart disease, pulmonary hypertension is the most dangerous. It is associated with a maternal mortality of 30–50%. Pregnancy should be avoided or interrupted. In particular, mitral stenosis from rheumatic heart disease is a common valvular defect. Twenty-five percent of women with pre-existing mitral stenosis develop pulmonary edema during pregnancy. The cardiac output is fixed in these women. If they require general or obstetric surgery during pregnancy, they can be managed with appropriate support of ventricular preload. If medical management of mitral stenosis is ineffective, percutaneous or closed valvulotomy can be performed with the same operative risk as in nonpregnant women. If this is not possible, valve replacement can be undertaken. Fetal loss occurs in 10–20% of these patients.

During pregnancy, reported complications of prosthetic valves include thromboembolism despite anticoagulants, red cell and platelet destruction by the prostheses, hemorrhage due to excessive anticoagulation, and bacterial endocarditis. Cardiac function may deteriorate, or the prosthetic valves may not function well or may even clot. Careful follow-up during gestation may minimize these complications. Cardiac surgery, if required, should be done before the third trimester, if possible.

Among the congenital lesions, surgery for coarctation of the aorta is the most important. Because of degeneration in the aortic media, ruptures may occur due to the hemodynamic changes of pregnancy. In patients who have not undergone correction prior to pregnancy, maternal mortality has been reported to be 3.5% due to rupture, congestive heart failure, endocarditic, or central nervous system (CNS) bleeding. Therefore, a newly discovered coarctation of the aorta during pregnancy should probably be repaired.

Marjan’s syndrome predisposes women to rupture of the aortic root. In fact, 50% of the aortic ruptures occur during pregnancy. Minimal cardiac involvement generally indicates
a safe clinical course during pregnancy. The risk of rupture is directly related to abnormalities of the aortic valve and a root diameter greater than 40 mm.

**TRAUMATIC INJURIES DURING PREGNANCY**

**Blunt Trauma**

Trauma is the leading nonobstetric cause of maternal mortality, accounting for 20% of maternal deaths. Minor injuries frequently occur, and do not seem to lead to fetal loss. Fetal demise from major blunt trauma increase from 8.8% in the first trimester, to 40–50% during the second and third trimesters.

Blunt trauma may result from rupture of the membranes and in preterm labor. In more serious injuries, the gravid uterus may be ruptured. Rupture of the uterus commonly occurs at the third trimester, but is rare before the second trimester. Occasionally, blunt trauma may result in fetal injury, particularly when the pelvis and lower abdomen receive large impact forces. Diagnosis of intrauterine fetal injury may be difficult. Fetal skull fractures and neurologic trauma are the most frequent findings at autopsy or at birth. Placental abruption is the most frequent cause of fetal demise when the maternal injuries are not lethal. The separation may manifest at the time of injury or later, with the great majority of them in the first 24 hours. For this reason, even seemingly moderate blunt trauma should be considered as an indication for fetal heart rate monitoring and observation for 24–72 hours. Placental abruption is the most common cause of acute disseminated intravascular coagulation after trauma.

In addition to placental separation, the fetal surface of the placenta may tear and lead to fetal hemorrhage. The fetal distress which results can be detected by fetal heart rate monitoring.

**Penetrating Trauma**

Damage to the uterus from penetrating trauma increases in frequency, as pregnancy progresses and is associated with a high fetal mortality rate. However, it is possible for the fetus to survive minor intrauterine injuries. Interestingly, intrauterine healing differs from that in the neonate. In early pregnancy, there is local mesenchymal proliferation without repair of the exposed tissues. There is no capillary proliferation, leukocyte infiltration, or formation of granulation tissue. After the 20th week of gestation, healing mechanisms become more like those in the neonate, except that wounds heal slowly. While penetrating injuries to the upper abdomen may cause damage to maternal intra-abdominal organs. Franger et al. recommended conservative management of gunshot injuries if:

- The mother is hemodynamically stable
- The entrance wound is below the uterine fundus
- There is no evidence of blood in the GI or urinary tracts
- The bullet can be demonstrated within the uterus.

This management scheme is even more applicable to knife injuries and parallels the development of conservative management of stab wounds in nonpregnant patients.
Critical Care in Obstetrics: An Overview

INTRODUCTION

Critical care or intensive care includes monitoring and definitive therapy of patients with acute but reversible life-threatening illnesses or injuries, and is reserved for patients with potential or established one or more multiple organ system failure (MOSF). The purpose of the intensive care units (ICUs) is to ensure timely and rapid intensive care that cannot be provided in general wards. Since the past 2 decades the importance of critical care in obstetric patients has been realized; however, there are few reports in the international literature of obstetric ICUs (OICUs), and most of the hospitals treat the critically ill obstetric patients in the general ICU (GICU) or the medical/surgical ICU. This is probably because critical care is expensive and the developing countries with high maternal mortality ratios (MMR), who actually need these OICUs, probably do not have adequate resources to establish them.

The MMR in India is 3 per 1,000 livebirths. The major causes of maternal death in India are hemorrhage (38%), sepsis (11%), abortion (8%), hypertensive disorders (5%), obstructed labor (5%) and other conditions (34%). Anemia and viral hepatitis are important indirect causes of maternal deaths in India. Preventive medicine can avert majority of these deaths; however, timely institution of critical care is important to prevent a significant number of these deaths.

Civetta has described three groups of patients for ICU care:
- Physiologically stable patients who need intensive observation
- Physiologically stable patients who need extensive nursing care and monitoring (frequently of an invasive nature)
- Physiologically unstable patients who require constant nursing and physician care.

Critically ill obstetric patients requiring admission to an ICU include those with:
- Hemorrhagic shock
- Septic shock
- Eclampsia and complicated preeclampsia
- Severe anemia with cardiac failure or pregnancy-induced hypertension (PIH) or sepsis or in labor
- New York Heart Association (NYHA) classes III and IV cardiac disease, especially those with PIH, anemia, or in labor
- Hepatitis with coagulation failure, encephalopathy or oliguria
- Disseminated intravascular coagulation
- Diabetic ketoacidosis
- Acute pulmonary injury and respiratory failure
- Severe hyperthyroidism.

The majority of reports state that hemorrhage, hypertensive disorders of pregnancy and sepsis are the main indications for admission to the ICU.

COSTS OF INTENSIVE CARE

Intensive care is expensive and the costs should be considered at the microeconomic and macroeconomic levels.
- Microeconomic cost is the cost of managing one patient in an ICU at the hospital level, and varies with the diagnosis and severity of illness. The cost in a tertiary ICU in India (1991) was reported to be ₹3,200 per day, but is now probably around ₹15,000 per day. In the USA although ICUs account for only 5% of all hospital beds, the cost of
care for these patients is approximately 20–28% of total hospital costs.¹³

- Macroeconomic cost is the cost of ICUs at the national or regional level. This is 0.2% of gross national product (GNP) in Canada and 0.8% of GNP in the USA.¹⁴ Data for India are not available.

To rationalize services and optimize resource utilization, health policies should ensure cost-effectiveness of an OICU. A prospective needs evaluation should be undertaken and there should be a demonstrated need for the proposed service. A hospital that caters to a small number of booked cases may not require an OICU; in such hospitals, special cubicles can be made to deliver these women in the GICU. In contrast, a tertiary or large government run hospital that caters to a large number of unbooked cases reporting in advanced pregnancy or in labor (majority from the low socioeconomic strata) would benefit from an OICU.

Reports in the literature have stated that the utilization rate of the ICU to range from 0.11% to 0.89% of all deliveries,¹²,⁶-¹¹ with majority reporting a rate of 0.2% of all deliveries.⁷,⁸,¹⁵,¹⁶ The maternal mortality amongst obstetric patients admitted to the ICUs is reported to vary from 3.3%³,¹⁷ to 28%;⁷ this probably reflects the differences between the patient populations.

It is important to emphasize that the recommended standards for an ICU should include the— in terms of space, staff and equipment; otherwise, the very purpose of the ICU will be defeated. I have described details regarding the organization of an OICU earlier.³

**NEED FOR AN OBSTETRIC ICU**

Care of the critically ill pregnant woman is a challenge to the clinician as these patients represent a potential mortality of 200% (mother and fetus). The patient’s disease and the therapy affect two individuals with vastly differing physiologies. The pregnant woman undergoes dramatic physiologic and physical changes that have to be borne in mind when instituting critical care. With improvement in antenatal care the number of ICU admissions for obstetric cases would decline in developing countries; however, this trend may be offset by the rising trend of increasing maternal age and pregnancies in women with complicated chronic medical disorders.

**INVESTIGATIONS TO BE DONE IN THE CRITICALLY ILL OBSTETRIC PATIENT**

These include those that can establish or rule out organ system failure (OSF) and those that are specific for the particular case. Tests for fetal viability and monitoring (after 30 weeks of gestation) should be performed when indicated. Various imaging studies including X-rays should be performed when indicated, keeping the exposure to ionizing radiation to the minimum and using a lead shield for the abdomen, whenever possible. These are listed in Table 1.

The frequency of testing will depend upon the condition of the patient.

**FACTORS AFFECTING OUTCOME OF CRITICAL ILLNESS**

The outcome of any illness depends upon the following patient factors—age, the specific disease and its severity, physiologic reserve and the response to therapy. Chronic diseases decrease the physiologic reserve. The type, timing and amount of therapy also determine the outcome. The key to success in the treatment of critically ill patients is the timely recognition of the need for intensive care and to administer it immediately by qualified personnel. The obstetric and anesthesiology staff has an important role to play in triaging women for intensive care. Obstetric patients at the extremes of the reproductive age (< 18 years and > 40 years) are at an increased risk for a poor outcome because of the associated social problems (unmarried pregnant teenagers and multiparous women with chronic diseases undergoing illegal abortion).

**ILLNESS SEVERITY SCORING SYSTEMS**

Prognostic stratification can help in determining the need for admission to the OICU and treatment decisions. Several scoring systems have emerged over the recent years to stratify severity of illness, and help in predicting outcome of illness.

### Table 1: List of investigations that should be done in critically ill obstetric patients

<table>
<thead>
<tr>
<th>Baseline, in all patients</th>
<th>Additional tests, as indicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin, hematocrit, white blood cell count, platelet count, PT, aPTT, serum sodium, potassium, creatinine, bilirubin, AST, ALT, ALP, blood urea, arterial pH, arterial HCO₃, PaO₂, PaCO₂ and blood sugar</td>
<td>Chest X-ray, ECG, creatinine clearance, serum proteins, serum albumin, serum ammonia, blood fibrinogen levels, blood levels of FDP, ultrasonography of uterus for fetal monitoring, NST and any other specific tests like CAT scan of brain</td>
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</table>

Abbreviations: PT, prothrombin time; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; HCO₃, bicarbonate; PaO₂, partial pressure of oxygen in arterial blood; PaCO₂, partial pressure of carbon dioxide in arterial blood; ECG, electrocardiogram; FDP, fibrin degradation products; NST, nonstress test; CAT, computed axial tomography
Emergency in Pregnancy

There are a few reports on the use of these scoring systems in pregnant women; the Acute Physiology and Chronic Health Evaluation II (APACHE II) score, has been evaluated maximally. Except for the study by El-Solh and Grant all other reports have shown that the actual mortality rate is lower than the predicted rate. Bhagwanjee et al. have shown that the Glasgow Coma Scale score reflects outcome in eclampsia cases better than the APACHE II score.

**MULTIPLE ORGAN SYSTEM FAILURE**

Knaus and colleagues defined OSF in 1985 and a modification by Rutledge and Sibbald is depicted in Table 2. Increased mortality rates are associated with an increase in the number and duration of OSFs. After only 24 hours, mortality in patients with three or more OSFs is reported to be 90%. Prompt recognition and treatment of patients with potential or established OSF can help in improving survival.

**INVASIVE HEMODYNAMIC MONITORING IN THE CRITICALLY ILL OBSTETRIC PATIENT**

This is seldom required. Indications for invasive monitoring include refractory or unexplained hypotension, oliguria, pulmonary edema and cardiac failure, selected cases of massive blood loss or replacement, acute respiratory distress syndrome (ARDS), amniotic fluid embolism and NYHA classes III and IV cardiac disease in labor or undergoing major surgery.

Invasive monitoring is usually performed through the external or internal jugular vein or the subclavian vein. The femoral and antecubital veins are used less frequently because of difficulty in positioning the catheter. The antecubital vein is preferred in the woman with a coagulopathy.

**Table 2: Definitions of individual organ failure**

<table>
<thead>
<tr>
<th>Organ system</th>
<th>Clinical signs, symptoms, or conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular failure</td>
<td>- Presence of one or more</td>
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<tr>
<td></td>
<td>- Heart rate ≤ 54 bpm</td>
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<td>- Congestive heart failure with chest radiograph and clinical evidence of pulmonary edema</td>
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<td></td>
<td>- Evidence of hypoperfusion with serum pH &lt; 7.30 with normal PaCO₂ or cardiac index &lt; 2.2 L/min/m²</td>
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<td></td>
<td>- Occurrence of ventricular tachycardia or fibrillation</td>
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<tr>
<td>Respiratory failure</td>
<td>- Presence of one or more</td>
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<tr>
<td></td>
<td>- Respiratory rate ≤ 5 breaths/minute or ≥ 40 breaths/min</td>
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<tr>
<td></td>
<td>- PaCO₂ ≥ 50 with pH &lt; 7.35</td>
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<tr>
<td></td>
<td>- A-aDO₂ ≥ 350</td>
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<tr>
<td></td>
<td>- Dependent on mechanical ventilation or CPAP &gt; 3 days</td>
</tr>
<tr>
<td>Renal failure</td>
<td>- Presence of one or more</td>
</tr>
<tr>
<td></td>
<td>- Serum creatinine &gt; 300 µmol/L</td>
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<tr>
<td></td>
<td>- Twice predmission creatinine in cases of chronic renal failure</td>
</tr>
<tr>
<td>Hepatic failure</td>
<td>- Elevated PT (not associated with vitamin K deficiency, DIC, or hemorrhage) with at least twice normal elevation of total bilirubin and elevated AST</td>
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<td></td>
<td>- Associated with metabolic encephalopathy</td>
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<tr>
<td>Hematologic failure</td>
<td>- White blood cell levels ≤ 1,000/mm³</td>
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<tr>
<td></td>
<td>- Platelets ≤ 20,000/mm³</td>
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<tr>
<td></td>
<td>- Hematocrit ≤ 20% without active bleeding</td>
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<tr>
<td>Neurologic failure</td>
<td>- *Glasgow coma scale score ≤ 6 in the absence of sedation or paralytic drugs</td>
</tr>
<tr>
<td></td>
<td>- Polyneuropathy of critical illness</td>
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<tr>
<td></td>
<td>- Encephalopathy</td>
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<tr>
<td>Gastrointestinal failure</td>
<td>- Presence of one or more</td>
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<td></td>
<td>- Stress ulceration</td>
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<td></td>
<td>- Acalculous cholecystitis</td>
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<td></td>
<td>- Pancreatitis</td>
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*Glasgow Coma Scale Score: Sum of best eye opening, best verbal and best motor responses. Scoring of responses are as follows:

- **Eye open:** Spontaneously (4), to verbal command (3), to pain (2), no response (1)
- **Motor:** Obeys verbal command (6), response to painful stimuli, localizes pain (5), flexion-withdrawal (4), decorticating rigidity (3), decerebrate rigidity (2), no response (1)
- **Verbal:** Oriented and converses (5), disoriented and converses (4), inappropriate words (3), incomprehensible sounds (2), no response (1)
- If intubated, use clinical judgment for verbal responses as follows: Patient generally unresponsive (1), patient’s ability to converse in question (3), patient appears able to converse (5).

Abbreviations: bpm, beats/minute; PaCO₂, partial pressure of carbon dioxide in arterial blood; A-a, alveolar-arterial oxygen gradient; DO₂, oxygen delivery; CPAP, continuous positive pressure airway pressure; PT, prothrombin time; DIC, disseminated intravascular coagulopathy; AST, aspartate aminotransferase
Complications of Venous Lines for Invasive Monitoring

- Misinterpretation or overinterpretation
- Pneumothorax—complicates 5% of subclavian and 0.01% of internal jugular vein insertions
- Lethal intrathoracic bleeding during subclavian vein cannulation, with injury to either arteries or veins
- Ventricular and supraventricular arrhythmias can occur during passage of the pulmonary artery catheter as it passes through the right side of the heart
- Massive hemorrhage can occur when the catheter or its introducer get disconnected from the intravenous (IV) lines
- Rare complications include pulmonary artery rupture, pulmonary infarction, sepsis, knotting of catheter, thromboembolism and balloon rupture

It is estimated that invasive monitoring is associated with major complications, including death, in 3% of patients.

Arterial Lines in Critically Ill Patients

These allow continuous monitoring of systemic blood pressure as well as allow easy access for arterial blood gas analysis.

Complications of Arterial Lines

- Sepsis
- Hematoma
- Vessel thrombosis
- Serious complications of gangrene and loss of digit or extremity occur in less than 1% of patients.

Table 3: Representative doses to uterus/embryo from common radiologic procedures

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Dose/study to uterus/embryo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plain X-ray:</td>
<td></td>
</tr>
<tr>
<td>Skull (AP and lateral views)</td>
<td>&lt;0.05 mrad</td>
</tr>
<tr>
<td>Chest (AP and lateral views)</td>
<td>0.02–0.07 mrad</td>
</tr>
<tr>
<td>Lumbar spine (AP and lateral views)</td>
<td>51–126 mrad</td>
</tr>
<tr>
<td>Lumbosacral spine (AP, PA and lateral views)</td>
<td>168–359 mrad</td>
</tr>
<tr>
<td>Abdomen (AP, PA and lateral views)</td>
<td>122–245 mrad</td>
</tr>
<tr>
<td>Hip (single, with AP and lateral views)</td>
<td>103–213 mrad</td>
</tr>
<tr>
<td>Fluoroscopic procedures:</td>
<td></td>
</tr>
<tr>
<td>Cerebral angiography</td>
<td>&lt;10 mrad</td>
</tr>
<tr>
<td>Barium meal</td>
<td>228 mrad</td>
</tr>
<tr>
<td>Barium enema</td>
<td>289–311 mrad</td>
</tr>
<tr>
<td>CAT scans:</td>
<td></td>
</tr>
<tr>
<td>Head (10 slices × 10 mm thick)</td>
<td>&lt;0.05 rad</td>
</tr>
<tr>
<td>Chest (10 slices × 10 mm thick)</td>
<td>&lt;0.10 rad</td>
</tr>
<tr>
<td>Abdomen (10 slices × 10 mm thick)</td>
<td>1.7 rad (5 mm gaps)</td>
</tr>
<tr>
<td>Lumbar spine (5 slices × 10 mm thick)</td>
<td>2.3 rad</td>
</tr>
<tr>
<td>Nuclear medicine studies:</td>
<td></td>
</tr>
<tr>
<td>Lung scan:</td>
<td></td>
</tr>
<tr>
<td>- Perfusion</td>
<td>50 mrad</td>
</tr>
<tr>
<td>- Ventilation</td>
<td>20 mrad</td>
</tr>
<tr>
<td>- Brain scan</td>
<td>700–800 mrad</td>
</tr>
</tbody>
</table>
Hemorrhage, sepsis and hypertensive disorders are important causes of maternal mortality and morbidity in India. Majority is associated with the lethal ARDS. A few points should be remembered with regard to the management of these conditions.

HYPERTENSIVE DISORDERS OF PREGNANCY

Severe cases of preeclampsia aim at lowering the blood pressure to 130/90 mm Hg, but not lower than this. IV drip of nitroglycerine should be started if the diastolic blood pressure is persistently above 120 mm Hg; this should be monitored by continuous electronic measurement (noninvasive) of the blood pressure. It is important to maintain an hourly urine output at 30 mL/hour in order to detect and treat oliguria at the earliest. IV fluids should be administered judiciously to avoid iatrogenic pulmonary edema. In the comatose patient, not responding satisfactorily to drugs, aimed at treating cerebral edema, fundoscopy should be repeated and a computed axial tomography (CAT) scan of the brain is essential. The Hemolysis, Elevated Liver enzymes, Low Platelet count (HELLP) syndrome and disseminated intravascular coagulopathy (DIC) should be diagnosed and treated early; "smoky" urine is often an indicator of a coagulopathy. Fresh whole blood, fresh frozen plasma (FFP) and platelet concentrates should be readily available when such patients are admitted in the ICU.

SEPSIS

Peritonitis due to puerperal sepsis and illegal abortion, and chorioamnionitis are frequently encountered in the obstetric population. These women are at very high risk of progressing to septicemic shock and ARDS. Early drainage of the pus, evacuation of infected uterine contents, termination of pregnancy by Cesarean section, or even hysterectomy in some cases are the mainstay of treatment. Broad-spectrum antibiotics that cover aerobic and anaerobic infections should be started in appropriate dosages. Patients will benefit from IV steroids for the prevention of septicemic shock. Maintaining good tissue perfusion and tissue oxygenation are crucial for the prevention of complications. Hemoglobin level should be maintained above 8.5 g/dL and coagulopathy should be diagnosed and treated at the earliest.

OBSTETRIC HEMORRHAGE

Hemorrhage is common in obstetrics. Blood loss is often underestimated by 30–50%. Patients suffering from antepartum hemorrhage (APH) are at high-risk for postpartum hemorrhage (PPH) and the two frequently occur in the same patient. Conservative treatment in APH should not be unduly prolonged—one can lose the mother as well as the...
fetus. Frequent recurrent bouts of bleeding in a woman who is anemic and undernourished is an indication to terminate the pregnancy irrespective of the period of gestation, because this patient does not have a good physiologic reserve to compensate for a massive bout of hemorrhage. Similarly, conservative measures to treat PPH should not be prolonged. Hysterectomy is lifesaving in cases of intractable PPH, but may not be so if performed too late.

It is important to recognize simple signs that can provide a clue to the severity of blood loss. Table 4 has been developed for the management of trauma patients, and can be applied to the obstetric patients as well.29

In acute hemorrhage, the immediate hematocrit may not reflect the actual blood loss till after 4 hours or more than 32 hours. However, with rapid infusion of crystalloids, more rapid equilibration occurs. The hourly urine output is one of the most important parameters to monitor in the hemorrhaging patient. In the absence of diuretics, the rate of urine output reflects the adequacy of renal perfusion, and in turn, the perfusion of other vital organs because renal blood flow is especially sensitive to blood volume changes. The urine output should be maintained at least at 30 mL/hour, and preferably at 1 mL/kg/hour. If the urine output is not satisfactory despite adequate volume replacement, dopamine should be infused at the dosage of 2 μg/kg/min.

Treatment begins with controlling the hemorrhage and prompt restitution of the blood volume. Crystalloids are used for initial volume replacement and 3 mL of fluid is used to replace 1 mL of estimated blood loss. Crystalloids are better than colloids for resuscitating the bleeding patient.30 Blood transfusion should aim at maintaining the hematocrit above 25% or a hemoglobin above 8 g/dL. Whole blood (preferably fresh) is ideal for the woman with acute blood loss.

In patients with massive blood loss31 FFP and platelet concentrates will be required, if enough fresh blood is not available, to avoid dilutional coagulopathy. Requisitions for these should be made well in advance to avoid delay. In these women, it may be prudent to transfuse screened and typed blood rather than cross-matched blood, as the former is readily available in lifesaving circumstances. Temperature controlled warmers for the fluid and blood (to 37°C) should be available, otherwise hypothermia will ensue.

Women suffering from hemorrhagic shock develop metabolic acidosis and hypothermia as a result of massive transfusion; these result in and exacerbate preexisting DIC. These women also are at high-risk for renal failure and ARDS, and these should be prevented by appropriate management including adequate volume replacement, maintaining the hematocrit above 25%, adequate oxygenation (which may require elective mechanical ventilation) and timely use of dopamine infusion.

Facility for autologous blood transfusion intraoperatively by using the cell-saver should be available in referral hospitals. The use of the military anti-shock trousers (MASTs) should be popularized in obstetrics, especially when the patient is being transferred to a higher center or is undergoing resuscitation before definitive surgery. The MASTs stop almost all bleeding (even arterial) below the renal arteries even in the presence of coagulopathy.32 They can be applied within 3 minutes with the patient in the bed or on the or table after a Foley catheter has been inserted. Usually a pressure of 25–35 mm Hg is sufficient and this can be maintained for 4–8 hours (up to 24 hours).

### ACUTE RESPIRATORY DISTRESS SYNDROME

This is the worst form of respiratory failure, and has a mortality of 40–50% in nonpregnant patients and can be as high as 90% if it was triggered by sepsis.2 Perry and colleagues33 reported a maternal mortality of 25%. Delivery does not improve maternal oxygenation.34 Timely recognition of the conditions that cause this condition, diagnosis in the early stage and prompt institution of appropriate therapy is crucial for lowering the mortality and morbidity due to ARDS. Infection, hemorrhage, preeclampsia and eclampsia are common causes of ARDS in pregnant women. Perry and colleagues noted that more than 70% of women with ARDS have a combination of sepsis, shock, trauma and fluid overload.33

Acute respiratory distress syndrome is a pathophysiological diagnosis, and includes pulmonary alveolar injury sustained via the airways and endothelial injury sustained via the pulmonary vasculature. Chemokines recruit the neutrophils to the site of inflammation; the neutrophils secrete cytokines and initiate tissue injury. This results in increased capillary permeability, loss of lung volume and shunting with arterial hypoxemia.2

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Class I</th>
<th>Class II</th>
<th>Class III</th>
<th>Class IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood loss (%)</td>
<td>15</td>
<td>20–25</td>
<td>30–35</td>
<td>40</td>
</tr>
<tr>
<td>Pulse (beats/min)</td>
<td>Normal</td>
<td>100</td>
<td>120</td>
<td>140</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>Normal</td>
<td>Normal</td>
<td>70–80</td>
<td>60</td>
</tr>
<tr>
<td>Mean arterial blood pressure (mm Hg)</td>
<td>80–90</td>
<td>80–90</td>
<td>50–70</td>
<td>50</td>
</tr>
</tbody>
</table>

### Table 4: Classes of hemorrhage
SECTION 3

36.6% of were methicillin-resistant following resistance rates: 80.8% of all Infection Control Consortium (INICC) ICUs showed the
aggregated data from all International Nosocomial Infections in the ICU

device-associated nosocomial infections in the ICU

These pose a great threat to patient safety, especially in developing countries. Rosenthal et al. reviewed these infections in 55 ICUs of eight developing countries (including India) and reported that 14.7% of patients were infected by these devices. The crude mortality for these infected patients ranged from 35.2% (for central venous catheter-associated bloodstream infections) to 44.9% (for ventilator-associated pneumonia). This report emphasizes the need for active infection control programs with proper surveillance of infection and treatment guidelines for every ICU.

Aggregated data from all International Nosocomial Infection Control Consortium (INICC) ICUs showed the following resistance rates: 80.8% of all Staphylococcus aureus were methicillin-resistant Staphylococcus aureus (MRSA), 36.6% of Pseudomonas spp. resistant to imipenem, 52.4% resistant to ciprofloxacin/ofloxacin, 56.8% Enterobacter spp. resistant to ceftazidime and 68.2% of Klebsiella spp. were resistant to ceftazidime.

THE NEED FOR AN ICU AT THE SUBDISTRICT AND DISTRICT HOSPITALS

A level I ICU with facility for short-term ventilation and 24 hours blood bank facility will go a long way in decreasing maternal mortality in India. Telemedicine can be utilized to provide continuous intensivist care to remote areas. The MAST suit should be recommended for the resuscitation of critically obstetric patients who are suffering from hemorrhagic shock.

CONCLUSION

There is a need for establishing obstetric ICUs in India, especially in the government-run hospitals catering to a large number of unbooked women from the low socioeconomic group. The obstetrician can play a vital role in the successful treatment of the critically ill obstetric patients by the timely recognition of the need for intensive care and ensuring that it is instituted immediately. Aggressive management of life-threatening complications is essential. The key to success is ensuring adequate tissue oxygenation by maintaining cardiac output, maintaining the hematocrit above 25%, and at times, mechanical ventilation.

REFERENCES

Emergency Obstetric Care for Reducing Maternal Mortality

Introduction

Maternal mortality continues to be a burning issue worldwide. Almost 600,000 women in the world die each year from pregnancy-related complications. Fifteen percent of all pregnant women develop life-threatening complications. The problem is more acute in developing countries leading to disability and death amongst women of reproductive years. Twenty percent of global maternal deaths occur in India. Besides every maternal death, there are twenty women who suffer severe morbidity so that their lives are not worth living. Since 70% of India’s population lives in rural areas, there is very high maternal mortality rate (MMR) in these settings due to lack of prompt and adequate treatment. Many programs have been instituted for identifying high-risk pregnancies by antenatal screening to try and address this major problem. Though useful, these efforts have not succeeded in reducing maternal deaths. This is because complications can develop in each and every pregnant patient (high-risk as well as low-risk). As a matter of statistical fact, majority of maternal mortalities are in low-risk patients and hence basic obstetric care must be made available at the grass root levels to all parturient women. Once an unpredictable complication occurs, she will require emergency services. Hence, to make a difference in saving women’s lives quality emergency obstetric care (EmOC) services are required to save a woman who develops life-threatening complications. Quality EmOC poses unusual challenge because EmOC must be available 24 hours a day, 7 days a week to be maximally effective. This is the only way in which we can help in reducing the MMR. Government of India has supported The Federation of Obstetric and Gynaecological Societies of India (FOGSI)/Indian College of Obstetricians and Gynaecologists (ICOGs) efforts of setting up EmOC training centers. This will help in making many first referral centers and district hospitals competent in providing emergency obstetric care. Hopefully, this public private partnership will help to reduce maternal mortality in India. Comprehensive EmOC certificate program has been implemented in 20 states of India.

Maternal Mortality: A Burning Issue Worldwide

Thirteen countries across Africa and South East Asia account for 67% of all maternal deaths. India tops the list. A million or more children are left motherless each year as a result of maternal deaths. Almost half (about 8 million) of perinatal deaths per year results from poor maternal health and inadequate delivery care.

India contributes nearly 47% of maternal death 253,000 deaths per year. One death in every 2 minutes, yet maternal mortality does not make headlines. Dr Fattalah, past president of International Federation of Gynecology and Obstetrics (FIGO) had rightly said that “women are dying because societies have yet to decide whether their lives are worth saving”.

Indian Scenario

India has an unacceptably high maternal mortality ratio of 200/100,000 livebirths as updated by CIA World Fact Book (2010). Twenty percent of Global maternal deaths occur in
India. Besides for every maternal death, there are twenty women who suffer severe morbidity so that their lives are not worth living. These women suffer from long-term disability such as chronic pain, vesicovaginal or rectovaginal fistula, impaired mobility and damage to reproductive system leading to infertility or prolapse of uterus. 70% of India’s population lives in rural areas where MMR is high due to lack of prompt and adequate treatment.

CAUSES OF MATERNAL DEATHS (FIG. 1)

Direct Causes (Fig. 2)

Hemorrhage (postpartum or antepartum) sepsis, complications of unsafe abortion, prolonged or obstructed labor, and hypertensive disorders of pregnancy, especially eclampsia are some of the complications, which can occur at any time during pregnancy and labor and without any forewarning.

These maternal deaths are preventable by evidence-based intervention. A swift and competent EmOC using resources effectively can have a significant impact on pregnancy outcome.

Other Problems that Contribute for Increased Maternal Mortality in India

Maternal mortality is not merely a health disadvantage but also a reflection of social and gender injustice. The low social and economic status of girls and women limits their access to education, appropriate nutrition as well as health and family planning services. All this directly impacts pregnancy outcomes. The overriding causes of high mortality in India are poor access to EmOC in case of a complication and absence of skilled birth attendant at delivery. Any skilled birth attendant also needs the backup of a functioning health system, i.e. having minimal infrastructure for managing life-threatening complications in pregnancy and labor like-availability of life saving drugs, safe blood, functioning operation theater with electricity, running water and anesthetist and 24 hours emergency obstetric care. These infrastructures are lacking in many small towns and villages of India.

KEY STRATEGIES TO SAVE LIFE OF PREGNANT WOMEN

- Skilled birth attendant at delivery
- Emergency obstetric care
- Timely and effective referral system
- Availability of safe abortion services.

WHY FOCUS ON EMERGENCY OBSTETRIC CARE?

Over the past several decades, maternal health programs have used antenatal screening to try to identify women at risk for complications. Though useful these efforts have not succeeded in reducing maternal deaths. It is proved by many studies that many women who develop complications do not have any known risk factors. Once an unpredictable complication occurs, she will require emergency services. As a result, 24 hours, quality EmOC services will be required to save a woman who develops life threatening complications.

There are three types of delays that can affect a woman’s chance of surviving an obstetric emergency.

1. Delay in problem recognition and decision making.
2. Delay in reaching a health facility.
3. Delay in receiving care at health care facility.

The last delay can be prevented by having a quality 24 hours EmOC services.

PUBLIC HEALTH CONCEPT

We have undertaken various public health intervention programs to reduce MMR for last 50 years (Fig. 3). Unfortunately
they have not yielded desired results. The emerging Public
Health evidences in the field of Reduction of MMR tell us a
different story. With the exceptions of prevention of anemia,
tetanus vaccination, universal availability of safe abortion
services and of course high quality family planning servic-
es, none, training of traditional birth attendants, high-risk
screening, can significantly reduce MMR. The public health
studies have clearly demonstrated that:
• Most critical complications occur amongst low-risk
  patients.
• They cannot be predicted or prevented effectively.
• They have to be managed effectively in time.

The management of critical complications need high
quality, accessible and timely interventions.
• This forms the basis of EmOC.
• It is proved by various studies that organization of such
  EmOC proves the cheapest (cost-benefit factor) to the
  administration with reference to the estimated maternal
death prevented (Fig. 4).

We have the greatest challenge to accomplish this
intervention successfully. If we analyze the components of
this intervention, we find that major deficit is in the sector of
human resources in the form of available qualified/trained
personnel to provide high quality comprehensive emergency
obstetric care.

Health Information of India 1999 (Table 1)

Present Need
6000 doctors competent in providing comprehensive
EmOC are required to make 2,000 first referral units (FRUs)
functional for 24 hours.
• Only 771 specialists of obstetrics and gynecology
  (Obs-Gyn)
• 25,506 medical officers (MO) in primary health center
  (PHC)
• Only 42% of days, obs-gyn services are available.
Emergency Obstetric Care for Reducing Maternal Mortality

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Present Status

Now if we wait for all community health centers (CHCs) and FRUs to be equipped with qualified specialist obstetricians, years would sail by. As against this challenge, we have the strength to huge pool of Medical Officers (MBBS) with us.

It sounds absolutely rational that this strength should be utilized to provide Quality EmOC by training them in the skill of EmOC.

DEFINING EMERGENCY OBSTETRIC CARE

Emergency obstetric care is often discussed in terms of basic and comprehensive care that is provided to a woman with obstetric complications.

Basic Emergency Obstetric Care

In basic, EmOC facility, skilled birth attendant should be able to administer parenteral antibiotics, parenteral oxytocic drugs, parenteral anticonvulsants for pre-eclampsia and eclampsia, perform manual removal of placenta, perform manual removal of retained products, manual vacuum aspiration and perform assisted vaginal delivery.

Comprehensive Emergency Obstetric Care

In comprehensive EmOC, the doctors on duty should be able to perform all the functions of basic EmOC and in addition, he should be able to perform emergency cesarean section to save the life of woman. The facility of safe blood and anesthetist should also be available in centers having comprehensive EmOC services.

Challenges in Addressing Emergency Obstetric Care in Low Resource Settings

There is lack of standard guidelines in training doctors and their supervision. There is shortage of continuous supply of drugs and repair of equipment in time. Besides, there is lack of technical and clinical decision making skills. There is no emergency preparedness. Infection preventive practices are poor and not enough training facilities nontrainers are available to train nonskilled MBBS doctors in emergency obstetric care.

Quality EmOC poses unusual challenge because EmOC must be available 24 hours a day and 7 days a week to be maximally effective. Therefore, a locum doctor must be available and constant efforts must be made to make all the emergency drugs available all the time.

FEDERATION OF OBSTETRIC AND GYNAECOLOGICAL SOCIETIES OF INDIA AND EmOC

Emergency obstetric care is an emerging concept of rural obstetrician to reduce maternal mortality and FOGSI is committed to working toward a significant reduction in MMR in the near future by addressing this issue.

The concept of rural obstetrics has developed during the past few years all over the world. The aim is to make basic obstetric lifesaving surgery within limited resources accessible to those who have no access to it under existing socioeconomic circumstances.

Current curricula of most medical colleges are generated toward hospital oriented medicine and cater to urban population while population living in rural areas is being catered by nonspecialized doctors. Most of skilled obstetricians prefer working in urban areas.

This leads to situations to take action to ensure training enough number of human resources/staff providing EmOC in rural India. This should be the key strategy to reduce maternal mortality.

Federation of Obstetric and Gynaecological Societies of India is an association with more than 22,000 members. The aims of federation being to provide knowledge amongst its members; have fellowship and give services to improve reproductive health care of Indian women. FOGSI and its academic wing, ICOG have commenced a certification course in EmOC to develop skilled personnel to reduce maternal mortality in rural areas. This is competency based course of 16 weeks in comprehensive EmOC and 3 weeks course in updating knowledge of those doctors working in rural areas with not sufficient skills in EmOC. With 700 public sector obstetricians and more than 20,000 public sector nonspecialized medical officers in rural areas, the vision of the project is massive. FOGSI aims to establish high quality training centers in each state of India to train rural non-specialized doctors in comprehensive EmOC.

Government of India has supported FOGSI/ICOGs efforts of setting up EmOC training centers. This will help in making many first referral centers and district hospitals competent in providing emergency obstetric care. Hopefully,
SUMMARY OF KEY POINTS

- Almost 600,000 women in the world die each year from pregnancy-related complications. Fifteen percent of all pregnant women develop life-threatening complications.
- The problem is more acute in developing countries leading to disability and death amongst women of reproductive years.
- Twenty percent of Global maternal deaths occur in India. Besides for every maternal death, there are twenty women who suffer severe morbidity so that their lives are not worth living.
- Seventy percent of India’s population lives in rural areas where MMR is high due to lack of prompt and adequate treatment. India has an unacceptably high maternal mortality ratio of 4–5 per 1,000 livebirths (SRS 1998)
- Maternal mortality is not merely a health disadvantage but also a reflection of social and gender injustice.
- The overriding causes of high mortality in India are poor access to EmOC in case of a complication and absence of skilled birth attendant at delivery also, inadequate backup of having minimal infrastructure for managing life-threatening complications in pregnancy and labor.

Key strategies to save the life of pregnant women are:
- Skilled birth attendants at delivery
- Emergency obstetric care
- Timely and effective referral system
- Availability of safe abortion services.

- There are three types of delays that can affect a woman’s chance of surviving an obstetric emergency:
  1. delay in problem recognition and decision making;
  2. delay in reaching a health facility; and
  3. most importantly a delay in receiving care at health care facility.

- Emergency obstetric care is often discussed in terms of basic and comprehensive care that is provided to a woman with obstetric complications.

- There are challenges in addressing EmOC in low-resource settings like lack of standard guidelines in training doctors and their supervision, shortage of continuous supply of drugs and repair of equipment’s in time, infection preventive practices are poor and most skilled obstetricians prefer to practice in urban settings.

- Quality EmOC poses unusual challenge because EmOC must be available 24 hours. a day and 7 days a week to be maximally effective. This is an emerging concept of rural obstetrician to reduce maternal mortality.

- The Federation of Obstetric and Gynaecological Societies of India (FOGSI) and its academic wing, ICOG have commenced a certification course in EmOC to develop skilled personnel to reduce maternal mortality in rural areas. This is competency based course of 16 weeks in comprehensive EmOC and 3 weeks course in updating knowledge of those doctors working in rural areas with not sufficient skills in EmOC.

- With 700 public sector obstetricians and more than 20,000 public sector nonspecialized medical officers in rural areas, the vision of the project is massive. FOGSI aims to establish high quality training centers in each state of India to train rural non-specialized doctors in comprehensive EmOC.

- Government of India has supported FOGSI/ICOGs efforts of setting up EmOC training centers. This will help in making many first referral centers and district hospitals competent in providing emergency obstetric care. Hopefully, this public-private partnership will help to reduce maternal mortality in India.

BIBLIOGRAPHY

Family Welfare and Contraception
INTRODUCTION

Since antiquity men and women have desired to regulate their fertility. Studies have shown that having a baby is the least frequent motivator for having sex for most people.\(^1\)

The earliest written references of contraception can be traced back to Egyptian medical manuscript *Ebers Papyrus*, Latin works of Dioscorides, Greek writings of Soranus and Arabic works of Al Razi and Avicenna. The various methods of contraception described in these ancient scriptures ranged from unscientific ineffective methods to reasonable scientific methods. Most of the birth control methods were developed by hit and trial. As dissemination of contraceptive knowledge was considered illegal and punishable in those times it was secretly passed from generation to generation.

A brief overview of the history and development of various contraceptive methods is described below.

NATURAL METHODS OF CONTRACEPTION

These methods have played an important role in family planning since ancient times. Abstinence, withdrawal, safe period method and breastfeeding are some natural methods of contraception.

Abstinence

People in ancient times believed pregnancy to be a magical event and had no idea of a connection between vaginal intercourse and reproduction. However, gradually as this relation was established, abstinence for birth control was promoted. Feminists in America promoted abstinence within marriage in 1870s, which resulted in an epidemic of sexually transmitted diseases (STDs).

Outercourse

Outercourse or alternatives to penile vaginal intercourse like masturbation were condemned by Early Christian Church. During the same time in India, Mallinaga Vatsayayana (400 CE) wrote *Kamasutra*, an Encyclopedia of procreative and nonprocreative sexual practices. It was translated in English by Sir Richard Burton in 1883 and circulated secretly amongst members of British Kamasutra Society. In 1960s this manual was published in US and became the bible of sexual revolution at that time.\(^2\)

Outercourse was revived in America in 1940s and 1950s but lost its popularity in 1960s with the availability of pill. In early 1980s, outercourse regained its popularity with the emergence of AIDS.

Withdrawal

It is one of the oldest methods of birth control. Coitus interruptus is the Latin name for withdrawal. Withdrawal was considered a sin by ancient Jews and Christians. However in 18th and early 19th centuries it was one of the most popular methods of birth control in the world.\(^3\)

The Catholics and Muslims have a religious sanction for coitus interruptus.
Fertility Awareness Based Methods

Avoidance of intercourse in fertile period for contraception has been practiced by the ancient Romans, Greeks, Africans and Hindus. However, the understanding of the fertile period at those times was inaccurate. The ancient Hindus believed that the most fertile period of a woman was just after or during periods. It was in 1929 Knaus from Austria and Ogino from Japan found that ovulation occurs 12–16 days before the next period. In 1960s Australian doctors John and Evelyn Billing came up with Billings’ cervical mucus method for identifying fertile period.\(^3\)

Lactational Amenorrhea Method

Extended breastfeeding has been used by women to space their pregnancies since prehistoric times. However, affluent Western women had higher fertility as they depended on their slaves for breastfeeding. Even today breastfeeding is more prevalent amongst poor rural women compared to urban dwellers. It provides protection to a significant number of fertile women in developing countries.

BARRIER CONTRACEPTIVE METHODS

In earliest times people used various plant and animal products to prevent pregnancy. Some substances used to block the cervix and absorb semen were vegetable seed pods, plugs of grass and crushed roots, sea weed moss, bamboo, empty halves of pomegranates, squeezed halves of lemon, sponge, tissue paper, bee wax, wool, rock salt, etc.\(^4,5\) With the advent of intrauterine devices (IUDs) and oral contraceptive pills (OCPs), barrier contraceptives became less popular. However, in 1980s with the emergence of AIDS they regained their lost popularity.

Condoms

The use of condom during sexual intercourse can be traced back to 12,000–15,000 years to a painting on the wall of a cave in France.\(^6\) Egyptians are considered to be the pioneers in the use of condoms for protection against STDs. The invention of condom is controversial. Several reports suggest that condom was named after Dr Condom who lived during the reign of Charles II in 18th century and recommended it to the King for protection against fathering illegitimate children and STDs.\(^7,8\) Others believe that the word condom was derived in 1717 from the Latin word “Condus” which means a receptacle.

The various milestones in the history of development of condoms are as follows:

- **19th century**: In 1843, Charles Goodyear and Hancock patented the vulcanization of rubber and introduced rubber condoms in 1870.\(^8,9\)
- **20th century**:
  - Earliest teat ended condoms were manufactured in 1901 by the trade name of “Dreadnought”.
  - Latex condoms were manufactured in 1930s.
  - Lubricated condoms were made available in 1960s. Silicon was used to produce semi-dry lubricated condoms.
  - In 1994, female condom became freely available in US.
- **21st century**: Female condom became available in India in 2007.

Japan leads the world in usage of condom followed by Scandinavian countries. Major condom producing countries are Japan, Great Britain, US, India, West Germany, Hungary, Korea and Thailand.

INTRAUTERINE CONTRACEPTIVE DEVICES

The discovery of modern IUD can be traced back to the Arabs who inserted pessaries into uteri of their camels to protect them against pregnancy during long journeys through the desert. The various milestones in the development of IUDs are as follows:

- **9th century**: A Persian physician recommended insertion of a paper wound tightly as a probe tied with a string and smeared with ginger water into cervix for contraception.
- **11th century**: Islamic scientist Avicenna used intrauterine pessaries for contraception in women.
- **19th century**: Stem pessaries with small caps which extended into uterus and blocked the cervix were used. They were made of wood, glass, silver, gold and ivory.
- **20th century**:
  - Dr Carl Hollweg of Germany in 1902, introduced wish bone shaped pessaries. They were associated with severe pelvic infection.
  - In 1909, Richard Richter from Germany introduced a ring shaped IUD of silkworm gut.
  - In 1926, German physician Dr Ernst Grafenberg introduced the first widely used ring shaped IUD of silkworm gut and silver wire.\(^10\) This IUD was without a tail.
  - In 1934, T Ota of Japan introduced a ring shaped device with a small disc in the center attached to the ring by three spokes made of gold or gold plated silver.\(^11\)
  - In 1936, Grafenberg and Ota rings were abandoned due to high risk of pelvic infection reported by European doctors.
  - In 1959, Oppenheimer of Israel and Isihama of Japan made the Ota and Grafenberg rings of plastic.
  - In 1962, Lazav Margulies and Jack Lippe from New York introduced IUDs made up of polyethylene, a biologically inert material.\(^12\) These devices were known...
as Marguiles coil and Lippes loop. Lippe also added barium sulfate to make it radiopaque and attached fixed nylon threads to it. These were followed by the introduction of several inert IUDs like Birnberg bow, soft coil, double coil, steel rings, etc.
- In 1967, Lernes and Davis designed the Dalkon Shield which became popular in US, but was later withdrawn due to severe infection and deaths associated with it.
- In 1969, Jaime Zipper and Howard Tatum developed medicated devices.
- Early 1970s saw the marketing and wide acceptance of first generation of medicated IUDs all over the world.
- In 1974, Multiload Cu 250 and hormone releasing IUD Progestasert was marketed. Progestasert was later replaced by a longer lasting LNG 20. It was popular in US and France.
- In 1979–1982 2nd generation Copper releasing IUDs with improved life span and effectiveness were introduced. They had silver core copper wires or sleeves.

Intrauterine devices are widely used all over the world. Almost one-third of users are from China alone. In developed countries, IUDs are most widely used in Europe. They are not very popular in US, Canada, Australia, New Zealand and Japan. Inert IUDs are still used in China, Indonesia, Pakistan and Turkey.

**HORMONAL CONTRACEPTIVES**

Women all over the world used herbs for preventing pregnancies. Over the years researchers have discovered a scientific basis of these herbs in preventing pregnancy. Pomegranate was one of the first oral contraceptives widely used by Greek women. Women in tropical India and Sri Lanka ate papaya to prevent pregnancy which was later found to contain an enzyme Papain which interacted with progesterone to prevent pregnancy. Generations of Mexican women ate wild yam to prevent pregnancy and later Russell Marker extracted progestin from this wild yam.

**Oral Contraceptive Pills**

Milestones in the development of OCPs are listed below:
- **20th century:**
  - In 1940s and 1950s Margaret Sanger followed the research on oral contraceptives by scientists Gregory Pincus and Min Chueh Chang.
  - The first successful clinical trials of the hormonal pill were conducted by Dr John Rock, eminent catholic gynecologist in 1956.
  - In 1960, FDA approved a combined OCP Enovid
  - From 1965–1975, studies established a relationship between OCPs and certain major complications like thromboembolic events, death, etc.
- Low dose pills with a reduced dose of estrogen and 2nd generation progestin were introduced in 1970s. These pills were safer.
- Noncontraceptive benefits of OCPs like prevention of ovarian cysts, ovarian and endometrial carcinoma, dysmenorrhea, etc. were highlighted in the period 1975–1985.
- Multiphasic pills with further reduction in dose of hormones per cycle and side effects were introduced in 1980s.
- Low dose pills with 3rd generation progestin and a further reduction in side effects were introduced in 1990s. Mini pills were also introduced during this period.
- **21st century:** Newer pills with decreased side effects and better efficacy, like drospirenone, seasonale, seasonique, etc. were introduced.

**Depot Medroxyprogesterone Acetate**

Soon after the pill was approved by FDA, an effort to develop a method to avoid daily intake of pill was made. The milestones in the development of injectable contraceptive—depot medroxyprogesterone acetate (DMPA) are described as below.
- **20th century:**
  - DMPA was submitted for the Food and Drug Administration (FDA) approval in 1967, which was delayed due to increased risk of breast and endometrial cancer documented in dogs and monkeys respectively with DMPA.
  - In 1971, DMPA was used all over the world except USA.
  - In 1988, FDA advisory committee discontinued the studies on dogs after realizing that dogs were pre-disposed to breast cancer.
  - WHO concluded that DMPA does not cause any additional risk of breast or endometrial cancer to women in 1991.

**Norplant**

The initial research on hormonal implants was successfully carried out in animals in 1950s followed by clinical trials on human beings in 1980s.
- **20th century:**
  - Norplant was approved by WHO in 1984.
  - In 1990, FDA approved Norplant.
  - By 1995, a large number of suits were filed against the manufacturer by users claiming that they were not apprised of the side effects. FDA reanalyzed the product and declared it safe and effective. Norplant II was introduced.
EMERGENCY CONTRACEPTION

The concept of emergency contraception is very old. As described in literature women used methods like wiping out the vagina of semen, sneezing and blowing nose several times, jumping backwards several times, forcefully contracting the vaginal muscles. Vaginal douching with chemicals like alum, plant products disinfectants, etc. was another ineffective but popular method used.

Another method of emergency contraception used was to induce menstruation by various herbs. The earliest reference to such herbs dates back to Hippocrates from Athens (460–377 BC). However, some of these herbs are still used worldwide.

The important milestones in the development of safe and effective emergency contraception are described as below:
- **20th century:**
  - In early 1970s, Dr Albert Yuzpe from Canada prescribed birth control pills for emergency contraception. FDA approved first emergency contraceptive pill product in 1998.
  - FDA approved the first progestin only emergency contraceptive pill in 1999.

MALE AND FEMALE STERILIZATION

Tubectomy

Although tubectomy is one of the most popular methods of contraception, it was the last to be accepted socially.

The various milestones in the history of development of tubectomy are described below:
- **17th century:** First tubal ligation was performed in US in 1880.
- **20th century:**
  - Up to 1930s female sterilization was used only for therapeutic indications.
  - From 1950–1960s female sterilization started gaining ground for fertility regulation.
  - Doctors observed the rule of 120 as a prerequisite for carrying out female sterilization till as late as 1960s. According to this rule a women could undergo sterilization only if her age multiplied by the number of her children equaled 120. That is for following a two child norm; the women had to be 60 years old to be eligible to undergo sterilization.
  - In early 1970s laparoscopic sterilization was introduced.
  - First mini laparotomy was performed in Bangkok in 1974.
  - In 1970s and 1980s tubal ligation as a contraceptive method started growing consequent to the scare about the side effects of oral pills and IUDs.
  - In 1990s tubal sterilization became the most popular method of contraception.

Vasectomy

The history of development of vasectomy as a contraceptive method has an association with force and coercion. Earliest references to male sterilization implied removal of testicles and sometimes penis as well. These castrated men guarded the women of royal families. Currently it is the major family planning method in the developed countries like USA, New Zealand, Australia and Canada. Milestones in development of vasectomy are as follows:
- **19th century:** First vasectomy was performed in UK for relieving a patient of swollen prostate in 1894.
- **20th century:**
  - From 1916–1940 Eugen Steinach, a Viennese Surgeon, began performing mass vasectomies with the aim to prevent aging.
  - In 1950s vasectomy was mainly performed to prevent men from performing sex crimes and transmit genetic diseases; however, vasectomy for birth control gradually became acceptable.
  - This movement gained momentum in 1960s and 1970s.
  - No scalpel vasectomy was introduced in China by Dr Li Shuangliang in 1974 and became popular all over the world since 1986.

History of development of contraception unfolds amazing facts about the knowledge of human beings of various methods of fertility regulation since antiquity and their changing attitude towards the same. The knowledge and understanding of the past events can shed light on modern-day issues regarding the same.

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INTRODUCTION

Fertility control is playing a pivotal role in reproductive health care of women. A successful fertility control program will enable us to face the future with an estimated 8–10 billion world population. Proper fertility control will also reduce maternal mortality rate by 25%.

At 00:00 hours of 1st March 2001, population of India stood at 1,027,015,247 comprising 531,277,078 males and 495,738,169 females. India added about 181 million persons between 1991 and 2001 thus outbeating Brazil also which is the most populated country in the world. Population density of India in 2011 was 382 persons/km².

July 2007 statistics showed total population of India as 1,129,866,154 there by adding 1 million and 30 lakhs. Of these, infants and 0–14 years old were 171,356,024 and 15–64 years old were 346,034,565. This indicates that there is long way to go before which we can achieve population stabilization.

Global trends in women’s health are that it is a state of physical and mental health and social well-being. For the first time in 1996 at the International Conference on Population and Development held in Cairo, Egypt, the consensus of gender equality and women empowerment were recognized as reproductive rights.

Women spend 30 reproductive years with 1 or 2 children and have to lead a sexually active role.

There are various Family Welfare Programs which provide a method by which couple can prevent childbirth.

Natural methods of contraception are those which do not use any appliance or medicine. Some of the methods are in vogue from prehistoric times. It is statistically proved that many couple practice natural methods of contraception worldwide.

The reason for greater compliance is that they do not need any medical appliance or medicine, involve no cost, can be practiced most secretly and without any religious bar.

With the increasing prevalence of sexually transmitted diseases (STDs) the role of natural and more so barrier methods has become important.

Various methods of contraception can be classified as:

• Natural methods
  - Natural family planning (NFP) methods
    - *Fertility awareness-based method (FAB):* This form of contraception includes all family planning methods that attempt to identify fertile time each cycle and then modify sexual behavior. When FAB methods involve sexual abstinence during the fertile time, this technique is called *natural family planning* whereas when these methods involve occasionally using a barrier method during the fertile time, the method is called *fertility awareness-combined methods—FACM.*

Because the ovum is probably susceptible to successful fertilization for only 12–24 hours after ovulation, periodic abstinence has intuitive appeal as a means of birth control. Pregnancy rates, however, with various methods of periodic abstinence have been estimated from 5 to 40 per 100 woman years. In other words, the unwanted pregnancy rate during the first year of use is approximately 20%.

• Lactation amenorrhea method (LAM)
• Withdrawal method
• Barrier methods of contraception.
Natural Methods of Family Planning: Barrier Contraception

NATURAL FAMILY PLANNING METHODS

Previously they were referred to as “safe period” and “rhythm period” based on periodic abstinence. In 1982, WHO advocated them to be referred to as “natural family planning methods”.

Natural family planning methods refer to methods of planning and preventing pregnancy by observing the naturally occurring symptoms and signs of the fertile and infertile phases of menstrual cycle.

Natural family planning has been in practice for ages. Of course the concept of correct ovulation time was not known.

In 1929, “Knaus” of Austria and Ogino of Japan found that ovulation occurs mostly between 12 days and 16 days. NFP methods are based on the premise that coitus should be avoided during this fertile period, timed correctly. Fertile phase is detected by:

- Rhythm method
- Basal body temperature (BBT) method
- Cervical mucus changes
- Symptothermal method correlates cervical mucus changes in BBT and intercourse in a chart form.
- Ultrasound follicular study detects ovulation time and is fool proof and convenient.

The Two-day Method

The two-day method has been developed by the Institute of Reproductive Health of Georgetown recently. It is a newly developed type of FAB method where women can determine whether they are fertile on any given day based on the presence or absence of cervical secretions. Cervical secretions are the key to women’s fertility without which sperms have difficulty traveling to the egg.

The two-day method is appropriate for women with cycles of any length, regardless of regularity, and suits couples who can avoid sex for about 10-15 days per cycle.

To use this method, a woman asks herself two questions each day:
1. Did I notice cervical secretions today?
2. Did I notice cervical secretions yesterday?

If she noticed secretions of any type either that day or yesterday, she should consider herself fertile and avoid unprotected sex. If she did not notice cervical secretions for two days consecutively, she would be unlikely to get pregnant from sex taking place that day. This is a simpler way of identifying the fertile days to either the Billing’ ovulation method or symptothermal method, which also involves observations of cervical secretions. Failure rate from correct use is 4% in 1 year and 14% from typical use.

After initial counseling, most participants (over 96%) are able to detect the presence or absence of cervical secretions. However, although simple this two-day method needs wider trial.

The Persona

Natural family planning enters the age of technology. Persona is basically a microcomputer attached to a microlaboratory. It is based on measurement of levels of luteinizing hormone and estrone-3 glucuronide (E3G) in early morning urine. Women can get an idea of ovulation time by dipping the test stick in her urine. It is widely used in UK and European countries.

With perfect use the failure rates are 6 per 100 woman years. It has to be perfectly programmed and is suited for couple who would follow NFP.

Natural Family Planning methods are applicable without any financial commitment and do not disturb the menstrual cycle. Recent studies in 1993 by WHO ruled out any chromosome or congenital anomalies as a consequence.

New technologies of ovulation prediction involve digital and electronic thermometers and most prefer the follicular study for pin pointing ovulation.

Lactational Amenorrhea Method

This could be effective traditional and popular concept when lactation is the only method of nutrition to the baby. The additional benefits are the antibodies in colostrum which are beneficial to baby. The raised level of prolactin inhibits LH but has no effect on FSH. The antifertility effect of prolactin during nursing may be due to erratic ovulatory cycle. The failure rate is unpredictable and is effective for 6 months only.

Additional benefit is it helps develop bonding between mother and child. Also, it helps in preventing development of breast cancer in later years.

Lactational amenorrhea method has got a very good place as a method of contraception in developing countries.

Counseling

All mothers following LAM should be encouraged to breastfeed fully. They should be informed that:

- Sexual intercourse during lactation is not harmful
- Breastfeeding should not be discontinued to start the use of contraception
- While breastfeeding gives protection against pregnancy, it is difficult to predict precisely the duration of lactational infertility of each woman
- Amenorrhea gives high degree of protection against pregnancy in fully nursing women during the first 6 postpartum months
- Breastfeeding on demand in the day and night can defer the onset of menses and fertility
- The risk of pregnancy increases with the first postpartum menses, the introduction of supplementary milk or food to the infant and after about 6 months of delivery
- Supplementary feeding is not recommended in the first 6 months unless there is affection of infant growth.
• Other contraceptive measures should be used as soon as any of the risks mentioned comes to be present or earlier if a woman wants better protection against pregnancy. The above points of counseling are based on the statement of the IPPF International Medical Advisory Panel issued in November 1989.

**Use Effectiveness**

Failure rate of LAM (for 6 months only) is less than 2% when correctly and consistently used but it is more otherwise. Many authorities believe nowadays that use effectiveness of lactational amenorrhea in fully breastfeeding mothers is as good as that of oral pills and barrier contraceptives, particularly in the first 6 months.

**Advantages**

• Lactational amenorrhea method effectively controls pregnancy for at least 6 months and perhaps longer if a woman keeps breastfeeding often, day and night.
• It can be used immediately after delivery.
• There is no interference at the time of sexual intercourse.
• No extra cost is needed for family planning or feeding the baby.
• No supplies or procedures are needed to prevent pregnancy.
• There are no hormonal side effects.
• The breastfeeding practices required by LAM have other health benefits for mother and baby:
  – It provides the healthiest food for the baby
  – It protects the baby from life-threatening diarrhea
  – It protects the baby from diseases like measles and pneumonia by passing on the mother’s immunities to the baby
  – It helps to develop a close relationship between mother and baby
  – It protects the mother from diseases like subinvolution of the uterus, fibroadenosis and fibroadenoma of the uterus. Breastfeeding reduces risks of breast cancer and epithelial ovarian cancer.
• The risk of breast cancer is reduced by 4% for each year of lactation, according to an analysis of 47 epidemiologic studies in 30 countries. This reduction is essentially the same in developing and developed countries. In addition, the risk of breast cancer is reduced by 7% for every birth a woman has. The incidence of breast cancer is much lower in developing than in developed countries, the study suggests that the larger families and patterns of prolonged breast feeding, typical in the developing world, explain much of the difference.

**Disadvantages**

• The effectiveness of LAM is not certain, and it is less acceptable.
• Frequent breastfeeding may be inconvenient or difficult for some women especially working mothers.
• It does not provide protection against STDs including HIV/AIDS.
• If the mother has HIV (the virus that causes AIDS), there is some chance that the baby will also be infected. Even so, in most parts of the world, particularly developing countries, babies are more likely to die from infectious diseases than from HIV in breast milk. Therefore, WHO recommends that a woman with HIV should breastfeed, but where the risk of infectious disease to the baby is slight and otherwise safe, affordable food is available, infected mothers should adopt a safe alternative method of contraception.

**Eligibility Criteria for Lactational Amenorrhea Method**

**Indications**

In general, most women can use LAM safely and effectively if they:
• Smoke cigarettes
• Are young or old
• Are fat or thin.

**Relative Contraindications**

Women with the following conditions can also use LAM:
• Benign breast disease
• Headaches
• High blood pressure
• Varicose veins
• Valvular heart disease
• Diabetes
• Iron deficiency anemia
• Gallbladder disease
• Malaria
• Sickle cell disease
• Thyroid disease
• Uterine fibroids.

**Absolute Contraindications**

Lactational amenorrhea method cannot be used under the following conditions:
• Baby 6 months or more old
• Mother cannot fully or near fully breastfeed day and night
• Menstruation starts (bleeding for at least 2 days after 8 weeks of childbirth)
• Mother being treated with mood-altering drugs, reserpine, antimetabolites, cortisone, radioactive drugs, cyclosporine and anticoagulants
• Viral hepatitis of mother
• Mother has HIV/AIDS (unless babies cannot be artificially fed properly).
Withdrawal Method

Coitus interruptus implies discharge of semen outside the female genitalia at intercourse. It is one of the oldest methods, practiced by primitive tribes also. There is no religious taboo. Combined with barrier method, NFP is the most effective for family planning. Motivation and proper technique by counseling go a long way for family welfare measures. As even one drop of semen can deliver many spermatozoa, it is not a fool proof method.

BARRIER METHODS

Barrier contraception was the main method of birth control in 1950s. With the introduction of pills and intrauterine devices their use declined. Lately with the fear of STD which are on the rise, the barrier contraceptives are becoming more and more popular.

The male condom is the most widely used and most popular method of contraception in the world.

It is highly acceptable in the developing countries including remote villages as there is no role of technical personnel.

The condom is the most effective method of contraception with failure rate being 2–3% per 100 women years. Addition of spermicides adds to the efficacy.

Condom is the oldest and most widely used birth control device in the world supposedly invented by Dr Condom for King Charles II and scientifically recommended by Italian physician Dr Fallopio in 1564. Later it evolved to the present form, with invention of latex in 1930s which revolutionized the concept.

The arrival of polyurethane condom is welcomed, due to added advantages over latex condoms. It is thin, odor free and with nonallergic effect. It is not corroded by oil-based lubricants.

The non-oxynol-9, a spermicide used as coating is being discontinued due to irritable reaction.

Condom use increased remarkably throughout the world as prevention measures against STDs and AIDS.

The contraception by vaginal sponge has been withdrawn due to the high incidence of anaerobic infection and spermicidal gel not based on non-oxynol-9.

A number of over the counter diaphragm/cervical cap devices (for example, Lea’s shield, Fem gel) may be marked shortly.

Barrier contraception is the main method of birth control and is being used more and more for the fear of STDs and AIDS.

Research should be continued to improve the quality and the type of barrier contraception.

The added advantages are availability without prescription and for elderly couples and adolescents with infrequent coitus.

Condom use provides protection from amniotic infections during pregnancy. It may reduce the chance of developing cervical dysplasia and cancer cervix at a later stage; as one of the theory is that smegma may be the cause of carcinoma cervix.

Female condoms are now available and usage can be propagated. Some of them are hormone impregnated and have dual advantage.

Proper counseling of the usage may further reduce the failure rate.

Counseling: Its role is crucial in any method of family planning. Enough time has to be spent and counseling to be done to the point, leaving the option of the method to the client.

CONCLUSION

Natural contraception has great potentiality for the control of population in India; mainly because they can be practiced without any special training and medical personnel. Motivation and propaganda are the need of the hour. Frequent and prolonged feeding without supplementary feeds to the baby with mid cycle abstinence is recommended. Barrier contraception and more so condom usage are helpful for their role in preventing STDs and AIDS.

Continued research to improve the quality of condoms should be undertaken.

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INTRODUCTION

The control of a woman’s procreative potential has advanced considerably over the past four decades. The introduction of newer, cheaper, safer and highly effective contraceptive agents following extensive research has not only led to increased awareness but a much higher acceptability amongst our population for the practice of fertility control.

As societies become more affluent, fertility decreases. This decrease is in response to the use of need-based contraception. Contraception is not new, but its widespread development and application are new.

An often asked question is “Why do we need contraception?” The answer is rather simple and short, “To avoid unwanted pregnancies!!” In addition, the regular practice of contraception, helps a couple to space their children and also allows a much needed rest to the “new” mother.

This chapter will briefly touch upon the various steroidal and nonsteroidal contraceptive methods presently available.

Steroidal Contraception

- Oral contraceptive pill (OCP):
  - Female
  - Male
- Injectable contraception
- Hormone-releasing intrauterine contraceptive device (IUCD)
- Others: Emergency contraception (EC)

Nonsteroidal Contraception

Temporary

- Natural methods of contraception
- Barrier contraception
- Oral contraceptive pill:
  - Female
  - Male
- Intrauterine contraceptive device
- Implants
- Vaginal rings

Permanent

- Female sterilization
- Male sterilization

Future Contraceptives

Within 2020 AD

- Gonadotropin releasing hormone (GnRH) analogs
- Antigestogens
- Patches
- Vaccines
- Male fertility regulation

Beyond 2020 AD

- Regulatory peptides
- Gene therapy
STEROIDAL CONTRACEPTION

Female Oral Contraceptive Pill

The OCP is a widely accepted and most effective method of fertility control, with over 100 million women using OCs all over the world. With the availability of newer progestogens like desogestrel and gestodene, coupled with lowered doses of estrogen (20 mg), the combined OC (COC) pill has made inroads in our country as well.

Oral contraceptive pills are broadly divided into two groups:
1. Combined OC pill
2. Progesterone-only pill (POP).

Combined Oral Contraceptive Pill

These are of two types:
1. Monophasic pill
2. Multiphasic pill.

Monophasic Pill

These pills contain an estrogen and a progestogen in the same amount in each pill. The most commonly used estrogen in the OCP is ethinyl estradiol (EE). The only other estrogen, which was tried with limited success in the earlier OCP was mestranol (3-methyl ester of EE), later discarded due to its higher risk of thromboembolism, and weak action as a result of its prior metabolism to EE in the body before eliciting its pharmacological action of inhibition of ovulation. The progestogens that are commonly used in OCs are norgestrel, levonorgestrel, desogestrel, gestodene or norgestimate. OCs can be broadly classified as low-dose or high-dose pills depending upon the EE content in each pill:
- Low-dose pill: EE content less than 0.05 mg (50 µg)
- High-dose pill: EE content of 0.05 mg (50 µg) or more.

High dose OCs have now been almost completely replaced for regular use, due to their greater side effects and major complications. However, they are still being used in the developing countries for 1–3 cycles, despite warnings of cardiovascular and other hazards.

In addition, a recent classification of COC pills based on epidemiologic studies have been proposed:
- First generation (high-dose) OCs: Products containing 50 mg or more of EE.
- Second generation OCs: Products containing levonorgestrel, norgestimate, and other members of the norethindrone (NET) group (norethindrone acetate, norethynodrel, ethynodiol diacetate, lynestrenol, norgestrel) and 30 or 35 µg EE.
- Third generation OCs: Products containing desogestrel or gestodene with 20 or 30 µg EE.

Although every attempt is being made to bring down the dose of EE to 15 µg, and even to 10 µg in the COC pills to minimize the side effects of estrogen, the only problem anticipated is whether such measures will provide acceptable cycle control, in addition to contraception. Extensive research is underway in this area at present.

- Spironolactone analog: A new progestin called drospirenone (DRSP) is derived from 17-α spironolactone, an analog of spironolactone. It has antiandrogenic and antimineralocorticoid activities. OCs containing DRSP and EE have been found to be highly effective and provide a safety level equivalent to that of other OCs. They also lessen acne, seborrhea and premenstrual syndrome. It is also being marketed as “Yasmin”.

Multiphasic Pills

These phasic formulations employ low doses and variable amounts of estrogen and progestogens in two (biphasic) or three (triphasic) periods of the menstrual cycle. The dose of the progestogens is low in the beginning and higher at the end, while the estrogen remains either constant or rises slightly in midcycle. The total dose of both steroids in a whole cycle is less in these pills.

Sequential pills, which contained only estrogen in the first 14 tablets and combined estrogen and progestogens in the next 7 tablets, have been withdrawn from the market because of high actual or probable incidents of endometrial carcinoma.

Choice of Estrogen and Progestogens in COC Pills

The universally accepted choice of estrogen in the COC pill is EE, as it provides consistent inhibition of ovulation and good cycle control in doses of 20–30 µg. The choice of progestogens in the present era depends upon not only in providing effective contraception but also in the lipid-friendly profile and positive health benefits (decreased androgenicity) of these molecules. The preferred progestogens are desogestrel and gestodene, although a large chunk of the COC pills prescribed contain levonorgestrel. The hazards attributed to the usage of the older progestogens having higher androgenicity are acne, oily skin, mild to moderate psychosexual disorders (depression, lassitude, decreased libido), negative effects on coagulation and lipid profile.

Mechanism of Action of COC Pills

- Inhibition of ovulation: This mechanism works by suppressing hypothalamic releasing factors leading to inappropriate secretion of follicle stimulating hormone (FSH) and luteinizing hormone (LH); estrogen preferentially inhibits FSH and is dose dependent while
Changes in the endometrium:

- This mechanism leads to alteration in the maturation of the endometrium rendering it unsuitable for the implantation of the fertilized ovum. The endometrial stroma becomes edematous and decidualized, while the glands become atrophic with less secretory activity.

- Changes in the cervical mucus: The cervical mucus becomes scanty, viscous and cellular with low spinbarkeit and no ferning. These changes impair sperm transport and penetration.

Effectiveness

Combined OCPs are very effective. The failure rate when correctly and consistently used is only 0.1% or 1 per 1,000 in the first year of use. The typical failure rate, as is commonly used, is 1.8%, which may increase to 8% or even more. Multicentric studies conducted by the World Health Organization (WHO) have found low-dose pills to be as effective as high-dose ones.

Drug failure: Failure of contraception due to the physico-chemical properties of the drug itself (ingredients, inappropriate or reduced dosage, formulation, etc.)

Method failure: Failure of contraception due to the method of administration of the drug (noncompliance of the patient: irregular pill taking, vomiting/gastroenteritis, nonadherence to pill-free days, etc.).

Pill Taking

Once a decision is taken with regard to the type of COC pill that the concerned woman will take, a decision is taken whether she would like to be a day 1 starter from the first cycle, or a day 5 starter. Starting OCPs from the first day of menses ensures immediate protection. In this regimen, the woman takes a pill every day from day 1 for 21 days, following which a gap of seven tablet-free days are observed, during which her menstruation usually starts. A fresh pack of 21 tablets is started thereafter, and continued cyclically. For a day 5 starter, the woman starts the first pill from the fifth day of the menstrual cycle for a period of 21 days, and continues in this cyclical way every month.

A more rational and effective method is to be a “day 3 starter” from the second month onwards (the woman starting her fresh pack of 21 tablets every month on the third day of her menstruation), as follicular recruitment with further growth of these follicles (up to 10 mm or more), subsequent ovulation and occasional pregnancy have been recorded with the commonly practiced seven tablet-free days.

There is no rational for recommending a pill-free interval (PFI) “to rest”. The serious side effects are not eliminated by PFI. This practice all too often results in unwanted pregnancies.

Irregular pill taking is a common occurrence. The commonly encountered situations are:

- If a woman misses one pill: She should take that pill as soon as she remembers (within the first 12 hours), and take the next pill as usual. No backup is needed.
- If a woman misses two pills in the first two weeks: She should take two pills on each of the next two days; it is unlikely that a backup method is needed, but the official consensus is to recommend backup for the next 7 days.
- If a woman misses two pills in the third week, or more than two pills are missed at any time: Another form of contraception should be used as backup immediately and for 7 days; if a Sunday starter (or, if she is more than 12 hours late with one or more pills), keep taking a pill every day until Saturday, and on Sunday start a new pack; if a non-Sunday starter, start a fresh pack the same day.

Even if no pills have been missed, the woman should be instructed to use backup method for at least 7 days after an episode of gastroenteritis.

Benefits and Advantages

- Prevention of pregnancy
- Cycle control
- Noncontraceptive benefits:
  - Cure of menstrual disorders like dysmenorrhea and ovulation pain (Mittelschmerz), some cases of polycystic ovarian disease
  - Protection against ovarian cancer by 40%
  - Protection against endometrial cancer by 50% (prevention of choriocarcinoma indirectly by preventing pregnancy)
  - Protection against benign tumors: Reduction of benign breast diseases like fibrocystic disease and fibroadenoma (25%), functional ovarian cysts (50%), corpus luteum cysts (80%), uterine fibroids (30%)
  - Protection against ectopic pregnancy (50%), pelvic inflammatory disease (50%), anemia (60-80%), endometriosis, acne, hirsutism, rheumatoid arthritis, osteoporosis.

- No affection of future fertility as it is easily reversible; regular ovulation returns within 3 months in 98% of women
- Simple to use, esthetically attractive, does not interfere with the sexual act.

Side Effects

- Minor: Nausea, vomiting, lack of appetite
- Menstrual irregularity: BTB, metrorrhagia, oligomenorrhea, and rarely, amenorrhea
- Breast changes: Edema, heaviness and tenderness
- Headache and migraine
- Chloasma: Hypopigmentation of the face and forehead
• Weight gain
• Others: Leg cramps, dimness of vision, hyperlipidemia.

Drawbacks
• Cost: Relative expensiveness
• Does not prevent sexually transmitted diseases
• Interference with biochemical and biopsy findings
• Myths about OCPs with respect to increased risk of cardiovascular disease and possible carcinogenicity.

Dispelling the Myths
Cardiovascular disease:
• All low-dose oral pills, regardless of the progestogens type, have an increased risk of venous thromboembolism, although the risk is lower than that reported earlier.
• Low-dose OCPs do not increase the risk of myocardial infarction or stroke in healthy, nonsmoking women, regardless of age; almost all myocardial infarctions and strokes occur in users of high-dose pills, or users with cardiovascular risk factors over the age of 35.

Possible Carcinogenicity
Cervix:
• Risk of dysplasia and carcinoma in situ increases with the use of OCPs for more than 1 year; hence, Pap smear surveillance is important, either annually or even 6-monthly for women using OCPs for 5 years or more.

Breast:
• Current and recent use of OCPs may be associated with about a 20% increased risk of early premenopausal breast cancer—this may be due to detection/surveillance bias and accelerated growth of already malignancies
• Previous OC use may be associated with a reduced risk of metastatic breast cancer later in life, and possibly with a reduced risk of postmenopausal breast cancer
• Oral contraceptive use does not further increase the risk of breast cancer in women with a positive family history of breast cancer or in women with proven benign breast disease.

Progestogen-only Pill
Progestogen-only pills or minipills contain small amounts of any one of the commonly used progestogens but no estrogen. These pills are much less used than the COC pills. The most commonly used progestogens are ethynodiol diacetate, NET, levonorgestrel and norgestrel. Recently, etonogestrel (3-keto desogestrel) is gaining wide popularity as an effective and safe POP.

Mechanism of Action
Progestogen-only pills produce their contraceptive effect in three ways:

1. By thickening the cervical mucus plug and making it impermeable to spermatozoa; the effect starts in 2–4 hours and lasts for 20–24 hours.
2. By inhibiting ovulation (60% of cases).
3. By involuting the endometrium making it hostile to implantation.

Indications:
• Lactating women
• Women more than 40 years.

Effectiveness
The average failure rate is 3–10% in the first year of use. When used effectively and consistently in lactating women, the failure rate is only 0.5% in the first year; the failure rates being higher in younger women than their older counterparts.

Administration
Progestogen-only pills should be started 6 weeks after delivery in a fully breastfeeding woman, and no backup contraceptive method (barrier/abstinence) is necessary. In other cases, POPs should be started on the first day of the period and a backup method must be used for seven days, with the POPs taken daily at the same time of the day.

Compositions and Proprietary Names
• Norethindrone: 0.350 mg (Micronor/Noriday)
• Levonorgestrel: 0.075 mg (Neogest)
• Norgestrel: 0.030 mg (Microval/Norgeston)
• Ethynodiol diacetate: 0.500 mg (Femulen)
• Desogestrel: 0.075 mg (Cerazette)

Comments (WHO, 2004) on Use of Progesterone-only Pills
• Pregnancy: No harm to the mother or fetus if POPs are used occasionally
• Adolescents: No definite evidence has been found on the effect of POPs on bone mineral density or bone mass levels.
• Obesity: No decreased effectiveness of depot medroxyprogesterone acetate (DMPA) or Jadella.
• Breastfeeding: There is concern that the neonate may have hormonal effects during the first 6 weeks postpartum. POPs do not affect breastfeeding performance and infant health and growth; nor do they increase depressive symptoms.
• Cervical intraepithelial neoplasia: Among women with human papillomavirus infection, long-term DMPA use (≥ 5 years) may increase the risk of carcinoma in situ and invasive carcinoma.
• Tuberculosis: Rifampicin is likely to decrease POP effectiveness.
Family Welfare and Contraception

- **Fibroids:** POPs do not appear to cause growth of fibroids.
- **Diabetes:** POPs may increase the risk of thrombosis, although less than COCs, in complicated diabetes or cases of more than 20 years duration.
- **Viral hepatitis and cirrhosis:** POPs may affect liver function, although less than COCs.
- **Rifampicin and certain anticonvulsants:** POPs may be less effective in women taking these drugs.
- **Antiretroviral therapy:** POPs may affect ARV therapy in AIDS patients. In these cases, a condom is preferable.

**Continuous Use Oral Contraceptives**

Studies have found that continuous use of monophasic pills reduces the number of times women experience monthly bleeding per year and reduces the number of bleeding days. Continuous use OCs also reduce the side effects including migraines, headaches, premenstrual syndromes, mood changes and heavy or painful menstrual bleeding which women experience while taking COCs for 3 weeks with 1 week off. However, in continuous use OC users incidence of breakthrough bleeding (BTB) or spotting is more which diminish after about 8 or 9 months of use.

One formulation, “seasonale” is packaged specifically for continuous use and is the US Food and Drug Administration (US FDA) approved. It contains 0.15 mg l-levonorgestrel and 0.03 mg EE (same doses as those of low-dose pills). Women take a pill every day for 84 days (12 weeks), and then take hormone-free pill for 7 days. This results in 4 withdrawal bleeds a year rather than 12. Seasonale has become a popular method of contraception in recent years. No extra pathologic change in lipid profile and endometrium has been found so far.

**Male Pill**

Within the next 5 years, a pill designed for male contraception could be available commercially. This is based on systemic administered steroid hormones which act by inhibiting the secretion of LH and FSH, thereby leaving testosterone secretion intact, thus rendering the man infertile but not impotent.

**Injectable Contraception**

Injectable contraceptives contain synthetic hormones that are administered by deep intramuscular injection, and are considered safe, effective and reversible contraception for most women. The injectable contraceptives that are available are:

- **Progesterone-only injectables (long acting):**
  - DMPA as a 1 mL injection containing 150 mg DMPA in an aqueous microcrystalline suspension, given once every 3 months
  - Norethisterone enanthate (NET-EN) as a 1 mL injection containing 200 mg DMFA in an oily preparation, given once every 2 months.

- **Combined injectables (short acting):**
  - Cyclofenyl Cycloprovera contains 25 mg of medroxy-progesterone acetate and 5 mg of estradiol cypionate, administered once a month
  - Mesigyna/Norigynon contains 50 mg of NET-EN and 5 mg of estradiol valerate, administered once a month

**Hormone-releasing Intrauterine Contraceptive Devices**

There are two hormone-releasing IUCDs:

**Progesterone IUCD**

This device called Progestasert is T-shaped, made of ethylene vinyl acetate (EVA) copolymer impregnated with barium sulfate. The vertical shaft is fitted with a capsule containing 38 mg of progesterone dispensed in silicone oil, delivering progesterone to the uterus at the rate of 65 µg per day. The contraceptive efficacy lasts for 1 year, although there is a possibility of increase of ectopic pregnancy. The use of Progestasert also leads to a decrease in menstrual loss.

**Levonorgestrel IUCD**

It is the “Gold Standard” IUCD amongst the hormone-releasing IUCDs, and is known by different names like LNG-20, Levonova and Mirena. It is long acting when compared to Progestasert, with a contraceptive effect lasting for 5 years, the pregnancy rates being very low at 0.1–0.4% per 100 women year in the first year. It is also T-shaped with a capsule on the stem, the core of the capsule containing a mixture of silicone rubber and 40–60 mg of levonorgestrel (LNG), releasing 20 µg of LNG per day. It has a protective effect against ectopic pregnancy, in addition to decreasing menstrual blood loss, sometimes resulting in complete amenorrhea, and is hence being actively promoted as treatment for menorrhagia.

**Emergency Contraception**

Emergency contraception refers to a method of contraception, used as an emergency measure to prevent unwanted pregnancy following unprotected intercourse or expected failure of contraception. EC is also referred to as “postcoital” or “morning-after” contraception, or interception.

Unwanted pregnancy can arise due to many reasons for which a woman may opt for EC. They are:

- Unplanned intercourse
- Forced intercourse
- Rape
- **Condom:** Slipped out/tore during coitus
• **OCPs:** Irregular pill taking/three or more missed pill without using any other form of contraception  
• **DMPA:** More than 2 weeks late for repeat injection  
• **NET-EN:** More than 1 week late for repeat injection

Emergency contraception can be provided by the following ways:
- Hormonal tablets
- Intrauterine contraceptive devices
- Others: Mifepristone (RU-486).

### Hormonal Tablets

Also known as emergency contraceptive pills, these are either COC pills or POP pills.

**Methods:**
- Two conventional COC pills (50 mg EE + 250 mg LNG) within 12 hours (1st dose) of unprotected intercourse, and then repeat the same dose 12 hours later (2nd dose): Yuzpe regimen.
- Four “low-dose” COC pills as 1st dose within 12 hours, 4 more 12 hours later (2nd dose).
- **POP:** 750 mg LNG as 1st dose (within 72 hours of unprotected intercourse) and repeat the same dose 12 hours later (2nd dose).

**Mode of action:**
- Delay or inhibit ovulation
- Alter tubal transport of sperm/egg or zygote (if fertilization has occurred).
- Impair endometrial ripening (makes the endometrium hostile for implantation of the embryo).

**Success rate of EC (when administered correctly):**
- Yuzpe regimen: 97–98%
- POP: 99%
- Cu-IUCD: 99.9%.

**Problems:**
- Nausea, vomiting (2%) with Yuzpe regimen
- Abdominal cramps
- Delayed periods
- Spotting.

**Intrauterine contraceptive devices:** Insertion of a copper (Cu) containing IUCD (Cu-T 200, Multiload Cu-250, Multiload Cu-375, Cu-T 380 series, etc.) within 120 hours (5 days) of unprotected intercourse. This not only provides effective interception (99.9%) but also can be continued as contraception for 3–5 years, depending on the type of IUCD used. It can only be used in parous women.
- **Mifepristone:** Mifepristone (RU-486) is a potent anti-progesterone agent (with five times more affinity for the progesterone receptor than progesterone itself). It has been used extensively and successfully as an intercourse since 1988. The original dosage schedule used was 600 mg as a single dose on day 27 of the menstrual cycle. Nowadays, reduced dosages of 50 mg, and even as low as 10 mg, have found popularity as an effective form of interception. In addition, the 10 mg dose regimen produced half the incidence of delayed periods for more than 7 days when compared to those women who were administered 600 mg (18% vs 38%). Ultralow dose therapy with 5 mg is now under clinical trial.

### NONSTEROIDAL CONTRACEPTION

#### Natural Methods of Contraception

Natural methods of contraception are those, which do not use any appliance of medicine. Some of these methods have been practiced throughout the world from prehistoric times. They are mentioned here only for completion, as their individual failure rates are high (10–35% women years), although when used effective and consistently, the failure rate can be lowered. The natural methods of contraception still practiced are:
- **Natural family planning methods:**
  - Rhythm method/safe period
  - Basal body temperature method
  - Cervical mucus method/ovulation method/Billings method
  - Symptothermal method.
- Lactational amenorrhea method
- Withdrawal method
- Others: Vaginal douching; abstinence

#### Barrier Contraception

Barrier contraceptives are family planning methods which act as barriers and prevent the fertilization of the ovum by the spermatozoa. They are of four types:

1. **Condom:**
   - Male
   - Female.
2. **Occlusive caps:** Vaginal diaphragms, cervical caps, Vault cap, Vimule cap.
3. **Vaginal sponge:** Nonoxynol-9.
4. **Spermicides:** Nonoxynol-9; chemical suppositories; foam tablets; aerosol creams.

#### Male Condom

The male condom is the only known contraceptive proven to prevent sexually transmitted diseases (STDs) and HIV infection which causes AIDS. Various types of latex rubber condoms are available: dry, lubricated, colored, flavored, scented, textured with or without spermicidal incorporation. The condoms are circular cylinders closed at one end with a small teat and open at the other with an integral rim, 15–20 cm in length, 3–3.5 cm in diameter and 0.003–0.007 cm
in thickness. Polyurethane and silicon condoms are now available, although expensive. The typical average failure rate of condom varies from 3% to 12%, but has been reduced to 1%, if a spermicidal product (nonoxynol-9) is used along with the condom. Condoms have a shelf life of 3 years.

**Female Condom (Figs 1A and B)**

The female condom has been a recent development. Various designs have been proposed, including the bikini-condom with its integral latex pouch, and more recently the Janesway panty-condom, with a latex pouch attached to frilly knickers!! The most successful product is Femidom (reality in the USA), first devised in Denmark. It is made of polyurethane and preloaded with an efficient silicone lubricant, 17 cm long, with an open outer end of 70 mm diameter with a ring attached to prevent it advancing beyond the vulva, and a 60 mm diameter inner ring at the inner closed end aiding retention within the vagina (squeezed like a diaphragm for insertion). The whole device thus forms a well-lubricated secondary vagina. Reports about its acceptability are high, although its use effectiveness (95% effective to 1 year of perfect use) is broadly similar to the male condom. The advantages proposed are:

- Over-the-counter method, not requiring fitting by any outsider
- Under the woman’s control
- One universal size
- Women of any age can use it
- Insertable pre intercourse
- Does not require an erect penis at outset
- Male sensations reported to be better than male rubber condom

- Odor free
- Complete barrier against STDs including viruses
- Worth suggesting if local soreness makes sex uncomfortable or during menses or postpartum lochia or during missing pill periods
- Shown to be less likely than the male condom to rupture in use
- Not damaged by any common chemicals.

The problems reported in use are:

- Prominence during foreplay
- The potential for the penis to become wrongly positioned (between the sac and the vaginal wall)
- It is rather noisy in use: Prompting the suggestion to “have the music on”!!

The female condom can be used with both water-based and oil-based lubricants. Male condoms should not be used concurrently because simultaneous use may cause friction that leads to condom slipping, tearing, and displacement. Following use, the female condom outer ring should be twisted to seal the condom so that no semen spills out.

The female condom has an acceptability rate of about 60% for women and 80% for men. However, the pregnancy rate is higher than with the male condom. The female condom has a 0.6% breakage rate. The slippage and displacement rate is about 3% compared with 3–8% for male condoms. In vitro tests have shown the condom to be impermeable to HIV, cytomegalovirus, and hepatitis B virus.

**Cervical Cap**

The Prentif cavity-rim cervical cap was approved for use by the FDA in 1988. The flexible, cup-like device is made of
natural rubber and is fitted around the base of the cervix. It can be self-inserted and allowed to remain in place for up to 48 hours. It should be used with a spermicide applied once at insertion. If properly fitted and used correctly, the cap is comparable in effectiveness to the diaphragm. The cervical cap is relatively costly, and overall, incorrect fitting and/or improper placement make it less effective than the diaphragm plus spermicide.

**Lea’s Shield**

Lea’s Shield (Yama, Inc., Union, NJ) is a reusable, washable barrier made of silicone, which is placed against the cervix (Fig. 2). The device comes in one size, which simplifies the fitting process. It may be inserted any time prior to intercourse and must be left in place for at least 8 hours afterwards. When used with spermicide, and adjusted for age, the reported 6-month life-table pregnancy rate was 5.6 per 100 users.

**Vaginal Sponge**

The most popular vaginal sponge available in the market is Today, a soft disposable foam sponge made of polyurethane, saturated with a powerful spermicide, nonoxynol-9. It is inserted high up in the vagina prior to intercourse, the spermicidal effect lasting for 24 hours (intercourse may be repeated as often as desired during this period). It must be removed and discarded after 8–24 hours but not before 6 hours of the last act of coitus. The failure rate varies between 9 and 27 per 100 women users in the first year. In addition to allergic reactions, vaginal dryness, soreness, the real danger of the sponge is the development of a rare life threatening complication, toxic shock syndrome (TSS). TSS is an extremely serious illness characterized by vomiting, diarrhea, high-grade fever, body rash and ultimately shock, caused by an endotoxin produced by *Staphylococcus aureus*.

**Nonhormonal Oral Contraceptive Pill**

**Female Pill**

The need for a safer alternative to estrogen-progestogen COCs was felt for over three decades. Researchers the world over have been designing and synthesizing nonsteroidal estrogen antagonists that would act by disturbing the delicate balance between estrogen and progesterone at the uterine level without interfering with the synthesis of blood levels. This led to the discovery of Centchroman, which marked a significant breakthrough in the sphere of contraception.

Centchroman is a novel nonsteroidal agent unrelated to any conventionally used contraceptive. Centchroman offers a unique combination of weak estrogenic and potent anti-estrogenic properties. In other words, Centchroman is a selective estrogen receptor modulator (SERM), and mediates its estrogenic effects through its estrogen receptor interaction. Central Drug and Research Institute (CDRI), Lucknow has the unique singular distinction to conceive, research and manufacture this molecule for the first time in the world. Centchroman is truly a “made in India” product.

**Mechanism of action:** Centchroman exerts its contraceptive action by the following ways:

- Acceleration of embryo transport through the fallopian tubes
- Suppression of endometrial proliferation and decidua- lization leading to a dyssynchrony between the embryo and uterine development
- Thickening of the cervical mucus

Centchroman has no effect on the hypothalamo-pituitary-ovarian axis and does not inhibit ovulation.

**Dose and administration:** The accepted regimen is one tablet of 30 mg twice a week for 3 months, followed by one tablet once a week for as long as contraception is desired. The first tablet has to be taken on the first day of the menstrual cycle and more importantly, the tablet should be taken on fixed days and at fixed times. The dosage should be strictly followed irrespective of subsequent menstrual periods.

Centchroman can be safely administered to lactating women after 6 months of delivery as a precautionary measure, although the concentration of the drug is below that of any which can have physiological consequences to the suckling baby.

**Contraindications**

- Polycystic ovarian disease
- Cervical hyperplasia
- Recent history of clinical evidence of jaundice or liver diseases
- Severe allergic states, chronic illness (tuberculosis, renal disease, etc.).
Effectiveness: Pearl index—1.07 (in a phase III study involving 26,899 women months of use).

Male Pill

The male pills, which are in use and under study, are:
- Gossypol
- Triptolide
- Styrene maleic anhydride.

Gossypol, or more commonly referred to as the “Chinese male pill”, has been used in China since 1972. It is a dissequiterpene aldehyde obtained from the seed, stem and roots of the cotton plant, and is now available in a highly purified form. Gossypol produces its effect by inhibiting spermatogenesis, decreasing epididymal sperm motility and affecting the conversion of proacrosin to acrosin. Restoration of fertility on stopping the drug is a problem and is associated with side effects, the most dangerous of which is hypokalemic paralysis seen in 1% of users.

WHO is investigating Triptolide, a compound extracted from the Chinese plant, Tripterygium wilfordii, for its antifertility effect.

Every attempt is being made to find chemical compounds having effects on sperms stored in the epididymis. A phase II clinical trial of a vas deferens injectable male contraceptive has been carried out. 60 mg of an agent containing styrene maleic anhydride (SMA) when administered bilaterally was shown to inactivate spermatozoa all along the length of the vas almost immediately for at least a 12-month-period. The method appears to be safe and yearly injections are required.

RISUG an acronym for “reversible inhibition of sperm under guidance” is a clear polymer gel made of SMA mixed with dimethyl sulfoxide (DMSO). It was developed in the Indian Institute of Technology and the All India Institute of Medical Sciences in India. RISUG is injected into the vas deferens in the testis; it partially blocks the vas, preventing sperms from coming into the ejaculate. It may act in some other way also. Results from Phase I and Phase II clinical trials suggest that use of RISUG is safe and effective as a contraceptive method. Animal studies have shown that sperms reappear when RISUG is flushed out with DMSO or sodium bicarbonate, or noninvasively by massage, vibration and low level electric current. Toxicological studies are being conducted.

Intrauterine Contraceptive Devices

Intrauterine contraceptive devices are an effective, safe and convenient method. They are made of plastic or metal or a combination of both of these materials, meant for insertion into the uterine cavity for contraception.

Indications
- Women who:
  - Want to delay pregnancy for a few years
  - Are breastfeeding
  - Have difficulty using other reversible methods
  - Prefer a method that does not require supervision or action before the act of coitus.

Intrauterine contraceptive devices are typically classified into three categories:
1. Inert IUCDs: Lippes loop, Saf-T coil, Ota ring
2. Copper-releasing IUCDs: Copper-7, Copper-T 200, Copper-T 220C, Multiload Cu-250, Multiload Cu-375, Copper-T 380A, Copper-T 380S.

The Cu-T 380 series is often considered as the “Gold Standard” IUCD amongst the categories mentioned above.

Based on contraceptive efficacy, IUCDs are divided into three groups:
1. Group I: Pregnancy rates greater than 2.0 but not less than 1 per 100 women years (Lippes loop, Copper-7)
2. Group II: Pregnancy rates less than 2.0 but not more than 1 per 100 women years (Multiload Cu-250, Copper-T 220C).
3. Group III: Pregnancy rates less than 1 (mostly less than 0.5) per 100 women-years: Multiload Cu-375, Copper-T 380A, Copper-T 380S, LNG-20.

Mechanism of Action
- Preventing sperms by impeding sperm transport and inhibiting their capacity to fertilize the ova
- Produce an inflammatory or foreign body reaction, which in turn causes cellular and biochemical changes in the endometrium, and in the uterine and tubal fluids.

Advantages
- No systemic undesirable side effects as in OCs
- Reversible: Fertility returns immediately following removal
- One time motivation
- Only one insertion every 3–5 years
- Cost-effective.

Implants

In order to increase contraceptive efficacy without corresponding dose increases, non-oral systems for sustained release of progestogens have been developed. Sustained-release progestogens implants (implantable contraceptives), are a new approach to meeting a worldwide need for more effective and acceptable birth control. This need stems from at least four background problems:
1. Rapid background growth
2. Environmental degradation
3. Persistent poverty
4. Unplanned pregnancy.

The implants which are available at present are non-biodegradable, (polydimethyl siloxane: silastic, EVA) which although are easy to insert, but terribly difficult in comparison to remove. Attempts are now on to discover newer implants, which are biodegradable. The WHO medical eligibility criteria are less restrictive for contraceptive implants than for OCs. In addition, implants are now considered to be probably the most efficacious method of all reversible contraceptives.

The implants currently available are:
- **Norplant**: Six silastic capsules releasing LNG, with a contraceptive efficacy of 5 years.
- **Norplant-2**: Two silastic covered rods releasing LNG, with a contraceptive efficacy of 3 years.
- Implanon consists of EVA rod releasing 3-keto desogestrel (etonogestrel), with a contraceptive efficacy of 3 years.
- Elcometrine Nestorone implant.

**Jadelle or LNG Rod**

This new system of contraceptive implant, the Jadelle or LNG rod, was earlier known as Norplant II. This type of implant as well as Norplant are research products of the Population Council, New York, and are manufactured by Leiras in Finland.

The LNG rod consists of two solid silastic rods, each 44 mm long. A total of 70 mg LNG is dispersed in the matrix of each rod. They are inserted and removed in the same way as the original Norplant, although both insertion and removal are much easier. The daily release of hormone too is almost like that of the original Norplant. The effectiveness and acceptability of the rod is same as that of Norplant capsules.

The failure rate of Jadelle or original Norplant is 0.05% (5 per 1000 women) in the first year of use and the continuation rate at 1 year is 84%.

The main points about the LNG rod are as follows:
- The LNG rod is a new product of its kind.
- It has approved effective life of 5 years rather than 3 years.
- The device is easier to insert and remove than the old Norplant system, as it does not become fragile through prolonged stay in a woman’s arm.

Although the LNG rod has been intensively tested and approved in USA, it is not yet available in the US market at the time of writing although is available through the private sectors in Europe and many developing countries including India.

**Efficacy**
- **Three years cumulative pregnancy rate**: 0%
- **Five years cumulative pregnancy rate**: 1%

**Benefits**
- Effective contraception
- Lower incidence of ectopic pregnancy
- Less lower genital tract infection (vaginitis, cervicitis)
- Less pelvic inflammatory disease.

**Problems**
- **Vaginal spotting/bleeding**: Common within the first year of use.
- **Amenorrhea**: Up to 75% after first year of use (less with LNG).
- **Headache, dizziness, mood changes, acne, weight gain**: 1–10%.

Other nonbiodegradable implants like ST-1345 implant (1 capsule) and Uniplant implant (1 silastic rod with nomegestrol acetate) are still in clinical trials. The main biodegradable implant, a single poly-e-caprolactone capsule with LNG (Capronor) with a contraceptive efficacy for 1 year, is under extensive study and ready for commercial availability. Finally, biodegradable subdermal NET pellets are being used in clinical trials with various ratios of NET to cholesterol (Annuelle: 4 pellets with 90% NET and 10% cholesterol).

**Implants Undergoing Trials and Research**

**ST-1435 single-rod implant or nestorone implant**: The Population Council is now testing a single modified silastic implant using a new progestogen ST-1435 which has contraceptive action and side effects similar to those of LNG. The implant contains ST-1435 crystals encased in a silastic capsule which releases the hormone at the rate of 100 µg/day. Early clinical trials have shown reliable contraceptive effect.

It is designed specifically for lactating women and has completed phase II clinical trial.

**Chinese no. 2 implant**: This system—also called sino-implant—is nearly identical to Jadelle but contains more LNG (150 mg instead of 140 mg).

**Vaginal Rings**

Steroid-containing vaginal rings have been in use intermittently for the last three decades. The vaginal rings available are:
- Levonorgestrel ring
- Progesterone ring
- Etonogestrel (3-keto desogestrel) ring
- ST-1435 ring
- R-2323 ring
- Combined estrogen-progestogen rings:
  - EE and etonogestrel
  - EE and LNG
  - EE and norethisterone acetate.
**Levonorgestrel Ring**

This ring has been tried by WHO since 1980 and are called Varlevo 20 rings or Silastic 382 rings. They are silicone rubber rings with a diameter of 55.6 mm and a cross section of 9.5 mm, and contain 5 mg of LNG with a daily release rate of 329 µg. It acts in three ways:

1. By changing the character of the cervical mucus to make it impermeable to sperms
2. By making the endometrium "out of phase"
3. Inhibiting ovulation (50% of women).

It is left in the vagina for 3 months continuously, after which it is replaced by a new one. The "first pass effect" on the liver is eliminated, lessening some side effects of the OCs. The other advantages are that they are convenient to use and reversible at will. The disadvantages include expulsion during defecation, irregular bleeding or spotting. The failure rate with the device in place is 3.7% women at the end of 1 year. The 1 year discontinuation rate is 50%.

**Hormonal Contraceptive Vaginal Rings**

Vaginal rings are a new method of steroid contraceptives. Some of them have recently been approved by the US FDA, and are on the market in some countries. Combined estrogen and progestogen rings offer good cycle control and deliver hormones more steadily than COCs.

Women can control the use of vaginal rings. A woman inserts the vaginal ring with her fingers in the higher part of vagina. The vaginal ring currently available for contraception is Nuva Ring.

**NuvaRing**

One of the most recently marketed methods is NuvaRing (Organon). It is a soft vaginal ring that release 15 µg EE and 120 µg etonogestrel, the active metabolite of desogestrel, per day as a controlled delivery system. Women keep the Nuva-Ring in the vagina for 3 weeks, and then remove it for 1 week, during which they have withdrawal bleeding. A new vaginal ring is needed for each 4 weeks cycle. If necessary the ring can be removed for intercourse, but it should not be outside the vagina for longer than 3 hours at a time during the scheduled 3 weeks use. When the period of non-use exceeds 3 hours, the manufacturers recommend an additional method of contraception for the next 7 days.

The contraceptive effect of NuvaRing is achieved through inhibition of ovulation. Concomitant use of vaginal antimycotics, spermicides or tampons does not appear to affect efficacy. The metabolic effects of NuvaRing are similar to those of low-dose COCs. The efficacy rate of NuvaRing is like that of COCs—the failure rate after perfect use is 0.3% within the first year of use and 8% after typical use.

One of the disadvantages is ring expulsion without the knowledge of the woman—sometimes resulting in pregnancy. Factors associated with expulsion are prolapse of the uterus cystocele, rectocele and severe or chronic constipation. The side effects include headaches, leukorrhea, vaginitis, nausea and breast tenderness. The high cost of NuvaRing is another disadvantage.

The advantages of NuvaRing include the low doses of hormones, avoidance of gastrointestinal disturbances and a rapid return to ovulation after discontinuation. Moreover, the ring is easy to insert and remove from the vagina; it is generally not felt by the partner during intercourse; it gives the women control without help from medical persons and is well tolerated.

However, NuvaRing is a new contraceptive method and further studies are needed to ascertain the long-term effects.

**Promising Trials and Development**

**Combined estrogen and progestogen vaginal ring**: It is a ring still at the stage of clinical trials and releases a combination of 150 µg of different progestogens, nestorone (ST-1435) and 15 µg of EE per day. The Population Council, with the help of US AID, is developing this ring specifically for use in developing countries. It will be effective for over 12 months. Women would keep the ring in the vagina for 3 weeks, then remove it for withdrawal bleeding and then reinsert the same ring for another 3 weeks. The early clinical trials are promising, and phase III trials are planned in 2005. There were 1.2 pregnancies per 100 women in the first year of use. The side effects were like those of COCs.

**Progestogen vaginal ring**: A vaginal progesterone-only ring called “Progering” has been developed and has been undergoing clinical trials since late 1990s. It contains natural hormone progesterone. These rings are slightly less effective than combined vaginal rings; however, they are very effective in lactating women because breastfeeding itself provides some protection against pregnancy. They do not contain estrogen which can reduce milk production. Each ring releases 10 mg of progesterone daily and lasts for 3 months. Women use these rings continuously for up to 1 year. Bleeding disturbances are common; other effects are almost the same as those of combined vaginal rings.

**Nestorone vaginal rings**: The Population Council is developing another progestogen-only ring containing nestorone (ST-1435), a more potent synthetic progestogen. These rings are particularly suitable for lactating women and provide effective contraception for up to 1 year like progering. However, clinical trials on these rings have lately been suspended.

**Permanent Methods**

- Female sterilization
- Male sterilization
Although a detailed discussion on the permanent methods of contraception is far beyond the scope of this chapter, a brief mention of the common methods in use are given below:

### Female Sterilization
- Minilaparotomy
  - Pomeroy’s technique and its modifications
  - Irving’s technique
  - Uchida’s technique
  - Kroener’s technique
  - Madlener’s technique
  - Parkland’s technique
- Vaginal tubectomy
- Laparoscopic sterilization
  - Falope/Yoon ring application
  - Hulka-Clemens/Fische clip application
  - Bipolar electrocoagulation method

The 10-year cumulative failure rates of female tubal sterilization methods are:
- Unipolar coagulation: 0.75%
- Postpartum tubal ligation: 0.75%
- Silastic (Falope/Yoon) ring: 1.77%
- Interval tubal ligation: 2.01%
- Bipolar coagulation: 2.48%
- Hulka-Clemens clip: 3.65%

### Male Sterilization
- Conventional vasectomy
- “No-scalpel” vasectomy

**No-scalpel vasectomy versus conventional vasectomy**: No-scalpel vasectomy, developed by Dr Li Shungiang of the Sichuan Province in China, is as effective as the conventional approach. Since 1986, this new technique has become more and more popular in many countries in the world. In China, more than 10 million men have undergone no-scalpel vasectomy. The new technique has some definite advantages over the conventional technique:
- The procedure takes less time, about 10 minutes
- Faster recovery
- Improved method of local anesthesia (vas block)—less painful
- Less tissue injury; less bleeding; decreased incidence of hematoma formation; less infection; less postoperative discomfort
- Psychologically a more acceptable procedure as there are no scalpels and stitches involved.

This technique, however, requires good practical training. On the whole, conventional or by the no-scalpel technique, vasectomy is safer, easier to perform, less expensive and has a lower failure rate than female sterilization. In addition, vasectomy reversal is associated with pregnancy rates as high as 70-80%, the best results achieved when the reversal is performed within 3 years of the vasectomy.

### FUTURE CONTRACEPTIVES

**Within 2020**

**Patches**
A new contraceptive method, “EVRA” patch containing EE and norgestimate is under advanced human trials. The patch is applied every week on a woman’s arm, upper chest, abdomen and buttocks, the drugs being released throughout the week. The patch has been found to be very effective, popular with fewer side effects, and expected to be available soon.

**Transdermal contraceptive patch**: A new contraceptive method, the patch, works transdermally by slowly releasing a combination of progestogen and estrogen through the skin. The only contraceptive patch available in the market now is “Ortho-Evra” (also called “Evra” outside USA, developed by Ortho-McNeil Pharmaceutical). It was approved by the US FDA in 1992 and is available in developed countries including USA. This combined patch delivers 150 µg of the progestogen norelgestromin and 20 µg of EE per day. A women wears a patch for 1 week, then replaces it by another one placed at a different site for a total of 3 weeks, followed by 1 week with no patch. The patches work by preventing ovulation, thickening the cervical mucus and suppressing endometrial growth.

Ortho-Evra is a square patch resembling a light-brown bandage. Each side is about 4.45 cm (1.75 inch) long. The patch is applied over dry skin on the buttocks, lower abdomen, upper outer arm or the upper body (front or back) but not on the breasts. The patch adheres well to the skin, allowing women to perform daily regular activities such as bathing, swimming, working and exercising without interruption even in warm, humid climates. It falls off in about 2% of cases.

It provides effectiveness and cycle control like those of OCs when used. The failure rate with typical use within the first year is 2 per 100 women and with perfect use 0.3 per 100 women (or 3 per 1,000).

The first patch should be applied within the first 5 days of menstruation. It should then be changed each week for 3 weeks, applying it each time to a new location. For the fourth week, no patch is worn, to allow for withdrawal bleeding. However, it may be used continuously, using a fourth patch in fourth week if the withdrawal bleeding is to be delayed.

Skin irritation or rash at the site of application is the most common side effect of Ortho-Evra. Other side effects are like those of COCs. The incidence of break through bleeding and spotting is low among users of Ortho-Evra patch, and further decreases with longer use.
**Vaccines**

In order to stabilize the present population and check further population explosion, particularly in developing countries like India, there appears to be tremendous need to develop an effective, reversible, long-lasting and easy to administer contraceptive method. Research is on to produce vaccines which can be manufactured at a relatively low cost, administered by paramedics, and have long lasting reversible contraceptive effects but with a selective effect on the reproductive chain limiting the risk of metabolic effects.

The contraceptive vaccines that are being extensively researched at present are:
- **Anti-human chorionic gonadotropin vaccine**
- **Anti-zona pellucida vaccine**
- **Anti-sperm vaccine**

**Promising Trials and Development**

*Transdermal contraceptive spray or gel:* The progestogen nestorone, appropriate for breastfeeding women, is being tried at (phase I clinical trial stage) as a spray-on approach for transferring a preset dose of fast-drying hormone on to the skin.

**Male Fertility Regulation**

The hormones that have been tried for male contraception are:
- **Androgens:** Testosterone enanathate 200 mg injections administered weekly; testosterone buciclate.
- **Progestogen:** DMPA
- **Antiandrogen and progestogen:** Cyproterone acetate.
- **Gonadotropin releasing hormone analogs:** Agonists; antagonists

Research is on in the field of producing biodegradable testosterone microcapsules and testosterone pellets, for the maintenance of sexual function.

In India, a multicentric phase III human clinical trial with an injectable contraceptive named RISUG (acronym for Reversible Inhibition of Sperm Under Guidance) is underway. RISUG is injected into the vas deferens, a single 60 mg injection of which can provide contraception for 10 years. A single dose is expected to cost ₹ 70/- with no side effects reported so far. Smaller doses of RISUG are also being tested for providing contraception for shorter periods, and possibly making it a reversible method of male contraception.

*Intra vas device:* Intra vas device (IVD), originally called Shug, is a device (plug) that is implanted in the vas deferens. Two plugs are implanted into each vas deferens. In animal studies, the IVD resulted in no sperm reaching the ejaculate, but after removal of the devices, all primates ejaculated normal numbers of sperm again. However, the method requires special technological skill like that of the ‘no-scalpel method’ of vasectomy. Wider trials are needed.

**Plant compound pills:** Attempts are being made to isolate newer isomers of gossypol and try their antifertility effects. The toxicity of these products will be keenly watched; however, the use of gossypol is being discouraged by some workers. Oral compound such as triptolide, extracted from the Chinese plant *T. wilfordii* is being investigated by the WHO for its antifertility effect.

**Beyond 2020**

- **Regulatory peptides**
- **Gene therapy**

Both regulatory peptides and gene therapy in relation to contraception are in their infancy, but hold great promise for the future.

**Male Vaccine**

Having failed to produce a safe, effective and reversible male contraceptive vaccine against hormones such as FSH and GnRH analogs, scientists are currently endeavoring to isolate, identify and produce antisperm surface antigens so as to develop a contraceptive vaccine which will hinder sperm-egg union without bad side effects. However, the development of such a method of contraception is not expected in the near future.

**CONCLUSION**

A recent International conference on the quality of care for family planning, reproductive health, and the three China National Comprehensive Programs (3 NCPs), held in Beijing, summed up the need for the “Program for Improving Quality of Contraceptive Care” project, where the participants reached a consensus to stress that:

- Informed choice and follow-up services are necessary
- Different contraceptive methods should be used at different ages
- Attention should always be paid to medical condition, lifestyle, and culture
- In addition to informed choice, all the other aspects of reproductive health care must be addressed. A specific example is the provision on the migrant population’s education about the prevention of STDs.

We, in India, can definitely learn from the tremendous success that China has achieved in controlling its population by proper planning and implementation of its family planning services, to hasten economic and social development.

Although it is almost impossible to cover all the areas of steroidal and nonsteroidal contraception in females and males in a single chapter, every attempt has been made to bring to light some of the existing methods and exciting new advances in the field of contraceptive technology. Newer molecules and drug delivery systems are on the anvil, some under research and others in phase II, III and IV clinical trials. We await the future of contraception with bated breath!!
REFERENCES

INTRODUCTION

Abortion care should be made available as close to people’s homes as possible and should be performed by the least specialized personnel who are adequately trained to perform it safely and well.\(^1\)

The benefits of this proposition are particularly relevant in a geographically large country like India, with its population of over a billion. In spite of having legalized Medical Termination of Pregnancy (MTP) over 3 decades ago, India still grapples with varied levels of facilities stretching unevenly over the subcontinent, to provide greater access to safe abortion. This presentation reviews the current status of abortion practice and outlines and summarizes possible solutions and directions for the future.

CURRENT STATUS OF ABORTIONS

More than 75 million women worldwide experience an unwanted pregnancy each year.\(^2\) Two-thirds of these women opt for induced abortions. Of these procedures, 20 million are deemed unsafe.\(^1\)

Approximately, 25% of the world’s population lives in countries where abortion is illegal without exception or is permitted only to save the life of a pregnant woman.\(^2\) While only 22% of the 190 countries in the world have laws allowing abortion on request, the Indian Medical Termination of Pregnancy Act with its acceptance of sociomedical indications rates amongst the most liberal.

Estimates of Abortion Prevalence

The reported worldwide abortion rate is around 35 per 1,000 women aged 15–44 years.\(^4\) It is estimated that 55,000 unsafe abortions take place everyday. Half of all women having illegal abortions live in Asia, 25% in Africa, 20% in Latin America and the remaining 5% in eastern Europe.\(^1\)

An estimated 6.7 million induced abortions take place each year in India. In contrast, national MTP records report approximately 0.6 million MTPs. This indicates a ratio of 10–11 illegal abortions for each MTP reported in national statistics.\(^1\)

This high ratio of illegal abortions may be attributed to a total lack of awareness regarding the legality of MTPs in India in the general population, paucity and inaccessibility of appropriate, recognized facilities and a tendency to seek services from easily approachable traditional birth attendants and quacks. Interestingly an ICMR survey on illegal abortion has highlighted a preference for qualified doctors and approved institutions. However, poor knowledge or inaccessibility of facilities, lack of courteous and compassionate interaction and a concern for secrecy deters clients from accessing public health facilities.\(^5\)

Ironically, a significant number of unreported MTPs are actually performed by qualified medical personnel, either because the well-equipped centers lack recognition or the accessory clinical documentation and paperwork is inadequate. These MTPs may be referred to as the safe illegal abortions, though in the eyes of the law their legal status is no different than any criminal abortion.

CHARACTERISTICS OF ABORTION SEEKER

The characteristic profile of women seeking abortion in India is of young, married women with at least 2 or more living children, who have failed to use contraception or in whom contraceptives have failed, and who do not want more children at all, or just at yet.\(^5\)
In marked contrast late abortions were more often sought in adolescent and unwanted pregnancies. A series of 2,055 second trimester MTPs represented 15% of all abortions over 10 years. While unmarried adolescents represented 5.5% of all MTPs, they accounted for 18.6% of second trimester MTPs. The MTP Act of 1971 has been beacon of social and medical legislation with far reaching positive benefits for the reproductive health of women. It is an empowering Act for the healthcare system and its beneficiaries, setting aside the application of the IPC in certain well-defined sociomedical situations.

Safe Abortion Services: Inadequate Availability

There exists great inequity in the availability of safe, legally recognized abortion services in India. This has led to a situation where only a tenth of an estimated 6.7 million abortions induced annually in India are being reported. This disparity exists at least in part due to the fact that there were just around 9,467 approved institutions for providing safe abortion services for the entire country in 1997. This problem of inadequate facilities is even more acute in the rural setting with only 1,800 out of over 20,000 primary health centers offering MTP facilities. This deficiency was attributed to the fact that the current overly medicalized requirements for conventional procedures demanded by the MTP Act and Rules are difficult to achieve and hence a hurdle to widespread availability of safe abortion.

Certification procedures for facilities were cumbersome and bureaucratic and have become the main hurdle to expanding safe abortion services through the private and NGO sectors. A FOGSI questionnaire on MTPs in clinical practice elicited 118 responses. While 28.8% centers reported easy recognition, 12.7% were recognized after delays from 1 year to 7 years, 44.1% reported difficulties in navigating the recognition process, while 11.9% of respondents were unaware of the need for center recognition. There was scope to simplify and streamline bureaucratic procedures by amending MTP rules and regulations. In what proved to be a stellar demonstration of government, professional organization and NGO partnership, the MTP Act was amended in 2002 and the rules were amended in 2003.

National Population Policy

A significant aspect of the National Population, 2000, was the serious thrust in establishing decentralized safe abortion services. It is proposed to achieve this by disseminating community level education about the availability of safe, legal abortion, increasing the geographic spread and enhancing affordability, adopting updated safe, easy and simple technologies, eliminating cumbersome registration of centers and establishment of additional training centers.

Amendments to the MTP Act and Rules

The amendments introduced in the Act in 2002 and in the rules in 2003, corrected longstanding discrepancies and addressed contemporary issues. The term lunatic was replaced by

LEGAL STATUS OF INDUCED ABORTIONS IN INDIA

Even today voluntarily “causing miscarriage” to a woman with child—other than in “good faith for the purpose of saving her life” is a crime under Section 312 of the Indian Penal Code (IPC), punishable by simple or rigorous imprisonment and/or fine.

Consequent sections (IPC Sections 313–316) relating to causing miscarriage without a pregnant woman’s consent or causing maternal death due to the procedure, are stricter, with punishments ranging from up to 10 years imprisonment and extending up to life imprisonment.

Legalization of Safe Abortion in India: Background Scenario

It was to stem the high maternal morbidity and mortality associated with illegal abortions that the Government of India set up the Shantilal Shah Committee, which after deliberating a wide range of evidence over 2 years recommended a broadening and rationalization of laws related to abortion in 1966.

Based on these, a MTP bill was introduced in the Rajya Sabha in 1969, referred to a Select Joint Committee Review and finally passed as the MTP Act in 1971.

The Medical Termination of Pregnancy Act, 1971

The MTP Act (Act No. 34 of 1971) has been defined in its opening lines as “An Act to provide for the termination of certain pregnancies by registered medical practitioners and for matters connected there with or incidental thereto.”

Legislated by Parliament on August 10, 1971, this central act was passed to extend to the whole of India except the State of Jammu and Kashmir and to be enforced across the country from 1st April 1972. In 1980, Jammu and Kashmir and Mizoram also adopted the MTP Act. However, it is still not applicable in Sikkim and Lakshadweep.

The purpose of this act is to define the situations and circumstances in which safe abortion could be legally performed and to empower medical practitioners and institutions delivering this service. The MTP Act, if adhered to completely, offers full protection to the medical practitioner from consequences of the IPC. However, this legal protection is only available, conditional to every requirement of the Act being fulfilled.

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mentally ill person (person in need of treatment by reason of any mental disorder other than mental retardation). This is a more pragmatic dispensation as compared to the definition from the Indian Lunatic Act, 1912. To ease the registration of centers, the power to register centers was delegated to a district level committee constituted by the government with the CMO or DHO as the Chairperson with a directive to complete inspection within 2 months of submission of application. By differentiating first trimester terminations (gynecology/labor table, back-up for treating shock and facilities for transportation) from second trimester terminations (operation theater table and instruments for abdominal and gynecological surgery, anesthetic equipment), the requirements for early abortions are now easy to fulfill. Medical methods for termination of pregnancy not exceeding 7 weeks may now be prescribed by a registered medical practitioner having access to any registered center.

For the first time, the concept of regulation and punishment was introduced with in the Act with rigorous imprisonment for a term not less than 2 years but which may extend to 7 years for termination by a person not an RMP and termination in place other than defined by the rules.

**TECHNICAL NUANCES OF MEDICAL TERMINATION OF PREGNANCY**

**First Trimester MTPs**

When performed in early pregnancy by well-trained practitioners in adequate facilities, abortion has an excellent safety record.\(^\text{13}\)

**Surgical Methods**

**Vacuum Aspiration: The Gold Standard**

Early abortions are undoubtedly the safest, with a fourfold increase in complications when abortions are performed late.\(^\text{1}\)

The effectiveness of vacuum aspiration for early induced abortion at over 98% is well established in large series and widely acknowledged in clinical practice. The results of meta-analytical study comparing vacuum aspiration with sharp curettage clearly established the undisputed supremacy of vacuum aspiration. Complications such as bleeding and cervical injury were reported to be twofold and uterine perforation sixfold higher with conventional curettage than with vacuum aspiration.\(^\text{14}\) Scientific evidence now suggests that it is time to abandon conventional D&C for induced abortions and the traditional check curettage after suction evacuation, in favor of an exclusive manual or electric vacuum aspiration.

**Resurgence of Manual Vacuum Aspiration in Medical Literature**

Recent medical literature is replete with references testifying to an increasing application of manual vacuum aspiration (MVA) in the practice of induced abortion throughout the first trimester.

Edwards and Carson reported MVA use for early pregnancy termination with postoperative inspection of the villi and transvaginal ultrasound with a 99% success.\(^\text{15}\) Westfall et al. performed MVA up to 12 weeks in a primary care office setting in 1,769 cases. They reported a 99.6% success with only a few minor complications such as retained products and infection.\(^\text{16}\)

**FOGSI Ipas Multicentric Study**

A prospective multicentric study was conducted in 27 purposively selected centers in nine cities and towns across the country over 6 months in 2004 to assess the effectiveness of using the double valve syringe to perform MVA throughout the first trimester. Of the 1,686 MVA procedures reported 1,203 (71.3%) were for MTP and 36% of the MTPs were for pregnancies of over 8 weeks. Complete evacuation with MVA was possible in 99.5% of cases below 8 weeks and 98.2% of cases over 8 weeks gestation. Incomplete abortions and other complications were reported in 2.9% of cases. Most procedures irrespective of gestation period were completed in less than 15 minutes and over half the cases were successfully managed under local anesthesia and/or sedation. The use of check curettage did not decrease the rate of incomplete abortion.\(^\text{11}\)

The multicentric study demonstrated that even in rural life service delivery settings with their inherent variations in clinical practice, instrument handling, case selection criteria and comfort levels of service providers using the equipment, MVA is an effective procedure with a few complications and is being used safely throughout the first trimester of pregnancy. This evidence is even more significant in the light of amendments in the MTP rules in 2003 rationalizing requirements for first trimester MTP provision thus providing an excellent opportunity to expand access to safe abortion through the use of this technology.

A useful observation by the contributors was the potential for reuse of both the MVA syringe and cannulae after simple sterilization procedures. Most centers continue to utilize the original syringe after completing over 50–75 cases.

**Essential Basic Procedure**

The effectiveness, safety and simplicity of the MVA procedure has earned it an endorsement as an essential basic procedure at the first referral unit (FRU) level.\(^\text{17}\) It is now well-established that outpatient MVA under local anesthesia increases access to safe abortions, shortens wait, reduces risk of complications and costs and facilitates links between emergency and contraceptive services.\(^\text{18}\)

**Medical Methods**

With the availability of mifepristone-misoprostol in India since it was approved 6 months ago, there now exists a valid...
option to a surgical procedure. Pioneering studies involving this technique were undertaken in India by Krishna and Coyaji. An interesting study reported its use in rural Indian villages between 1995 and 1998. A total of 294 cases were studied with a 95.9% success. This proved the method to be feasible, safe and effective in varied settings. There is hence great promise of medical methods with MVA backup to promote widespread availability of safe abortions.

Medical abortion technologies have low failure rates, however, it is essential that providers of medical abortion to establish standing arrangements for backup with vacuum aspiration.

Second Trimester MTPs
While late abortions have traditionally been induced by numerous methods, practitioners in India probably have the largest experience of using extra-amniotic ethacridine lactate. Described as the most common and most widely accepted method with documented safety, the main disadvantage is a relatively prolonged induction-abortion interval. A number of combinations have been tested to overcome this. The most effective was the use of extra-amniotic ethacridine lactate with supplementary extra-amniotic 15-methyl PGF₂α (250 g after 6 hours). A study of 315 cases reported an increase in successful termination from 92% to 98% and a reduction in induction-abortion interval from 35 hours to 19 hours with prostaglandin supplementation.

While still resorted to occasionally, effective non-surgical methods have made hysterotomy obsolete and discredited as a primary procedure. There remains a marginal role for aspirotomy in early second trimester during the gray zone when medical methods are not quite effective. These procedures are best performed under USG guidance, to enhance safety.

ABORTION RELATED COMPLICATIONS
Between 1 and 5 of every 10 women undergoing unsafe abortions, need medical care for complications such as sepsis, hemorrhage and trauma. Unsafe abortions result in an estimated 50,000 to 100,000 maternal deaths and many more injuries each year. About a fifth of this burden is borne by India.

TRAINING INTERVENTIONS
The most important strategy to make abortions safe is to increase the number of trained persons who can do the job. In 1997, there were only 163 designated MTP training centers in the country, with a capacity to train around 20 doctors percentage each year, since every trainee had to have practical experience of at least 25 MTPs.

Expansion of the pool of trained abortion providers to include midlevel clinicians has been suggested as an additional way to address the provider shortage.

For any successful mass introduction of safe abortion techniques, it is necessary to enhance training capacities by involving peripheral institutions and nongovernmental organizations besides the teaching hospitals.

Manual Vacuum Aspiration at Primary Health Centers: Pilot Project
A partnership between the Ministry of Health and Family Welfare, Government of India (GOI), State Governments, FOGSI and the World Health Organization (WHO) has been evolved to enhance the delivery of safe abortion services at the district and primary health care (PHC) level in chosen districts. This is to be achieved by training medical officers in government service at the districts and PHCs to decentralize early safe abortion services by introducing MVA services at the grass roots level in the health care system.

Safe Abortions Save Lives
Unsafe abortion endangers health in the developing world and merits the same dispassionate, scientific approach to solutions as do other threats to public health. There is an ample evidence that allowing abortion on liberal grounds reduces maternal morbidity and mortality. India has successfully overcome legal and ethical challenges to induced abortion services, by having in place landmark legislation. Now remains the process of decentralizing and disseminating abortion through establishment of centers throughout the country and training available staff to deliver safe abortion services.

VISION FOR THE FUTURE
That every woman should have access to high quality comprehensive reproductive health services and no woman, even in the remotest corner of rural India, should have to die a preventable death as a result of an unsafe abortion and that every woman must have the right to choose and access safe abortion services with ease and dignity.

REFERENCES
INTRODUCTION

Since the time Medical Termination of Pregnancy (MTP) Act, has been passed in India in 1972, this procedure of termination of an unwanted pregnancy has gone through extensive clinical trials. Various methods have been tried and today some old methods have been replaced by newer and safer techniques. Today more emphasis is on medical methods than surgical methods, especially in the western countries to reduce the cost of hospitalization and to reduce the risk of anesthesia and surgical trauma. However, in our country due to high cost, many clinicians prefer surgical methods for 1st trimester termination, as they are quicker, safer and are considered as “one time procedure”.

As far as methods for 2nd trimester terminations are concerned the search is still on, for an ideal method. The method of choice for 2nd trimester termination today, is combination of extra-amniotic instillation of ethacridine lactate and newer prostaglandins (PGs). The intra-amniotic instillation of hypertonic saline is given up, as it causes severe complications like hypernatremia and disseminated intravascular coagulation (DIC), leading to death. Once again there is revival of “Menstrual regulation” (MR), currently known as “Manual vacuum aspiration” (MVA), specially in developing countries with availability of better MR syringes. This MVA seems to be very promising especially in rural and remote areas where electric power supply is either inadequate or erratic. Abortion is an impressively safe procedure in countries where it is legal, accessible and performed under modern medical conditions. The overall abortion related mortality rate among developed countries is less than 1/100,000 procedures. Reports published from North America and Scandinavia, consistently indicate complication rates for 1st trimester abortion of less than 10/100 operations.1

In a United States (US) report of 170,000 1st trimester surgical abortions performed in low risk women by experienced providers, complication rates requiring hospitalization was 0.71/1,000 cases and minor complication rate was 8.46/1,000 cases.2

In contrast, mortality and morbidity from unsafe abortion persist as major problem in most of the developing world. The World Health Organization (WHO) estimates between 50,000 and 100,000, women die annually as a result of illegal abortion with morality rate of 250–500 deaths/100,000 procedures.

Common complications include infection, hemorrhage and uterine injury. In India, in spite of liberalization of abortion since 1972, even after 30 years many more abortions are carried out illegally and under unsafe conditions, according to Chhabra and Nuna.3

In India, illegal abortion today outnumber the legal procedures, by a ratio of 11 is to 12 with a high maternal mortality of 15%. According to WHO, over 20,000 Indian women die annually due to unsafe abortions.4

According to Ford Foundation Study (1995),5 the number of illegal abortions has risen dramatically, from 6.5 million in 1971 to 7.5 million in 1981, to 8.5 million in 1991.

Factors that increase the risk of abortion-related complications include older age, multiparity and advancing gestational age,6 the methods of abortion, skill of the surgeon, accessibility and quality of medical facilities to treat complications and added procedures like tubectomy or
insertion of intrauterine contraceptive devices (IUCDs) also increase the complication rates.

In a large prospective study of 2nd trimester abortion complications, dilatation and evacuation (D & E) was safer than instillation procedures using PG or hypertonic saline.\textsuperscript{7}

According to legal abortion mortality data collected by Centers for Disease Control and Prevention (CDC), US from 1972 to 1987 the number of deaths per 100,000 abortions was 0.5 for 1st trimester vacuum curettage procedures, 3.7 for surgical dilatation and evacuation (D & E), 7.1 for instillation procedures and 51.6 for hysterotomy/hysterectomy.\textsuperscript{8}

Tyler\textsuperscript{9} calculated that between 16 weeks and 20 weeks gestations the risk of death is 25 times greater than before 8 weeks gestation. Similarly, mortality increases during the 2nd trimester on an average of 20.1 per week, for major complications.\textsuperscript{10}

Complications can be broadly divided as methods:
- Complications due to surgical methods
- Complications due to medical methods.

**COMPICATIONS DUE TO SURGICAL METHODS (TABLE 1)**

The complications can be divided into:
- Early (within 1 month of abortion)
- Late (occurring after 1 month of abortion).

The “early” complications are further subdivided into “immediate” and “occurring not during the procedure but within 1 month”. If the procedure is done under anesthesia there can be complications due to anesthesia also and will depend upon the type of anesthesia used.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Timing</th>
<th>Gravity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inability to dilate the cervix</td>
<td>Immediate</td>
<td>Not serious in itself</td>
</tr>
<tr>
<td>Inability to complete the abortion</td>
<td>Immediate</td>
<td>Generally not serious if recognized</td>
</tr>
</tbody>
</table>
| Uterine perforation               | Immediate but may not be recognized until later | Varies from asymptomatic to very serious:  
|                                   |                         | potentially life-threatening           |
| Anaphylaxis                       | Immediate               | Potentially life-threatening            |
| Seizure                           | Immediate               | May be serious or not serious depending on etiology and seizure type |
| Embolism                          | Immediate               | Potentially life-threatening            |
| Cervical laceration               | Early                   | Usually not serious                    |
| Disseminated intravascular coagulation | Early            | Deep lacerations or cervical fracture can be potentially life-threatening |
| Uterine atony                     | Early                   | Potentially very serious                |
| Hematometra                       | Early or delayed        | Depends on amount of blood loss        |
| Failed abortion                   | Early or delayed        | Usually not serious                    |
| Ectopic pregnancy                 | Early of delayed        | Not serious if pregnancy is intact     |
| Endometritis                      | Delayed                 | Serious: potentially life-threatening  |
| Incomplete abortion               | Delayed                 | Usually not serious if treated promptly |
| Postabortal triad                 | Delayed                 | Usually not serious                    |
| Septic incomplete abortion        | Delayed                 | Serious: potentially life-threatening  |

**Complications According to the Methods of Abortion**

**Menstrual Regulation\textsuperscript{11}**

As the procedure is performed before pregnancy is confirmed by pregnancy test, the procedure is performed unnecessarily on 27–59% of cases.

As these patients were not pregnant, this misdiagnosis of pregnancy can be reduced by using sensitive pregnancy test, using beta human chorionic gonadotropin ($\beta$hCG) specific assays, using ultrasonography and examination of aspirated material.

- **Failure abortion:** This is also common complication when MRD is performed very early as gestation sac can be completely missed, if situated in cornual region. The incidence reported is 3–12%. This can be reduced by doing MR under ultrasound control. Also all the products should be carefully examined and patient should be called for follow-up after 1 month, so if pregnancy is continuing it can be diagnosed and the procedure repeated.

- **Incomplete abortion:** This is also very common specially, if the surgeon is inexperienced or MR surgical procedure is not properly performed. The incidence varies from 5% to 30%.

- **Hemorrhage**

- **Trauma:** Cervical trauma or uterine perforation incidence are very low as plastic cannula is used.

Fracture of the tip of the cannula a very rare but can occur, if disposable cannula is used. Dilation and curettage will be required to remove the tip of the cannula.
Complications and Sequelae of Medical Termination of Pregnancy

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CHAPTER

Complications due to Dilatation and Suction Evaluation

Early Complications Occur during Operations

- Incomplete evaluation
- Trauma
  - Trauma to cervix: Cervical laceration or tear could occur. The injury to cervix can be reduced by using a traumatic tenaculum or priming the cervix with either PGs. Cervical tears near internal os, can cause severe hemorrhage and must be sutured immediately.
  - Uterine perforation (Fig. 1): Uterine perforations are common in cases of multiparity or advanced pregnancy more than 14 weeks gestation or when uterus is previously scarred like with previous cesarean sections, metroplasty, etc. Uterine perforation is suspected when instruments pass further than expected without any resistance or when bleeding is excessive or when bowel or omentum is seen outside the cervix.
  - Injury to surrounding structures like urinary bladder intestines, omentum, etc. specially if there is uterine perforation with sharp curette or aspiration cannula.
- Hemorrhage: Uterine hemorrhage associated with abortion indicates cervical laceration, perforation, retained pregnancy tissue, uterine atony, placental abnormality or coagulopathy. Definition of hemorrhage varied in different studies from blood loss of 250 cc or 500 cc more to patient requiring hospitalization or blood transfusion. The incidence varies from 0.07% with gestational age less than 13 weeks to 12% when gestation age is 13–15 weeks. Advances in operative technique and prophylactic use of intramuscular (IM) injection, PG half hour prior to procedure reduces the incidence of hemorrhage.
- Infection.

Role of Ultrasound

Ultrasound plays a very important role to MTP in knowing the exact size of the uterus, diagnosis of fibroid with pregnancy, diagnosis of twins and multiple pregnancy or vesicular mole and also diagnosis of uterine malformation. Ultrasound also plays important role during surgical evacuation specially in cases of extremely obese patients, bulky uterus pregnancy and when patient has undergone previous cesarean sections. Ultrasound helps in prevention of perforation and ensures complete evacuation thus, reduces chances of retained product and hemorrhage.

The management of uterine perforation depends upon amount of bleeding, types of instrument that caused perforation and, whether intestine or bladder is injured or not. Immediate laparoscopy is performed to assess the size of perforation and injury to other organs. If perforation is small and there is no active bleeding, patient is observed for 24 hours and discharged, if stable but if perforation is large and there is excessive bleeding or bowel or bladder is injured, immediate laparotomy is carried out. Perforation bladder injury that is also properly sutured is sometimes, necessary as a life-saving procedure.

Aspirotomy

Aspirotomy is a combination of section, aspiration and embryotomy carried out under paracervical block injection of adrenaline and saline in lower uterine segment to reduce the blood loss. It is also known as D & E procedure. It is normally carried out when uterine size is more than 14 weeks and up to 20 weeks of pregnancy. It is a good method for 2nd trimester termination as its procedure is quick and complete and patient can go home in 2–3 hours. It is very popular in western countries specially Europe as cost of anesthesia is used by many obstetricians but requires proper training and use if aspirotomy forceps. The method was tried at MR Wadia Maternity Hospital by Dr MR Parikh and his team. They have performed more than 500 aspirotomy procedures, without major complications.12,13

Complications

These include cervical trauma, laceration uterine perforation and incomplete abortion specially retention of bony fragment
as pregnancy is advanced, there can be severe hemorrhage as uterus will be larger. The aspirotomy should be performed by an experienced gynecologist and must always be done in a good set-up with facility for laparotomy control to ensure the complete evacuation and to prevent perforation.

**Hysterotomy**

It is rarely done as a primary procedure for abortion but is carried out for failed 2nd trimester termination, especially when instillation procedures are used. It is a major operation which requires anesthesia and proper hospital facilities.

**Complications**

It is an invoice procedure. Hemorrhage can occur if uterine incision is not properly sutured.

*Infection:* Normally occurs due to failed termination and prolonged induction abortion interval.

**Hysterectomy**

Rarely done for 2nd trimester termination. It is selectively done in cases of failed terminations, with severe sepsis or hemorrhage. Sometimes, it is done as a primary procedure in multiparous patient with gynecological problems like multiple fibroids and dysfunctional uterine bleeding (DUB) or pregnancy with carcinoma cervix.

**Complications**

It is a major surgical procedure and carries, with if the high incidence of morbidity and mortality. Hemorrhage can occur due to increased vascularity. Maternal mortality can occur due to severe hemorrhage or due to anesthesia complications.

**Delayed Complications due to Surgical Methods**

- Retained products of conception or incomplete evacuation. This is one of the most common complications seen in about 5% of suction evacuation. It can lead to hemorrhage and infection if not treated. The diagnosis is made with help of ultrasound, which shows retained products of conception. Treatment is readmission, report dilatation and evacuation. The incidence of incomplete evacuation can be reduced by doing “check curettage” or by doing MTP under ultrasound control, especially with early abortions or less than 6 weeks and late abortions after 12 weeks.
- *Pelvic infection:* Worldwide rates of infection after 1st trimester termination, varies from 0.1% to 4.7%. It is usually due to pre-existing pelvic infections either due to chlamydial infection, gonorrhea, bacterial vaginoses and the rare but extremely serious infections such as *Clostridium perfringens* and synergistic necrotizing infections. Sepsis, if not controlled can lead to septic shock and acute respiratory distress syndrome (ARDS). It can also be due to incomplete evacuation or if proper aseptic precautions are not used. The incidence of infection can be reduced by using all aseptic precautions, complete evacuation of the uterus and use of prophylactic antibiotics.
  - *Amniotic fluid embolism:* It is very rare but fatal occurs in 1/10,000–1/80,000 pregnancies.
  - *Pulmonary embolism:* A retrospective CDC study described 10 cases of fatal pulmonary embolism for the period, 1972–75 occurring 2–50 days after induced abortion. Patient had one or more risk factor like obesity, hypertension and recent use of oral contraceptives or family history of embolism.

**Complications due to Anesthesia in Surgical Procedure**

- Vasovagal reaction
- Anaphylaxis
- Asthmatic reactions
- Seizures
- Bronchospasm
- Cardiac arrest.

**COMPLICATIONS DUE TO MEDICAL METHODS OF TERMINATION**

**Medical Methods for First Trimester**

The common method used is combination of mifepristone (RU-486) and misoprostol. Mifepristone 600 mg followed by 36–48 hours later, with 1 mg of gemeprost vaginal pessary or misoprostol tab 200 µg.

**Complications**

- Headache, malaise, skin rash.
- Adrenal failure
- *Bleeding:* Irregular bleeding normally occurs from 1 day to 10 days. Patient must be called for follow-up and if bleeding is severe patient requires admission and blood transfusion, the reported incidence is 1 in 2,000 cases—0.85%.
- *Failed attempted abortion:* Seen in about 1–2% of cases of patients with pregnancy less than 7 weeks. Patients are called for follow-up and advised to undergo surgical evacuation because of potential teratogenic effect on the fetus. PGs cause constriction defects in distal limbs.
- Next menstruation may be delayed by 10–15 days.

Intramuscular methotrexate and intravaginal misoprostol is also used as a medical method of abortion. Incidence of failed abortion varies from 3% up to 49 days of gestation.
and less than 12% at 50–56 days of gestation.\textsuperscript{15} However, as methotrexate is toxic drug, it is not widely used. If pregnancy continues patient is advised to undergo suction evacuation because of the potential teratogenic effect on the fetus.

Complications of Second Trimester Abortions

1. **Intra-amniotic instillation of hypertonic saline 20% NaCl 200 mc**: This method is associated with some major complications including maternal mortality and therefore, not used in big cities where prostaglandins are available. However, in smaller places and in some centers in big cities it is still used as prostaglandins are expensive.

   **Immediate complications**
   - **Incomplete abortion requiring curettage**: For about 3.3–13% patients will have incomplete abortion and will require D & E under anesthesia.
   - **Failed abortion**: About 1–3% will have failed abortion after 48 hours cut-off point and will require reinstallation.
   - **Hemorrhage**: This could be due to retained placenta, atomy of the uterus or due to DIC. The incidence of bleeding, following saline instillation is about 16\% (Tietze and Lewit).\textsuperscript{16}
   - **Hypernatremia**: This occurs due to accidental injection of saline into blood vessel. This leads to immediate cardiovascular collapse or cerebral edema followed by convulsions, hypoxia and failure of one of the vital organs. However, the incidence is very low 1:4,000.\textsuperscript{17}
   - **Disseminated intravascular coagulation**: This is also a serious complication leading to severe bleeding and the incidence with hypertonic saline is 658/100,000 abortions.\textsuperscript{18}
   - **Uterine wall necrosis**: This occurs due to accidental injection of hypertonic saline into uterine wall. This is also a serious complication and can lead to death.
   - **Maternal mortality rate varies from 0 to 8/1,000 instillations. The causes are hypernatremia, endotoxic shock, DIC and cerebral hemorrhage.**

2. **Intra-amniotic instillation of 40% urea**: It is an inert substance and therefore, no harm occurs even, if accidentally injected into vein or uterine muscle. Therefore, many prefer this method over hypertonic saline instillation.

   **Complications**
   - **Failed abortion**: Success rate of the method is 86%. Retained placenta and incomplete abortion with urea prostaglandin F2 (PGF2) the reported incidence is 35–46\%.\textsuperscript{19}
   - **Hemorrhage**: Rare with urea, but can occur sometimes, but severity is less than saline.
   - **Urea**: is hepatotoxic and toxic to kidneys therefore, cannot be used for patients with renal or liver disease.

   **Extra-amniotic Instillation of Ethacridine Lactate**

   This is the method of choice for 2nd trimester abortion in India, in majority of centers, as it is safe, cheap and ethacridine is easily available.

   **Complications**
   - **Failure of abortion**: This is common and sometimes abortion does not occur even after 72 hours. This can be reduced by combined with PGs.
   - **Incomplete abortion**: The reported incidence is about 10\%. Dilatation and evacuation is done to complete the abortion.
   - **Renal damage and death**: If excess of ethacridine is injected, i.e. more than 50 mL, it can lead to renal toxicity and death. However, this is a very rare and so far only 1 death is reported from Gujarat.

   Pytel et al.\textsuperscript{20} from Soviet Union have reported 5 cases of acute renal failure following large volume of ethacridine lactate more than 500–700 mL. These patients were treated with hemodialysis.

   **Prostaglandins**

   They are used quite frequently nowadays in India as they are easily available and are effective in producing abortion. They are used either alone or as combination with urea or ethacridine lactate. They can be given by various routes intra-amniotic instillation, intravenous (IV), IM and now newer analogs can be given vaginally, intracervical or even orally.

   **Complications**
   - Side effects like gastrointestinal disturbances are very common—vomiting, diarrhea. Sometimes, it can be very severe and patient needs IV fluids infusion.
   - **Cervical tears**: Occur in many cases, specially bucket handle type. The incidence of cervical laceration, reported is 1%.
   - **Transverse rupture of the posterior uterine wall**: This is a serious complication. The rupture occurs because of the tetanic type of contractions with PGs.
   - **Hemorrhage**: Either due to lacerations or tear of the cervix or rupture or due to retained products.
   - **Convulsions**: Can occur sometimes.
   - **Incomplete abortion**: Sometimes placental tissue is retained. This requires dilatation and curettage.
   - **Expulsion of the live fetus**.
   - **Sudden maternal death**: Cases of sudden maternal deaths have been reported with use of sulprostone. Also when used in combination with RU486, three women developed myocardial infarction. Therefore, sulprostone is no longer used for termination of pregnancy. It is also advised that PGs should not be used in women who are obese, heavy smokers and have history of hypertension.
SECONDARY INFERTILITY:

Due to infection following MTP, leading to PID and tubal blockage. Chlamydia organism is the most common cause of secondary infertility following abortion. Examination for chlamydia is now routine in most hospital and clinics and if necessary patient is treated before abortion is carried out.

INCOMPETENT OS LEADING TO REPEATED ABORTIONS OR PRETERM DELIVERIES:

Occurs either following repeated MTPs or sometimes with aspirotomy procedure.

ASHERMANN’S SYNDROME:

This is due to vigorous curettage or postabortal infection, this complication is seen rarely if proper care is taken while doing MTP.

RH ISOIMMUNIZATION:

Usually occurs in a Rh negative patient if Rh anti D immunoglobulin injection is not given. It is advisable that prior to all MTPs whether 1st trimester or 2nd trimester, blood grouping and Rh typing should be done to avoid occurrence of Rh isoimmunization.

PSYCHOLOGIC SEQUELAE:

Seen in women with a previous history of psychiatric disorder or when MTP is done against the desire of the women. It is also seen in Muslim and Christian as their depression is psychologic.

ECTOPIC PREGNANCY FOLLOWING PID.

REFERENCES

INTRODUCTION
Contraceptive methods today are very safe and effective. However, we remain decades away from a perfect method of contraceptions for either men or women. Because reversible contraceptive methods are not perfect, sterilization is now the most commonly used method of contraception worldwide.

Vasectomy accounts for only a small percentage of sterilization procedures in developing countries except in India and China, worldwide, the ratio of female to male sterilization is 3 to 1.

History
James Blundell proposed in 1823, in lectures at Guy’s Hospital in London, that tubectomy should be performed at lower segment cesarean section (LSCS) to avoid repeat LSCS.

Madlener procedure, was the first technique devised in 1910, since it was associated with many failures, it was not popular.

Ralph Pomeroy described the technique in 1929.

Laparoscopic method was introduced in 1970s. When the risk of pregnancy from the contraceptive failure is taken onto account, sterilization is the safest of all contraception methods.

Vasectomy
Surgical sterilization of male: Vasectomy remains the most reliable, safe and cost-effective method of contraception. Failure rates are comparable with that of female tubal ligation. With improvement in vasectomy technique like no-scalpel technique, nonsurgical technique for vasectomy may become more acceptable.

Eligibility Criteria
The eligibility criteria are shown in Table 1.

Counseling
After selecting appropriate case for vasectomy, surgeon should provide information to the patient regarding permanence of the procedure, he should be reaffirmed that there will be no effect on masculinity, sexual activity and also has no demonstrable long-term deleterious effects.

Table 1: World Health Organization medical eligibility criteria for male sterilization

- **Contraindications:**
  - No permanent contraindication
- **Delay:** Procedure should be delayed until the condition has been successfully treated or no longer exists.
  - Intra-scrotal mass
  - Filariasis; elephantiasis
  - Signs/symptoms of STD
  - Infection of the operative area
  - Acute systemic infections
- **Refer/special precautions:** The procedure should be performed only in a facility well equipped and staffed to handle any potential difficulties or complications or it may be postponed.
  - Previous scrotal injury
  - Large varicocele
  - Large hydrocele
  - Inguinal hernia
  - Coagulation disorders
  - Previous surgery for cryptorchidism

*Abbreviation: STD, sexually transmitted disease*
CHAPTER

Permanent Methods of Sterilization

Technique

**Conventional Vasectomy**

It is done under aseptic precautions in the theater setup. Local anesthesia is usually used. Lignocaine 2% is injected into the area of incision at the junction of the upper third and middle third of median raphe to raise a 2 cm wheal over the vas. Vas deferens is fixed with fingers and lignocaine is injected into perivasal tissues. The skin and muscles overlying the vas are incised to about 1 cm transversely. The vas is grasped and isolated by incising longitudinally on the overlying sheath to expose the vas. The exposed vas is occluded and a segment of 2–3 cm is resected. The same procedure is performed on the other side. Incisions are closed.

**No-scalpel Technique**

Introduced in China, a simple no-scalpel technique reaches the vas through a puncture in the scrotum, rather than through a scalpel incision. Special instruments required for this procedure are—a vas deferens dissecting forceps and extra cutaneous fine vas fixing clamp. This procedure is done under local anesthesia with aseptic precautions. The vas is grasped with a ringed clamp, applied extra cutaneously to hold the vas in place. A puncture is made over the vas using the dissecting forceps. The forceps is then stretched and vas is lifted up. Vas is occluded as with other techniques. The puncture site needs no closure. This procedure also called “minimally invasive no scalpel” (MINS) vasectomy is less painful; less infection, less postoperative discomfort and takes less time compared to conventional vasectomy. This small variation reduces the chance of bleeding. However, MINS needs good practical training of doctor.

**Alternative**

Nonsurgical technique for vasectomy involves the injection of a polyurethane elastomer plug into vas via percutaneous puncture. Injection of silicon rubber has also been investigated. Other surgical alternative include, use of occlusive devices like plugs, clips, valves, etc.

Another variation is the open ended vasectomy, in which only the abdominal end of the severed vas is coagulated, while the testicular end is left open. This is associated with less chance of epididymitis.

**Postoperative Advice**

Unless warranted there is no need for antibiotics. Analgesics for pain can be advised for 2–3 days. Patient should be advised to avoid strenuous exercise for 2 days and cycling for 1 week. Scrotal support will reduce discomfort. Wound should be cleaned with soap water daily. Contraceptive measures should be advised for 3 months or 20 ejaculations which ever comes first. Protected coitus may be started 3 days following surgery.

**Efficacy**

Vasectomy is very effective method of contraception. Many of the failures are due to lack of precautions before semen becomes sperm-free. Technical failure may be due to spontaneous recanalization of vas, division of wrong structure, duplication of vas. Failure rate is 0.15 pregnancies/100 men in the 1st year after procedure.

**Complications**

Common minor short-term complications of surgery are:
- Pain in the scrotum
- Swelling and bruising
- Discomfort for 2–3 days.

These are often related to degree of patient’s apprehension. Significant pain is experienced in 1% of patients and may be associated with hematoma.

Bleeding, infections at incision site or inside the incision are uncommon complications. Clinical infection is noted in 1%. Rarely, abscess formation may require drainage.

Small hematomas or subcutaneous ecchymosis develops in few patients. They usually resolve within 1–2 weeks. Hematoma large enough requiring drainage may develop in less than 1% of patients.

Sperm granuloma may present in up to 1–3% of vasectomies. They may account for some vasectomy failures. They are painful and on occasion require excision.

Antisperm antibodies are formed in 40% of vasectomized patients. This phenomenon has been associated with failure of reversal.

Postvasectomy pain syndrome or chronic testicular pain is described but poorly understood.

Vasectomized men are not more likely to develop cancer, heart disease or other illness.

**Reversal**

Vasectomy is amenable to reversal by vasovasostomy. Patency rates of 80% can be achieved. However, pregnancy rates are lower than 5%.

The longer the interval since the vasectomy, the poorer the chance of reversal.

**Female Sterilization**

For couples desiring no more fertility this is one of the most effective and the best methods of contraception. Female sterilization is a permanent method of sterilization, a procedure which involves ligation with or without resection or blocking of both fallopian tubes.
It comprises around 94% of total number of voluntary sterilization in India.

**Selection of Cases**

Medical eligibility criteria were laid down by World Health Organization (WHO) in 1996.

- **Contraindication:** No permanent contraindication
- **Delay the procedure:** Delay the procedure till the underlying medical condition is treated and resolved. Temporary methods should be provided till then.
- Known or suspected pregnancy
- Active pelvic infection, peritonitis
- Pelvic inflammatory disease (PID) within 3 months
- Acute systemic infection
- Acute liver or gallbladder disease
- Current cerebrovascular
  - Postpartum, 7–42 days
  - Sexually transmitted diseases (STDs) infection
  - Severe anemia (< 7 g/dL)
  - Current, acquired immunodeficiency syndrome (AIDS) related illness
  - Unexplained vaginal bleeding suggestive of serious condition
- Any other temporary operative risk
- Any psychiatric condition that may impair decision making
- **Following pregnancy conditions:**
  - Puerperal sepsis
  - Premature rupture of membrane (PROM) more than or equal to 24 hours
  - Pregnancy with persistent hypertension
  - Postpartum psychosis
  - Severe trauma to genital tract
  - Recent septic abortion
  - Severe postabortal hemorrhage
  - Unhealthy newborn/stillbirth
- Special conditions need referral to a center where an experienced surgeon can perform in a setting equipped for general anesthesia (GA).

- Conditions that increase surgical difficulties:
  - Past cardiovascular disease
  - Chronic respiratory problems
  - Hyperthyroidism
  - Diabetes with vascular disease
  - Complicated valvar
  - Heart disease
  - Moderate anemia
  - Severe chronic liver disease
- Cautions mean procedure can be performed in a routine setting but with extra preparation with precautions depending on the condition:
  - Mild raise of blood pressure (BP) (140/90–159/99 mm Hg)
  - Past stroke or heart disease due to blocked arteries
  - Valvular heart disease without complications
  - Epilepsy on treatment
  - Diabetes without vascular disease
  - Hypothyroidism
  - Sickle cell anemia
  - Kidney disease
  - Obesity
  - Lack of nutrition.

Female sterilizations are mainly performed by two different types of procedures, namely:
1. Tubal ligation
2. Laparoscopic sterilization.

**Timing of Sterilization**

Sterilization can be performed:
- At the time of cesarean section
- Puerperal sterilization that is shortly after delivery in early puerperium. During this period, sterilization is technically easy as tubes can be approached through a small incision. This should be ideally done within 48 hours following delivery, but not beyond 7 days.
- Interval sterilization: Interval sterilization is done any time in nonpregnant women or 6 weeks after delivery. Tubal ligation should be done within 7–10 days of menstruation.
- Postabortal sterilization is done following induced abortion or after evacuating incomplete abortion.

**Counseling**

The following features of the sterilization procedure must be explained to the patient according to the Government of India, Family Welfare:
- It is a safe and simple procedure
- It is a permanent procedure for preventing future pregnancies
- It is a surgical procedure that has a small risk of complications requiring further treatment
- It does not affect sexual pleasure, ability or performance
- It will not affect the patient’s strength or his ability to perform normal day-to-day functions
- It has a small chance of failure, even if performed under optimum circumstances
- After vasectomy, it is necessary to use a back-up contraceptive method, either for 20 ejaculations or for a period of 3 months.
- Sterilization does not protect against STD/AIDS
- Patient must be told that a reversal of this surgery is possible, but the reversal involves a major surgery and its success cannot be guaranteed.

**Consent**

The written consent of spouse is not required for sterilization.
Preoperative Evaluation
Proper consent of the women should be obtained. The work up also includes careful history and physical gynecological examination. Pregnancy should be excluded at the time of sterilization.

SURGICAL APPROACH

Minilaparotomy for Tubal Ligation
Minilaparotomy approach for tubal ligation can be used in the interval, postabortal or postpartum period. In postpartum minilaparotomy, abdomen is opened by a 2 cm subumbilical incision 2 cm below the fundus.

Three centimeter midline transverse suprapubic incision 2.5 cm above the symphysis pubis. A uterine manipulator is placed just before surgery and is used to bring the uterus towards the incision. Trendelenburg’s position can be used to enhance exposure.

In either situations, the tube is identified first by the fimbrial end, and then mid portion of the tube is grasped with Babcock’s forceps and elevated through the abdominal incision. Tubal ligation is done by one of the following methods:

- **Pomeroy technique:** A loop is formed 2 cm lateral to fundus. Avoiding blood vessels, a round-bodied needle with no. 0 plain catgut is passed through mesosalpinx. The base of the loop is tied, leaving 2 cm of loop above the tie. 1.5 cm of loop is removed. The rationale of this procedure is based on prompt absorption of the ligature and subsequent separation of several tubal ends. Failure rate is 1/400 procedure.

- **Parkland technique:** This was designed to avoid the initial intimate approximation of the cut ends of the tube. After identifying the tubes, it is doubly ligated 2.5 cm apart with no. 0 chromic catgut and the intervening tube excised. Failure rate is 1/400 procedures.

- **Madlener procedure:** The Madlener procedure is similar to Pomeroy operation except that knuckle of the tube is crushed and ligated with nonabsorbable suture but not resected. Failure is about 7%.

- **Fimbriectomy:** Recommended by Kroener involves removal of all of the distal tube. This has a high failure rate of 2%. Other techniques not commonly used are Irving technique, Uchida technique.

Laparoscopic Sterilization
Because laparoscopy permits direct visualization and manipulation of the abdominal and pelvic organs with minimal abdominal discomfort, it offers many advantages.

- Surgeon has an opportunity to inspect the pelvic and abdominal organs for abnormalities.
- However, laparoscopic sterilization is not without disadvantages, which includes the need of expensive fragile costly equipment. Special training is required for the personnel. Finally, the risks inherent to procedure like inadvertent bowel or vessel injury are there.

Laparoscopic sterilization can be achieved by:

- **Electrocoagulation:** Unipolar method of sterilization creates a dense area of current, under the grasping forceps of the unipolar electrode. Isthmic pole of the tube is grasped and elevated away from the surrounding structures and the electrical energy applied until the tissue branches swells and then collapses. This procedure is repeated till 2–3 cm of tube has been coagulated. However, there is increased risk of ectopic pregnancy due to fistula formation. In bipolar method, current density is more at the point of forceps contact with tissues as current leaves the body via the same forceps. So more applications of grasping forceps are necessary to coagulate the same length of tube than with unipolar coagulation. Bipolar cautery is safer than unipolar. However, both are associated with thermal bowel injury.

- **Clips:** Two types of clips are widely used are:
  1. The spring loaded clip (Hulka-Clemens clip)
  2. Silicone—Titanium clip (Filshie clip).

  Filshie clip made of titanium lined with silicone is locked over the tube using a special instrument. Upper jaw latches under a hook in the lower jaw. Only 4 mm of tube is destroyed, providing good chance of recanalization. Hulka clip made of lexan has two jaws held together by a stainless steel spring. This should be applied at a 90° angle to include some mesosalpinx at the proximal isthmus of tube.

- **Rings:** Fallope ring, most popularly used in India at present is made of nonreactive silastic rubber band. Application needs a specially designed endoscopic applicator. A knuckle of tube is grasped and silastic ring is realized into 2.5 cm loop of tube. After devascularization, this portion of tube becomes anoxic and resorbs over time. Apart from included tube very little destruction is caused to the remaining tube.

  Failure rates are about 1% after 2 years. Mesosalpingeal bleeding is most common complication of silastic ring application. Occasionally, ring may be placed on structures other than tube, e.g. round ligament, mesosalpingeal folds leading to failure.

COMPLICATIONS

Common Intraoperative Complications

- Vasovagal shock
- Respiratory depression/arrest
- Cardiac arrest
• Bleeding from mesosalpinx
• Injury to urinary bladder
• Injury to intra-abdominal viscera
• Uterine perforation
• Reaction to local anesthesia.

Immediate Postoperative Complications
• Wound sepsis
• Hematoma in the abdominal wall
• Paralytic ileus, peritonitis/intestinal obstruction.

Delayed Complications
• Chronic PID
• Menstrual irregularities
• Incisional hernia
• Psychological problems
• Post-tubal ligation syndrome: This term is used for abnormal menstrual bleeding, dysmenorrhea following sterilization. This is said to be because of disturbance in ovarian blood supply and thus dysfunction. The existence of which is doubtful.
• Ectopic pregnancy: One-third of pregnancies following sterilization are ectopic
• Regret following sterilization is not uncommon
• Failure: Pregnancy is more common after first year.

Causes
• Luteal phase pregnancy
• Tubal anastomosis
• Clips wrongly placed on round ligaments, mesosalpinx.

Advantages of Permanent Sterilization
• Permanent birth control
• Immediately effective
• Allows sexual spontaneity
• Requires no daily attention
• Not messy
• Cost effective.

Disadvantages of Permanent Sterilization
• Does not protect against STD/AIDS
• Requires surgery
• Risks associated with surgery
• More complicated than male sterilization
• May not be reversible
• Possible regret
• Possibility of post-tubal ligation syndrome.

Reversal
Microsurgery for tubal anastomosis is associated with excellent results, if only small portion of tube is damaged. Success rate is about 70–80%, lowest with electrocoagulation.

Recent Advances
Potential new technologies for female sterilization by tubal occlusion have appeared, namely:
• Transcervical use of chemicals like quinacrine
• Hysteroscopic methods, including silicone implants
• Ablation of the uterine horn endometrium with neodymium-doped yttrium aluminum garnet (Nd:YAG)
• Transcervical placement of metal microspindles through fluoroscopic guidance
• Essure.

WHAT IS ESSURE?
• Hysteroscopic approach to place micro-inserts into the fallopian tubes
• Tissue growth in and around the inserts blocks the fallopian tubes achieving tubal occlusion
• Food and Drug Association (FDA) approved in November 2002.

Steps to Essure Placement
• Paracervical block is administered
• Hysteroscope with attached camera is inserted through the cervix
• Catheter is passed through the hysteroscope and directed to the ostium of the fallopian tube
• Micro-insert is positioned in the proximal portion of the fallopian tube and then detached
• Over the next 3 months, the tissue response and tissue in growth occludes the fallopian tubes
• Hysterosalpingogram (HSG) is done after 3 months to confirm occlusion and location.

Mechanism of Action
Micro-insert is flexible and dynamic and accounts for differences in women. The diameter of the micro-insert is larger trailing into the uterus than within the tubal lumen. This difference in the diameters is intended to prevent migration toward the peritoneal cavity.

Benefits
• No GA required
• No incisions required
• Speed of procedure
• May be performed as an outpatient
• Quick recovery
• Effective.
Considerations

- Patients must use another form of birth control, for at least 3 months after the procedure
- Removal requires surgery
- Reversal is not achievable: In vitro fertilization (IVF) is only option to conceive
- Not all women will achieve successful placement of both micro-inserts
- Physician learning curve.

BIBLIOGRAPHY

INTRODUCTION
Human being is a social animal. Yes, an animal but social. We have been learning this especially from our primary school days. It was also taught that we form and stay in a community which is similar to any other ecosystem that we see in the environment. Evolution is a constant process and one can appreciate that in the society and the social situation.

Health happens to be the prime component of human life and therefore health care services are for the, by the, and of the community. Social work we all have to understand is something that is closely interspersed with this health care. As doctors we have developed a sort of false and egoistical attitude that we are the health care system but it is important that we understand that we are mere a small component of the society, the health care system and what it actually implies.

WHAT IS SOCIAL WORK?
The dictionary meaning goes; “organized work intended to advance the social conditions of a community, especially of the disadvantaged by providing psychological counseling, guidance and assistance especially in the form of social services. Let us consider the various components of this definition; advancement of social conditions, disadvantaged strata, psychological counseling and assistance. Through social work one can promote a social change, solve problem in human relationships, and empower and liberate people to enhance well-being. Utilizing theories of human behavior and social systems, social work intervenes at the points where people interact with their environments. Principles of human rights and social justice are fundamental to social work.

What we are doing through our everyday jobs as a medical professional itself to an extent is social work. But then there also exists a lot of disparity.

Let us go a little in the past. How did hospitals come into being? The elite in the society had family or personal physicians taking care of ailments. The poor and the destitute were through social awareness at that time taken into alms houses to be looked after through the means that society felt appropriate and could shell out. Gradually the elite of the society, the so-called reformers felt the need of having a place for the ill and the ailing to be looked after in better conditions. This thought also was propelled further by some fractions of the society being ready to pay for such services. Thus hospitals mushroomed. But all these primary institutions were essentially charitable institutions and supported by the public sector. In the very recent past when tuberculosis was a dreaded disease without any drugs to treat it we saw the sanatoriums as a major solid socialistic evolution for managing the affected.

An ailing person is not always an easy task to handle. Looking after any ill person mentally or physically is a drain on material as well as emotional resources. It is difficult to handle the ill for various reasons and one can see lot of money being exchanged for such services. The ones who can afford to pay, the ones who cannot are helpless. Added to it increased awareness of health, emergence of newer diseases, early diagnosis of many diseases and availability of many modern treatment modalities have all led the simple caring and nurturing into a huge health care industry (transformation from Vaidyas to Modern Medicine).

Even if it is now a business we cannot forget and are not allowed to ever forget that we are closely entwined with the society in its basics through our profession. Therefore social work is an extremely important part of our existence as
Social work in the medical scenario is an important link connecting the professional to the patient through his environment. This especially becomes relevant in financially and socially challenged situation or in the scenario of government agencies failing in their manifesto of primary care for the needy and poor or the socially deprived. Social work bases its methodology on a systematic body of evidence-based knowledge derived from research and practice evaluation, including local and indigenous knowledge specific to its context. It recognizes the complexity of interactions between human beings and their environment, and the capacity of people both to be affected by and to alter the multiple influences upon them including biopsychosocial factors. The social work profession draws on theories of human development and behavior and social systems to analyze complex situations and to facilitate individual, organizational, social and cultural changes.

As gynecologists we have an altogether a different aspect to deal with. We care for women and the main stay of our practice is closely related to the family. Family or women through whom the society actually is born. Our responsibility actually begins from the birth of a girl child. We as a professional are actually powerful socialists and it is important that each one of us realizes this at the earliest in his practice. Even if we spend few minutes of our consultation with the client in evaluating her social situation, it becomes easy to communicate, to assess, to understand and to treat her disease in a much better way.

One cannot limit our clinical consultation only to the disease process in our clients. Many of our references are based on experiences of our western colleagues and very often we follow these practices blindly. They have set these standards on sound evidence and here again one must attribute this to social work. If one looks at social work as a profession and decides to train for it one will realize that the curriculum is basically and predominantly research-oriented. Everything, the design, the teaching and the practice of social work training is based on research.

Social work addresses the barriers, inequities and injustices that exist in society. It responds to crises and emergencies as well as to everyday personal and social problems. Social work utilizes a variety of skills, techniques and activities consistent with its holistic focus on persons and their environments. Social work interventions range from primarily person-focused psychosocial processes to involvement in social policy, planning and development. These include counseling, clinical social work, group work, social pedagogical work, family treatment and therapy as well as efforts to help people obtain services and resources in the community. Interventions also include agency administration, community organization and engaging in social and political action to impact social policy and economic development. The holistic focus of social work is universal, but the priorities of social work practice will vary from country to country and from time to time, depending on cultural, historical and socioeconomic conditions.

This is the biggest disparity in medical training. The realization dawns very late as a professional and no due returns and lack of time mostly come in the way of research. This is where one could entwine-trained social workers in our establishments. Like we have certain must have professionals as associates from the allied branches like the anesthesiologists, pathologists, pediatricians, etc. we must have a social worker as an important associate. Firstly, we have to realize that we are dealing with that fraction of society which is socially deprived in many ways. Secondly, even a little lateral thinking in every deal with our client we can contribute toward a change for betterment in the society and that itself is social work.

Let us not go on to oncology or psychiatric illnesses where we think the clinical practice rests mainly on social workers. Let us take an example of antenatal patient. From sensitizing her to seek care to plan for her confinement and all this to acquire with relevance to her social situation is where a social worker can help the professional, but such practice we see only in large institutions. The financial constraints are usually the reason given and thought about in small nursing homes as the need has not been completely realized.

What then can we do as far as social work is concerned? We over a period of our training as professionals and practicing in our field acquire a lot of knowledge which could be easily disseminated in the society. Small talks, lectures, camps, informal events all go a long way in doing social work as an individual. That little extra if can be spared, which may not give you much probably in way of material returns immediately, can go a long way in giving back to the society that you live in. What has the society given us would be the next question? Our existence throughout our lifetime is given to us by the society and we owe her that much.

This is on an individual basis. But we are fortunate to be associated to organizations like the Federation of Obstetric and Gynaecological Societies of India (FOGSI) which is strong force to reckon with. Successful and senior professionals through their experiences set examples to follow. Every such new project has gone a long way in creating a social ripple. If all of us join hands we can create a wave. Examples like the Adolescent Health Awareness Programme, the Anemia Chale Jaon Drive, the medicolegal concept go a long way in creating a social change. Our experienced seniors are invited by the policy makers in important health issue like the Prenatal Diagnostic Techniques Act (PNDTA) as an example. THIS TOO IS SOCIAL WORK. IF WE JOIN HANDS TOGETHER we
can then fulfill the important part of the definition “integrated and organizational work”.

The Lord of the universe says: “While constantly struggling for more and more wealth, finally you arrived in your grave. Now you will know the fact” (Holy Quran: 102). It is true that when we realize or know facts about spiritual or economic matters, it is too late. Let us not be too late and start being socially aware and savvy.

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Intrauterine Contraceptive Device

INTRODUCTION

An intrauterine contraceptive device is also known as an IUCD. It is a device placed in the uterine cavity and is the world’s most widely used method of reversible birth control. Nearly 15% of women of reproductive age use IUCDs. It is popular because of its effectiveness combined with its long duration. The most widely used IUCDs are copper-bearing IUCDs. Currently nearly 160 million women use this method, over two-thirds of whom are in China where it is the most widely used birth control method, surpassing sterilization. In India, the use of IUCDs by contraceptive users among married women of reproductive age (MWRA) has come down from 13% in 1969 to 4% in 1979, although since the introduction of Copper-T (Cu-T) its use has increased slightly to 5.4% in 1984. According to government publications, IUCDs in the form of Lippes Loop were introduced in the National Family Welfare Program of the Government of India (GOI) in 1965 and have always been considered an important spacing method. Based on the results of clinical trials conducted by the Indian Council of Medical Research, Cu-T 200B was introduced in the program in 1975; subsequently in 2002, Cu-T 380A was introduced replacing Cu-T 200B.

In India, only 1.8% of MWRA use IUCDs. Despite the fact that the government offers IUCD services free of cost, it remains largely underutilized.

Intrauterine contraceptive devices (Fig. 1) are devices made of plastic or metal or a combination of these materials, meant for insertion into the uterine cavity for contraception.

HISTORY AND DEVELOPMENT

From ancient times, different materials have been introduced into the uterus of animals and human beings for prevention of pregnancy. For example, there are quotes that pebbles inserted in the uteri of camels by Arabs and Tweks during long journeys through deserts to protect them from pregnancy. Although it has no basis in history and was meant only for entertainment purposes.

In the 19th century, various stem pessaries, originally meant for treatment of infertility and correction of position of the uterus, were also used to prevent pregnancy. Stem pessaries had small caps, which covered the opening of the cervix, and a stem, which extended up into the lower part of the uterine body and cervical canal. The materials like wood, glass, silver, gold and ivory were used to prepare it. In 1902, Dr Carl Hollweg of Germany introduced wishbone shaped pessaries and tried it in 700 women for prevention of pregnancy. Some of these pessaries were used to procure abortion also. The use of wishbone pessaries was followed by severe infection and brought a bad name upon pessaries.

A German physician, Richard Richter, first introduced the intrauterine device as a contraceptive method for women...
in 1909. The device was ring-shaped and was made of silkworm gut but he never marketed his product and so never got appreciation like Gräfenberg.

The first widely used IUCD was introduced in Germany by Ernst Gräfenberg and became popular in the late 1920s. This was a ring of silkworm gut and silver wire. This device was found to be quite effective. In 1930 at the 7th International Birth Control Conference in Zurich, Switzerland, Gräfenberg presented his illuminating paper. Dr Gräfenberg reported a lower pregnancy rate of 1.6% among 600 women.

In 1934, Japanese physician Tenrei Ota, introduced a device made of gold or gold-plated silver. The device was a ring with a small disc in the center, attached to the ring by three spokes. The Ota ring was used extensively in Japan. The addition of this central disc lowered the IUCDs expulsion rate. These devices still had high rates of infection, and their use and development was further stifled by World War II politics—contraception was forbidden in both Nazi Germany and axis-allied Japan. Both Gräfenberg and Ota rings were criticized so much so that in 1936 the Japanese government condemned the Ota ring, and Gräfenberg was forced to abandon his ring after severe criticism by European doctors for risk of pelvic infection.

The first plastic IUCD, the Marguiles Coil or Marguiles Spiral, was introduced in 1958. This device was somewhat large, causing discomfort to a large proportion of women users, and had a hard plastic tail, causing discomfort to their male partners. The Lippes Loop, a slightly smaller device with a monofilament tail, was introduced in 1962 and gained popularity over the Marguiles device.

The Population Council of the USA conducted a major research and development program for IUCDs and spent about one and a half million dollars between 1959 and 1962. The first international conference on the IUCD was held in New York in 1962, conducted by the Population Council and attended by physicians all over the world who reported their favorable experiences with IUCDs. At this conference Lazav Marguiles of Mount Sinai Hospital, New York and Jack Lippe of Buffalo, New York described their experiences. Both these devices could be inserted through narrow tubes without cervical dilatation into the uterine cavity where on being released they resumed their shapes. Lippe further added barium sulfate to polyethylene so as to render the device radiopaque and fixed nylon threads to the device, which hung through the cervix for easy detection and removal when needed.

At the second world conference in 1974, the Population Council established the cooperative statistical program (CSP) under the direction of Christopher Tietze to undertake evaluation of IUCDs. The CSP studied several types of IUCDs including Lippes Loops A, B, C and D, the Marguiles coil, Birnberg Bow—large and small, Saf-T coil or double coil, steel rings and many others. A life table analysis was carried out of the critical events, pregnancies, expulsions and removals, per 100 women at 1, 2 or 3 years of use. It was concluded that the IUCD was a safe and effective method of contraception and appropriate for use in national family planning programs. From this CSP study, Tietze and Lewit concluded that no single type of IUCD was superior to the others so far as the critical events were concerned. In 1967, Lernes and Davis designed the Dalkon shield, which had a central membrane to increase the area of contact with the endometrium. It soon become very popular in the USA, but was later withdrawn from the market on being found to cause severe infection, which sometimes proved fatal. There are reports of 110 septic spontaneous abortions in women with the Dalkon Shield in place, seven out of them died. Robins stopped international sales of the Dalkon Shield in April 1975.

By the mid-1970s, a second generation of devices also called medicated or bioactive devices, started to be developed and were used to reduce some of the drawbacks such as high expulsion rate, removal rate due to bleeding and pain, and pregnancy rates. In these bioactive devices, plastic IUCDs become carriers for other substances such as metals, hormones and antibleeding agents.

Jaime Zipper from Chile and Howard Tatum developed the first medicated devices in 1969. In these, Copper wires were wrapped around the “T” and “7” devices having a small surface area to reduce bleeding and pain, and to improve efficacy. The addition 200 mm² of exposed copper to the “T” or “7” devices improved the quality. T-shaped devices had lower rates of expulsion due to their greater similarity to the shape of the uterus. Worldwide today, with the exception of the new GynFix, this is the only type of IUCD available.

The multiload Cu-250 and multiload Cu-375 are being tried in different sizes; they have different shapes, and inserters of the withdrawal type.

Since 1973, IUCDs containing hormones are being used. The progestasert contains a reservoir of 38 mg of progesterone in silicone oil and is approved by the USFDA with an effective life of 1 year. Newer devices containing progesterone, effective for 3–10 years, are being tested.

Another group of pharmacological agents being added to IUCDs with a view to reduce bleeding are the fibrinolytic inhibitors tranexamic acid (AMCA) and epsilon aminocaproic acid (EACA).

Various researches are being conducted throughout the world to improve the inserter, the shape and size of IUCDs and by adding different compounds to improve on the present type of IUCDs. An ideal version is still to be invented.

**TYPES OF INTRAUTERINE CONTRACEPTIVE DEVICES**

As we have seen in the history, there are several types of IUCDs developed so far (Figs 2A and B). But only few of them were used consistently. Many of them were discarded in short span because of their serious complications.
There are three types of IUCDs:

**First Generation IUCDs**
Inert IUCDs like Lippe’s loop, Saf-T coil. These are also called as first generation IUCDs.

**Second Generation IUCDs**
Copper containing devices like Cu-T 380A, Cu 7, Multiload Cu-T, Nova T, etc., which are second generation IUCDs.

**Cu-T 380A**
Copper-T 380A intrauterine device (IUD) is a T-shaped device composed of a polyethylene frame measuring 36 mm by 32 mm with 176 mg of electrolytic copper wire wrapped around its vertical stem and two copper sleeves of 68.7 mg of copper, placed on each of the horizontal arms, for a total surface area of 380 ± 23 mm² of copper. The device has a monofilament polyethylene string tied at the base of the stem to create two tail strings that aid in monitoring device’s position and in its removal. The frame contains barium sulfate to permit radiographic visualization. The Cu-T 380A IUCD is Food and Drug Administration (FDA) approved for 10 years of use, although clinical studies indicate high efficacy for at least 12 years and as long as 20 years.

**Efficacy:** The cumulative 5 years pregnancy rate is between 0.3% and 0.6% for the Cu-T 380A IUCD. It is the most effective copper-bearing IUCD in the world. The 10 years cumulative pregnancy rate for the Cu-T 380A is 1.9–2.2%. Because IUCDs act their efficacy is maintained even in women with class 3 obesity.

**Contraindications:** The Cu-T 380A IUCD is not appropriate for women with copper allergies and is not recommended for women with copper storage defects (Wilson’s disease). Labeling states that the Cu-T 380A IUCD should not be used by women at high-risk for sexually transmitted infections (STIs); however, in that situation, concurrent condom use may enable IUCD use. A recent retrospective study of women with a history of sexually transmitted diseases (STDs) or active infections showed that both the IUCDs were safe and effective. HIV-infected women are also appropriate candidates for IUCDs.

Expulsion rates are highest in the first few months after placement and depend on insertion technique and timing of placement within the menstrual cycle. Overall, first-year expulsion rates with the copper T 380A are 5.7% among all users and 2.3% among parous women. After the first year, expulsion rates decline.

**Third Generation IUCDs**
Third generation IUCDs are hormone based devices that work by releasing a progesterone like Mirena, Progestasert.
Most nonhormonal IUCDs have a plastic T-shaped frame that is wound around with pure electrolytic copper wire and/or has copper sleeves. Cu-T 380A is most popular.

Intrauterine contraceptive device today and seen in Figures 3A and B. Cu-T 380A is 32 mm (1.26”) in the horizontal direction (top of the T), and 36 mm (1.42”) in the vertical direction (leg of the T). In some IUCDs, such as the Nova T 380, the pure copper wire has a silver core which has been shown to prevent breaking of the wire. The arms of the frame hold the IUCD in place near the top of the uterus. All copper-containing IUCDs have a number as part of their name. This is the surface area of copper (in square millimeters) the IUCD provides.

In the United Kingdom, the term IUCD only refers to inert or copper-containing devices. There, hormonal uterine contraceptives are considered a different form of contraception than copper IUCDs, and they are distinguished with the term intrauterine system or IUS.

**Fourth Generation IUCDs**
Newer IUCDs or fourth generation frameless IUCDs are not yet in clinical use. The frameless IUCDs are made without
the plastic T-shaped frame common to most other types of IUCDs and consists of several copper cylinders tied together on a string. It is anchored 1 cm deep into the fundus (top) of the uterus. This design is intended to cause less pain and bleeding than framed devices.

**GyneFix**

GyneFix, the newest frameless IUCD, was introduced in Europe in the early 1990s, following 15 years of research to improve ease of insertion and attachment to the uterine wall. It is also available in China and through Marie Stopes International Programs in Latin America, Asia and Africa. Its developer plans to apply for US FDA approval.

Small, noncomparative studies demonstrate promising results for GyneFix in minimizing menstrual blood loss and discontinuation. Randomized controlled trials involving GyneFix have not yet provided clear support for the benefits expected and the expulsion rates have been higher than found in early clinical trials.

The frameless IUCDs require an entirely different insertion technique than the framed IUCDs and the level of skill required to insert them is high. Providers face difficulty with insertion even with the use of a new inserter mechanism, introduced by the developer to simplify insertion. The frameless IUCD is less likely to be expelled when inserted by an experienced provider.

Another frameless IUCD in development, FibroPlant-LNG, releases the progestin levonorgestrel. Based on the design of the GyneFix IUCD, it too is anchored into the fundus of the uterus. FibroPlant-LNG delivers 14 µg of levonorgestrel daily and prevents pregnancy for at least 3 years. Initial studies suggest that FibroPlant-LNG would be highly acceptable and may reduce bleeding.

**INTRAUTERINE SYSTEM**

Hormonal uterine devices do not increase bleeding as inert and copper-containing IUCDs do. Rather, they reduce menstrual bleeding or prevent menstruation altogether, and can be used as a treatment for menorrhagia.

Progestasert was the first hormonal uterine device, developed in 1976 and manufactured until 2001. It was replaced annually, and had a failure rate of 2% per year. As of 2007, the LNG-20 IUS, marketed as Mirena, is the only IUS available. First introduced in 1990, it contains 60 mg of levonorgestrel which elutes 20 mg daily and may be used for 5 years.

A lower-dose T-shaped IUS named Femilis is being developed by Contrel, a Belgian company. Contrel also manufactures the FibroPlant-LNG, a frameless IUS.

Table 1 gives comparison and summary of IUCD and IUS where major difference is of cost.

**MECHANISM OF CONTRACEPTION**

The precise mechanism of action of IUCD is still unknown. It could be a combination of the following:

- Within 24 hours of insertion, there is inflammatory reaction in the endometrium. Phagocytic leukocytes engulf sperms and ova. All unmedicated and copper devices produce an inflammatory or foreign body reaction in the uterus. Numerous polymorphonuclear leukocytes followed by giant cells, mononuclear cells, plasma cell and macrophages appear in the endometrium and uterine fluids, mostly around the devices. Macrophages adhering to the devices are also a source of prostaglandins. In 1969, Wynn and Sawaragi postulated that increased prostaglandin levels produced asynchronous development of the endometrium and increased uterine activity; which may be responsible for the contraceptive effect.

- Copper alters the trace element and enzyme content of the endometrium and is spermicidal. Copper ions are also toxic to sperms.

- There is alteration of uterine and tubal fluids to impair viability of gametes and impede fertilization. The presence of a device in the uterus prompts the release of leukocytes and prostaglandins by the endometrium. These substances are hostile to both sperm and eggs.

- IUCDs containing progesterone maintain high local progesterone levels and in consequence relatively low estrogen levels. They thereby keep the endometrium in the decidual or progestational phase, which hinders implantation. The small amount of progesterone released by these devices does not appear to effect ovarian function. This type of IUCD also alters the cervical mucus, which, in turn, inhibits sperm from passing through the cervix.
Earlier it was suggested that IUCDs act by accelerating ovum transport through hyperperistalsis of the oviducts so that the fertilized ovum cannot be implanted owing to the unpreparedness of the endometrium. This theory could not become substantial.

**EFFECTIVENESS OF CONTRACEPTION**

All second-generation copper-T IUCDs have failure rates of less than 1% per year and cumulative 10-year failure rates of 2–6%. A large WHO trial reported a cumulative 12-year failure rate of 2.2% for the Cu-T 380A with average failure rate of 0.18% per year over 12 years, equivalent to a cumulative 10-year failure rate of 1.8% following tubal ligation.

Mirena is also 99% effective in preventing pregnancy.

The Cu-T 380A device remains effective for up to 10 years; the multiload copper IUCD remains effective for up to 5 years; the levonorgestrel-releasing IUCD is effective for at least 5 years. Most women can use IUCDs safely throughout their reproductive years, if the woman is satisfied with the method and has no problems with it.

**TIMING OF INSERTION**

**Postmenstrual Insertion**

Some doctors prefer to insert the IUCD immediately after menses or during menstruation to verify that the woman is not pregnant at the time of insertion. However, IUCDs may safely be inserted at any time during the menstrual cycle as long as it is reasonably certain that the woman is not pregnant. So the best time is the time convenient for the potential user.

**Postcoital Insertion**

To prevent or interrupt pregnancy following unprotected intercourse IUCDs have been inserted with successful results, even when inserted up to 5 days after coitus.

**Postabortal Insertion**

Studies in various countries including the US, India, Finland, Sweden by the WHO revealed no increased incidence of infection, perforation, expulsion, bleeding or other events.

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**Table 1: Comparison of intrauterine contraceptive devices and intrauterine system**

<table>
<thead>
<tr>
<th>Method of action</th>
<th>IUCD - Gold standard is the branded T Copper 380A</th>
<th>IUS (Mirena)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method of action</td>
<td>Prevents fertilization and inhibits implantation&lt;br&gt;Releases copper ions that reduces sperm motility&lt;br&gt;May disrupt normal division of oocytes</td>
<td>Prevents implantation mainly by thinning and suppressing endometrium&lt;br&gt;Thickens cervical mucus&lt;br&gt;Also alters sperm function</td>
</tr>
<tr>
<td>Duration of action</td>
<td>5–10 years, if contains 380 mm copper&lt;br&gt;Until no longer requires contraception</td>
<td>5 years and until no longer requires contraception</td>
</tr>
<tr>
<td>Failure rate</td>
<td>Less than 2 per 100 women for 5 years&lt;br&gt;Expulsion in &lt; 1 woman in 20/5 years</td>
<td>Less than 1 per 100 women per 5 years&lt;br&gt;Expulsion in less than 1 in 20 per 5 years</td>
</tr>
<tr>
<td>Risks</td>
<td>50% request removal within 5 years&lt;br&gt;Mainly due to bleeding or pain.&lt;br&gt;PID incidence is less than 1%, if low risk for STI&lt;br&gt;Perforation incidence is less than 1 per 1000&lt;br&gt;Ectopic pregnancy risk is 1 in 20, if pregnant with IUD in situ</td>
<td>60% request removal within 5 years&lt;br&gt;Due to bleeding, pain or hormonal problems&lt;br&gt;PID risk is less than 1%, if low-risk for STI&lt;br&gt;Perforation risk is less than 1 per 1000&lt;br&gt;Ectopic pregnancy risk is 1 in 20, if pregnant with IUS in situ&lt;br&gt;Increased risk of acne</td>
</tr>
<tr>
<td>Effect on menses</td>
<td>Increased menstrual loss and dysmenorrhea</td>
<td>Irregular bleeding and spotting for first 6/12 months&lt;br&gt;Oligomenorrhea</td>
</tr>
<tr>
<td>Return to fertility</td>
<td>No delay</td>
<td>No delay</td>
</tr>
<tr>
<td>Advice given at fitting</td>
<td>Pain and discomfort last few hours, followed by light bleeding for a few days&lt;br&gt;Watch for signs of perforation&lt;br&gt;Follow-up in 3–6 weeks&lt;br&gt;Return if concerned&lt;br&gt;Check threads</td>
<td>Pain and discomfort last few hours, followed by light bleeding for a few days&lt;br&gt;Watch for signs of perforation&lt;br&gt;Follow-up in 3–6 weeks&lt;br&gt;Return if concerned&lt;br&gt;Check threads</td>
</tr>
</tbody>
</table>

( Abbreviations: IUCD, intrauterine contraceptive device; IUS, intrauterine system; PID, pelvic inflammatory disease; STI, sexually transmitted disease)
following insertion of IUCD after spontaneous and induced abortion. In an Indian study of 1,000 cases where IUCDs were introduced after menstrual regulation, the expulsion rate and failure rate were found to be much less with the Cu-T200 than with the Lippes Loop. Postabortal insertion has a high acceptance rate. However, there is 5–10 times more chance of expulsion of the IUCD when inserted after second trimester abortion.

**Postpartum Insertion**

Fitting after a delivery is either immediately postpartum, which is not a common practice for obvious reasons or at 4–6 weeks postnatal. But insertion of the IUCD in the postpartum period has a number of advantages, including ease of insertion and convenience to the user; it is particularly of value in developing countries including India, where postnatal care is not satisfactory. Both postpartum and interval insertion after cesarean delivery have been found to be safe and effective. There is no increased risk of perforation, infection or heavier menstrual bleeding following insertion of the IUCD within 10 minutes of delivery of placenta or after delay of 6–8 weeks postpartum as compared to insertion in the interval between menses. The disadvantages of postpartum insertion of the IUCD is its higher expulsion rate and more chances of perforation. Immediate postpartum insertion (within 10 minutes of delivery) seems to be associated with lower rates of expulsion than insertion at other times of puerperium. Various attempts have been made to reduce expulsion rates by experimental IUCDs with added catgut sutures of biodegradable projections, but none has been found to have a lower expulsion rate following postpartum insertion than the conventional Lippes Loop or Cu-T. Careful postpartum insertion technique, placing the IUCD high up in the fundus transversely, is more important than the type of IUCD whether modified or not. Immediate postpartum insertion of the IUCD is best done by means of a sponge-holding forceps or just manually. There is no need of long inserters such as were used earlier.

**Counseling**

Before insertion every woman should be told about the advantage and drawbacks of the procedure and advised to try it and to get it out any time she does not like it. False hopes about hundred percent safety should never be given. Bad counseling is one of the main causes of the lowering of acceptability and continuation rates in countries like India.

**Insertion Technique**

It is advised that medical personnel trained in IUCD insertion should insert IUCDs. The selection of patients, choice of device, timing of insertion and skill of the inserter is critical to the success of the device and can affect how it is accepted and also determine its continuation of use. Rarely during insertion some patients may get syncope and so good resuscitation facilities should be available.

Other research has looked at improving IUCD services by training nonphysicians to provide IUCDs. IUCD insertions by trained nonphysicians are increasing, and some countries, such as the Philippines, have initiated training programs specifically for nonphysicians. Studies in Brazil, Turkey, and the Philippines found that trained health care workers can provide IUCDs as safely and effectively as physicians in many settings. Additional training may be required to ensure correct placement of the IUCD in the uterine fundus to reduce the likelihood of expulsions. Training nonphysicians to provide IUCDs safely and effectively could result in higher use of this method. But at the same time it carries risk in difficult cases as we all know that every case is different.

Most IUCDs are supplied with their inserter in prepacked sterilized plastic containers. The shelf life of the Cu-T 380A IUCD is 7 years. If the date on that IUCD sterilized packaging has expired, the device and its inserter should be discarded.

Perform a bimanual examination to assess the position of the uterus and to rule out pelvic infection. Place the speculum in the vagina. Clean the cervix and vagina with betadine or a similar antiseptic solution. Place a tenaculum on the anterior lip of the cervix. Explore the uterus with a uterine sound. Do not move rod. The Cu-T device and the inserter with the plunger are taken out under sterile conditions just before insertion. The horizontal arm of the device is folded. The tail, the vertical rod and the folded horizontal arm of the device are introduced.
at the top end of the inserter. The adjustable collar is adjusted so the size of the portion of the inserter above it corresponds to the size of the uterine cavity as determined by the introduction of the uterine sound. The solid rod plunger is now introduced into the inserter tube up to the lower end of the vertical arm. The inserter loaded with the device is now negotiated into the uterine cavity till it touches the fundus and the collar touches the external os. The plunger is held firmly with the left arm, and the outer inserter tube is retracted over the plunger with the right hand for about 2 cm, so that the Cu-T device is left high up in the fundus and lies transversely. This is withdrawal technique, which minimizes risk of perforation. The plunger is withdrawn followed by removal of the inserter tube and thread is trimmed so as only 2 cm lies outside external os. In puerperal insertion or in cases with previous uterine surgery, special care is needed.

The woman should be told that the IUCD will not interfere with her sexual act nor will her male partner feel it during intercourse. To detect expulsion she should watch her pads during the next few periods and also watch for falling of T-shaped device during other acts like voiding. Additionally she can feel the tails following menstruation as long as she uses the IUCD (Fig. 5). But at many times it is found that women are not very comfortable for this rather they find it embarrassing.

The woman should report if she cannot feel the tail or if she feels a part of the IUCD inside the vagina or if IUCD is expelled. Though it is common that first few cycles could be slightly heavy she should also report if she experiences persistent irregular bleeding, discharge or if she develops severe pain in the lower abdomen with or without fever. It is necessary to tell about failure of IUCD and rare possibility of pregnancy with IUCD in situ and accordingly she should come for consultation if her period is missed.

The woman should have a routine check-up after the next period and then after 3 months and then every 6 months. Medicated devices should be replaced at intervals depending upon the recommended effective life span of the devices. Table 2 gives the list of situations when she should report health provider for consultation.

**REMOVAL**

The woman can come for removal anytime she desires to have her next pregnancy. If she is not happy with IUCD use or is not convinced with appropriate counseling she can come for removal but it is necessary to offer another suitable method of contraception. If she has continued IUCD use till menopause then it is advisable to remove it 18 months after menopause, if she is less than 50 years or 12 months after menopause, if she is more than 50 years.

**INDICATIONS**

- Its main use is contraception but there are many other indications for which IUCD is used.
- Intrauterine devices can be used as emergency contraception to prevent pregnancy up to 5 days after unprotected sexual intercourse. Insertion of a Cu-T IUCD as emergency contraception is more than 99% effective, making it more effective than emergency contraceptive pills.
- Following adhesiolysis in Asherman’s syndrome, IUCD is inserted to prevent re-adhesions. It is used for 3 months.
- It is also used after hysteroscopic resection of uterine septum, to avoid Asherman’s syndrome.
- Mirena, progestogen IUCD is used in menorrhagia as it reduces menstrual loss.

**ADVANTAGES**

- A single decision leads to effective long-term prevention of pregnancy.
• It is particularly useful for spacing pregnancies and as a real alternative to hormonal contraception in couples in long standing mutually monogamous relationships.
• It is long-lasting. The most widely used IUCD, Cu-T-380A, lasts at least 10 years. Inert IUCDs need never be replaced.
• They are very effective immediately after fitting. No daily action or user motivation is needed. IUCDs are appropriate for women who desire a “forgettable” method of contraception.
• No interference with sex and its use is nonintercourse related. Instead there is increased sexual enjoyment because there is no need to worry about pregnancy.
• Nonhormonal IUCDs are considered safe to use while breastfeeding.
• It can be inserted immediately after childbirth except hormone releasing IUCDs or after induced abortion if there is no evidence of infection.
• It has very low morbidity and mortality.
• Some women especially those using hormonal contraceptives experience 74–90% decrease in menstrual bleeding and reduced menstrual cramping.
• IUCDs are a safe and effective method of reversible, long-term contraception for most women.
• It protects against endometrial cancer.
• It is cost effective.

DISADVANTAGES AND SIDE EFFECTS

Common Side Effects
Menstrual changes which are common in the first 3 months but likely to lessen after 3 months are:
• Longer and heavier menstrual periods
• Increased watery or mucoid discharge
• Bleeding or spotting between periods
• More cramps or pain during periods.

Other Uncommon Side Effects
• Severe cramps and pains beyond the first 3–5 months after insertion.
• Heavy menstrual bleeding or bleeding between periods, possibly contributing to anemia.
• The string may be felt by some men during intercourse. If this is problematic, the provider may cut the strings flushing with the cervix, so they cannot be felt.
• Expulsion of IUCD is noticed in 2–10% cases. This risk is more in nulliparous women or if it is a postpartum insertion.
• Perforation of the wall of the uterus is very rare if the IUCD is properly inserted. The incidence is 1 in 1,000 fittings.
• Does not protect against STDs including HIV/AIDS. Not a good method for women with recent STDs or with multiple sex partners.
• Pelvic infection—not increased when risk of STDs is low. But on high-risk, pelvic inflammatory disease (PID) is more likely to follow STD infection if a woman uses an IUCD. It is advisable to rule out infection before insertion as this PID can lead to infertility.
• Risk of ectopic pregnancy is less than in patients using no contraception for obvious reason that there are fewer fertilizations in patients using IUCDs. However, patients who use copper IUCDs are less protected against ectopic pregnancy than oral contraceptive users or those using other methods.
• With hormonal IUCDs, women may experience changes in bleeding pattern, headache, breast tenderness, acne, weight changes or mood changes. But these changes usually decrease over time.
• It is possible to minimize these side effects by avoiding use of IUCDs in following situations.

CONTRAINDICATIONS

Absolute
• Active pelvic infection or history of infection within last 3 months
• Suspected pregnancy
• Suspected genital malignancy
• Previous classical cesarean section.

Relative
• Uterine fibroids, specially grossly distorted cavity
• Congenital anomalies of the uterus, when cavity is less than 5 cm
• Previous ectopic pregnancy
• Menorrhagia, unless it is mild
• Metrorrhagia
• Severe dysmenorrhea
• Severe cervical stenosis
• Moderate to gross anemia
• Copper allergy including Wilson’s disease
• Valvular heart disease especially previous history of endocarditis
• Insulin dependent diabetes
• Immunosuppressive therapy.
  If there is a history of ectopic pregnancy or if there is heart disease or in nulliparas, it is better to avoid IUCDs. In 1985, the American College of Obstetricians and Gynecologists had advised not to use IUCDs in women who have not had children or who have multiple partners, because of the risk of PID and possible infertility. But in other cases it can be used even in nulliparous women.

The WHO medical eligibility criteria for contraceptive use and RCOG Faculty of Family Planning and Reproductive Health Care (FFPRHC) UK, medical eligibility criteria for contraceptive use lists the following as conditions where
insertion of a copper IUCD is not usually recommended or conditions where a copper IUCD should not be inserted.\textsuperscript{30,41}

**Conditions where the Theoretical or Proven Risks usually Outweigh the Advantages of Inserting a Copper IUCD**

- **Postpartum:** Between 48 hours and 4 weeks (increased IUCD expulsion rate with delayed postpartum insertion)
- Benign gestational trophoblastic disease
- Ovarian cancer
- Very high individual likelihood of exposure to gonorrhea or chlamydial STIs
- AIDS (unless clinically well on antiretroviral therapy).

**Conditions which Represent an Unacceptable Health Risk if a Copper IUCD is Inserted**

- Pregnancy
- Postpartum puerperal sepsis
- Immediately following postseptic abortion
- Before evaluation of unexplained vaginal bleeding suspected of being a serious condition
- Malignant gestational trophoblastic disease
- Cervical cancer (awaiting treatment)
- Endometrial cancer
- Distortions of the uterine cavity by uterine fibroids or anatomical abnormalities
- Current PID
- Current purulent cervicitis, chlamydial infection, or gonorrheal STIs
- Known pelvic tuberculosis.

While nulliparous women are somewhat more likely to have side effects, this is not a contraindication for IUCD use.

**COMPLICATIONS**

**Infection**

Some barrier contraceptives protect against STDs. IUCDs do not protect against STDs or PID.

On the contrary, insertion of the IUCD may introduce bacteria into the uterus. The insertion process carries a small, transient increased risk of PID in the first 20 days following insertion.\textsuperscript{42} It is very important that the provider use proper infection-prevention techniques during insertion.

Recent studies also have investigated the possibility that the increased menstrual bleeding and upper genital tract infections associated with IUCDs may increase the risk of HIV among IUCD users. Data from several studies, however, have not demonstrated an increased risk.\textsuperscript{43}

**Heavy Menstrual Periods**

After IUCD insertion, menstrual periods are often heavier, more painful, or both—especially for the first few months after it is inserted. On average, menstrual blood loss increases by 20–50% after insertion of a Cu-T IUCD; increased menstrual discomfort is the most common medical reason for IUCD removal.\textsuperscript{44} But in fact in many cases, bleeding gets controlled in 2–3 cycles.

**Uterine Perforation**

It is generally caused by an inexperienced provider and is very rare. It usually occurs during insertion itself due to faulty technique. It is a myth that IUCD travels in abdominal cavity.

If the patient complains of sudden significant pain during the insertion procedure or uterine sounding or if the loaded IUCD inserter tube passes into the uterus beyond 9–10 cm without fundal resistance being felt, stop the procedure and remove the IUCD if it has been inserted. Observe the patient for signs of intra-abdominal bleeding (e.g. falling BP, rising pulse, severe abdominal pain, tenderness, guarding, and rigidity). Take the patient’s blood pressure and pulse every 15 minutes for 90 minutes. If there are signs of intra-abdominal bleeding, it is managed accordingly. Otherwise schedule a return checkup after 1 week and help the patient choose another contraceptive method in the meanwhile. Reinsertion can be attempted after the next menstrual cycle.

It is to be remembered that if the IUCD device has been inserted into the abdomen, then the IUCD needs to be removed, preferably by laparoscopy. Copper-containing IUCDs induce an inflammatory reaction causing adhesions and therefore should be removed promptly. Progesterone-containing devices do not induce similar intraperitoneal adhesions; however, most providers also prefer prompt removal.

**Expulsion**

This is more common in younger women, women who have not had children, and when an IUCD is inserted immediately after childbirth or abortion. Women should check the string of the IUCD at least once per menstrual cycle to verify that it is still in place.

**Missing or “Lost” Threads**

It indicates:

- Pregnancy
- Expulsion
- Threads drawn up into the uterus.

Assessment of the patient with examination, ultrasound scan, or X-ray if necessary, will be required. It is managed in this way:

- Always consider the woman with lost threads to be either already pregnant, or at risk of being so
- Determine whether patient is pregnant
- Explore cervix with narrow artery forceps, under direct vision. Gently open and close jaws and withdraw. The majority of threads will be found with this procedure.
- If unsuccessful consider ultrasound to establish position or proceed to exploration of uterine cavity with retriever
hook. Needs appropriate analgesia, e.g. mefenamic acid 500 mg.
- If still unsuccessful, refer for ultrasound, hysteroscopy or laparoscopy if extrauterine.
- If patient elects for termination of pregnancy, the IUCD can be removed at time of surgery.
- If patient is pregnant with IUCD in situ and wishing to proceed to full-term, gentle removal in the first trimester has been found to halve the miscarriage rate.\textsuperscript{45}

**Ectopic Pregnancy**

The risk of ectopic pregnancy to a woman using an IUCD is lower than the risk of ectopic pregnancy to a woman using no form of birth control. However, if pregnancies that do occur during IUCD use, a higher than expected percentage (3–4%) are ectopic.

However, there are many reports saying that, IUCD use is not associated with an increased risk of PID, or ectopic pregnancy, or of subsequent infertility.

**Failure**

If pregnancy does occur, presence of the IUCD increases the risk of miscarriage, particularly during the second trimester. It also increases the risk of premature delivery. These increased risks are reduced if the IUCD is removed after pregnancy is discovered. IUCDs are also not associated with birth defects or other pregnancy complications. Before 12 weeks there is a 50/50 chance of miscarriage whether the device is removed or not, but early removal prevents possible midtrimester miscarriage. Removal very early carries a lower than 50% association with miscarriage.

**Allergic Reactions**

A few case reports have attributed eczematous dermatitis and urticaria in users of copper-releasing IUCDs to systemic copper allergic contact dermatitis, but some dermatologists are skeptical of this because the amount of copper released daily by an IUCD is only a small percentage of the required amount of copper (an essential trace mineral) absorbed daily from the diet, and because copper is an extremely rare cause of allergic contact dermatitis with a low sensitizing potential.\textsuperscript{46}

**Risk of Cervical or Endometrial Cancer**

Although it was hypothesized that irritation of the cervix and endometrium by an IUCD might cause cancer, no association has been found. On the contrary, The Cancer and Steroid Hormone Study of the Centers for Disease Control and Prevention found a protective effect against endometrial cancer (OR = 0.50; 95% CI, 0.3–0.8) with IUCD use.\textsuperscript{47} This protective effect increased with duration of use but did not reach statistical significance. Several other studies have also demonstrated a protective effect of the IUCD against endometrial cancer. It is hypothesized that the IUCD introduces structural changes in the endometrium, thereby altering its sensitivity to circulating hormones.

**SUMMARY**

Table 3 depicts summary of commonly used IUCD, Cu-T 380A.

The IUCD is a safe, cheap, effective and convenient method of contraception, needing no repetition and not interfering with sexual activity. In spite of this its acceptability

<table>
<thead>
<tr>
<th>Table 3: Summary of commonly used intrauterine contraceptive device</th>
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<td><strong>Background</strong></td>
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<td></td>
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<tr>
<td><strong>Risks</strong></td>
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</table>

*(Abbreviations: BC, birth control; STD, sexually transmitted disease)*
is not up to the mark, mainly because of drawbacks such as bleeding, pain, expulsion and infection. Its continued use depends a lot upon the attitude and social customs of the patient towards slight irregular bleeding, which happens commonly in the first few months, and also upon the attitude of the operator and the availability of other methods of contraception.

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Emergency Contraception

DEFINITION
Postcoital contraception or emergency contraception (EC) as it is called now, is a method of using contraceptives to prevent pregnancy following unprotected or unintended intercourse.

Various methods that can be used are either hormonal [estrogens, oral contraceptive pills (OCPs), progestin-only pills (POPs), danazol], nonhormonal (RU-486, Ormeloxifene) or mechanical (IUD). The exact mechanism of action of these agents is dependent on the event of ovulation and its relation to the timing of intercourse and the use of any of the methods.

Added to the World Health Organization (WHO) list of essential drugs in 1996, EC is now recognized as an essential component of contraceptive choice. If EC is used when a couple is at risk of an unintended pregnancy, half of the estimated 3.5 million unintended pregnancies could have been prevented.

INDICATIONS
Situations in which EC is indicated are:
- No contraceptive was used when intercourse took place
- A male condom slipped, broke or leaked
- Diaphragm or cervical cap was incorrectly inserted, dislodged during intercourse, was removed too early, or was found to be torn
- Missing one or more combined oral contraceptive pills (COPs) at the beginning or the end of the pack so that the pill free interval is prolonged beyond 7 days
- Missing one or more POPs
- Improper insertion or removal of a female condom
- Placement of penis in-between female condom and vaginal wall
- Error in practicing coitus interruptus or periodic abstinence
- Partial or total expulsion of intrauterine device (IUD)
- Exposure to possible teratogen such as a live vaccine or cytotoxic drug
- In cases of rape or incest.

Out of these, contraceptive accidents form the major component.

An ongoing pregnancy is the only contraindication to most methods of EC.

A consensus statement sponsored by Family Health International, The Population Council, International Planned Parenthood Foundation and the World Health Organization was published in 1995. This group of 24 experts identified the following three hurdles that have to be overcome, in order to make EC available to all women.

1. Inform patients and doctors about EC so that women know about it before they need it.
2. Manufacturers of EC to provide more publicity and information.
3. All health care providers to change their concept on mode of action. Emergency contraception prevents pregnancy rather than acting as an abortifacient.

EPIDEMIOSOCIAL ASPECTS
On the basis of the six nationally representative studies, the United Kingdom has the highest rates (12%) of women ever using emergency contraception. By contrast, 4% of women in Finland reported the same, and only 1% of women in the United States of America and Nigeria said they have used the method.

Studies also reveal that emergency contraception is indeed popular with young people when they know about it. A study of a teen clinic in Nottingham, UK found that 17% of the clinic visits were for emergency contraception. Perez, who conducted a study of youth center clinics in three cities in Spain, found that 25% of the visits were for emergency contraception.
CHAPTER 58

Emergency Contraception

MODE OF ACTION

Estrogen, combination OCPs, POPs and danazol act in different ways to prevent a pregnancy, depending on when the method is administered. If administered before ovulation, disruption of follicular growth, development and maturation is noted. This disruption can lead to anovulation or delayed ovulation with a change in hormone production during the luteal phase of the menstrual cycle. Postovulatory treatment probably has an effect on the endometrium. However, these methods cannot hamper an ongoing pregnancy.

Estrogens

In 1920s, the estrogen components of ovarian extracts were used for their ability to prevent pregnancies. Since then various schedules were tried. But, the side effects in estrogen users were more severe, hence are not in use at present.

Oral Contraceptives

Combination Pills

In 1977, Yuzpe and Lance published their first article that showed that 500 µg (0.5 mg) of ethinyl estradiol (EE) and 2 mg of levonorgestrel (LNG) in two divided doses over the course of 12 hours within 72 hours of unprotected intercourse could be used as a method of EC. The primary advantage of this regimen, which came to be known as the “Yuzpe Method” (Table 1) is a 125-fold reduction in the EE content and a decrease in overall length of drug administration.

In this landmark study, 608 women were treated, of which 464 admitted to regular menstrual cycles and only 152 had unprotected intercourse at the midcycle. Only one pregnancy was documented in a woman who was exposed at midcycle and started the medication 70 hours after intercourse. The pregnancy was terminated by vacuum aspiration and pathologic evaluation of placenta revealed fibrinoid necrosis of majority of the chorionic villi. Sixty-six percent of patients experienced nausea and 19% emesis.

The various mechanisms by which this regimen seems to act are:

- Suppression or delay of ovulation
- Disruption of luteal function or luteolysis
- Desynchronization of endometrium through the effect on endometrial enzymes and the effect of endometrial progesterone receptors with interference of downregulation
- Accelerated ovum or zygote transport through the tube.

Five years later, Yuzpe et al. published as a follow-up study that documented 11 pregnancies in 692 women who adhered to previous protocol. Of this group, 451 patients were noted to have regular cycles. Of these women with regular cycles, 101 were exposed before midcycle, 217 at midcycle and 133 after the midcycle. Of the 11 pregnancies, 9 were in women with regular cycles and 2 were in those with irregular cycles. In those exposed after the midcycle, one pregnancy occurred in a woman who vomited after she took the pills. Nausea and/or emesis occurred in 51.7% of all patients. Other side effects were minimal.

Trusell et al., analyzed the results of nine published studies in which the effectiveness of this regimen was assessed when treatment was initiated one, two and three days after midcycle unprotected intercourse. The analysis showed that the first tablet needs to be taken immediately after intercourse, allowing the women to go to a health care facility to receive medication the day following unprotected intercourse without a decrease in effectiveness.

In a large Canadian study, 30% of the subjects treated with this regimen reported having nausea without vomiting and another 20% experienced both nausea and vomiting. These investigators included an antiemetic (50 mg tab of dimenhydrinate) in the package and instructed the women to take it along with the second dose of OCPs, if they experienced nausea after the first dose. The time of onset of subsequent menses was also slightly decreased in the users of this regimen.

This regimen is associated with lower rates of side effects such as abnormal bleeding, delayed menses and gastrointestinal (GI) disturbances. In addition, due to a one day treatment regimen, patient compliance is much improved. As a result, this method is more widely used than high dose estrogens for EC. Grossman et al. have reported an underutilization of this method in the US due to lack of public awareness. The WHO criteria (medical eligibility criteria) for emergency contraceptive pills is presented in Table 2.

Progestin-only Pills

Pills containing levonorgestrel have been shown to be equally effective as the Yuzpe method for EC. Ho and Kwan, randomized 424 women to use the Yuzpe method and 410 to the levonorgestrel group. Comparative study between Yuzpe regimen and progestin-only pills (POPs) as EC is shown in Table 3.
Levonorgestrel is administered as 0.75 mg tablet within 72 hours of intercourse and is to be repeated after 12 hours. Though 18.2% of the combination pill users and 19.3% of the progestin-only pill users continued to have intercourse during the cycle, only 3.5% of the Yuzpe group and 2.9% of the POP group became pregnant.

In 1998 WHO published a well-designed randomized controlled trial showing higher efficacy for the progestogen-only method compared with the Yuzpe method. Failure rates were 3.2% and 1.1% respectively.

Hence, when compared with the Yuzpe method, the progestogen-only regimen is equally effective with lesser incidence of side effects such as nausea, emesis and breast tenderness which are caused due to estrogen, and are hence not encountered.

Vomiting following LNG administration is unusual, occurring in only 1% of women. Nausea is reported more frequently (14%). If a woman vomits within 2 hours of taking levonorgestrel emergency contraception (LNG EC), she should take a further dose as soon as possible. Antiemetics are not routinely recommended. An IUD should be considered for a woman experiencing persistent vomiting with oral EC.

Cycle disturbances are common after LNG EC. In the WHO trial, 16% of women experienced bleeding (unrelated to expected menstruation) in the 7 days following treatment. Around 50% of women menstruated a few days earlier or a few days later than their expected practice as women and clinicians generally rely on the reassurance of menstruation as confirmation that EC has been effective and pregnancy has not ensured. It may be difficult to differentiate between nonmenstrual bleeding in the early days after EC and actual menstrual bleeding. Clinicians and women should always err on the side of caution, and undertake pregnancy testing if there is any doubt that menstruation has followed EC use.

Ectopic pregnancies have been identified following administration of LNG EC in case series, however the overall risk does not appear to be increased following LNG EC. There is insufficient postmarketing data to allow accurate assessment of risk. Clinicians and women should be alert to the possibility of an ectopic pregnancy, but the risk is likely to be small.

At the present moment, the United States Food and Drug Administration (USFDA) has approved both combined OCPs and POPs for EC use. These drugs have been marketed as a four tablet pack along with a pregnancy test device in most countries. At the Consortium of Emergency Contraception which was held in New Delhi, India, in January 2001, this regimen was selected as a “dedicated product”.

A WHO multicentric trial was conducted in order to simplify the LNG regimen. A single dose of 1.5 mg of LNG was as effective as doses given 12 hours apart up to 120 hours after exposure.

### Intrauterine Device

The use of IUD as postcoital contraceptives is also referred to as mechanical postcoital contraception. It was first used in 1976 by Lippe et al. as a postcoital contraceptive. Intrauterine device can be used as an effective method of EC up to 7 days after exposure.

The exact mechanism is not precisely known, but the various postulated mechanisms are as follows:

- **Intrauterine device may have an effect on tubal ciliary motility to disrupt the transport of the oocyte or the embryo.** The IUD itself or its copper ions may also hamper the ability of an embryo to implant. It acts before implantation because there was no evidence of a rise in beta human chorionic gonadotropin (β hCG) level following IUD insertion as EC. Copper is also known to be both spermicidal and blastocidal. All these factors contribute to its effectiveness up to 7 days after intercourse has occurred.

- **Intrauterine devices (IUIDs) with banded copper on the arms and containing at least 380 mm² of copper have the lowest failure rates and should be the first-line choice, particularly if the woman intends to continue contraception.**

- **Fasoli et al. summarized the results of four published studies from nine countries involving 875 women who utilized this technique.** Only one pregnancy resulted in these women following copper-IUCD insertion.
The failure rate was consistently less than 0.1% in most studies. Hence, IUDs have the lowest failure rate of any method of EC.

- The primary side effects associated with this method are uterine cramping and vaginal bleeding or spotting.
- One of the biggest advantages of IUDs is that it can be used as an ongoing method of contraception. However, it should not be used in patients in whom the device would be contraindicated like women who have pelvic inflammatory disease (acute, recent or recurrent), distorted uterine cavity, or multiple sexual partners.
- Though IUDs have been shown to be effective, they are infrequently used. When physicians were polled regarding the utility of IUDs for EC, they stated that they thought the obstacles of using the IUD were the possible risk of pelvic inflammatory disease or the amount of time it took to place the device (Fig. 1). This study demonstrated that physicians should become more comfortable with IUD use and should consider IUD for use as an EC. So far, no manufacturer of IUDs has yet applied for USFDA approval to market IUDs as an EC product. Hence, it is infrequently prescribed by clinicians and very few women are aware of its utility, effectiveness, accessibility and safety as an EC.

**Danazol**

Danazol is an androgen analogue that primarily has been used in daily dosage ranging from 400 mg to 800 mg for patients for endometriosis, inducing a pseudomenopausal state.

Studies concerning the effectiveness of danazol as an EC have not been encouraging. Incidence of nausea and emesis were lower than that seen with Yuzpe method. Nevertheless, the effectiveness of danazol as an EC was unacceptable.

In those women, who desire a continuing need for contraception after the cycle in which these drugs (i.e. danazol and LNG) are used, one of the conventional methods needs to be prescribed. Ormeloxifene has also been used as an EC in a dose of 60 mg (2 tab) within 72 hours and 2 tablets within the next 12 hours.

**Antiprogestins (RU-486: Mifepristone)**

Antiprogestins are a family of compounds that block the progesterone receptor. Progesterone is important in endometrial development, ovulation and pregnancy continuation. Any disruption to the progesterone receptor could produce an adverse effect on follicular development, implantation and maintenance of pregnancy.

The most commonly studied antiprogestin as an EC is RU-486 (mifepristone). When RU-486 is administered as a single dose of 600 mg, within 72 hours of unprotected intercourse, it is as efficacious as the Yuzpe method or Danazol.

In the three studies that examined all three methods the failure rates were RU-486 (0–0.4%), Yuzpe method (1.3–2.6%) and Danazol (3.5–4.7%). Also, compared with Yuzpe method, RU-486 users had low rates of nausea (70% vs. 37%) and emesis (22% vs. 3%). Women using Yuzpe method had a higher rate of irregular bleeding, while those using RU-486 had delayed menses. Because of this delay, further intercourse should be avoided. The patient is to be reassured that a postponed cycle may not be a result of pregnancy. If menses do not occur by 3 weeks, a pregnancy test is mandatory.

Greater utility of RU-486 as an EC, will help improve patient compliance, decrease adverse effects and as a result medical or surgical abortions and the social implications brought on by the delivery of an unwanted pregnancy.

A dose of only 10 mg has been shown to be a highly effective method up to 5 days after unprotected coitus.

### CONTRAINDICATIONS

The WHO Medical Eligibility Criteria for Contraceptive Use advises that there are no medical contraindications to the use of hormonal EC. The Summary of Product Characteristics (SPC) advises caution in women with hepatic dysfunction, hereditary problems of galactose intolerance, the Lapp lactose deficiency or glucose-galactose malabsorption. Women with severe malabsorption syndromes (such as Crohn’s disease) may experience a reduction in efficacy of oral EC. Additionally, any women known to have hypersensitivity to LNG or any of the other components of the tablet should use oral EC with caution.

Use of an IUD for EC carries the same contraindications as does routine IUD insertion. For most women, benefits of IUD use outweigh risks (WHO Category 1, “unrestricted use”) or (WHO Category 2, “benefits generally outweigh risks”). Risk of sexually transmitted infections (STIs), previous ectopic pregnancy, young age, and nulliparity are not contraindications to IUD use.
DRUG INTERACTIONS RELEVANT TO EMERGENCY CONTRACEPTIVE USE

- Women using liver enzyme-inducing drugs should be advised that an IUD is the preferred option for EC.
- Women who are using liver enzyme-inducing drugs who are given 0.75 mg tablets of LNG should be advised to take a total of 2.25 mg (three tablets) as a single dose, as soon as possible and within 72 hours of unprotected sexual intercourse. This use is outside the product license.
- Women who are using liver enzyme-inducing drugs who are given 1.5 mg tablets of LNG (Levonelle 1500) should be advised to take a total of 3 mg (two tablets) as a single dose, as soon as possible and within the 72 hours of unprotected sexual intercourse. This use is outside the product license.
- Women using nonliver enzyme-inducing antibiotic (short- or long-term) should follow the normal LNG regimen (1.5 mg within 72 hours of unprotected sexual intercourse).
- There are no drugs that are known to affect emergency IUD use.

PRACTICAL MANAGEMENT FOLLOWING A REQUEST FOR EMERGENCY CONTRACEPTION

1. Detailed history about:
   - Last menstrual period (LMP)
   - Past menstrual cycles
   - Timing of unprotected acts/acts of coitus
   - Failure of contraceptive method
   - Sexual history
2. Assess the necessity for EC
3. Explain proper use
4. Discuss effectiveness and failure rates
5. Discuss side effects
6. Counsel regarding need for ongoing contraception.

AFTER CARE AND FOLLOW-UP

Usually, follow-up is recommended within 3 to 4 weeks of treatment. However, the patient should report immediately if she has heavy bleeding or lower abdominal pain. She should also seek immediate help if her next period is exceptionally scanty or is delayed. In such a scenario, pregnancy should be ruled out and if not pregnant, confirm that the woman is correctly using an effective contraceptive method.

Following LNG EC, more than 80% of women menstruate before, or within 2 days after, their expected date; and 95% menstruate within 7 days after their expected date. Women should be advised to have a pregnancy test if menstruation is delayed by more than 7 days, or is lighter than usual. Clinicians should always consider the possibility of ectopic pregnancy in such women.

An emergency IUD can be removed after the next menstruation without risk of pregnancy, provided no unprotected sexual intercourse has occurred since menses or if hormonal contraception was started within the first 5 days of the cycle. In the case of a woman who has not menstruated following emergency IUD insertion, the device can be removed after 3 weeks as long as it is reasonably certain that she is not pregnant.

In the case she is pregnant, counseling regarding pregnancy should be done. If the woman desires termination of pregnancy (which most women will desire), she should be counseled about the various techniques of medical termination of pregnancy (MTP).

Long-term contraception should be discussed. Combined oral contraceptive pills can be started on the 1st day of the next period. Barrier methods and IUCDs can be used immediately. Injectables can be initiated within a week of the next period. Advance provision of LNG can be offered to women to increase early use when required.

ROLE OF VARIOUS ORGANIZATIONS IN EMERGENCY CONTRACEPTION (FLOW CHART 1)

The WHO expert committee on the use of essential drugs added EC in its list in December, 1995. In June 1996, an advisory committee of the US FDA declared the Yuzpe regimen safe and effective and urged its wider availability.

A national consensus on EC was organized under the auspices of WHO and AIIMS, New Delhi, India, in January 2001 to develop a strategic approach and to plan guidelines for EC.

The Indian Council of Medical Research (ICMR) and the Department of Family Welfare, Government of India have decided to undertake projects in order to obtain information for the purpose of introducing EC in the National Family Planning Program.

In 2003, the Federation of Obstetric and Gynaecological Societies of India (FOGSI) in association with Reliance Mobile initiated an Emergency Help Line for EC. This helpline was available in more than 600 towns and cities all over India with the cost of that of a local phone call only.

However, the promotion of EC in India needs careful planning and infrastructure for an effective implementation. Government agencies, medical bodies, NGOs and women groups need to have cooperative and synergistic role in order to enhance the accessibility of EC.

CONCLUSION

Postcoital contraception has a definite place in the prevention of unwanted pregnancies in modern society. Hormonal methods are all very effective, but IUDs are the “gold standard”.

The use of EC as a repetitive method of contraception should be strongly discouraged. At the time of EC administration, plans should be made to use an ongoing contraceptive pill or device and further acts of unprotected coitus should be discouraged.

In developing countries, the use of this method will have tremendous impact, if the drugs are supplied to the patient via medical or paramedical staff. Through such measures, people can be better motivated or induced to use usual contraceptive measures; thus EC can be used as a recruitment service. Future liberalization in the distribution of emergency contraceptive as over-the-counter drugs (OTCs) will lead to a larger utility of EC. Increased female literacy and health educational programs, will lead to greater community based awareness.

**BIBLIOGRAPHY**

Women are not dying because of diseases we cannot treat. They are dying because societies have yet to make the decision that their lives are worth saving.

—Mahmoud Fathalla MD PhD, 1997

PROBLEM OF UNSAFE ABORTION

Unwanted/unplanned pregnancies are a fact of life. Human beings in the reproductive age group are more often than not exceptionally fertile. Even if contraceptive coverage were to be encompassing all, there would still be unplanned pregnancies due to method or human failure attributable to the contraceptive methods.

It therefore stands to reason and is also borne out by statistics that women need safe services for induced abortion. Approximately 6.7 million induced abortions take place in India annually. When abortion is safe, it is an exceptionally simple procedure with an exceedingly low mortality. However, unsafe abortions are a major killer of women.

Unsafe abortion by itself accounts for at least 13% of maternal mortality worldwide and as much as 20% in parts of Africa and Asia, making it one of the leading causes of maternal death.

About 4 million (40 lakhs) illegal/unsafe abortions take place in India. It is estimated by the World Health Organization (WHO 1994) that in the Indian subcontinent 15–24 unsafe abortions takes place per 1,000 women aged 15–49 years. It is estimated (WHO, 1994) that in India 70–89 women per 100,000 live births die from unsafe abortion, the risk of death is 1 in 250 procedures.

BACKGROUND

It is a completely unfounded belief that restricting abortions legally can bring down the number of abortions. Some of the world’s highest abortion rates are in countries where the procedure is most restricted, such as Chile, Peru, Nigeria and the Philippines. Some of the lowest rates are in countries like the Netherlands, Sweden and France, where abortion is an accepted part of comprehensive women’s healthcare.

Up until the medical termination of pregnancy (MTP) act was passed, providing abortion remained punishable under the Indian Penal Code (IPC, 1860) Section 312 which stated that “Any one voluntarily causing miscarriage to a woman with child, other than in good faith for the purpose of saving her life is punishable by imprisonment (simple or rigorous) and/or a fine”.

Sections 313-316 of the IPC dealt with the punishment to be meted out when there was a death due to procedure as up to 10 years imprisonment and fine, extending up to life imprisonment where the abortion was conducted without consent.

The Shantilal Shah Committee was set up to stem the high maternal morbidity and mortality associated with illegal abortions and it recommended a broadening and rationalization of laws related to abortion in 1966. The MTP Bill was introduced to the Rajya Sabha in 1969, referred to Joint Select Committee Review and finally passed as the MTP Act in 1971. The Act was enforced nationwide from April 1, 1972 and adopted by Kashmir and Mizoram in 1980. At present all States and Union Territories except Sikkim are implementing the Act.
THE MEDICAL TERMINATION OF PREGNANCY ACT

Although a relatively brief piece of legislature the MTP act is rich with meaning and implications for all healthcare providers. It is not possible for this article to cover the act in every detail and nuance but I hope that the gist of the act can be distilled and presented to you in the following paragraphs:

The stated aim of the act was “An Act to provide for the termination of certain pregnancies by registered medical practitioners and for matters connected there with and incidental thereto.”

There are a few important facts to be kept in mind whilst analyzing the MTP act.

The first is that it does not as yet confer upon women the right to have an abortion legally. It is a wrong impression that abortion is available on demand in our country. What the act does, is lays down certain indications, albeit liberal, which may make abortion services available to most women. As a counterpoint to this is the second fact that the act makes the service of providing safe abortion almost completely provider centric where the onus on decision making for the abortion is legally with the provider. Thus the thrust of the act needs to be changed to make it easier for those seeking the service and make it woman centric.

The other fact is that up until now the act was a protective act for qualified service providers. This protection was extended provisional to the provider meeting all the demands of the act. The punishments for not following the act were as would be laid down in the IPC. The amendments however, have changed this and punishment is now incorporated into the act itself. There is provision for rigorous imprisonment for a minimum of 2 years which may be extended up to 7 years under the amendments to the act.

When Pregnancies may be Terminated?

According to Section 3 (2) based on opinion formed in good faith, “pregnancies not exceeding 12 weeks can be terminated with single opinion. Pregnancies between 12 weeks and 20 weeks require opinion of not less than two medical practitioners.”

This section indicates that any induced abortion after 20 weeks is illegal, except to save maternal life as per Section 5. Thus whatever else may be the indication a pregnancy beyond 20 weeks may not be terminated except to save maternal life.

Grounds for terminations as per Section 3 (2) allowed for the following indications:

- Risk to life or risk of grave injury to physical or mental health
- Substantial risk of physical or mental abnormalities if the child were born

This section indicates that the responsibility to judge the necessity and indication lies with the physician who has to opine in good faith regarding valid legal indication for the termination of pregnancy.

Explanation 2 of the section specifies that “Where any pregnancy occurs as a result of failure of any device or method used by any married woman or her husband for the purpose of limiting the number of children, the anguish caused by such unwanted pregnancy may be resumed to constitute a grave injury to the mental health of the pregnant woman”. The explanation does not elaborate on the method of contraception. It is quoted as being the most common indication on records for an MTP.

The Issue of Consent

Consent has always been a controversial issue to the practicing gynecologist particularly when it relates to matters of reproductive health. However, the act is unequivocal about the type of consent required and the format (Form C) for the same.

Valid legal consent as per Section 2 (4) is mandatory. In the case of majors (women above the age of 18) termination of pregnancy can proceed with their valid consent. It is important to note here that the law does not require spousal or anybody else’s consent for women who are majors. Thus the practice of taking consent from either the spouse or any other family member is legally not valid.

In the case of clients below the age of 18 or mentally ill persons termination can only proceed with the consent of guardian. However, the definition of guardian is tenuous at best.

By Whom Pregnancies may be Terminated?

The act is quite clear as to the qualifications required for a provider to perform MTP’s.

Qualifications of a practitioner registered in the State Medical Register are defined in Section 2 (d) of Rules as a doctor trained in the allopathic system of Medicine (any recognized medical qualification as defined in clause (h) of section 2 of the Indian Medical Council Act, 1956 (102 of 1956, whose name has been entered in a State Medical Register) who further has:

- PG degree or diploma in Gynecology and Obstetrics
- Registered before commencement of Act with 3 years experience in the practice of gynecology and obstetrics
- Registered after commencement of the Act if:
  - House surgeon (6 months) in gynecology and obstetrics
  - Experience of over 1 year in gynecology and obstetrics
  - Assisted or performed 25 MTPs in a training Institute (observed 10, assisted 10 and performed 5 procedures under supervision)
This has been one of the contentious sections as it disregards the talents and potential of the doctors trained in the alternative systems of medicine who have undergone structured training. Consideration should be given to this thought and training systems devised to bring them into the ambit of structured healthcare programs. Needless to say this may be made possible only after rigorous training.

Where Pregnancies may be Terminated?

There is no ambiguity in the act that an MTP performed in a center which is not registered is an illegal abortion. The provider who performs the MTP in an unregistered center steps out of the protection that the MTP act offers and is liable to punishment. It is therefore essential that both the place where the procedure is performed and the provider fulfil the requirements of the Act.

Registration of place has constantly been one of the bureaucratic bugbears for expanding access to safe abortion. On the one hand the country is faced with inadequate and inequitable access and on the other hand the process of registering the center for performing MTP's was, to say the least cumbersome and time consuming. The amendments to the MTP act address this issue and the registration process has now been decentralized.

Section 4 of the MTP Act defines settings where abortion may be provided legally as:

- A hospital established or maintained by the Government
- A place for the time being approved for purpose of this Act by the Government or a District Level Committee constituted by the government with the chief medical officer or district health officer as the chairperson. The district level committee shall consist of not less than three and not more than five members as may be specified from time to time.

Although a breakthrough in terms of policy, the decentralization and formation of district level committees has taken place as of now only in very few places in the country. Teething problems to form the committee have held up formation of these at most places and awareness within the system needs to be raised.

The Legal Status of the Medical Methods of Medical Termination of Pregnancy (Medication Abortion)

Medical methods for termination of pregnancy are recognized in an explanation in the amendments to the MTP Act. They are allowed to be administered up to 7 weeks (49 days) into the gestation by a registered medical practitioner as prescribed under Section 2 (d) and Rule 3, having access to a place approved by the Government under Section 4 (b) and Rule 5 of MTP Rules.

This means that even if a place is not registered an RMP as defined by the act can prescribe medical abortion here provided he/she displays a certificate proclaiming that he/she has access in terms of surgical backup to a place which is formally registered for MTP.

Documentation and Records

According to the MTP Regulation (Regulation 5) centers are required to maintain an Admission Register in the prescribed format (Form III) and preserved for 5 years. This is a secret document to be kept in safe custody. It is important for all practitioners of MTP to maintain good records and report them sincerely. Besides being a legal requirement there are several data gaps in our current databases which need to be filled. This data is significant for future planning, advocacy and monitoring progress.

Protection of Action Taken in Good Faith

The MTP Act (Section 8) protects the medical practitioner from suits or other legal proceedings for any damage caused or likely to be caused by anything done in good faith under the act. The important, thing to note is that to avail of the protection the provider has to be strictly within the framework laid down in the act and therefore the importance of sticking to the act in providing MTP services.

Further Changes

The MTP act stands out as an act which is wise, liberal and has the potential to relieve untold suffering to many women. Having said that, several lacunae which need to be addressed with further amendments still exist, e.g.:

- Requirement of two opinions for second trimester termination is now a formality and could be dispensed.
- A qualified extension of up to 22 weeks to accommodate terminations after prenatal diagnosis of birth defects simply because a large majority are diagnosed after this time.
- There is immense work to be done in terms of simplifying bureaucratic procedures to speed up the registration process.
- The subsection in Section 2 which elaborates on the failure of contraception specifies “married” couples who have a failure of contraception as eligible to undergo an MTP. The word married needs to be omitted.

These are only a few of the changes which need to be incorporated into the act.

CONCLUSION

We live in a structured society and it is important for each of us to appreciate and know as well as we can the rules that
govern our professional life. Not knowing the rules can hardly be termed as an excuse to break them.

We in India are fortunate to have a liberal law for provision of safe abortion. This inspired piece of legislature was in need of some changes and these came about as the MTP (Amendment) Act 2002. The Federation of Obstetrics and Gynecological Societies of India (FOGSI) was proud to play a significant role in the evolution of the amendments of the MTP act and will continue to be involved in updating and implementing the act.

Besides policy we also have to look at the ground realities which exist after policy is in place. Although the MTP act has greatly benefited the women of our country much work still remains to be done. We all have a role to play in achieving the goal of giving our mothers the freedom to make their choices safely. They deserve no less.
INTRODUCTION

With increasing awareness, information and education, male partner involvement in family planning and welfare is on the rise. Today, couples are able to discuss the family planning options amongst themselves and with their doctor and make a logical decision about the method of contraception both temporary and permanent.

Apart from condoms and spermicidal gels, with no reliable male contraceptive pill available, vasectomy remains one of the safest and the most effective permanent contraceptive method available and is a popular male option. As compared to tubal ligation done in females, vasectomy is easier, safer, does not require opening of the abdominal cavity, quicker and can be done as an outpatient office procedure. Under local anesthesia (LA) contraception is effective, reliable and reversible. In spite of all the advantages, it is less commonly performed than tubal ligations in most countries.

Population reports (2003) have found that apart from India and China, less than 1% of women in the developing countries rely on male sterilization as a contraceptive method. In India, the figure is 2%, Nepal 6% and China 8%. Male sterilization is a major family planning method (more than 40%) in the developed countries like United Kingdom (UK), United States of America (USA), Canada, Australia and New Zealand. The reason for the lower incidence in the developing countries could be gender bias, male dominance and misconceptions. Vasectomy is still shrouded with fear and ignorance and many associate this procedure with loss of virility.

With the improvements and evolution in techniques such as NSV Li et al., vasectomy has surpassed tubal ligations in some provinces of China. Also vasectomy reversal has better success rates than before. Technical success as evidenced by live spermatozoa in the ejaculate is achieved in greater than 95% of the patients operated by trained urologists. Studies suggesting increased incidence of prostatic cancer and also increased levels of antisperm antibodies have been discounted. All these factors have led to an increase in acceptance of vasectomy as a choice of voluntary permanent sterilization.

INDICATIONS

Vasectomy is indicated as a permanent sterilization method in couples or individual male who desires no further children. The concerned individual must be in a fit mental state and able to understand the consequences of his decision.

Eligibility Criteria [World Health Organization (WHO)—International Planned Parenthood Federation (IPPF)]

Contraindications

No permanent contraindication (irrespective of age and number of children).
Delay

Delay: Until condition is successfully treated or no longer exists
• Infection of operative area or acute systemic infections
• Signs and symptoms of sexually transmitted disease (STD)
• Filaria—elephantiasis
• Intrascrotal mass.

Special precautions: To be done in a facility well-equipped to handle complications
• Previous scrotal injury
• Large varicocele
• Large hydrocele
• Previous surgery for cryptorchidism
• Inguinal hernias
• Coagulation disorders.

Counseling and Preoperative Information

Males should be encouraged to undergo vasectomy as a permanent family planning procedure particularly if the female partner is weak, anemic, suffering from any systemic disease, heart problems or intra-abdominal adhesions and previous pelvic operations.

Vasectomy Procedure

• Complete preoperative counseling of patient.
• Perfect choice of technique and surgery without complications at a suitable center by a trained individual.
• Confirmation of success by semen examination showing sperm ejaculate.

The following information must be given to the patient:
• Vasectomy is a permanent male contraception method.
• It is done by a short simple office procedure under LA and does not require admission
• It does not mean castration
• It has no effect on masculinity, sexual activity, semen volume or general health.
• Millions of men have undergone this safe procedure in the last 50 years.
• Sterility does not occur immediately, hence other contraception like condoms must be used until ejaculate becomes sperm-free.
• There is a failure rate of 0.5%.
• Reversal is possible with 70% success rates in good hands.
• There is a 2% wound infection and hematoma rate.
• There is no long-term effect such as testicular or prostatic cancer.

Selection of Cases

Detailed history taking followed by local examination should be done. Local infection, scrotal problems, scrotal filariasis, hernias, hydrocele should be looked for. Psychiatric problem must be noted. Anemia, diabetes, blood pressure, recent cardiac diseases should be detected. Every attempt should be made to make vasectomy safe and avoid mortality, morbidity and subsequent discredit to the family planning program.

TECHNIQUE OF VASECTOMY

Anesthesia

Local anesthesia using up to 10 mL 2% lidocaine is injected using 24 gauge needle in the 2 cm area of the incision under the median raphe. Two to three milliliter of lidocaine is also injected along side the vas (into the vas sheath). Occasionally, general anesthesia (GA) may be used in extremely sensitive patients.

There are two methods of vasectomy:
1. Conventional vasectomy (CV)
2. Nonscalpel vasectomy (NSV)

Conventional Vasectomy

Steps

• A 1 cm incision is done in the skin in the median raphe upper end.
• The vas is rolled between the thumb and two fingers in the cord and palpated and brought under the skin incision.
• The vas is grasped with the Allis forceps. A longitudinal incision is made on the vas sheath and vas is pulled, dissected, exposed and held between the Allis forceps or towel clamp and brought out.
• A segment of vas is cut (0.5–1 cm) and both the ends tied. Various ligature methods are described. Hemoclips may be used or cauterization of the cut ends done. Fascial interposition (FI) may be done to prevent the cut ends from approximating. The distance between the two cut ends must be at least 2–4 cm. Too tight ligatures must be avoided as there may be chances of cut through.
• Hemostasis done, procedure repeated on the other vas and skin closure done (Figs 1A to D).

Nonscalpel Vasectomy

Steps

• The vas deferens is fixed under the skin at the median raphe using a specially designed ring forceps. It holds the vas extracutaneously and directly without injuring it.
• A dissecting forceps with a sharp-pointed tip similar to a curved mosquito forceps is used to puncture the skin directly overlying the vas contained within the ring forceps.
• The puncture hole is enlarged to twice the diameter of the vas deferens.
• The next step involves a delicate but firm grasping of the vas with the puncturing instrument and deliberately rotating the vas in a clockwise manner to make it bare and
The net result is a no incision, no stitch vasectomy with minimal dissection using only three instruments (vas fixation forceps, vas dissection forceps and a scissor) (Fig. 2) as compared to nearly 14 instruments required in CV.

The NSV is being implemented in India to help male sterilization and thus promote male participation in the family welfare program. Ensuring availability of this new technique in the peripheral rural areas will help increase the acceptance of male sterilization in the country. The project is being funded by the United Nations Fund for Population Activities (UNFPAs) who has contributed 9.15 crores. The Government of India will contribute in kind toward providing centers for training and making available necessary infrastructure at the training sites.

**Advantages of Nonscalpel Vasectomy over Conventional Vasectomy**

- It takes less time (about 10 minutes)
- Causes faster recovery
- Less painful
- Less chances of bleeding and hematoma formation
- Only three instruments required
- No stitch required.
  However, some training and special instruments are needed.

Complications include pain, swelling, discomfort, bleeding and hematoma formation. Infections may occur, sperm granuloma may result in a palpable lump. Antisperm antibodies have been demonstrated in 40–60% of men.

**Fig. 1A to D:** Step of conventional vasectomy. (A) Incisions on the skin, (B) The sheath of the vas is cut open, (C) A portion of the vas is removed, (D) The vas is ligated at the cut ends

**Fig. 2:** Steps of nonscalpel vasectomy
undergoing vasectomy. Failure of vasectomy may occur in 0.1–1.2% of the cases.\textsuperscript{5,6} A small percentage of people (less than 10%) have chronic testicular pain after vasectomy.\textsuperscript{7}

**Postoperatively:** About 15–20 ejaculates contain sperms and 2–3 months are required to become sperm-free during which time alternative contraceptive method must be used.

### RECENT DEVELOPMENTS

The two main components of vasectomy are isolation of the vas deferens from the scrotum and subsequent vas occlusion. However, more than 30 different combinations of vas occlusion (Figs 3A to H) have been described.\textsuperscript{8} Poor quality studies, heterogeneous study designs and conflicting results have made it difficult to determine which are the most effective.\textsuperscript{8} The most common technique especially in low resource settings is future ligation with excision of a small segment of vas.\textsuperscript{8} Recent evidence from Asia suggests that 95% of all vasectomies in India are done using ligation and excision.\textsuperscript{10} In contrast, data available indicates that only 18% of the vasectomies in the US are done using this technique.\textsuperscript{11} Although vasectomy has traditionally been thought to have overall failure rates of 1–3%,\textsuperscript{12–14} recent research indicates higher failure rates for ligation and excision.\textsuperscript{15–17} A meeting of vasectomy experts held in December 2003 came to the following conclusion:

- Ligation and excision of a small segment of the vas lumen is also more effective than ligation and excision alone.
- Recent evidence indicates that cautery plus FI is more effective than ligation and excision and FI but FI is technically challenging.

**Fascial Interposition**

This is a new technique in which the sheath covering the vas is pulled over one-severed end and the sheath is closed to create a natural tissue barrier (Figs 3A to H). The testicular end of the vas lies within the sheath and the prostatic end lies outside. Many practitioners prefer it the other way round.

### Review of Literature

Review of literature is based on author’s conclusion after extensive Medline, Embase review, textbooks and book chapters evaluation.

**Vasectomy Surgical Techniques\textsuperscript{18}**

Current evidence supports NSV as the safest surgical approach to isolate the vas when performing a vasectomy. Adding FI increases effectiveness beyond ligation and excision alone. Occlusion effectiveness appears to be further improved by combining FI with cautery.

### Scalpel versus Nonscalpel Vasectomy\textsuperscript{19}

The nonscalpel approach to the vas, resulted in less bleeding, hematoma, pain and infection, as well as shorter operative time than the traditional incision technique. Although no difference in effectiveness was found between the two approaches, the sample sizes might have been too small to detect the differences. Additional well-conducted randomized trials are needed.

### CONCLUSION

- Vasectomy is a simple method of permanent sterilization in males and is gradually gaining more acceptance.
- Nonscalpel vasectomy is the new method promoted by the Family Planning Association of India (FPAI)—it is quicker, safer and an office procedure which can be done under LA. However, it requires a trained surgeon.
- Failure rates are directly related to the experience of the operating surgeon.
- Ligation, excision of a segment and vas occlusion with cautery seems to be the best combination.
- Fascial interposition is a new technique which reduces failures.
- Making vasectomy absolutely safe with minimum complication and failure rate will boost the family planning program.

### REFERENCES

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General Gynecology
## INTRODUCTION

Abnormal uterine bleeding is defined as any bleeding from the uterus which is not normal cyclical menstruation. It is a common clinical problem with many different causes. However, with a sound knowledge of menstrual physiology and a scientific approach to differential diagnosis, we can evaluate and manage the problem with confidence.

## MENSTRUAL PHYSIOLOGY

The typical menstrual cycle has two phases: (1) proliferative and (2) secretory. The proliferative phase is characterized by a predominance of estrogen over progesterone and a buildup of endometrium. The secretory phase begins after ovulation triggers progesterone production. This phase is marked by a reaction to the combination of estrogen and progesterone and stabilization in the thickness of the endometrium.

Menstrual bleeding occurs after secretion of estrogen and progesterone tapers off. Early during menses, thrombin plugs restrain blood loss, but later, vasoconstriction of the spiral arterioles is responsible for hemostasis. When ovulation does not take place, progesterone levels do not rise; therefore, typical cyclic withdrawal of estrogen and progesterone cannot occur.

Normal menstrual cycles are characterized by a cycle length of 28 days (±7 days), a duration of flow of 4 days (±2 days), and a blood loss of 40 mL (±20 mL) (Fig. 1).³

### Causes

Several types of abnormal uterine bleeding² are described in Table 1.
Whenever a woman presents with abnormal menstrual bleeding the differential diagnosis should be kept in mind as shown in Table 2.

### Diagnostic “Rules”

The list of differential diagnostic considerations in abnormal uterine bleeding is extensive, but systematic consideration of each of the five categories has led to our set of six diagnostic “rules”. Following an algorithm (Flow chart 1) of these simple diagnostic rules will enable the gynecologists to come to a diagnosis with minimum testing and minimum interventions.

**Rule No. 1: Consider Pregnancy**

All women of reproductive age should have a urine or serum pregnancy test.

**Rule No. 2: Consider Coagulopathy**

All adolescents with menorrhagia severe enough to require hospitalization or significantly reduced hemoglobin levels (to < 10 g/dL) should undergo evaluation for coagulopathy. Disorders of both platelet number and function may cause menorrhagia. von Willebrand disease, a defect in platelet adhesion and a deficiency of factor VIII, is the most common bleeding disorder, affecting about 1% of the population. Diseases causing thrombocytopenia include idiopathic thrombocytopenic purpura, leukemia and aplastic anemia. In adolescents, the prevalence of a primary coagulation disorder requiring hospitalization for abnormal uterine bleeding ranges from 3% to 20%.

**Rule No. 3: Consider Pelvic Lesions**

In women with evidence of ovulation, abnormal uterine bleeding should prompt suspicion of benign pelvic lesions. These patients should undergo thorough endometrial evaluation for pelvic lesions when there is no obvious alternative cause of abnormal bleeding.

**Rule No. 4: Consider Malignancy**

Without exception, perimenopausal or postmenopausal women with abnormal uterine bleeding should undergo endometrial evaluation. Until malignancy has been ruled out, it should be considered the cause. About 20–25% of cases of endometrial carcinoma occur before the menopause.

**Rule No. 5: Consider Hypothyroidism**

Hypothyroidism is an uncommon, although important, cause of metrorrhagia or menorrhagia. Women with unexplained severe menorrhagia should undergo thyrotropin assay.

**Rule No. 6: Consider Dysfunctional Uterine Bleeding**

Dysfunctional uterine bleeding is a diagnosis of exclusion. In the vast majority of cases, it is secondary to anovulation, which is more common at the extremes of reproductive age (i.e. during the postmenarchal and perimenopausal periods). Chronic anovulation may also be associated with thyroid or prolactin disorders, premature ovarian failure, adult-onset
CHAPTER

Approach to Abnormal Uterine Bleeding

congenital adrenal hyperplasia, or polycystic ovary syndrome. Some common causes of hypothalamic anovulation are weight loss or gain, eating disorders, stress, chronic illness and excessive exercise. Women with chronic anovulation that is not attributable to any of these causes are considered to have idiopathic chronic anovulation.

Anovulatory bleeding can be thought of as estrogen breakthrough bleeding. This type of bleeding is related to the levels of estrogen stimulating the endometrium. For example, high levels of estrogen for prolonged periods result in amenorrhea followed by acute intermittent heavy bleeding, and continually low levels of estrogen availability result in intermittent spotting.

EVALUATION

A logical sequence of evaluation for abnormal uterine bleeding can be constructed on the basis of the preceding information.

STEPS FOR EVALUATION

1. Complete history taking with age and complaints of the patient
2. Physical examination (clinically and pelvic examination)
3. Diagnostic testing (CBC, urine pregnancy test, thyroid assay)
4. Pap smear and cervical cultures
5. Endometrial evaluation
6. Hysteroscopy
History Taking

The specifics of the bleeding pattern should be elicited on history taking. The frequency, duration and severity of flow should be ascertained. It is also critical to determine if the bleeding is acyclic or cyclic, the latter being more consistent with ovulation. Other important considerations include patient age, sexual history (which determines risk for sexually transmitted diseases), previous gynecologic disease, likelihood of pregnancy, use of medications or hormonal contraceptives and the presence of chronic medical problems.

Physical Examination

Evidence of systemic diseases; signs and symptoms of hypothyroidism, liver disease, hyperprolactinemia, eating disorders and coagulopathies warrant special attention. A thorough pelvic examination, including a Pap smear, is essential. If indicated by history or physical findings, cervical cultures for Neisseria gonorrhoeae and Chlamydia trachomatis should be obtained. Benign lesions of the uterus may be obvious. For example, uterine myomata may result in an irregularly contoured, enlarged uterus that is palpable on bimanual examination.

Diagnostic Testing

In most cases, laboratory evaluation is limited to a complete blood cell count. However, all women of reproductive age who have abnormal uterine bleeding should have a urine or serum pregnancy test. Other tests are done only if indicated by the results of history taking and physical examination.

Endometrial Evaluation

Further investigation of abnormal uterine bleeding is guided primarily by the patient’s age. Adolescents who are not pregnant do not require additional workup.

More controversial is evaluation of abnormal bleeding in nonpregnant women who show no obvious cause (i.e. no abnormal findings on pelvic examination, no evidence of systemic disease and no use of medications that interfere with menses). Investigators disagree over two issues: (1) whether all patients need further endometrial testing and (2) whether this testing should include visualization of the endometrial cavity (i.e. ultrasound) or sampling of the endometrial tissue.

Most investigators recommend that further evaluation of abnormal uterine bleeding in nonpregnant women be based on risk for endometrial neoplasia. Therefore, women who are under 35 years of age and have no identifiable risk factors for neoplasia can be assumed to have dysfunctional uterine bleeding and treated accordingly. However, perimenopausal and postmenopausal women and women who are younger than 35 years of age but have a history of chronic anovulation or obesity are considered at high risk, and endometrial biopsy or transvaginal ultrasound is required to rule out endometrial hyperplasia or cancer. Some investigators are firm in the more conservative recommendation that any woman over 35 years of age with abnormal uterine bleeding undergo endometrial evaluation.

Endometrial Biopsy

Sampling techniques using small, flexible, disposable devices are adequate for obtaining endometrial tissue. To ensure accuracy, the procedure must be done before any hormonal treatment is given, and multiple areas of the endometrium must be sampled (Figs 3A to C).

Most endometrial biopsy results fall into one of four categories (Table 3). The presence of atypia is the most important risk factor for development of cancer. Carcinoma has been found to develop in 25% of patients with atypia but only 2% of patients without atypia. All patients with atypia should therefore be referred for gynecologic evaluation.

Patients who have hyperplasia but no evidence of atypia should be treated with progestins, and surveillance endometrial biopsy should be done every 3–6 months. The presence of normal secretory endometrium on biopsy indicates that the patient is having ovulatory cycles. This finding should raise suspicion that the bleeding is from a cause other than anovulation (e.g. a benign pelvic lesion).

Before in-office biopsy is done, pregnancy and significant cervical stenosis must be ruled out. Patients with significant stenosis may be better evaluated with use of transvaginal ultrasound.

Endometrial Aspiration

Endometrial aspiration can be done with the help of devices, like Pipelle® curette, Sharman’s curette, Gravlee jet washer, Isaac cell sampler, Vabra® aspirator, etc. The diagnostic accuracy of endometrial aspiration using Pipelle® device is 92–98% when compared with subsequent D&C. Since no dilatation of the internal os is required prior to insertion at the time of endometrial aspiration, the procedure can be performed as an outpatient procedure without any requirement of anesthesia. Following the procedure, the endometrial sample obtained is sent for histopathological examination (Figs 4A and B).

Table 3: Common findings on endometrial biopsy

- Proliferative, secretory, benign, or atrophic endometrium
- Simple or complex (adenomatous) hyperplasia without atypia
- Simple or complex (adenomatous) hyperplasia with atypia
- Endometrial adenocarcinoma.
### Approach to Abnormal Uterine Bleeding

#### Ultrasound

The use of transvaginal ultrasound (Fig. 5) in women at high risk for endometrial neoplasia is gaining popularity because it is an inexpensive, noninvasive and convenient way to indirectly visualize the endometrial cavity and measure endometrial thickness. This technique has been studied most extensively in postmenopausal women, but investigators are beginning to examine its use in premenopausal women as well. A recent meta-analysis of uterine bleeding in postmenopausal women concluded that the sensitivity of transvaginal ultrasound compares favorably with that of endometrial biopsy. In this population, a threshold of 5 mm of endometrial thickness was associated with 96% sensitivity for cancer detection and 92% sensitivity for detection of endometrial disease (e.g. cancer, hyperplasia, polyps). This false-negative rate of 8% compares favorably with the 5–15% false-negative rate with endometrial biopsy.

Evaluation of abnormalities in premenopausal women who have an endometrial thickness greater than 5 mm is controversial. About 10% of such patients have hyperplasia and about 40% have myomata or polyps.

Nondirected outpatient endometrial biopsy may miss a significant percentage of benign endometrial lesions. For this reason, some clinicians recommend proceeding immediately to a more directed endometrial evaluation, such as saline-infusion sonohysterography or dilation and curettage with hysteroscopy. Others perform an endometrial biopsy and, if...
results are normal, treat for presumed dysfunctional uterine bleeding. Patients for whom medical therapy fails are then evaluated with directed biopsy.

Hysteroscopy
Hysteroscopy is the gold standard for evaluation of endometrial cavity. It provides direct visualization of the cavity (Fig. 6). It can be used for both diagnostic and operative purposes for directed biopsies and excision of polyps.

Saline Infusion Sonography
Saline infusion sonography involves direct extension of uterine cavity with saline to enhance visualization of the endometrial surface. It is a noninvasive method to diagnose endometrial polyps and submucous myomatas (Fig. 7).

CT-scan and MRI
CT-scan and MRI primarily used in patients with suspected malignancy or adenomyosis.

TREATMENT OPTIONS
Complications of Pregnancy
If beta-hCG is positive, a careful pelvic examination must be performed and USG should be done to determine the possibility of ectopic pregnancy, threatened abortion, inevitable or missed abortion. Any patient who is hemodynamically
unstable and bleeding heavily may require surgical interventions like D and C or laparoscopic surgery for ectopic. Antimicrobial prophylaxis is a must. If any signs of infection are present, a broad spectrum coverage should be given. Woman with missed or incomplete abortion who is stable and not bleeding heavily may be treated with misoprostol.

**Benign Pathology**

Fibroids are the most common uterine neoplasms. They present with abnormal uterine bleeding mostly menorrhagia. Commonly done surgical procedures for treatment are: myomectomy, hysterectomy or myolysis. Polyps are generally endometrial lesions which tend to be asymptomatic. If symptomatic they usually cause premenstrual or postmenstrual spotting. Polyps are removed by operative hysteroscopy.

**Malignant Pathology**

Endometrial cancers are rare. They occur in older age after 40 years of age. They must be suspected in postmenopausal women. Treatment—total abdominal hysterectomy with bilateral salpingo-oophorectomy is the standard therapy. The need for postoperative radiation therapy depends on the stage. Treatment of cervical carcinoma depends on the staging—surgical resection, chemotherapy, radiation or combination.

**Systemic Diseases**

- **Disorders of coagulation:** von Willebrand disease is the most common inherited bleeding pathology. Test performed to diagnose are factor VIIIC activity, vWF antigen, platelet function tests and bleeding time. OCPS, desmopressin, and antifibrinolytic agents are treatment options.
- **Endocrinopathies:** Endocrine disorders can cause anovulation and produce an environment of unopposed estrogen. Hypothyroidism and hyperprolactinemia are common disorders. Bromocriptine or surgical resection of macroadenoma pituitary may relieve hyperprolactinemia. Thyroid replacement therapy may be necessary for hypothyroidism.
- **Liver failure:** Decreased metabolism of estrogen may lead to endometrial glandular and stromal break down causing endometrial hyperplasia. If possible underlying liver disease it should be treated. Progesterone therapy may be beneficial.

**Drug Induced**

Drug induced various medications like antipsychotic, OCPS, anticoagulants, digitalis, phenytoin, Depo-provera may cause abnormal uterine bleeding.
Intrauterine Devices
Copper intrauterine contraceptive devices (IUCDs) may increase average monthly blood loss. It can be treated by nonsteroidal anti-inflammatory drugs (NSAIDs).

Dysfunctional Uterine Bleeding
Dysfunctional uterine bleeding (DUB) is the diagnosis of exclusion. It is usually treated by long-term OCPS, HRT, Danazol, NSAIDs or antifibrinolytic agents (Table 4).

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Copper intrauterine contraceptive devices (IUCDs) may increase average monthly blood loss. It can be treated by nonsteroidal anti-inflammatory drugs (NSAIDs).

**Dysfunctional Uterine Bleeding**

Dysfunctional uterine bleeding (DUB) is the diagnosis of exclusion. It is usually treated by long-term OCPS, HRT, Danazol, NSAIDs or antifibrinolytic agents (Table 4).
Table 4: Medical treatment options for dysfunctional uterine bleeding

<table>
<thead>
<tr>
<th>Type of bleeding</th>
<th>Treatment option</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td>Oral contraceptive, 1 tablet PO bid or tid × 7d; allow withdrawal bleed, then 1 tablet PO qd × 3 months</td>
<td>Use low-dose (35-microgram) monophasic formulation; some clinicians omit withdrawal bleed to avoid exacerbating anemia</td>
</tr>
<tr>
<td>Chronic</td>
<td>Oral contraceptive, 1 tablet PO qd</td>
<td>Perimenopausal women should use 20-microgram pills</td>
</tr>
<tr>
<td></td>
<td>Medroxyprogesterone acetate, 10 mg PO qd × 10 days/month (last 10 days)</td>
<td>Bleeding occurs 2–7 days after last dose</td>
</tr>
<tr>
<td></td>
<td>Clomiphene citrate (Clomid, Milophene, Serophene), 50–150 mg qd on days 5–9</td>
<td>Use for patients who wish to become pregnant; if pregnancy does not occur in 3 to 6 months, consider referral</td>
</tr>
</tbody>
</table>


choice of treatment depends on whether bleeding is acute or chronic. When bleeding is acute, the first step is to determine if the woman’s condition is hemodynamically stable. A patient with signs of hypovolemia should undergo volume resuscitation, be hospitalized, and be given high-dose intravenous estrogen. The estrogen promotes rapid endometrial regrowth over the denuded epithelial surfaces. If this treatment fails, most clinicians proceed to dilation and curettage, which quickly controls bleeding.

The hemodynamically stable patient with acute heavy bleeding should also be treated with estrogen. The most convenient method of estrogen administration is use of low-dose monophasic oral contraceptives. Nausea and vomiting from the high doses of hormones can be minimized by adding an antiemetic agent such as promethazine (Anergan, Phenergan) or chlorpromazine hydrochloride (Thorazine).

After finishing the course of oral contraceptives, the patient typically experiences a heavy, crampy period. Patient should continue to take low-dose oral contraceptives for at least another 3 months and then undergo re-evaluation to determine whether treatment for chronic bleeding is indicated.

In patients with an absolute contraindication to estrogen (e.g. a 36-year-old smoker with history of deep vein thrombosis), some clinicians use high-dose progestins to control bleeding. There are no randomized, placebo-controlled trials to support this practice.

Treatment of patients with chronic recurrent bleeding is based on their reproductive desires. Patients who want birth control can use low-dose monophasic oral contraceptives. If contraception is not desired, use of cyclic progestins for the first 10 days of each month is the treatment of choice (Table 4). Patients wishing to become pregnant are candidates for clomiphene citrate (Clomid, Milophene, Serophene).

If any of these regimens fails to control what has been assumed to be dysfunctional uterine bleeding, other diagnoses, specifically structural abnormalities of the endometrium, must be considered. Often, endometrial biopsy does not detect reproductive tract abnormalities such as endometrial polyps and submucosal fibroids. In this situation, further evaluation may be performed with endovaginal ultrasound or saline-infusion sonohysterography. The latter procedure involves instilling fluid into the uterus during an endovaginal ultrasound examination to enhance image resolution. This purely diagnostic procedure can be done in the office using only local anesthesia, but skill in its performance and interpretation is required for consistently accurate results.

For patients at high risk for complications of anesthesia, sonohysterography is a reasonable option. Patients who are good surgical candidates, however, may opt to proceed directly to a dilation and curettage with hysteroscopy, which allows simultaneous diagnosis and treatment.

In the few cases in which dysfunctional uterine bleeding does not respond to any of the management options described, hysterectomy or endometrial ablation can be done. A hysterectomy is indicated when a patient has associated pelvic abnormalities such as leiomyomas and does not wish to preserve fertility. Endometrial ablation is a less costly, safer alternative to hysterectomy for women with no uterine lesions. Ablation can be performed on an outpatient basis with a laser or electrocautery device (roller ball).

CONCLUSION

The approach to diagnosis of abnormal uterine bleeding is guided by a sound knowledge of menstrual physiology and differential diagnosis. Often, simple anovulation is the underlying problem, although the possibility of pregnancy, endometrial hyperplasia with atypia, or benign reproductive
tract disease must be considered. In the majority of cases, abnormal uterine bleeding can be fully evaluated and effectively treated medically without the need for gynecologic referral.

REFERENCES

INTRODUCTION

Uterine leiomyomas (fibroid/myoma/leiomyofibroma) are the most common benign, monoclonal tumors of the smooth muscle cells of the myometrium in women, affecting 20–50% of reproductive age population. Examination of hysterectomy specimens by serial sectioning at 2 mm intervals suggests prevalence of 77%. Despite their prevalence, the disease has remained enigmatic, with the natural history and progression incompletely understood. Recent research on molecular biology of myomas has enabled us to understand better the pathophysiology of this tumor.

EPIDEMIOLOGY

The frequency of clinically obvious fibroids is an underestimation because majority are asymptomatic. The incidence of pathologically diagnosed fibroids increases steadily with age. The chance of being diagnosed with fibroids increases with age until about 50 years and then declines sharply.

There are significant differences in prevalence of fibroid between women of different racial and ethnic background. A carefully conducted case-control study found self-reported African-American heritage to be associated with a relative risk (RR) of fibroids of 9.4 compared to white women. Both Hispanics and Asians had risks similar to whites. Fibroids are diagnosed at a younger age, are more often multiple and tended to be larger in African-Americans.

Fibroids are 2–3 times more frequent when there is a family history. A Japanese study examined the prevalence of fibroid in first degree relatives of women undergoing surgery for fibroids. Thirty-one percent of women undergoing fibroid surgery reported a first degree relative with fibroids, as opposed to 15% of controls. The risk also increases as age at menarche falls.

Oral contraceptives (OCs) are protective with the RR decreasing in a dose-dependent fashion to the duration of OC use. However, exposure of OC at age 13–16 years has a higher risk. Starting OCs at a younger age could be a marker for other risk factors for fibroids rather than a cause itself. Depot medroxyprogesterone has been associated with protection whereas tubectomy slightly increases the risk.

For the majority of postmenopausal women with myomas, hormone therapy will not stimulate uterine growth. If the uterus does grow, it is more likely related to the dose of progesterone than estrogen.

Obesity increases while smoking diminishes the risk of fibroid probably due to higher and lower endogenous estrogen levels respectively. The Nurse Health Study II (NHS II) showed an increased risk for fibroid with increasing BMI. Risk of myoma increased 21% with each 10 kg increase in body weight. Although red meat increases and green vegetables decrease the risk, dietary interventions are not protective.

Several studies have shown a protective effect of pregnancy on the development of fibroids, with parity decreasing the risk of fibroids up to fivefold. However, these numbers may be deceptively high, given the known decrement in fertility attributable to fibroids. Age at first pregnancy is not a risk factor. A longer interval from the last child birth increases the risk. Childbearing during the mid-reproductive years (age 25–29 years) provides the greatest protection against myoma...
development. The increased number of menstrual cycles is the risk factor in nulliparous and less parous women. It is not clear whether fibroid is a cause or consequence of infertility. Recently, the association with nulliparity and infertility were found only with submucous tumors.11

A recent study demonstrated an intriguing link between diastolic blood pressure and fibroids.12 It is suggested that elevated blood pressure could cause injury or cytokine release in the uterine smooth muscles that promotes fibroid growth. The increased risk is related with degree and duration of hypertension.

There is positive association between fibroid and pelvic infections. A history of pelvic inflammatory disease increases the risk of fibroids, with the risk increasing with the number of infectious episodes. It seems that the intrauterine irritation may contribute to fibroid growth.

**PATHOLOGY**

Leiomyoma, essentially a smooth muscle tumor, contains variable amounts of fibrous tissue and collagen matrix. The latter is responsible for the misnomer “fibroid.” They arise from the body of the uterus in majority of cases, but may be cervical (3.8%). They may be single but are more often multiple. They originate from the uterine muscle layer and may remain intramural or become subserous or submucous. Subserous fibroids may become pedunculated. Rarely, they lose their uterine attachment gaining new blood supply from another organ (wandering/parasitic fibroid). Arising from lateral uterine wall they may grow into a broad ligament tumor.

Submucous fibroids comprise just 5% of all tumors but are often symptomatic. They may also be pedunculated, distend the cervical canal or may prolapse through the cervix. Rarely, they can cause inversion.

**Macrosopically,** fibroids are usually spherical, well circumscribed, white, firm lesion(s) that protrude from the cut myometrium. The cut surface has a lighter color than normal myometrium and has a whorled appearance with intersecting fascicles of smooth muscle bundles. A typical intramural fibroid is separated from the adjacent normal myometrium by a thin layer of connective tissue—the so-called false capsule (there is no true capsule). Small nutrient arteries penetrate the capsule although a single larger artery provides the major blood supply.

**Microscopy:** Leiomyomas are made-up of interlacing bundles of elongated eosinophilic smooth muscle cells with pink fibrillar cytoplasm and blunt ended cigar shaped nuclei that have an even chromatin pattern and inconspicuous nucleoli. Occasional mitosis is seen. These cells are surrounded by varying amounts of collagenous fibrous connective tissue containing rather thick walled blood vessels. Fibrous tissue cells have less cytoplasm, are without fibrils and the elongated spindle shaped nuclei have more pointed ends.

The term cellular leiomyoma is used when the density of the smooth muscle cells is significantly greater than usual but there are no atypical features such as increased mitotic count, abnormal mitosis, coagulative necrosis or cellular pleomorphism. These latter features characterize the classical leiomyosarcomas that show a more variegated cut surface and a more invasive irregular margin. Lesions intermediate between classical leiomyoma and leiomyosarcoma with unpredictable clinical outcome are called smooth muscle tumors of uncertain malignant potential.

**Degenerative Changes**

Majority lack clinical significance and occur secondary to circulatory alterations, postmenopausal atrophy or infection. A most acute form is red/carneous infarction, causing pain and localized peritoneal irritation, most often in mid pregnancy.

The risk of sarcomatous change is 0.1%, but majority of these are symptomatic with pain, malaise, vaginal bleeding and postmenopausal enlargement. Genetic differences between myomas and leiomyosarcomas indicate that they most likely have distinct origins and that leiomyosarcomas do not result from malignant degeneration of myomas.13

### ETIOPATHOGENESIS

Despite the prevalence of leiomyomas, relatively little is understood about their development and growth. Unlike the quiescent myometrium, leiomyoma exhibits elevated rates of mitotic activities and S-phase fractions.14 Growth of these tumors is believed to depend on ovarian hormones. These hormones may exert their growth stimulatory effects through some intermediate elements such as cytokines and growth factors. Estrogen and progesterone may regulate gene expression of these cytokines and growth factors which in turn modify the transcription of other genes.

**Cytokines and Growth Factors**

The abnormal production of cytokines and growth factors results in increase in cell proliferation, accumulation of extracellular matrix or combination of these phenomena.

Another potential mechanism, decreased apoptosis is responsible for development of fibroid. Bcl-2 protein—an apoptosis inhibiting gene product is abundantly expressed on fibroid and progesterone upregulates this Bcl-2 protein.15

<table>
<thead>
<tr>
<th>Table 1: Secondary changes in fibroid</th>
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<tbody>
<tr>
<td>• Hyaline</td>
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<tr>
<td>• Myxomatous</td>
</tr>
<tr>
<td>• Cystic</td>
</tr>
<tr>
<td>• Calcification</td>
</tr>
<tr>
<td>• Red</td>
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<tr>
<td>• Sarcoma</td>
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However, estrogen has a downregulatory effect. GnRH antagonist up regulates apoptosis.

Each tumor results from a single progenitor smooth muscle cell which undergoes a somatic mutation (Step I). The subsequent growth occurs by clonal expansion of the mutated myocyte (Step II). Multiple myomas within the same uterus are clonally unrelated. The initiator(s) of Step I are unknown but genetic predisposition and ovarian hormones may have a role in both formation and growth of fibroids. A large number of growth factors (Table 2) have been identified which cause tumor expansion (Step II). The pathobiology involves alterations in:

a. Smooth muscle cells (SMC): Proliferation and differentiation.
b. Fibroblast (proliferation) and extracellular matrix (deposition): Overexpression of collagen, fibronectin and glycosaminoglycans contributes to the formation and growth of the tumor.
c. Angiogenesis: To support growth, proliferation and migration of endothelial cells.

Fibroids have increased levels of both Estrogen (E) and Progesterone (P) receptors. The SMCs show both higher mitosis and decreased apoptosis. Both E and P are important. Estrogen does not induce mitosis in follicular phase; instead it maintains a differentiated state and essentially benign nature of the tumor. Increased mitosis seen during luteal phase suggests P as mitogen. Myomas show higher mitotic activity in women treated with P compared to women treated with E and P or in women receiving no hormones. Progesterone may also expand tumors by down regulating apoptosis, by increasing expression of bcl-2 protein (an apoptosis inhibitor).

Although blood levels of estrogen and progesterone are similar in women with or without clinically detectable myomas, levels of estradiol within myomas are higher than in normal myometrium. De novo production of estrogen within myoma tissue is suggested by increased level of aromatase, an enzyme that converts androgens to estrogen. Low levels of enzyme that convert estradiol to estrone have been found in myoma cells and may promote accumulation of estradiol within the cells, leading to upregulation of estrogen and progesterone receptors and myoma growth.

**Genetics (Flow Chart 1)**

Fibroid is not a single gene disorder. However non-random chromosomal changes such as translocations, duplications and deletions have been identified in nearly 40% of tumors
by cytogenetic analysis. Abnormal myoma when compared with normal myoma are generally more cellular, have a greater mitotic index and lower DNA content and also fail to produce a decrease in DNA content after GnRH agonist therapy. The remaining 60% of myomas, which are chromosomally normal, suggests that genetic aberrations may be submicroscopic for these tumors.

In examining fibroid with abnormal karyotypes certain correlations between tumor genotype and clinical phenotype have been observed. Only 12% of submucosal fibroids have chromosomal rearrangements, followed by subserosal (29%) and intramural (35%). However, in spite of lower frequency of karyotypic rearrangements, submucosal fibroids are highly symptomatic. Thus far, no correlation has been established in fibroid between type of cytogenetic aberration and patient age or parity.

Several genes have been implicated in the molecular pathogenesis of leiomyoma including the sex-steroid associated genes, estrogen receptor α, estrogen receptor β, progesterone receptor A, progesterone receptor B, growth hormone receptor, prolactin receptor, extracellular matrix gene and collagen gene. Chromosomal rearrangements in fibroid have been noted in the High Mobility Group I Proteins including those encoded by HMG 2A (formerly HMG 1C) and HMG 1A (formerly HMG 1Y). High levels of these closely related low molecular mass proteins are detected in fibroid but not in the adjacent myometrium.

### CLINICAL FEATURES

Majority of fibroids are asymptomatic. Around 20–50% of fibroids produce symptoms (Table 3).

The most common symptom is menorrhagia reported by 30% of women with fibroids.

### Bleeding

Irregular bleeding is not characteristic of myoma and should be investigated to rule out endometrial disease. Pedunculated submucous tumors with infection or surface ulceration can however produce acyclical bleeding. Submucous myomas are the most likely to cause menorrhagia. Some studies suggest that only 40% hysterectomy specimens done for fibroid with menorrhagia have submucous tumors.

### Infertility

The conviction that myoma cause infertility derives mostly from observational studies in which about half of patients who undergo myomectomy subsequently conceive. None of these studies are controlled. Around 25–40% of women with fibroids are infertile, but other causes of infertility are present in majority of cases. Submucous fibroids decrease fertility: pregnancy rate decreases by 70% and their removal increases fertility to baseline rates. Some recent studies of women undergoing IVF suggest that even intramural tumors may be contributory.

### Pelvic Pain/Pressure

Uncomplicated myomas do not produce pain. The pelvic-abdominal discomfort, often called pressure depends on fibroid location. Urinary symptoms arise from anterior myomas (frequency and rare retention), while posterior ones can cause low backache, rectal tenesmus or constipation. Cervical and broad ligament tumors produce no menstrual disturbances but only pressure symptoms including ureteric obstruction. Some large tumors may be discovered by the patient herself.

Exceptionally fibroids produce acute pain due to torsion (subserous tumors/regeneration/infection). Attempted expulsion of pedunculated submucous tumor through cervix may cause uterine cramps/dysmenorrhea.

In premenopausal women, rapid uterine growth almost never indicates presence of uterine sarcoma. Most women found to have uterine sarcoma are clinically suspected of having a pelvic malignancy.

### Problems during Pregnancy

Very rarely does the presence of a fibroid during pregnancy lead to an unfavorable outcome. Possible effects of fibroid on pregnancy are shown in Table 4.

**Effect of pregnancy on fibroids:** Contrary to expectation, majority of fibroids remain unchanged/decrease in size. Only 20–30% fibroids increase in size; and the increase is no more than 25% in volume and occur mostly in first trimester.

### Table 3: Symptoms of fibroid

- Abnormal bleeding
- Pelvic pain/pressure symptoms
- Infertility
- Problems in pregnancy

### Table 4: Effects of fibroid on pregnancy

<table>
<thead>
<tr>
<th>Effect of fibroid on pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abortion(s)</td>
</tr>
<tr>
<td>Preterm labor</td>
</tr>
<tr>
<td>Preterm pre-labor rupture of membranes</td>
</tr>
<tr>
<td>Placental abruption</td>
</tr>
<tr>
<td>IUGR</td>
</tr>
<tr>
<td>Antepartum hemorrhage</td>
</tr>
<tr>
<td>Malpresentation</td>
</tr>
<tr>
<td>Obstructed labor</td>
</tr>
<tr>
<td>Cesarean section and cesarean hysterectomy</td>
</tr>
<tr>
<td>PPH</td>
</tr>
<tr>
<td>Fetal injury attributed to mechanical compression by myoma—very rare</td>
</tr>
</tbody>
</table>

**Abbreviations:** IUGR, intrauterine growth restriction; PPH, postpartum hemorrhage.
There is no relationship between initial fibroid volume and fibroid growth during gestational periods. Most fibroids remain uncomplicated but 10% undergo red degeneration.

Anemia is the major consequence of menorrhagia. Rarely secondary polycythemia is possible (elaboration of erythropoietin by tumor tissue).

Palpation of an enlarged, firm, irregular, non-tender uterus with some mobility by abdominal and vaginal examination gives away the diagnosis in 95% of cases. Submucous myoma may cause symmetric uterine enlargement; subserous pedunculated tumor may mimic adnexal mass. Consistency may be altered by degenerative changes and mobility may be restricted by coexistent disease (e.g. endometriosis).

The most common differential diagnosis includes pregnancy, adenomyosis and ovarian tumor.

INVESTIGATIONS

Investigations confirm the diagnosis and may decide mode of treatment (Table 5). Ultrasonography (USG) assesses size(s), location(s), interval growth, adnexal anatomy and excludes hydronephrosis. Submucous myoma often requires saline-infusion sonography, hysteroscopy or MRI for definitive diagnosis. Differential variegated echogenicity in the myometrium is characteristic of fibroids; cystic/calcific degeneration may also be revealed. Transvaginal sonography (TVS) evaluates the endometrial cavity better and it is the most readily available and least costly technique and may be helpful for differentiating myomas from other pelvic conditions.

Laparoscopy is useful if uterus is not larger than 12 weeks of gestation and there is associated infertility or pelvic pain. MRI represents the most accurate method to determine size, location and route of removal and with low inter-observer variability in interpretation. It can differentiate fibroid from adenomyosis (sensitivity 64%, specificity 88%) and was superior to TVS (sensitivity 59%, specificity 79%). For most indications, the extra cost is not justified and USG should be the initial evaluation.

The preoperative diagnosis of leiomyosarcoma may be possible with total serum lactate dehydrogenase (LDH), LDH isoenzyme 3 and gadolinium-enhanced MRI.

<table>
<thead>
<tr>
<th>Table 5: Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>• USG, TAS, TVS</td>
</tr>
<tr>
<td>• HSG</td>
</tr>
<tr>
<td>• Sonohysterogram</td>
</tr>
<tr>
<td>• Doppler</td>
</tr>
<tr>
<td>• MRI</td>
</tr>
<tr>
<td>• Laparoscopy</td>
</tr>
<tr>
<td>• Hysteroscopy</td>
</tr>
</tbody>
</table>

Abbreviations: USG, ultrasonography; TAS, transabdominal sonography; TVS, transvaginal sonography; HSG, hysterosalpingography

CONCLUSION

Despite the frequency and the morbidity they can cause, fibroids remain a frontier for gynecologic investigations. New research into basic biology, especially the role of growth factors and genetic mutations hold promise for new therapeutic options.

REFERENCES

Fibroids are the most common neoplasm of the uterus and therefore understanding appropriate therapy for these is important. Newer researches are opening better avenues for therapy in this condition and as we progress further reappraisal and understanding of the cellular mechanisms and growth influences of fibromyomas is essential to better treat our patients.

More than 50% of women have leiomyomas and most of the times they are asymptomatic. If surgical specimens are serially sectioned, about 77% of women who come to hysterectomy will have myomas, many of which are occult. Many a times fibroids are incidental findings on clinical evaluation making us wonder whether treating them is mandatory.

Advanced age of marriage and late pregnancies have increased the need of conservatively managing fibroids either surgically or medically. Also availability of various treatment modalities (Table 1) has increased the need to understand the advantages and disadvantages of these and their appropriate place in the given clinical situation. Increased awareness and availability of diagnostic modalities has also increased the incidence of myomas being diagnosed, not always mandating treatment and therefore could require expectant management. It is therefore essential to tailor appropriate treatment exclusively to the presenting clinical situation basing the decision on sound evidence.

**TREATMENT FOR MYOMAS MODALITIES**

**Expectant Management**

This consists of serial history taking and clinical evaluation at regular intervals. The initial evaluation could be undertaken at 3 or 6 monthly interval to determine the rate of growth. Yearly follow-up intervals can be undertaken if the tumors are documented to be stable or slow growing after 1–2 years of observation.

Women with menorrhagia, dysmenorrhea, pelvic pain and pressure symptoms can be treated with nonsteroidal anti-inflammatory drugs (NSAIDs), combination pills (low-dose) and progestins after ruling out endometrial pathology with suitable diagnostic modality.

**Medical Management**

Fibroids are tumors sensitive to hormonal influences. Based on this proposition many hormonal and non-hormonal modalities of therapy have been used. Fibroids are estrogen sensitive tumors growing at a slow rate. Sometimes they grow faster and this rate of growth is semi-quantitatively linked to

### Table 1: Treatment for myomas: modalities

<table>
<thead>
<tr>
<th>Expectant</th>
<th>Medical</th>
<th>Surgical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regular evaluation</td>
<td>Oral contraceptives</td>
<td>Myomectomy</td>
</tr>
<tr>
<td>Symptomatic treatment</td>
<td>Progestogens</td>
<td>Laparoscopic</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>NSAIDs, antifibrinolytics</td>
<td>Myolysis</td>
</tr>
<tr>
<td>Androgens</td>
<td>Anti-Progestogens</td>
<td>Electrical</td>
</tr>
<tr>
<td>Aromatase inhibitors</td>
<td>GnRH analogs</td>
<td>Thermal</td>
</tr>
<tr>
<td>Growth factors</td>
<td>SERMs</td>
<td>Ultrasound MRgFUS</td>
</tr>
<tr>
<td>SPRMs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Girija Wagh, Sanjay Gupte
(Chapter updated by Rekha Rani)
the number of estrogen and progesterone receptors (PRs). Rapid growth raises the possibility of malignant change within the tumor although this is extremely rare. It is clear that hormonal factors play an important role in this disease. How steroid hormones influence the disease pathophysiology is the current area of research. Following are the proposed hormonal influences shown in Table 2.

Progestosterone or progestin commonly available like the oral, depot preparations and the LNG-IUD have been used. These were used as progestosterone has many actions which are anti-estrogenic. But none of these showed consistent response. On the contrary these were shown to influence the growth adversely leading to the understanding of the existence of PRs in myoma cells. Biochemical studies suggest that progestosterone, progestins modulate myoma mitotic activity.

Likewise came the understanding necessitating specific hormonal receptor modulators. Selective estrogen receptor modulators (SERMs), like Tamoxifen, Raloxifene, seemed promising by repressing growth, reducing proliferation, and there was also a tumor reduction by 50%. But this lasted temporarily. The reason for this was found to be absence of apoptosis. The method of growth inhibition in response to estrogen deprivation is as shown in Table 3.

Thus, the data on in vitro study suggests that creation of a hypoestrogenic milieu within leiomyomas reduces tumor volume independent of apoptosis and therefore is less effective. It is well understood that leiomyomata are unicellular in origin with identical glucose-6-phosphatase-dehydrogenase electrophoretic type cells arising from a single neoplastic smooth muscle cell. Cytogenetic studies have revealed consistent abnormalities including translocations and deletions involving several chromosomes but most commonly the chromosome 12. These mutations could be the cause of absence of apoptosis.4

Selective progesteron receptor modulators (SPRMs) represent a new class of PR ligands. These are also known as “mesoprostogens”. SPRMs exert clinically relevant tissue selective progesterone agonist, antagonist or mixed agonist/antagonist effects on various progesterone target tissues. Asoprisnil (J867) is the first SPRM to reach an advanced stage of clinical development for the treatment of symptomatic uterine fibroids and endometriosis.

Thus wide choice of drugs has now become available to treat myomas. They can be undertaken as part of expectant management, for alleviation of symptoms, to reduce the size as adjuvant to surgery and sometimes as an alternative to surgery (Table 1). Prior to medical management, one must be sure of the diagnosis.

The aims of medical management are as follows:
• Expectant management with alleviation of symptoms
• Improve the hemoglobin status and menorrhagia before surgery
• Minimize the size and vascularity before surgery to facilitate surgery
• To facilitate hysteroscopic or laparoscopic surgery
• Alternative to surgery in perimenopausal women with high risk factors
• Postponement of surgery.

### Drugs for Medical Management

#### Oral Contraceptives

High dose estrogens contribute to the growth of fibroids. Low estrogen containing pills like the low dose pills decrease the size of fibroids and reduce the endometrial thickness. Thus combined pills can be used to treat small fibroids causing menorrhagia. This could be attributed to subphysiologic concentrations of estrogen.5 Low dose cyclic or continuous estrogen and progesterone pills can be used after GnRH-Ag therapy as “add-back” but such usage is still investigational.

### Progestogens

Useful in an ovular menorrhagia and achieve reduction in size of fibroids.

*Norethindrone acetate* in the dose of 5–10 mg daily from day 5 to day 20 of the cycle can be used.

*Injection DMPA*: *Depot medroxyprogesterone acetate*—After 6 months use: effects.

• 30% Amenorrheic
• 70% Improvement
• 15% Had increase in Hb levels
• 48-33% Reduction in mean uterine volume

*LNG-IUD (Mirena)*: It is an alternative route of using progesterone. It is a prostagastert with 52 mg Levonorgestrel which acts directly on the endometrium. The endometrium becomes thin and inactive. There is a reduction in the size of small fibroids. After 3 months of usage, the average blood loss is 85% less and after 12 months it is 97% less.6 It has been licensed for 5 years usage. Although there are no randomized trials of LNG-IUS in women with fibroids this option could be considered for women with heavy uterine bleeding caused
predominantly by intramural fibroids and who are poor surgical candidates.

**Fibroplant:** It is a progestasert similar to Mirena but is unique as it is frameless. It releases levonorgestrel at the rate of 14 μg/day. Its frameless nature increases its compliance. It is associated with a low incidence of amenorrhea and thus is one step ahead of framed progestasert. More trials are required for its usage in fibroids.

Progesterone is known to cause leiomyoma cell proliferation and growth in vitro and in vivo.⁷ MPA blocked the fibroid shrinking effect induced by GnRH agonist.⁸ Thus progesterone has self-contradicting clinical results. The reason that progestogen containing therapies achieved symptomatic relief as seen in the past was more due to correction of hormonal imbalance or reduced vascularity.

**Androgens**

**Danazol:** Isoxazole of 17 b-ethyl testosterone exerts androgenic action by suppressing sex hormone binding globulin. It is given in the dosage of 100–200 mg daily for 3–6 months. Several studies have shown that Danazol reduces the size of fibroids by 20–25%. Danazol inhibits aromatase in leiomyomata⁹ and may promote fibroid regression.¹⁰ It has androgenic as well as hypoestrogenic side effects and therefore is not popularly recommended.

**Gestrinone:** It is a trienic steroid with both anti-estrogenic and anti-progestogenic properties. Large doses are required to reduce the size of fibroids. There is a Brazilian study which included 24 patients with large fibroids. It was observed that all patients had menstrual suppression and the uterine volume reduced from 724.9 cm³ to 450.73 cm³ in 6 months. This effect was achieved within 2 months and lasted up to a year after treatment.¹¹ Minor androgenic side effects were seen with a mean weight gain of 3.4 kg in 6 months. No menopausal symptoms were seen. Not popularly used due to severe androgenic side effects especially water retention.

**Antifibrinolytics**

Tranexamic acid is a synthetic derivative of amino acid lysine. In the dose of 2–4 gm/day given in divided doses, it reduces blood loss associated with fibroids significantly. It has no effect on blood coagulation. As per the Cochrane review antifibrinolytics therapy causes a greater reduction in objective measurements of heavy menstrual bleeding.

**GnRH Agonist**

Goserelin, Leuprorelin, Buserelin are commonly used drugs. Agonist creates a pseudo menopause like state, thus reduces the size of fibroids by about 12.5 mL on an average. It reduces intraoperative blood loss and is efficacious in women awaiting in vitro fertilization (IVF) cycles or nearing menopause with uterine fibroids.

Following benefits were observed: Improved hemoglobin concentration, relief of pressure symptoms and reduction in the vascularity of the tumor leading to reduced blood loss at myomectomy. It also reduces the size of the fibroids.¹²

**GnRH Antagonists**

Cetrorelix and Ganirelix are the most common used antagonists. They cause immediate suppression of pituitary. The basic advantage is reduction in treatment time and faster restoration of ovarian activity. GnRH antagonistic therapy has certain drawbacks like:

- Excessive fibrosis makes capsule identification difficult
- Incomplete removal of fibroid
- High recurrence rate in treated (65%) as compared to untreated (28%) women
- Prolonged pituitary suppression
- Prompt increase in the size of fibroids after discontinuation
- Adverse hypoestrogenic effects
- Not cost effective.

**Mifepristone**

Mifepristone or RU486 is an anti-progestogen drug which blocks the effect of progesterone at the receptor level. It reduces the size of fibroids and is as effective as a GnRH analog when used for 3 months. It is cost effective, has fewer side effects and greater patient acceptability. In a non-randomized study, a daily dose of 10 mg RU486 reduced the volume of myomas by 40% in 3 months with minimal side effects and with no effects on bone mineral density.¹³ A trial comparing GnRH agonist and 12.5 mg RU486 revealed 20% reduction in the myoma volume, but the GnRH group had a higher recurrence rate after cessation of therapy.¹⁴

**Newer Drugs**

**Growth factors** This plays a relevant role in the pathophysiology of fibroids by inhibiting growth through its effect on the myometrium. This would be the basis of future therapy.

**SERMS:** Low estrogenic states are associated with regression of myoma size. The treatment of premenopausal women with an estrogen receptor (ER) antagonist, however, has produced disappointing results. Fulvestrant is a pure ER antagonist that binds to and promotes dramatic ER down regulation. A prospective randomized controlled trial found no inhibition of fibroid growth when comparing fulvestrant with placebo in premenopausal women with uterine fibroids requiring hysterectomy.¹⁵Raloxifene has shown reduction in the size of fibroids in postmenopausal women but in another randomized controlled trial it has shown no effect on myoma size or menstrual pattern after 6 months of treatment in premenopausal women.¹⁶

**SPRMs:** New class of PR ligands. The PR exists in two isoforms: (1) PR-A and (2) PR-B. PR-A decreases estradiol responsive-
Aromatase inhibitors: It is observed that aromatase, the enzyme that converts testosterone (T) to estradiol (E2) and androstenedione (A) to estrone (E1), is expressed in higher levels in myoma tissue than myometrium. Inhibition of aromatase could potentially reduce myoma size.

Fadrozole: It is an aromatase inhibitor tried in the dose of 2 mg daily and reduced myoma volume by 71% in a perimenopausal woman after 2 months of treatment. But this is a case report and more study is needed.

Pifenidone: This is an agent that inhibits DNA synthesis, cell proliferation, and collagen synthesis in both normal myometrial and leiomyomas smooth muscle cells, probably through inhibitory effects on growth factors implicated in fibroid growth. It is used as an antifibrotic in patients with pulmonary fibrosis and has shown reasonable safety. It can be an effective non-steroidal treatment for fibroids as it inhibits myometrial and fibroid cell proliferation. It is currently under trial.

Surgical Management of Myomas

The most common symptoms for which treatment is sought:

- Excessive uterine bleeding
- Pelvic pressure and pain
- RPL
- Occasionally infertility.

Indications for surgical management of uterine myomas: American College of Obstetricians and Gynecologists (ACOG) and American Society for Reproductive Medicine (ASRM).

- Abnormal uterine bleeding not responding to conservative treatments.
- High level of suspicion of malignancy.
- Growth after menopause.
- Infertility with distortion of the endometrial cavity or tubal occlusion.
- Pain or pressure that interferes with quality of life.
- Urinary tract frequency or obstruction.
- Iron deficiency anemia related to abnormal uterine bleeding.

Myomectomy

Myomectomy for removal of intramural and subserosal myomas solely to improve or to treat infertility has been controversial. The potential risks and consequences like postoperative adhesions that may reduce fertility and the need for cesarean delivery are real. The data from studies of IVF outcomes in women with or without myomas certainly suggest that historical skepticism regarding the value of myomectomy in infertile women is justified. Results of two myomectomy series also challenge the therapeutic value of myomectomy in otherwise asymptomatic infertile women with intramural and subserosal myomas. In both studies it was observed that cumulative results of over the first two postoperative years related primarily to duration of infertility and presence or absence of other infertility factors but not to the size or site of the large myoma removal.

There are recent studies though which have evaluated the reproductive outcome before and after laparoscopic or abdominal myomectomy for submucous or intramural myomas. Campro et al. studied 41 out of 128 patients who underwent myomectomy as only these matched the criteria of the study designed. They concluded that myomectomy significantly improved pregnancy outcome in patients with subserous or intramural fibroids probably removing a plausible cause of altered uterine contractility or blood supply. The main determinants of pregnancy rate after surgery are patient age, diameter and intramural localization of the myomas and type of surgery.

Keeping these controversies in mind there are guidelines designed for myomectomy by the ACOG (Table 4).

Myomectomy by any route is still a controversial subject. According to the available evidence based on a comprehensive review slightly less than two-thirds of the women with uterine leiomyomas and otherwise unexplained infertility conceived after myomectomy. There is a renewed interest in the procedure due to postponement of pregnancy until later age thus myomas getting a chance to thrive. Also with the advent of minimal access surgery and better imaging modalities choice of route requires to be addressed. Comparison between laparoscopic and abdominal myomectomy is shown in Table 5.

<table>
<thead>
<tr>
<th>Table 4: ACOG criteria for myomectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication:</strong> Leiomyoma in infertile patients as a probable factor due to its size or location</td>
</tr>
<tr>
<td>If RPL after investigating all other causes</td>
</tr>
<tr>
<td><strong>Prerequisites of the procedure:</strong></td>
</tr>
<tr>
<td>- Evaluate other causes of male and female infertility or recurrent pregnancy loss</td>
</tr>
<tr>
<td>- Evaluate the endometrial cavity and fallopian tube, e.g. HSG</td>
</tr>
<tr>
<td>- Document discussion that complexity of disease process may require hysterectomy</td>
</tr>
</tbody>
</table>

"Table 4: ACOG criteria for myomectomy"
**Table 5: Comparison between laparotomy and laparoscopic myomectomy**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Laparotomy myomectomy</th>
<th>Laparoscopic myomectomy (Figs 1A to D)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal incision/access</td>
<td>Pfannenstiel incision is many a times sufficient with all its advantages</td>
<td>Primary port access could be through the umbilical tube either by open technique (preferred) or with prior pneumoperitoneum. In large tumors veress could be inserted through the palmar’s point and the optical port may have to be taken in the supraumbilical region. Additional 10 mm access could be sought in the suprapubic region or just a little medially to the Mc Burney’s point. This helps to use additional energy source/needle holder and can be enlarged to use the morcellator.</td>
</tr>
<tr>
<td>Abdominal incision/access</td>
<td>Maylard’s or any other muscle cutting incision could be chosen. Vertical midline incision may be required in some cases</td>
<td></td>
</tr>
<tr>
<td>Hemostasis</td>
<td>• Bonney’s clamp curve up or down at the level of the internal os or a rubber catheter tourniquet. (duration not &gt; 20 min)</td>
<td>Injection vasopressin at both the cornual ends or in the myoma. Can cause systemic hypertension leading to death. Caution essential 0.25% bupivacaine with epinephrine is used. In both approaches prior use of:</td>
</tr>
<tr>
<td></td>
<td>• Additional sponge holders on the ovarian vessels</td>
<td>• Tranexamic acid</td>
</tr>
<tr>
<td></td>
<td>• Injection vasopressin at both the cornual ends or in the myoma. Can cause systemic hypertension leading to death. Caution essential 0.25% bupivacaine with epinephrine is used. In both approaches prior use of:</td>
<td>• GnRH analogs</td>
</tr>
<tr>
<td></td>
<td>• Uterine artery cannulation can be done</td>
<td>• Uterine artery cannulation can be done</td>
</tr>
<tr>
<td>Uterine incision</td>
<td>• As low as is possible</td>
<td>• Right handed surgeon may prefer a midline longitudinal incision making it easy to suture</td>
</tr>
<tr>
<td></td>
<td>• Posterior more difficult for suturing</td>
<td>• Posterior horizontal incision may also be chosen in superiorly placed tumor</td>
</tr>
<tr>
<td></td>
<td>• Anterior for cervical fibroids always after opening the UV fold of peritoneum can protect against adhesions</td>
<td>• Anterior oblique incision from the right upper pole to the left lower pole can be easier to suture</td>
</tr>
<tr>
<td></td>
<td>• Large myometrial surfaces can be approximated with the Bonney’s hood</td>
<td>• In any case the incision should be well away from the tubal origin</td>
</tr>
<tr>
<td>Energy source</td>
<td>• Blended to be used</td>
<td>• The harmonic scalpel and use of bipolar in correct quantum has revolutionized this modality</td>
</tr>
<tr>
<td></td>
<td>• Caution not to use close to the endometrial cavity</td>
<td>• Monopolar current should not be used</td>
</tr>
<tr>
<td></td>
<td>• Hemostatic sutures can reduce the need of energy source</td>
<td></td>
</tr>
<tr>
<td>Suturing</td>
<td>• Three layers with 2-0 vicryl</td>
<td>• Suturing with good approximation needs to be mastered.</td>
</tr>
<tr>
<td></td>
<td>• Assured approximation</td>
<td>• Thorough suturing in 3 layers to be done for comparable results: deep myometrium, superficial myometrium and serosa.</td>
</tr>
<tr>
<td></td>
<td>• Reliable scar integrity</td>
<td>• If endometrium avulsed then four layer suturing (4-0 vicryl) to be done</td>
</tr>
<tr>
<td>Postoperative recovery</td>
<td>• Slow</td>
<td>• Fast</td>
</tr>
<tr>
<td></td>
<td>• VAC scores poor</td>
<td>• Early ambulation</td>
</tr>
<tr>
<td>Adhesion prevention</td>
<td>Good peritoneal toileting: Ringer’s lactate is proposed to be better than the commonly used normal saline. Gotex and interceed can also be used. Studies have shown increased incidence of adhesions</td>
<td>• Interceed has good results</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Gotex believed to be superior but requires suturing in place and removed after a while</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Peritoneal drying due to CO₂</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Pneumoperitoneum can be prevented by humidifiers and continuous irrigation</td>
</tr>
<tr>
<td>Scar integrity</td>
<td>Good</td>
<td>Good in experienced hands</td>
</tr>
<tr>
<td>Removal of the specimen modifications</td>
<td>Easier due to large incisions</td>
<td>• Morcellation with modern devices has made it easy. Expensive gadgets can be replaced by techniques of spiral cut or using other cutting instruments and energy. Posterior colpotomy or a small abdominal incision can be used</td>
</tr>
<tr>
<td></td>
<td>Minilaparotomy incision can be used and maneuvering achieved by use of uterine manipulators</td>
<td>• Removal of myoma can be through a small incision and the uterine suturing too can be done through this incision either in the abdominal wall or vagina</td>
</tr>
</tbody>
</table>
There are various factors which influence the choice of route of myomectomy:
- Size, number and site
- Expertise of the surgeon
- Control of hemorrhage
- Suturing technique and the resultant scar integrity
- Available facilities.

Contraindications for laparoscopic myomectomy:
- Medical conditions likely to be worsened with abdominal distension and Trendelenburg position for a long period
- Diffuse leiomyomas
- More than three myomas equal to or more than 5 cm
- Uterine size more than 16 weeks of gestation
- Myoma more than 15 cm in diameter
- Incision totaling to more than 15 cm.

There are quite a few authorities now not strictly adhering to these criteria and no clear-cut offs exist to determine the approach. The decision is situational.

The two most important prerequisites before a myomectomy requiring consideration are:
- Preoperative treatment with GnRH analogs
  A Cochrane Review suggests that the use of GnRH analogs for 3–4 months prior to surgery reduces both uterine volume and fibroid size. They are of benefit in reducing iron deficiency anemia if present and also help in reducing the intraoperative bloodloss. Reduction in size facilitates the procedure to be completed by laparoscope. The disadvantage is the extensive dense fibrosis which may occasionally develop. Also in our experience it does not help much in those fibroids which have already undergone cystic degeneration.
- Clear and informed consent
  Clear discussion and the choice of route should be discussed with the patient. The risk of vascular and visceral injury should be discussed. Also sometimes the necessity of hysterectomy should be discussed. Some authors have quoted the risk of hysterectomy to be as high as 1 in 100.

For subserous myomas laparoscopy can offer a minimal invasive alternative to laparotomy (Figs 2A to E). It is associated with faster postoperative recovery and potentially less postoperative adhesions (Fig. 3). Main concern remains with respect to removal of the myoma after it has been removed either by ligation or use of energy. But it is definitely satisfying to use laparoscopic access in these fibroids. Asymptomatic subserosal fibroids do not always necessitate surgery. Myomectomy for intramural fibroid is an issue requiring appropriate modality of treatment. Laparoscopy has certain important advantages especially with respect to adhesions. At the time of second look laparoscopy, adhesions were found less frequently and were less extensive in patients who had laparoscopic myomectomy. The critical risk factors were found to be the posterior location of the myoma and the number of incisions.

Recent evidence favors safety and reliability of laparoscopic approach. Prospective randomized controlled trials comparing laparoscopic myomectomy with laparotomy myomectomy will clarify the status further. Bullett and coworkers compared postoperative adhesions after laparoscopic versus laparotomy myomectomy in a prospective controlled trial and found it to be advantageous.

**Advantages of Laparoscopic Myomectomy**
- Shorter hospitalization
- Faster postoperative recovery
- Reduced postoperative pain
- Reduced ileus and thromboembolic phenomenon.

**Limitations of Laparoscopic Myomectomy**
- Deep intramural fibroids may not be localized due to lack of tactile sensation; intraoperative transvaginal sonography could be undertaken for the same.
- **Skills of the surgeon**: Experience and sound suturing skills are essential.
- Number of instruments and various angles of insertion to approach the surgical site are limited, posing technical difficulties.
- Removal of myoma from the abdominal cavity may be difficult.
- Accurate edge apposition may be difficult.
- Operating time.
As for submucosal fibroid (Figs 4A and B) hysteroscopy approach is the current gold standard. Currently the main indications for hysteroscopic myomectomy (Table 6) in infertile patients or in candidates for HRT are the presence of abnormal uterine bleeding and submucous myomas, including asymptomatic cases.

Grading of these myomas is essential to better plan the surgery. Based on dimensions and site, the European Society of Hysteroscopy has proposed the classification shown in Table 7.

G0 can be handled by an inexperienced surgeon. G2 requires considerable skills. This classification however does not mention the dimension of the fibroid. The operability depends on the intramural component of the tumor. The thickness of the peritoneum remaining between the inner deep margin of the tumor and the serous peritoneum of the uterus is important. The safety margin set by most is at 0.5–1 cm. Also the angle proposed by Donez et al. proves less accurate as it does depend on the dimensions of the myoma.

There is therefore one more classification proposed to evaluate the viability of hysteroscopic surgical treatment.\(^{29}\)

The new classification (NC) is based on the subjective analysis of parameters that make surgery more difficult. The four criteria, as discussed in Table 8, were considered.
Table 6: Indications for hysteroscopic myomectomy
- Abnormal uterine bleeding
- Infertility (including asymptomatic cases)
- Candidates for HRT (including asymptomatic cases)

Table 7: Classification of intrauterine myomas by the ESH

<table>
<thead>
<tr>
<th>Grading</th>
<th>Myoma with development limited to the uterine cavity, pedunculated or with limited implant base</th>
<th>G0 Grade 0</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Myoma with partial intramural development, i.e. endocavitatory component more than 50%, angle of protrusion between the myoma and the uterine wall &lt;90</td>
<td>G1 Grade 1</td>
</tr>
<tr>
<td></td>
<td>Myoma with predominantly intramural development, i.e. endocavitatory component 50%, angle of protrusion between the myoma and uterine wall &gt;&gt;90</td>
<td>G2 Grade 2</td>
</tr>
</tbody>
</table>

Table 8: Criteria for NC
- The penetration of the nodule into the myometrium
- The extension of the base of the nodule with respect to the wall of the uterus
- The size of the nodule
- The topography of the nodule

Table 9: The classification and scoring of myomas

<table>
<thead>
<tr>
<th>Points</th>
<th>Penetration</th>
<th>Size</th>
<th>Base</th>
<th>Third</th>
<th>Lateral wall (+1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>&lt; 2 cm</td>
<td>&lt;1/3</td>
<td>Lower</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>&lt; 50%</td>
<td>&gt;2–5 cm</td>
<td>&gt;1/3–2/3</td>
<td>Middle</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>&gt; 50%</td>
<td>&gt;5 cm&gt;2/3</td>
<td>Upper</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Accordingly the myomas are scored and classified as in Table 9. The scoring of the myomas is done and then the treatment is suggested as follows (Table 10).

Both these studies require to be compared on a larger patient group. They can actually complement each other.
Myomectomy at C-Section

Traditional teaching has always been to remove only subserous or pedunculated myomas at the time of C-section. Torrential hemorrhage and infection later on were the prime concerns with intramural fibroids. There is renewed interest in the recent past with the advent of superior surgical techniques and better antibiotics. Intramural fibroids have been successfully removed at the time of cesarean section. We have attempted ligation of the uterine artery at the time of C-Section a keen to uterine artery embolization (UAE). Our observation has revealed increased febrile morbidity in these patients. We require to statistically evaluate our data.

Alternative Surgical Treatment: Myolysis

Electrical, thermal and ultrasound energy sources have been used to coagulate and devascularize symptomatic fibroids. Most such techniques involve laparoscopy directed placement of energy probes. LASER has been used giving rise to dense adhesions. Bipolar energy so far has given better results. Magnetic resonance guided focused ultrasound surgery of uterine fibroids (MRgFUS) is one such modality but without laparoscope. None of these myolysis approaches have established safety in women desiring fertility.

Magnetic Resonance Guided Focused Ultrasound Surgery of Uterine Fibroids

It is a noninvasive, outpatient procedure which uses high doses of focused ultrasound waves to destroy uterine fibroids without affecting any of the other tissues around the fibroid. MRI mapping of the fibroids is done prior to the procedure. The focused ultrasound energy is directed to a small volume of the fibroid raising its temperature high enough to cause thermal ablation without impacting other tissues. Pulses of energy are repeated until the entire volume is treated.

This method suffers from lack of sufficient evidence with respect to volume of the studies, follow-up, comparisons with other modalities, etc. It is proposed that 50% of the fibroid tissue is destroyed which still require to be quantified. Also one wonders whether such partial destruction of fibroid is beneficial to alter the pathogenesis of the disease. This treatment cannot be used for fertility preservation or enhancement.

Use of adjuvant therapy with the GnRH agonists potentiates the thermal effects of MRgFUS in women undergoing treatment of uterine fibroids. Transvaginal probe guided sonications have been tried, and hysterectomy specimens have revealed no serosal heating or burning and hold some promise and are currently under evaluation.

Table 11: Complications of UAE

- Related to angiography: DVT, pulmonary embolism
- Amenorrhea
- Premature ovarian failure
- Perforation
- Infection
- Tissue necrosis

Uterine Artery Embolization

Uterine artery embolization has been used in the treatment of postpartum hemorrhage (PPH) since the 1970s, but is relatively a new option for the treatment of fibroids. It entails angiographically guided occlusion of the uterine artery with pellets, which decreases the size of the fibroids. Complications can arise as discussed in Table 11.

The fertility rate after this procedure when performed for PPH were not adversely affected. The risks associated with this procedure included hysterectomy, premature ovarian failure and infertility from radiation exposure following UAE as per the earliest studies that evaluated the fertility potential and labor performance of women. It concluded that the risks associated with UAE compared favorably with those associated with myomectomy. There are multiple case reports of successful pregnancy outcomes after UAE. However, numerous complications also have been reported. A review of 50 such published cases after UAE reported the following complications:

- Malpresentation (17%)
- SGA (7%)
- Cesarean section (56%)
- Premature delivery (28%)
- PPH (13%).

Safety of UAE with respect to fertility conservation is still controversial. An ACOG Committee opinion from 2004 states: “there is insufficient evidence to ensure its (UAE) safety in women desiring to retain their fertility, and pregnancy-related outcomes remain unstudied. The ACOG considers this procedure investigational or relatively contraindicated in women wishing to retain fertility...” Myomectomy remains the standard of care in patients who wish to retain fertility. UAE’s effect on fertility and pregnancy needs to be studied further. Meanwhile this technique should be used only in those patients desiring to retain fertility without any other feasible option.

Hysterectomy

The definitive treatment for uterine myoma is hysterectomy though at the cost of functionality. Hysterectomy as a modality can be chosen only when fertility is not desired by the patient. The risk of mortality associated with hysterectomy is
Table 12: ACOG criteria for hysterectomy for leiomyomas

- Asymptomatic myoma which are abdominally palpable
- Excessive uterine bleeding leading to flooding, clots or frequent and long lasting or leading to anemia
- Myomas causing pelvic discomfort

approximately 1/1,000 procedures. Mere presence of a fibroid does not warrant a hysterectomy. Also hysterectomy in the case of myoma requires considerable surgical expertise. Proper patient selection is mandatory and unindicated intervention should be avoided. The ACOG Committee has developed certain criteria (Table 12) for hysterectomy in leiomyomata of uterus.

The guidelines also mention certain important preoperative prerequisites such as:
- Confirm the absence of cervical malignancy
- Eliminate an ovulation and other causes of abnormal bleeding
- Confirm the absence of endometrial malignancy in the presence of abnormal bleeding
- Surgical risk assessment due to anemia and treat it if necessary
- To consider patient’s medical and psychological risks concerning hysterectomy.

Management Guidelines

Management of the uterine myomas must be individualized. The factors to be considered are:
- Symptoms
- Size
- Fertility status
- Rate of growth.

Asymptomatic Patients

In these patients, we would like to give prime importance to expectant management, as this is the one, which is easily forgotten. Lately there is increasing tendency to remove every fibroid seen on the uterus just because it can be done easily especially with newer modalities. However, we must remind ourselves that fibroids are a very occurrence. More than 50% of women would have one or two fibroids by the time of menopause and many of them are entirely asymptomatic.

In our series of 216 cases of fibromyomas, 180 were in premenopausal group, and we encouraged expectant management with medical and surgical management when required. It was observed that among the asymptomatic cases even with large (more than 6 cm) tumors, 39% did not require surgery. Among symptomatic and large tumors, 28.5% could be managed non surgically, while among asymptomatic and small (less than 6 cm) tumors, 63.3% did not require surgery. Patients without symptoms with uterine enlargement less than or equal to 12 weeks gestational size and slow uterine growth (< 6 weeks size in 1 year) should be managed expectantly regardless of fertility status.

Patients desiring pregnancy can be counseled that myomas rarely impair fertility or complicate pregnancy. Asymptomatic women with myoma greater than 12 weeks gestational size who desire pregnancy should attempt conception. Myomectomy may be considered for women who fail to conceive after unprotected cohabitation or who have repeated pregnancy losses if a thorough workup for infertility or RPL is negative.

Currently no data supports routine performance of myomectomy for arbitrary sized myoma in asymptomatic women desiring fertility and therefore these can be managed expectantly.

Traditionally, large asymptomatic fibroids in women not desiring pregnancy have been managed by hysterectomy. This decision is based on the following rationale:
- Large myomas interfere in the clinical evaluation of adnexa which could delay the detection of ovarian malignancy
- It would help in early detection of sarcomas
No data supports this rationale
Any treatment offered to asymptomatic patient should be evaluated and be of clearcut benefit with minimum risks.

Symptomatic Patients

It is essential to establish that the symptoms are attributed to the myoma. Many a times myomas are an incidental finding not necessitating intervention. Myomectomy may be offered to women desirous of fertility but proper criteria should be adhered to before undertaking any definitive treatment modality.

In conclusion, there are a plethora of treatment modalities available for treating leiomyomas. It is important that each clinician keep himself updated with these advanced data to better treat our patients. One should keep an open mind to different aspects of therapy, base diagnosis on sound clinical judgment and offer treatment based on evidence based data. Proper patient selection and individual tailor made treatment should be the aim.

REFERENCES

5. ACOG educational and technical bulletin, p. 869.
Genital prolapse is at least as old as Egyptian mummy.

Prolapse simply means downward descent. While from the angle of a physicist its root cause would be incessant pull of gravity; from the viewpoint of a gynecologist it would be failure of normal structural, functional and positional antigravity mechanism and/or operation of some progravity force (e.g., any chronic downward force) from above on the organs in question. Anyway, before getting down into the pathological anatomy and surgical anatomy of prolapse (as the chapter heading demands) a review of the other types of pelvic anatomy is essential because these are all inseparably interrelated (Fig. 1).

CONCEPTUAL TYPES OF FEMALE PELVIC ANATOMY

- Structural anatomy
- Positional anatomy
- Functional anatomy
- Pathological anatomy
- Surgical anatomy.

STRUCTURAL ANATOMY

This means the structures—“as is and where is” undisturbed by any pathological process or force. Since to any postgraduate (to whom this book is directed) this kind of descriptive anatomy is expected to be all too known this will not be detailed here exhaustively except through drawings for the purpose of comparison with pathological anatomy (Fig. 2).

However, one misconception that many gynecologists tend to suffer in connection with prolapse is that—they subconsciously take the structural anatomy as it is found in a young nulliparous woman only “as normal” and any deviation from it makes their perfectionist mind somewhat unhappy—
Prolapse: Pathological Anatomy and its Bearing to the Selection of its Treatment

whereas, in real life, even normal structural anatomy varies with parity and age.

**POSITIONAL ANATOMY**

Since prolapse is a matter of position (i.e. downward descent from normal position) review of some important facts about the positional anatomy of the organs concerned is necessary—not only to label a case as one of prolapse but also to allocate degree to it. Besides, it is also necessary in order to precisely plan the repair.

**Positional Anatomy of Uterus**

In adult woman in erect posture, except in approximately 15%, uterus lies in a forwardly bent attitude, i.e. in anteverted and anteflexed state. It is noteworthy that of this natural state, it is specially the feature of anteversion which acts as an inherent mechanism against occurrence of prolapse even under great downward stress. This is because in an anteverted position the axis of the cervix meets the axis of vagina at approximately 90° angle and so, when a woman is standing, the cavity of the uterus is more horizontal than vertical (Fig. 3) and hence it never comes under vertical downward stress. Besides, the above fact also implies that, for uterine prolapse to occur, the axes of the above two organs has to come more or less in the same line by some mechanism.

Secondly, in a standing woman, the internal os is found to lie approximately in level with the upper border of symphysis pubis and the external os at about the level of ischial spines. Hence, logically, any descent of uterus from the levels mentioned above should be labeled as a case of prolapsed uterus.

**Positional Anatomy of Vagina**

*Not a vertical canal:* Normally, vaginal canal extends obliquely upward and backward from the vulva at an angle of 60–70° to the horizontal or in other words, it is not a vertical canal. Hence, any rise in intra-abdominal pressure has the closing effect on vaginal canal by causing apposition of anterior and posterior vaginal wall.

*Not a straight canal:* In connection with prolapse another important positional feature of vagina to appreciate is—that its canal is not straight. It is actually angulated backward at about halfway of its length (called vagino-pelvic angle—Fig. 4), which means that upper half of the vagina is more or less horizontally placed. This is again another mechanism by which vagina not only escapes the vertically downward stress but under stress its upper half tends to close.

*Not a canal at all:* The third point to note in this context is, specially the lower part of the vagina is H-shaped in cross-section which means that its anterior and posterior walls normally lie in apposition thereby obliterating its canal (Fig. 5). Vaginal canal assumes this configuration because it is fixed (suspended) laterally by the lowermost part of Mackenrodt’s ligaments.

Obviously, for prolapse to occur whether uterine or vaginal or both, nature’s above well-engineered positional anatomy has got to be disturbed first.

**FUNCTIONAL ANATOMY**

While this is the ace matter both from physiological and therapeutic (surgical and nonsurgical) angle, besides its far reaching psychological, social and sexual implications, it is not yet fully understood because of the following reasons:

- The correlation between somatic and autonomic neuromuscular activity of pelvic floor muscles cannot yet be fully explained.
- Agonist and antagonist activity of pelvic floor musculature do not satisfactorily explain the functional anatomy.

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*Fig. 2: Structural anatomy of female reproductive tract*

*Fig. 3: Normally, the axis of cervix and that of vaginal canal cut each other almost at right angles, which is an inherent positional mechanism for prevention of prolapse*
may be noted that the altered anatomy should only be taken as pathological if it makes “the patient” unhappy (not the gynecologists), e.g. if she has seen or even felt something at her introitus and/or has noticed some undesirable alteration of some function of that region, e.g. that of micturition, defecation, coitus, etc. then only the anatomy may be called as pathological.

**Purpose**

A precise knowledge of pathological anatomy is absolutely essential to plan appropriate treatment, i.e. whether the patient requires nonsurgical or surgical treatment, and, if surgery—what surgery and to what extent it should be carried out.

**Assessment**

For assessing the precise pathological anatomy in a case, besides clinical examination in unstressed and also stressed condition (e.g. asking the patient to strain in lying and if necessary, sitting, squatting or even standing position) investigations like ultrasound, both abdominal and transperineal, intravenous urography specially for determining the position of ureters, back pressure changes, etc. urodynamic studies, even MRI—to assess the extent of muscular and fascial damage may be employed in suitable cases. Of course, per rectal examination is a must specially to differentiate rectoceles from enterocele.

**ORGANWISE DESCRIPTION**

**Pathological Anatomy of Anterior Vaginal Wall Prolapse**

Prolapse of anterior vaginal wall most commonly presents as cystocele (Fig. 6). However, rarely, through its lowermost part—the posterior wall of urethra may bulge, when it is called urethrocele. Disruption or degeneration of the layer of normal fascial condensation around the vaginal canal is the cause of such prolapse and to prevent recurrence after repair this fascial tissue has to be repaired.

**Pathological Anatomy of Posterior Vaginal Wall Prolapse**

**Upper Third Prolapse**

This includes enterocele of various degrees and post-hysterectomy vaginal vault prolapse (Fig. 7).

These two conditions constitute true pelvic hernia because these have peritoneum lined sac and hence the basic principles of hernia repair apply, i.e. dissection of the hernial sac, closure of the neck of the sac and building
local support (usually by plication of what is felt of the uterosacral ligament) to prevent recurrence. In the cases of vault prolapse, where necessary, support may be sought from the anterior longitudinal ligament that lies on the anterior surface of sacrum through a sling of Decron or Mersilene tape—a procedure which must be done through laparotomy. Recently, however, transvaginal colpopexy with sacrospinous ligaments of both sides is being preferred for the purpose—this being much simpler and easier.

As a preventive step to this form of herniation some gynecologist routinely plicate the uterosacral ligaments in the midline by a few stitches.

**Middle Third Prolapse**

This presents as rectocele. Colpoperineorrhaphy up to 1.5 cm beyond the limit of the bulge of rectocele with plication of rectovaginal fascia and tightening of levator ani (puborectalis) is the commonly practiced approach to tackle this. Recently, a new approach about repair of rectocele. Recently, for cases of isolated rectocele without significant perineal or levator laxity, the author has been doing “site specific repair” which means circumscribed repair of the weak and sacculated area only. This avoids performance of routine perineorrhaphy which is known to have many side effects (see below). None of the six cases done over last ten years have come back with recurrence.

**Lower Third Prolapse**

This includes cases of lax introitus, wide open introitus and lax perineum. All these patients have underlying perineal tissue tear. These patients usually complain of unsatisfactory intercourse, excess exposure and local vulvovaginal dryness. They need just good perineorrhaphy with buttressing of levator ani.

**The Debate about “Routine” Perineorrhaphy**

A concept prevailed for many years that no operation for prolapse is complete unless one has done perineorrhaphy with it—be it repair of cystocele, be it a case of simple uterine prolapse or any other kind of prolapse. This myth has been dispelled by Jeffcoate. He found this procedure is required only in 50% operations for prolapse. The practice of routine perineorrhaphy was based on the postulate that uterus is supported by vagina and the vagina (both its anterior and posterior wall) is supported by the perineum, which have been found to be unproven (see under supports of vagina later).

The advantages of avoiding perineorrhaphy (where it is not specifically required) are as follows:

- Patients are remarkably free from local postoperative pain and discomfort
- Occurrence of postoperative retention of urine and consequent cystitis are quite rare
- The chance of occurrence of anatomical dyspareunia later due to narrowing of introitus and lower vagina and also that from painful and/or hypersensitive perineal scar is virtually eliminated.

**An Important Note about Site-Specific Repair**

The proponents of this type of repair believe that pathologically there are two types of vaginal prolapse as follows:

1. Distension prolapse
2. Displacement prolapse.
**Distension Prolapse**

This occurs due to attenuation of vaginal wall ‘only’ without any loss of its fascial attachments. So, here the vaginal rugae will be lost and vaginal wall will look smooth.

**Displacement Prolapse**

This results from loss of attachment of lateral vaginal walls from the pelvic side walls and hence here vaginal rugae will be intact.

**Local Vaginal Pathology Consequent to Prolapse**

In long-standing vaginal prolapse, vaginal walls get keratinized due to constant exposure and friction; some also develop pigmentation, even decubitus ulcer. In postmenopausal women, signs of vaginal atrophy are present and these patients get benefited by preoperative topical estrogen therapy.

**Pathological Anatomy of Uterine Prolapse**

The three degrees of descent of uterus from its normal position has been depicted in Figure 8. Uterine prolapse can occur on its own due to weakness of direct supports of uterus, i.e. that of Mackenrodt’s and uterosacral ligaments in which case cystocele and rectocele may not be associated. However, in the same case if there has also occurred disruption of vesicovaginal or rectovaginal fascia, cystocele and rectocele are also present.

Primary prolapse of uterus is almost always associated with some degrees of elongation of supravaginal cervix due to chronic pull of cardinal ligaments on it to check the descent and also due to interference with venous and lymphatic drainage from this part. If the supravaginal elongation is much, though cervix may be seen outside the introitus, the actual uterus may still be positioned up in the pelvis.

**SURGICAL ANATOMY**

This means pathological anatomy with surgical plan superimposed in it. This entails, on the part of the surgeon, to find out the exact pathological anatomy so as to be able to plan the technique and extent of surgery keeping in mind that he/she has not only to put the structural anatomy right but also to ensure restoration of previous functions or at least the functions desired by the patient as required for meeting her social, psychological and biological situation.

Besides this, particularly for prolapse repair operation, a gynecologist must also have a clear concept about the various supports of the female reproductive tract (see later). To this end he/she also needs to do purposeful local examination in order to assess what supporting structures are presently available for use to repair and reconstruct. In this context a precise knowledge about the bones of the pelvis particularly the ligaments in and around the pelvic girdle is also essential because in some cases these may have to be utilized to organize support of the prolapsed organs. For example:

- pubic bones in the context of repair of stress incontinence
- sacrospinous ligaments (Fig. 9) for support of the posterior vaginal wall prolapse and vault prolapse (Fig. 9)
- anterior longitudinal ligament of sacrum for vault prolapse, etc.

In addition to above, the gynecologist also has to carefully assess the structural and functional state of the viscera intimately related to the prolapsed reproductive organs (Fig. 10) like that of the bladder, of the ureters, the urethra, the rectum, the anal canal and even that of the peritoneal recesses like POD. The purpose of this are twofold:

1. Ensuring their rehabilitation
2. To be able to take adequate care to avoid injury to these during the course of repair.

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**Fig. 8:** Stages of uterine prolapse

**Fig. 9:** Sacrospinous ligament
A Brief Note on Neuromuscular Anatomy in Relation to Surgical Treatment of Prolapse

- It is nearly impossible to restore neuromuscular function or lost reflex activities by restoring the anatomy surgically.
- *The vulnerability of “Levator ani nerve”: This nerve arises from the sacral roots and courses on the superior surface of the coccygeus muscle where it lies approximately 3 cm medial to the ischial spines. This important nerve is vulnerable to surgical injury during the following two operations for prolapse:
  - Sacrospinous ligament fixation and
  - Paravaginal defect repair.
  If this happens, this may result in chronic pelvic pain and/or dysfunction due to atrophy of this rather large vital muscle.
- The possible reason why some women develop ‘just’ pelvic organ prolapse and others develop urinary or fecal incontinence—different innervation of the levator ani and that of the striated urethral and anal sphincter.

Supports of Female Reproductive Tract and Their Relation with Pathological Anatomy of Prolapse

Most undergraduate books give neat structural classification of supports of uterus as upper group (round ligament and broad ligament), middle group (Mackenrodt’s ligament and uterosacral ligament) and lower group (pelvic diaphragm and urogenital diaphragm) which is helpful, but for postgraduate level one has to understand the supporting mechanism from the functional angle and also to critically assess the reality about the checking role of the various supporting structures in the occurrence of prolapse. From this point of view supports of uterus can be classified as:
- Static group of supports
- Dynamic group of supports.

Static Group of Supports

This means support by nonmobile, nonstretchable (hence susceptible to breakage under extreme stress) static structures, and ligamentous support constitute this category. These structures, which are generally very strong, hold the organs in their right place at all time, i.e. in both stressed and unstressed condition. The examples of these are—Mackenrodt’s ligament, uterosacral ligament and pubocervical ligaments (Fig. 11). In fact, this group constitutes the most important and the only real direct support for the uterus. Structurally, these are condensation of pelvic cellular tissue with some plain muscle fibers in them. Given below is a brief description of these ligaments.

*Mackenrodt’s Ligament (Transverse Cervical Ligament)*

Medially it is attached to supravaginal cervix and vault of vagina and laterally to a wide area in lateral pelvic wall (Figs 11 and 12). It lies in the space between the broad ligament above and aponeurosis on the pelvic floor muscles namely those on levator ani and obturator internus below. This is the thickest and the strongest support of the uterus.

*Uterosacral Ligament*

It stretches from the supravaginal cervix and posterior vault—to the front of the sacrum encircling the rectum (Fig. 13). This ligament is, in fact, the thick posterior margin of the Mackenrodt’s ligament. Under downward stress, due to the above attachment of the ligament, the vaginopelvic angle...
of vagina, become more acute which has occlusive action on vaginal canal. Besides, in standing position, the cervico-isthmic attachment of this ligament keeps the projection of the cervix oriented toward the central tendinous point of perineum, which, through dynamic support mechanism, works as complementary antigravity back up.

**Pubocervical Ligament**

Normally, this is not a well-defined ligament but usually become discernible in the presence of cystocele and anterior vaginal wall prolapse.

**Controversy about Vaginal Fascia**

There are two large reviews which have challenged the existence of structures like—pubovaginal fascia, bladder-pillar, pubovesical fascia, mesovaginal fascia, uterovesical ligament, musculofascial hammock, etc.  

**Dynamic Group of Supports**

A complex muscular apparatus that is formed by the muscles of pelvic diaphragm and the urogenital diaphragm constitute the dynamic support system (Figs 14 to 16). The system is mediated by a ‘tonic’ and ‘phasic’ reflex activity through type I (fast twitch) and type II (slow twitch) muscle fibers integrated at central nervous system. This comes into play for every effort involving Valsalva maneuver like defecation, lifting, running and other forms of sports activity and also for every incidence of increased intra-abdominal pressure like coughing, laughing, sneezing, etc. It has been found that any situation where the intra-abdominal pressure exceeds 100 cm of water it strains the pelvic supporting mechanism. Besides above, pelvic muscles also directly take the weight of the uterus, vagina, etc.
Of the above apparatus, which acts in a concerted manner, it is particularly the reflex contraction of puborectalis part of levator ani which plays the most important role in the following ways:

- Causes elevation of the central tendinous point of the perineum (to which it is inserted) which in turn effects the following—occlusion of the vagina, alteration of vaginopelvic angle which offsets the directional effect of stress, works as a supporting cushion for the vagina
- By directly opposing the expulsive forces
- By protecting the relatively stiff and therefore fragile static group of supports (see above) from overstretching and disruption.

Central tendinous point of perineum, being such a strategic supporting structure of female reproductive tract, its various attachments need a review. Attached to this are the following—superficial and deep perinei muscles, bulbocavernosus muscles and pubococcygeus muscles of both sides and also sphincter ani externus and the superior and inferior layer of urogenital diaphragm (together called triangular ligament).

Controversy about the Role of Levator Ani and Central Tendinous Point of Perineum

In the experience of Jeffcoate (1981) and many others, complete perineal tear with consequent diavirication of levator ani do not lead to development of either uterine or vaginal prolapse, not even rectocele.

The Reality about Pathological Anatomy/Etiology of Prolapse

The author proposes that in this disorder of displacement in majority of cases the anatomy is probably congenitally pathological, i.e. in most women who develop prolapse the supporting system of their reproductive tract is probably inherently weak. Any other etiological factors, e.g. trauma of repeated vaginal birth, menopausal atrophy or disruptive force of chronic severe stress, are just incidental insults unmasking or precipitating the prolapse. They are not the primary factors. Here is the logic behind the above proposition:

Points in Favor of Familial and Racial Factor

- Familial incidence of prolapse has been reported, and prolapse has been found to occur in sisters
- Chinese women have been found to have more sturdy pelvic floor
- Obviously, in nulliparous prolapse the cause is inherent weakness
- There are some known developmental anatomical features that favor occurrence of prolapse, e.g.
  - Short vagina
  - Deep pouch of Douglas
  - Axial uterus, i.e. axis of cervical canal and vaginal canal are (relatively more) in one line than at right angles (Fig. 17).

Points against Obstetrical Stretch Injury as the Dominant Cause

- Not all, only a small proportion of multiparous women develop symptomatic prolapse (laxity-yes). These women are perhaps the very women whose support systems were inherently weak. For others who do not develop prolapse, it is reasonable to assume that their support systems must have been strong enough to withstand the stress
Jeffcoate\(^2\) found prolapse often follows easy rather than difficult labor pointing to some inherent pre-existing factor.

While it is true that 90% prolapse patients are parous; over 80% middle aged women are parous in any case\(^2\).

Current trend of allowing second stage of labor to prolong even up to 6 hours (under epidural analgesia) is testimony that stretch injury cannot be a very significant factor.\(^6,9\)

**Points against Menopausal Atrophy of Support as the Primary Case**

While this biological change occurs in 100% women, severe prolapse (not mere laxity) occurs only in a small percentage, i.e. perhaps only in those whose supports were already inherently weak.

**Points against the Factor of Chronic Stress as the Primary Cause**

Mere chronic stress succeeds in causing prolapse only when it is of severe degree and usually in those women whose supporting system was already inherently off the mark.

**Would Routine Prophylactic Forceps/Vacuum or Elective Cesarean Prevent Prolapse and Pelvic Floor Dysfunction?**

The idea here is not to stress the perineum. Here is what the literature says about it—“Because elective episiotomy and operative vaginal deliveries have not been shown to be beneficial, and potential harm is great, use of these procedures should be avoided when possible.”\(^10\)

If all women underwent cesarean section, there would undoubtedly be less future pelvic floor dysfunction. However, most women do not develop pelvic floor dysfunction.

A policy of elective CS would subject many women to a potentially dangerous procedure to prevent a condition that they never would have developed.\(^10\)

**Some Recent Findings about Pathological Anatomy of Prolapse**

- Biopsies of puborectalis muscle taken during operation for prolapse have demonstrated dystrophic type of lesions in the muscle and also structural change of neurogenic origin.\(^2\)
- EMG studies done on pelvic floor muscles in patients with prolapse showed tracings suggestive of neurogenic myopathy.\(^3\)
- Studies of sacral potential have demonstrated (in patients with stress incontinence)—prolonged latency in reflex response to stimuli.\(^3\)
- Operation of anterior fixation of uterus has been found to cause enterocele by exposing the pouch of Douglas to the expulsive forces.
- Anterior colposuspension (Burch’s operation) has been found to promote severe uterine prolapse within a very short time.\(^3\)

**REFERENCES**

INTRODUCTION

Considerations of etiopathology, incidence, clinical features and investigations as described in the previous chapter will provide a basis for management. This is essentially surgical unless unwillingness or unfitness prevent surgery, which includes exercises, palliative and medical treatment. It is important to recognize that the asymptomatic patient cannot be made to feel better by medical or surgical therapy. A corollary could be one cannot assess the success of therapy without comparing signs and symptoms before and after therapeutic intervention.

Surgical treatment becomes pointless if risk factors are not identified and modified. Belief that the treatment ends with surgery must be changed. Obesity, heavy lifting, constipation and pelvic floor muscle atrophy are among other factors that need to be addressed. If these are not, we are putting our patients right back into same situation and environment that contributed to their condition.

The crucial undertaking is to correctly define and assess the descent of the uterus and/or vaginal wall, and the herniation of genital and abdominal organs. Unlike hernias elsewhere (where functional consequences are minimal), pelvic support defects are commonly associated with alteration in bladder, bowel and sexual function. Prolapse of the bladder (cystocele) or urethra (urethrocele) through the anterior vaginal wall and/or prolapse of intestines (enterocele) or rectum (rectocele) through the posterior vaginal wall can be associated with uterine prolapse. Vaginal wall prolapse can occur without prolapse of the uterus, but uterine prolapse is invariably associated with vaginal wall prolapse. It is necessary to establish the presence or absence of cystocele, rectocele, urethrocele, paravaginal defect, SUI, procidentia principally, and then ascertain the degree and combination. What is always present in true procidentia is the enterocele.

As a recent advance, understanding of anatomy and physiology of supports of uterus is better, as is the knowledge about compromise of pelvic floor, muscle, connective tissue and nerve, by vaginal childbirth, especially if prolonged. There are three mechanical principles, which explain how the uterus and vagina are normally held in place:

1. The uterus and vagina are attached to the walls of pelvis by the endopelvic fascia that suspends the organs from the pelvic sidewalls.
2. The levator ani muscles constrict the lumina of these organs until they are closed, forming an occlusive layer on which the pelvic organs can rest.
3. Third supportive effect called a flap valve results from the above structural arrangements. With the vagina suspended in such a way that it rests against the supporting wall adjacent to it, increases in pressure force the vagina against the wall, thereby pinning it in place.

The top layer of the pelvic floor is created by the endopelvic fascia, which attaches the pelvic organs (especially the vagina and the uterus) to the pelvic walls, thereby suspending them. This is a viscerofascial layer. The part that attaches to the uterus is called “parametrium”, and that which attaches to the vagina is called paracolpium. The parametria are made up of what we refer to as the Mackenrodt’s ligament and uterosacral ligament. The paracolpium is responsible for suspending the apex of vagina after hysterectomy (level 1 according to DeLancy).
The function of the levator ani muscles can be compromised in two ways. First, there can be a direct injury to the muscle resulting in mechanical disruption of the entire muscle. Second, damage to the nerve supply of the muscles can lead to their inability to contract, even though they themselves remain intact. As small nerves are torn away from their muscle fibers, the ability of the muscle to contract is diminished and normal function is lost.

For the pelvic muscles to support the pelvic organs, they must not only have their normal structure, but must also have intact sensory and motor innervation. The recognition that neurologic damage occurs during child birth is one of the science's significant contributions to the study of pelvic floor.

Etiopathology of prolapse in relation to management also encompasses congenital weaknesses of supports of uterus and estrogen deficiency. In young women in the childbearing age group, a single vaginal delivery may be followed by the unremitting load of abdominal pressure that stresses them.

Epidemiologic studies point to vaginal delivery as the strongest risk factor, although the etiology is multifactorial. The pathophysiological mechanism of prolapse have not been fully elucidated, but it is likely that damaged or malfunctioning skeletal muscle, smooth muscle, connective tissue and nerves all play a role in the progression of this disease.

**Site-Specific Defect Theory**

Support for the site-specific defect theory (SSDT).

Advocates of the SSDT changed the definition of enterocele to an area in the vagina (typically at the apex) where there is a gap between the anterior pubocervical fascia and the posterior rectovaginal fascia. In this site, the peritoneum comes in contact with the vaginal wall epithelium. This could be identified surgically and repaired by suturing pubocervical fascia to rectovaginal fascia.

**POSTHYSTERECTOMY APICAL PROLAPSE**

Posthysterectomy apical prolapse was felt to represent detachment of the vaginal apex from the uterosacral ligament.

Here repair emphasizes the ipsilateral attachment of the vagina to the uterosacral ligaments without plication of the uterosacral ligaments across the midline.

Shull reported a greater than 90% success rate in the treatment of apical vaginal vault prolapsed with vaginal site-specific enterocele repair and uterosacral "ligament suspension".

Laparoscopic site-specific fascial defect repair of enterocele in vaginal apex prolapse showed an 88% success rate at 6 month follow-up.

**RECTOCELE**

Rectocele was newly defined as a gap in the rectovaginal fascia where the rectum comes in contact with the vaginal wall epithelium. Various breaks or detachments of the rectovaginal fascia were identified at gross surgical dissection and repaired individually. Reconstruction of the perineal body was also emphasized. Narrowing of the levator hiatus is not performed in the surgical case series documenting outcomes of site-specific rectocele repairs.

**CYSTOCELE**

If the anterior vaginal wall is prolapsed and there was a detachment laterally at the arcus tendineus fascia pelvis, then lateral support of the vagina with sponge stick will correct the cystocele. If there is primarily a midline tear in the anterior vaginal wall, the vaginal wall epithelium overlying the muscularis will be stretched and there will be loss of the rugated appearance of the epithelium. Richardson documented a greater than 90% success rate when repairing...
anterior vaginal wall prolapse and stress urinary incontinence by this approach.

CONCLUSION

Site-specific defect theory of POP has helped to advance our concepts about the etiology and surgical repairs. Unfortunately, parts of this theory have been proven inaccurate by current studies.

Most women with POP have both neuromuscular injury and connective tissue injury to their pelvis. Proponents of site specific defect have underemphasized the neuromuscular injury component, later part of which may be responsible for the high recurrent rate of POP. Proper evaluation of “defects” and incorporation of new procedures is now essential. Probably, further prospective evaluation might answer this theory of “site-specific repair”. Adequate stress should be given to the patient’s perspective in this evaluation, taking her bladder, bowel and sexual function into account apart from correction of prolapse.

The precipitating factors are:
- Repeated unsupervised/home deliveries
- Precipitate delivery
- Prolonged second stage of labor
- Instrumental delivery, especially before cervix is fully dilated
- Strenuous work in farms like lifting heavy weight or prolonged work in squatting position
- Chronic cough or chronic constipation
- Chronic anemia and malnourishment
- Increased intra-abdominal pressure due to tumor or ascites.

Certain associated conditions should always be noted, ruled out or treated before surgery.
- Genuine stress incontinence (GSI)
- Urinary tract infection (especially cystitis)
- Any other associated organic pathology, e.g. fibromyomata, endometriosis, Ca cervix, adnexal pathology (ovarian tumor)
- Pelvic inflammatory disease
- Decubitus ulcer
- Vulval or perineal pathology.

All conditions mentioned above modify the treatment of prolapse.

INVESTIGATIONS

Thorough examination is done before surgery. Hemogram, blood group with Rh, urine analysis with culture and sensitivity, Pap smear, intravenous pyelography (IVP), X-ray chest. Sonography should be a mandatory modern investigation as it rules out adnexal, other pelvic organic pathologies and pyometra (rare but important). Sonography would also rule out any associated kidney, ureteric, bladder or abdominal pathology. Sophisticated investigations like urodynamic studies, visecrograms, colpocystograms, defecography, dynamic fluoroscopic pelvic floor evaluation, advanced USG and MRI are relevant but not routinely possible. Investigations to establish fitness for anesthesia/surgery are essential.

POINTS TO REMEMBER

Preoperative

- Prior medical treatment of chronic cough/chronic constipation is a must.
- Presence of decubitus ulcer on the cervix could mean altered vascularity and associated infection, which needs treatment with glycerine-acriflavine pack or ring pessary. Both help by repositing the uterus to its normal anatomical position, thus relieving kinking of uterine vessels, cervical congestion and ulcer formation. The surgical procedure should be delayed till the congestion and infection around ulcer show arrest or regression. This will reduce excessive intraoperative bleeding and flaring up of infection postoperatively.
- Associated urinary tract infection and pelvic inflammatory disease (PID) must be treated aggressively.
- Preoperative estrogen therapy should be given to patients, especially the elderly, where the vaginal epithelium is very thin and inflamed.
- Antiseptic vaginal douches not less than a day before surgery.
- Full dose of antibiotics 2 hours before surgery to be given IV (e.g. 1 gram ampicillin, 80 mg gentamicin, 500 mg of metronidazole) to prevent incidence of postoperative pelvic infection.
- In diabetic cases, a higher antibiotic (Cefotaxime, Ciproflaxcin) may be considered.

Intraoperative (for Vaginal Operations)

- Thorough painting of vagina, vulva, perineum, medial aspect of thighs and lower abdomen.
- Proper vulval retraction with skin stitches.
- Keeping anal canal away by stitching fourchette with drape.
- Adequate illumination with addition of fiber optic directed cold light is desirable.
- Infiltration of pericervical and forniceal areas with normal saline alone, or with adrenaline, if the patient is not hypertensive, to facilitate dissection in proper plane and reduce intraoperative bleeding.
- Proper identification of lower limit of the bladder using a metal catheter/bladder sound.
- Use of 1.0 vicryl for pedicles.
- Use of chromic catgut 1 for vaginal suturing.
- Proper hemostasis at every step of the operation.
- retracting the anterior vaginal wall with Sim’s speculum provides excellent exposure of the posterior peritoneum.
Now, enterocele repair is ensured by closing the peritoneum as high as possible at a level identified by extraperitoneal pad of fat.

- Forming a good trough by tying opposite pedicles together especially the uterosacral ligaments. The opposing uterosacras should be further united by insertion of two sutures along their length posteriorly. In effect, the gap between them is closed for prevention of future enterocele.
- At this juncture, encerclage of the uterosacrals by these sutures should be scrupulously avoided to prevent ureteric injury or kinking.
- The uterosacral sutures are to be anchored to the vagina for vault suspension.
- While repairing cystocele, avoid excessive dissection into paraurethral, paravesical or retropubic spaces to avoid damage to the venous plexuses.
- Bladder neck is to be supported by a buttress stitch such as Kelly’s to treat stress incontinence if present or to prevent its iatrogenic occurrence (2–3%).
- To rest the bladder for 2 days after cystocele repair and for 3–5 days after Kelly’s stitch with self-retaining catheter.
- While a minimal rectocele may be required, over-enthusiasm should be avoided when tightening relaxed perineal outlet, otherwise dyspareunia will result.
- Dissection of rectum to be gentle, careful and slow even if deemed easy.
- Perineorrhaphy for lax perineum is best done by approximating both levator ani bellies together with #1 PGA sutures. Beware of rectal injury at this step.
- Frequently, bleeding is encountered during colpoperineorrhaphy, so proper hemostasis is to be ensured at each stage. Diathermy can be advantageous or complicating.
- Vaginal pack (optional ?), retained up to 24 hours, is advantageous to prevent inevitable oozing.
- Examination per rectum at the conclusion of procedure is mandatory.

Postoperative

- Sedatives and analgesics as per requirement, generous if required and permissible
- Antibiotic cover for 7 days
- Metronidazole for 48 hours
- Early ambulation
- Plenty of fluids orally
- Early feeding with semisolids and solids
- Repeat hemogram, PCV, urine examination routine at 48 hours
- The issue of early discharge should be individualized.

**Surgical Procedures**

Various surgical procedures can be classified as shown in Table 1.

<table>
<thead>
<tr>
<th>1. Conservative</th>
<th>Abdominal</th>
<th>Vaginal</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Nonconservative</td>
<td>Abdominal</td>
<td>Vaginal</td>
</tr>
<tr>
<td>3. Laparoscopic</td>
<td></td>
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The choice of the surgical procedures depends on the following:

- Age
- Desire for further child-bearing
- Desire for preservation of menstruation
- Degree and type of prolapse
- Degree of cervical elongation
- Associated organic/adnexal pathology
- Associated medical/surgical problem.

*It is beyond the scope of this article to go into the details of every surgical procedure. Some are briefly described for their principles, applicability, popularity, results, reporting and evaluation in the Indian context. Each procedure should be discussed at length with the patient, explaining the advantages and disadvantages. Proper counseling should enable the patient to make her own decision and provide informed consent.*

**Conservative Techniques for Very Old, and Especially Those Unfit for Major Anesthesia**

**Le Fort’s Operation**

It was deemed an operation of choice.

**Dani’s Stitch** *(Introital Tightening)*

It is easier and simpler than Le Fort’s operation. It is a simple minor procedure and can be performed under local anesthesia. Slightly increased risk of SUI after this stitch can be minimized by proper suburethral placement of the stitch to lift the urethra slightly. Initially, #1 monofilament nylon was used. The occurrence of the stitch cutting through was subsequently minimized by local estrogen therapy preoperative and postoperative, use of polylactic acid material (Vicryl #1 or 2) and going sufficiently deep in tissues around the introitus.

**Conservative Techniques for Young Patients**

**Vaginal**

*Fothergill’s operation* *(Manchester repair): This operation is an option in a wide age group where the patient desires preserving organ function. It can correct prolapse up to second degree. It consists of amputation of cervix and shortening of Mackenrodt’s ligaments along with anterior colporrhaphy and/or posterior repair. This operation was initially advocated for young women who were desirous of
child-bearing. Also, it is an operation of choice when cervical elongation and/or chronic cervicitis is present. However, cervical amputation may adversely affect subsequent conception (infertility, cervical stenosis) and/or pregnancy outcome (repeated second trimester abortions, preterm labor, cervical dystocia or precipitate labor). For these reasons, this repair is not considered as an operation of choice in India. However, techniques avoiding cervical amputation, viz. modified Fothergill’s or Shirodkar modification of Fothergill’s can be considered.

Abdominal

These consist of various types of sling operations.

Shirodkar’s Posterior Sling Operation

This operation is a “milestone” in the surgery for prolapse, perhaps a “gold standard”. Newest techniques are based on his principle that the uterosacral ligaments are the most important supports of uterus. This ligament not only holds the uterus at a higher level, but also maintains it in an antverted position. Mackenrodt’s ligaments hold the uterus up but their role in keeping uterus antverted is doubtful. Therefore, Shirodkar designed his operation by creating artificial uterosacral ligaments. The difficult part of his surgery was the left sided sling where a psoas hitch has to be formed. It has inherent potential for complications like injury to ureters, major vessels, genitofemoral nerves and the sigmoid.

Soonawala’s Unilateral Posterior Sling Surgery

We reproduce the originator’s personal communication below.

In case of nulliparous prolapse or prolapse in parous young women where function of the uterus is to be preserved, vaginal approach is not suitable for surgical correction as the results are not satisfying. Abdominal approach to fortify the uterosacral ligaments is one procedure which gives excellent results. A number of variations of this are described. The technique described here is simple, easy to perform and has given excellent results with low recurrence rate. It strengthens the main support of the pelvic fascia responsible to keep the uterus in its normal antverted position and preventing its descent.

Procedure: By a Pfannenstiel incision, the abdomen is opened and bowel loops are packed to give the pelvic cavity a good exposure. Promontory is identified and peritoneum over the first sacral vertebra is incised, fibroareolar tissue is dissected to visualize the anterior longitudinal ligament. Prolene loop, a special suture which is two strands of No. 1 prolene on a large atraumatic needle, is used. This is anchored to the anterior longitudinal ligament. The needle is then passed extraperitoneally along the right uterosacral ligament to the isthmus of the uterus taking a bite of the uterine wall. The path is retraced extraperitoneally to come into the area of the first sacral vertebra. The two ends are tied back securely pulling the cervix of the uterus up toward the sacrum. The incised peritoneal edges are apposed and abdomen is closed in layers.

Conclusion: For second and third degree uterine prolapse where function of the uterus is to be maintained, procedure to fortify the anatomical uterine support, uterosacral ligament, is most satisfying. Since the supporting sling does not encircle the uterine isthmus, it does not restrict dilatation of the cervix and normal delivery can take place. It does not constrict the rectum as it is only on the right side of the pelvis. Mersilene tape can be advantageously substituted for prolene loop.

Purandare’s Cervicopexy

Here, slings are formed from the rectus sheath and fixed on the anterior surface of the uterus near isthmus.

Disadvantages of this operation are:
- It does not cause effective anteversion of the uterus.
- Interference with vaginal delivery.
- High recurrence rate, because the slings can get stretched and attenuated with age.
- If cesarean section is required, the sling has to be incised.

Joshi’s Sling

Through a Cherney incision, the uterus is suspend-
ed to the pectineal ligament on both sides with Mersilene tape. Burch colposuspension can be done in selected cases.

Technique: Using a stout curved Mayo needle, Mersilene tape is anchored as its midpoint to the anterior surface of the uterus just above the level of internal os. A long artery forceps is passed subperitoneally from the retropubic space, just below the lateral end of the round ligament, toward the lateral edge of the peritoneal incision over the uterus, to grasp the lateral end of the Mersilene tape on that side. Lateral end of the tape is now drawn to the retropubic space. This procedure is repeated on the other side. Threaded into a curved cutting Mayo needle, the lateral end of the tape is passed through adequate thickness of pectineal ligament on each side as laterally as possible. The two ends of the tape are now drawn taut to elevate the uterus adequately and are anchored to the pectineal ligaments using 3 or 4 knots. The knots are fixed with “0” prolene sutures to prevent loosening and the excess portion of the tape is cut-off. This results in anteflexion and elevation of the uterus.

Comments
- The uterus is effectively elevated without compressive effect on any organ.
- The weight of the uterus is shared by two strong ligamentous anchoring points minimizing the chance of recurrence.
The technique involves minimal dissection away from structures like ureter, rectosigmoid, and median sacral vessels.

Most patients deliver vaginally and cesarean can be done without cutting the tape.

**Virkud’s Sling**

Here, one end of the Mersilene tape (30 cm long) is fixed to the sacral promontory posteriorly with two strong linen stay sutures. It is then passed subperitoneally on right side of pelvic wall, then through broad ligament and fixed to posterior surface of the isthmus of the cervix with # 20 Barbour linen stay sutures. The tape is then passed between left broad ligament through left internal inguinal ring, piercing the transversalis fascia and turned medially at linea semilunaris between the rectus muscle and sheath, where it is sutured with # 20 Barbour linen to rectus sheath. The left uterosacral ligament is then plicated with linen, in order to correct the dextrorotation of the uterus. According to the author this helps in maintaining anteversion. The advantages of this operation are: it provides a double support, *static:* bone (sacral promontory), *dynamic:* rectus sheath. It is technically easier to perform and being an open sling, there is no risk of bowel obstruction later on.

In fact, this operation is a combination of Shirodkar’s posterior sling on right side, and Purandare’s sling on the left side.

**Khanna’s Sling**

In this operation the tape is fixed posteriorly to the isthmus with three sutures of # 4.0 black silk. With the help of uterine packing forceps, one end of this tape is drawn laterally across the iliac fossa retroperitoneally between the leaves of the broad ligament. Same step is repeated on the other side. Two ends of the tape are held tight, buried and sutured to the lateral end of the inguinal ligament close to the anterior superior iliac spine. # 3.0 black silk suture is used and care is taken to leave the knots deeper to the inguinal ligament. The author claims that this works like a transverse cervical ligament (Mackenrodt’s ligament) and therefore not only elevates the uterus but also maintains anteversion.

All components need proper identification and adequate correction.

**Causes**

- Missing the diagnosis of enterocele preoperatively.
- Failure to take due precautionary steps to support the vault in surgical technique during hysterectomy.

Higher closure of the posterior peritoneum and suturing both the uterosacral ligaments to each other and then to the vault with vicryl are the two most important steps to prevent vault prolapse.

Prophylactic sacrospinous fixation of the vault at the end of vaginal hysterectomy for prolapse has been practised and advocated.

**Management of Vault Prolapse**

It is essentially surgical, either vaginal or abdominal.

**Vaginal Colpoplasty**

This consists of dissection, plication of enterocele with anterior and posterior vaginal wall repair. Support of the vault with uterosacral is an integral part of the repair. However, the uterosacral are difficult to identify and may not be strong enough to give lasting support.

- It can be difficult due to fibrosis.
- Injury to the rectum and bladder may occur.
- Loss of vaginal coital potential.

**Sacrospinous Colpopexy: Commonly Unilateral**

It involves dissection of pararectal space, identification of sacrospinous ligament and suspension of the vault using # 1 prolene aided by special instruments like Miya hook.

**Advantages**

- Vaginal axis and coital potential are maintained.
- Low recurrence rate.

**Disadvantages**

- It involves many blind steps which may predispose to injury to pudendal nerve and vessels, sacral nerves, rectum and ureter.
- Technically difficult in recurrent vault prolapse because of fibrosis and shortened vagina.

**Abdominal route**

- Sacral colpopexy using prolene or Marlex mesh.
- Soonawala’s sling: as discussed previously.
- Joshi’s unilateral vault-pectineal suspension: posterior culdoplasty is mandatory.
- Endoscopic vault suspension has been reported recently with encouraging results.
**Laparoscopic Surgery for Repair of Pelvic Floor Defect**

One of the primary goals of laparoscopic reconstruction is to reproduce proven abdominal techniques in a minimally invasive way without compromising safety or efficacy. Compromising traditional surgical technique for the sole purpose of accomplishing the repair laparoscopically should be discouraged. A laparoscopic procedure may not be appropriate if there is history of a multiple abdominal surgery or pelvic infection (e.g., ruptured appendicitis, pelvic inflammatory disease) suggesting the presence of adhesion. Transvaginal surgery may be preferred in elderly, obese and other high-risk situations where general anesthesia should be avoided.

The surgical techniques which are employed laparoscopically are:

- Paravaginal repair for cystocele.
- Uterosacral ligament uterine suspension and sacrocervicopexy for management of uterine prolapse.
- Sacrocolpopexy for treatment of vaginal eversion.
- Enterocoele repair.

**Complication:** Vascular and bowel injury are most common complications during access in any laparoscopic procedure. Injury to urinary tract is an additional complication of procedure for repair of pelvic floor defect. Intraoperative cystoscopy should be a routine part of the surgery.

**William-Richardson’s Operation**

Here, a strip of external oblique aponeurosis is dissected free, brought inside the abdominal cavity extraperitoneally and fixed to the lateral fornices of vagina with the linen or silk suture so as to elevate the vault of vagina.

**Posterior Intravaginal Sling Plasty (IVS)**

This minimally invasive transperineal technique developed by Petros aims at restoring the three anatomical levels of vaginal support described by Delaney. It involves the implantation of tension-free polypropylene tape to create an artificial uterosacral neo ligament for the support of vaginal vault prolapse. In short-term follow-up 91% cure rate has been reported.

**Surgical Principles of Suture Materials**

Collagen is central to wound healing and the weaker more elastic type III is laid down first. With maturation, type I replaces type III, but the new tissue is never as strong as original. Fascia will only have regained 15% of its original strength by 14 days and takes 3 months to regain 70%. However, the most common suture material used for vaginal repair is rapidly absorbable such as polyglycolic acid and polyglactin. Hence, first principle, tells surgeons to use a longer acting material. Gynecologists are slow in utilizing the newer synthetic sutures now available. Only delayed absorbable sutures should be used, though more data on suture material in pelvic reconstructive surgery is required.

**THE USE OF PROSTHETICS IN PELVIC RECONSTRUCTIVE SURGERY**

With a reoperation rate of 30% for prolapse surgery attempts are being made to improve the outcome of primary surgery. The introduction of synthetic and biological prosthesis has been proposed to reduce recurrence rate whilst maintaining vaginal capacity and coital function.

There is growing opinion that conventional surgery for prolapse without a graft is like attempting to repair damaged tissue with poor vascular supply, predisposing to surgical failure.

**CLASSIFICATION**

I. Synthetic material

1. Macroporous, nonabsorbable (e.g., Marlex, Prolene): The pore size is more than 75 nm to allow infiltration by macrophage fibroblast, new vessels and collagen fibers. They are mainly used for prolapse surgery. The problem is mesh erosion.

2. Absorbable-polyglactin (vicryl): No complication of mesh erosion; however, long-term results are doubtful.

II. Biological material

1. Autologous materials include rectus fascia, fascia lata.

2. Xenografts may be porcine: New prosthetic systems have been introduced for the management of vaginal prolapse, e.g., (1) posterior intravaginal sling plasty; (2) apogee/perigee.

**Mesh Erosion**

The risk of erosion is one of the factors that have made the use of synthetic prosthesis controversial. The management of erosion depends on amount of mesh exposed, the type of material and associated infections.

Erosion presents with vaginal discharge, bleeding, pain and dyspareunia. Initially topical estrogens (in postmenopausal women) and broad spectrum antibiotics can be tried. Small erosion less than 5 mm may be closed with this management alone. If this fails or if erosion is up to 2 cm in size surgical recovering is required. For erosions more than 2 cm, removal of prosthesis and reapproximation of vaginal tissue is required.

*Every honest surgeon of extensive and long experience will have to admit that he is not entirely and absolutely satisfied with his long-term results of all his operations for prolapse and allied conditions.*

—Richard TeLinde
The corollary could be the surgeon is satisfied but the patient is not, very rarely, the patient is satisfied but the surgeon is not. Together, the first chance is the best.

—Authors

REFERENCES

For the past two decades, Obstetricians and Gynecologists have strongly advocated discontinuing the use of the term “pelvic inflammatory disease” (PID). In the initial conceptualization, PID was used to designate upper female genital tract infection caused primarily by Neisseria gonorrhoeae. Centers for disease control (CDC) definition of PID is “PID comprises a spectrum of inflammatory disorders of the upper female genital tract, including any combination of endometritis, salpingitis, tubo-ovarian abscess and pelvic peritonitis”.

In November 1999, the International Infectious Disease Society for Obstetrics and Gynecology—USA (IIDSOG—USA) formed a 7-member panel to address growing concerns regarding this disease entity. The recommendations put forward by the panel were subsequently reviewed and approved by the society. The society recommended to use the term “upper genital tract infection” (UGTI) instead of “PID”. Recognizing how ingrained the term PID is and the massive education effort required to effect a change, an interim solution was proposed. For the term “PID” to be used the following criteria need to be fulfilled:

Anatomic designation: Disease must involve at least the endometrium and Fallopian tubes (Figs 1A to C).

Causative designation: The term is restricted to disease in which the primary causatives are major sexually transmitted disease microorganisms that share common demographic features and consequences. Organisms taking part via superinfection would be addressed in the recommendation on staging of the disease. For bacteria (such as Streptococcus pneumoniae or Group A Streptococcus) that on rare occasions fulfill the anatomic requisites, the diagnostic designation would be “UGTI due to relevant bacteria”.

Pelvic inflammatory disease is defined as the inflammation of upper genital tract organs typically involving the Fallopian tubes, ovaries and surrounding structures. According to the IIDSOG—USA, the PID is defined as “an inflammatory process of infectious etiology which shares a common epidemiological profile (sexual risk factors), which specifically involves at least the uterine and/or Fallopian tube sites, and which may result in relatively comparable long-term sequel. Disease due to bacteria not meeting these requirements will be termed UGTI and the designation of specific etiology cited”. The society also approved the following staging of acute PID. The necessity of the staging is to implement a rational and appropriate therapeutic regimen.

- **Stage I**: Patients who fulfill the CDC major diagnostic criteria with one or more of its minor criteria but do not have overt peritonitis, as demonstrated by the absence of rebound tenderness, and have not had a prior documented sexually transmitted UGTI.
- **Stage II**: Patients who meet the above criteria but who have peritonitis.
- **Stage III**: Patients with demonstrable tubo-ovarian complex/tubo-ovarian abscesses by either physical or USG examination.
- **Stage IV**: Patients who have ruptured tubo-ovarian abscess.

**CAUSATIVE ORGANISMS**

Sexually transmitted organisms, especially *N. gonorrhoeae* and *Chlamydia trachomatis* are implicated in most cases; however, microorganisms which are usually part of vaginal flora (e.g. anaerobes, Gardnerella vaginalis, Haemophilus influenzae, enteric Gram-negative rods and *S. agalactiae*) can also cause PID. In addition *Mycoplasma hominis* and *Ureaplasma urealyticum* may also be causative organisms.
PREVALENCE

Being the main gynecological cause of acute lower abdominal pain, PID has a prevalence of 9–27 per 1,000 fertile women.  

DIAGNOSTIC CONSIDERATIONS

Due to the wide variation of symptoms and signs, acute PID is difficult to diagnose. Delay in diagnosis and also initiation of treatment leads to inflammatory sequel in the UGT. Goal of diagnosis is to establish guidelines that are sufficiently sensitive to avoid missing mild cases but at the same time sufficiently specific to avoid giving antibiotic therapy to women who are not infected.  

Laparoscopy has been considered the gold standard for PID diagnosis, but its sensitivity varies depending on the stage of illness—being less sensitive in the mild form, where diagnostic criteria are less objective.  

So PID diagnosis is based on certain clinical criteria proposed in 1983 and modified in 1991. Data indicate that positive predictive value of a clinical diagnosis is 65–90% compared with laparoscopic diagnosis. In all settings, however, no single historical, physical or laboratory finding is both sensitive and specific for the diagnosis of acute PID. Combinations of diagnostic findings that improve either sensitivity or specificity do so only at the expense of the other. For example, requiring two or more findings excludes more women who do not have PID but at the same time reduces the number of women with PID who are identified. Because of the difficulty in diagnosis and potential for damage to the reproductive health of women, by even apparently mild

Figs 1A to C: Modes of causation of pelvic inflammatory disease
cases, health care providers should maintain a low threshold for the diagnosis of PID.

**CRITERIA FOR THE DIAGNOSIS OF ACUTE PID (CDC, MAY 2002)**

**Minimum Criteria**
Uterine/adnexal tenderness or cervical motion tenderness.

**More Elaborate Criteria**
These additional criteria may be used to enhance the specificity of minimum criteria.

- **Routine criteria for PID diagnosis:**
  - Oral temperature greater than 38.3°C or 101°F
  - Abnormal cervical or vaginal mucopurulent discharge
  - Raised ESR
  - Increased C-reactive protein
  - Laboratory documentation of cervical infection with *N. gonorrhoeae/C. trachomatis*
  - Presence of WBC in saline preparation of vaginal secretion

- **Specific criteria for PID diagnosis:**
  - Histopathological evidence of endometritis in endometrial biopsy
  - TVS/MRI showing thickened fluid filled tubes with or without free pelvic fluid or tubo-ovarian complex or Doppler studies suggesting pelvic infection (e.g. tubal hyperemia). Laparoscopic abnormalities are consistent with PID.

**RISK FACTORS FOR ACUTE PID**
- Multiple sexual partners
- Past history of sexually transmitted infection (STI)/PID (Westrom and Eschenbach, 1998)
- Vaginal douching (Westrom and Eschenbach, 1998)
- Use of drugs or alcohol, especially with sexual activity
- Lack of consistent condom use
- Lack of contraceptive use (oral contraceptive and DMPA are protective against PID not STI (Speroff, Glass and Kase, 1999)).

**PREVENTION OF PID**
Theoretically, the majority of PID cases can be prevented by screening all women at high risk (based on age or other factors) by using DNA amplification on cervical specimens (in women receiving pelvic examination) and on urine specimens (in women not undergoing pelvic examination). Although bacterial vaginosis (BV) is associated with PID, it is not clear whether treatment of BV can reduce the incidence of PID.

**SEQUELAE OF PID**
- Infertility
- Ectopic pregnancy
- Chronic pelvic pain

**DIFFERENTIAL DIAGNOSIS**
- Ectopic pregnancy
- Appendicitis
- UTI and pyelonephritis
- Constipation
- Gastroenteritis
- Rupture, bleeding or torsion of an ovarian cyst
- Mittelschmerz
- Inflammatory bowel disease (rare)
- Renal colic (rare).

**INVESTIGATIONS**
- Complete blood count
- Urine pregnancy test
- High vaginal swab
- DNA Polymerase Chain Reaction
- Ultrasonography
- Laparoscopy
- Endometrial biopsy

**TREATMENT**
Treatment regimens for PID must provide empiric, broad spectrum coverage of likely pathogens. Several antimicrobial regimens have been effective in achieving clinical and microbiologic cure in RCT and short-term follow-up. However, only a limited number of studies have assessed and compared these regimens with regard to elimination of infection from the endometrium and Fallopian tubes or estimated the incidence of long-term complications (e.g. tubal infertility and ectopic pregnancy) after antimicrobial regimens. Need to eradicate anaerobes from women who have PID has not been determined definitely. Anaerobic bacteria have been isolated from UGT of women with PID and in vitro studies have revealed that some anaerobes (e.g. *Bacteroides fragilis*) can cause tubal and epithelial destruction. Until treatment regimens that do not adequately cover these microbes have demonstrated to prevent long-term sequel as successfully as the regimens that are effective against these microbes, the use of regimens with antianaerobic activity should be considered. The physician should take into account the cost, availability, acceptance and susceptibility of the medicine while selecting a treatment regimen.
TREATMENT REGIMENS
(RCOG GUIDELINES 32, MAY 2003)

Outpatient Treatment (Grade B Recommendation)

Oral ofloxacin 400 mg bid + oral metronidazole 400 mg bid × 14 days
OR
Intramuscular (IM) ceftriaxone 250 mg stat or IM cefoxitin 2 g stat with oral probenecid 1 g, followed by oral doxycycline 100 mg bid + oral metronidazole 400 mg bid × 14 days.

In-Patient Treatment

Criteria for Hospitalization (CDC 2002)

• Surgical emergency cannot be ruled out
• Pregnancy
• No clinical response to oral antibiotic therapy
• Inability to follow or tolerate an outpatient oral regimen
• Severe illness, nausea, vomiting or high fever
• Tubo-ovarian abscess.

Inpatient therapy is based on IV regimens which should be continued until 24 hours after clinical improvement and followed thereafter by oral therapy.

Recommended Parenteral Regimens (COG May 2003) (Grade B Recommendation)

IV cefoxitin 2 g tid + IV doxycycline 100 mg bid (oral doxycycline may be used if tolerated; doxycycline infusion in painful), followed by oral doxycycline 100 mg bid + oral metronidazole 400 mg bid for a total of 14 days.
OR
IV clindamycin 900 mg tid + IV gentamicin 2 mg/kg loading dose followed by 1.5 mg/kg tid (a single daily dose of 7mg/kg may be substituted), followed by either oral clindamycin 450 mg qd to complete 14 days oral doxycycline 100 mg bid + oral metronidazole 400 mg bid to complete 14 days.
OR
IV ofloxacin 400 mg bid + IV metronidazole 500 mg tid for 14 days.

If parenteral gentamicin is used, serum drug level and renal function should be monitored. Evidence of the efficacy of antibiotic therapy in preventing the long-term complications of PID is currently limited.

TREATMENT IN PREGNANCY
(RCOG, MAY 2003)

Pelvic inflammatory disease in pregnancy is extremely rare condition except in septic abortion. Treatment will depend upon organisms isolated. Drugs known to be toxic in pregnancy, e.g. tetracycline, should be avoided.

TREATMENT IN YOUNG WOMEN
(RCOG, MAY 2003)

Based on data on animal studies, it is said that ofloxacin should be avoided while bone development is still occurring. No problems have been reported in human subjects and the British National Formulary currently recommends ofloxacin in children where other options are limited. Doxycycline can safely be used in children greater than 12 years of age.

TREATMENT IN A WOMAN WITH AN INTRAUTERINE DEVICE

Grade B recommendation, RCOG 2003

An intrauterine device (IUD) may be kept in site in mild PID, but should be removed in severe disease. IUD increases the risk of development of PID only in the first few weeks after insertion.¹⁵

SURGICAL TREATMENT (GRADE B RECOMMENDATION RCOG 2003)

Surgical treatment is considered in severe cases or where there is clear evidence of a pelvic abscess. Help of laparoscopy or laparotomy may be taken for adhesiolysis or drainage of pelvic abscess. USG guided aspiration of pelvic abscess is less invasive and equally effective.

MANAGEMENT OF SEX PARTNERS

Male sex partners of women with PID caused by N. gonorrhoeae or C. trachomatis are often asymptomatic; so they should be examined and treated if they had sexual contact with the woman during the 60 days preceding the woman’s onset of symptoms. Sex partner should be treated empirically with regimens effective against both of these organisms, regardless of the etiology of PID or pathogens isolated from the infected women. Patients should be advised to avoid intercourse until they and their partners have completed the treatment schedule.

PID IN WOMAN WITH HIV

Contrary to the previous belief that HIV infected women get more severe PID, recent studies show that there may be minor differences and they respond equally well as of the women who are not infected with HIV.¹⁶

PID IN POSTMENOPAUSAL WOMEN

Pelvic inflammatory disease is a rare entity in this age group. Extragenital pathology in addition to genital tract malignancy
must be considered in these patients. Direct extension of infectious processes from adjacent intra-abdominal viscera is more likely to be associated with PID in older women. Forgotten IUD may be associated with a serious genital tract infection. Postmenopausal women are less likely to harbor a sexually transmitted organism than the premenopausal counterpart. In most reported cases the organisms frequently encountered were *Escherichia coli* (76%) and *Klebsiella* (43%). Other isolated bacteria included *Pseudomonas* (14%) and *Staphylococcus aureus* (< 5%). Broad spectrum antimicrobial therapy should be started and appropriate imaging studies obtained. Surgical intervention should be considered if there is no clinical improvement within 48 hours. Aggressive treatment in these seriously ill patients may lead to decrease in mortality and morbidity in this disease.

**FOLLOW-UP**

Patients should show definite clinical improvement within 3 days of starting of therapy. If it does not happen, she should be hospitalized and re-evaluated with the help of laparoscopy if needed (for alternative diagnosis) and parenteral therapy must be started. Some physicians advocate rescreening for *C. trachomatis* and *N. gonorrhoeae* 4–6 weeks after therapy is completed in women with documented infection by these pathogens (August 4, 2006/55 [RR 11]:1-94). All women diagnosed as acute PID should be offered HIV testing.

**REFERENCES**

Ectopic Pregnancy: Current Concepts

INTRODUCTION

Ectopic pregnancy (EP) is an enigma, wrapped in mystery, presents in a bewildering variety of anatomical, physiological and clinical expressions. Natural course is equally unpredictable. While the medical fraternity grapples with unpredictability of the trophoblastic behavior, EP continues to be an important cause of maternal deaths. Just as the hyperactive trophoblasts rapidly invade the delicate tubal wall causing rupture and massive hemorrhage, the hypoactive ones remain treacherously dormant with a dangerous potential for fatal flare-ups. Mercifully, some of them resolve spontaneously, without bothering the clinician. EP thus is extremely difficult to diagnose early before tubal rupture.

Gupta and his colleagues (1992) observed that 60% had tubal rupture and only 4% had intact tubal gestation during surgery. Less than 50% conceived again and 12–18% reported with recurrent EP (Stabile et al. 1990). The incidence of EP is rising alarmingly “almost reaching epidemic proportions” (Makinen JI, 1987); a 4.5% increase has been observed in USA alone over the 70s (Ory, 1991). However, the case fatality rate decreased from 35.5 deaths per 10,000 cases in 1970 to 2.6 per 10,000 cases in 1992 (Sepilian V).

ETIOPATHOLOGY

Anything that hampers the migration of embryo to the endometrial cavity predisposes to ectopic gestation. Common conditions that increase the risk of EP include the following:

- **Pelvic inflammatory disease (PID):** Previous tube infections (salpingitis), risk EP 4-fold, the most common organisms are *Chlamydia trachomatis* followed by *Neisseria gonorrhoeae*. The successive attacks of PID increase the likelihood of another EP by 7–13 folds.
- **Prior history of tubal pregnancy** treated conservatively; there is a roughly 10-fold increase in tubal pregnancy.
- **History of tubal surgery and conception after tubal ligation:** 35–50% of patients who conceive after a tubal ligation are reported to experience EP.
- **Infertile subjects undergoing ovulation induction** with different ovulogens has been linked with a 4-fold increase in risk of EP with increased number of heterotopic pregnancy.
- **Salpingitis isthmica nodosum:** Microscopic presence of tubal epithelium in myosalpinx like small diverticula protrudes through tubes predispose to EP.
- **Other causative factors:** Intrauterine contraceptive device (IUCD) (3–4% risk), dermal-epidermal separation (DES) exposure, rupture appendix, etc.

CLINICAL PRESENTATIONS

Ectopic pregnancy has three distinct clinical groups:

1. **Acute:** Nearly one-fifth of all EPs require urgent intervention.
2. **Asymptomatic high-risk:** Less than one-fifth constitute this group; with history of impaired tubal function, previous tubal surgery, previous EP and infertility cases undergoing ovarian hyperstimulation in assisted reproductive technology (ART), etc. As they become biochemically pregnant, they are screened, followed up and managed very early before symptoms develop (Ankum et al. 1996). Refer to Table 1 for important landmark.
3. **Subacute cases:** Nearly 60–70% constitutes this major group. They present with or without amenorrhea, irregular vaginal bleeding and abdominal pain. For the rest of our discussion, we will focus our attention on the last two groups of EPs, which are most difficult to diagnose early.
CURRENT DIAGNOSTIC APPROACH

The focus now is on an awareness to detect not only EPs early, but to follow them in a controlled way, monitoring blood concentration of β-hCG under sonographic guidance. The objective is to treat the patients with minimal invasive surgery or without the aid of laparoscopy using medicine and to send them back to their normal day-to-day life at the earliest directed to restore tubal function. Application of serial quantitative β-hCG concentration correlating with the first sonographic appearance of intrauterine pregnancy (IUP) (discriminating zone) further helped early detection. The potential diagnostic dilemma was further eased with the use of high-resolution TVS. To understand this intricate pathophysiology we focus our attention what happens in normal pregnancy.

Serum β-hCG Level in Normal Pregnancy

Human chorionic gonadotropin is a glycoprotein secreted by the trophoblasts in the body; contains alpha and beta subunit. The serum testing for beta subunits is more accurate. As the pregnancy grows, exponential rise in hCG level takes place, becomes double every 60 hours (roughly 2 days) and attains the peak by eight menstrual week followed by slow declines. A strong correlation exists between the size of gestational sac (GS), hCG level and gestational period before sonographic visualization of embryo (Daya S 1987, Nyberg et al. 1985).

Discriminatory hCG Level and Sonographic Correlation (Table 1)

The following thumb rule exists regarding the identification of important landmarks:
- Biochemical pregnancy is established almost immediately after nidation at 5 mIU/mL of β-hCG level on 22nd–23rd postmenstrual day of a regular 28 days cycle.
- On day 26–28, urinary pregnancy test becomes positive (detection limit at 25–50 mIU/mL).
- A tiny 2–3 mm GS can be discerned in a thick shining echogenic endometrium by TV probe on day 32–33 at 1,000–1,500 mIU/mL of β-hCG level (discriminatory level).

Kadar and his associates (1981) enunciated the vital principle that whatever ultrasonography (USG) equipment is used, there is a serum β-hCG value above which GS is always visible, a level below which GS is never detectable; an uncertain zone exists in between. This concept of “discriminatory level” is a path-breaking third epoch making step, forming the basis for a host of diagnostic algorithms.

A paired serum β-hCG samples taken at least 48 hours apart may indicate fall, flattening or a rising trend of hormone concentration. If the increase is less than 66% over 48 hours (equivalent to doubling time of 2.7 days), EP is indicated and laparoscopy is recommended for confirmation (Kadar et al. 1988).
What Happens in Ectopic Pregnancy?

Ectopic pregnancy (EP), like a failed IUP causes impaired β-hCG production in comparison to normal pregnancy, displaying longer doubling time which produces a slow rise or attains a low plateau or slow decline as shown in Figure 1. Serial β-hCG measurement therefore, is mandatory than a single value and offers four types of pictures rendering different prognostic values.

Prognostic Evaluation of Serial β-hCG Assay

Serial β-hCG assay offer four different possibilities:
1. β-hCG above discriminatory zone with empty uterus always suggests EP. On the other hand, the presence of intrauterine GS virtually excludes the possibility of extrauterine pregnancy by extension. Heterotopic pregnancy is extremely rare in spontaneous conception (1:30,000) (DeVoe et al. 1948). We should remember that EPs are more (1 in 10,000 to 1 in 15,000 pregnancies) associated with concomitant IUPs in subjects undergoing artificial reproductive techniques (Richards et al. 1982, Gambardella et al. 1989).
2. β-hCG below the discriminatory zone limits the diagnostic capability of TVS since intrauterine GS won’t be evident. They are low risk patients but can enter high-risk zone with rising hormone level, thus they demand serial scans correlating with serum hormone level.
3. Subnormal rise indicates degenerating trophoblasts likely to resolve spontaneously.
4. Rapidly growing β-hCG level signals danger and suggests functionally active trophoblasts likely to grow further and rupture vide Figure 1.

Pelvic Scan by Transvaginal Sonography and Transabdominal Sonography (Figs 2 to 7)

The accuracy of high resolution-high frequency TV probes over TAS in the early diagnosis of EP has been well documented (Nyberg et al. 1987, Rempen A 1988, Timor et al. 1989, Das et al. 1993).

Transvaginal sonography offers two types of findings:
1. Specific findings: Discern GS, cardiac flicker, yolk sac and other embryonic structures displaying tubal outline.
2. Nonspecific: Like empty uterus, complex adnexal mass and fluid in postoperative day (POD). A high resolution TV probe with its close proximity to the target organ offers an amazingly sharp clear picture not only to characterize the indirect findings better, but displays the tubal outline, identifies the direct findings in about 87% cases (Rottem et al. 1991; Das et al. 1995, Das et al. 2000).
Fig. 2: Day 1: Empty uterus with discrete extrauterine gestational sac display tubal outline.

Fig. 3: Day 1: Note corpus luteum with distinct gestational sac containing yolk sac.

Fig. 4: Day 1: Extrauterine gestational sac displaying increased color mapping and typical low impedance high flow trophoblastic blood flow RI = 0.466.

Fig. 5: Day 1: Left ovary shows corpus luteum blood flow separate from gestational sac.

Fig. 6: Scan on 3rd day after two doses of intramuscular methotrexate 50 mg.

Fig. 7: Day 7: Uterine cavity displaying shedding off endometrium and blood and wrinkled gestational sac.
A living extrauterine embryo is always associated with higher level of hCG. Less specific finding like adnexal mass or intraperitoneal bleeding, however, may occur at any hormone level. The mass is often due to edema, blood clots, necrotic tissue, rather than trophoblasts. Cacciatore and coworkers (1990) diagnosed EP with adnexal mass combined with a serum $\beta$-hCG level at 1,000 mIU/mL (IRP) or above with a sensitivity of 97%, specificity of 99%. It will be pertinent to note here that with the growing refinement of technology, TVS can now identify EPs about 1 week earlier at a much lower hormone level vis-à-vis TAS at 6,500 mIU/mL (Kadar et al. 1981).

**Transvaginal Color Doppler Sonography**

The recent introduction of transvaginal color Doppler sonography (TVCD) added yet another tool to display the increased vascular areas randomly dispersed in the adnexal complex mass and assess the trophoblastic activities, which correlate well with the $\beta$-hCG titer (Kurjak et al. 1994). The test prognosticates trophoblastic invasiveness and can differentiate an active trophoblast from nonviable IUP and pseudogestational sac (Das et al. 2001).

**Uterine Curettage**

Failed intrauterine or molar pregnancy may offer indeterminate sonography findings (doubtful nonviable IUPs).

Chorionic villi can be detected simply by floating uterine curettage in normal saline. A simple bedside “saline test” offers valuable information. The left out placental tissue obtained by suction aspiration floats whereas endometrial tissue sinks in the normal saline. Histopathology report after a couple of days confirms the saline test (Das et al. 1995).

### CURRENT THERAPEUTIC APPROACH

The therapeutic approach over the last decade has gone through four distinct phases: Radical salpingectomy® Conservative tubal surgery® Expectant management® Medical treatment (Table 2).

**Surgical Treatment**

Once diagnosed early, salpingostomy or microsurgery through laparoscopy or laparotomy are common to salvage the tube. Laparoscopic approach to surgical management has been developed and described with increasing frequency and improved outcome. Laparotomy is indicated in hemodynamic unstable condition due to massive hemorrhage or extensive intra-abdominal adhesion. After conservative surgery, however, the risk of persistent trophoblastic disease remains in about 5–10% cases (Lundorff et al. 1991) (Table 3).

The author (BK Mitra and KK Das) has observed that a prior single dose intramuscular methotrexate (IM MTX) carried out

<table>
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<th>Table 2: Diagnostic and therapeutic tips</th>
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<td><strong>Steps</strong></td>
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| 1. | If semi-quantitative urinary pregnancy test is positive with a lower detection limit at 25 mIU/mL (Pregnancy test, early icon, velocity, etc.) | Pregnancy located unequivocally within the uterus | • Practically excludes EP  
• Still look for the adnexal region to exclude concomitant EP (1:30,000) |
| | | Tubal gestational sac displays embryonic structures like cardiac flicker, yolk sac, etc. | • Unequivocally suggest EP → high risk and is likely to rupture  
• May be false positive pregnancy test  
• May be too early to discern the pregnancy be it IUP or ectopic |
| | Serum $\beta$-hCG below discriminatory level (<1,000–1,500 mIU/mL) | Pelvis entirely normal and no visible adnexal mass | Paired sampling (48 hours apart) to note the $\beta$-hCG trend and prognosis |
| 3. | Serum $\beta$-hCG above discriminatory level (>1,000–1,500 mIU/mL) | Complex adnexal mass with or without fluid in the POD/no IU gestational sac and poorly defined | Needs serial scan correlated with hCG titer medical treatment or laparoscopy/ laparotomy |
| 4. | If serum $\beta$-hCG level falling and → | Intrauterine findings nondiagnostic | Failed IUP?  
Pseudogestational sac? Endometrial aspiration → bedside saline test → HP examination to identify placental tissue |
| 5. | If post D and C shows rising serum $\beta$-hCG and → | Intrauterine findings nondiagnostic | • Indicates active EP  
• Medical/surgical treatment suggested |
Table 3: Four golden rules for nonlaparoscopic presumptive diagnosis of EP

1. Demonstrable tubal GS with embryonic structures
2. Empty uterus above discriminatory zone (1000–1500 mIU/mL IRP)
3. Uterine curettage and saline test in indeterminate TVS → no chorionic villi
4. hCG titer continues to rise after D and C

2–5 days before laparoscopic surgery, makes the procedure easier to perform, induces less bleeding and oozing from the gestational bed. This procedure practically eliminates the risk of persistent EP. The fertility outcome following conservative surgery (78.9%) compares well with that of medical treatment (80.7%) (Debby et al. 2000) and corroborates our experience.

Surgically-administered Medical Treatment

Several chemotherapeutic agents have been used directly in EP using endoscopes, radiological or echo-guided techniques to arrest tubal damage without the risk of systemic side effects. Commonly used drugs for salpingocentesis are methotrexate, potassium chloride, prostaglandins, hyperosmolar glucose or mifepristone. The patient must be hemodynamically stable, tubal diameter should be less than 4 cm, and initial hCG level below 15,000 mIU/mL (Bhatt and Taylor, 1997).

Expectant Management

About 20–30% of tubal pregnancies, resolve spontaneously; if these subjects are identified expectant management become the treatment of choice (Ylostalo et al. 1993).

Criteria for expectant management:
- Falling level of serum hCG at 2 days interval,
- No sign of IUP,
- A diameter of EP less than 4 cm, and
- No signs of rupture or active bleeding by TVS.

Patient selected for expectant management must be closely monitored until spontaneous resolution is complete. Tubal pregnancies have been known to rupture even when the serum β-hCG levels are low (Tulandi et al. 1991). The slow resolution, prolonged follow-up and the need for frequent monitoring, coupled with uncertainty, limits the usefulness and cost effectiveness of this technique (Das et al. 1997).

Medical Management

Methotrexate, an anti-folic acid metabolite, has been successfully used in the treatment of gestational trophoblastic diseases for last four decades. Tanaka and his colleagues in 1982 first used this agent systemically in the treatment of interstitial pregnancy. Since then, MTX has been the most commonly used drug administered intravenously, intramuscularly or orally employing different regimens with folinic acid rescue claiming a success rate of around 60–70% (Goldenberg et al. 1993) (Figs 8 to 11).
Single dose MTX IM (1 mg/kg of body weight) proves to be quite useful in majority of selected cases in ambulatory patients (Stovell et al. 1993). Medical treatment with MTX has many advantages—is effective, less costly, simple, and preferable to surgery and thus more acceptable to the patient (Das et al. 2001). However, key to the success of expectant or medical treatment is our ability to diagnose EP presumptively without the aid of laparoscopy. Once laparoscopy is required to confirm diagnosis, medical treatment becomes less attractive (Das et al. 1997).

The above guidelines depend heavily on the availability of two important resources:
1. Presence of a reliable hormone laboratory
2. The service of an accomplished endovaginal sonographer.

For a developing country with limited resources, a semiquantitative pregnancy kit, close monitoring with pelvic scan and an increased awareness can detect more number of EPs early which may go a long way to salvage tubal potentiality. This is particularly important until in vitro fertilization is more available and affordable with increased success rates (vide a case report given below).

The clinician may adopt variable algorithms. If an early hormone report is not available, a paired sample 5–7 days apart may be helpful, provided the patient’s condition remains stable. The first author (KK Das) observed how amazingly the symptoms settle down within 2–3 days after single dose of MTX therapy in majority of the cases. Post MTX abdominal cramps on day 2–3 is a common finding but alone without hemoperitoneum is not an indication for surgical intervention. However, very rarely one may find the POD fluid (hemoperitoneum) continues to increase with deteriorating general condition, surgery should be performed. It is needless to emphasize that the clinician must motivate the patient, offer proper counseling so that she understands the possible risks involved. Clinician must obtain her informed consent and ensure access to 24 hours emergency treatment.

Serum Progesterone

To avoid the hassles of prolonged TVS and serial hCG measurement, assessment of circulatory progesterone is a second choice to differentiate normal from abnormal pregnancy, takes only 2–3 hours. (Hahlin et al. 1991, Buck et al. 1988, Stovall et al. 1989). A single value of 25 ng/mL or more exclude EP in 95.5% of clinically suspected cases. A concentration of 5 ng/mL is almost 100% correlated with abnormal or nonviable pregnancy. However, there is no cut off value between normal IUP and EP. Concentrations between 10 ng/mL and 20 ng/mL are common and have little differential value.

WHAT FUTURE HOLDS?

- Effective vaccination against *Chlamydia trachomatis*. Once clinically available, it should have a dramatic impact on the frequency of EP and overall health of the female reproductive system (Sepilian V).
- “No other pelvic condition gives rise to more diagnostic errors” as such we are desperately in search of a “specific ectopic markers” (Stabile et al. 1990).
- In another area, attempts are being made to relocate successfully an EP to the uterine cavity: is it a dream or reality? (Wallace CJ 1917, Shettles LB 1990, Pearce et al. 1994, Grudzinskazs JG, et al. 1994).

CONCLUSION

In the recent years, significant improvement has taken place in the understanding of pathophysiology and management of EP. Early diagnosis is possible and we are now embarking in a new era, which promises to remove most EPs from the hands of gynecological surgeons. If medical treatment proves successful in ambulatory patients, laparoscopic diagnosis and surgical treatment (except in rare instances) will become the thing of the past.

ACKNOWLEDGMENTS

We duly acknowledge the help from Dr KC Samanta and Anjan without which this manuscript would not have been possible.

CASE STUDY

Mrs Salimunnisha, 26 years, (Reg. No. 1775) P0 + 1, referred to us on June 15, 2000 for possible conservative treatment suspecting a repeat “ectopic pregnancy”. An infertile subject she was provisionally diagnosed without laparoscopic aid. Earlier she had open salpingo-ophrectomy for tubal rupture and life-threatening hemorrhage 1 year back. The serial images below display how she was managed successfully with two doses of MTX IM and monitoring serum $\beta$-hCG concentration under sonographic guidance (Figs 2 to 11).
BIBLIOGRAPHY

INTRODUCTION

Endometriosis is a chronic, recurring disease, often associated with infertility. It is defined as the presence of endometrial-like tissue outside the uterus, which induces a chronic, inflammatory reaction. It can affect women at any stage in their lives, but is most common in the reproductive years from all ethnic and social groups. Despite high incidence figures, the causes of endometriosis are still open to debate. In addition to uncertainty over pathogenesis of the disease, endometriosis is often misdiagnosed leading to delays in treatment, sometimes for several years. This delay may result in disease progression. The associated symptoms in endometriosis can impact on the physical, mental and social well-being of the woman. However, some women may have no symptoms at all.

INCIDENCE

True prevalence of endometriosis is not known owing to a lack of well-defined epidemiologic studies. It is estimated to affect 71% of women with pelvic pain and 84% of women who have infertility as well as pelvic pain. In asymptomatic women, histologically confirmed endometriosis has been reported to occur in 45–50% of patients at the time of laparoscopy for investigation of infertility.

PATHOGENESIS

A complete understanding of endometriosis has defied researchers, but there are various theories regarding its etiology. The theories have been proposed in an attempt to explain the pathophysiology of endometriosis. Unfortunately, no single theory adequately explains the pathogenesis of this disease.

Transplant Theory

The most frequently cited mechanisms in the development of endometriosis are transplantation of exfoliated endometrial cells and coelomic metaplasia. The transplant theory hypothesizes that, during menstruation, endometrium is deposited in ectopic locations via retrograde menstruation or dissemination through the lymphatic or vascular systems. Multiple studies have demonstrated that endometrial cells within the fallopian tube and peritoneal cavity are viable and capable of implantation. In addition, animal and human studies have confirmed that placement of endometrial tissue into ectopic sites results in histologic transformation into endometriotic lesions; however, transplantation alone does not explain why endometriosis develops in only 5–10% of women when efflux of menstrual fluid has been documented to occur in 76–90%.

Coelomic Metaplasia

The coelomic metaplasia theory cites transformation of the coelomic epithelial lining of the peritoneal cavity, which is composed of differentiated cells capable of dedifferentiating into endometrial-type tissue. Research has not supported that peritoneal cells can undergo transformation, and most metaplastic processes in humans increase with advancing age, whereas endometriosis is usually found in women of reproductive age. The mechanism of coelomic metaplasia may explain the occurrence of endometriosis in women with Müllerian agenesis, postmenopausal women, and women who have undergone hysterectomy.

Genetic Predisposition

The association between genetic predisposition and endometriosis has been based on retrospective analysis of
family histories indicating a polygenic and multifactorial inheritance pattern. In probands from affected families, the onset of endometriosis occurs earlier in life, with more severe disease at the time of diagnosis. First-degree female relatives have a 6–9% occurrence rate versus a 1% rate for nonrelated controls.

**Immunology**

Investigators have also found alterations in cell-mediated and humoral immunity in women with endometriosis. Affected patients have been shown to exhibit increased macrophage activation, decreased T-cell and natural killer cell function, and increased levels of autoantibodies. The significance of autoantibodies and dysfunction of the immune system are controversial and unclear.

**Environmental Toxins**

An increasing area of interest is the role of environmental toxins, such as dioxin, in inducing endometriosis. Human studies have confirmed elevated dioxin levels in patients with endometriosis versus control patients. Molecular aberrations in steroidogenic enzyme function have been implicated in the development of endometriosis. Endometrial tissue from women with endometriosis expresses aromatase P450, whereas endometrium from women without identifiable endometriosis does not. The presence of aromatase within endometriosis results in higher local production of estrogen necessary to maintain lesions.

Rather than one theory explaining the etiology of endometriosis, it is likely that a multitude of factors contribute to its formation. Retrograde menstruation and transplantation of endometrium into ectopic sites may be necessary in activating metaplastic transformation of the coelomic epithelium. In patients with immune dysfunction, genetic predisposition, or prior environmental toxin exposure, clearance of endometrial tissue may be impaired, allowing implantation and growth of lesions. On transformation into endometriotic lesions, aromatase expression may allow continued growth and spread of endometriosis.

Endometriosis is an estrogen-dependent disease; therefore, factors that reduce estrogen levels (e.g. menstrual disorders, decreased body fat content and smoking) are associated with a reduced risk for developing the condition.

**CLINICAL PRESENTATION**

Endometriosis is associated with a wide variety of clinical symptoms and signs, although many patients are asymptomatic. Symptoms of endometriosis are often confused with conditions such as pelvic inflammatory disease, irritable bowel syndrome or even psychosomatic problems.

The classic triad of dysmenorrhea, dyspareunia and infertility has been described as a characteristic of the disease.
formation causing marked distortion of pelvic anatomy. There is usually no correlation.

**DIAGNOSIS**

The classic diagnosis of endometriosis is made by identifying endometrial glands and stroma in extraterine locations or within the musculature of the uterus, defined as adenomyosis. The pelvic structures most often affected by endometriosis in decreasing order of frequency are the ovaries, the anterior and posterior cul-de-sac, the posterior surface of the broad ligament, the uterosacral ligaments, the fallopian tubes, the sigmoid colon, the appendix and the round ligaments. The cervix, vagina and bladder are less frequently affected. The clinical features of endometriosis are shown in Table 1.

Endometriosis is asymptomatic in many women. Pelvic pain caused by endometriosis falls into three categories:
1. Secondary dysmenorrhea, with pain commencing before the onset of the menstrual cycle
2. Deep dyspareunia that is exaggerated during menstruation
3. Sacral backache, worse during menstruation.

The remaining symptoms classically described in endometriosis, such as pelvic pain and painful defecation were similarly distributed in infertile women with and without endometriosis, whereas dyspareunia even showed a trend to a protective effect. This fact could be the result of an increased prevalence of the aforementioned symptoms in infertile women or to a different behavior of endometriosis associated with infertility in regard to the other varieties of endometriosis. The presence or absence of dysmenorrhea or of the remaining clinical symptoms in an infertile woman is of no value to suspect or discount endometriosis.

A number of the findings classically described as suggestive of endometriosis are as follows:
- Painful cervical mobilization
- Uterine lateralization and limitation of uterine mobility
- Painful ovarian palpation
- Adnexitis.

But these clinical features are also present in women with and without endometriosis. There is a higher frequency of uterine retroversion and nodularity in the pouch of Douglas in endometriosis cases. The presence of a fixed uterus in the pelvic examination is often seen in endometriosis. Uterosacral nodularity and uterosacral tenderness are the only findings that are significantly increased in endometriosis cases. Their frequencies are much higher than in infertile women without endometriosis (odds ratio > 11.7 and odds ratio = 4.6). The association between severity of endometriosis and severity of symptoms is controversial. Many of the differences can be attributed to the different methodologies and populations studied.

The predictive value of any one symptom or set of symptoms is uncertain, as a significant proportion of affected women are asymptomatic. Establishing the diagnosis of endometriosis on the basis of symptoms alone can be difficult because the presentation is so variable.

Definitive diagnosis of endometriosis depends on visual inspection of the pelvis at laparoscopy (Figs 2A and B). It is good to use an instrument such as a grasper, via a secondary port, to mobilize the pelvic organs and to palpate lesions, which can help determine their nodularity. It is also important to document in detail the type, location and extent of all lesions and adhesions. It is unnecessary to obtain a positive histological diagnosis, visual inspection is usually adequate.

When compared with laparoscopy, transvaginal ultrasound has limited value in diagnosing peritoneal endometriosis but it is a useful tool both to make and to exclude the diagnosis of an ovarian endometrioma.

**MANAGEMENT (FLOW CHART 1)**

The treatment of women with endometriosis can be a challenge. Therapeutic strategies must be tailored to the individual symptoms, age, and desire for fertility. Endometriosis can be managed effectively with medical therapy, surgery or a combination of both. Therapy is directed toward the severity of symptoms, the extent of disease, the location of disease and desire for fertility.
Endometriosis

Flow chart 1: Management of endometriosis

MEDICAL MANAGEMENT (TABLE 2)

The observation that endometriosis is rarely seen in hypoestrogenic postmenopausal women, led to the concept of treating the disease by inducing a pseudomenopausal state. Treatment is directed toward the estrogen responsiveness of endometriosis, thus the goal of therapy is to induce either a pseudopregnancy (oral contraceptives, progestin) or a menopausal state [gonadotropin-releasing hormone (GnRH) analog] to inhibit or delay progression.
The role of medical therapy in the treatment of women with endometriosis has changed dramatically. In the 1980s, the development of GnRH agonist created a breakthrough in the management of endometriosis.

These approaches are supported by spontaneous regression of endometriosis and associated symptoms during menopause in most patients secondary to a decrease in estrogen production. Medical therapy continues to be based on endocrine treatment such as oral contraceptives, progestins, danazol and GnRH agonists.

Unfortunately, recurrence rates are high after discontinuation of therapy. Recent clinical research on GnRH analogs plus add-back therapy has produced favorable results. Long-term treatment of patients using this approach has successfully reduced pain while minimizing symptoms of hypoestrogenism and adverse metabolic effects such as loss of bone mineral density (BMD). Currently, GnRH analogs given with add-back therapy seems to be the most effective long-term approach to the treatment of symptomatic endometriosis. In the future, other modalities, such as medicated vaginal rings, inhibitors of steroidogenic enzymes and GnRH antagonists, will be the most likely options.

**Oral Contraceptives**

The initial management of the patient suspected of having endometriosis based on history and physical examination who does not currently desire fertility may be treated with oral contraceptives. But endometriosis can remain active despite oral contraceptives, and some patients will continue to complain of symptoms. If the patient fails to experience relief of symptoms within 3 months of initiating oral contraceptive therapy, a more aggressive medical modality is warranted. No evidence supports switching from one oral contraceptive formulation to another in an attempt to improve response.

**Progestins**

Progestins are frequently used in the management of endometriosis. Progestational agents inhibit endometriotic tissue growth by causing an initial decidualization and eventual pseudonecrosis or atrophy. Progestins oppose the growth-promoting effects of estrogen by altering clearance of the nuclear estrogen receptor and inducing 17 beta-hydroxysteroid dehydrogenase, which converts estradiol to estrone. At high doses, progestins will also inhibit gonadotropin secretion and ovarian hormone production, inducing an amenorrheic state.

Associated side effects include weight gain, fluid retention, headaches and depression. All of these effects resolve after discontinuation of therapy. Oral administration of medroxyprogesterone acetate, 50 mg daily, improves symptoms in 80% of patients with moderate to severe endometriosis. Unfortunately, recurrence rates have been reported to reach 42% after 2 years of therapy. As an alternative to medroxyprogesterone acetate, one may choose to administer norethindrone acetate, 5 mg daily for 6 months. A similar response can also be achieved with 40 mg of megestrol acetate daily. Parenteral medroxyprogesterone acetate depot may also be given at a dose of 100 mg every 2 weeks for 3 months followed by 200 mg monthly for 3–6 months.

**Danazol**

Danazol, a synthetic derivative of 17 alpha-ethinyltestosterone, was introduced into clinical practice in 1971. Danazol directly inhibits steroidogenic enzymes, endometriotic implant growth and pituitary gonadotropin secretion, and interacts with androgen and progesterone receptors. Sex hormone-binding globulin (SHBG) levels are also reduced, resulting in elevated free testosterone levels, which promote androgenic side effects such as acne and hirsutism. Danazol produces a hypoestrogenic-hyperandrogenic environment that is unfavorable for the growth of endometriotic lesions.

Other side effects of danazol include weight gain, hot flushes, mood changes, depression, muscle cramps, decreased breast size, decreased high-density lipoprotein (HDL) levels and increased liver enzymes.

More than 80% of patients experience relief or improvement of pain symptoms within 2 months of starting treatment with danazol. Danazol has been shown to reduce pain better than placebo for up to 6 months after discontinuation of therapy. Unfortunately, the recurrence of symptoms within 4–12 months of discontinuation of therapy approaches 50% in most studies.

Danazol is given orally in divided doses ranging from 400 mg to 800 mg daily for 6 months. A 6-year prospective study evaluating the effectiveness of danazol at 400 mg and 800 mg found no difference in side effects between the two doses, and gross resolution of the disease was similar.

A recent study investigated the use of a vaginal danazol ring for the treatment of endometriosis. Eighty-eight percent of participants with deep endometriosis had a decrease in dysmenorrhea, and 92% had a decrease in tenderness of the cul-de-sac within 3 months. Preliminary data suggest that danazol rings are effective in treating severe endometriosis while avoiding androgenic side effects.

Trials evaluating the effect of danazol on fertility in comparison with expectant management have shown no increase in pregnancy rates. Concerns have been expressed...
regarding the androgenic action of danazol and potential harm to a developing female fetus. Despite anovulation owing to decreased gonadotropin secretion, patients are encouraged to use barrier contraception.

**Gonadotropin-releasing Hormone Agonists**

The most predictable form of medical therapy that inhibits estrogen production by the ovaries is GnRH agonist. Continued exposure to GnRH leads to a hypogonadal state with decreased release and suppression of estradiol from the ovaries. GnRH agonists bind to receptors in the pituitary gland, initially resulting in a release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), followed by modulation, a decrease in gonadotropin secretion, and, eventually, cessation of estrogen production by the ovaries. In a hypoestrogenic environment, endometriosis will undergo quiescence and atrophy with improvement in symptoms.

Gonadotropin-releasing hormone may also be used as a diagnostic test to determine whether pelvic pain is estrogen-related, in patients who continue to suffer pain when laparoscopy is unrevealing. The decrease in mean serum estradiol concentration was also more significant with GnRH analog than with danazol.27

Gonadotropin-releasing hormone therapy is also associated with a recurrence of symptoms, as is true for other medical modalities. Dysmenorrhea returns in 57% of patients within 6 months of discontinuation of therapy. Histologically proven relapse has been observed in 13.3–15.6% of women after GnRH analog therapy. Patients with severe forms of endometriosis are more likely to have recurrence of pain, with an overall recurrence rate of 43.8%.

Gonadotropin-releasing hormone agonist formulations are available as nasal sprays or injection. The usual dose is 400–800 µg daily for nasal nafarelin, 3.6 mg for monthly subcutaneous goserelin and 3.75 mg for monthly intramuscular leuprolide.

Gonadotropin-releasing hormone agonists do not have androgenic or progestogenic side effects or negative impact on lipid profile; however, the side effects associated with a hypoestrogenic state may be severe. These effects include vaginal dryness, hot flushes, insomnia, depression, libido changes, headache and fatigue. A decrease in trabecular bone density of up to 6% in 6 months has been reported. This effect is largely reversible after discontinuation of therapy but limits the time this agent can be used. The long-term effect of multiple courses of GnRH analog therapy in young women is unknown, and there is potential for delayed adverse effects on BMD.

The addition of add-back therapy to GnRH analog treatment has gained wide acceptance and minimizes the hypoestrogenic side effects of the analog while preserving therapeutic efficacy. The ultimate goal is to decrease vasomotor symptoms and detrimental effects on bone density to enhance compliance with prolonged duration of therapy. The addition of progestin alone was first employed as add-back therapy.28 Vasomotor symptoms and bone density loss could be reduced with a 100 mg daily add-back of medroxyprogesterone acetate but apparently not with lower doses. Several studies have shown that transdermal 17 beta-estradiol or conjugated equine estrogens administered with medroxyprogesterone acetate result in decreased vasomotor symptoms and decreased bone loss without increasing pain. The addition of bisphosphonates to norethindrone also eliminates BMD loss; however, in light of the cost of bisphosphonates and concerns over long-term effects in young women who desire future fertility, further studies are indicated before this adjunct can be used as a standard approach. Unfortunately, after discontinuation of GnRH agonist and add-back therapy, recurrence rates are similar to the rates reported for other medical therapies.

Repeat therapy or extended periods of treatment with GnRH agonists has previously been limited due to their effects on BMD. However, the loss of BMD does show a gradual return toward baseline following treatment discontinuation. By giving add-back using an estrogen/progestogen preparation with a GnRH agonist:

- The impact of treatment on BMD loss is reduced
- Vasomotor symptoms such as hot flushes are relieved
- Efficacy of treatment on endometriosis symptoms is unaffected.

**Aromatase Inhibitors as a Treatment for Endometriosis**

Recently aromatase inhibitors are prescribed for women with endometriosis who have not had success with other treatments or who cannot use other treatments because of their side effects. At this moment, the treatment of endometriosis with aromatase inhibitors is still in the research stage.

Aromatase is a protein in the body that is responsible for producing estrogen. Normally, it is found in the ovaries, and to a much lesser extent in the skin and fat. Research has shown that aromatase is also found in high levels in the ectopic endometrial tissue of women with endometriosis, which contributes to their growth. Aromatase inhibitor suppresses the growth of endometriosis and reduces the associated inflammation. This, in turn, significantly reduces their pelvic pain.30–33

It has been established that medical treatment does not improve the chance of pregnancy for subfertile women with endometriosis. It has also been established that medical treatment of endometriosis-associated pain is effective, although little or no difference exists among the various medical treatment modalities available: continuous combined oral contraceptives, danazol, gestrinone, androgens, progesterone derivatives and GnRH analogs. Many have considered the beneficial effect on pain to correlate with a therapeutic effect on subfertility. However, a causal relationship between endometriosis and subfertility remains to be established.
Mirena as a Treatment for Endometriosis

The Mirena is increasingly being used to treat women with endometriosis. It contains levonorgestrel that is released into the uterus over a period of 5 years. Only a few studies have been published, the studies indicate that it is an effective treatment for endometriosis, and may have the potential to be a long-term treatment for women who want to postpone pregnancy. It offers several potential advantages over other current treatments.

Most common side effect of Mirena is irregular vaginal bleeding, frequent spotting or light bleeding between periods. However, these problems usually settle after 3–6 months.

SURGICAL TREATMENT (TABLE 3)

Surgical treatment is no longer the first-line therapy. Surgery is indicated in patients who have failed medical therapy and who have physical findings of extensive endometriosis such as endometriomas. Ovarian cystectomy, oophorectomy, hysterectomy and total hysterectomy are radical options, which, while often curative but are unsuitable for women wishing to retain fertility.

Treating early stage endometriosis to improve fertility is still controversial. Some studies have suggested that laparoscopic surgery is effective in increasing the incidence of pregnancy. In patients with significant physical findings or symptoms, the threshold for laparoscopy should be lower.

Total abdominal hysterectomy and bilateral salpingo-oophorectomy remain a definitive cure for symptomatic endometriosis but only possible in patients who have completed their families. In extensive endometriosis, surgical intervention requires extreme care and is best attempted by experienced and skilled surgeons. Following radical surgery involving oophorectomy, patients often require hormone replacement therapy.

Laparoscopic Excision

Over the last decade, laparoscopic surgery is gradually getting wider acceptance in the surgical management of endometriosis. The advantages of the laparoscopic approach are obvious. The aim is complete ablation or excision of the active endometriotic tissue and correction of anatomical distortion induced by the adhesions and cystic ovarian lesions and this should be achieved with minimum damage to the healthy tissue.

The most effective laparoscopic technique, excision, coagulation or vaporization is still being debated but it does not appear to be crucial for the eventual outcome. As endometriosis is an invasive disease and occasionally infiltrates deeply in the surrounding structures, ablation is as dangerous as excision. One should be able to identify the disease and to use the most effective surgical modality for each location and each patient. The following modalities are generally used:

- **Adhesiolysis**: This is the most important step in endometriosis.
- **Excision**: The lesions are identified and carefully excised usually after prior coagulation.
- **Vaporization**: The CO₂ laser is the best instrument to vaporize peritoneal implants.
- **Coagulation**: Occurs with lower energies as in a bipolar cautery and results in lower temperature at the tissue levels.

Laparoscopic surgery can be used to excise endometriosis from any pelvic location. Resections of uterosacral ligaments, excision of endometriomas, bowel lesions and ovaries or tubes are possible through the endoscopy. Excision techniques and procedures are the standard surgical techniques used at laparotomy. Very dense or widespread adhesions or some bowel lesions may require laparotomy in some patients.

Endometrioma

Endometriomas most frequently occur in the ovary and may present as an asymptomatic pelvic/abdominal mass.

Several surgical treatments are available for endometriomas:

- **Simple puncture**: This procedure is completed by draining the chocolate colored fluid from the cyst. Endometriomas have been shown to recur in about 50% of the patients treated with simple puncture, hence a more aggressive surgical approach is now recommended.
- **Ablation**: Another approach is to drain the cyst and remove its base with laser or electrosurgery.
- **Excision of the cyst wall**: This is the procedure of choice to decrease recurrence of disease. Endometriomas may recur in 8% of the patients treated with this procedure. Results from several different prospective studies have reported pregnancy rates of 50% over 3 years. There are no randomized clinical trials comparing these different treatment methods.

ENDOMETRIOSIS AND CANCER RISK

Women with endometriosis have a mildly increased risk for development of epithelial types of cancer of the ovary. This
risk seems to be highest in women with endometriosis and primary infertility, but the use of oral contraceptive pills, which are sometimes used in the treatment of endometriosis, appears to significantly reduce this risk.

The reasons for the association between endometriosis and ovarian epithelial cancer are not clearly understood. One theory is that the endometriosis implants themselves undergo transformation to cancer. Another possibility is that the presence of endometriosis may be related to other genetic or environmental factors that also increase women’s risk of developing ovarian cancer.

**ASSISTED REPRODUCTION IN ENDOMETRIOSIS**

Patients diagnosed as suffering from endometriosis should be referred for assisted reproduction early. The results are encouraging in a younger couple seeking advice early in the course of their treatment. Intrauterine insemination (IUI) improves fertility in minimal-mild endometriosis: IUI with ovarian stimulation is more effective. In vitro fertilization (IVF) is appropriate treatment especially if tubal function is compromised, if there is also male factor infertility, and/or other treatments have failed.

Laparoscopic ovarian cystectomy is recommended if an ovarian endometrioma greater than or equal to 4 cm in diameter is present to confirm the diagnosis histologically; reduce the risk of infection; improve access to follicles and possibly improve ovarian response. The woman should, however, be counseled regarding the risks of reduced ovarian function after surgery.

**CONCLUSION**

The enigma that is endometriosis requires decision making at every stage by physician and patient alike. The complexities surrounding diagnosis, when to treat, sequence and combinations of treatment all add up to a truly mysterious disease.

Current evidence suggests that pain caused by endometriosis can be mostly managed medically. Progestins, danazol, oral contraceptives, nonsteroidal anti-inflammatory drugs and GnRH agonists have all been shown to reduce the size of lesions. However, no medical therapy has been proved to eradicate the lesions.

Surgery for women with endometrial pain is associated with significant reduction in pain during the first 6 months following surgery. However, up to 40% of women experience a recurrence of symptoms within 1 year.

The following recommendations from the American College of Obstetricians and Gynecologists (ACOG) are based on Level A (good and consistent) scientific evidence:

- For pain relief, treatment with a GnRH agonist for at least 3 months or with danazol for at least 6 months appears to be equally effective in most women.
- When relief of pain from treatment with a GnRH agonist supports continued therapy, the addition of add-back therapy reduces or eliminates GnRH-induced bone mineral loss without reducing the efficacy of pain relief.
- Therapy with a GnRH agonist is an appropriate approach for the management of the woman with chronic pelvic pain, even in the absence of surgical confirmation of endometriosis, provided that a detailed initial evaluation fails to demonstrate some other cause of pelvic pain.
- For pain relief, oral contraceptives and oral or depot medroxyprogesterone acetate are effective and may be equivalent to other more costly regimens.
- Hormone replacement therapy with estrogen is not contraindicated following hysterectomy and bilateral salpingo-oophorectomy for endometriosis.
- For severe endometriosis, medical treatment alone may not be sufficient.

Because endometriosis often is unpredictable and may regress, expectant management may be appropriate in asymptomatic patients.

So long as we do not understand the exact pathogenesis of endometriosis, rational treatment will remain elusive. Also, the natural course of the disease is enigmatic: Why does endometriosis not progress beyond the minimal/mild stage in most women? Why, when and how does it resolve spontaneously with time, if at all? Why, when and how does it cause pain (dysmenorrhea, dyspareunia, chronic pelvic pain)? Endometriosis is a disease that waxes and wanes. Until we understand what makes endometriosis start and why it stops again spontaneously after some time, we will not be able to understand the disease or devise a permanent cure.

**REFERENCES**


INTRODUCTION

Urinary tract infections (UTIs) are common in women. Usually UTIs are benign and easily treated. But recurrent and persistent infections can lead to serious disease. The incidence of UTI is 1% among school children (aged 5–14 years), increases to about 4% by young adulthood and by an additional 1–2% per decade of age. In addition, the older a woman, the more likely she is to have a reinfection. UTIs are important because 20% of women aged 20–65 years suffer one attack per year and approximately 80% of women develop a UTI during their lives. The probability of recurrent UTIs increases with the number of previous infections and decreases in inverse proportion to the time elapsed between the first and second infections. Of these recurrent infections, 71–73% are caused by reinfection with different organisms, rather than recurrence with the same organism. UTIs account for more than 40% of all nosocomial infections. 12–25% cases of chronic renal failure are attributed to chronic pyelonephritis. UTIs can be hazardous when associated with an abnormal urinary tract, in pregnancy or in the presence of underlying diseases such as diabetes and hypertension. Acute symptomatic urinary infections are common in women between 20 years and 50 years of age while asymptomatic bacteriuria (ASB) is more common in elderly women.

TERMINOLOGY

The term bacteriuria is used to define the presence of living bacteria in freshly voided urine or urine obtained via suprapubic aspiration. Although 50% of women with lower UTI have 100,000 or more organisms per milliliter cultured from urine, approximately one-third of women who present with symptoms of acute dysuria, frequency and urgency have between 100 and 100,000 organisms per milliliter by properly obtained culture, and yet warrant a diagnosis of UTI. Studies of bladder urine specimens obtained by suprapubic aspiration or by transurethral catheterization demonstrated that smaller number of organisms in symptomatic women is associated with bacteriuria, pyuria and a predictable response to UTI therapy. The concept of significant bacteriuria or a single organism colony count of 100,000 or more organisms per milliliter is appropriate when applied to ASB or acute pyelonephritis. In 1956, Kass proposed that the isolation of more than 100,000 colony forming units (cfu) or organisms per milliliter of midstream voided urine should be used to differentiate probable contamination from ASB.

Asymptomatic bacteriuria is the term used to describe the condition in which there is significant bacteriuria although the patient remains asymptomatic. It is found in approximately 5% of young women and increases with age, reaching a prevalence of 22–43% in elderly women. In general it is not thought to be of clinical significance, except in certain clinical circumstances such as pregnancy, instrumentation of the lower urinary tract and renal transplant patients. It is more likely to be present in those patients with a chronic indwelling catheter.

Recurrent UTI is the term used to describe a symptomatic infection that follows the resolution of a previous UTI, generally after treatment. It occurs in 12–27% of women after their first UTI and in 48% of women who have had a previous UTI. The ratio of recurrent UTI to pyelonephritis has been estimated to range between 18:1 and 28:1.

Recurrent infection may be due to relapse of the original organism or to reinfection with the same or a different organism. As it is often difficult to differentiate between
relapse and reinfection, a relapse is defined as a recurrent UTI caused by the same organism, and a reinfection as a recurrent UTI caused by a different organism. Around 80–90% of recurrent infections are due to reinfections, with one-third being with the same organism.

Complicated lower UTIs are infections that may be related to other pathology (Table 1). One of the most common forms of complicated UTI is related to the use of catheterization. The incidence of bacteriuria associated with an indwelling urinary catheter is 3–10% per day, and the duration of catheterization is the most important risk factor for developing infection of the lower urinary tract. Whereas less than 5% of catheter-induced episodes of bacteriuria result in bacteremia, they represent a huge reservoir of resistant bacteria in the hospital environment.

Cystitis indicates inflammation of the bladder but is often used by patients to indicate any UTI. A symptom of dysuria, urgency and frequency unaccompanied by significant bacteriuria has been termed the “acute urethral syndrome” and is sometimes interchangeable with “frequency dysuria syndrome (FDS)”. Acute bacterial pyelonephritis indicates acute infection of the kidneys. The term chronic pyelonephritis indicates chronic inflammation of the renal and tubular tissues, with scarring and shrinkage secondary to interstitial fibrosis. There is accompanying reduction in the glomerular filtration rate and tubular function.

**Table 1: Conditions associated with complicated lower urinary tract infection (UTI)**

<table>
<thead>
<tr>
<th>Structural</th>
<th>Community (%)</th>
<th>Hospital (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urolithiasis</td>
<td></td>
<td></td>
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<tr>
<td>Malignancy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ureteric stricture</td>
<td></td>
<td></td>
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<tr>
<td>Urethral stricture</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bladder diverticulae</td>
<td></td>
<td></td>
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<tr>
<td>Renal cysts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fistulae</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary diversions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foreign bodies</td>
<td>Indwelling catheter</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ureteric stent</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nephrostomy tube</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>Diabetes mellitus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pregnancy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Renal failure</td>
<td></td>
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<td></td>
<td>Renal transplant</td>
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<tr>
<td></td>
<td>Immunosuppression</td>
<td></td>
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<tr>
<td></td>
<td>Multidrug resistance</td>
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<tr>
<td></td>
<td>Hospital-acquired (nosocomial) infection</td>
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</tr>
</tbody>
</table>

**Table 2: Common uropathogens in general practice and hospital**

<table>
<thead>
<tr>
<th>Organisms</th>
<th>Community (%)</th>
<th>Hospital (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escherichia coli</td>
<td>77.5</td>
<td>62.9</td>
</tr>
<tr>
<td>Proteus mirabilis</td>
<td>4.5</td>
<td>4.5</td>
</tr>
<tr>
<td>Klebsiella-Enterobacter spp.</td>
<td>4.7</td>
<td>9.3</td>
</tr>
<tr>
<td>Enterococcus spp.</td>
<td>4.9</td>
<td>9.2</td>
</tr>
<tr>
<td>Staphylococcus spp.</td>
<td>1.0</td>
<td>2.7</td>
</tr>
<tr>
<td>Others (Ureaplasma, Mycoplasma, Chlamydia)</td>
<td>7.4</td>
<td>7.6</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>3.8</td>
<td></td>
</tr>
</tbody>
</table>
Bacterial Virulence Factors

Uropathogens have the ability to survive and multiply in the bladder, as well as being able to adhere to the bladder epithelium. Adherence of the organism to the bladder wall triggers an acute inflammatory response by the activation of cytokines. These in turn stimulate the production of an intracellular adhesion molecule, which by leukocyte adhesion causes migration of cells to the point of infection. This prevents the organism from being “washed out” and, by increasing their nutrient supply, they divide more efficiently.

The structure of bacteria is also known to be important when considering virulence and pathogenicity. Various bacterial adhesions, surface receptor sites and attachment properties of bacteria have been identified. Pili and fimbriae are found on the outer membrane of some bacteria and promote binding, using an adhesion molecule on their tip. P-fimbriae mediate adherence to the glycolipids in the urothelium whilst type I fimbriae confer the ability to adhere to the mucous layer within the bladder. Enterobacteriaceae have an antigenic structure that induces an antibody immune response. The outer cell membranes contain O antigens, which, together with endotoxins, initiate the immune response in the bladder wall by stimulating cytokine production. Capsular (K) antigens on the surface of the bacteria help to inhibit phagocytosis and immunoglobulin A (IgA) and IgG in the urothelium. Finally some bacteria are able to break down bladder mucin and invade the urothelium beneath.

Host Factors

Flora, particularly coliforms from the gastrointestinal tract colonize the vagina and periurethral area and ascend into the bladder. The female urethra appears prone to colonization with colonic Gram-negative bacilli, owing to its proximity to the anus and its short length (about 4 cm). Natural defenses against the bacterial adherence to and the ascent into the urinary tract include various substances produced by the urinary tract, local immunoglobulins, competitive bacterial flora and normal voiding patterns.

The bladder mucosa is thought to have a bactericidal action and produces a surface layer of mucus, providing an antibacterial barrier. The lamina propria of the bladder wall and urethra has also been shown to synthesize IgA, and this also has a bactericidal effect by preventing bacterial adherence. Finally, Tamm-Horsfall protein, a mucoprotein shed from the renal tubular cells and excreted in the urine, has been shown to bind and trap E. coli and to be increased in patients with pyelonephritis and vesicoureteric reflux. The maintenance of an infection-free urinary tract relies first on regular and complete flushing of the system with a steady flow of urine from the kidneys and secondly the presence of friendly flora in the vagina and vulva. Anatomical abnormalities and neurological diseases may interfere with flushing. The friendly flora is disrupted by sexual activity, particularly when spermicides are used.

Among sexually active women, lower UTIs are associated with sexual intercourse. Urethral massage, as occurs during sexual intercourse causes introduction of bacteria into the bladder and appears to be very important in the pathogenesis of urinary infection in younger women. In recently married, consummation of marriage may traumatize the urethra and bladder base causing dysuria and “honeymoon cystitis”. Large proportions of susceptible women become symptomatic within a short period of time after intercourse. Strom et al. found that sexual intercourse in the previous 48 hours had an odds ratio for UTI of 58.1 and was the single most important factor in the development of UTIs. Use of diaphragm and spermicidal-coated condoms has been linked to an increased incidence of UTIs caused by E. coli. Handley et al. found that the largest risk of UTI was associated with exclusive condom use and use of nonoxynol-9-coated condoms.

Urinary infections are detected in 2–8% of pregnant women. Nearly 5% of women at their first antenatal visit have ASB. 20–30% of women with ASB develop acute pyelonephritis during pregnancy; have lower hemoglobins, which improves with eradication of the ASB and hypertension is more common, especially in association with renal scars. A significant number of patients with ASB have chronic renal disease. There is also a greater risk of prematurity and an increase in perinatal mortality. This predisposition to upper UTI during pregnancy results from the decreased ureteral tone and peristalsis and temporary incompetence of the vesicoureteral valves seen in pregnancy. Bladder catheterization during or after delivery without proper asepsis may cause additional infections. Sickle-cell anemia and sickle-cell trait in pregnant women has been correlated to an increased incidence of UTIs.

Although the symptoms of acute UTI resolve within a few days of starting antibiotics, the epithelium may take weeks to recover completely. During this recovery period its resistance to further infection is impaired and recurrent infection is more likely. Approximately 20% of women with UTIs have recurrences of symptoms within variable periods of time. Recurrences are most often reinfections, demonstrated by culture negativity between episodes and by the isolation of different organisms as shown by determining the biotype and the sensitivity patterns in each episode. Recurrences develop in characteristic clusters of symptomatic UTI, often during 6–12 month time periods.

Less frequently recurrent symptoms result from the persistence of the same organism after therapy is halted and is referred to as relapse. Close intervals of 10–14 days between symptomatic recurrences may indicate upper UTI. Persistence of single organism raises the concern of congenital or acquired structural or functional abnormalities of the urinary tract.
PRESENTATION

Symptoms

Adult women with dysuria, frequency, urgency and suprapubic pain usually have acute cystitis. In some cases, the patient recognizes that sexual intercourse may be the precipitating factor. In acute pyelonephritis, symptoms generally develop rapidly over a few hours or a day and include fever which is often 38°C or greater, with chills, nausea and vomiting. Though loin pain and fever are more common, symptoms of cystitis may coexist.

Patients with recurrent UTIs must be instructed to keep a record of the time of the day and volume every time the woman passes urine. This introduces an objective measurement, which is useful when assessing the severity of her symptoms and monitoring the response to treatment.

Physical Signs

In acute cystitis/urethritis, suprapubic tenderness is often present and palpation in this region may provoke a desire to pass urine. In adult pyelonephritis, the patient looks ill, has tachycardia and fever, which is often greater than 38°C. Physical examination reveals marked tenderness on deep pressure in one or both costovertebral areas. In some signs and symptoms of Gram-negative sepsis predominates and patients may have hypotension accompanying the tachycardia.

DIAGNOSIS

Urine Analysis

Infected urine may look cloudy. Commercial “stick test” is useful to detect glycosuria, proteinuria and hematuria. A positive leukocyte esterase test is 75–95% sensitive and 95% specific in detecting more than 10 WBCs/mL, consistent with a UTI. Some sticks can also reveal the presence of nitrites in the urine, which indicates Gram-negative bacterial infection if positive it has a specificity of greater than 92% for UTI.

Urine Microscopy and Culture

Microscopy of a fresh specimen of urine from a patient with UTI will detect bacteria and pus cells in abundance. The presence of casts indicates renal disease. The presence of pus cells and subsequent failure to isolate a pathogen is called sterile pyuria and alerts the clinician to the possibility of tuberculosis. The majority of women with symptomatic UTI who later are documented to have bacteriuria have pyuria with more than 8–10 WBCs/mL in unspun urine and 2–5 WBCs/HPF in spun urine sediment. The presence of hematuria in the absence of pus cells or bacteria suggests pathologies other than infection, e.g. renal calculi, bladder polyps and carcinoma. A midstream clean voided urine sample obtained after washing the introitus with tap water without soap and water is inoculated on a selective culture medium such as MacConkey within 20 minutes. If delayed, the urine must be refrigerated to 4°C. If lower UTI is associated with bacterial counts between 100 and 100,000 colonies/mL, contamination of specimens with other organisms may confuse the interpretation of culture results. Counts obtained between these two limits should be interpreted considering each specific clinical setting. Urine cultures that reveal 100,000 or more colonies/mL of a single pathogen support the diagnosis of UTI in asymptomatic women whereas cultures that reveal 100 or more colonies/mL of a single pathogen support the diagnosis of UTI in symptomatic women.

A quantitative estimate of the degree of bacteriuria can be made by direct microscopic examination of a Gram’s stain of uncentrifuged, freshly voided urine. If bacteria can be found by this method, it may be assumed that the number present approximates 100,000/mL. Identification and antibiotic sensitivity testing complete the microbiological report.

If there is a significant delay between collecting a sample of urine and platting it on culture medium some clinicians use a dip slide system. A slide coated with solid culture medium is dipped into the urine specimen and then transported to the laboratory in a sealed container. This technique has a false-positive rate of up to 10% and false-negative rate of up to 3%.

Imaging

Imaging studies are useful for detecting congenital anomalies of the urinary tract, obstruction, calculi and vesicoureteral reflux. Indications for imaging studies are children with UTI, adults suspected to have an upper UTI and adults with lower UTIs who fail to respond to treatment, have recurrent episodes of UTI or have symptoms suggesting some urinary tract pathology such as obstruction or calculi.

Ultrasound Examination

It is used to measure the dimensions of the kidney and to detect obstruction of their drainage. It will also reveal residual urine following incomplete bladder emptying. It is a well-tolerated, noninvasive investigation. Transvaginal ultrasound should be performed to exclude the possibility of a pelvic mass.

Plain Abdominal Radiograph

Most calculi and calcification seen in some chronic infections such as tuberculosis can be detected.

Intravenous Urography

Intravenous (IV) urography now has limited application in the investigation of the urinary tract, as relatively high doses
of radiation are a definite disadvantage and has not been shown to influence treatment in majority of the cases. It is usually used to demonstrate precise anatomic relations of the ureter. This may be helpful in planning surgeries involving the ureters.

**Computed Tomography Scan**

It displays cross-sectional anatomy and clearly delineates renal and perirenal pathology. It is particularly helpful in detecting renal and perinephric abscesses, acute focal bacterial nephritis and emphysematous pyelonephritis.

**Cystoscopy**

It is indicated in women with recurrent urinary infections and symptomatic women without significant bacteriuria. Other causes of lower urinary symptoms, such as carcinoma in situ, interstitial cystitis or tuberculosis can be detected and a biopsy undertaken to confirm the diagnosis.

**Approach to Imaging**

The combination of a plain abdominal radiograph and ultrasound has been compared with traditional IV urography in the investigation of patients with UTI. Both have similar sensitivities and concur in 96% of cases. IV urography involves a greater dose of radiation and is more expensive. It is wise to commence with a plain abdominal radiography and ultrasound. In most cases of UTI in adults this will be normal and no further imaging is warranted. If any abnormality is detected other imaging studies may be done.

**Blood Tests**

Plasma creatinine and urea concentrations are important measurements of renal function and should be performed in all cases other than solitary episodes of cystitis in adult women. The fasting plasma glucose concentration and oral glucose tolerance test are superior to tests for glycosuria when considering diabetes mellitus.

### MANAGEMENT

**General Measures**

The management of lower UTI is aimed at treating the current infection and preventing further recurrences. The aims of treatment are as follows:

- Symptomatic relief
- Clinical cure
- Microbiological cure
- Detection of predisposing factors
- Prevention of upper urinary tract involvement
- Management and prevention of recurrence.

The management and prevention of UTIs are closely related. Local hygiene is very important in the success of treatment and prevention of reinfection. Women must be told that perineal toilet should be done by wiping the perineum from the vagina toward the anus so as to avoid fecal contamination of the urethra, especially during an episode of diarrhea. Potentially irritant vaginal deodorants and bubble baths should be avoided and a high standard of perineal hygiene maintained. Patients with recurrent UTI should have plenty of oral fluids. Regular and complete bladder emptying must be taught and the concept of double micturition emphasized to those with residual bladder urine after voiding.

The complaint of postcoital UTI symptoms provides the ideal opportunity to review contraceptive methods. Oral contraceptives must be advised rather than condom if there is much irritation with the latter. The women must be instructed to void as soon as possible after intercourse.

Cranberry juice has also been shown to be an important factor in the prevention of lower UTIs. Regular intake of at least 300 mL/day has been associated with a reduced risk of UTIs. Cranberry juice is thought to act by reducing bacterial adherence to the bladder wall.

**Antimicrobials**

An antimicrobial should be selected that has the appropriate sensitivity and is also able to achieve a high concentration within the urinary tract. Ideally the drugs should be rapidly absorbed and not induce bacterial resistance (Table 3).

**Asymptomatic Bacteriuria**

Pregnant women and women with renal scars from previous infection with ASB need treatment. ASB should be demonstrated with at least two positive cultures before treatment is given. Seven days of an oral agent to which the organism is sensitive should be given initially. If bacteriuria persists, it can be followed without further treatment in most patients. In patients who may be at high-risk because of

<table>
<thead>
<tr>
<th>Table 3: Common antibiotic sensitivities</th>
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<tbody>
<tr>
<td><strong>Gram-negative bacilli</strong></td>
</tr>
<tr>
<td>- Norfloxacin</td>
</tr>
<tr>
<td>- Ciprofloxacin</td>
</tr>
<tr>
<td>- Gentamicin</td>
</tr>
<tr>
<td>- Sulfonides</td>
</tr>
<tr>
<td>- Cotrimoxazole</td>
</tr>
<tr>
<td>- Trimethoprim</td>
</tr>
<tr>
<td>- Nitrofurantoin</td>
</tr>
<tr>
<td><strong>Pseudomonas</strong></td>
</tr>
<tr>
<td>- Norfloxacin</td>
</tr>
<tr>
<td>- Ciprofloxacin</td>
</tr>
<tr>
<td>- Gentamicin</td>
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</tbody>
</table>

...
neutropenia, compromised host defenses, renal transplant or previous development of pyelonephritis or bacteremia, further treatment with either 6 weeks of oral therapy or 4–6 weeks of combined parenteral and oral therapy should be given.

**Acute Uncomplicated Cystitis**

More than 90% of infections are due to *E. coli* and most strains are sensitive to many antibiotics. Amoxicillin, trimethoprim, sulfa or a quinolone may be a good first choice. The latter two should not be used in women at risk for pregnancy or pregnant (Table 4). Cephalosporins have an unacceptably high-risk of precipitating vaginal candidiasis and should be avoided in this setting.

Several studies have proved that single dose of medication is sufficient to treat approximately 80% of uncomplicated lower UTI. Appropriate single-dose agents include amoxicillin (3 g), trimethoprim (400–600 mg), sulfasoxizole (2 g), and trimethoprim-sulfamethoxazole [2 double strengths (DS)]. Cephalosporins are not effective as single-dose agents. Single-dose therapy should not be used in women with symptoms or signs of pyelonephritis or in women with urologic abnormalities or stones. Most practitioners and their patients will find a 3 days course with either trimethoprim, norfloxacin, ciprofloxacin or ofloxacin acceptable.

Treatment of acute urethritis in women depends on the etiological agent involved. In Chlamydial infection, tetracycline (500 mg orally QID for 7 days) or azithromycin (1 g) as a single oral dose should be used.

**Acute Pyelonephritis**

Treatment may require hospitalization, IV antibiotics and hydration. A 10–14 days course of trimethoprim-sulfamethoxazole, trimethoprim alone, an aminoglycoside, third generation cefephalosporin, augmentin or ciprofloxacin usually provides adequate therapy. Antibiotics must be given intravenously and should be continued for at least 24 hours of a febrility followed by oral antibiotics.

**Recurrent Cystitis or Pyelonephritis**

Women with recurrent or persistent UTIs, especially those with diabetes, immunosuppression or urinary obstruction require antibiotic prophylaxis. Taking antibiotics every night or every other night has been found to decrease the incidence of recurrent UTI. The suppressive dose usually employed is one-quarter or one-third of that given for the management of an acute episode. Some women may relate the development of UTIs to coitus. Single postcoital doses of antibiotics, including trimethoprim, sulfamethoxazole, ciprofloxacin or other quinolones has shown to decrease the recurrence of UTIs (Table 5).

**Lower Urinary Tract Infections in Pregnancy**

When treating lower UTIs in pregnancy penicillins and cephalosporins have been shown to be safe in the first and second trimesters. As it is a folate antagonist, trimethoprim should be avoided in the first trimester, although it may be used safely in late pregnancy. Conversely nitrofurantoin and sulfonamides are safe in early pregnancy, although they should be avoided in third trimester when the former may cause a hemolytic anemia and the latter hyperbilirubinemia and kernicterus. Tetracyclines should be avoided because of their chelating action, which will lead to hypoplasia and staining of the teeth. Whilst in general erythromycin is considered safe, the estolate salt may be associated with cholestatic jaundice. Finally fluoroquinolones may affect fetal cartilage formation, and chloramphenicol may be associated with neonatal cardiovascular collapse.

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**Table 4: Antibiotics for first or uncomplicated urinary tract infection (UTI) or cystitis**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Acceptable in pregnancy</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin</td>
<td>250–500 mg TID</td>
<td>Yes</td>
<td><em>E. coli</em> resistance rates of 25% have been reported</td>
</tr>
<tr>
<td>Cephalexin</td>
<td>250–500 mg TID</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>50–100 mg BID to QID</td>
<td>Yes</td>
<td>Good for penicillin allergic</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>250–500 mg BID</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>400 mg every 12 hours or 800 mg QD</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>100 mg every 12 hours</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Trimethoprim/sulfamethoxazole</td>
<td>One DS BID</td>
<td>No</td>
<td></td>
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</tbody>
</table>

*Abbreviation: DS, double strength (trimethoprim 160 mg and sulfamethoxazole 800 mg)*
Urinary Tract Infections in Women

The female genital and urinary tracts arise from the primitive urogenital sinus and develop in close proximity. Urological and vaginal symptoms due to urogenital aging often parallel each other, because they originate from a common fetal structure. Human and animal studies have identified estrogen receptors in the tissues of the vagina, urethra, bladder and pelvic floor. Estrogen deficiency, particularly when prolonged is associated with a wide range of urogenital complaints including frequency, nocturia, incontinence, UTIs and the "urge syndrome". These may coexist with vaginal symptoms of dryness, itching, burning and dyspareunia. Iosif and Bekassy20 studied 2,200 women aged 61 years and found that the incidence of lower genital tract disorders was high with 49% of women having some symptoms. UTIs are also very common in older women, leading to substantial morbidity.

### Effect of Aging on the Urinary Tract

In women, older age (and presumably concomitant lower estrogen concentrations) is associated with several genitourinary changes, such as atrophy of the bladder trigone, diminished sensitivity of the α-adrenergic receptors of the bladder neck and urethral sphincter and thinning of the urethral mucosa. Urodynamic studies have shown that the urethra and bladder become less efficient with age. Elderly women have a reduced urine flow rate and increased residual urine volume. In addition, detrusor pressures at urethral opening and closure during voiding fall. With a decline in blood flow due to estrogen deficiency, important immune system functions may also be affected, facilitating in combination with the wide urethra, microbial migration into the urinary bladder. This together with the vaginal reservoir of urinary pathogenic microorganisms makes it understandable that there is a high frequency of symptomatic and ASB as well as recurrent cystitis.21

### Estrogens and Recurrent Urinary Tract Infections

Alternations in the vaginal flora following menopause, place women at an increased risk of UTIs, particularly if they are sexually active. There is a rise in vaginal pH and a fall in the number of lactobacilli, allowing colonization of Gram-negative bacteria which act as uropathogens. Many studies have shown that estrogen reverses these changes, an effect which enables it to be used for either treatment or prophylaxis of recurrent UTI.

### Management

The first step is a careful consideration of the history and analyzing symptomatology. A careful gynecological examination will assess the degree of atrophy and the presence of infection. A wet vaginal smear, Pap smear and an analysis of midstream urine sample are performed if indicated. Local estrogen therapy is suitable for urogenital atrophy and the symptoms caused by it. Estrogen preparation in the form of vaginal cream, pellets or rings can be prescribed. If the patient is satisfied with the relief it provides, maintenance dosage can be given for a more prolonged period. Micronized estriol cream 0.5 mg/day has a specific action on vaginal and lower urinary tract epithelium. It does not cause endometrial proliferation and hence there is no withdrawal bleeding and no supplementary progesterone is required.

If the symptoms are not relieved after 4 weeks of topical estrogens the patient needs further evaluation. Estrogen therapy may be stepped up. In addition to local estrogen, systemic therapy may also be started if there are no contraindications.

### Conclusion

Urinary tract infections are very common in women. These infections must be identified, treated and sterility proven. Recurrent UTIs should be treated rigorously and may be

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
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<tr>
<td><strong>Postcoital single-dose prophylaxis</strong></td>
<td></td>
</tr>
<tr>
<td>Trimethoprim/sulfa</td>
<td>Half DS or one regular strength tablet</td>
</tr>
<tr>
<td>Sulfamethoxazole</td>
<td>500 mg</td>
</tr>
<tr>
<td>Cephalexin</td>
<td>250 mg</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>50 mg</td>
</tr>
<tr>
<td><strong>Chronic prophylaxis</strong>: Take every night or every other night</td>
<td></td>
</tr>
<tr>
<td>Trimethoprim/sulfa</td>
<td>Half DS or one regular strength tablet</td>
</tr>
<tr>
<td>Sulfamethoxazole</td>
<td>500 mg</td>
</tr>
<tr>
<td>Cephalexin</td>
<td>250 mg</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>50–100 mg</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>200 mg</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>250 mg</td>
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</table>

*Contraindicated in pregnant women and should not be used in fertile women who are not using an effective method of contraception. Abbreviation: DS, double strength
able to be prevented. Estrogens may be effective when used for prophylaxis against recurrent UTIs in postmenopausal women.

REFERENCES

INTRODUCTION
In clinical practice, the gynecologist is presented with a variety of urinary disturbances related to the bladder and the urethra. In order to understand these, it is essential to understand the physiology of micturition and its control. In this chapter, we will first deal with the micturition physiology followed by problems of urinary incontinence and their management in detail.

MICTURITION
Micturition is defined as the process by which the urinary bladder empties itself when it becomes filled. The main actions involved in micturition are:

- Progressive filling up of the urinary bladder till the tension in the wall crosses a threshold value.
- This is followed by a nervous reflex known as micturition reflex (Fig. 1) (Flow charts 1A and B) which causes micturition or at least a conscious desire to urinate.

Once the micturition reflex becomes powerful enough it causes another reflex through the pudendal nerves to the external urinary sphincter to inhibit it. If this inhibition is more powerful than the voluntary constriction signals to the external sphincter from the brain, urination will occur.

Approximate normal cystometric values in women (Fig. 1):

**Point 1**: Residual urine—Less than 50 mL
**Point 2**: First desire to void—150–250 mL
**Point 3**: Cystometric capacity—400–600 mL
**Point 4**: Maximum detrusor pressure during filling—Less than 15 cm of H$_2$O
**Point 5**: Bladder compliance index—20–100 mL/cm of water measured 60 seconds after reaching cystometric capacity

**Point 6**: Maximum detrusor pressure during voiding—Less than 70 cm of H$_2$O
**Point 7**: Peak urinary flow rate—More than 15 mL/sec
**Point 8**: Absence of systolic detrusor contractions during bladder filling.

Bladder Muscles
The bladder consists of a smooth muscle chamber made up of two parts, viz.

1. The body, which is the main portion of the bladder in which the urine collects.
2. The neck, a funnel shaped extension passing anteriorly and inferiorly into the urogenital triangle and connects to the urethra.
The smooth muscle of the bladder is made up of muscle fibers extending in all directions with cells fusing with each other such that an action potential can spread throughout the detrusor muscle leading to contraction of the entire bladder muscle at once.

**Bladder Sphincters**

- Internal sphincter is 2–3 cm long and is composed of detrusor muscle interlaced with large amount of elastic tissue. It keeps the bladder neck and posterior urethra empty thus preventing bladder emptying till the bladder pressure goes above a critical threshold.

- External sphincter is made up of voluntary skeletal muscle and is under voluntary control of the nervous system thus preventing urination even against the involuntary controls.

**Bladder Innervation**

This is mainly by way of pelvic nerves connecting the spinal cord through the sacral plexus mainly to segments S2 and S3. These nerves contain both sensory and motor fibers. The former are mainly responsible for detection of stretch signals especially from the posterior urethra initiating reflexes causing bladder emptying. The motor fibers consists mainly of parasympathetic fibers innervating the detrusor muscle. The skeletal motor fibers of the external sphincter are supplied by body somatic nerves fibers via pudendal nerves (Fig. 1).
Tone of the Bladder and the Cystometrogram

Cystometrogram is the solid curve which shows the approximate changes in the intravesical pressure as the bladder fills up with urine. Cystometry is the technique which studies the pressure-volume relation of the bladder and is used to assess bladder sensation, bladder compliance and detrusor activity.

THEORIES OF FEMALE CONTINENCE

Pressure Transmission Hypothesis
- Female urethra—intra-abdominal portion and extra-abdominal portion
- Increase in intra-abdominal pressure
- It is transmitted simultaneously to the bladder and the proximal urethra to prevent leakage of urine.

Hammock Hypothesis

This hypothesis emphasizes anatomical principles of female continence. According to this hypothesis, continence is maintained by compression of urethrovesical junction against the hammock of the anterior vaginal wall and the pubocervical fascia during an increase in the intra-abdominal pressure.

URINARY INCONTINENCE

Urinary incontinence is defined as the involuntary loss of urine posing a social or hygienic problem and which is objectively demonstrable.
- Stress urinary incontinence (SUI) is defined as urinary loss which occurs with sudden elevations of the intra-abdominal pressure without detrusor contractions.
- Genuine stress incontinence is defined as involuntary loss of urine when the intravesical pressure exceeds the intraurethral pressure in the absence of detrusor activity. This term is used only for a patient who has undergone urodynamic testing. The new term recommended by the international continence society is urodynamic stress incontinence.

Incidence

Stress urinary incontinence can affect women of all ages but has a prevalence of 10–30% in women between the ages of 15 years and 64 years.

Factors Contributing to Stress Incontinence

Basically SUI is determined by an interaction of three determinants:
1. The biologic strength of the sphincteric mechanism
2. The level of physical stress placed on the continence mechanism
3. The woman’s personal and cultural expectations about urinary incontinence.

Factors Contributing to Urethral Integrity

Extrinsic Factors
- Endopelvic fascia and integrity of its lateral attachments
- Levator ani muscles and their strength
- Connections of levator muscle complex with the endopelvic fascia
- Coordination of levator muscle contraction with factors which increase the intra-abdominal pressure.

Intrinsic Factors
- Sympathetic innervation and tone (α-adrenergic)
- Striated urethral muscle
- Mucosal coaptation of the urothelium
- Vascular congestion of submucous venous plexus
- Smooth muscle of urethral wall and blood vessels
- Elasticity of urethral wall.

Evaluation of Stress Urinary Incontinence

- Stress urinary incontinence may be mild requiring an increase in pressure by 70–80 cm of water for it to occur or may be very severe requiring only 20–30 cm of water rise in the pressure.
- The amount of urine lost at a given time is only a few drops which is a very important feature of the diagnosis.
- Soreness and excoriation of the vulva due to frequent repeated leaking of urine.
- Patient feels a social outcast and avoids leaving the house.
- Frequent attempts at emptying the bladder to keep herself dry
- Incontinence occurs irrespective of the degree of fullness of the bladder although very high pressure may be required to cause urinary leakage when the volume in the bladder is low.

Demonstration of Stress Urinary Incontinence Clinically

As the factors contributing to SUI become more and more clearly understood, SUI can be separated into three broad types:
1. SUI due to anatomic hypermobility of urethra
2. SUI occurring due to intrinsic sphincteric deficiency or weakness
3. Fixed urethra with failure of the intrinsic sphincter.
   The former is more prevalent and occurs due to faulty urethral closure under situation of stress. It accounts for 80–90% of all cases of SUI. The latter although less common, is more difficult and challenging as far as treatment is concerned. Thus, while demonstrating SUI, the main factor
METHODS OF EVALUATION OF URETHRAL SUPPORT

Clinical Examination

This is the quickest and simplest way of evaluation of urethral support. It involves inspection of the urethra and bladder neck while the patient is at rest and then during maximum straining.

Rotational descent of the bladder neck can be easily demonstrated. Leakage of urine with increase in the intra-abdominal pressure can also be demonstrated provided the patient has not emptied the bladder immediately before examination.

It is important to note that urinary leakage in some patients can be demonstrated only when the patient is standing and this makes it necessary to examine the patient in standing position as well. The character and timing of urethral leakage should also be noted.

Q Tip Test

It is a simple test to evaluate urethral axial mobility. A sterile lubricated cotton tipped swab is placed in the urethra up to the bladder neck. The resting angle of the urethral axis is first measured using a goniometer. The patient is then asked to strain maximally and the angle of excursion of the swab is measured. If the maximum straining angle is more than 30°C, it provides significant evidence of urethral hypermobility. However, it is to be kept in mind that this test is indicative of urethral hypermobility and not diagnostic of SUI.

Bonney’s Test

This test, discussed by the late Victor Bonney, aims at seeing whether an uplift of the urethrovaginal stem will stop the incontinence during times of raised intra-abdominal pressure, thus giving a guidance to the type of surgery required. With the patient in dorsal position, light pressure is applied at the sides of the upper urethra without causing an uplift. A positive test is indicated by control of urinary leakage from the vagina with closure of the internal sphincter by pressure. The main usefulness of this test is not to demonstrate patient remaining dry but to find patient who continue to leak in spite of correction of normal anatomic support, thus suspicious of having a significant element of intrinsic urethral sphincter weakness or deficiency.

Investigations

- **Fluoroscopy** of the bladder for identification of patients in whom the bladder neck is gaping open at rest, in standing position. These patients are at high-risk of failure to improve from standard supportive bladder neck suspension procedures.
- **Lateral urethrocytography** (Micturating cystourethrogram or micturating cystogram) involves filling of the bladder with a radiopaque contrast medium through a urethral catheter and then taking lateral radiographs, at rest, while straining and during micturition. In a normal person, the posterior urethrovaginal angle is lost during voiding such that the urethra and the trigone come into line opening up the bladder neck. In patients with incontinence, the posterior urethrovaginal angle is also lost. This may be apparent when the woman is standing or sitting quietly in severe cases; in mild to moderate case it is apparent only with straining.
- **Cystourethroscopy** can be used in identification of poorly functioning urethras, e.g. scarred urethras in which the urethral lumen remains open throughout the examination making visualization of the bladder interior possible from the distal urethra.
- **Urethral pressure profile** involves measurement of the pressure along the entire urethral length using a special catheter with 3 microtop pressure transducers placed 6 cm apart pulling it out from the bladder to the outside through the urethra at a fixed rate. All along the transducer keeps measuring the intravesical pressure till it enters the urethra when the pressure rises and peaks at the point of maximum urethral pressure. The difference between the maximum urethral pressure and the intravesical pressure gives the maximum urethral closure pressure, i.e.

  $$ \text{Maximum urethral closure pressure} = \text{Maximum urethral pressure} - \text{Intravesical pressure} $$

However, urethral pressure profile determination test is not very sensitive as the pressure readings can vary depending on the orientation of the transducer, the rate of withdrawal of the catheter, the bladder volume, the patient’s position, etc. Also there exists an overlapping of the pressure values between normal patients and those with SUI. Hence, this test could not stand the test of time and search for more sensitive tests continued.

- **Leak point pressure determination** is the total intravesical pressure required to produce SUI in a patient. According to McGuire, patients with leak point pressures of less than 60 cm of water have severe incontinence due to intrinsic sphincteric deficiency.

Other Varieties of Incontinence

- **Ure incontinence**: It refers to urine loss which is accompanied by a strong desire to urinate (urgency)
- **Reflex incontinence**: Abnormal spinal cord reflex activity in the absence of a normal desire to micturite
- **Overflow incontinence**: Passive elevation of the bladder pressure above maximum urethral pressure due to vesical distension
- **Detrusor instability**.
Stress Urinary Incontinence

MANAGEMENT

• Careful history and examination (as already described) including:
  - Chief complaints
  - Duration
  - Any special circumstances or precipitating events leading to SUI
  - Progression.
• History of previous attempts at treatment and some idea of severity
• Frequency volume bladder chart or maintenance of a urinary diary, this should include:
  - Volume of each void
  - Time at which voiding occurred
  - Time and amount of fluid intake
  - Any episodes of incontinence and any special events leading to them to be noticed
  - Episodes of frequency (more than 7 voids/day), nocturia (awakening from sleep with the need to urinate), etc.
• Treatment history
  - Medical
  - Surgical
• Complete examination
  - General
  - Neurologic screening tests especially lower limbs and perineum
  - Urogynecologic examination
  - Investigation
  Management of SUI is almost always considered to be surgical although this is not always required or true. Surgery should be advised and undertaken only when the problem is severe enough warranting correction and when the patient is fit for the same.
  Although the complete interaction between the urethral tone, bladder neck and urethral mobility and the state of pelvic innervation remains incompletely understood, recent understanding of pelvic anatomy suggest that the main support of this region comes from the pelvic musculature especially the levator ani complex. The periurethral fibers of these muscles maintain tone over a long period of time and increase the tone suddenly to compensate for any increase in the intra-abdominal pressure. Thus, improvement in the strength of these muscles by rehabilitation through physiotherapy and exercise can increase its ability to cause effective urethral closure and maintain continence.

Kegel’s Exercises

Aim

• To strengthen the striated urogenital sphincter
• Improve the support of the proximal urethra.

Principles

• It must be supervised, done regularly and aided by some form of feedback to provide judgement of progress, e.g. pneumatic biofeedback perineometer.
• It requires an intensive program for 3 months with pre- and post-treatment urodynamic evaluations.
• It involves tensing the musculature for 5 seconds each 15–20 times per session and three such sessions per day.
• Gardener and Fonda have stated that urinary incontinence in older age can be cured or significantly improved in 60% of cases with conservative management.
• Dougherty et al. showed that 16 weeks of pelvic floor exercises produces significant improvement in urinary incontinence.

Pharmacological Treatment

• As the adrenergic activity from the sympathetic nervous system is the main element maintaining the tone of urethra and bladder neck, an adrenergic agonist can be used to treat SUI.
  The agents tried till date are:
  - Ephedrine 25–50 mg QDS
  - Pseudoephedrine HCl 30–60 mg QDS
  - Phenylpropanolamine HCl 50–75 mg BD
  - Imipramine 10–25 mg TDS
  - Main side-effect: Hypertension due to increase in vascular tone by these agents.
• Anticholinergic agents:
  - Propantheline bromide 15–30 mg QDS
  - Methantheline bromide 50 mg QDS
  - Hyoscine sulfate 0.37–0.75 mg BD/tabs
• Calcium-channel blockers: Anticholinergic action (e.g. Terodiline HCl 12.5–25.0 mg BD).

Estrogen Replacement Therapy

This therapy can be adopted in case of postmenopausal women with urogenital atrophy due to estrogen depletion.

Electrical Nerve Muscle Stimulation Therapy

This involves the passage of an electric current either transvaginally or transrectally in a continuous or intermittent manner to the muscles of pelvic floor causing their contraction and reflex inhibition of detrusor activity.

In Case of Associated Detrusor Instability

• Bladder retraining/bladder drill regime
• Drug therapy like antispasmodic agent, e.g. oxybutinin chloride 5–10 mg TDS/QDS, flavoxate HCl 200 mg QDS.
• Prostaglandin synthetase inhibitor, e.g. mefenamic acid.
**Treatment of any Associated UTI**

Surgical treatment of SUI: More than 200 different surgeries have been described so far for the treatment of SUI and this itself suggests that an ideal surgery applicable to all patients has not been devised yet.

**CLASSIFICATION OF OPERATIONS FOR STRESS URINARY INCONTINENCE**

- Anterior colporrhaphy with Kelly’s plication of paravesical tissue at the bladder neck
- Abdominal bladder neck suspension procedures designed to correct urethral hypermobility
  - Retropubic bladder neck suspension
    - Marshall Marchetti Krantz surgery
    - Burch colposuspension
  - Paravaginal bladder neck suspension
    - Paravaginal defect repair
    - Vaginal obturator shelf-procedure
  - Needle suspension procedures
    - Pereyra procedure
    - Modification of Pereyra procedures—Raz, Stamey, etc.
- Operations to correct intrinsic sphincteric deficiency:
  - Sling operations
    - Organic materials: Autologous—rectus fascia and lata, etc. Heterologous—procrine dermis, ox dura, etc. Synthetic—polypropylene
    - Tension free vaginal tape
  - Artificial urinary sphincter
  - Mechanical devices.

**Anterior Colporrhaphy**

First described by Howard Kelly in 1914.

- It is an attempt to cure SUI by stabilizing the suburethral fascia thus preventing urethral hypermobility.
- It probably works by supporting the urethra and the bladder neck elevation of the bladder neck, preferably above the lowest bladder level or by supporting the bladder neck and kinking the urethra.
- The main indication is in frail elderly women with prolapse and mild genuine SUI.

**Advantages**

- Low morbidity
- Less postoperative pain
- Early mobility.

If genuine SUI is more marked, it can be combined with Stameys repair or periurethral injections with very little increase in morbidity.

This surgery has led to dissatisfaction as far as the results are concerned due to higher recurrence rate and potential narrowing and scarring of vagina postoperatively.

**Abdominal Bladder Neck Suspension Procedures Designed to Correct Urethral Hypermobility**

**Techniques for Retropubic Bladder Neck Suspension**

First described by Dr Marshall, Marchetti and Krantz (MMK) of Cornell University Medical Centre in 1949. These operations correct bladder neck displacement and urethral hypermobility by surgical suspension of these structures using an operation performed in the space of Retzius which is a potential space outside the peritoneal cavity within the bony anterior pelvis and is full of loose areolar connective tissue with varying amount of fat. The main underlying principle is stabilization of the endopelvic fascia to various fixed points in the retropubic space.

- The MMK procedure consists of taking a series of sutures in the endopelvic fascia along the urethra up to the level of bladder neck and fixing it into the periosteum of symphysis pubis.
- The Burch procedure includes fixation of the endopelvic fascia to the ilipectineal ligament of Cooper.
- The paravaginal repair involves reattaching the endopelvic fascia to the arcus tendinous.
- The vaginal obturator shelf procedure described by Turner Warwick consists of suturing the endopelvic fascia to the fascia covering the obturator internus muscle.

**Mechanism of continence with bladder neck suspension procedures:**

- The MMK procedure works by elevation of the bladder neck along with restoration of the urethrovescical anatomy leading to a valvular effect due to movement of the bladder neck and trigone behind the symphysis.
- Burch’s colposuspension works by an increase in the outflow resistance.

**Complications of retropubic bladder neck suspensions:**

- Kinking of urethra in unnatural position
- Postoperative voiding difficulty
- Osteitis pubis (in case of MMK operation)
- Chronic irritative voiding symptoms
- Uncorrected cystocele
- Predisposition to enterocoele
- Increased residual volumes and reduced flow rates
- De novo detrusor instability.

**Results of colposuspension (from different authors):** The continence rate following colposuspension reported by various authors ranges from 73% to as high as 90.3%.

**Results of colposuspension as secondary procedure:** When performed as a secondary procedure, the continence rate was between 63% and 82.5%.
Randomized study of Burch versus abdominal paravaginal defect repair showed a 100% versus 72% success rate.

**Needle Suspension Procedures**

- First described by Armand Pereyra in 1959.
- It consists of urethral suspension by a combined abdomino-vaginal approach in which a special long needle is used to carry the suture through the space of Retzius and this suture is fixed at two points viz. the perivesical fascia and the abdominal fascia. The bladder neck is thus suspended between the two sets of sutures.

  **Stamey’s modifications:**
  1. Use of intraoperative cystourethroscopy to avoid trauma to the bladder and to ensure that the suspensory suture is not passing through the bladder. Also may help in determining the tightness of the sutures.
  2. Use of small (1 cm) Dacron bolster threaded over the suspensory sutures to act as a buttress or a stopper avoiding pulling out of the suture. Closure of the vaginal incision should be done with absorbable material before the suspension sutures are lifted up and tied over the abdomen as the vaginal incision becomes inaccessible and recedes behind after the suspensory sutures have been tied off.

**Complications**

- Voiding difficulty postoperatively due to pulling of the sutures very high or tying them very tightly
- No definite endpoint of sutures elevation, thus it may remain too loose or too tight
- Pull through of the sutures in patients with poor peri-urethral and perivesical tissue
- Chronic pain due to twisting or pulling of the sutures
- Infection, erosion or granulation formation if dacron bolsters are used
- Hemorrhage from the veins in the space of Retzius
- Damage to bladder or urethra.

**Advantages**

- Quick procedure
- Technically easy
- Can be easily combined with other surgeries like vaginal hysterectomy
- Useful in morbidly obese patients where other procedures may be technically difficult.

**Long-term Results**

- Kevelighan et al.—subjective cure rates of 45% at 2 years, 18% at 4 years and only 6% at 10 years.
- Kohli N et al.—comparison of anterior repair versus transvaginal needle suspension showed a recurrence rate of 7% in the former against 33% in combined procedures.

**Bone Anchors and Needle Suspension Techniques**

Nowadays, commercially available kits have been introduced for performing bone anchored suspension procedures, e.g. vesica technique—device used to anchor the abdominal end of the sutures to the pubic bone.

**Advantages**

- Easy to perform
- Fast procedure
- Avoids the potential weakness at the rectus fascia by using bone as the anchoring point
- Low surgical morbidity and fast recovery
- Very good short-term results.

**Disadvantages**

- Costlier procedure
- Risk of osteomyelitis
- Long-term success results are still awaited.

**OPERATIONS TO CORRECT INTRINSIC SPHINCTERIC DEFICIENCY**

**Sling Surgery**

These procedures are mainly designed to compensate for intrinsic sphincter weakness or deficiency although it prevents abnormal urethral descent to some extent.

**Indications**

- Complicated SUI cases
- Previously failed surgery for SUI
- SUI following pelvic fracture
- SUI with chronic obstructive pulmonary disease (COPD)
- Massive genital prolapse with associated SUI
- Congenital urethral abnormalities.

**Principle**

Supporting the urethral bladder neck in a hammock providing both elevation and partial compression of the urethra.

**Procedure**

Insertion of a sling using a combined vaginal and abdominal procedure, a vaginal approach alone or a supra-pubic technique alone with blind dissection beneath the urethra and bladder base have been described. The common feature of sling surgery is to pass a strip of material beneath the urethra or the bladder neck.

- **Goebel Stock Frangenheim operation:** It involves the placement of a fascia lata sling under the bladder neck
and anchoring its two ends to the rectus fascia through the space of Retzius on either side.

- **Adridge procedure**: It involves fixation of strips of rectus fascia to the endopelvic fascia through the space of Retzius using small permanent sutures.
- **McGuire’s pubovaginal sling**: Uses a small piece of rectus fascia as the hammock in which the urethra rests.

### Tension Free Vaginal Tape

Tension free vaginal tape (TVT) is a new sling procedure which is minimally invasive and involves passage of polypropylene tape around the mid-urethra through a vaginal incision providing a resilient platform under the mid-urethra to maintain continence against an increased abdominal pressure.

#### Indications for Tension Free Vaginal Tape

- Intrinsic sphincteric efficiency
- Previous failed anti-incontinence surgery
- Co-existent morbidities viz. COPD, obesity, etc.

#### Procedure

- Done under sedation or GA or spinal anesthesia or ethylene dibromide
- Bladder drained by 18 F catheter which is left in situ for the initial part of the procedure
- 0.5 cm incisions made at the superior margin of the pubic bone, 2.5 cm from the midline on either side
- 1 cm midline incision in the vaginal mucosa under the mid-urethra
- 1 cm tunnel created between vaginal mucosa and pubocervical fascia lateral to the mid-urethra on both sides
- First needle with tape attached is passed through the suburethral incision into the left tunnel and then going upward through retropubic space in close contact with posterior surface of pubic bone till it penetrates the suprapubic incision on left side
- Foleys removed, bladder filled with saline and cystoscopy performed for evidence of needle perforation
- Foleys reinterted and procedure repeated on opposite side after ensuring that the tape is placed flat under the mid-urethra without any twist
- Both ends of the tape are cut from their needles and grasped with clamps
- 0.5 cm gap created between the mid-urethra and the tape using a clamp to ensure tension free placement
- Plastic sheath over the tape removed
- Each end of the tape is cut just below skin level
- Skin closed with 4-0 suture
- Vaginal mucosa closed with 3-0 suture
- Postoperative trial of voiding and measurement of residual volume (aim at residual of less than 100 ml.).

### Complications and Risks

- Postoperative voiding difficulty
- Bladder perforation, bowel injury, urethral injury
- Urethrovaginal fistula
- Bladder erosion unrecognized at the time of surgery
- Vascular injury and hemorrhage
- Rarely ilioinguinal nerve entrapment, urethral erosion, vaginal erosion, necrotizing fasciitis, delayed bowel erosion.

### Outcome

- Similar objective cure rates on comparison with Burch colposuspension at 2 years postoperatively (81% for TVT, 80% for Burch).
- Women with recurrent SUI after failure of previous surgery can benefit from TVT. Cure rates of 81–85% reported.
- Effective for intrinsic sphincteric deficiency: Up to 74% cure rates and 12% significant improvement reported.

#### Transobturator Tape Sling

- Placement of a polypropylene sling under the mid-urethra using a curved needle inserting the tape around the ischiopubic ramus in horizontal plane through obturator foramina.
- Cure rates similar to TVT with lesser incidence of bladder injury.

#### Suprapubic Arc Sling

- Involves placement of a polypropylene mesh under the mid-urethra.
- The technique involved is different from a TVT in that it employs passage of a needle above the pubic bone down through a suburethral vaginal incision. The tape is then attached to the needle and pulled up above the pubic bone.

### Complications

- Retropubic bleeding and hematoma formation occasionally requiring drainage and/or transfusion
- Small bowel injury
- Bladder injury
- Postoperative voiding difficulty.

#### Periurethral Injections (Bulking Agents)

Periurethral injections was first described by Murless using phenol in 1938.

**Mechanism of action**: Bulking up the bladder neck tissues causing the urethral mucosa to coapt in situations of raised intra-abdominal pressure and increases urethral closure pressure.
Stress Urinary Incontinence

**Procedure**
- Outpatient procedure
- Done usually under local anesthesia
- Transurethral or periurethral injection under cystoscopic guidance with a 22 gauge spinal needle with bevel facing medially and angled toward the bladder neck
- Usually 20 mL of material is required
- Similar procedure repeated on the opposite side.

**Materials Used**
- Teflon
- Autologous fat
- Contigen—Glutaraldehyde cross linked with bovine collagen
- Urethrin—Polytetrafluoroethylene micropolymer particles
- Micronized silicone rubber particles.

**Complications**
- Urinary infection
- De novo detrusor instability—rare
- Hypersensitivity especially to bovine collagen
- Expensive
- Long-term effects are difficult to assess.

Berman CJ et al. showed a 26.7% rate with collagen injection versus 71.4% success rate with fascia lata sling surgery.

**POSTOPERATIVE MANAGEMENT**
- Adequate bladder drainage without overdistension of a traumatized bladder which may lead to long-term voiding dysfunction and affect the success of the surgery. The catheter is left undisturbed for at least 24 hours before any attempts at voiding. The purpose is to provide regular and complete voiding without overdistension at any point.
- Adequate nursing care.
- All patients should be taught clear intermittent self-catheterization which can be done after each void to judge the progress of voiding allowing modification of the voiding schedule.
- Placement of a suprapubic catheter or silicone Foley catheter through a bladder incision. When voiding trials are begun, the patient is asked to record the volume of urine voided while the suprapubic has been kept closed. Thereafter the suprapubic is opened up for about 20 minutes to see the post void residual volume. When the voided volumes are large and the post void residual volume is low, the suprapubic can be removed.
- Adequate antibiotic cover.
- Pharmacological measures to treat urgency, frequency and urge incontinence which may occur in the first few weeks.

**FAILURES OF SURGERY**

**Causes**
- Episodic incontinence
  - Stress incontinence
  - Recurrence of SUI
  - Detrusor instability
- Urge incontinence
  - Prior to surgery
  - Detrusor instability
  - Wet without warning
  - Detrusor instability
  - Defective voluntary control
- Continuous incontinence
  - Retention with overflow
  - Fistula (urethral, vesical, ureteric)

**CAUSES OF RECURRENT STRESS URINARY INCONTINENCE**
- Failure to elevate bladder neck
- Failure of alignment of the urethra to posterior aspect of the pubic symphysis
- Lack of support to the proximal urethra and bladder
- Postoperative surgical fibrosis
- Properly elevated bladder neck—sling procedure
- Functionless rigid urethra—artificial urinary sphincter
- Detrusor instability—antispasmodic therapy, e.g. Oxybutynin, flavoxate, etc. bladder ret raining regimes.

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Genital Fistula

**CHAPTER 71**

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*(Chapter updated by Urvashi Verma)*

**INTRODUCTION**

Genital fistula is one of the most tragic occurrences of a woman’s life making her a social outcast. It is basically an abnormal communication between urinary or gastrointestinal and genital tract, either acquired or congenital with involuntary escape of urine or feces into the vagina. The incidence of genital fistulae varies from region to region as do the causative factors.

Genital fistulae may be divided into two broad categories:

1. Urinary fistulae
2. Fecal fistulae

Uterocutaneous fistulae is a rare entity. Most fistulae result either from obstetric trauma or during gynecological surgery.

**URINARY FISTULAE**

Depending on the anatomical site they may be divided into the following:

- **Ureters:**
  - Ureterovaginal
  - Ureterocervical
  - Ureterouterine
- **Bladder:**
  - Vesicovaginal fistula (VVF)—High, mid, low, massive
  - Vesicocervical
  - Vesicouterine (Fig. 1)
- **Urethra:**
  - Urethrovaginal.

**INCIDENCE**

Incidence of genitourinary fistula is 0.5–3% among gynecological admissions in referral hospitals of the developing countries although accurate figures are difficult to obtain.

Five hundred new cases a year are currently being treated at the Addis Ababa Fistula Hospital (J Hamlen 1982, personal communication).^3^ Newcastle survey of 1969–1970 (Lawson 1977, personal communication) shows that 350 vesicovaginal fistulae are treated each year in England and Wales.^3^ In the developing countries fistulae are most common due to obstetric causes while in developed countries it is injury at gynecological surgery which is the main contender. Obstetric fistulae due to obstructed labor were seen in 0.3–3.7% of admission to gynecological wards in India and Nepal (Shah 1989).^4^ Prema Naidu from Hyderabad (India) reported that out of 208 fistulae examined by her in 1962, obstetric causes accounted for 201 cases.^5^ Rao (1972),^6^ Abbo and Mukhtar (1975)^7^ Gunarathe and Mati (1982),^8^ Taheib (1983)^9^ also reported an 85% incidence of obstetrics fistulae from Asia and Africa.

In contrast, in Moir’s series of 350 vesicovaginal fistulae in the UK, 268 were due to gynecological causes and only...
82 were a result of obstetric trauma. Similarly in the United States, 82% of VVF are small fistulae in vaginal vault that appear after total abdominal and vaginal hysterectomy for benign disease.

### ETIOPATHOGENESIS

#### Obstetrical Factors

Vesicovaginal fistula (Fig. 2) is the most common type of fistula. In developing countries most common cause is obstetrical trauma, although various etiopathological factors are as follows.

**Obstructed Labor**

In obstructed labor it results from prolonged compression effect on the bladder base between the presenting part and the symphysis pubis followed by ischemic necrosis of the tissues, which slough off leading to fistulous communication. Such fistulae present within a week of delivery.

**Traumatic**

- Injury to the bladder may occur in destructive procedures such as craniotomy, decapitation, evisceration either by instrument itself or by bony spicules of the fetal skull
- Difficult forcep delivery may result in trauma to the soft tissues
- Symphysiotomy
  
  Such type of fistulae present within 24 hours of delivery.

**Rupture Uterus**

Distal extension of the rupture itself may involve the bladder and cause fistulae formation.

- Besides fistula formation between bladder and genital tract, fistula can also occur between ureter or urethra and genital tract
- Urethral sloughing can occur in prolonged second stage of labor, especially in obstructed labor. Injury to urethra can occur even during urethral coitus or illegal abortion. Urethra can avulse also during vaginal delivery
- Injury to ureter can also occur while applying forceps before full dilatation of cervix or during cesarean section or cesarean hysterectomy

*Postpartum use of intravaginal caustic agents may also cause erosion of vagina leading to VVF.*

#### Obstetrical Abdominal Operations

- Cesarean section especially repeat cesarean section can result into fistula formation because of presence of adhesions.
- Cesarean hysterectomy done for rupture uterus can also cause fistula formation when bladder is edematous and high up. Injury may be direct or ischemic following a part of bladder wall being caught in the suture or due to inadequate mobilization of the bladder.
- Retrovesical hematomas may also result into fistula formation. Such fistulae present from 7 days up to 3 months.

#### Gynecological Surgical Injuries

**Abdominal Hysterectomy**

Vesicovaginal fistula develops in 0.5–1% of patients undergoing an abdominal hysterectomy. The chances of development of VVF are more in total abdominal hysterectomy because of close proximity of cervix with bladder. Injury to bladder base is more common due to the following points (Fig. 3):

- Inadequate mobilization of bladder inferiorly and laterally
- Vigorous and blunt dissection in an improper plane between the base of bladder and pubovesicocervical fascia covering the cervix
- At the time of vault closure suture may take a bite through the bladder base leading to gradual necrosis of bladder wall and formation of VVF, which manifests after first week of surgery
- Use of prolonged or deep diathermy for hemostasis at bladder base may also lead to fistula formation
- Abdominal hysterectomy done in previously irradiated tissues or previous cesarean section, or in women with pelvic inflammatory disease, diabetes mellitus, concurrent infection, vasculopathy or tobacco abuse are more at risk.
Genital Fistula

and sloughing of neoplastic tissue in vesicovaginal septum leading to fistula formation. Radiotherapy, even as a latent effect in 1–2 years time causes end arteritis obliterans leading to ischemic necrosis and sloughing. These fistulae are usually located at the bladder neck and upper urethra. Malaplication of brachytherapy implants may also lead to fistula formation.

Infections

Chronic granulomatous lesion may lead to fistulae formation.

Vaginal Tuberculosis

Formation of granulomas and scarring may lead to weakening of wall and formation of VVF.

Lymphogranuloma Venereum

*Lymphogranuloma venereum* causes vesicopustular eruptions leading to ulceration and fibrosis involving bladder wall and formation of urethrovaginal fistula (UVF).

Actinomycoses

A gram-positive anerobic slowly progressive bacterial infection, which causes violation of normal tissue plane creating draining sinuses which may reopen to form a fistula.

Others

Endometriosis: Congenital

*Symptoms and diagnosis:* The typical history of a fistula due to pressure necrosis is that of a prolonged labor (often unattended) resulting in a stillbirth with incontinence of urine and in some cases also feces a few days later.

Following direct injury during surgery, incontinence usually appears immediately after the delivery or surgery. In postradiation cases, fistula may form many years later.

With a small fistula the urinary leakage is slight and sometimes depending on the position of the patient the woman may be able to void urine in good quantities.

With larger fistulae the woman suffers from a true incontinence of urine, i.e. continuous dribbling of urine.

Most fistulae are painless but fistulae resulting from irradiation can cause severe pain which may be aggravated by movement.

Bladder injury must be suspected in postoperative patients with abdominal pain, distension, paralytic ileus, hematuria or severe bladder irritability.

Continuous trickle of urine down the vagina produces vaginitis and vulvitis with attendant soreness. Incrustation of phosphates may form in the vagina, and in long-standing cases there may be extensive excoriation of vulva, groin and thighs.
On examination, care must be taken to distinguish between the true incontinence of a fistula and overflow or stress incontinence. Most fistulae can be easily visualized on a per speculum examination. Filling the bladder with a dilute solution of methylene blue may help in visualizing small fistulae.

Moir’s three tampon test is useful in differentiating between a ureterovaginal and a VVF and in identifying the level of a VVF. In this test, three cotton tampons are placed in the vagina in tandem. Methylene blue is instilled in the bladder. The patient walks about for 10–15 minutes, and the tampons are removed and examined. If the lowest tampon is wet and stained blue, the patient may be presumed to have transurethral urinary incontinence and no fistula. If the upper tampon is wet and blue, a VVF is indicated. If the upper tampon is wet but not blue, a ureterovaginal fistula is the likely diagnosis.

Cystoscopy is useful in identifying the level of a fistula and its relation to ureteric orifices but it is difficult in large fistulae as the bladder cannot be distended adequately. In these cases the air method of Kelly and the carbon dioxide technique of Robertson are useful modifications. At times more than one VVF may be present. If the single fistula is identified it cannot be assumed that it is the only one present.

Excretory urography is useful in delineating the exact site and number of fistulae. Sonography has recently been shown to be complementary to above investigations in evaluation of patients with obstetric fistulae. Various genital abnormalities not revealed by intravenous urography were detected by sonography. These included cervical injuries and VVF showing ‘flat tire’ sign and hourglass deformities.

A urinalysis and urine culture must be done to identify the presence of a concomitant infection. In case of a small fistula sample may be collected by a midstream clear catch method or by catheterization to avoid continuous dribbling, urine may be collected on a sterile speculum and sent for analysis.

When injury is suspected at the time of surgery then intravenous indigo carmine must be injected to check the integrity of the urinary tract.

**URETEROVAGINAL FISTULA**

Close anatomical association between ureter and genital organs may lead to ureteric injury during gynecological surgery.

*Incidence: 0.5–1% of all pelvic operations.*

- At or below the pelvic brim
- Along the course of ureter on lateral pelvic wall above the uterosacral ligaments

- In the base of broad ligament where the ureter passes beneath the uterine vessels, about 1.5 cm lateral to cervix at the level of internal orifice
- Beyond the uterine vessels as the ureter passes in the tunnel in Mackenrodt’s ligament and turns anteriorly and medially to enter the bladder
- In the intramural portion of bladder

**Nature of Injury which can Lead to Ureterovaginal Fistula**

- Ischemia from trauma to ureteric sheath endangering its blood supply
- Ligature incorporation
- Crushing injury by clamps—necrosis
- Segmental resection either accidental or planned
- Thermal injury when diathermy or laser is used
- Injury by staplers during laparoscopic surgery

**Gynecological Operations Causing Ureterovaginal Fistula**

- *Radical hysterectomy:* Extensive surgery leading to devascularization and ischemic necrosis of the wall of terminal ureter resulting into UVF.
- *Abdominal hysterectomy:* To remove
  - A tubo-ovarian abscess
  - Extensive pelvic endometriosis
  - An intraligamentary leiomyoma
  - Ovarian remnant

**URETHROVAGINAL FISTULA**

Small isolated fistulas are caused by:

- Anterior colporrhaphy
- Urethroplasty
- Suspension or sling operations for stress incontinence
Prevention

For Obstetric Fistulae

- Community awareness for institutional deliveries can go a long way toward preventing obstetric fistulae. The fact is proven by the low incidence of such fistulae in developed countries.
- Once the patient does come late in obstructed labor such cases must be dealt by the most experienced obstetricians in the hospital to reduce the occurrence of complications.

For Gynecological Surgery

There has been a move promoting subtotal hysterectomy over total hysterectomy for benign gynecological conditions, to reduce bladder trauma. Another very important technique taught to students in gynecology is to always apply clamps as close to the uterus as possible during hysterectomy. Clamps must never be applied blindly. When bleeding occurs, proper exposure must always be obtained. Sharp dissection must be used to isolate the bladder. The performance of intrafascial hysterectomy may also help avoid bladder injury. In a series of 867 women who underwent intrafascial abdominal hysterectomy there was a bladder injury incidence of 0.4%.\(^\text{15}\)

Consequences of Genital Fistulae

Genital fistulae are a psychologically debilitating condition making the woman a social recluse, disrupting sexual relations and leading to depression and low self-esteem. Goh et al.\(^\text{16}\) concluded that all women with genital tract fistulae must be routinely subjected to psychological/psychiatric assessment and treatment.

Fecal Fistulae

Depending on the anatomical location these may be classified into:
- Enterovaginal
- Sigmoidovaginal
- Rectovaginal
- Anovaginal.

Incidence

Rao (1989) reported that 5% of urinary fistulae are associated with rectovaginal and anovaginal fistulae.\(^\text{17}\)

Etiology

Obstetric

- Third or fourth degree perineal laceration
- Prolonged labor
- Difficult forceps
- Precipitous delivery.

Surgery

- Difficult abdominal hysterectomy
- Vaginal hysterectomy
- Perineorrhaphy.

Malignancy

Cervix, vagina, rectum, uterus.

Irradiation

Inflammatory processes:
- Crohn’s disease
- Diverticulitis
- Perirectal and pelvic abscess
- Tuberculosis
- Lymphogranuloma venereum.

Others

- Vaginal trauma
- Leukemia
- Aplastic anemia
- Agranulocytosis
- Systemic lupus erythematosus
- Endometriosis.

Symptoms and Diagnosis

A small rectovaginal fistula may be entirely asymptomatic, a slight leakage of gas and seepage of feces in the vaginal discharge go unnoticed. When the fistula is a bit large there is complaint of passage of flatus per vaginum and fecal odor in vaginal discharge. Patient may complain of fecal incontinence when she has diarrhea. Larger fistulae may result in the entire contents of the bowel being evacuated through the vagina.

Rectovaginal fistulae are normally painless except those following irradiation or due to inflammatory diseases particularly Crohn’s disease.

A fistula between the ilium and vagina usually causes intense excoriation and redness of vaginal and vulvar tissues due to irritation by secretions from the small intestine.

As in urinary fistulae methylene blue is useful in delineating the fistulous tract. Barium enema, proctoscopy and barium meal are other useful investigations.

A simple test has been described for identification of small fistulae not visible on routine examination. Patient is laid in slight Trendelenburg position and a 20F urinary Foley’s catheter is placed in the anal canal with a 5 mL balloon. Air is pushed through the catheter while the water filled or soap covered vagina is observed for air bubbles.

Though comparatively less common than urinary fistulae but fecal fistulae are equally traumatic for the woman and the principles of obstetric management outlined for prevention of urinary fistulae apply in to prevention of fecal fistulae.
REFERENCES

INTRODUCTION
Genitourinary fistulas are marked by leakage of urine through the vagina and can cause great suffering and emotional distress in a woman. Occasionally, renal function can be impaired when a ureter is involved due to injury or due to inflammatory fibrosis leading to ureteric obstruction. Treatment of this morbid condition continues to evolve with medical opinion constantly debating the pros and cons of various techniques and approaches. Genitourinary fistulas can be classified into vesicovaginal, ureterovaginal, urethrovaginal and utero-vesical. In this chapter attention is directed to the diagnosis and treatment of vesicovaginal and ureterovaginal fistulas, but the basic principles remain applicable in all cases.

INCIDENCE AND ETIOLOGY
There are broadly two classes of genitourinary fistulas: (1) obstetric and (2) gynecological.

Obstetric fistulas result from prolonged obstructed labor due to cephalopelvic disproportion with resulting pressure necrosis of the anterior vaginal wall, bladder neck and proximal urethra. Obstetric fistulas occur more often in developing countries because of several factors:
- Social cultures favor early marriages—immature and relatively small pelvis bear the brunt of childbearing
- Poor nutrition resulting in stunted or distorted pelvic growth in the mother
- Lack of competent prenatal and obstetric care.

The incidence of vesicovaginal fistulas in the developing world has been estimated to be about 0.3–0.4% of all deliveries.

Genitourinary fistulas resulting from gynecological surgery are commoner in developed nations where gynecological surgery is more available. About 80% of gynecological fistulas occur after hysterectomy, especially abdominal hysterectomy. Other procedures that have been responsible for urinary fistulas are general surgical operations in the pelvis, anterior colporrhaphy or cystocele repair, anti-incontinence surgery or other urologic procedures.

Postradiation fistulas may develop several decades after completion of radiation treatment. The median interval from completion of radiation therapy to presentation of the vesicovaginal fistula is about 8.7 months.

Trauma to the bladder can occur by:
- Inadvertent cystotomy during sharp dissection or a laceration during blunt dissection
- Thermal necrosis during electrocauterization especially during laparoscopic surgery
- Suture placement through both the bladder and the vaginal wall during closure of the vaginal cuff or during an attempt to control pelvic bleeding.

Leakage of urine collects in a pelvic urinoma which ultimately drains out through the vaginal cuff.

Ureteral injuries are almost always in the distal ureter and occur usually during procedure for benign as opposed to malignant conditions. The risk of ureteral injury appears to be greatest during laparoscopic hysterectomy, followed by abdominal, and then by vaginal hysterectomy. The risk of iatrogenic ureteral injury during major gynecological surgery is estimated to range from 0.5% to 2.5%.

MANAGEMENT
Successful treatment of genitourinary fistulas is based on three steps:
1. Perform a thorough evaluation of the fistula and the patient’s general condition.
2. Plan an individualized course of treatment with clear indications for conservative treatment versus operative intervention. The timing and the method of surgical repair should confirm to a deliberate policy.

3. Comfort the patient through the morbidity of urinary leak while she awaits a surgical cure.

**Evaluation**

Detailed evaluation of a genitourinary fistula begins with a focused clinical examination. This is followed by imaging studies and finally by cystoscopy.

**Clinical Examination**

Faced with a postoperative urinary leak from the vagina, one should proceed with clinical examination in a logical sequence. The first step is to carry out a good pelvic examination with visualization of the vagina. Methylene blue is instilled into the bladder. A vaginal leak of the same readily confirms a vesicovaginal fistula. Should there be no such leak, it becomes necessary to ascertain whether the leaking fluid is urine (and not peritoneal fluid, lymphorrhea, or inflammatory exudates), and also whether the leak is from a ureterovaginal fistula. This involves intravenous injection of indigo carmine or methylene blue or the oral administration of phenazopyridine (Pyridium). A stained vaginal swab confirms both suspicions. The three vaginal swab test is useful to indicate the presence of a ureterovaginal fistula, but it does not influence the need for imaging studies which in any case are necessary.

An essential part of the clinical examination is to assess the state of the local tissues (slough, foreign body, inflammatory process, infection and residual tumor). Accessibility of the fistula from the vaginal route should also be taken note of.

**Imaging Studies**

Every genitourinary fistula needs radiological imaging. Three functions need to be served:
1. To ascertain that there is no ureteric involvement either during the initial injury or due to subsequent fibrosis.
2. To examine the surrounding tissue planes for abscess formation or unresolved urinoma.
3. To search for residual malignancy in postradiation fistulas.

A spiral CT scan with 3-D reconstruction is now the standard of care. Its scores over a conventional urogram and cystograms because it can reveal in addition to renal and ureteric anatomy, fluid collections, abscesses, and residual tumor. It also offers detailed perspectives of fistula site in any desired plane. Intravenous urograms, cystograms and even only ultrasonography may be valid options where facilities are restricted.

**Cystoscopy**

Cystoscopy is indispensable. A diligent examination should document the following:

- The number and size of the vesicovaginal fistulas, with their exact location in relation to the ureters and the bladder neck
- The state of the margins of the fistula (slough, suture material, infective debris, residual tumor). If needed a biopsy can be taken from the margin of a postradiation fistula.
- If ureteric involvement has been shown on imaging studies, a retrograde ureterogram and double J stenting can be attempted. For this reason, imaging studies should precede cystoscopy.

**PLAN FOR TREATMENT**

**Conservative Treatment**

Conservative or nonoperative treatment has obvious appeal, but succeeds only occasionally (7–12.5%).

- In a recently developed vesicovaginal fistula, urinary drainage by indwelling catheter, anticholinergics, and antibiotics may be tried for up to 3 weeks. If the fistula does not heal, then catheter should be removed. Persisting with an indwelling catheter for prolonged periods prevents resolution of local infection, prevents regressing of inflammatory edema and ultimately compromises surgical repair.

- Established vesicovaginal fistulas with epithelialized tracks of a diameter less than 3 mm, may be cured by ablating the epithelial lining and draining the bladder for 2–3 weeks. The epithelium may be curetted by an ordinary metal screw or electrocauterized. Fibrin sealant can then be injected into the track. Closure occurs by fibrosis.

- Ureterovaginal fistulas often heal if a double J stent can be maneuvered across the injured ureteral segment and left indwelling for 8 weeks. An aggressive attempt should be made to pass a double J stent across the defect, employing ureteroscopy if called for.

**Surgical Treatment**

Once it becomes clear that conservative measures will not succeed, surgical repair has to be planned. Two issues need clear decisions:
1. When to repair?
2. How to repair?

**Timing of Repair**

A distinctly different approach is used to schedule surgical repair for vesicovaginal fistulas as compared to ureterovaginal fistulas.

**Surgical Repair**

**Vesicovaginal fistulas**: There is an emotionally driven need to seek early relief from the embarassing predicament that the patient and her physician have landed into. A number
Successful fistula surgery is based on these tenets:

- Adequate preoperative correction of anemia, nutritional state, and infection. Local urinomas and abscesses should have been fully resolved.
- Appropriate surgical approach, vagina, abdominal, or laparoscopic.
- Adherence to certain surgical principles during handling of tissues.

**Surgical Approach (Figs 1 to 4)**

Repairs of vesicovaginal fistulas through the vagina is successful, less traumatic (no cystotomy and no repeat laparotomy), less expensive (shorter hospital stay) and significantly easier on the patient (less postoperative discomfort). In only special circumstances should the abdominal route be employed in preference to the vaginal route.

Clear indications for abdominal repair are as these:
- Recurrent fistula and postradiation fistulas which necessarily require the interposition of omentum
- Vesicovaginal fistula repair where a ureter needs to be reimplanted
- Complex uroenteric fistulas
- Severe scarring makes vaginal access difficult
- Shrunken bladders which require augmentation cystoplasty.

Laparoscopic surgery now offers the advantages of abdominal repair at a much reduced morbidity. Procedures like omental interposition and ureteral reimplantation are well within the ambit of laparoscopic repair.

**Tissue Handling Techniques**

- Wide separation of the plane between bladder and vagina to allow multilayered tension-free closure of the defect and also to allow interposition of a viable tissue buttress (omentum or Martius flap).
- Avoid excision of the fistula track as this will enlarge the tissue defect and may even compromise local vascularity when cautery is used for hemostasis. In addition in chronic fistulas, a strong fibrous ring forms outside the epithelialized track that maintains some strength through the repair if this layer is incorporated into the closure.
- Use of adjuvant flaps and grafts to allow the interposition of healthy tissue during vesicovaginal fistula repair.
- Uninterrupted and secure postoperative urinary drainage, using a suprapubic catheter as well as a urethral catheter when required.

**PREVENTION OF GENITOURINARY FISTULAS**

- Ensure an empty bladder during all gynecological operations by constant catheter drainage.
Figs 1A to F: Repair of a high vesicovaginal fistula: vaginal approach
- Perform sharp dissection along anatomical tissue planes; dissect and develop extraperitoneal spaces
- Clamp, cut, suture under direct vision while avoiding large tissue pedicles
- Avoid frantic “blind” attempts to clamp and ligate bleeding vessels. Sustained application of pressure will almost always control the bleeding to allow accurate identification and control of the bleeding vessel
- Avoid excessive use of monopolar electrocautery during laparoscopic surgery

- When planning to operate difficult cases, take care of the following:
  - Position, prepare and drape the patient so as to allow both abdominal and vaginal access
  - Identify the course of each ureter and safeguard it from injury. Preoperative placement of ureteral catheters is neither practical nor desirable as the catheters themselves can cause injury to the ureteral mucosa or impart stiffness to a ureter that may predispose it to devascularization or laceration.\(^8\)
Figs 3A to E: O’Conor’s abdominal repair of vesicovaginal fistula

The bladder is repaired in two layers with absorbable sutures. The first layer skirts the mucosa and approximates the full thickness of the bladder muscle.

The second layer (Lembert like) picks up the seromuscular layer to bury the first suture line.
- Intraoperative testing of the integrity of the urinary tract should be readily resorted to, so that primary repair may be immediately undertaken. This can easily be done by instillation of methylene blue into the bladder or into the ureter. Intraoperative cystoscopy and even cystotomy should be practiced with hesitation.

CONCLUSION

Genitourinary fistulas are an old bête noire that have caused disquieting moments to many a gynecologist. Despite the great advances that this specialty has made, genitourinary fistulas obstinately occur with relentless regularity (about 1 out of 1,800 gynecological procedures).

A slew of new initiatives are establishing themselves.

- Spiral CT scan with 3D reconstruction is emerging as the imaging modality of choice
- The traditional 3–6 month wait with diapers is being discarded in favor of earlier repair
- Laparoscopy is upstaging the stalwart open abdominal repair.

REFERENCES

INTRODUCTION

Hysterectomy is one of the most common and major operations in women, and it is therefore vital to make evidence-based decision to choose the appropriate technique of hysterectomy. For years the abdominal route remained the unquestioned traditional route for a hysterectomy with the vaginal route being used in less than a fourth of the population, in the presence of uterovaginal prolapse, and in the absence of the possible need for oophorectomy. This persisted through the years in spite of evidence that was forthcoming in favor of the vaginal route.\(^1\)

The debate on whether the uterus should be removed vaginally or abdominally was sparked when Langenbeck first performed a vaginal hysterectomy (VH) in 1813.\(^2\) Historically, the reason gynecological surgery became a specialty in its own right was its extensive use of the vaginal route. The vaginal approach has always been the hallmark of the gynecological surgeon.

Although VH is the procedure associated with the quickest operating time, the shortest hospital stay, and the lowest hospital costs,\(^3\) many surgeons do not feel comfortable with this approach. Table 1 argues in favor of the vaginal route from the study; still only 20–30% of hysterectomies are carried out vaginally in the western world.\(^4\)

Magos et al.\(^5\) reviewed 500 women who had undergone a hysterectomy by both techniques; 76% were by the abdominal route in the absence of an absolute contraindication (CI) to VH. Among the women operated by the abdominal route, the following characteristics were found; lack of uterine prolapse (76%), fibroid uterus (45%) and need for oophorectomy (43%). It was concluded that with adequate surgical training, more than two-thirds of the patients could have had a VH.

The indications for hysterectomy and the associated conditions are given in Table 2. The fact remains that most cases can be done vaginally if the operator chooses to train himself in the minutiae of the technique. In Brown’s series (cited Sheth SS, 2005)\(^6\) from Australia, 79% of the hysterectomies were completed vaginally. Qureleu and Kovac (cited Sheth SS, 2004)\(^7\) reported 77% and 89% hysterectomies respectively performed by the vaginal route and in the first authors personal series of 7,334 hysterectomies in India,

<table>
<thead>
<tr>
<th>Complication</th>
<th>Complication vaginal (n = 568)</th>
<th>Rate (%) abdominal vaginal (n = 1283)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile morbidity</td>
<td>15.3</td>
<td>32.3</td>
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<tr>
<td>Transfusion</td>
<td>8.3</td>
<td>15.4</td>
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<tr>
<td>Atelectasis</td>
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<td>Ileus</td>
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<tr>
<td>Wound dehiscence</td>
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<tr>
<td>Neuropathy</td>
<td>0</td>
<td>0.2</td>
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<tr>
<td>Deep vein thrombosis/thrombophlebitis</td>
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<table>
<thead>
<tr>
<th>Indications</th>
<th>Number</th>
<th>Associated conditions</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Menorrhagia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Dysfunctional uterine bleeding/Adenomyosis</td>
<td>3,167</td>
<td>Nulliparous</td>
<td>328</td>
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<tr>
<td>• Uterine fibroids</td>
<td>1,886</td>
<td>Previous abdominal surgery</td>
<td>1154</td>
</tr>
<tr>
<td>• Severe mental handicap</td>
<td>115</td>
<td>Previous vaginal surgery</td>
<td>112</td>
</tr>
<tr>
<td>• Cervical polyp/fibroid</td>
<td>36</td>
<td>High risk</td>
<td>162</td>
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<tr>
<td>2. Uterine prolapse</td>
<td>580</td>
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</tr>
<tr>
<td>3. Benign adnexal pathology*</td>
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<tr>
<td>4. Carcinoma in situ of the cervix</td>
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<td>5. Endometrial cancer</td>
<td>16</td>
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<td></td>
</tr>
<tr>
<td>6. Benign hydatidiform mole</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>6,044</strong></td>
<td><strong>1,756</strong></td>
<td></td>
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</tbody>
</table>

* Generally, a contraindication to vaginal hysterectomy (VH), it is performed only after counseling as trial VH with laparoscopically-assisted vaginal hysterectomy (LAVH) or laparotomy facility available.

6,044 (82%) were carried out vaginally of which 92% were in the absence of uterovaginal prolapsed.\(^6\)

The preferred method of removing the uterus is almost always determined by the surgeon’s training, preference and experience in a particular technique. However, a gynecologist is now frequently recognized for his/her level of expertise in a particular type of hysterectomy—the one using a laparoscope is looked upon as the most updated and laparoscopic hysterectomy (LH) is being looked upon as the pinnacle of surgical skills, which in reality is far from true. It is unfortunate that abdominal hysterectomy (AH)—the least preferred technique of hysterectomy—is being performed in all categories of patients where vaginal or laparoscopically-assisted vaginal hysterectomy (LAVH) can be performed.

There is little doubt that VH is a more difficult technique to teach and learn than AH, because some steps require careful observation to achieve familiarity with the tissue planes, whereas LH, which is technically more difficult, is aided by the excellent visualization afforded by the modern laparoscopes and television monitors. For VH, the crux of the issue lies in friendliness with the anterior and posterior pouches, i.e. getting access to peritoneum.

The complication rate for AH is 70% higher than that for VH. Western Australia study of 83,000 hysterectomies shared that the occurrence of a serious complication were 20% lower for vaginal hysterectomies compared with abdominal procedures.\(^8\)

In the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) study of 3,798 hysterectomies from the UK, the overall operative complication rate for VH was 3.07% while 3.57% of AH patients were reported to have a complication of surgery and 6.07% of women treated by LAVH experienced a complication.\(^9\) Overall complication rate was 5.3% for VH and 12.6% for AH as concluded from study of 1,427 hysterectomies between 1988 and 1993.\(^10\)

One conclusion of the VALUE study is that laparoscopic techniques tend to be associated with higher complication rates than other methods. Major concern is toward urinary tract injuries. Cystotomy and ureteric injury rate is 1.38% and 0.91% respectively.\(^11\) This rate is far too high when compared with conventional VH. In a review of 1,372 articles in the world literature between 1970 and 1996, the incidence of bladder injury was highest with LH. Postoperative fever which often matters to patient as well as relatives was significantly higher in the abdominal group (18%) compared with 9% and 8% respectively in the vaginal and LAVH groups.\(^6\) Wound infection, which is unlikely after VH, adds 3.5 days to the hospital stay after AH.\(^7\) The chances of leaving behind a sponge are remote with VH. The Collaborative Review of Sterilization Study (CREST) report shows an overall rate for the complication of bleeding of 2.6% with VH and of 1.6% with AH. The CREST study shows that complication of bleeding is more by 1% with VH than with AH.\(^6\) Blood loss is more when VH is associated with repair than without. However, blood transfusion rate is higher with AH than with VH. Operative morbidity, cosmesis and recuperation favor the vaginal approach. It has advantages in recovery, cost, hospital stay, absence of scar and is the least invasive and minimal accessed hysterectomy.

**Stay**

Hospital stay for VH and LAVH is similar, and both are significantly shorter than for AH.\(^12\) Abdominal hysterectomy
will have hospital stay longer by 24–72 hours and this can matter to patient, relatives, hospital and insurance company. In an interesting study, Summitt et al.\textsuperscript{13} showed that, following simple VH, the total hospital stay could average 9.4 hours with 100% patient satisfaction. This study clearly announced that hospital stay can be considerably reduced, to less than 48 hours.

**Cost**

All studies comparing laparoscopic and VH reported laparoscopic hysterectomy to be more expensive\textsuperscript{6} and VH is the least expensive.\textsuperscript{14} Kovac\textsuperscript{10} has contended that if size, access and adnexa are evaluated, 90% of hysterectomies for benign indications could be safely done vaginally, thus saving more than $200 billion each year in the United States—easily more than $1,000 per hysterectomy.

The advent of LH has increased the incidence of recourse to the vaginal route, since the vaginal part of the procedure, (if the correct indications have been followed) is actually much more difficult than performing a VH with a prolapse or with good access. Sutton\textsuperscript{15} emphasizes that what is achieved laparoscopically does not make the vaginal part of the surgery easy. One study has been published assessing the impact of introducing LAVH into a community based gynecological practice, where the rate of VH prior to the advent of LAVH in 1991 was 27.7% and later the incidence had doubled to 53%.\textsuperscript{3} The number of cases of AH has been reduced by 29% with a concomitant increase in the number of VH.\textsuperscript{16} The incidence of AH precipitously fell to 12% from 66% with concurrent rise of LAVH from 0% to 40%\textsuperscript{3} or rise in laparoscopically-assisted Doderlein hysterectomy. This blatantly reflects the down of LH and the generally preferred direction of the route for hysterectomy.

**Randomized Controlled Trials**

Evidence-based medicine shows that the first randomized controlled trial (RCT) was reported by Richardson\textsuperscript{17} from the Royal Free Hospital in London. They had 45 patients in their study and the operating time was much longer with the LAVH, and other measures of recovery and morbidity were similar in the two groups. The other slightly larger study is reported by Summitt et al.\textsuperscript{13} In this study, 56 patients were included who had adequate uterine mobility and a good shaped pelvis. As expected, the operating time in the LAVH group was longer than in the conventional VH group, but other measures suggested little difference between the two approaches, apart from the fact that operative blood loss after conventional VH was significantly greater. This resulted in overall reduction of AH and a corresponding rise in LAVH with automated rise in VH, bringing forth the importance of VH as a technique of first choice.

A randomized study of total abdominal hysterectomy (TAH), VH and LAVH by Ottosen et al.\textsuperscript{18} showed that mean stay in hospital and mean time to recovery was significantly longer for TAH compared with VH and LAVH. It was possible to remove uteri under 600 gm with all three methods.

There are 20 RCTs comparing TAH and VH with LH and 16 RCTs comparing LH with TAH. Almost all trials indicate that LH takes more surgical time with lesser stay and shorter recovery period. Conclusion from 27 trials with 3,643 was, where VH is not possible LH is preferable to AH, although it brings a higher chance of bladder or ureter injury.\textsuperscript{19} Another four studies, though not randomized, clearly suggest that VH should be preferred for hysterectomy, unless specific indications in favor of the abdominal or laparoscopic route are present. Recent papers by Clayton and the Cochrane database reviewed evidence-based hysterectomy studies and Reich concluded that VH is preferable to AH. There is no evidence to support the use of LH if VH can be done safely.\textsuperscript{18–21}

**Quality of Life and Satisfaction**

A prospective study from the technology assessment group at Kaiser Permanente, which examined quality-of-life (QOL) measures, found that patients who had VH returned to normal activity much sooner and had more favorable pain, activity, and function outcomes than patients who underwent either LAVH or AH.\textsuperscript{22} LH had lower mean increase in quality adjusted life years (QALYs) than VH.

Thus, when all clinical decisions are equal, VH appears to provide the most satisfactory outcomes from the patient’s point of view, although QOL outcomes for the laparoscopic procedure were often as favorable and both were superior to AH. Before concluding, results require proof—evidence that convinces and this has accrued out of RCTs and various studies.

### INDICATIONS OR ASSOCIATED CONDITIONS

- For following, benign indications, in absence of contraindication, vaginal route should be a primary route for hysterectomy and performing alternative is certainly not in the best interest of our patient. They are:
  - Dysfunctional uterine bleeding
  - Adenomyosis
  - Fibroid
  - Uterine prolapse
  - Polypsis
  - Carcinoma in situ (CIN III) of cervix
  - High-risk with early endometrial cancer.

- Following associated conditions should never deter gynecologist in selecting vaginal route as primary route for hysterectomy:
  - Nulliparity
  - History of cesarean section
  - Oophorectomy
Indications for Abdominal Hysterectomy

- Uterine size greater than 20–24 weeks size of gestation (VH contraindicated and LAVH risky or very difficult)
- Associated dense adhesions due to endometriosis or pelvic inflammatory disease (PID) or following cesarean in past
- Suspicion of malignancy, e.g. in a rapidly growing tumor
- Adnexal pathology
- Adnexal pathology suspicious of malignancy
- Broad ligament fibroid.
- Associated extragenital surgery or incisional hernia repair from a scar compatible for hysterectomy.

Evidence recommend that AH is indicated when the clinical as well as under anesthesia findings indicate that VH is unsuitable and should not be done, i.e. contraindicated, and LAVH is risky or very difficult.

Contraindications

These are few to take away the option of choosing vaginal route as primary route for hysterectomy. They are:

Common

- Uterus more than 12 weeks’ size or uterine volume more than 250–300 cm³
- Restriction of uterine mobility
- Adnexal pathology.

Uncommon

- Cervix flush with the vagina or past Fothergill’s operation makes the cervix look most unlike a cervix.
- Invasive cancer of the cervix.
- Vesicovaginal and/or rectovaginal fistula repair.

Inaccessible cervix: Uncommonly, after repeated uterine surgery, particularly, past cesarean section, there are dense adhesions between the uterocervical surface, the bladder and the lower abdominal wall (Fig. 1) which makes the cervix inaccessible to an approach by the vaginal route. These adhesions can be anticipated by simple speculum examination by the presence of Sheth’s cervicofundal sign (Fig. 2). With a rise in the cesarean section rate, gynecologists should be aware of such adhesions.

- Uterocervical angles of 90°. Globular uterus mimicking small melon perched on top of cervical stump typically angles between the lateral cervical surface and the
ascending uterine wall from the cervix. When the angle is reduced from usual 140° or more to 90° or thereabout (Fig. 3)23 chances of failing to perform a VH rise sharply. Diagnosis comes from clinical and more so from almost identical all three dimensions on sonography when uterus is larger than 18 weeks size.

Many gynecologists are reluctant to undertake VH under the following circumstances, although they are in no way contraindications to this technique for hysterectomy. They appear more like excuse to condone oneself.

**Excuses for Avoiding Vaginal Route**

- Nulliparous women
- Absence of uterine prolapse
- Uterine enlargement, either with adenomyosis or myomas or dysfunctional uterine bleeding (DUB)
- Previous pelvic surgery such as cesarean section, myomectomy
- Cases wherein oophorectomy is indicated.

**Nulliparity**

The best guidance in these cases for suitability of VH is obtained from careful examination under anesthesia. Occasionally, laparoscopic evaluation will resolve any doubt. Not uncommonly, young women with severe mental handicap or learning disability provide classical example of possible VH in nulliparous virgins.24 At worse, laparoscopic assistance will be a far better choice than opening of the abdomen. Very few series of vaginal hysterectomies had more than 10% nulliparous patients before the advent of LAVH, this has now gone up to 40%.25 In a series of 365 women without prolapse who underwent attempted VH, Agostine reported an overall success of 96.2% in nulliparous and 99.7% in multiparous women.26

**Absence of Uterine Prolapse**

Presence of uterine prolapse is never a prerequisite for undertaking vaginal route for hysterectomy. Every gynecologist needs to be aware that every uterus, in absence of pelvic pathology, has a certain degree physiological descent to initiate VH. Careful examination under anesthesia will clear the doubt about descent and remove apprehensions regarding this aspect.

**Uterine Enlargement**

Several techniques have been described to deal with the enlarged uterus at the time of vaginal hysterectomy, including bisection, morcellation, myomectomy, organized debulking and coring when the uterine mobility and access are adequate.3,23,27 This situation would arise only when size is greater than 10–12 weeks or uterine volume is greater than 250–300 cm³. Another way of facilitating the operation is to shrink the fibroids preoperatively with gonadotropin-releasing hormone agonists.3 Vercellini et al. found that VH was possible in 80% of treated patients versus 16% of untreated patients.

Flow chart 1 demonstrates the clear approach for selecting the technique of hysterectomy when the uterus is enlarged.

**Previous Pelvic Surgery or Cesarean Sections**

Currently, 20% or more of the deliveries are carried out by cesarean section in most countries.28 One of the techniques that the author finds most useful in circumventing dense adhesions is use of the lateral window or the uterocervical broad ligament space described by Sheth (Figs 4 and 5).29

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**Flow chart 1:** Algorithm for hysterectomy for enlarged uterus/uterine fibroids uterus (size in weeks)

- **≤ 12**
  - VH

- **> 12**
  - 13–16
    - Experienced vaginal surgeon trial VH
    - LAVH TLH TAH

- **17 to 22–24**
  - LAVH TLH TAH ? Trial VH

- **> 22–24**
  - TAH

---

**Abbreviations:** VH, vaginal hysterectomy; LAVH, laparoscopically assisted vaginal hysterectomy; TLH, total laparoscopic hysterectomy; TAH, total abdominal hysterectomy
This allows access to the vesicouterine fold of peritoneum from the lateral aspect. It can be used to comfortably gain access to the bladder without risk of bladder trauma. Magnetic resonance imaging (MRI) studies confirm the presence of this space or window. Sizzi and Rossetti and also Khung note that “a safer approach is from the lateral, the surgical window described by Sheth which allows a safe, sharp dissection also through laparoscopy, starting from both sides going medially toward the medial portion of the vesicouterine space” (Fig. 6). However, if operator is apprehensive about possible anterior adhesions, laparoscopic evaluation can guide as well as instill confidence to perform a trial vaginal hysterectomy. LAVH will be a more scientific approach than opening of the abdomen. Laparoscopically assisted vaginal hysterectomy may be needed for adhesiolysis, if there are significant pelvic adhesions from previous cesarean delivery,7 other abdominal procedures, PID or endometriosis. VH is safe for women who have a history of previous cesarean delivery. LAVH is usually not needed by these women except on those rare occasions in which the lower part uterus is densely adherent to the lower abdominal wall. Laparoscopic dissection of the bladder is not indicated, because vaginal dissection is actually anatomically more correct and should be less likely to result in bladder injury. Previous vaginal delivery in women undergoing VH provides protection from complications.

**Oophorectomy**

The additional step of vaginal oophorectomy, by any technique, is safe in the hands of the surgeon at VH and does not add to the patient’s morbidity. Experienced vaginal surgeons can achieve safe oophorectomy during VH and should adhere to the indication for this procedure as if working through an abdominal incision.32 Essence lies in cutting round ligaments separately and distally from the uterus so as to get an access to infundibulopelvic ligament (Figs 7 and 8). The ovaries can be accessed and excised vaginally in many ways other than by conventional clamping and cutting,6,33 all without laparoscopic assistance. American College of Obstetrics and Gynecology (ACOG) guidelines clearly defines that LAVH is needed only when oophorectomy at VH is difficult. In other words, it can be done at VH and in few cases—in genuinely difficult cases, LAVH rescues.34
Flow chart 2: Algorithm for prophylactic oophorectomy at vaginal hysterectomy

**Abbreviations**: IPL, infundibulopelvic ligament

or LAVH. Preoperative counseling and intraoperative frozen histopathology facility will prove asset. 

Clinical findings can be strengthened and guided by:
- Examination under anesthesia (EUA)
- Ultrasonography (USG)
- Laparoscopic evaluation.

**EXAMINATION UNDER ANESTHESIA**

“Reliable findings of EUA can give an unambiguous decision on the approach or route for hysterectomy”. This is a singularly important examination, which should form an integral part of the management of a patient needing hysterectomy.

Examination under anesthesia should include the following:
- Exclusion of any contraindication to the vaginal route
- Assessment of uterine mobility, size and physiological descent
- Vaginal and pelvic evaluation in patients with a history of previous pelvic surgery or doubtful adnexal pathology. Diagnostic dilatation and curettage provides an excellent opportunity for careful examination under anesthesia and evaluation of the route for hysterectomy. This must be utilized by the experienced and novice gynecologists alike.

Examination under anesthesia is performed, after placing the patient in the lithotomy position, by careful speculum examination using a volsellum or tenaculum on the cervix and bimanual examination and not as often performed on a patient lying in supine position. 

Algorithm desired in Flow chart 3 indicates how a decision on technique of hysterectomy can be reached based on clinical examination, pelvic sonography and findings obtained on assessment under anesthesia.

Table 3 indicates the preferred approach or route for hysterectomy in various indications and associated conditions.
Table 3: Choice of hysterectomy indications or associated situations

<table>
<thead>
<tr>
<th>Conditions/Situations</th>
<th>Vaginal</th>
<th>Trial vaginal</th>
<th>LAVH</th>
<th>Abdominal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysfunctional uterine bleeding</td>
<td>•</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenomyosis</td>
<td>•</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibroid(s): uterus up to 12 weeks’ size</td>
<td>•</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibroids: uterus up to 13–16 weeks’ size</td>
<td>o</td>
<td>•</td>
<td></td>
<td>●</td>
</tr>
<tr>
<td>Fibroids: uterus 17 to 22–24 weeks’ size</td>
<td>●</td>
<td>●</td>
<td></td>
<td>o</td>
</tr>
<tr>
<td>Endometrial hyperplasia (with or without atypia)</td>
<td>●</td>
<td>●</td>
<td></td>
<td>o</td>
</tr>
<tr>
<td>Polyp: Cervical/Endometrial</td>
<td>●</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nulliparity/Severe mental handicap</td>
<td>●</td>
<td>o</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Cervical intraepithelial neoplasia</td>
<td>●</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endometrial malignancy</td>
<td>●</td>
<td>o</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Early endometrial malignancy in high risk</td>
<td>●</td>
<td>o</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Benign adnexal pathology</td>
<td>o</td>
<td></td>
<td>●</td>
<td></td>
</tr>
</tbody>
</table>

* First choice, o First alternative, ● Second alternative

Abbreviation: LAVH, laparoscopically-assisted vaginal hysterectomy

Flow chart 3: Algorithm indicates how a decision on technique of hysterectomy can be reached based on clinical examination, pelvic sonography and assessment under anesthesia findings

Ultrasonography

This can:
- Confirm clinical findings
- Help to exclude contraindications
- Provide information on endometrial thickness, which is a “must” in all women with menorrhagia and/or suspected endometrial pathology, especially in postmenopausal.
- Detect pathology such as endometrial cyst in an ovary, gall bladder stones, and renal tract pathology.
- Assessment of the total uterine volume provides information on possible surgical approach and possible outcome\(^5\) (Table 4). It can guide the experienced vaginal surgeon in difficult situations either to avoid or attempt the vaginal route for hysterectomy, besides leading to adequate counseling of the patient. Fallacious findings
will lead to misguidance about the approach. Beware of people behind new machines.

**Role of Laparoscopic Evaluation**

When the clinical findings are not conclusive, especially in the early years of practice, the gynecologist may take advantage of laparoscopy as a diagnostic tool to evaluate the feasibility, for hysterectomy via the vaginal route or the need for laparoscopic assistance during VH.

- Vaginal hysterectomy appears possible (i.e. not contraindicated) but the operator has some doubt or apprehension.
- In some cases where trial VH has been planned.
- **Adnexal pathology:** When an experienced vaginal surgeon plans to excise a benign, mobile adnexal mass at vaginal hysterectomy, laparoscopy will evaluate the earlier findings, exclude malignancy and tuberculosis and confirm if removal via the vaginal route is possible.²³

Laparoscopic evaluation needs to be differentiated from laparoscopically-assisted surgery which is operative laparoscopy and wherein the surgical steps taken are part of a VH in progress or to be performed.

**Trial Vaginal Hysterectomy or Tentative Vaginal Route for Hysterectomy**

Even in experienced hands, there are times when it is felt that, although difficult, a VH may succeed. A trial by the vaginal route is undertaken with full preparation to switch over to the abdominal route, if necessary. It is best to discuss this in advance with the patient and her relatives. Failure to do so can result in the patient losing confidence in the surgeon.⁷,³⁶

**Table 4: Uterine volume in cm³ and vaginal hysterectomy (VH)**

<table>
<thead>
<tr>
<th>Uterine volume (cm³)</th>
<th>Possibility of VH</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>Easy, average gynecologist should be able to do it</td>
</tr>
<tr>
<td>101–200</td>
<td>Interested gynecologist should be able to do it easily</td>
</tr>
<tr>
<td>201–400</td>
<td>Best performed by gynecologist with expertise/experience</td>
</tr>
<tr>
<td>300–350</td>
<td>Needs debulking</td>
</tr>
<tr>
<td>301–400 and more</td>
<td>Be scheduled as tentative or trial VH; needs debulking consider/availability of LAVH and/or abdominal hysterectomy</td>
</tr>
</tbody>
</table>

Cases likely to fall into this category are:
- Those with uterus greater than 12–14 weeks in size or uterine volume greater than 300–400 cm³.
- Those who have had earlier cesarean section and/or myomectomy and/or uterine rupture
- Nulliparous women
- Those who have had previous surgery for uterine prolapse or suspension
- Those with doubtful adnexal pathology or benign, mobile adnexal mass
- During the early part of the surgeon’s learning curve. It is comparable to a trial forceps delivery in obstetrics. Such a plan will considerably reduce the number of abdominal hysterectomies, gradually reduce number of LAVH, enhance the surgeon’s experience and sharpen his or her judgment on when to undertake VH.

**Laparoscopically Assisted Vaginal Hysterectomy**

**Indications**

- Uterine size greater than 12–14 weeks and less than 22–24 weeks
- Benign adnexal pathology
- Pelvic endometriosis or adhesions
- Excessive vaginal narrowing
- Large and/or not easily accessible fibroid at VH
- Endometrial malignancy—selected cases

ACOG Guidelines give crystal clear picture of place of LAVH.

LAVH is required when:

- Lysis of adhesions
- Treatment of pelvic endometriosis
- Uterine fibroids that complicate the performance of VH
- Ligation of infundibulopelvic ligaments to facilitate difficult ovary removal
- Evaluation of the pelvic and abdominal cavity before hysterectomy.³⁴

In other words, LAVH may be the method of choice when hysterectomy by the vaginal route is contraindicated. Usually LAVH is used to undo that which makes VH contraindicated, difficult or risky. Only when LAVH is contraindicated, risky or difficult is the, abdominal route to be considered. When hysterectomy is possible by both methods, LAVH is superior and preferred technique to performing AH.

**Subtotal Hysterectomy**

There is a recent trend toward saving the cervix at hysterectomy (subtotal hysterectomy or supracervical hysterectomy). Subtotal hysterectomy may be abdominal, laparoscopic or vaginal.

Subtotal hysterectomy is less easy to perform vaginally than total vaginal hysterectomy. Under the circumstances, it is not worthwhile recommending it, especially since the advantages of the retained cervix are nebulous. Recently, Sutton¹⁵ has drawn attention to the fact that laparoscopic
subtotal hysterectomy is associated with a large number of secondary procedures to remove the cervical stump.

It is worth noting that 20% of women experienced vaginal bleeding after subtotal abdominal hysterectomy and more women suffered from urinary incontinence after subtotal than TAH and there was no difference in sexual satisfaction with type of hysterectomy. Several prospective, randomized trials from United States, England, Holland and Denmark suggest that preservation of the cervix does not help bladder, bowel and sexual function. Dr Parker, commented in no uncertain terms that supracervical hysterectomy was an operation devised by and made for incompetent surgeons. Authors wonder at laparoscopic surgeons commending subtotal hysterectomy. Is hysterectomy subtotal because of lack of surgeon’s confidence to safeguard ureters and bladder at laparoscopic surgery and later advocating better sex life and/or preserving uterine ligaments intact a marketing device? Morrow rightly asks: “Is the conventional wisdom that teaches that the cervix be removed with the uterus to be disregarded for the technology costs and reduced recovery time?” Nevertheless, subtotal hysterectomy is indicated in the following circumstances:

- The patient’s condition demands a rapid hysterectomy
- In the presence of inseparable adhesions that increase the danger of trauma to the sigmoid colon or ureters
- When the patient insists on retaining the cervix.

**IMPORTANT POINTS TO REMEMBER WHEN CHOOSING THE ROUTE FOR HYSTERECTOMY**

All uteri that can be removed vaginally can be removed by the abdominal route or by LAVH, but the reverse is not true. In practice, more than 70–80% of hysterectomies can be carried out via the vaginal route and only in the remaining recourse to LAVH or the abdominal route is required. Laparoscopic surgery is a boon and a great addition to our armamentarium as it has demonstrated the superiority of the vaginal over the abdominal route beyond reasonable doubt.

Examination under anesthesia should become the gold standard. Reliable USG findings coupled with clinical and EUA findings can guide the gynecologic surgeon and when in doubt laparoscopic evaluation will provide further information. Flow chart 4 shows the stages for developing operative technique in vaginal hysterectomy starting from a straight forward normal-size parous uterus with third-degree descent to more difficult presentations and more complex procedures.

Today, surgeons advocating AH are becoming laparoscopic surgeons and learning to perform a VH so that they can perform LAVH; on the other hand, those advocating vaginal hysterectomies are expanding the indications and reducing the contraindications for VH, using a better and preferred method surgery and having fewer complications than abdominal surgery.

Evidence suggests only when VH is contraindicated, should LAVH be considered and when LAVH is not possible, AH is to be considered. If hysterectomy is possible by all three approaches, in the best interests of the patient, the order of preference would be vaginal, LAVH and abdominal.
REFERENCES


Endocrinology
Female Endocrinology and its Clinical Relevance

INTRODUCTION

Female endocrinology is a very complex system. In this chapter the author has tried to explain the whole physiological process of the development of a female fetus into an adult female and the physiology of normal menstrual cycle in a simplified form.

TWO-CELL SYSTEM (FIG. 1)

Theca cells secrete androgens in response to luteinizing hormone (LH). This androgen diffuses into the granulosa cells, and in granulosa cells aromatization of androgen produces estrogen. Insulin-like growth factor (IGF) helps in both the processes—production of androgen and its conversion to estrogen. Activin helps to produce follicle stimulating hormone (FSH) and its receptors. Inhibin enhances the action of theca cells. So, estrogen secretion prior to ovulation is a result of combined FSH and LH stimulation on two cells—theca cells and granulosa cells.

Majority (69%) of the sex steroid hormones, estradiol (E2) and progesterone are bound to protein carrier known as sex hormone binding globulin (SHBG), produced mainly in liver. Another 30% is bound to albumin and only 1% is unbound, i.e. free.

Hyperthyroidism, pregnancy and estrogen increase SHBG and so decrease free hormonal levels while corticoids, androgens, progestin, growth hormone, insulin and IGF-1 decrease SHBG levels and increase free hormonal levels. Weight gain and hyperinsulinemia can decrease the levels of SHBG, and low SHBG is a predictor of type II diabetes mellitus.

Estrogen Metabolism

Androgens are common precursors to estrogen. Androstenedione is converted into testosterone through 17β hydroxysteroid dehydrogenase activity. Testosterone is rapidly aromatized to estradiol which is the major estrogen secreted by ovary. Estradiol also comes from estrone which is a derivative of androstenedione as shown in Figure 2, showing steroidogenesis. Estriol is a peripheral metabolite of estrone and estradiol. So how estrogens are produced is shown in Figure 1.

Free androgens are converted into free estradiol in skin and adipose tissues. Central obesity produces more androgens. In females, adrenal gland remains a major source of androstenedione.

In a normal woman, estradiol is produced at the rate of 100–300 mg/day. Production of androstenedione is 3 mg/day. Twenty to thirty percent of androstenedione is converted to estrone per day. Therefore, as shown in Figure 2 in female, circulatory estrogens are a sum of ovarian secretion of estrogens and peripheral conversion of androgens to estrogen.

Progesterone Metabolism

Peripheral conversion of steroids to progesterone is not seen in a nonpregnant female. Progesterone comes from...
adrenals and ovaries. Before ovulation, progesterone levels are lower than 1 mg/day. During luteal phase, production of progesterone reaches as high as 20–30 mg/day. About 10–20% of progesterone is excreted as pregnanediol. This is the compound which is used as basis for home pregnancy test kits.

Progesterone level in preovulatory phase is lower than 1 ng/mL and in luteal phase it is 3–15 ng/mL. In congenital adrenal hyperplasia, progesterone levels are 50 times higher above normal, and because of the enzymatic defect of 21 hydroxylase, 17α hydroxylase level also increases. Its level normally in preovulatory phase is lower than 100 ng/dL and in luteal phase it is 200 ng/dL. In congenital adrenal hyperplasia it is 10–400 times the normal values.

\[
\text{Progesterone} \rightarrow 17\text{-hydroxyprogesterone (17-OHP)}
\]

\[
\text{Pregnanediol} \quad \text{Pregnanetriol}
\]

**Androgen Metabolism (Fig. 3)**

The major androgen products of the ovary are androstenedione, dehydroepiandrosterone (DHA) and very little testosterone. Androgen level rises at the time of ovulation.

Adrenal sex steroids are normally intermediate products for corticosteroids and glucocorticoids. Therefore, excessive steroids from adrenals are due to neoplasm or enzyme deficiency. About 50% of androstenedione and DHA comes from adrenals. Other 50% of androstenedione is from ovary, while for DHA, 25% comes from ovary and 25% from peripheral tissue.

Testosterone secretion is 0.2–0.3 µg/day and out of total secretion 50% comes from peripheral conversion of androstenedione, 25% is secreted from ovary and 25% from adrenal. Androgens are excreted in urine as 17-ketosteroids.

Total testosterone level may be normal in hirsutism and this is because of low levels of SHBG because of which free testosterone level is high. Sometimes, free testosterone may be normal but its conversion to dihydrotestosterone by 5α reductase may be high and represents as hirsutism. This can be diagnosed by high levels of 3α androstenediol which indicates increased activity at target tissue.
Neuroendocrinology

There are two major sites of action within the brain that are important in the regulation of reproductive function—the hypothalamus and the pituitary gland. The hypothalamic-hypophyseal portal circulation is responsible for neurohormonal transmission. Gonadotropin releasing hormone (GnRH) stimulates gonadotropin synthesis and secretion as well as activin, inhibin and follistatin secretion. Activin enhances and follistatin suppresses GnRH activity and gonadotropin response can be blocked by follistatin. Prolonged GnRH stimulation causes downregulation of pituitary. Increasing GnRH pulsatile frequency first increases FSH production and then with high frequency or continuous GnRH stimulation follistatin production is increased which suppresses gonadotropins.

Pulsatile GnRH secretion must be within a critical range for frequency and concentration (amplitude). This is absolutely necessary for normal reproductive function. Gonadotropin releasing hormone has only positive actions on the anterior pituitary: synthesis and storage activation, and secretion of gonadotropins. Gonadotropins are secreted in a pulsatile fashion in response to similar pulsatile release of GnRH. Lower GnRH pulse frequencies favor FSH secretion and higher GnRH pulse frequencies favor LH secretion. Low levels of estrogen enhance FSH and LH synthesis and storage, have little effect on LH secretion, and inhibit FSH secretion. High levels of estrogen induce the LH surge at midcycle and high steady levels of estrogen lead to sustained elevated LH secretion. Low levels of progesterone acting at the level of pituitary gland enhance the LH response to GnRH and are responsible for LH surge at midcycle. High levels of progesterone inhibit pituitary secretion of gonadotropins by inhibiting GnRH pulse at the level of hypothalamus. In addition, high levels of progesterone can antagonize pituitary response to GnRH by interfering with estrogen action.

OVARY

Ovary goes through the following phases:
- Fetal ovary
- Neonatal ovary
- Ovary in childhood
- Adult ovary.

Ovary is a dynamic endocrine organ which expands and shrinks depending on stimulation of tropic hormones so it has different characteristics and functional abilities in different phases of life.

Fetal Ovary

It has four stages of development.

Indifferent Gonad Stage

At 5 weeks of gestation, gonadal ridges are formed which cannot be distinguished into testes or ovary. It contains germ cells and somatic cells which later on become follicular cells. Somatic cells come from epithelial and mesonephric cells.

Stage of Differentiation

At 6–9 weeks the gonads differentiate into testes or ovaries.

Period of Oogonal Multiplication and Oocyte Formation (Fig. 4)

There is rapid mitotic multiplication and gives 6–7 million oogonia by 16–20 weeks. By mitosis, germ cells give rise to oogonia. The oogonia are transferred to oocytes as they enter first mitotic division and arrest at prophase. They reach to diplotene stage. A single ovum is formed from two meiotic divisions of oocyte, one just before ovulation and second at the time of sperm penetration.

Stage of Follicle Formation

Follicular formation starts by 18–20 weeks. Perivascular cells surround the oocyte which have completed first stage of meiosis and form primordial follicle. So in primordial follicle oocyte is arrested in prophase of meiosis enveloped by a single layer of spindle-shaped pregranulosa cells surrounded by basement membrane. Primordial follicle becomes primary follicle and then preantral follicle by 6 months of pregnancy. Antral follicles are characterized by a fluid filled space and are present in the fetal ovary at the end of gestation. Even in fetal life, follicular formation, ripening and atresia occur. But full maturity and ovulation does not occur.

Unlike male, gonadal steroid production is not required for development of normal phenotype. The development of Müllerian duct into Fallopian tubes, uterus and upper third of vagina are independent of the ovary.

Withdrawal of estrogen from placenta may cause gonadotropin surge which in turn may develop cysts in neonatal ovary. Ovary develops receptors for gonadotropins only in second half of pregnancy. Follicle stimulating hormone circulating peak levels are observed at 28 weeks of gestation.
Neonatal Ovary

Germ cells fall in number to 1–2 million by birth from 6–7 million within last 20 weeks. The gonad on right side is larger and heavier in protein and DNA content. Postnatally FSH rise is more marked than LH because of withdrawal of fetoplacental steroids. This may cause ovarian cyst which is the most common cause of abdominal masses in fetus and newborns. Afterwards gonadotropin levels reach to a nadir during early childhood, i.e. within 1–2 years of age and then rise slightly between 4 years and 10 years.

Ovary in Childhood

This is characterized by low levels of gonadotropins, little response to GnRH and maximum hypothalamic suppression. But number of follicles reaching up to antral stage may decrease in ovaries. Because of atresia of follicles there is increase in weight by 10 folds in ovaries. There is no evidence that ovarian function is necessary up to puberty.

Adult Ovary

At the onset of puberty, germ cell mass is reduced to 3–5 lac units. In the next 40 years, 400–500 will be selected to ovulate. In the last ten years before menopause, there is a rapid loss of follicles. This is secondary to increased FSH and release of inhibin B and IGF-1. For every follicle to mature, approximately 1000 follicles end in atresia which is called apoptosis. From primary follicle to ovulation the follicle takes 85 days.

Ovary is distinguished from adrenal gland in that it is deficient in 21 hydroxylase and 11β hydroxylase reaction, so glucocorticoids and mineralocorticoids are not produced in ovary.

Preantral Follicle

Follicle progresses to preantral stage as the oocyte enlarges and is surrounded by a membrane, the zona pellucida. The granulosa cells undergo a multilayer proliferation as theca layer continues to organize from the surrounding stroma. Initial follicular development occurs independently of hormone influence. Follicle stimulating hormone stimulation rescues a cohort of follicles from apoptosis, propelling them to the preantral stage. FSH-induced aromatization of androgen in the granulosa results in the production of estrogen. FSH and estrogen increase FSH receptor content of the follicle and stimulate the proliferation of granulosa cells.

Antral Follicle

Under the influence of FSH, estrogen, a fluid filled cavity surrounded by granulosa cells develops and cumulus is found surrounding the ova. For continuous follicular growth FSH is necessary and it produces estrogen which continues the growth. But if FSH is low or absent, androgen predominates and causes atresia of follicle.

Synthesis of steroid hormone can be explained by the “two-cell, two-gonadotropin” theory.

Ovarian steroidogenesis is LH dependent. Luteinizing hormone allows low-density lipoprotein (LDL) cholesterol in the cell to form androstenedione and testosterone. Presence of P450c17 only in theca cells and P450arom only
in granulosa cells is the definitive evidence of the “two-cell, two-gonadotropin” theory. It explains the theory of estrogen production.

**Dominant Follicle**

Final stages of maturation are optimized by LH, increasing the amount of androgen substrate for estrogen production and promoting the growth of dominant follicle while hastening the regression of smaller follicles. Estrogen causes negative feedback of FSH and so FSH level decreases, in turn estrogen level decreases causing atresia of less mature follicles. This process is known as apoptosis. Tumor necrotizing factor (TNF) is secreted from granulosa cells which also inhibits FSH stimulation of E2 secretion except in dominant follicle. Anti-Müllerian hormone (AMH) also helps in selecting the dominant follicle and inhibits growth of primordial follicles.

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**Chapter 74**

**Female Endocrinology and its Clinical Relevance**

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**PUBERTY**

**INTRODUCTION**

Puberty has been a time of celebration. Because of improved nutrition and living conditions the age of puberty is earlier nowadays. Puberty is a process of developmental endocrinology that marks the evolution of a child into a sexually mature adult capable of reproduction.

**PHYSIOLOGY OF PUBERTY**

- Period of infancy and childhood
- Prepubertal period
  - Adrenarche
  - Decreasing repression of gonadostat
  - Gonadarche
- Puberty
  - Timing of puberty

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**PERIOD OF INFANCY AND CHILDHOOD (FIG. 5)**

From fetal life to prepubertal stage, hypothalamus, pituitary and ovary can secrete all the hormones. Up to second trimester FSH and LH hormones increase during fetal life. But because of high levels of estrogen and progesterone, inhibitory effect establishes and it causes fall of FSH and LH. Separation of the newborn from mother deprives it of estrogen and progesterone which causes negative feedback to stimulate FSH and LH. So there is transient E2 secretion for 2–4 months. But by one year full negative feedback is achieved and by 2 years they remain very low till 6–8 years. Estradiol is very low up to 10 pg/mL. Gonadostat is highly sensitive to negative E2 and gonadotropins are kept at low levels. The other mechanism causing low gonadotropin is central suppression of endogenous GnRH and gonadotropin synthesis.

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**PREPUBERTAL PERIOD**

**Adrenarche**

Increased production of adrenal androgen causes growth of pubic and axillary hair. This is known as adrenarche or pubarche. There is progressive increase of dehydroepiandrosterone (DHA), dehydroepiandrosterone sulfate (DHAS), androstenedione associated with 17β hydroxylase and 17-20 lyase activity (P450c17 enzyme) from age 6–7 years to adolescence (13–15 years). Adrenarche precedes growth spurt by 2 years, increases estrogen and gonadotropin, and menarche. Therefore, adrenal androgen may be initializing event in pubertal transition. Adrenarche is not under the

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Fig. 5: Hormone levels from fetal life to childhood

Abbreviations: FSH, follicle stimulating hormone; LH, luteinizing hormone; DHA, dehydroepiandrosterone; hCG, human chorionic gonadotropin
direct control of adrenocorticotropic hormone (ACTH) or gonadotropins. Controlling factors of adrenarche and gonadarche are different. Pituitary androgen stimulating factor has been suggested as the agent stimulating adrenarche.

There is prominence of zona reticularis which secretes DHA and DHAS and there is relative deficiency in 3β hydroxysteroid dehydrogenase activity which is maintained in adult life and its higher level prevents adrenarche in earlier life.

**Decreasing Repression of Gonadostat**

There is decrease in central nervous system (CNS)—pituitary gonadostat, pituitary becomes responsive to GnRH, FSH and LH initiates follicular reactivity.

Up to 8 years FSH and LH are suppressed to a very low level. This is because of very high sensitivity of negative feedback of low levels of estrogen on hypothalamus and pituitary sites and central inhibitory influence on GnRH. Decrease in GABA (γ-aminobutyric acid) and neuropeptide Y increases secretion of GnRH and there is onset of female puberty.

Another postulation is reduction of melatonin from pineal body which causes reversal of central suppression. This is not proven in humans to initiate puberty.

**Gonadarche**

The normal pubertal timing of gonadarche results from combined reduction of intrinsic suppression of GnRH and decreased sensitivity to negative feedback of estrogen. Gonadotropin releasing hormone secretion increases and causes secretion of FSH and LH from anterior pituitary. Luteinizing hormone responses are much greater than FSH responses to GnRH. As gonadotropin secretion increases ovarian follicle starts secreting estrogen. By midpuberty, estrogen enhances LH secretory response to GnRH (positive feedback) while combining with inhibin to maintain relative inhibition (negative feedback) of FSH response. The secretion of biologically active LH rises more than immunologic LH. Frequencies and amplitudes are more common during night in initial phases and later on by late puberty, they are more in day time.

**Timing of Puberty**

- It is decided by genetic factors
- Geographic location at equator, exposure to light, lower altitude, good health and nutrition (urban areas), obesity and psychological factors promote early puberty and vice versa
- Age of menarche depends on menarche of mother and sisters
- Earlier the onset, longer the duration of puberty
- Central mechanism brings hypothalamo-pituitary ovarian axis which stimulates growth to critical weight and increases body fat
- Leptin level increases and regulates eating behavior and energy balance. Leptin is secreted from adipose tissue. Therefore, higher the leptin, earlier is menarche
- Leptin has important relation with nutrition and reproduction.

**Stages of Pubertal Development**

Pubertal sequence requires period of 4–5 years (range 1.5–6 years).
- Breast and pubic hair: 7–8 years
- Menarche: 11–12 years
- Thelarche: 9–10 years (7–10)
- Adrenarche: 9 years (7–11)

The first sign of puberty is acceleration of growth.

**Breast Development (Table 1)**

- Breast budding
- Enlargement and elevation of nipple and areola
- Elevation of breast
- Formation of final adult contour

**PUBERTY**

Release of pulsatile GnRH from prepubertal feedback and central negative inhibition leads to increase in gonadotropin levels and steroids causing appearance of secondary sexual characteristics and menarche ovulation. Between the age of 10 years and 16 years, endocrine sequences observed are release of gonadotropins, increase in pulsatile peak of LH, episodic peak of estradiol, menarche, followed by maturation of positive feedback between estradiol and LH leading to ovulatory cycles.
### Table 1: Tanner staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>Breast</th>
<th>Pubic hair</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1 (prepubertal)</td>
<td>Elevation of papilla only</td>
<td>No pubic hair</td>
</tr>
<tr>
<td>Stage 2</td>
<td>Elevation of breast, papilla as small mound, enlarged areola diameter, Age: 9.8 years</td>
<td>Sparse, long, pigmented hair chiefly along labia majora Age: 10.5 years</td>
</tr>
<tr>
<td>Stage 3</td>
<td>Further enlargement without separation of breast and areola, Age: 11.2 years</td>
<td>Dark, coarse, curled hair, sparsely spread over mons: 11.4 years</td>
</tr>
<tr>
<td>Stage 4</td>
<td>Secondary mound of areola and papilla above breast Age: 12.1 years</td>
<td>Adult type hair, abundant but limited to mons: 12 years</td>
</tr>
<tr>
<td>Stage 5</td>
<td>Recession of areola to contour of breast Age: 14.6 years</td>
<td>Adult typespread and quantity distribution: 13.7 years</td>
</tr>
</tbody>
</table>

### Growth

The growth spurt in adolescent girls occurs two years earlier than boys. Growth peak occurs two years after breast bud and one year prior to menarche. Growth is due to estrogen, growth hormone and IGF-1. Growth in puberty is influenced by growth in utero.

Normally, growth hormone is stimulated by sex steroids. Calcium supplementation in puberty causes increase in bone density. Growth is slower after menarche. The concentration of hormones in blood during different stages of female puberty is shown in Table 2.

### Menarche

Decline in the age of menarche is due to improved nutritional status and healthier living conditions in developed countries. There has been shift of body composition to a greater percent of fat (from 16% to 23%). So, moderately obese girls get earlier menarche. Delayed menarche or amenorrhea is seen in low weight and exercising girls. Blind girls get earlier menarche.

The final hallmark of puberty is development of positive estrogen feedback on pituitary and hypothalamus. It stimulates midcycle LH surge required for ovulation. Anovulation may last for 2–4 years after menarche. The differentiating point between GnRH dependent and independent precocious puberty are basal FSH/LH levels. These are high in non GnRH dependent precocious puberty and are low in GnRH dependent precocious puberty.

With premature adrenarche do 17-OHP to rule out 21 hydroxylase deficiency. The treatment of GnRH dependent precocious puberty is GnRH agonist, antagonist are under trial.

In noncentral precocious puberty suppression of gonadal steroid is done by medroxyprogesterone acetate or aromatase inhibitors.

### Precocious Puberty (Table 3)

Puberty changes before 8 years and menarche before 10 years of age are known as precocious. Adrenarche and Thelarche before 6 years of age requires evaluation. Increased growth may be the first sign of puberty but sometimes menarche may be the first sign. It may be GnRH dependent or independent.

In 75% of cases, it is idiopathic but CNS lesions should be ruled out. Ovarian tumors, adrenal disease, McCune-Albright syndromes are to be ruled out.

It causes adults with short status. Thyroid evaluation in all these cases is a must.

### Table 3: Classification and relative occurrence of precocious puberty

<table>
<thead>
<tr>
<th>Category</th>
<th>Female (%)</th>
<th>Male (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic</td>
<td>74.0</td>
<td>41.0</td>
</tr>
<tr>
<td>CNS problem</td>
<td>7.0</td>
<td>26.0</td>
</tr>
<tr>
<td>Ovarian (cyst or tumor)</td>
<td>11.0</td>
<td>—</td>
</tr>
<tr>
<td>Testicular</td>
<td>—</td>
<td>10.0</td>
</tr>
<tr>
<td>McCune-Albright syndrome</td>
<td>5.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Adrenal feminizing</td>
<td>1.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Adrenal masculinizing</td>
<td>1.0</td>
<td>22.0</td>
</tr>
<tr>
<td>Ectopic gonadotropin production</td>
<td>0.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>
**Preovulatory Follicle**

Preovulatory follicle produces increasing amount of estrogen. This estrogen level reaches to a peak 24–36 hours prior to ovulation. The onset of LH surge starts with peak levels of estradiol and it seals the fate of other follicles. This LH surge inhibits further cell growth of remaining follicles and promotes steroidogenesis along with the secretion of IGF.

Luteinizing hormone promotes luteinization of the granulosa cells in dominant follicle which produces progesterone. This small amount of progesterone has a significant importance. Along with LH this progesterone also limits granulosa cell proliferation. Progesterone facilitates not only positive feedback of estrogen and subsequently LH but also is responsible for midcycle FSH surge. This ensures completion of FSH function on the follicle.

There is a rise of 17α-hydroxyprogesterone. This indicates rise in androgen from theca cells which is required for estrogen production. This androgen rise is due to effect of LH on follicles undergoing atresia, the theca cells of which are converted to stromal tissue, which produce androgen. Androgen is also responsible for atresia of smaller follicles and increase in lutein in preovulatory period.

**Ovulation**

Ovulation occurs after 10–12 hours of LH peak and 24–36 hours after the estradiol peak. Onset of LH surge is an indicator that ovulation would occur in 34–36 hours. This surge is responsible for full maturation of the oocyte and lasts for 48–50 hours.

Up to the age of 30 years ovulation alternately occurs from both ovaries, but right ovary ovulates more frequently.

Luteinizing hormone surge causes expansion of cumulus, synthesis of prostaglandins and other substrates required for follicular rupture and initiation and continuation of meiosis. Luteinizing hormone-induced cyclic adenosine monophosphate (cAMP) activity overcomes inhibitory effect on oocyte because of oocyte maturation inhibitor (OMI) and luteinization inhibitor (LI, i.e. endothelin-1). Therefore, OMI, LI and activin together prevent premature luteinization of the follicle by suppressing progesterone before the LH surge.

Cumulus oophorus has no LH receptors and no progesterone production. Oocyte controls the cumulus cells and prevents premature luteinization.

Progesterone increases distensibility of follicular wall. Follicle stimulating hormone, LH and progesterone increase the proteolytic activity resulting in digestion of collagen. These changes with histamine release induce ovulation. Ovulation is a result of proteolytic digestion of follicular wall.

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**Fig. 7: Endocrinology of ovulation**

*Abbreviations: FSH, follicle stimulating hormone; LH, luteinizing hormone; 17-OHP, 17-hydroxyprogesterone*
apex, a site called “stigma”. FSH peak is totally dependent on preovulatory progesterone. Gonadotropin (FSH) surge stimulates granulosa cells to produce “plasminogen activator” which converts plasminogen to plasmin and helps ovulation. Hyaluronic acid matrix is also produced in follicle due to FSH rise, which frees the ovum from follicular attachments to help in ovulation. Hyaluronic acid and FSH also produce adequate LH receptors. Therefore, low FSH in follicular phase will in turn have less LH receptors resulting into inadequate luteal phase.

Prostaglandin synthesis is due to LH surge. It is increased by interleukin B. If prostaglandins are not synthesized, follicle will not rupture and ovulation will not occur in spite of luteinization and steroidogenesis, and results in luteinized unruptured follicle (LUF). Therefore, prostaglandin synthesis inhibitors are always avoided during infertility treatment.

High level of LH suppresses estradiol production. Progesterone also prevents granulosa cell proliferation decreasing E2. Decrease in LH is because of decrease in estradiol and negative feedback of progesterone. The level of LH is controlled by a short negative feedback of LH on hypothalamus and gonadotropic surge inhibitory factor (GSIF) from ovary.

**Luteal Phase**

After ovulation, granulosa cells enlarge and become vacuolated with deposition of lutein pigment. Capillaries begin to penetrate into the granulosa layer after cessation of LH surge and reach the central cavity. Angiogenesis is mediated by vascular endothelial growth factor (VEGF) produced by granulosa lutein cells.

By day 8–9, vascularization is at the peak along with peak estradiol and progesterone levels. Corpus luteum has highest blood flow per unit mass in the body and so corpus luteum hematoma is a serious complication causing acute surgical emergency particularly for those who are on anticoagulants like aspirin.

When fertilization occurs, human chorionic gonadotropin (hCG) is secreted by fertilized ovum which starts between day 9 and 13 and prevents corpus luteal regression. Human chorionic gonadotropin maintains steroidogenesis from corpus luteum till 9–10 weeks of gestation. Luteinizing hormone regulates LDL receptor expression which helps in synthesis of progesterone. Presence of leukocytes in corpus luteum are rich source for cytolytic enzymes, prostaglandins and growth factors involved in angiogenesis, steroidogenesis and luteolysis. In view of the known estrogen requirement for synthesis of progesterone receptors in endometrium, luteal phase estrogen may be necessary to allow the progesterone-induced changes in endometrium after ovulation. Inadequate progesterone receptor content due to inadequate estrogen priming of the endometrium is an additional possible mechanism for infertility or early miscarriage, another form of luteal phase insufficiency.

**Luteal Follicular Transition**

Two days before the onset of menses there is selective rise of FSH, which directs the recruitment of a new ovulatory follicle. Decrease in luteal steroids and inhibit in change in GnRH pulsatile secretion helps in rise of FSH from midluteal phase. This FSH was supposed due to inhibit B in midluteal phase. During the early growth of follicles, LH is not required. This increase in FSH is responsible for rescuing approximately 70 days old group of follicles, allowing the dominant follicle to begin its emergence.

**REFERENCES**


INTRODUCTION

Menstrual disorders in adolescent age are quite different than in adult women, both for diagnostic and therapeutic management. We need to take into account the problems in normal initiation of menarche, hematological problems, general endocrine problems, and fragile emotional status at this tender age. We also need to keep in mind the anxious parent, long-term sequel of therapy and the effects on reproductive career of the girl.

There are some major limitations in diagnosis of menstrual disorders in adolescent age. The young and sexually nonactive age precludes vaginal examination and transvaginal sonography—the current mainstays of accurate gynecological diagnosis. In planning a therapy also one needs to tread a cautious path when a surgical option is considered, which is not accepted easily by the young girl and her parents.

MENSTRUATION IN ADOLESCENCE

Menarche usually occurs at 12–13 years of age and generally coincides with Tanner stage 4 developments of breast and pubic hair. Of late a trend toward early menarche has been noticed and is attributed to early weight gain as a result of improved nutrition. The relatively higher stress of urban existence also brings an early menarche. Environmental estrogens found in chemicals, pesticides and even the hair products have contributed to early body changes of puberty. However, detailed analysis has shown that the menarchal age has remained static over last few decades.

The menstrual cycle can be quite irregular in first 1–2 years, after which it stabilizes. The menstrual cycle length averages about 33 days in women below 21 years of age compared to 26 days by age 40. Thin girls tend to have longer cycles whereas girls who drink alcohol regularly have shorter cycle length. The duration of period averages 6.6 days in young girls compared to shorter duration in older age. Smokers have longer periods while athletes tend to have shorter periods.

Menstrual problems are perhaps the main cause for which adolescent girls seek medical advice in India. The commonest menstrual disorders observed in this age are:

- Dysmenorrhea (painful menstruation)
- Amenorrhea or oligomenorrhea (absent or reduced menstruation)
- Dysfunctional uterine bleeding (DUB), menorrhagia (excessive and/or irregular menstruation).

The initiation of menstruation is a relatively complicated and sometimes frightening event for the young adolescents. Young adolescent girls are quite curious of knowing this mechanism through which menstrual cycle occurs. This provides the physician an excellent opportunity to review the basic anatomy (with the use of models and charts) and then discuss the functions of hormones estrogen and progesterone with young girls. A thorough explanation and understanding of the menstrual cycle and its variations can be very helpful in reducing the fear and stress associated with this event.

The hypothalamic-pituitary-gonadotropin system is the mediator of menstrual cycle. A failure of this system may lead to amenorrhea or sometimes variation in menstruation (DUB). Menstrual problems are common during adolescence...
Due to slow maturation of the hypothalamic-pituitary-ovarian axis and can last 2–5 years after menarche. Adolescents usually lack the positive feedback mechanism to induce luteinizing hormone (LH) surge and subsequent ovulation despite increased follicular estrogen levels. Negative estrogen feedback is intact as evidenced by suppression of follicle-stimulating hormone (FSH), LH and gonadotropin-releasing hormone (GnRH) levels by high estrogen. This indicates that pubertal anovulation is probably a hypothalamic malfunction rather than a pituitary one.

Although most problems are explained by anovulation, other causes must be considered and excluded in a logical and cost-effective manner.

**DYSMENORRHEA**

Dysmenorrhea is one of the common gynecological complaints during adolescence. Around 60% of girls of 12–17 years age group complain of dysmenorrhea; however, only 15% of these seek medical assistance. Girls on average miss out 25% more classes in school compared to boys due to pain during menses.

First few periods are generally pain free due to anovulation. A heavy dragging pelvic pain is more common than actual dysmenorrhea during periods. This pain is due to the new phenomenon of pelvic vascular engorgement under the effects of sex steroids. The typical sites of period pain are shown in Figure 1.

Most cases of dysmenorrhea in adolescents are of primary dysmenorrhea, which develops early after menarche—within first 2 years. Possible etiological causes are endocrine, myometrial disturbed action, prostaglandins and vasopressin. It is also observed that there is high intrauterine tone, elevated intrauterine active pressure, frequent uterine contractions as well as in-coordinate myometrial action in girls suffering from primary dysmenorrhea. Pain is usually described as crampy and lasts from a few hours to a couple of days. Often quoted cervical stenosis does not appear to be playing any role in primary dysmenorrhea. Girls who are overweight have twice the risk of having severe and prolonged cramping compared to girls who are not over weight, and smokers have 50% higher risk than nonsmokers. Interestingly those who start menstruating at age 11 or younger are at higher risk of severe pain, longer periods and longer menstrual cycles.

Secondary dysmenorrhea may occur many years after menarche. The pain is usually more severe and can precede periods by several days. The common conditions leading to secondary dysmenorrhea are endometriosis, genital infections and congenital genital tract malformations. Colicky pain before the flow and relieved with menstruation is classic presentation of secondary dysmenorrhea.

The accurate cause of dysmenorrhea can be diagnosed through a very careful history. One needs to look at the emotional conditioning by the mother. Although a pelvic examination is avoided in a very young girl the presence of severe symptoms do warrant a gentle vaginal examination. Upon good counseling a majority of these young girls allow adequate vaginal examination, which even though performed by one finger is far superior in clinical terms compared to conventionally advocated per-rectal examination. One can diagnose major genital tract malformation, presence of rectovaginal nodule or pelvic masses, vaginal and pelvic infections with reasonable accuracy. An abdominal ultrasound scan will also be very valuable in diagnosis of dysmenorrhea. If pain is atypical, severe or incapacitating and when the pain continues for more than 6 months in spite of therapy, a diagnostic laparoscopy is indicated to rule out endometriosis and pelvic inflammatory disease (PID) (in case of sexually active teenagers). This is very vital to prevent the aftermath of infertility and chronic pelvic pain, if these conditions are left untreated.

**Treatment Approach**

Treatment approach would be:

- A detailed explanation about the pathophysiology of primary dysmenorrhea
- Diet: Salt restriction, reduced caffeine intake, sugar, and alcohol may be beneficial. Increased amount of fish in diet may help reduce menstrual pain. In one Danish study, menstrual pain was greater in girls with low levels of omega 3 fatty acids, which is found in fish and supplements of fish oil appeared to reduce heavy and painful bleeding in adolescent girls.
• Exercise in moderation and back massage appears to reduce menstrual pain. Stress reduction, acupressure, Yoga and meditation are all helpful in selected cases.

• Thermal therapy: A continuous low level topical heat provides great pain relief in the form of a heat wrap. The device: “Therma Care” which delivers a constant, safe 104°F temperature, is worn for 8 hours and provides pain relief for 24 hours. In a blinded, active-controlled study of acetaminophen (1,000 mg/day) versus heat therapy for dysmenorrhea, the heat wrap was found to be superior in relieving pain, muscle tightness, and cramping.

• Simple analgesic like paracetamol is effective (about 30% relieved) in case of milder discomfort.

• Antiprostaglandin agents like benzoic acid derivatives (e.g. aspirin), butyrophenones (e.g. phenylbutazone), indole acid derivatives (e.g. indomethacin) and propionic acid derivatives (e.g. mefenamic acid and flufenamic acid). The last group is superior whenever a concomitant menorrhagia is present. All these substances are equally effective and pain relief is to the tune of 70%.

• Spasmolytics like drotaverine HCL 80–240 mg/day give excellent results. Guaifenesin, a common ingredient of cough medicines has smooth muscle relaxant effect along with mucolytic effect on cervical mucus. In a dose of 600 mg/day has shown significant amelioration of pain.

• Inhibition of ovulation: Oral contraceptive pills (OCP), progesterone only pill, danazol.

• Laparoscopy to treat endometriosis or PID.

• Psychologist’s help may at times be sought.

AMENORRHEA

Primary amenorrhea is one when a girl does not start menstruation by age of 16. However, by age 14, if the girl has never menstruated, one needs to conduct a preliminary clinical check-up and an ultrasound scanning to rule out major problems like general endocrine disorders, cryptomenorrhea, absence of uterus, etc. Once reassured of absence of these, a more detailed check-up is deferred up to 16 years. One needs to be quite alert to pick up cryptomenorrhea early, as any delay in treating these problems may have profound effects on the future reproductive functions of the girl.

If absence of uterus is noted or if the ovarian follicles are not seen at laparoscopy, and in case of streak gonads, an ovarian biopsy is indicated. These young girls may require estrogen replacement for a long time.

Secondary amenorrhea is diagnosed when there is an absence of menstruation for 6 continuous months; however, for clinical purposes, one should start investigating the case whenever menses is more than 3 months delayed.

Evaluation of Amenorrhea

Figure 2 summarizes the evaluation of amenorrhea.

![Fig. 2: Approach to menstrual disorders](image)
Causes of Amenorrhea

- **Central nervous system disorders:** Hypothalamic: Systemic illness/chronic disease, tumors (e.g., craniopharyngioma, glioma), mass lesions like granuloma, central nervous system irradiation, congenital lack of GnRH-anorexia nervosa, drugs (antihypertensives, antidepressants, chemotherapeutic drugs and narcotic drugs), OC pills, competitive athletes, athletic triad, stress.
- **Pituitary:** Hypopituitarism, tumors (e.g., prolactinoma), hemochromatosis.
- **Thyroid dysfunction:** Both hyperthyroidism as well as hypothyroidism.
- **Adrenal dysfunction:** Congenital adrenal hyperplasia, tumor, Cushing syndrome.
- **Ovarian:** Premature ovarian failure, gonadal dysgenesis, 47XXX, polycystic ovary (PCO), androgen producing tumors (arrenoblastoma, theca cell tumor).
- **Outflow tract dysfunction:** Uterine agenesis, Asherman’s syndrome, cervical/vaginal agenesis, imperforate hymen.
- **Pregnancy** in sexually active teenage girls should always be suspected.

Clinical Features of Amenorrhea/ Oligomenorrhea

The discrepancy between bone age and chronological age, presence of chronic illness, genitourinary anomaly or history of sexual activity, recent weight change or medication use are all very useful in arriving at diagnosis. On examination one needs to look out for the signs of virilization, height and indifferent sexual characters (Tanner staging and body habitus), absence of menses in presence of secondary sexual characters, thyroid swelling, galactorrhea, obesity, exercise levels and emotional stress levels. Lab studies are tailored according to the suspicion of etiology.

Once the systemic causes are ruled out, a detailed gynecological check-up is warranted. On ultrasound scan the presence of follicles and growing endometrium are quite reassuring. Laparoscopy and/or hysteroscopy may be employed as required. A norethisterone test (progesterone challenge test) by noting the withdrawal bleeding within 7 days following ingestion of 10 mg/day × 5 indicates a plasma estradiol level of more than 150 mmol/L (40 mg/mL) and will be very vital in diagnosis of underlying problem.

A syndrome known as female athlete triad is associated with eating disorders, amenorrhea and osteoporosis in girls who exercise or dance excessively (girls running for > 20 hours/week for more than 3 months). On closer scrutiny it was found that exercise in fact was not to blame but the poor calorie intake and low fat stores were responsible for amenorrhea and osteoporosis. The primary cause for amenorrhea was found to be low level of the hormone leptin. **Leptin** is released by fat cells and interferes with reproductive hormones, particularly LH. This may be a primitive protective biological mechanism designed to prevent potentially harmful pregnancies during the times of famines. These girls respond very promptly to addition of calories to their diet and should not be advised to refrain from exercise or intensive dance practices!

Management

Sympathy and gentleness are very necessary to ease the extreme anxiety of both the girl and her wards. These girls should be counseled for change in habits, especially for exercise and food intake when necessary. Estrogen + progesterone is used in sequential manner. A combined OCP should generally be avoided as occasional post-pill amenorrhea is noted. In case of galactorrhea-bromocriptine and in selected cases pyridoxine are the drugs of choice. Hysteroscopic lysis of adhesions in Asherman’s syndrome gives very good results.

Polycystic Ovaries and Polycystic Ovarian Syndrome

Polycystic ovaries is an ultrasound diagnosis, whereas polycystic ovarian syndrome (PCOS) is a clinical syndrome involving a PCO with either amenorrhea, oligomenorrhea, hirsutism, anovulation and other signs of androgen excess like acne and crown pattern of baldness.

Oligomenorrhea, amenorrhea and prolonged erratic menstrual bleeding are all aspects of the menstrual disturbances that occur in PCOS. Although the majority of girls having anovulation will have PCOS, weight-related amenorrhea and hyperprolactinemia should be considered as part of the differential diagnosis. The prevalence of PCO in asymptomatic volunteers is 21–23% and in these cases of PCO the PCOS is present to the tune of about 59–76%.

There is evidence of autosomal transmission of responsible genetic sequences for PCOS. It is possible that gene (or series of genes) may render ovary susceptible to insulin stimulation of androgen secretion while blocking follicular maturation. The basic pathophysiology of PCOS seems to be the disordered activity of the enzyme cytochrome P450C 17α, which catalyzes 17 hydroxylase and 17/20 lyase activities, the rate limiting step in androgen biosynthesis.

Concept of Spectrum

There is continuum or spectrum of clinical presentations. At one end of the spectrum are the women who may have PCO and yet ovulate and who have no dermatological manifestations such as acne or hirsutism. At the other end of the spectrum there may be women with menstrual disturbances, oligoamenorrhea, increased hair growth, acne, crown pattern of baldness and evidence of insulin resistance.

The presence of a woman in this continuum is probably predetermined by genetic factors, but her position on the
Disorders of Menstruation in Adolescent Age

continuum is likely to be related to lifestyle and, in particular, body mass index. Although the exact “trigger” that causes the expression of the syndrome is unknown, it is likely that body mass index is involved and women at the PCO end may move to the PCOS end if they increase their bodyweight. Weight reductions in a woman with PCOS will often return her to the other end of the spectrum with ovulatory cycles and improved hirsutism.

In clinical practice asymptomatic nonobese woman who is diagnosed with PCO on ultrasonography (USG) should be counseled about the advisability of maintaining a normal body mass index in the future. Should symptoms of amenorrhea or hyperandrogenism develop, specialist attention should be sought regardless of weight.

**Diagnosis**

*Hormone assays* for raised LH + testosterone, LH: FSH ratio of greater than 2:1, *absolute LH value* are all used for diagnosis of PCOS and the last one appears to be most useful. Limitations of “hormone assays” are that the LH is released in a pulsatile manner and hence, measuring hormone levels only once may be misleading.

**Ultrasound Criteria for Diagnosis of Polycystic Ovaries**

- **Ovarian length, utero-ovarian index** (uterus width: ovarian length ratio), **sphericity index** (ovarian width: ovarian length), **ovarian area assessment**, **ovarian volume** are all tried but to get accurate measurements of these parameters is very difficult and hence this is not very popular.
- **Polyfollicular pattern:** Excessive number (> 10) of small echoless regions less than 10 mm in diameter is strongly suggestive of PCO. In young patients these follicles are more peripherally placed giving the “necklace” appearance.
- **Ovarian stromal hypertrophy and hyperechogenicity** are the most reliable USG signs to distinguish between PCO and multifollicular ovary (stromal area > 380 mm²). Ultrasoundography is simple, noninvasive and allows repeatable measurements. It can assess both the follicles near the surface as well as dense stroma. Transabdominal USG fails to detect PCO in 30% cases as compared to 100% diagnosis by transvaginal USG. MRI, 3D and Doppler have been used with varying results.

**Treatment**

*Lifestyle changes* will remain the hallmark of management of this lifelong problem. The girl should be apprised of the possible problems of weight gain and disease progression. The key will be to keep the body mass index in the normal range of 19–25, preferably at its lower end. This single measure is most effective to ward off all the manifestations.

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**Menorrhagia and Dysfunctional Uterine Bleeding**

The clinical syndrome of DUB occurs quite frequently in adolescent age and is usually associated with anovulatory cycles. About 55.7% of cycles in first year after menarche are anovulatory, decreasing to about 18% in girls who are menstruating for more than 4 years. Anovulatory bleeding is painless and often irregular. The irregularity may be in the amount of bleeding, duration of period or in the interval between two periods. The anovulation is either due to inappropriate maturation of hypothalamus, or persistent anovulation with high LH due to ovarian immaturity. Additional causes are PCO, drugs, stress and excessive exercise.

Fortunately only 10% of women less than 20 years of age have an organic cause for menstrual problems. Of all menorrhagia in adolescent age 75% are due to anovulation and 20% are due to coagulation problems. However, in the first year after menarche 50% of menorrhagia is due to coagulation defects. Spotting or light bleeding in between periods (at ovulation time) is common in girls just starting menstruation probably due to transient fall in estrogen levels. Interestingly the feedback between FSH and estrogen is intact and spontaneous and that maintains normal cycle regularity in early anovulatory years.

**Etiological Factors of Puberty Menorrhagia and Dysfunctional Uterine Bleeding**

Menorrhagia generally is defined as excessive bleeding, either in duration or quantity of blood lost or both (> 8 days and/or > 80 mL) at regular intervals. The commonest causes leading to excessive menstruation in pubertal age are...
anovulation and bleeding disorders, whereas reproductive tract infections and pregnancy-related complications are the chief causes in later age. The cycle irregularity (metrorrhagia) however is very commonly associated with the menorrhagia of pubertal age.

**Anovulation**

With better understanding about menarche and subsequent menstrual rhythm we now know that approximately 55.7% of cycles in first year after menarche are anovulatory, decreasing to about 18% in girls who are menstruating for more than 4 years. Anovulatory bleeding is painless and often irregular. The irregularity may be in the amount of bleeding, duration of period or in the interval between two periods. The anovulation is either due to inappropriate maturation of hypothalamus, or persistent anovulation with high LH due to ovarian immaturity. Additional causes are PCO, drugs, stress and excessive exercise. Fortunately only 10% of girls less than 20 years of age have an organic cause for menstrual problems. Of all menorrhagia in adolescent age 75% are due to anovulation. If menorrhagia sets in, the blood loss is likely to be much higher due to the unopposed estrogenic effects of endometrial growth and vascularization.

**Blood Dyscrasias**

Of all menorrhagia in adolescent age 20% are due to coagulation problems. However, in the first year after menarche 50% of menorrhagia is due to coagulation defects. Idiopathic thrombocytopenic purpura is the commonest hematological problem observed in India as compared to “von Willebrand’s Disease” quoted most commonly in Britain and USA. Thalassemia and sickle cell anemia also contribute to milder forms of menorrhagia, which are refractory to therapy.

Other common causes of menorrhagia in pubertal age are listed in Box 1.

### Clinical Features

**History**

The age of menarche and a detailed menstrual calendar should be evaluated. The importance of maintaining a menstrual calendar needs to be emphasized greatly to these young patients. A detailed history should include the color and amount of bleeding, pelvic pain, dietary and weight loss practices (excessive laxatives, bulimia), medical history of chronic diseases, medications, and family history of bleeding disorder or endocrine disorder.

With increasing trend to earlier sexual activity, one may need to enquire into contraceptive and sexual history, postcoital bleeding and vaginal discharge. Pregnancy-related causes must be ruled out even in absence of positive sexual history. In traditional communities like ours, the girls may have concerns about confidentiality or may be victims of sexual coercion and missing the diagnosis of pregnancy, in such hemorrhaging adolescents may lead to severe consequences.
Disorders of Menstruation in Adolescent Age

Use of hormones, such as OCPs or progesterones and use of other medications such as coumadin, aspirin should also be enquired into.

Symptoms of anemia (fatigue, dizziness, shortness of breath, light-headedness, headaches, ringing in the ears—tinnitus, irritability, pale skin, restless legs syndrome, palpitation and mental confusion) as well as indicators of coagulation disorders (i.e. easy bruising, epistaxis or gum bleeding) should be evaluated. Recent social stressful events, recent weight changes and a family history of menstrual disorders should also be inquired into.

A review of all the pubertal milestones (thelarche, pubarche, adrenarche, menarche and overall body growth) should be evaluated to assess the maturational state of the hypothalamic-pituitary-ovarian axis. Presence of chronic illnesses, especially tuberculosis must be enquired about as TB accounts for a high rate of menstrual problems in India.6

Examination

The examination in a very young girl should be carried out in presence of the mother; however, this option is left to the girl herself. It is observed that girls in later age (14+) generally avoid being examined in presence of a close relative.

**General examination** should include the estimation of body habitus, stage of secondary sexual characters and bleeding disorders. Evidence of acne and/or hirsutism would alert one to the diagnosis of PCO or adrenal problems. General assessment for endocrine diseases, vital signs for severity of anemia, tanner staging, thyroid palpation, assessment of vulva, hymen and pelvic organs are all checked for.

**Abdominal examination** should be performed to rule out pregnancy or neoplastic diseases. Although refrained upon, at times a pelvic examination need be performed, albeit gently with one finger, to palpate the cervix and fornices. A per-rectal examination can also be quite useful.

**Pelvic ultrasonography** is performed in almost all cases and can be of great help in confirming the diagnosis of PCO, uterine fibroid and ovarian cyst. One may need to resort to a laparoscopy sometimes for confirmation as well as simultaneous therapy for acute pelvic infection, fibroids, endometriosis and ovarian cysts. A vaginoscope or even a hysteroscope inserted in vagina can be of great help in arriving at a diagnosis.

The **laboratory** includes complete blood count, endocrine tests (thyroid, prolactin, LH/FSH, androstenedione), pregnancy test—Pap smear and vaginal cultures in sexually active girl, bleeding time—prothrombin time and partial thromboplastin time.

Treatment

The objective of treatment is to stop the bleeding and prevent recurrences. At the same time a lot of effort is needed for the correction of anemia.

After a thorough evaluation, treatment for mild cases should be supportive. A confident reassurance and explanation of physiology will alleviate the anxiety of both the girl and her mother to a great degree. Patient should be educated about proper diet, exercise and stress management.

**Management of anemia** should be simultaneously employed. In a very young adolescent who has a history of menarche for less than 2 years and no history of underlying chronic disease or sexual activity and when the presentation is mild (i.e. without evidence of anemia or homodynamic changes) reassurance and maintenance of menstrual calendar along with basal body temperature charts for several months may be helpful in determining the necessity of detailed work-up and possible use of steroidal hormones. Usually this situation is resolved within 1–2 years with onset of spontaneous ovulation. These patients should be reviewed on 6 monthly bases.

**Diet and trace elements:** The general guidelines for a healthy diet apply to everyone; they include eating plenty of whole grains, fresh fruits and vegetables, and avoiding saturated fats and commercial junk foods.

**Iron:** Menorrhagia can lead to iron deficiency, but iron deficiency can also lead to or aggravate menorrhagia by reducing the capacity of the uterus to stop the bleeding. Supplementing with iron decreases excess menstrual blood loss in iron-deficient women (to the tune of 75%) who have no other underlying cause for their condition.8,15

**Vitamin A:** In a study of women with menorrhagia who took 25,000 IU of vitamin A twice per day for 15 days, 93% showed significant improvement and 58% had a complete normalization of menstrual blood loss.14

**Vitamin E:** Supplementing with 100 IU of vitamin E every other day can correct the problem of menorrhagia within 10 weeks (63% responded within 4 weeks).2

Both vitamin C and flavonoids protect capillaries (small blood vessels) from damage. In so doing, they might protect against the blood loss of menorrhagia. In one small study, 88% of women with menorrhagia improved when given 200 mg vitamin C and 200 mg flavonoids three times per day.9

Various herbal preparations have been used traditionally for alleviation of symptoms of menorrhagia. Cinnamon has been used historically for the treatment of heavy menstruation.3

**Steroid hormones:** In severe cases and in those with associated anemia, a hormone therapy is indicated. For quick arrest of heavy bleeding estrogen depot preparations are used. Once the bleeding ceases progesterone alone are preferred as hormone therapy. Progestins are antiestrogenic and they induce enzyme 17-hydroxysteroid dehydrogenase in endometrial cells, to convert estradiol to estrone. They also inhibit the augmentation of estrogen cytosol receptors, which modulate estrogen action and thereby inhibit the
growth of endometrium. Medroxyprogesterone acetate can be used as 10 mg/day for 10 days every month (from day 15 to 25 of menstrual cycle), which induces stromal stability and is followed by withdrawal flow. This is used cyclically for 3–6 months. A continuous progesterone therapy (from day 5 to 25) is also employed by some to reduce the menstrual flow significantly. Combined OCPs are also used preferred by some doctors and they have an added advantage of regulating cycles along with reducing the menstrual blood flow by 60%.

An acute episode of bleeding can be controlled by 50 mg estrogen containing OCP. One pill every 6 hours till bleeding stops and then gradually tapered to one pill every day. If bleeding is not stopped within 48 hours one must look for causes other than anovulation.

Hospitalization is necessary in situations of acute or heavy bleeding with altered vital signs. Blood transfusion may be required when hemoglobin levels are below 7 g/dL.

A bolus dose of intravenous estrogen (progynon depot or premarin) 25 mg is very effective for prompt arrest of bleeding. Estrogens stop bleeding by enhancing platelet aggregation, increasing fibrinogen levels, increasing factor V and IX and decreasing effectiveness of bradykinin. Once the bleeding is arrested, the patient should be prescribed cyclical OCPs or cyclic progestins. The OCPs may be started at one tablet four times a day for 4 days and then gradually tapered to one per day given cyclically for additional 2 months. In the event of nonresponse to hormonal therapy, one needs to re-evaluate the case for presence of a coagulopathy or an anatomic disorder.

A time-tested therapy for arrest of acute bleeding is the use of two testosterone injections 12 hours apart. A switch to estrogen, progesterone or a combination is made once the bleeding stops or significantly reduces in amount.

To prevent heavy active bleeding in a crisis situation especially in presence of blood dyscrasias, desmopressin nasal spray (dose 1.5 mg/mL) may be lifesaving. This also obviates the possible spread of AIDS/hepatitis that may occur in case of systemic preparations. Desmopressin is a synthetic analog of neurohypothalamic nonpeptide arginine vasopressin.

In a large reported series (n. 238 cases) the success rates quoted were 92% for cases of menorrhagia. It can be given intravenously also, in a dose of 0.3 mg/kg diluted in 50 mL of normal saline and administered over 15–30 minutes. This results into a rapid rise of coagulation factor VIII with peak levels at 90–120 minutes and lasts for approximately 6 hours. These compounds inhibit the prostaglandin endoperoxide synthase decreasing the total amount of prostaglandin levels. These compounds may be prescribed with cyclical hormonal therapy for a dual action. They are given at the first sign of menses or with the first cramping episode at the time of menses and continued during menstrual cycle. Of special interest is mefenamic acid in daily divided doses of 1.5 g during the bleeding.

Recent introduction of tranexamic acid, a synthetic form of the amino acid lysine that enhances clotting and working at capillary level has also shown promise in a dose of 1.5 g three times in a day. For an acute episode an intravenous bolus is also used in conjunction with hormone therapy for quick arrest of bleeding.

In situations of prolonged uncontrolled bleeding not responding to hormonal therapy or when hormonal therapy is contraindicated, GnRH analogues can be used. They suppress gonadotropin secretion and subsequent estradiol secretion, which stops menstruation completely and produces a state of amenorrhea. Osteoporosis and lipoprotein changes are drawbacks of long-term use of this therapy, and it should be limited to a maximum period of 3 months.

Fortunately endometrial cancer is yet to be reported in an adolescent girl! Curettage is generally a last resort option and is performed only if other measures fail for 6 months. In rare case a balloon hemostasis may be achieved successfully even in adolescent age! The surgical option is very limited if at all open in puberty menorrhagia. The advent of endoscopic surgery is a boon to young girls having fibroids, ovarian cysts and endometriosis with minimal impact on future reproductive functions.

Follow-Up

On a long-term follow-up of DUB in adolescence (192 cases) an interesting fact emerged! DUB was present in 60% cases after 2 years of its appearance, 50% after 5 years and a whopping 30% even after 10 years. This amazing study makes one ponder on the possibility of a genetic or a persistent environmental factor operating! This also underscores the importance of long-term monitoring of these patients in adult life, as one in three will need further medical assistance.

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Disorders of Menstruation in Adolescent Age


Hormone Therapy: Current Concepts

THE BASKET OF HORMONES

The origin and constituents of conventional hormone therapy (HT) are simple. In earlier days, the concept of HT lay in the replacement of a woman’s deficient gonadal (ovarian) hormones. Since the predominant circulating reproductive (gonadal) hormones were known to be estrogens, progestogens and, to some extent, androgens—HT implied replacement with just these hormones and was termed hormone replacement theory (HRT). If only the predominant hormone estrogen was replaced, it was specifically called estrogen replacement therapy (ERT); if both estrogen and progestogen together were replaced, it was termed estrogen progestogen replacement therapy (EPRT). When taken cyclically in a sequential manner, the term was sequential EPRT (SEPRT). When taken on a continuous combined daily basis it was continuous combined HRT (CCHRT). Then there was the occasional use of androgen replacement therapy (ART). Terminology has now been modified from HRT to HT. The rationale for the change in terminology is that since there is a decline in hormones after menopause, naturally the term replacement is technically incorrect because in that phase in a woman’s life, she does not have hormones in any case. Hence, treatment with hormones thereafter is now quite simply termed “hormone therapy” the word “replacement” having been dropped, akin to “insulin” therapy (not insulin replacement therapy). Effects of menopause on the female body is illustrated in Figure 1.

With the passage of time, estrogen and progestogen receptors have been discovered. Today, we have more therapies in this “basket” of hormones. Multiple divergent drugs that act selectively on different receptors at variable sites, collectively called selective estrogen receptors modulators (SERMS), are placed in this same basket.

Tibolone, a gonadomimetic, is a synthetic steroid with weak estrogenic, progestogenic and androgenic properties. It is described as a selective tissue estrogenic activity regulator (STEAR).

Hormonal Therapies (Table 1)

Broadly hormones may belong to the following groups:
- Gonadal HT (estrogens, progestogens and androgens)
- Hormone simulants/selective hormones (SERMS)
- Gonadomimetics (STEAR)
- Natural plant hormones (phytoestrogens)

In essence, the HT basket is filling with different “goodies”—each “goodie” or agent unique in its own right with its own benefits and problems—some identified and some not. The
comprehensive metabolic and clinical profiles of the various forms of HT still need to be clearly defined. Effects on various tissues, organs and functions of the body of the different agents need to be understood clearly and differentiated one from the other.

As per the proposals of the International Menopause Society in March, 2003, hormonal therapies are defined as follows:

- **Combined continuous estrogen-progestogen therapy (CCEPT)**
- **Combined sequential estrogen-progestogen therapy (CSEPT)**
- **Estrogen-androgen therapy (EAT)**
- **Estrogen progestogen therapy (EPT)**
- **Estrogen therapy (ET)**

When the term HT is used, it is vague and serves as a general term unless qualified. We need to ask ourselves which specific hormone types are we referring to—a conventional HT, a gonadomimetic, or a SERM? Even amongst the broad classes of estrogens, progestogens or androgens, their different forms vary in their actions. Natural progesterone is lipid neutral versus norethisterone. Similarly, the different routes of administration offer different benefits. Oral estradiol which gets converted in the gut to estrone is different from nonoral estradiol, which undergoes the first pass metabolism in the liver and is absorbed as such. Estradiol has the advantage of having less effect on the coagulation parameters and hypertension than the less potent estrone. The relevance for indicating the specific hormone type at all times lies in the fact that each of these may have varying specific effects or actions at different sites of the body. Hence, clubbing together of all hormones when analyzing clinical, experimental, observational and other data along with its application to the practice of menopausal medicine may be fraught with error. Lack of differentiating the hormone types may lead to the automatic extrapolation of the actions of conventional form of HT of a particular type to all hormone types and vice versa. If raloxifene is prescribed for its osteoprotective effect because it is considered safe for the breast, one has to be aware that all the other so far documented benefits or risks and problems (i.e. actions) of conventional EPT may not necessarily be applicable to raloxifene. They may not have yet been studied in or established for raloxifene. On the other hand, when considering the risks of HT, it may be quite incorrect, e.g. to translate the increased breast cancer detection risk of EPT to raloxifene because the evidence so far suggests that the net effects on breast tissue of raloxifene are minimal. Likewise, the other actions are not yet investigated and unknown; so far may also be somewhat different.

Nonhormonal therapies that are commonly used as complements or as supplements to hormones in menopausal women are not hormonal in their nature and action. They include:

- Herbs
- Micronutrients
- Antioxidants
- Calcium
- Bisphosphonates
- Calcitonin
- Others

These therapies do not constitute HT and are not replacement for the resulting estrogen deficiency of menopause.

### Table 1: Hormone therapy regimes

<table>
<thead>
<tr>
<th>1. <strong>Full replacement:</strong></th>
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<tbody>
<tr>
<td>• Estrogen</td>
</tr>
<tr>
<td>- CEE: 0.625 mg</td>
</tr>
<tr>
<td>- Micronized estradiol: 1 mg</td>
</tr>
<tr>
<td>- Estradiol valerate: 2 mg</td>
</tr>
<tr>
<td>- EE: 0.05 mg</td>
</tr>
<tr>
<td>- Estradiol patch: 0.05 mg</td>
</tr>
<tr>
<td>• Progesterone</td>
</tr>
<tr>
<td>- Medroxyprogesterone: 2.5 mg or 5 mg daily</td>
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<tr>
<td>- Micronized progesterone: 100 mg daily</td>
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<tr>
<th>2. <strong>Half replacement:</strong></th>
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</thead>
<tbody>
<tr>
<td>• Estrogen</td>
</tr>
<tr>
<td>- CEE: 0.3 mg</td>
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<tr>
<td>- Micronized estradiol: 0.5 mg</td>
</tr>
<tr>
<td>- Estradiol patch: 0.025 mg</td>
</tr>
<tr>
<td>• Progesterone</td>
</tr>
<tr>
<td>• Medroxyprogesterone: 1.5 mg</td>
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</tbody>
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<tr>
<th>3. <strong>Estrogen-progesterone combination:</strong></th>
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<tbody>
<tr>
<td>• Cyclic (along with estrogen)</td>
</tr>
<tr>
<td>- Medroxyprogesterone: 5–10 mg from day 10 to 14 of each month</td>
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<tr>
<td>- Norethindrone</td>
</tr>
<tr>
<td>- Micronized progesterone 100 mg morning and 200 mg in the evening</td>
</tr>
<tr>
<td>• Continuous combined</td>
</tr>
<tr>
<td>- 0.625 mg CEE + 2.5 mg MPA</td>
</tr>
<tr>
<td>- 0.05 mg EE + 1 mg norethindrone acetate</td>
</tr>
<tr>
<td>- Micronized estradiol (0.5 mg) + norethindrone acetate (2.75 mg) transdermal patch, twice weekly</td>
</tr>
</tbody>
</table>

**Abbreviations:** CEE, conjugated equine estrogen; EE, ethinylestradiol; MPA, medroxyprogesterone acetate

A classification which is mandatory prior to the use of the term HT is based on need. Why or what for is the HT being considered? Is it purely for symptomatic relief (**therapeutic HT**) or is it for its preventive long-term benefit (**preventive HT**), e.g. local HT use for prevention of genitourinary problems. The earlier long-term preventive use of systemic HT for cardioprotection, benefits on quality of life amongst others are no longer recommended and are
on hold by all menopausal societies and expert groups in light of the results of the Women’s Health Initiative (WHI) trial. Attaching this prefix to the use of hormone therapies is useful. Unless specified at the very outset with the appropriate prefix, the term HT may conjure up visions of long-term breast cancer risks in the minds of both doctors and in those women considering it. HT for symptom relief is usually prescribed short-term and necessary for varying periods of 6 months to 2 years or even more before it is slowly tapered off over another period of 2–12 months. Hence, breast cancer risk in this scenario may be quite different to the increase in breast cancer detection rates after 5 years of estrogen use. Local vaginal HT may be used intermittently for short periods of time for life.

In our experience with menopausal women we find it useful to define the multifocal functional indications of HRT use and thus differentiate it into the following need-based categories:

- **Short-term therapeutic HT** for 2 to 3–5 years, like that of a sprinter in a 100 meters race as with treating the menopausal symptoms.
- **Short-term preventive HT** for up to 5 years, as with surgical menopause.
- **Long-term preventive HT** for more than 5 years. Like a marathon race which may go on even for life as to “the grave” as the use of with local vaginal estrogens for vaginal symptoms.
- **Intermittent therapeutic or preventive HT**, for example, urogenital symptoms, which can occur lifelong from chronic estrogen deficiency.
- **Relayed placement (therapeutic or preventive)**: We have coined this term for use when the types of hormones and therapy used are changed over time—for instance every 5–7 years—in a planned manner in a pattern that follows the style of a relay race. Shifting from the initial use of EPT in the immediate postmenopause to gonadomimetics or raloxifene to finally local vaginal estrogen use in older women. After initial relief of menopausal symptoms, HT should be tapered off gradually and nonhormonal agents be advised, particularly where osteoporosis is a concern.

This option of placement of various therapies over time in a woman’s postmenopausal lifespan as an intended plan of action may be used with a view to maximizing benefits and minimizing risks. It allays fears with regards to continuous long-term use of a single hormonal agent. If one considers the various stages of woman’s health and aging, different health therapies can be placed, as necessary for the different issues in each phase of a woman’s life.

- **Concomitant multiple HT (therapeutic or preventive)**: This term may be used for the simultaneous administration of one form of HT along with one or more other forms, e.g. estrogen, progestogen or raloxifene or estradiol combined with local estriol. This is useful because an additional function or benefit is obtained by the concomitant use without increasing the dose of one hormone.
- **Multidimensional therapy (therapeutic or preventive)**: Hormone therapy may be variably combined with other therapeutic modalities (e.g. HT with biphosphonates and calcium; HT with antioxidants, micronutrients, multivitamins, calcium). These combinations may be considered for either prevention or therapy. Their intended duration of use would vary along with the risk benefit connotations and choices of the individual women.

### TISSUE SELECTIVE RATIONALE OF HORMONE USE

The mechanism of action of hormones has been relooked at recent research has shown that estrogens manifest their biological activity through at least two distinct receptors—ER alpha (the original) and ER beta (the later discovered receptor). Progestogen and androgen receptors are also present in different tissues.

These receptors have different cellular distributions and therefore different actions. As an example, estrogen receptors are considered. They are present in almost all tissues in the female body from crown to toe. Their concentration, however, is different in various organs, e.g. being very densely present in certain areas of the genitourinary tract and sparse in some areas of the brain. Though somewhat similar in structure, the ligand binding domain on the two estrogen receptor types—alpha and beta is very different. Moreover, different estrogens have different ligand binding affinities. As an example, the potential benefits of an ER-beta selective ligand is that it is central nervous system (CNS) selective and hence beneficial for Alzheimer’s disease (AD) and cognition and has also been postulated to be beneficial for the endothelial cells of the cardiovascular system.

Each target cell (as in the brain, bone or uterus), therefore, is uniquely positioned to respond to different compounds. Once the active ligand receptor diiner has bound with the adapter, it enters the target gene resulting in the synthesis of the special protein by the cell. Different proteins are synthesized depending on the different “fits” received into the genes. Hence, the estrogen receptor ligands differentially affect transcription in different tissue cell types.

In essence, steroid hormone receptors are ligand-dependent transcription factors that affect cell function. Classification of compounds as agonists or antagonists is tissue/cell dependent. The new science of estrogen action supports the concept that different estrogens acting through the same receptor can induce different biological activity.

Evidence is also emerging that estrogen, in addition to acting via receptors, can rapidly influence the physiology of the cell through other nongenomic mechanisms. The implication again is that no two estrogens act in the same manner.
The mechanism of estrogen action is not the same in all cells. It has therefore been possible to develop tissue selective estrogens and other gonadomimetic agents.

**Tissue selectivity of tibolone:** Tibolone, a gonadomimetic, is a unique compound with tissue specific action. It is a synthetic steroid with weak estrogenic, progestogenic and androgenic properties. It is described as STEAR. Its metabolites, 3α- and 3β-OH tibolone, bind with estrogen receptors. The D4 tibolone isomer binds with progesterone and androgen receptors without any affinity for estrogen receptors and has no estrogenic properties. Tibolone intake has an estrogen-like action on the lower genital tract, bone and vasomotor symptoms; a progesterone-like or antiestrogenic action on the endometrium where tibolone is converted to its D4 isomer. Tibolone metabolites are potent inhibitors of local estradiol production in the breast tissue due to enzymatic inhibition of sulfatase and 17β-hydroxysteroid dehydrogenase (HSD) and via stimulation of cell differentiation and apoptosis. It has an androgenic action on mood and libido. Its effect on lipoprotein profile is that it decreases triglycerides, total cholesterol and Lp(a); the low-density lipoprotein (LDL) remains unchanged. On the downside, the high-density lipoprotein (HDL) is lowered. There is an increase in fibrinolytic activity with tibolone.

**Tissue selectivity of SERMs:** Raloxifene is a SERM that has estrogenic activity on bone, total cholesterol and LDL, and antiestrogenic activity on endometrium and breast tissue.

To simplify molecular jargon into clinical relevance, the take home message is that different estrogens acting through the same receptors can induce different receptor conformations resulting in different biologicals and hence, different effects on the various tissues of the female body. Remember whilst prescribing that all estrogens are not equal. Some are more equal than others! It also depends on the action or effect you are looking for in your patient. Do you want estrogenic effects on urogenital tissues only and are not “fussed” whether it is osteoprotective as long as it does not have any effect on the breasts, or do you want osteoprotection along with all the other benefits as well? You will then have to select the therapy for your patient accordingly.

### THE CURRENTLY ENLARGED CANVAS OF HORMONE THERAPY ACTIONS

#### Osteoporosis

Estrogens and bones are old friends. The osteoprotective benefits of ERT are well established. The earlier a woman is started on EPT the better, as more osteoprotection is achieved by early initiation of therapy. Delaying the start of conventional EPT to 9 years after menopause increases the odds ratio (OR) for hip fractures to 0.62 (0.33–1.18) from 0.35 (0.24–0.54) in current users, as shown by the Swedish hip fracture study group.

On the other hand, it is now recommended (post WHI trial) that conventional EPT should be initiated for its osteoprotective action only in women with other menopausal symptoms and not for prevention and treatment of osteoporosis alone. A 4% increase in bone mineral density (BMD) with EPT had been demonstrated in elderly women (over the age of 65 years) started on continuous low dose conjugated equine estrogen (CEE) (0.3 mg/day) combined with 2.5 mg medroxyprogesterone acetate (MPA). This was a larger response than was typically seen with early menopausal women (50–55 years). However, in the elderly at 65 years, with other options available for osteoprotection unless the reasons for selecting estrogen progestogen are compelling, the option of combining biphosphonates with local estradiol therapy for genitourinary effects may be more prudent.

An enhanced effect on BMD has been demonstrated by combining CEE with biphosphonates.

Osteoprotective benefits have similarly been demonstrated with tibolone and raloxifene. There may be additive effects of raloxifene with alendronate. The Multiple Outcome of Raloxifene Evaluation (MORE) trial showed a 30–50% reduction in the risk of vertebral fractures with raloxifene usage. The amount of 60 mg/day of raloxifene use causes less reduction in vertebral fractures as compared to 120 mg/day [relative risk (RR) 0.7 vs 0.5]. Tibolone causes a 50% decrease in fractures.

Conclusive data regards phytoestrogens is not available regards osteoprotection and decreased fracture risk.

#### Alveolar Bone and Tooth Loss

Sophisticated studies have revealed that conventional EPT reduces alveolar bone loss and tooth loss. Although, the prevention of periodontal disease and maintaining good oral hygiene is the most important factor in maintaining teeth, it has been hypothesized that some tooth loss may occur as a result of resorption of the alveolar bone and therefore may reflect osteoporotic bone loss. The strongest evidence of EPT benefit against tooth loss comes from a prospective study of 14,171 women in the nurses’ health study where the RR (adjusted for age and smoking) for tooth loss amongst current estrogen users was 0.76 (0.72–0.80). This protection disappeared with time after discontinuation of traditional HT. There is some evidence that BMD in postmenopausal women is correlated with the number of teeth.

Studies also suggest that estrogen may provide protection against tooth loss and periodontal disease in both post users and current users. One study that examined estrogen deficiency as a risk factor for periodontal disease involved 412 women (236 postmenopausal, aged 50–74 years and 176 perimenopausal aged 25–49 years). The postmenopausal group included 59 ET users and 177 women who were not. Because cigarette smoking is the single most significant risk factor associated with severity of periodontal disease, only nonsmokers were included. Only 6.3% of the premenopausal...
women and 11.9% of the postmenopausal women using ET had severe attachment loss, compared to the 18.6% of the non-ET women.\textsuperscript{11} It is suggested that ET promotes oral health by inhibiting gingival inflammation, periodontitis and consequent loss of teeth.

No data has yet been published regards the benefit of tibolone, raloxifene or phytoestrogens on alveolar bone and tooth loss.

\textbf{Estrogen Benefits on Vision Disorders}

One thinks, “vitamin A may be...but estrogens and eyes??”. Yes, it is true.

- A number of ocular symptoms may be observed and can be associated with the very onset of menopause itself. An example illustrating this is a study of 1,287 women who visited a menopause clinic for relief of a variety of complaints. These women were questioned about ophthalmic symptoms. Four hundred thirty (35\%) of these women reported problems with their eyes that were associated with the onset of menopause. Out of the 19 reported ophthalmic complaints, the two most common problems noted were deterioration in visual acuity and dryness. Ninety eight women underwent ophthalmic examination and received cyclical EPT for 3 months. A significant improvement or complete relief from ophthalmic complaints was reported by most of the women who were followed up by the end of 3 months. In addition to this, increased lacrimal fluid, and improved convergence and fusion (which denotes improved visual acuity) was objective evidence of improvement noted by a physical examination.\textsuperscript{14}

On the contrary, a study has demonstrated a detrimental effect of estrogen on the tear film in the eyes which can result in the development of the dry eye syndrome.\textsuperscript{15} A study published in the Journal of American Medical Association reported that women who use HRT, particularly estrogen alone, are at increased risk of dry eye syndrome.\textsuperscript{15} The odds of having dry eyes were 70\% more if postmenopausal women used HRT. Each 3-year increase in the duration of HRT use was associated with a 15\% increase in risk of having dry eyes.

Possible role of androgen is documented, but androgen use is not recommended, because of its side effects.

There is evidence that receptors of estrogen are present in human lens epithelial cells. This suggests a possible mechanism for a direct estrogen effect on the lens. Estrogen inhibits transforming growth factor-beta (TGF-beta). TGF-beta has been shown to induce cataract. Several estrogens have also been shown to have significant antioxidant properties and therefore it may protect against free radical damage (like carotenoids, vitamin C, etc.).

- Results from the Beaver Dam eye study\textsuperscript{16} indicate a slight protective effect of estrogen exposure on the female lenses. The odds scale ratio of this study indicates that current use of ET is allied with a lessened risk of more severe nuclear sclerosis. It has also been illustrated that the longer the duration of ET, the less the severity of the disease—in fact women who reported 20 years of postmenopausal estrogen use had (on an average) 65\% of the risk of those reporting no use at all.\textsuperscript{16}

On the other hand, strong correlations were not found in terms of a connection between estrogen and prevalent cataracts (nuclear, cortical and posterior subcapsular) in an evaluation of data from the Blue Mountains eye study (Australia).\textsuperscript{17} No association in any of the women was found between EPT and cataract. However, for EPT users of 65 years and above, the OR for cortical cataract was 0.4 (0.2–0.8). The OR for posterior subcapsular cataract was 2.1 (1.1–4.1) for current traditional EPT users who had nonsurgical menopause.\textsuperscript{18}

The protective effect of estrogen on lens transmittance amongst postmenopausal women is indicated by the observation that lens transmittance was significantly higher in estrogen users and lens autofluorescence was significantly lower.\textsuperscript{19}

- Estrogen has also been reported to reduce glutamate toxicity which is a significant contributor to glaucoma. A review article evaluating the hormonal regulation of intraocular pressure (IOP) found copious studies showing a small decline in IOP with ET. Initially, glaucoma was thought to be increased by estrogens but 1 in 6 cases has normal IOP. Recent data which points at glutamate toxicity as one of the major contributors to glaucoma promotes the notion of the protective role of estrogen against glutamate toxicity and hence glaucoma. At the molecular level, glutamate (an excitatory neurotransmitter) promotes rapid firing in nerve cells—if excess glutamate is produced—nerves are stimulated “to death”. If glutamate, does indeed (as data suggests), underlie the pathology of glaucoma, estrogen may provide menopausal women a benefit by protecting against glutamate toxicity.\textsuperscript{20–22}

One study found that HRT reduces eye pressure by 8–13\% in menopausal women after about 12 weeks of HRT.\textsuperscript{23} Supporting a role for the beneficial effect of female sex hormones is the finding that early menopause is associated with a higher risk of open-angle glaucoma, especially true if women went through menopause before reaching the age of 45 years\textsuperscript{24} from the widely regarded Rotterdam study. The relation between primary open-angle glaucoma and gender is still controversial. In the Baltimore eye survey,\textsuperscript{25} the Beaver Dam eye study\textsuperscript{26} and the Blue Mountains eye study\textsuperscript{27} no significant difference was found between prevalence of primary open-angle glaucoma in men and women. However, in the Framingham eye study,\textsuperscript{28} the Barbados eye study\textsuperscript{29} and the Rotterdam study\textsuperscript{30} up to a two-fold higher prevalence was found in men.

- The most current study from the same eye disease case control study group above, examined risk factors among 198 women with idiopathic macular holes (IMH) with
The evidence of the association between menopause and AMD is found in other epidemiological studies. The Beaver Dam eye study found that increasing number of years of HT use was associated with reduced maculopathy. The eye disease case-control study evaluated a range of possible risk factors for women, including estrogen use, oral contraceptive use, history of hysterectomy and parity. A large protective effect was found for women who formerly or currently used HT and an increased risk was found for women who had one or more children. Yet another disease that may benefit from estrogen use (the list seems endless!) is age-related macular degeneration (AMD). The evidence of the association between menopause and AMD is found in a Rotterdam Study where results indicate that women with a younger age at menopause had a 90% increased risk of exhibiting signs of late AMD compared to women who had a later menopause. The data in this study is from a large case-controlled study of end-stage of disease and suggests that EPT reduces the risk of AMD developing.

Findings from the Rotterdam Study suggested that early menopause due to surgical removal of the ovaries increased the risk of macular degeneration which could be due to an early decline in estrogen production. Other evidence supporting the slight reduction by ET of early and late stages of AMD comes from smaller studies such as the Beaver Dam eye study. The Beaver Dam eye study found that increasing number of years of HT use was associated with reduced maculopathy. Data from the Beaver Dam eye study did not support this association. In conclusion, HT on balance may seems to help in visual acuity, visual symptoms, while the effect on cataract, glaucoma and macular degeneration is controversial, and may increase dry eye symptoms. There is no circumstance where HT will be considered solely for aging eye related diseases.

No data is available that regards the effects of tibolone, raloxifene or phytoestrogens on any of the ophthalmic effects.

### Emerging Facts and Figures About Colon Cancer

Our third stop of the seemingly never-ending benefits of ET/HT is at the colon cancer junction. In a nutshell, the risk of colorectal cancer is prevented and largely decreased by estrogens. A majority of studies indicate an inverse, protective effect of EPT on this cancer, particularly with current use. One of the largest studies found that whether current or former, the duration of estrogen use increased the protective effect.

Estrogen reduces the incidence (up to 50%) and the mortality from colon cancer. It has also been known (along with aspirin) to reduce the incidence of adenomatous polyps. The highest reduction in risk is observed for tumors of the proximal colon. The control for screening has not eliminated an inverse association. Epidemiologic evidence does support the fact that conventional EPT both lowers the risk of colorectal polyps and inhibits promotion of existing cancers. The WHI trial—a prospective randomized controlled trial has confirmed this also.

Again no evidence of the role of tibolone or raloxifene or phytoestrogens in colon protection has been studied.

### Estrogens versus Combined Estrogen Progestogen for Cardioprotection

Long-term research and observational studies on estrogen only CEE use and cardiovascular disease had suggested a role for primary cardioprotection in preventing cardiac morbidity and mortality in normal and at risk women.

Several secondary prevention and epidemiological studies had also shown results where ET use in women had reduced the risk of mortality by 50–90%. This degree or reduction was marked and comparable to that observed following successful treatment of LDL cholesterol elevations. Two studies involved estrogen use in postmenopausal women with angiographically defined coronary artery disease (CAD). Women using estrogen had significantly less coronary artery stenosis as compared to those women not using estrogen. Patients with the most advanced CAD had been shown to benefit the most from ET usage.

However, one arm of the randomized controlled WHI trial had used continuous combined 0.625 mg of CEE and 2.5 mg MPA in an older population of women, mean age 63.3 years, and had failed to demonstrate any primary cardioprotective role. This trial was in fact terminated at 5.2 years. The other arm, which used only CEE, continued and was prematurely terminated after 6.8 years of follow-up. Overall, coronary outcomes among the CEE and placebo groups were not statistically significant. These results show convincing trends of estrogen cardioprotection in women who began oral CEE treatment at ages 50–59 which were of no statistical significance, most probably because of the small power of the study and a design that did not allow for statistical differentiation of coronary events among the groups.

The heart and estrogen/progestin replacement study HERS II (also a randomized controlled double blind prospective study) and HERS II had also shown that the continuous combined use of the same combination of 0.625 CEE and 2.5 MPA had no secondary cardioprotective
benefits with up to 6.8 years of use. However, no increase in cardiac morbidity was seen either.

In relation to restenosis and angioplasty outcome, the effects of EPT are not constant. Interestingly, two studies present contradictory outcomes. In one, a reduction by 50% was seen in restenosis rate following atherectomy but not following angioplasty. Another study showed a highly significant long-term benefit in the 7 year mortality, although no effect was seen on the occurrence of myocardial infarction after angioplasty. Another study showed a highly significant long-term benefit in the 7 year mortality, although no effect was seen on the occurrence of myocardial infarction after angioplasty.

To Summarize

The findings from the WHI and HERS trials are consistent with previously known observational data regarding the real but small risks from continuous combined use of 0.625 CCE and 2.5 MPA to individual women of thromboembolism, stroke, breast cancer detection. Lack of secondary cardioprotection was demonstrated from the HERS I study. The WHI trial demonstrated the lack of primary cardioprotection with the use of this continuous combined EPT regimen (Table 2).

Evidence-based Recommendations Regards Use of Estrogen Therapy and Estrogen Progestogen Therapy

Where do we stand today?

- Menopausal women in the fifth decade of their live’s who are symptomatic, may continue to be advised oral estrogen-progestin combinations for short-term therapy which varies from around 2–5 years. This should be gradually tapered off to minimize chances of recurrence of symptoms. One could consider using micronized progesterone in view of the minimal effects on lipid profile of this progestrone.

- As demonstrated in the WHI trial, the risk of pulmonary embolism (PE) is greatest in the first 2 years and the risk of stroke appears in the second year. The women considering short-term HRT would hence need to be counseled regards these issues. Though the RR for PE is 2.13 in 5.2 years, the absolute true increased risk is only 0.17%/year for an individual woman. This can also be translated to connote eight extra cases of PE per 10,000 women per year, i.e. less than one per 1,000 women per year.

- With regards to considering this therapy long-term, for preventive health measures, it must be clarified that there are no demonstrated primary or secondary cardioprotective benefits, although in the long-term there no additional cardiac risks either. The relative and absolute risks of PE, stroke and breast cancer detection should be explained. The documented additional risks for these are eight cases of each of these per 10,000 women per year, i.e. less than one per 1,000 women per year. This combination should not be recommended to women seeking to initiate or continue HRT for cardioprotection, particularly if they belong to the “at greater risk for developing coronary heart disease (CHD) group”. Instead alterations in lifestyle measures, such as weight reduction, appropriate exercise and diet, avoidance of excessive alcohol and stress, no smoking, and the use of statins and aspirin should be recommended as first line measures.

- Because randomized controlled trials are not yet available for other health issues, it does not necessarily imply that the value of all the previous observational trials which have demonstrated multiple beneficial effects should be discarded.

- Since other hormones and different regimens and doses have not yet been subjected to rigorous prospective randomized controlled double blind trials, neither can they be absolved from these problems nor can these results be extrapolated to them. Large well designed prospective studies covering all aspects are required to resolve these issues, which may take years before we have the answers.

Knowledge of associated risks, albeit small with this therapy, is in a way an advantage over unknown and unstudied effects of other EPT combinations, regimens and hormones. This combination has been subjected to the rigorous test of time and scientific clinical assessment and studied unlike other hormones. “Forewarned is forearmed!” Careful evaluation and monitoring can prevent, detect early and deal with the problems when and if they occur. We are all aware that even paracetamol or aspirin do not come without their risks.

- Women who are already on combination therapy—whether less than or more than 5 years, should be counseled individually and a personalized decision taken in light of their needs, requirements, risk factors and the latest consensus on available medical evidence. Physicians, and the women themselves, should not be unduly alarmed as the risks to an individual are small. The women should be reassured and counseled appropriately as such.

<table>
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<tr>
<th>Table 2: Observations of Women’s Health Initiative Study</th>
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<tr>
<td>• 41% increase in stroke</td>
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<tr>
<td>• 29% increase in heart attacks</td>
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<tr>
<td>• Doubling of venous thromboembolism</td>
</tr>
<tr>
<td>• 26% increase in breast cancer</td>
</tr>
<tr>
<td>• 37% reduction in colorectal cancer</td>
</tr>
<tr>
<td>• One-third reduction in hip fracture</td>
</tr>
<tr>
<td>• 24% reduction in total fracture</td>
</tr>
<tr>
<td>• No difference in total mortality</td>
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• **Consideration should be given to switch to micronized progesterone**, preferably the vaginal or rectal route, if acceptable to the woman.

• **The women who are taking only CCE without the MPA should really not be unduly concerned.** Since, the estrogen-only arm of the WHI trial has failed to demonstrate relative harm.

• **To assess latent cardiac risk factors** in those women who are keen to do so and who can afford it financially, the following tests could be performed: complete lipid profile, LDL cholesterol subfractions, homocysteine, lipoprotein(a) [Lp(a)], plasminogen activator inhibitor-1, fasting insulin, blood sugars and C-reactive protein.

• **To assess an inherent risk of thromboembolism**, the following tests could be performed: protein C, protein S, antithrombin III, lupus anticoagulant, anticardiolipin antibody immunoglobulin G (IgG) and IgM. Those women identified as at risk for these should be counseled regards the implications of these results, explained about the impact of lifestyle measures and discouraged from taking HT.

*Until conclusions from other randomized controlled studies are available, it is currently recommended that EPT not be initiated or continued for the purpose of primary or secondary cardioprotection, but may be used for short-term therapeutic relief of symptoms after complete explanation to the women. The choice of the progesterone should possibly be micronized progesterone. However, if a woman has been on EPT already, there is no reason for alarm. One could consider switching over to micronized progesterone. The women should rediscuss the personalized need, desires, risks and benefits of continuing with HT. EPT may be advocated for its multiple other indications and preventive advantages.*

There are no results of randomized controlled trials looking at the cardiovascular disease endpoints with the use of tibolone, raloxifene or phytoestrogens. Therefore, when these are prescribed, it has to be clarified that information regarding this aspect is unavailable at the moment.

### Novel Anti-inflammatory and Other Actions of Conjugated Equine Estrogen on the Brain

Estrogen has been shown to have beneficial action on the brain. In the animal model, CEE has a protective effect against amyloid-beta-induced inflammatory reaction in AD. The decrease in prevalence of AD in women on ET may be partially explained by modulation of the normal age related increase in cell membrane breakdown and decline in serotonergic function. Women taking EPT have milder symptoms than those who do not. EPT decreases the risk and delays the onset of AD. The use of estrogen for longer than 1 year reduces the risk of developing AD by 5% annually. Estrogens have also been shown to improve verbal and visual memory.

Several recent epidemiological studies provide the best evidence relating estrogen deficiency to AD. A 40–60% reduction in the risk of AD in women who have taken ET has been demonstrated individually by each of the five independent studies. It must also, however, be noted that the majority of these hormone users received unopposed estrogens.\(^ {53-58} \)

With the loss of estrogen at menopause, it is hypothesized that a selective neuronal loss within the hippocampus (a region of the brain which subserves memory that is uniquely sensitive to hypoglycemia as evidenced by autopsy studies of insulin dependent diabetics) results from a decrease in estrogen dependent glucose transport to the CNS.

*As seen above, estrogens do have some neuroprotective actions. However, there is no conclusive data on tibolone, raloxifene or phytoestrogens on these issues yet.*

### Re-evaluating the Breast Cancer Issues

There exists a baseline incidence of breast cancer in any population. This incidence of breast and gynecological cancers rises with the advent of menopause and with advancing age.

The relationship between EPT and breast cancer is complex. A prospective randomized placebo controlled trial\(^ {59,60} \) conducted albeit a small study failed to demonstrate any deleterious effect of sequential EPT on breast cancer. On the other hand, the recent WHI trial\(^ {52} \) demonstrated an increased risk of breast cancer detection with the continuous combined use of 0.625 mg CCE and 2.5 mg MPA as did with the million woman study.

Some of the women participating in the WHI trial had either been past or current HT users with a family history of breast cancer. Again, their behavior with regards to breast cancer may have been altered somewhat in view of this.

It was also observed that there was no increase in the incidence of breast and gynecological cancers supporting the theory of hormones potentiating the development of invasive breast cancer rather than initiating it.

The second arm of the WHI trial is looking at the effect of estrogen only.

The effects of all HT need not necessarily be the same. The gonadomimetic agent, tibolone has been shown clearly to be advantageous to breast tissue as seen in experimental studies on breast cell lines. The mammographic changes also do not show any increase in breast density with the use of tibolone whereas with the use of estrogen-progestogen this increase in density has been seen.

### Baseline Breast Cancer Risk Increases with Age (Table 3)

In women, the chance of breast cancer increases with age, especially after menopause. The cumulative incidence by age 85 years is a lifetime risk of breast cancer of 11%.

Up to 50 years of age, the baseline breast cancer risk is 18/1,000 women (approximately 2%). After 50 years of age,
which is also usually the age around menopause, the baseline breast cancer risk increases approximately by 2/1,000/year of increasing age (0.2%).

Factors Affecting Breast Cancer Risk Seen in Perspective (Table 4)
The risk of HT on breast cancer must be viewed in perspective and compared to that of other prevalent factors that affect it, like excessive consumption of alcohol, failure to take regular exercise, increased body mass index (BMI) (increased weight) and late menopause.

Increased Probability of Breast Cancer Diagnosis: Tumor Promotion versus Tumor Initiation
The increased probability of breast cancer diagnosis should be differentiated from increased risk of actual initiation of breast cancer development (cancer initiation). The two do not necessarily have the same connotation.

Breast cancer is usually present for many years (5–10 years) before it is clinically diagnosed—the “theory of the dormant malignant cell”. Therefore, during the subclinical periods, there may be a prolonged exposure to estrogens—both exogenous and endogenous. It has been seen that EPT users are younger at the time of breast cancer diagnosis than never-users. It is postulated that estrogens may have merely accelerated the growth of pre­existing tumors rather than initiating the development of the tumor. It is possible that estrogens and EPT influence expression and transcription in normal breast cells and cancerous breast cells of growth factors, oncogenes and other factors of the cell cycle. Thereby EPT may have a role in the promotion of tumor proliferation rather than in its initiation. Promotion of tumour proliferation in a pre-existing tumor is quite different from initiation of tumor development.

Effect of Current/Recent Use of EPT on Breast Cancer Incidence and Diagnosis (Tables 5 and 6)
It has been demonstrated that up to 5 years of use there is no increased probability of breast cancer diagnosis. Current counseling is based on combined reanalysis of 51 epidemiological studies on 52,705 women. This reanalysis has included 90% of all popular studies. The risk has been shown by these epidemiological studies to increase beyond 5 years of EPT use. The results of the WHI trial have confirmed the RRs to be 1.26 at 5.2 years of use of continuous combined CCE and MPA.

The average increase in RR of breast cancer observational studies per year of use is 0.023, i.e. 2.3% [95% confidence interval (CI) 1.1–3.6] and 0.08% per year of use by the results of the WHI trial.

After 5 years of discontinuation of EPT, no increased risk remains and has not been demonstrated.

The excess number of breast cancers seen amongst users of EPT (current/recent), starting at age 50 years, is tabulated below. This information must be clearly put to a woman who is being counseled about EPT and other therapies to enable her to get the right perspective regards the effect of this on breast cancer incidence before she decide to go on any type of HT.

<table>
<thead>
<tr>
<th>Duration of EPT use</th>
<th>Increased relative risk of breast cancer</th>
</tr>
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<tbody>
<tr>
<td>Short term (1–4 years)</td>
<td>1.05 (95% CI 0.99–1.12)</td>
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<tr>
<td>&gt; 5 years (average 11 years)</td>
<td>1.35 (95% CI 1.21–1.49)</td>
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<table>
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<tr>
<th>Years taking EPT</th>
<th>Breast cancers over 20 years (age 50–70)</th>
<th>Excess breast cancers in EPT users</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never use (Baseline risk)</td>
<td>45 per 1000</td>
<td>–</td>
</tr>
<tr>
<td>5 years</td>
<td>47 per 1000</td>
<td>2 per 1000</td>
</tr>
<tr>
<td>10 years</td>
<td>51 per 1000</td>
<td>6 per 1000 and 8 per 1000 by WHI trial</td>
</tr>
<tr>
<td>15 years</td>
<td>57 per 1000</td>
<td>12 per 1000</td>
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Hormone Therapy Use Improves Breast Cancer Prognosis

On the other hand, the nature and direction of tumor proliferation with estrogens has been shown to be less aggressive than those not exposed to estrogens. Smaller sized tumors, localized tumors with less metastatic potential are seen when they are associated with HT use. A lower grade of breast cancer has been seen in HT users compared to never users with a lower proliferation rate. The tumors in the HT users are less aggressive and less invasive.

Contrary to popular belief, the prognosis of breast cancer cells matched for stage at diagnosis, has been seen to be better with raised endogenous estrogen levels in premenopausal women who have a better prognosis as compared to postmenopausal women who have lower estrogen levels and yet a worse prognosis. Therefore, increased estrogen levels are not necessarily detrimental to breast cancer, as popularly believed! The relationship between breast cancer and estrogen may not be a simplistic direct relationship but be a complex relationship influenced by other coexisting factors such as the reproductive phase of a woman’s life, her weight, smoking, lifestyle and other factors.

Hormone Therapy and Recurrence in Breast Cancer Survivors

The recurrence rate in HT users has been shown to be lower (6.2%) compared to that in non-HT users (29.3%). No increase in cancer progression of breast cancer recurrence was seen. However, in an anecdotal study, the progression of breast cancer recurrence was halted in four patients on stopping their HT.

Summary of Effects of HT on Breast Cancer

The available data on the exogenous use of estrogens and HT on breast cancer can be summarized as follows:

- There is an increased probability of breast cancer diagnosis with EPT use.
- No role of EPT in malignant transformation (initiation) has been demonstrated so far.
- EPT is associated with promotion of an already existing breast cancer.
- However, the kind of breast cancer which may have been promoted with EPT use is less aggressive.
- Prognosis of breast cancer is not worsened with the use of EPT, in fact it is improved.
- There are no deleterious effects of EPT on the course of breast cancer.
- The course of breast cancer is not worsened with EPT.
- Clinically less advanced disease is seen in EPT users.
- A reduced mortality with improved survival is seen in EPT users compared to never-users.

- EPT may be used in patients who have earlier been diagnosed to have breast cancer which was estrogen-progestogen receptor (ERPR) negative.
- The efficacy of treatment modalities (surgery, irradiation, chemotherapy) of breast cancer are not affected by EPT use in these cancer patients.
- Whether or not EPT should be suspended during the active treatment of breast cancer, needs to be established by trials. However, till such guidelines are clear, it may be wise to temporarily withhold EPT on these patients and after initial control of disease initiate EPT, only if necessary after comprehensive counseling.
- EPT may be used in patients with benign breast disease.
- EPT may also be used in patients with a family history of breast cancer under strict surveillance.
- Monitoring for breast cancer detection is mandatory for all women on EPT.
- Results of the recent WHI randomized double blind prospective trial has shown that the RR of breast cancer detection with continuous combined CCE 0.625 mg and 2.5 mg MPA is 1.26 at 5.2 years. In the estrogen only arm of the WHI study, invasive breast cancer was decreased by estrogen treatment. The hazard ratio was not statistically significant: 0.77 (CI 0.59–1.01). An older, small randomized trial with sequential 2.5 mg CCE and 10 mg MPA has shown the RR to be 0.46.

Hormones Provide Relief in Other Gynecological Cancers

There is no associated risk between EPT, cervical cancer, vaginal cancer, vulval cancer and leiomyosarcoma. The 5-year survival, recurrence rates and prognosis are unaffected with EPT even in adenocarcinoma of the cervix. EPT may be used as it does not seem to affect prognosis contrary to speculation.

Hence, in all those women suffering from severe estrogen-deficiency symptoms from chemotherapy or local pelvic changes from radiotherapy, EPT can be safely used to treat these symptoms. Quality of life for these women is greatly improved and the EPT associated benefits are profound.

The emerging data on risk of ovarian cancer is controversial at the moment. EPT has been shown to increase survival in ovarian cancer patients, especially with endometrioid and clear cell carcinomas of the ovary. No negative influence is noticed with the disease free interval in these patients with EPT use.

Distinct from initiating use of HT in women with demonstrated ovarian cancer may be the chance of development of ovarian cancer in HT users. A recent report of a cohort study of former participants in the Breast Cancer Detection Demonstration Project identified 329 women who had developed ovarian cancer. They found that short-term estrogen-progestin use had not increased risk of ovarian cancer in these women but high doses of estrogen only...
(unopposed estrogen) for 10 years or more increased the risk of ovarian cancer by 0.07 per year of use.

**TAILORING THERAPY: INVESTIGATIONS PRIOR TO STARTING HORMONE THERAPY, FOLLOW-UP AND MONITORING**

**Assessment and Evaluation Before Hormone Therapy (Table 7)**

It is very essential to individualize the HT and to choose the right drug from the wide range available now.

A thorough history, evaluation of the woman’s needs, evaluation of the woman’s individual risk factors, thorough physical examination, performing some pre-HT tests along with opportunistic screening tests should be carried out prior to starting HRT.

Certain tests are reserved for special indications only. Routine physical examination should include documentation of height, weight, BMI and measurement of blood pressure (BP). A detailed breast and pelvic examination should also be performed.

**Routine Screening Tests**

*Pre-Hormone Therapy—The following tests are recommended prior to starting HT:*

- Mammography, ultrasound of breasts
- Transvaginal sonography (TVS) for endometrial thickness and morphology
- Lipid profile, particularly serum triglyceride.

*Additional tests for menopausal health which may be considered as opportunistic screening are:*
- Pap smear
- Serum TSH, if indicated
- Urine tests—routine and culture
- Stool for occult blood
- Blood sugars
- Complete blood count (CBC)

*The following tests (Table 8) are performed as indicated in the individual.*

*The follow-up schedule for monitoring patients on HT is:*

- First follow-up should be after 1 month, followed by an evaluation after another 3 months and subsequent follow-ups should be tailored to the individual woman 6-monthly or annually, as appropriate.
- At each follow-up visit, it is important to ascertain the relief of menopausal symptoms.
- Compliance with therapy should be assessed along with documentation of patterns of vaginal bleeding and occurrence of any side effects. Weight should be measured and changes in weight/BMI recorded at each visit.
- Blood pressure measurement should be used as opportunistic screening, especially with pre-existing hypertension.
- Clinical breast examination with mammography and breast sonography is ideally required annually for women on HT. All women should also be counseled about monthly breast self-examination.
- Annual lipid profile, especially estimation of triglycerides is essential, if a woman is on oral estrogen and HDL, if she is on tibolone. Initially, these should be assessed after 1–3 months to assess the trend. Blood sugars, thyroid function should be rechecked as indicated.
- Pelvic ultrasounds (preferably transvaginal/transrectal) should be done annually in order to measure endometrial thickness in millimeter and morphology, along with

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<th>Table 7: Contraindications of hormone therapy</th>
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<tr>
<td>Absolute contraindications</td>
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<tr>
<td>- Active hepatic disease</td>
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<tr>
<td>- History of thrombosis</td>
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<tr>
<td>- History of breast cancer</td>
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<tr>
<td>- Undiagnosed vaginal bleeding</td>
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<tr>
<td>- Previous myocardial infarction</td>
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<tr>
<td>- Previous stroke</td>
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<tr>
<td>- History of pulmonary embolism</td>
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<table>
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<tr>
<th>Table 8: Tests to be performed before starting hormone therapy</th>
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<tbody>
<tr>
<td>1. TSH</td>
</tr>
<tr>
<td>2. FSH and estradiol</td>
</tr>
<tr>
<td>3. Tests to assess increased risk of thrombosis</td>
</tr>
<tr>
<td>4. Endometrial biopsy</td>
</tr>
<tr>
<td>5. Bone mass measurement</td>
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<td>6. LFT</td>
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screening for ovarian size and masses, and assess the growth of fibroids, if any.

- Bone density (Dexa) scan is advisable annually or every 2 years
- At each visit, it is sensible to reassess and document the indication of HT, its dosage schedule, assess individual risks and benefits of continuing therapy, and discuss any recent developments and alternate therapies made available in the market.
- All women taking HT should be monitored regularly and regularly reassessed for a changing individualized risk benefit ratio.
- *Some tests* that may need to be performed, if indicated in light of developments, since the last visit of the patient are coagulation profile for thrombophilia, endometrial sampling and hysteroscopy.
- The number of office visits and procedures should be kept to the minimum necessary to reduce the stress on the patients and on the health care system.
- It is important to remind women at each visit that first line treatment for prevention of heart disease and cancer is to incorporate lifestyle changes and encourage them to maintain a normal BMI, perform routine exercises, take a healthy diet and stop smoking.

**Absolute Contraindications**

Absolute contraindications to HT include a known or suspected pregnancy, undiagnosed abnormal vaginal bleeding, endometrial/gynecological/hormone dependent cancers, breast cancer, severe active liver disease with impaired/abnormal liver function and acute vascular thrombosis/thrombophlebitis in past or present.

**Relative Contraindications**

Relative contraindications to HT are those when hormones can be prescribed but with careful assessment and monitoring because of their adverse effects such as migraines, headaches, thrombophlebitis, strong family history of breast cancer, the presence of uterine fibroids, endometriosis, gall bladder disease and past history of pancreatitis are important considerations to make when tailoring HT.

Metabolic differences exist between different types of steroids and different routes of administration. These should be borne in mind and hormones prescribed accordingly.

**Side Effects of Hormone Therapy**

Side effects associated with estrogens and progestogens may be subdivided broadly into predominantly estrogenic or progestogenic side effects.

The common estrogenic side effects are leg pain, breast tenderness, headache, bloating, nausea, dyspepsia and vaginal discharge.

The progestogenic side effects may be physical, like acne, bloating, backache, breast tenderness, headache, dizziness, generalized aches and pains, greasy skin, fatigue, poor sleep, weight pain, backache, abdominal cramps; or psychological, like anxiety, confusion, depression, forgetfulness, irritability, panic attacks, poor concentration and restlessness.

**Informed Decisions, Acceptance and Continuation of Therapy**

When counseling women and advising hormones, it is wise to indicate and document the reason for prescribing the hormone replacement therapy. It is also prudent to explain the possible adverse effects of therapy prescribed. This helps the patient identify and report the problems and not get unduly alarmed. The importance and need of tailoring therapy to an individual will then be understood and will result in a greater chance of continuation with therapy. The long-term problems of increased breast cancer detection rates and thromboembolism must be discussed. This ensures the woman understands and can reflect on why she is taking the treatment. It is also wise to clearly record the results of the investigations performed prior to starting, and to clarify the time when she needs to come back for reassessment and follow-up. For every woman, the risk-benefit ratio should be personalized.

Myths abound regarding "HRT"! Evidence-based counseling and management with hormones will enhance acceptance and continuation of therapy and help prevent a lot of suffering whilst adding quality of life to this difficult phase in a woman’s life.

**REFERENCES**

INTRODUCTION

Prolactin is a single chain polypeptide of 199 amino acids, somewhat similar in structure to growth hormone and placental lactogen. Prolactin is encoded by a single gene in the short arm of chromosome 6. The anterior pituitary cells that produce prolactin are said to be responsible for secretion of growth hormone (GH) and thyroid-stimulating hormone (TSH) as well.

Prolactin release in humans varies in various physiological states and in response to different stimuli. Prolactin secretion is influenced by chronic inhibitory control exerted by Dopamine secreted by hypothalamus (HT). Dopamine is delivered through the pituitary portal circulation from the HT to the pituitary gland and this can be interrupted by any lesion that involves the stalk. There is also an increasing evidence that prolactin secretion is positively regulated by a variety of releasing factors like thyrotropin-releasing hormone (TRH), vasoactive intestinal peptide (VIP) and angiotensin II. Prolactin is secreted in a pulsatile fashion with the pulses synchronizing with luteinizing hormone (LH) pulses throughout the menstrual cycle and follicular-stimulating hormone (FSH) pulses during the follicular phase.

Circulating prolactin is present in glycosylated and non-glycosylated forms. Larger forms of prolactin have also been discussed as a “Big” prolactin and a “Big Big” prolactin. The “Big Big” prolactin form is found in macroprolactinemia in a condition where elevated prolactin levels are relatively asymptomatic.

The normal level of prolactin in prepubertal level is 2–12 ng/mL and in adult of 3–30 ng/mL. Sleep increases the prolactin level which comes down to normal after 2 hours of waking up. Exercise, stress, sexual activity and nipple stimulation increases prolactin levels. In pregnancy, prolactin increases steadily from 7th week onwards and at term reaches to 20 times the basal level, probably in response to increasing level of estrogens. The prolactin level returns to basal region within 4 weeks of delivery if there is no breastfeeding. In nursing mothers the prolactin level remains high upto 80–100 days or even more. Prolactin level decreases in postmenopausal women.

Hyperprolactinemia is a common endocrine disorder frequently leading to gonadal dysfunction which presents as menstrual disturbances like oligomenorrhea and amenorrhea, galactorrhea, loss of libido, dyspareunia and infertility.

The restoration of prolactin levels to normal using medical therapy results in ovulation with a pregnancy rate of 70%.

CONDITIONS ASSOCIATED WITH INCREASED PROLACTIN SECRETION

- Hormone disturbance caused by:
  - Delivery of exogenous or endogenous estrogens
  - Increase in TRH caused by primary hypothyroidism
  - Administration of oral contraceptive pills (OCPs).
- Use of Dopamine receptor blocking agents like:
  - Phenothiazines
  - Haloperidol
  - Metoclopramide, etc.
  - General anesthesia.
- Dopamine depleting agents like:
  - Reserpine
  - Alpha-methyldopa
  - Opiates.
- Histamine H₂ receptor antagonists like Ranitidine.
- Stimulation of serotonergic system by amphetamines and hallucinogens.
Other conditions like pituitary tumors can cause inappropriate prolactin secretion. Tumors of prolactin secretory cells (prolactotroph adenoma) directly increase prolactin levels. Tumors arising in the neighborhood of prolactotrophs within the pituitary gland can compress or defunction the prolactotrophs and cause hyperprolactinemia, while tumors of the pituitary or the hypothalamus that grow towards the pituitary stalk can produce lesions similar to stalk transection and prevent Dopamine reaching the pituitary gland. Such tumors increase prolactin level by interrupting the chronic inhibitory action of Dopamine.

Administration of TRH promptly stimulates prolactin secretion. So in cases of primary hypothyroidism, which results in hypothalamic release of TRH, hyperprolactinemia is a common sequel. In this condition, administration of thyroid hormone automatically results in normoprolactinemia.

One of the most frequent pathological causes of hyperprolactinemia is prolactinoma which is also the most common hormone secreting tumor of the pituitary.1

 MANAGEMENT OF HYPERPROLACTINEMIA (FLOW CHART 1)

The treatment of elevated prolactin not only corrects menstrual disturbance but also resolves other problems related to estrogen deficiency. In women suffering from osteoporosis with hyperprolactinemia, return of gonadal activity restores trabecular bone structure and calcification.

The prolactin producing tumors of pituitary gland are classified as microadenoma, if less than 10 mm in diameter. Microadenomas are very common; so common, that their presence may be ignored unless they are producing unacceptable symptoms. They rarely grow during pregnancy nor do they progress to macroadenoma. They also have a significant recurrence rate after surgery. Dopamine agonist treatment can reduce their size and serum prolactin levels, but they form again after the treatment is over. Their natural course is never affected by Dopamine agonists. So, microadenoma may be ignored and should be treated only when the patient is intolerant of galactorrhea or if she is infertile.

Prior to the development of Dopamine agonist, women with prolactinomas routinely underwent surgery. In a group of highly selected patients, transphenoidal pituitary surgery is still effective, but recurrence rate of hyperprolactinemia after surgery is high and there is no assurance of long-term cure.3 Development of Dopamine agonists has revolutionized the treatment of prolactinomas and virtually alleviated the need for surgery.

The two commonly available Dopamine agonists are bromocriptine, an ergot derivative which has been in use for over 20 years and Cabergoline, a nonergot agonist available only for the last 11 years. Both the drugs act by binding to the cell surface receptors of the pituitary lactotrophs and reduce prolactin levels. Both drugs can cause nausea, nasal stuffiness and orthostatic hypotension; but these symptoms are worse in patients taking bromocriptine.

Although bromocriptine is the less expensive of the two drugs, it also has the drawback of requiring twice daily dosing unlike cabergoline which needs to be given once or twice weekly.

The choice of Dopamine agonist depends on whether restoring fertility is the goal. In patients who wish to conceive, the safety record of bromocriptine makes it the first drug of choice since it has been used in over 6,000 pregnancies with no increase in incidence of spontaneous abortions, ectopic pregnancy, multiple pregnancy or congenital anomalies.4,5 In contrast, pre-pregnancy Cabergoline has been used in only about 300 patients; in view of this, more long-term studies are required.

Patients are usually advised to discontinue bromocriptine as soon as pregnancy is diagnosed but there have been several women who have used bromocriptine throughout pregnancy without any fetal complications.6,7 If infertility is not the issue, then the goals of therapy in these women with amenorrhea and/or galactorrhea, is to restore gonadal function and prevent bone loss. Cabergoline appears to be more effective in these patients. Normalization of prolactin level occurs in 83% of patients with cabergoline as compared to 59% treated with bromocriptine. Restoration of ovulation occurs in 72% of patients treated with cabergoline as against 52% in bromocriptine treated patients.8 Cabergoline being more potent than bromocriptine is also the treatment of choice in patients with large prolactinomas. But the drug may not be given if microadenomas continue to remain small without showing any symptoms of increase in size like headache, neurological symptoms or symptoms of hypopituitarism. If restoration of fertility is not the goal of the treatment and there is no evidence of macroadenoma, one may not treat this condition at all, because 95% of small prolactinomas tend to remain small. Side effects and cost of Dopamine agonist drugs and the relatively asymptomatic condition of the disease makes it difficult for patients to continue to have long-term adherence to drug regimes.

Most young patients would like to have their menses regularized and the physician should also be worried about long-term effects of hypoestrogenism in these patients. In view of this, an OC pill can be used to satisfy both these concerns. OC pills are less expensive and better tolerated than the Dopamine agonist drugs.8,10 Estrogen therapy does induce mild hyperprolactinemia and lactotroph hyperplasia, but short term OC pill administration are not known to produce tumor growth.

During usage of either drug it is important to start on a low dose and step-up the dosage depending upon the response like the degree of remission of symptoms viz. galactorrhea,
amenorrhea and irregular menses—once in 5–7 days for bromocriptine and once in 2 weeks for cabergoline. The maximum dosage advisable for bromocriptine is 7.5 mg per day and for cabergoline it is 1 mg twice weekly.

It has also been found that women with microprolactinoma who have at least had one pregnancy are more likely to get long term or complete tumor regression compared with those who have had no pregnancy at all.\textsuperscript{11,12}
There has been an increasing trend towards conservatism in the management of microprolactinomas as majority of them never grow. Dopamine agonist treatment is reserved for those tumors which show rapid growth in size or those that are already large. These lesions are frequently associated with prolactin levels of more than 100 ng/mL.

The initial X-ray evaluation in suspected cases of tumors of pituitary is to get a coned down lateral view (CDLV) of sella turcica. If the prolactin level is more than 100 ng/mL and if CDLV of the sella turcica is abnormal, a computed tomography (CT) scan or magnetic resonance imaging (MRI) may be required. Since, the prolactin producing cells are situated in the inferolateral aspect of the pituitary gland, one often looks for a double floor of sella in the coned down view (CDV), but in the absence of enlargement of sella or demineralization of the bone, it is interpreted as a normal variation rather than asymmetrical depression of the sella floor by tumor.

Increased use of CT scan and MRI have revealed other silent pituitary masses which pose no adverse effects on a person’s general health; because not only they are inert, but they grow ever so slowly. These are called as pituitary “incidentalomas,” seen in 9–27% of autopsy specimens.\textsuperscript{13-15} The benign course of these tumors are arguments in favor of noninterference or “wait and watch policy” and this also applies to microprolactinoma. Long-term surveillance is required by reassessment of MRI or CT scan on 1, 2, and 5 years. If there is no change in size, no further radiological studies are required; but hormonal studies like assay of prolactin, TSH, 24-hour urinary cortisol and dexamethasone tests may be done at intervals of 1–2 years.

Large tumors of pituitary gland visible on MRI or computed axial tomography (CAT) scan associated with a prolactin level of less than 100 ng/mL are unlikely to be prolactinomas. The increase in serum prolactin is more due to a non-prolactin producing tumor extending upwards and compressing upon the stalk than the tumor caused by prolactin producing cells.

A macroadenoma can cause visual problems and bifrontal, retro-orbital or bitemporal headaches. Treatment is required in order to relieve the patient of symptoms and also of the fear of further growth. Bromocriptine binds with high affinity to the Dopamine receptors on both normal and adenomatous lactotroph cells and it is the treatment of choice for prolactinomas of all sizes.\textsuperscript{16,17}

Tumor shrinkage is observed to occur within 2 weeks of therapy in some women. Most women become free from symptoms within 3 months of therapy. These include not only freedom from headache and visual symptoms, but also return of menstrual cycles, ovulation and even onset of pregnancy.

The patients must be counseled that the micro- or macroadenoma can increase during pregnancy and that they should watch out for symptoms of headache and visual disturbances. Since estimation of prolactin level ceases to be a marker during pregnancy (because of physiological hyperprolactinemia), one must watch the effect of tumor expansion on intracranial tension (headache) and pressure on neighboring structures like the optic nerve (visual disturbance). It is a useful exercise to have a preconceptional documentation of visual fields as a baseline so that any deviation from pre-pregnancy chart can be compared critically. The increase in tumor growth can be confirmed by pituitary imaging and also by disturbance in visual field. In the rare event of increase in size of prolactinoma whether it is micro- or macroadenoma, bromocriptine may be started once again without fear of any teratogenicity to the fetus.

The normal pituitary gland increases by 35% in weight and about 60% in size due to an increase in the number and size of lactotrophs during pregnancy. This is meant to prepare the breast for lactation and prolactin levels rise up to 6–20 times the normal preconceptional level.

Gemzell and Wang\textsuperscript{18} studied 217 pregnancies on 198 women with prolactinomas. 85 women with microadenoma had 91 pregnancies. None of them had received either prior surgery or irradiation. Only five of them developed signs of tumor enlargement like headache or visual disturbances (5.5%). Among 46 women with macroadenoma who had neither surgery nor medical treatment, 20 of them showed tumor enlargement during pregnancy giving an incidence of 35.7%. Whereas, among 67 women with macroadenoma, who had been pretreated either with surgery or irradiation or both, there were five pregnancies with tumor enlargement giving an incidence of 7% (Table 1).

Till now there has been no teratogenic effect noticed on the fetus with administration of bromocriptine therapy during pregnancy but the policy adopted is to discontinue therapy as soon as pregnancy is diagnosed. However, reports are available of using bromocriptine successfully in the event of tumor expansion in pregnancy. All patients must be counseled regarding the possibility of tumor expansion whether it is a microadenoma or a macroadenoma during pregnancy.\textsuperscript{19,20} Repeated visual field examination during pregnancy may not prevent the complication of visual loss which may occur very rapidly and unpredictably. It has not been proven that preconceptional surgery or radiation therapy is superior to Dopamine therapy as a prophylactic measure against tumor expansion during pregnancy. Moreover, megavoltage irradiation to pituitary gland can cause destruction of other cells along with tumor producing lactotroph cells. The risk for patients with microprolactinoma and macroprolactinoma confined to pituitary fossa is below 5% either to warrant radiotherapy or to give continued Dopamine treatment during pregnancy.
SUMMARY

The algorithm supplied gives the approach to management of hyperprolactinemia which is a relatively easy condition to treat with the free availability of bromocriptine. Bromocriptine can act as an ovulation inducing agent in women with hyperprolactinemia. A patient having amenorrhea can become pregnant while on bromocriptine therapy even before the onset of menstrual cycles. Bromocriptine is simply stopped when pregnancy is diagnosed and there is no fear of teratogenicity. Patients who have been treated adequately for hyperprolactinemia before embarking on pregnancy have less than 5% chance of tumor expansion during pregnancy. If it does occur, bromocriptine can be given throughout pregnancy.

Asymptomatic hyperprolactinemia per se need not be treated if the symptoms are not severe. A level less than 100 ng/mL of prolactin usually means that it is a microadenoma which need not be treated. The patient should be counseled regarding the requirement of regular follow-up.

REFERENCES

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common reproductive endocrinopathy of women during their childbearing years with a reported prevalence of 4–8%. It is a major cause of infertility, amenorrhea or oligomenorrhea. Classical symptomatology is a result of excessive ovarian androgen production and chronic anovulation. Hyperandrogenism may present as hirsutism, acne or male pattern alopecia. Anovulation manifests as irregular menstrual cycles and infertility.

The classic work of Stein and Leventhal in 1935 first brought attention to this disorder when it was diagnosed on the basis of oligomenorrhea, hirsutism, obesity, and the presence of polycystic ovaries, which were considered pathognomonic for the disorder. They performed ovarian wedge resection which resulted in return of ovulatory cycles in some cases. The enlarged sclerocystic ovaries were observed by pneumoroentgenography or by laparotomy. With development of sonography, laparoscopy and radioimmunoassay techniques and introduction of ovulation induction drugs such as clomiphene citrate and gonadotropin there was a great change in the method of diagnosis and management of this problem. Assisted reproductive technology has also been helpful to overcome this problem in a significant number of women.

Polycystic ovarian syndrome is characterized by disruption of the regular process of ovulation and is associated with hyperandrogenism, hyperinsulinemia, normal or elevated estrogen levels, and raised LH secretion leading to increased luteinizing hormone (LH): follicle stimulating hormone (FSH) ratio. Macroscopically, the ovaries are usually, but not always, enlarged. On histological examination the ovaries contain atretic follicles, theca cell hyperplasia and increased stroma. On ultrasound examination, the ovaries are characterized by peripheral distribution of multiple subcapsular cysts. However, these are not specific for PCOS. Clinically PCOS presents in many patients with hirsutism and obesity in addition to oligomenorrhea. Approximately 2% of women in the general population and about 30% of women presenting with infertility have this syndrome. In the past only abnormally regulated LH levels were believed to account for these symptoms. However, recent evidence suggests that hyperinsulinemic insulin resistance plays a pathogenic role in PCOS by increasing the circulating androgen by P450c 17-α stimulation, thus impeding ovulation.

PATHOPHYSIOLOGY

No single etiologic factor fully accounts for the spectrum of abnormalities in PCOS. PCOS may arise from a variety of causes. Once established, there is a well-described chronicity and self-perpetuating nature of the syndrome.

Anovulation and LH Abnormality

Amongst disorders of ovulation, PCOS is unique as it is associated with normal or elevated estrogen levels. This estrogen may arise from the ovary and also peripherally from fatty tissue. An abnormal estrogen environment could feedback on gonadotropin secretion, leading to a relative excess of LH secretion and suppression of FSH. This
disturbance may lead to a failure of ovulation and increased androgen production. The increased ovarian androgen production is a result of complex biochemical processes with disordered activity in the enzyme cytochrome P450C 17-α which catalyzes 17-α hydroxylase and 17/20 lyase activities. Chronic exposure of the ovary to this hormonal environment could lead to the development of the typical picture of PCOS. Patients with elevated androgen levels may have normal LH. It is suggested that the bioactivity of LH is increased or that the ovarian LH receptors are increased.

Since the FSH level is not totally suppressed, new follicular growth will continue, but not to the point of full maturation and ovulation. As these follicles undergo atresia, they constantly and to the stromal compartment of the ovary.

**Insulin Resistance**

Fifty to seventy percent of patients with PCOS have insulin resistance. Normally when insulin binds to its receptor, tyrosine residues on the receptor undergo phosphorylation to initiate insulin action. In PCOS, this process is altered in favor of serine phosphorylation which results in decreased insulin action within the cell. This accounts for the insulin resistance and the resultant hyperinsulinemia. The cause for the serine phosphorylation is uncertain but could presumably have a genetic basis.

Our understanding has advanced with the realization of the central role that insulin plays in PCOS. Insulin resistance represents a common component of the syndrome that is present not only in obese PCOS, but also in normal weight PCOS, in adolescent girls with hyperandrogenism, in women with multifollicular ovaries, and in apparently normal women with polycystic ovaries. Partial resistance to metabolic activities of insulin leads to derangement of the regulation of androgen synthesis preventing the down regulation of LH receptors and stimulating the activity of P450C17 coenzyme. This result in the increase of androgen and estrone secretions, which coupled with the reduction of SHBG, produces hyperestrogenism and gonadotropin abnormalities that perpetuate the syndrome. There is development of lipid abnormalities in oligomenorrheic women with PCOS and hypertriglyceridemia is also a direct result of the insulin resistance. Besides, there is disturbance in cholesterol metabolism due to alterations in sex-steroid concentrations. Gjonnaess found a 27-fold increase in the incidence of gestational diabetes amongst women with PCOS who conceived after ovarian electrodiahtermy. The hypothalamic pituitary ovarian axis and the role of insulin are explained in Figure 1.

Hyperinsulinemia is associated with increased levels of plasminogen activator inhibitor type 1 (PAI-1). Raised PAI-1 levels increase the risk for coronary artery disease. Evidence suggests that insulin resistance is the likely link between PCOS and the metabolic syndrome. The most commonly encountered marker is an increase in the serum testosterone concentration.

Dehydroepiandrosterone sulfate (DHEAS), which is exclusively secreted by the adrenal, is elevated in about 50% of anovulatory women with PCOS. About 25% of these women will have mildly elevated prolactin levels also due to the abnormal estrogen feedback to the pituitary.

Follicular recruitment, growth and selection of the dominant follicle are all deranged, increased density of both resting and growing follicles in the ovary of PCOS women compared to normal women. The early follicular development in the FSH independent stage is initiated by hyperandrogenemia.

- Low Activin A levels leads to low FSH secretion. This is augmented by high follistatin levels which binds activin and inhibits its action.
- Defective inhibin biosynthesis.
- Premature responsiveness of the small follicles to high LH levels. This premature follicle luteinization promoted by hyperinsulinemia causes follicular arrest.

The oocyte secreted growth differentiation factor-9 (GDF-9) which promotes granulosa cell proliferation and preantral follicular growth is found to be reduced in PCOS.

**Leptin and PCOS**

Leptin is a 167 amino acid protein produced mainly in adipocytes. Insulin is a potent stimulator of leptin production. In PCOS this insulin stimulated leptin secretion is limited by the insulin resistance in the adipocytes. Furthermore the amount of visceral fat is more in PCOS and visceral fat has been shown to secrete less leptin than subcutaneous fat (Vauhkonen et al. 1998b, Van Harmelen et al. 1998). Leptin inhibits Neuropeptide Y, a hypothalamic neuropeptide which serves as an effector molecule in mediating the downstream effects of activation of central leptin receptors. Neuropeptide Y is a potent stimulator of food intake. The insulin resistance in PCOS which results in lower leptin levels in turn leads to higher Neuropeptide Y levels leading to decreased satiety signals in the hypothalamus, permitting further development of obesity (Jacobs and Conway 1999).

**Genetic Basis of Polycystic Ovary Syndrome**

Polycystic ovary syndrome has a genetic component to its etiology. Studies over the last 30 years have shown familial clustering. A study suggested an autosomal dominant mode of inheritance. Sixty-six percent of first-degree female relatives were affected. However, the picture is somewhat more complex and it appears that PCOS can best explained by the interaction of a small number of causative genes, the so-called oligogenic mode of inheritance. A study on 35 pairs of twins suggested that PCOS is not the result of a single autosomal dominant genetic defect, but may be
Increased ovarian androgen biosynthesis in the polycystic ovary syndrome results from abnormalities at all levels of the hypothalamic-pituitary-ovarian axis. The increased frequency of luteinizing hormone (LH) pulses in the polycystic ovary syndrome appears to result from an increased frequency of hypothalamic gonadotropin-releasing hormone (GnRH) pulses. The latter can result from an intrinsic abnormality in the hypothalamic GnRH pulse generator, favoring the production of LH over follicle-stimulating hormone (FSH) in patients with the polycystic ovary syndrome, in whom the administration of progesterone can restrain the rapid pulse frequency. By whatever mechanism, the relative increase in pituitary secretion of LH leads to an increase in androgen production by ovarian thecal cells. Increased efficiency in the conversion of androgenic precursors in theca cells leads to enhanced production of androstenedione, which is then converted by 17β-hydroxysteroid dehydrogenase (17β-HSD) to form testosterone or aromatized by the aromatase enzyme to form estrone. Within the granulosa cell, estrone is then converted into estradiol by 17β. Numerous autocrine, paracrine, and endocrine factors modulate the effects of both LH and insulin on the androgen production of theca cells; insulin acts synergistically with LH to enhance androgen production. Insulin also inhibits hepatic synthesis of sex hormone—binding globulin, the key circulating protein that binds to testosterone and thus increases the proportion of testosterone that circulates in the unbound, biologically available, or “free”, state. Testosterone inhibits and estrogen stimulates hepatic synthesis of sex hormone—binding globulin. The abbreviation SCC denotes side-chain cleavage enzyme, StAR steroidogenic acute regulatory protein, and 2β-HSD 3β-hydroxysteroid dehydrogenase. Solid arrows denote a higher degree of stimulation than dotted arrows.


X-linked or autosomal recessive, with the influence of environmental factors.13 Numerous metabolic studies have shown that women with PCOS have abnormalities of both insulin secretion and action, and therefore gene coding for insulin may have a role in etiology of PCOS. The genetic abnormality of the insulin receptor/post-receptor signaling is involved in the etiology of PCOS and there is impaired sensitivity to insulin action. A plausible hypothesis is that there is a common etiology for both insulin resistance and hyperandrogenism in PCOS.14 Although several genetic loci have been proposed as being linked to PCOS including CYP11A, the insulin gene and follistatin, the evidence substantiating linkage is weak. The mode of inheritance of the disorder is still uncertain. However,
the majority of studies indicate that PCOS has an autosomal dominant pattern, modified by environmental factors.

HYPERANDROGENISM AND HIRSUTISM

Excess of testosterone or related steroids such as androstenedione and DHEAS leads to hyperandrogenism which causes several problems. Hirsutism is defined as an increase in facial and body hair in a woman when fine, soft and unpigmented vellus hair is transformed to coarse, pigmented and longer terminal hair. Testosterone is the biologically important extracellular androgen. It is metabolized into biologically active metabolites which are dihydrotestosterone (DHT) formed intracellular through 5α-reduction of testosterone, estrogen and estradiol. The other androgens D5 androsterone 3-β, 17-β diol, androstenedione, DHEAS are androgenic as they are converted to testosterone and/or DHT. There may be subtle increase in terminal body hair, virilization and even defeminization. The effects depend on the severity and duration of androgen excess together with the intrinsic sensitivity of androgen specific tissues. Hirsutism results from an interaction between androgen level and the sensitivity of the hair follicle to androgen. Most women with androgen level twice the upper limit of normal or higher have some degree of hirsutism.

CLINICAL FEATURES

Early clinical manifestations are shown in Figure 2. The syndrome is characterized by occurrence of a single or multiple features such as disturbances in menstruation, truncal obesity, acne, hirsutism, male pattern alopecia (frontal and sagittal scalp hair loss) and anovulatory infertility.

In women with PCOS, menstrual dysfunction is primarily characterized by irregular, infrequent or absent menstrual bleeding. This is highly suggestive of anovulation. Typically, the inception of irregular cycles can date back to the menarche and the postpubertal phase. It is now recognized that the disruption of the normal menstrual bleeding is not uniform in all PCOS. Some will have normal ovulatory function. Hirsutism is present in about 70% of PCOS patients. Onset is gradual in young women who become aware of excess hair on upper lip, chin, neck, periareolar areas, lower abdomen or upper thighs. Some women do not develop hirsutism in spite of elevated androgen levels. Skin 5α-reductase activity largely determines the presence or absence of hirsutism, which is influenced by racial characteristics. Therefore the prevalence of hirsutism (70%) reported in United States of America and Europe decreases to 10% with oriental population. Acne (30%) is present in addition to hirsutism. Evidence of frank virilization does not occur in PCOS. Acanthosis nigricans is a mucocutaneous eruption characterized by hyperkeratosis, papillomatosis and increased pigmentation and occurs in about 5% of women with PCOS. This leads to skin with velvety contour and there may be plaques in the axillae, the nape of the neck as well as under the breasts. The term HAIRAN syndrome has been coined to describe the constellation of symptoms of hyperandrogenism, insulin resistance and acanthosis nigricans. Hyperandrogenism in the adolescent has special problems with cosmetic, social and psychological concerns.

Obesity has been reported to occur in about half of PCOS patients. The obesity of PCOS is characterized by an increased waist to hip ratio or android appearance. Obesity is correlated with decreased SHBG which increases free circulating testosterone and estradiol. The risk of dyslipidemia increases cardiovascular risk. Also obesity is associated with insulin resistance which may progress to DM. The adverse effect increases with body mass index (BMI) greater than 30 kg/m². The data from the third National Health and Human Examination Survey III (NHANES III) shows a high prevalence of the metabolic syndrome in the range of around 50% in

Fig. 2: Clinical manifestations of PCOS
these women between the ages 20 and 40 years. American Association of Clinical Endocrinology recommends routine screening for diabetes with glucose tolerance test (GTT) by the age of 30 years for all women with PCOS (Table 1).

**DIAGNOSIS OF PCOS**

Before confirming the diagnosis, exclusion of related disorders would mean ruling out other causes of androgen excess such as nonclassical adrenal hyperplasia (NCAH) adrenal tumors, Cushing’s syndrome, ovarian androgen secreting neoplasms, etc. Ovulatory dysfunction due to hypothyroidism, hyperprolactinemia as well as those due to intake of drugs should also be excluded (Table 2).

A 2003 Rotterdam international reproductive medicine consensus workshop recommended using polycystic ovaries as an alternative criterion to either hyperandrogenism or anovulation. Diagnosis of PCOS can be made if two out of the following three criteria are present after exclusion of other hyperandrogenic disorders:

1. Oligo- or anovulation
2. Clinical and/or biochemical signs of hyperandrogenism
3. Ultrasonographic evidence of polycystic ovaries.


**Ultrasound Features**

The diagnosis of PCOS is established by imaging polycystic ovaries by ultrasonography. Magnetic resonance imaging (MRI), CT scan, 3-D sonography and Doppler ultrasonography are rarely required. It is important that the sonologist is well trained. In fact a good number of cases are now detected by chance even when they are asymptomatic.

**The Sonographic Criteria**

Polycystic ovaries are commonly detected by ultrasound (Fig. 3), but this does not confirm the diagnosis of PCOS unless it is associated with the clinical and biochemical features which define the syndrome. The presence of 12 or more follicles measuring 2–9 mm in diameter seen in at least one ovary, and/or an increased ovarian volume (> 10 cm³) is considered to be the criteria of polycystic ovary.

The increase in LH/FSH ratio (> 2:1) is seen in 20–60% of women. It is also important to remember that this increase may not be seen in the other 40%.
• Microcysts (< 10 mm) more than 5, generally more than 10, homogeneous in appearance
• Hypertrophied and mainly central stroma with microcysts pushed towards the periphery (necklace pattern) or dense stroma infiltrating the microcysts (cogwheel appearance)
• Increase in ovarian size with a cross-sectional area of greater than 10 cm²
• Increase in ovarian volume greater than 11 cm³
• Follicular dominance not evidenced, thus both ovaries equally prominent
• Uterine width: Ovarian length less than 1
• The endometrium is usually estrogenized, either proliferative or hyperplastic, seldom hypoestrogenic.

Although these features are very well identified by transvaginal sonography, it is often necessary to use the transabdominal route with a full bladder giving a panoramic view of pelvic cavity, especially in young unmarried girls. It also excludes any associated uterine or ovarian abnormalities. However, the inner echo-structure of the ovaries is better visualized by transvaginal sonographic (TVS) approach, particularly in obese patients.

Computerized quantification of ovarian stroma allowing selective calculation of the stromal area by subtraction of cyst area from the total ovarian area on a longitudinal ovarian cut is possible. However, in practice it is not necessary. MRI does not provide more information but is helpful when there is severe hyperandrogenism. Its main role is exclusion of virilizing ovarian tumor. Doppler allows detection of the vascularization network within the ovarian stroma and the blood flow may be more frequently visualized in PCOS than in normal patients. The increased stroma component in PCOS seems to be accompanied by higher visualization reflected by an increased peak systolic velocity and a decreased pulsatility index (PI).

### Laboratory Diagnosis

Laboratory investigations will be required to confirm the clinical suspicion of PCOD. When atypical features of PCOS exist, additional investigations are warranted (see differential diagnosis).

- Day 2 serum:
  - Raised LH, N/Decreased FSH/LH > 3:1
  - LH/FSH
- Serum prolactin: Raised
- Serum testosterone: Raised
- Serum DHEA: Raised
- Serum insulin: Raised

### Laparoscopy

Classically, ovaries are enlarged with smooth walled pearly white capsule (oyster ovaries). Thick sclerotic capsule is found in long-standing cases. There is no evidence of corpus luteum or stigmata of ovulation. However, for the diagnosis of PCOS, sonography has replaced laparoscopy.

### Differential Diagnosis

The differential diagnosis of hirsutism and oligomenorrhea includes congenital adrenal hyperplasia, Cushing’s syndrome, benign and malignant androgen secreting tumors of the adrenals or ovaries and hyperthecosis ovarii. The major features which distinguish them are time...
of onset, the medical presentations, the extent of virilization, associated obesity, hyperinsulinemia and the level of FSH, LH, testosterone, adrenocorticotropin hormone (ACTH) suppression test and imaging findings, etc.

**MANAGEMENT**

**Lifestyle Factors**

As PCOS is a combination of familial and environmental factors that interact causing menstrual and metabolic disturbances, certain changes in lifestyle are necessary along with pharmaceutical treatment. Weight loss, altered diet and exercise are important aspects. It is also necessary to discontinue smoking and improve psychological attitudes.

**Weight Loss**

There is a strong relationship between obesity and PCOS. Approximately 50% of the women have a BMI of more than 30 kg/m² (Norman et al. 2003). Whether obesity is the cause or effect of the disorder is uncertain. Obese women (BMI > 30 kg/m²) should be encouraged to loose weight. Long-term lifestyle modification with an appropriate low calorie diet with reduced carbohydrate intake with regular and moderate exercises are necessary for weight loss. In obese women with insulin resistance agents like metformin may help some loss of weight. With loss of weight the symptoms of PCOS are reduced, endocrine profile is improved and there is resumption of ovulation in a significant proportion of women. Among women with amenorrhea and anovulation and menstrual disturbances, obesity has been found 1.5 times more frequent than among women in the normal weight range, in a study of 26,638 women. Obesity is also associated with increased risk of miscarriage as shown by a study of over 13,000 women during their spontaneous pregnancy. Besides, there is an increased risk of hypertension in pregnancy, gestational diabetes and macrosomia. With increasing BMI, the women with PCOS have risk of glucose intolerance and gestational diabetes. Weight loss induces regular menstruation in a good proportion of women. This has been confirmed by several other studies. Besides dieting, exercise programs are necessary, as redistribution of fat and weight is an important factor. Consequent to weight loss, 12 of 13 women with PCOS anovulation, ovulated by 6 months and the majority became pregnant within a year.

**Diet Modifications**

- Include more complex carbohydrate and fiber. Avoid simple sugars.
- Improve the quality of fat by avoiding saturated fat and increasing poly unsaturated oils
- Include ω3 oils
- Small more frequent meals
- Reduce alcohol intake.

Pharmacological agents which enhance satiety as well as those which inhibit the absorption of fat from the gastrointestinal tract can help in weight reduction. Sibutramine: Caution should be exercised orlistat.

- Sibutramine caution should be exercised
- Orlistat.

For women with morbid obesity who do not respond to diet modification and medicines bariatric surgery should be considered.

**Cigarette Smoking**

There is convincing data that apart from the well-known hazards of smoking on cardiovascular and respiratory system, there is associated reduction of fertility potential. It is therefore, prudent to motivate the women to change their lifestyles even before embarking on ovulation induction treatment, as the treatment is then more likely to be successful and also improve their long-term health.

**TREATMENT OF PCOS IN ADOLESCENT GIRLS**

The origin of most PCOS cases is in adolescents. Anovulation, insulin resistance, acne and hirsutism have their impact on the physical and mental well being of young girls. The clinical definition is based on the Consensus Conference of the National Institute of Health and National Institute of Child Health and Development. The consensus was that there are “definite or probable” criteria for the diagnosis of PCOS. Definite criteria included menstrual dysfunction and androgen excess and excluded congenital adrenal hyperplasia and other causes. Factors such as insulin resistance, elevated ratio of LH to FSH and ovaries appearing polycystic on ultrasonography were considered to be “probable criteria”. In their personal experience of adolescent girls over 3 years, PCOS was diagnosed by ultrasound in approximately 30%. Amongst the girls found having PCOS on ultrasound, 50% had evidence of hyperandrogenism, 25% were overweight and 91% had menstrual irregularity. Treatment of PCOS in adolescents is directed towards reduction of ovarian androgens and weight reduction as well as establishing monthly menstrual periods. The effect of estrogen with nonandrogenic progesterone (combined OCs) is an effective form of treatment for hirsutism, if maintained for adequate duration. Estrogen suppresses gonadotrophin secretion, ovarian androgen secretion and adrenal steroid biosynthesis. Metformin is helpful to reduce insulin resistance and also helps weight loss. As most young girls do not need immediate fertility, it is important to counsel them and explain the rationale of the treatment.
TREATMENT OF MENSTRUAL DISTURBANCES

About 70% of women with PCOS have menstrual disturbances. The menstrual cycle may be scanty, irregular or heavy. Women with oligo or amenorrhea may be relieved with the use of a low dose combined oral contraceptive pill (COC) or with cyclical progestogen therapy. In women who have anovulatory amenorrhea the unopposed estradiol action on the endometrium may have a long-term effect of endometrial hyperplasia and carcinoma. So they may require periodic withdrawal bleeding with progestogens. The alternative option in these women could also be levonorgestrel releasing intrauterine system.

In women with features of hyperandrogenism in addition to menstrual irregularities the administration of cyproterone acetate (2 mg) and ethinyl estradiol (35 µg) will regularize bleeding, reduce acne and hirsutism and provide contraception.

HIRSUTISM

The most common method of evaluating the severity of hirsutism is by using the visual score based on the modified Ferriman and Gallwey scoring system. In this system, nine body areas namely the upper lip, chin, chest, upper back, lower back, upper abdomen, lower abdomen, arms and legs are considered (Fig. 4).

A score of 0–4 is given based on the density of terminal hair in these areas. A score of 0 represents absence of terminal hair whereas 4 denotes extensive terminal hair. A score greater than 8 is classified as having hirsutism (Table 4).

Hirsutism and androgenic alopecia can be distressing and cause depression. The choice of therapy should be based on severity of the condition and results of the endocrine investigations. The therapy can be a combination of hormonal treatment to decrease androgen production or antiandrogen drugs to block the androgen effect at the hair follicle and/or local treatment.

Pharmacological treatment to suppress the androgen secretion does not lead to loss of established hair but the duration of hair cycle is prolonged. The treatment must be carried out for 12–18 months to judge the optimal effect. There is peripheral blockade of androgen action by androgen receptor antagonist such as cyproterone acetate or spironolactone. 5α reductase inhibitors such as finasteride can also be effective. Other drugs such as flutamide, though effective antiandrogens, have severe liver toxicity. GnRH analog can reduce androgen production but are not used as they are expensive, need parenteral route and cannot be given for a prolonged period.

Cyproterone acetate is an effective anti-androgen. Traditionally this agent has been used in a reversed sequential method. 50 mg of cyproterone acetate is prescribed for the first 10 days of a 21-day course of estrogen. Estrogen is then interrupted for 7 days during which withdrawal bleeding occurs and the cycle is repeated. Side effects include breast discomfort, weight gain and decreased libido. Recently, continuous low doses have been used effectively in combination with estrogen to provide anti-androgen effect together with effective contraception. Cyproterone acetate 2 mg daily for a 21-day cycle combined with 35 mg ethinyl estradiol (Dianess 35) is effective in providing an improvement of approximately 50% in hirsute scores over 6–9 months with fewer side-effects.

Alternatively, spironolactone 50–100 mg/day, a mineralocorticoid antagonist with anti-androgenic property is used as continuous therapy. As it causes irregular menstruation, it is combined with an oral contraceptive pill. It is particularly useful in hypertensive women. It is unusual for electrolyte disturbances to develop but patients should be monitored for development of postural hypotension, hyperkalemia or hyponatremia.

Adrenal suppression (dexamethasone 0.25/0.5 mg each night) is unique amongst the treatments of hirsutism, as it facilitates ovulation. All other forms of treatment are associated with ovarian suppression, or are treatments where pregnancy is contraindicated (anti-androgens).

With medical therapy it takes several months to show effect hence concomitant local treatment like waxing, bleaching, electrolysis and laser therapy should be encouraged.

Efflornithine hydrochloride (11.5%) topical cream is used to reduce facial hair without systemic side effects.
TREATMENT OF INFERTILITY

Treatments used include medical therapy in the form of antiestrogens, adrenal suppression, gonadotropins, GnRH analogs, metformin and surgical therapy.

Medical Therapy (Table 5)

Table 5: Drugs used in hirsutism

<table>
<thead>
<tr>
<th>Ovarian suppression agents</th>
<th>Androgen receptor blocking agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Oral contraceptives</td>
<td>• Spironolactone</td>
</tr>
<tr>
<td>• Cyproterone acetate</td>
<td>• Flutamide</td>
</tr>
<tr>
<td>• GnRH agonist/antagonist</td>
<td>• Cyproterone acetate</td>
</tr>
</tbody>
</table>

5α-reductase inhibitors

• Finasteride

Anti-estrogens

Clomiphene Citrate

This is considered the first line therapy for anovulatory infertility. The dose is 50–100 mg/day from day 2–6 of natural or progestogen induced bleeding.

Inhibition of estrogen feedback at the hypothalamic-pituitary level leads to a surge in FSH with growth of the Graafian follicle and increase in estrogen. When successful the follicle continues to enlarge and eventually ruptures releasing an ovum, i.e. ovulation.

It can be used along with hCG to improve midcycle LH surge.

- **Ovulation rates**: 80%
- **Pregnancy rates**: 40%

The disparity between the ovulation and conception rates may be due to the antiestrogenic effects of clomiphene on the endometrium and cervical mucus or due to high basal levels of LH which prevent conception.33

**Multiple pregnancy rates**: 10% twins and 1% triplets.34

Pretreatment of patients with progestogen, e.g. medroxyprogesterone acetate or combined OCs has improved the ovulation and pregnancy rates in patients subsequently treated with clomiphene citrate.

Approximately 20–25% of women do not respond to clomiphene and are called clomiphene resistant.30 The nonresponders are mainly obese women with insulin resistance and hyperandrogenemia.30

Preliminary trials suggest that letrozole, an aromatase inhibitor may be effective for ovulation induction in PCOS.35

They do not have the antiestrogenic effects of clomiphene36 but the possible teratogenicity is still to be carefully evaluated.38 Anastrozole is also being studied as an alternative.30

Tamoxifen

Some women who experience troublesome side-effects with clomiphene benefit from tamoxifen 20–40 mg, days 2–6. Monitoring should be same as for clomiphene citrate.

Adrenal Suppression

Polycystic ovary syndrome patients with hirsutism and hyperandrogenism would benefit with glucocorticoid administration (dexamethasone 0.25/0.5 mg each night). Ovulation rates are 60%.37 This is associated with an improvement in the hormonal status and also an improved pregnancy rate and a lower miscarriage rate. Combination treatment of dexamethasone and clomiphene is associated with a higher rate of ovulation than is achieved with either treatment used alone.

Gonadotropin Therapy

Patients who fail to respond to clomiphene citrate therapy can be offered gonadotropins for ovulation induction. Available preparations include combination of LH and FSH or purified FSH, which is preferred in view of high endogenous LH. Exogenously administered gonadotropins stimulate the ovary directly resulting in follicular maturation, and hCG is then given to trigger release of mature ovum. Because of the increased cost of therapy and risk of hyperstimulation and multiple-pregnancy, specialist supervision and close monitoring is mandatory. The pregnancy rate for gonadotropin therapy in clomiphene-resistant PCOD is approximately 20%. Risk of multiple pregnancy correlates with the number of dominant follicles (4% when two dominant follicles are present, increasing to 18% with 3 to 4 dominant follicles).34 Pretreatment with a GnRH agonist to prevent premature luteinization has been associated with higher pregnancy rates.38 The incidence of spontaneous miscarriage following gonadotropin therapy may be as high as 30%.39

In order to overcome the problems associated with conventional gonadotropin therapy in PCOD, namely low pregnancy rates and increased risk of hyperstimulation, multiple pregnancy and miscarriage, alternative regimes have been proposed. Franks et al. 19967,40 advocated the low dose regime with a starting dose of 52.5 IU of FSH maintained up to 14 days. The step-down protocol attempts to mimic the FSH profile seen in natural cycles. Starting with a conventional high dose, the dose is gradually reduced as follicles develop. No hyper-stimulation was reported and the incidence of multiple pregnancies was down to 7%; however, the pregnancy and miscarriage rates were disappointingly similar to the conventional regimes.
**GnRH Agonist**

GnRH agonist has been used as an adjunct for induction of ovulation with gonadotropins. Results are promising, but it is unclear if this is any more effective than use of gonadotropins alone. GnRH agonist has also been beneficial when used prior to induction of ovulation with pulsatile GnRH in clomiphene resistant cases.

**Metformin**

An improvement of clinical and endocrine features of the syndrome has been obtained by using metformin or troglitazone, an agent that decreases insulin resistance. Use of metformin 500 mg three times daily allowed resumption of normal menses in most (91%) previously amenorrheic women with PCOS. Nestler et al. 1998 demonstrated an increased ovulatory response to clomiphene in obese women with PCOS. Long-term administration of metformin might be helpful in treating insulin resistance, thus reducing the risks of type 2 NIDDM and cardiovascular disease in PCOS patients.

**SURGICAL TREATMENT**

Although Stein and Leventhal, in 1935 offered surgical treatment of wedge resection, better understanding of the syndrome brought in useful medical management. In the last two decades, electrocautery of the ovaries has been introduced. The cauterization of cystic areas through the external surface of the ovaries is associated with a decline in testosterone and LH levels and an increase in FSH levels, resumption of ovulation and the occurrence of pregnancy. However, the miscarriage rate associated with pregnancy following electrocautery is similar to that of pregnancies occurring following gonadotrophin treatment. The patients following this surgical procedure were more responsive to clomiphene treatment. Thus this form of therapy has expanded the options available for treatment. There are some possibilities of tubo-ovarian adhesions but it is certainly necessary when the patient is resistant to medical treatment or the patient develops ovarian hyperstimulation syndrome (OHSS) or there are financial constraints for gonadotrophin injections.

Armar develops a strategy of minimizing the number of diathermy points to four per ovary avoiding the hilum, for 4 seconds at 40 watts. With this technique there was a low rate of adhesion formation, but the pregnancy rates were not satisfactory. Women with greatly enlarged ovaries need more ovarian reduction which can be achieved by increasing the number of punctures.

In 778 ovarian biopsies the pregnancy rate was 31.8%. In 1984 Gjonnaess proposed the use of laparoscopic multi-electrocauterization in PCOS. The ovulation rate in this study was 92% and the pregnancy rate 69%. The procedure involves making multiple punctures on the ovarian surface using a monopolar needle with 40 W cut current. The number of punctures varies depending on the ovarian size and the number of follicles, usually 10–15 per ovary (Fig. 5). The same author reported the results of 252 women with ovarian electrocauterization during 1979–1991 with ovulation obtained in 92% and pregnancy in 84%. The response was influenced by body weight with an ovulation range of 96–97% for the slim and moderately obese women, decreasing to 70% in the very obese ones. It is important to note that this procedure can occasionally lead to ovarian hemorrhage due to trauma of ovarian blood vessels and rarely lead to problems due to electric spark causing perforation of bowel.

Laparoscopic laser drilling has been used in treatment of PCO for the last 15 years. The laser provides controlled label power density and more predictable thermo damage and may diminish the risk of adhesions. Carbon dioxide laser, argon and YAG lasers have been used. Donesky and Adashi, in 1995, reviewed 29 relevant studies in the English language. Pregnancies after laparoscopic ovulation induction procedures have been reported in an average 55% of treated subjects (range 22–65%). Lower spontaneous abortion rates were reported in several studies with laparoscopic series compared to medical treatment.

Laparoscopy must not be considered as the first line of treatment. Clomiphene citrate remains the first line of therapy for an anovulatory patient with PCOS. For resistant patients, the laparoscopic techniques may have the advantages over gonadotrophin therapy and can be offered. However, if laparoscopy is done for infertility and PCOS is observed, cauterization of the ovaries may be done at the same time to avoid a secondary surgical laparoscopy.

**In Vitro Fertilization for Patients with PCOS**

When women fail to conceive despite ovulating for more than 6 months, IVF could be offered. When ovarian stimulation
is required for IVF; a different approach to therapy is necessary because the objective is to achieve multifollicular development, resulting in the collection of several appropriately mature eggs, but without causing OHSS. As OHSS is a particularly important problem in women with PCOS, IVF may be a good solution. This is specially so also for women who do not conceive either with oral clomiphine citrate or gonadotropin therapy. A recent meta-analysis of eight randomized studies of patients undergoing IVF, suggested that treatment with FSH, resulted in 50% higher pregnancy rates than treatment with hMG with an overall odds ratio of 1.71 (95% CI 1.12–2.62).

THE PREGNANCY OUTCOME FOR WOMEN WITH PCOS

Of all clinical pregnancies about 15% end in first trimester miscarriage. The incidence of PCOS amongst women with recurrent miscarriage is high. Several studies have shown a clear relationship between raised serum LH in association with PCOS and early pregnancy loss. Besides, the problem of multiple pregnancy and association of gestational diabetes and pregnancy induced hypertension in these women is high.

LONG-TERM HEALTH IMPLICATIONS IN WOMEN WITH PCOS

The association of insulin resistance, obesity, hyperandrogenism, irregular ovulation with continuous effect of estrogen on endometrium, certainly have long-term impact of the metabolic disturbances associated with this disorder on women’s health. These range from obesity and related problems, risk of endometrial and breast cancer and some increased risk of epithelial ovarian cancer. Hyperandrogenism and hyperinsulinism lead to the possibility of diabetes and long-term risk of cardiovascular problems such as hyperlipidemia and hypertension. These women therefore need long-term monitoring. Although PCOS has molecular genetic factors responsible, modification in lifestyle, proper treatment and monitoring can minimize the problems very significantly (Fig. 6).

CONCLUSION

The PCOS is a heterogenous familial disorder. There are extraovarian factors involved but ovarian dysfunction is the main pathology. Obesity, hirsutism, alopecia and infertility are common distressing symptoms. The clinical management should be individualized and should be symptom oriented.

REFERENCES


INTRODUCTION AND DEFINITION

“Luteal phase defect (LPD) is historically defined as a lag of more than 2 days in histologic development of the endometrium compared to the day of the cycle.” The original description of LPD in clinical settings was published by Jones in 1949. Jones described two forms of luteal phase inadequacy, the first due to a deficiency of progesterone output and the second due to a defective endometrial response to hormonal stimulation. A positive correlation was found between luteal inadequacy and frequency of nonobstructive sterility.

INCIDENCE AND ETIOPATHOLOGY

Luteal phase defect is found in 30% of isolated cycles of normal women, 3–4% of infertile women, 5% in women with a history of recurrent abortion; significant if found repeatedly. LPD in natural cycles occurs more often in women at extremes of reproductive life and in athletic women, women with hyperprolactinemia, hypothyroidism, post-danazol; soon after abortion or delivery. Induction of ovulation with clomiphene and gonadotropins are special occasions when LPD is quite frequent.

Luteal phase defect is characterized by inadequate endometrial maturation, results from a qualitative or quantitative disorder of corpus luteum function. In turn, normal corpus luteum function is dependent on normal follicular and ovulatory phase endocrine events.

OVULATORY EVENTS AND LUTEAL PHASE

- Normal luteal function requires optimal preovulatory follicular development [adequate follicle-stimulating hormone (FSH) stimulation] and continued tonic luteinizing hormone (LH) support.
- Follicle-stimulating hormone induces aromatization in granulosa cells and E2 synthesis and also LH receptors on granulosa cells. Midcycle FSH stimulates LH surge in late follicular phase.
- The LH surge stimulates continuation of reduction division in the oocyte, luteinization of the granulosa; synthesis of progesterone and prostaglandins within the follicle causes rupture of the follicular wall and ovulation.
- Progesterone levels rise sharply after ovulation reaching a peak after 8 days. Progesterone causes endommaturation, inhibits neofolliculogenesis. It has a uterorelaxing effect which improves successful implantation and pregnancy outcome.
- If pregnancy occurs, human chorionic gonadotropin (hCG) from the blastocyst rescues the corpus luteum to be maintained to provide the hormonal support into early pregnancy. hCG rescue of the luteum occurs at approximately 9–10 days of the luteal phase.

Cellular Structure of Corpus Luteum

Cellular structure explains the basis of interaction of various hormones and corpus luteum (Table 1).

<table>
<thead>
<tr>
<th>Large cells</th>
<th>Small cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>More than 20 µm diameter</td>
<td>Less than 20 µm diameter</td>
</tr>
<tr>
<td>Secretion of the progesterone</td>
<td>Have low basal progesterone secretion</td>
</tr>
<tr>
<td>These cells are few in number</td>
<td>These cells are plenty in number</td>
</tr>
<tr>
<td>Have greater aromatase activity</td>
<td>Have lower aromatase activity</td>
</tr>
<tr>
<td>Stimulated by FSH and not by hCG</td>
<td>Stimulated by hCG</td>
</tr>
</tbody>
</table>

Abbreviations: FSH, follicle stimulating hormone; hCG, human chorionic gonadotropin.
PATHOPHYSIOLOGICAL MECHANISMS OF LUTEAL PHASE DEFECT

Luteal phase defect could be the consequence of disturbances at various levels in the events of ovulation.

Altered Follicular Phase Events

Deficient follicular phase FSH levels and alterations in inhibin feedback and LH levels affect the development of follicles. Increased follicular phase LH pulse frequency has been observed in patients with luteal deficiency.\(^5\)

Alterations in Luteal Phase Events

- Deficient mid-cycle surge and luteal phase LH levels
- Hyperprolactinemia
- Deficient luteotropic stimulus
- Accelerated luteolysis
- Intrinsic cellular defects of the corpus luteum
- Inadequate endometrial progesterone receptors.

LUTEAL PHASE DEFECT AND CLOMIPHENE CITRATE

The antiestrogenic properties of clomiphene citrate (CC) have been used to increase endogenous FSH in response to perceived estrogen deficiency by the hypothalamus and this results in ovulation. Clomiphene exerts antiestrogenic effects on ovary, endometrium and endocervix and this is unfavorable. Inadequate dosage of clomiphene may result in ovulation, but there may still be inadequate luteal function leading to LPD. An increase in dosage on one hand may correct the LPD but it could also lead to LPD due to the direct antiestrogenic action of the drug itself.\(^6\) CC can also cause premature luteinization of the follicle.

Extended half-life of CC may lead to residual levels of CC in the luteal phase causing delayed endometrial maturation and inhibition of progesterone production. LPD may be the reason for the disparity between excellent ovulation (80%) and mediocre pregnancy rates (50%) after CC therapy. In clomiphene cycles with thin endometrium, progesterone support is of dubious value while favorable results are observed with gonadotropin therapy.

LUTEAL PHASE DEFECT IN CONTROLLED OVARIAN HYPERSTIMULATION

When the ovulating process does not occur spontaneously (anovulation, types I and II, polycystic ovarian disease), common treatment consists of providing early follicular gonadotropin stimulation with human menopausal gonadotropin (hMG) or recombinant FSH. Extension of this treatment scheme referred to as controlled ovarian hyperstimulation (COH) now has been universally adopted in assisted reproductive techniques (ART) and with intratertiary insemination (IUI), thus harvesting numerous oocytes. The supraphysiological levels of E\(_2\) and other ovarian peptides thereby produced can possibly hamper endometrial receptivity to implantation.\(^7\) Altered estrogen-progesterone ratio has been noticed. About 14% of all treated cycles were characterized by shortened luteal phase probably due to a defective corpus luteum. Alterations in the endometrial morphology seen (or suspected) in COH can be referred as “iatrogenic LPD” and account for the suboptimal pregnancy rates seen in COH cycles including in vitro fertilization (IVF).\(^8\)

Gonadotropin-releasing hormone (GnRH) agonists work by preventing premature surges of endogenous LH during IVF cycles through pituitary suppression, allowing time for a larger number of oocytes to reach maturity prior to harvesting. This suppression of pituitary LH secretion lasts for as long as 10 days after the last dose of agonist. Without this LH signal, the corpus luteum may be dysfunctional, and subsequent progesterone and estrogen secretion may be abnormal.

Gonadotropin-releasing hormone antagonists have been gaining popularity in ovarian stimulation for ART for prevention of LH surge in IVF. Whether GnRH antagonists cause down regulation of pituitary GnRH receptors is a subject of investigation; these have been found to cause down regulation of pituitary GnRH receptors in rats.\(^9,10\) Albano et al. analyzed that GnRH antagonist and hMG cycle with no luteal supplementation showed a short luteal phase and low E\(_2\) and progesterone concentration in 3 of 6 patients.\(^11\) They showed that different doses (0.5 mg or 0.25 mg–Cetrorelix) of antagonist do not have any negative impact on luteal phase when hCG is given as luteal support. Progesterone level did not differ in the two groups. Whether there is any need to supplement the luteal phase after the use of GnRH antagonist for ovarian stimulation is still unanswered.

On the basis of findings that antagonists do not cause a prolonged pituitary suppression, the low LH levels seen in luteal phase may be attributed to negative feedback from hCG.\(^12\) This is also observed by Tavaniotou et al. who studied hMG alone versus hMG and Cetrorelix.\(^13\)

DIAGNOSIS OF LUTEAL PHASE DEFECT (FLOW CHART 1)

Luteal phase defect is suspected in women with normal cycles and unexplained infertility, women with short luteal phase as studied by basal body temperature (BBT) or ultrasonography (USG), women on ovulatory agents and women with recurrent abortions. Diagnosis of LPD is tricky and the concept of LPD in women with normal cycles is controversial.

Basal Body Temperature

There is usually an increase of 0.4–1°F during luteal phase with the number of days of thermal increase less than 10 LPD.
is suspected. Though BBT is a simple noninvasive method, it is cumbersome and patient dependent.

**Serum Progesterone Levels**

Mid luteal progesterone of less than 10 ng/mL (taken 1 week prior to menstruation) denotes LPD. Since progesterone is secreted in a pulsatile fashion, this measurement may not be accurate. An average of 15 ng/mL for three mid-luteal samples has been suggested as an alternative method. Salivary progesterone estimation has been described.

**Endometrial Biopsy**

Endometrial biopsy (EB) is considered to be the gold standard for the diagnosis of LPD. Biopsy should be of full thickness of endometrium from the fundus (anterior or posterior wall). The ideal day for biopsy is 26th day or 2 days prior to menstruation, where there is a lag of more than 2 days in the histology of the endometrium (by Noye’s criteria) compared to the day of the cycle, LPD is suspected. For the diagnosis of the LPD to be established, two biopsies must be greater than 2 days out of phase in two menstrual cycles. Some patients have abnormal EB despite seemingly normal folliculogenesis and periovulatory events. Accuracy rate of the endometrial biopsy to diagnose luteal inadequacy is 25–35%. Hence, its utility is questioned and it is difficult to put women through repetitive biopsies.

The value of estimation of endometrial protein, estrogen, progesterone receptor and integrins is under study.

**Ultrasonography**

Ultrasonography defines the beginning of luteal phase; endometrium if more than 6–7 mm thickness with good triple line indicates adequate folliculogenesis. Doppler indices, e.g., high pulsatility index of corpus luteum blood flow may be a useful index of luteal function. USG being noninvasive is a practical method of grading the endometrium for receptivity.

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**Flow chart 1: Diagnosis and treatment of luteal phase defect**

- Infertility
  - Luteal phase length
    - <12 days
    - 12 to 16 days
      - Measurement of midluteal serum progesterone levels and endometrial stripe by transvaginal ultrasound
        - Progesterone >9 ng/mL and/or endometrial stripe ≥8 mm with diffuse pattern
          - Progesterone <10 ng/mL and/or endometrial stripe <8 mm
            - Endometrial biopsy between cycle days 24 and 27
              - Abnormal in 3 consecutive cycles
              - Normal
                - No luteal phase defect
                  - Clomiphene
                  - Gonadotropins
                  - Progesterone
TREATMENT OF LUTEAL PHASE DEFECT
(FLOW CHART 1)

Given the disagreement about the incidence and diagnosis, the treatment of LPD remains controversial. The therapeutic approach to luteal phase inadequacy depends upon:

- Identifying specific causes and correcting the hormone deficiency (thyroid, prolactin)
- Improving follicular dynamics (CC and gonadotropins)
- Luteal phase supplementation (hCG, progesterone, estrogen, GnRH analogs).

Pregnancies can occur without treatment in women who are diagnosed as having LPD.

Clomiphene and Gonadotropins

Based on finding that low FSH values prior to ovulation can be associated with LPD, it seems reasonable to use CC and/or gonadotropin in selected cases. CC is the first choice of many clinicians for the treatment of LPD. If dysovulation is not corrected by CC or if LPD is suspected while on clomiphene, it is wiser to change over to gonadotropins.

When LPD appears to be linked to faulty follicular recruitment in the ovulatory process, it is reasonable to consider a more global approach and augment the stimulus recruiting the developing follicle by administration of exogenous gonadotropin (hMG or rec FSH) in the context of COH protocols. Overall the experience gained by using COH protocols (hMG or FSH) in unexplained infertility (or failed CC cycles) has revealed that pregnancy rates were reasonably high which ultimately supports the practical value of this approach.

Progesterone Support

Since LPD is defined as the inadequate output of progesterone by the CL, progesterone supplementation is a logical treatment modality. Progesterone supplementation has proven effective in correcting abnormal endometrial histology in more than 80% of cases and pregnancy rates in treated infertile patients have ranged from 50% to 80%. To prove the endometrial defect has been corrected, a repeat biopsy can be obtained in the treatment cycle. Progesterone administration did not increase fetal anomalies.

In patients of LPD, progesterone therapy should commence after ovulation to avoid early pregnancy wastage. Treatment is continued until menstruation or up to 8–10 weeks of a pregnancy.

Synthetic progesterone agents should not be used to treat LPD, since they may have a luteolytic effect on the CL and can produce glandular stromal disparity, thereby worsening rather than improving the situation.

Route and Dosage of Progesterone Supplementation

Intramuscular

Progesterone has been traditionally used by intramuscular (IM) route. The dosage is 50 mg or 100 mg daily in IVF cycles beginning from the day of or the day after oocyte retrieval.

Oral and Nasal

The bioavailability of oral micronized progesterone and even nasally administered progesterone preparations has been demonstrated; available as dydrogesterone 10 mg or micronized progesterone 100–200 mg/tablet.

Intravaginal Progesterone

Vaginal preparation in the form of micronized tablet, suppositories and gel are available. Dosage is 400 mg or 600 mg per day. Vaginal progesterone therapy is simple, easy and well tolerated. Vaginal progesterone is absorbed rapidly. The hepatic metabolism is avoided. It has uterine first pass effect and has high bio-availability than IM or oral preparation. Women are more receptive to vaginal progesterone, since it avoids the pain of IM injections, though it can cause vaginal irritation or discharge.

Human Chorionic Gonadotropin Injection

Human chorionic gonadotropin (hCG) readily stimulates progesterone production in normally functioning corpus luteum, whereas its stimulatory effect is minimal on malfunctioning CL. The timing dose and frequency of hCG are somewhat empirical. Premature hCG injection may cause atresia of the follicle. Human chorionic gonadotropin (hCG) has been commonly used in a dosage of 1,500–5,000 IU once in 3–5 days. As per Royal College of Obstetricians and Gynaecologists (RCOG) guidelines revised in May 2003, the use of progesterone or hCG for luteal phase support in recurrent abortions is uncertain.

Luteal Phase Support in IVF Cycle

Ovarian stimulation for IVF profoundly alters luteal phase endometrial development. Luteal phase supplementation with a variety of steroid hormones has significantly improved fertility outcomes compared with no treatment. A meta-analysis of the randomized controlled trials (Pritts and Atwood) suggests that luteal supplementation is beneficial. IM progesterone is no more effective than hCG, but more effective than vaginal progesterone. Because of the risks of ovarian hyperstimulation syndrome (OHSS) associated with hCG administration in the luteal phase, IM progesterone seems
to be the drug of choice for luteal phase supplementation (Table 2).

Ludwig M and Diedrich L concluded that vaginal progesterone is as effective as IM progesterone and vaginal progesterone should be the standard choice for luteal phase support. Manno M and Tomei et al. observed in a study of 385 patients of intracytoplasmic sperm injection (ICSI), greater implantation and pregnancy rate with vaginal progesterone compared with IM progesterone.

Intramuscular hCG added to a standard dose of vaginal progesterone, compared with vaginal progesterone alone in the luteal phase, was examined in two studies. When the long GnRH agonist was used, continued pregnancy rate (CPR) was no different between the groups. There was no difference in CPR or spontaneous abortion when the short GnRH agonist was utilized.

### Estrogen Support in Assisted Reproductive Techniques

Estrogen and progesterone are the key elements in the development of uterine receptivity. Several investigators have noted that serum estrogen levels are also low in the luteal phase of GnRH agonist IVF cycles (Smitz et al.). Addition of estrogen to luteal progesterone supplementation has been addressed in the literature in varying protocols, including estrogen and progesterone versus progesterone alone.

Theories for the destructive effect of low estrogen levels in luteal phase:
- Estrogen suppresses the apoptosis of corpus luteal cells by its antioxidant property.
- It also influences the expression of HOX A-10 homeobox gene which improves the receptivity of the endometrium.

Farthi et al., Lukaszuk et al., Unfer et al., Jung and Roh, Pritts and Atwood concluded that the addition of estrogen to progesterone improved pregnancy and implantation rates. Study by Gleischer N et al. showed that the benefit of estrogen substitution was restricted to young primiparous and/or women below 38 years, whereas Lewin et al., Fatemi et al. did not favor supplementation to improve pregnancy and implantation rate. The role of estrogen supplementation on reducing the miscarriage rate was favored as per the study by Kaider and Coulam.

### GnRH Agonist

In cycles where GnRH was not part of pituitary desentization and it was observed that GnRH agonist itself could induce the LH surge and therefore final oocyte maturation and is not associated with luteal phase insufficiency (Pirard C, Donnez J and Loumayo). Here intranasal buserelin (100 µg thrice a day for 15 days) was found to be as effective as hCG in providing luteal phase support in patient undergoing ART.

### Table 2: In vitro fertilization (IVF) luteal support comparing hCG with intramuscular or vaginal progesterone: Fertility outcomes

<table>
<thead>
<tr>
<th>Questions</th>
<th>Outcome measure</th>
<th>Author(s)</th>
<th>No. of studies</th>
<th>No. of patients</th>
<th>RR</th>
<th>95% CI</th>
<th>Meta-analysis</th>
<th>Power # 2</th>
<th>Power # 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>hCG versus progesterone (IM)</td>
<td>CPR (long protocol)</td>
<td>Albert et al., 1991; Claman et al., 1992; Araujo et al., 1994; Artini et al., 1995; Loh and Leong,1996</td>
<td>5</td>
<td>486</td>
<td>0.98</td>
<td>0.68–1.42</td>
<td>Yes</td>
<td>0.99</td>
<td>0.74</td>
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<td>hCG versus progesterone (IM)</td>
<td>CPR (flare protocol)</td>
<td>Golan et al., 1993</td>
<td>1</td>
<td>56</td>
<td>6.07</td>
<td>0.84–130.80</td>
<td>No</td>
<td>0.36</td>
<td>0.13</td>
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<td>hCG versus progesterone (IM)</td>
<td>OPR (long protocol)</td>
<td>Artini et al., 1995</td>
<td>1</td>
<td>88</td>
<td>1</td>
<td>0.22–4.58</td>
<td>No</td>
<td>0.54</td>
<td>0.18</td>
</tr>
<tr>
<td>hCG versus progesterone (IM)</td>
<td>DR (long protocol)</td>
<td>Claman et al., 1992</td>
<td>1</td>
<td>121</td>
<td>1.7</td>
<td>0.52–6.27</td>
<td>No</td>
<td>0.68</td>
<td>0.24</td>
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<tr>
<td>hCG versus progesterone (IM)</td>
<td>DR (flare protocol)</td>
<td>Golan et al., 1993</td>
<td>1</td>
<td>8</td>
<td>0.86</td>
<td>1.00–10.76</td>
<td>No</td>
<td>0.09</td>
<td>0.06</td>
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<tr>
<td>hCG versus progesterone (IM)</td>
<td>SAB (long protocol)</td>
<td>Artini et al., 1995; Ludwig et al., 2001; Martine et al., 2001; Ugur et al., 2001</td>
<td>4</td>
<td>707</td>
<td>0.9</td>
<td>0.72–1.14</td>
<td>Yes</td>
<td>0.99</td>
<td>0.89</td>
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<tr>
<td>hCG versus progesterone (vaginal)</td>
<td>OPR</td>
<td>Artini et al., 1995; Ludwig et al., 2001</td>
<td>2</td>
<td>235</td>
<td>1.08</td>
<td>0.54–2.19</td>
<td>Yes</td>
<td>0.94</td>
<td>0.45</td>
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<tr>
<td>hCG versus progesterone (vaginal)</td>
<td>SAB</td>
<td>Artini et al., 1995; Ludwig et al., 2001</td>
<td>2</td>
<td>43</td>
<td>0.69</td>
<td>0.23–2.10</td>
<td>Yes</td>
<td>0.28</td>
<td>0.11</td>
</tr>
</tbody>
</table>

Source: Pritts and Atwood

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Table 2: In vitro fertilization (IVF) luteal support comparing hCG with intramuscular or vaginal progesterone: Fertility outcomes

- **hCG versus progesterone (IM):** CPR (long protocol) - Albert et al., 1991; Claman et al., 1992; Araujo et al., 1994; Artini et al., 1995; Loh and Leong, 1996
  - RR: 0.98, 95% CI: 0.68–1.42
  - Meta-analysis: Yes
  - Power # 2: 0.99
  - Power # 1: 0.74

- **hCG versus progesterone (IM):** CPR (flare protocol) - Golan et al., 1993
  - RR: 6.07, 95% CI: 0.84–130.80
  - Meta-analysis: No
  - Power # 2: 0.36
  - Power # 1: 0.13

- **hCG versus progesterone (IM):** OPR (long protocol) - Artini et al., 1995
  - RR: 1, 95% CI: 0.22–4.58
  - Meta-analysis: No
  - Power # 2: 0.54
  - Power # 1: 0.18

- **hCG versus progesterone (IM):** DR (long protocol) - Claman et al., 1992
  - RR: 1.7, 95% CI: 0.52–6.27
  - Meta-analysis: No
  - Power # 2: 0.68
  - Power # 1: 0.24

- **hCG versus progesterone (IM):** DR (flare protocol) - Golan et al., 1993
  - RR: 0.86, 95% CI: 1.00–10.76
  - Meta-analysis: No
  - Power # 2: 0.09
  - Power # 1: 0.06

- **hCG versus progesterone (IM):** SAB (long protocol) - Artini et al., 1995; Ludwig et al., 2001; Martine et al., 2001; Ugur et al., 2001
  - RR: 0.9, 95% CI: 0.72–1.14
  - Meta-analysis: Yes
  - Power # 2: 0.99
  - Power # 1: 0.89

- **hCG versus progesterone (vaginal):** OPR - Artini et al., 1995; Ludwig et al., 2001
  - RR: 1.08, 95% CI: 0.54–2.19
  - Meta-analysis: Yes
  - Power # 2: 0.94
  - Power # 1: 0.45

- **hCG versus progesterone (vaginal):** SAB - Artini et al., 1995; Ludwig et al., 2001
  - RR: 0.69, 95% CI: 0.23–2.10
  - Meta-analysis: Yes
  - Power # 2: 0.28
  - Power # 1: 0.11

Source: Pritts and Atwood

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A study by Engmann L et al. where ovarian stimulation protocol consisted of GnRH agonist trigger after antagonist cotreatment combined with luteal phase and early pregnancy support with estrogen and progesterone showed a decreased risk of OHSS and better implantation and ongoing pregnancy rate in comparison with hCG trigger after GnRH agonist protocol.38

CONCLUSION

In summary, it seems that the need for luteal supplementation is real, with both hCG and progesterone conferring benefit to fertility in women undergoing modern ART cycles. Luteal estradiol deficiency and its replacement may represent a somewhat unknown cause of infertility. The benefit of these agents in normal cycles and recurrent abortion is yet to be proven.

REFERENCES


CHAPTER 80

Hyperandrogenism

ANDROGEN EXCESS IN REPRODUCTIVE LIFE

Androgens are present in females in early fetal life when adrenal gland secretes significant quantities of dehydroepiandrosterone sulfate (DHEAS). In the middle of the first decade at about 6–7 years of age these begin to rise again. This phase is termed as "adrenarche" and is clinically manifested by the appearance of pubic and axillary hair. In normal girls the androgen levels continue to rise throughout the second decade and are maintained at relatively steady levels until the menopause. These contribute in maintenance of body fat and weight, libido and normal functioning of the reproductive system in terms of ovulation. On the other hand excess of androgens, either by overproduction or reduced clearance may hamper reproductive performance.

ANDROGENS PRODUCTION IN FEMALES

Androgens are produced in females in three compartments (Fig. 1):
1. **Ovary:** Ovarian stroma and theca cells.
2. **Adrenal:** Zona fasciculata and reticularis.
3. **Periphery and liver:** Periphery includes skin, fat, pilosebaceous unit and blood.

Ovarian Androgen Secretion

The theca interna and the stromal cells of the ovary synthesize the androgens. The ovaries secrete mainly androstenedione and testosterone and small quantities of dehydroepiandrosterone (DHEA). The menopausal ovary, which is devoid of oocytes and follicles, still secretes androgens from the stromal cells and the hilum. Testosterone is secreted mainly by the ovaries and is used as a marker of ovarian androgen secretion. Luteinizing hormone (LH) controls androgen synthesis in the ovaries.

Adrenal Androgen Secretion

The adrenals mainly secrete DHEA, DHEAS and androstenedione, (5 and 11 androstenedione). Small quantities of testosterone also are secreted directly by the adrenals. DHEAS and 11-androstenedione are not secreted by the ovaries and, therefore, are used as markers of adrenal androgen secretion. The control of their secretion clearly is under the control of adrenocorticotropic hormone (ACTH). However, prolactin, estrogen, and a hypothetical pituitary hormone; cortical androgen-stimulating hormone (CASH) or adrenal androgen-stimulating hormone (AASH), have been proposed as separate regulators of adrenal androgen production.

Peripheral Androgens

The principal circulating androgens are testosterone and its metabolite dihydrotestosterone (DHT), androstenedione and DHEAS. All are C19 steroids derived from the conversion of cholesterol in either the ovaries or the adrenal. DHT is the most biologically potent, followed by testosterone. Androstenedione and, to some degree, DHEA are converted to testosterone in the skin. Twenty-five percent of circulating testosterone is secreted directly by the ovaries, 25% directly by the adrenals and the remaining 50% is derived from peripheral conversion of androstenedione to testosterone. Androstenedione, DHEA and DHEAS are comparatively weak androgens with minimal effect on skin and hair growth under normal circumstances. DHT is derived exclusively from peripheral conversion of circulating testosterone.
and androstenedione in a reaction catalyzed by enzyme 5α-reductase in the pilosebaceous unit which then is metabolized further to 5-androstanediol. The relative activity of the 5α-reductase enzyme can be determined by measuring 5-androstanediol glucuronide in either urine or blood.1

Androgens are bound in blood to the sex hormone-binding globulin (SHBG) and albumin. Androgens circulate in a bound and an unbound fashion. In healthy women, 80% of testosterone is bound to SHBG, 19% is bound to albumin and 1% circulates free in the bloodstream.2 In women who are hirsute, 79% is bound to SHBG, 19% is bound to albumin and 2% circulates free. In men, 78% is bound to SHBG, 19% is bound to albumin and 3% circulates free. Only the free and non-SHBG-bound androgens are thought to be biologically available.2 The following conditions and drugs affect the levels of SHBG:2

- Increase
  - Estrogens
- Decrease
  - Androgens
  - Synthetic progestin’s (norethindrone, norgestrel, desogestrel, norgestimate)
  - Hypothyroidism
  - Hyperinsulinemia
  - Prolactin

### VARIOUS ANDROGENS PRESENT IN FEMALES (FLOW CHART 1)

- Testosterone (T)—25% from ovary, 25% from adrenal and 50% by conversion of androstenedione (A) and DHEA in extra glandular tissue (blood, skin, liver)
- Androstenedione—50% from ovary and 50% from adrenal
- Dehydroepiandrosterone—10% from ovary and 90% from adrenal
- Dehydroepiandrosterone sulfate—100% from adrenal only
- Dihydrotestosterone is formed by peripheral conversion of T and A by the action of 5α-reductase

### ESTIMATION OF ANDROGENS

Until recently, adrenal androgen secretion has been assessed by measurement of urinary 17-ketosteroid secretion which comprise mainly of DHEA, DHEAS, androstenedione and breakdown products of T.

- Developments of radioimmune assays now estimate all these in blood
- Total T = SHBG + free T
- In females the normal index is 1%, which means the ratio of free to total testosterone is 1:100. Methods of measuring free T are cumbersome while measurement of total T and SHBG is much easier therefore these are undertaken to determine free T levels.2

### ANDROGEN EXCESS MANIFEST IN TWO WAYS

1. Reproductive system:
   - Ovary: Ovulatory disorders extending to chronic anovulation and amenorrhea
- Uterine endometrium: Unopposed estrogen action with resultant endometrial hyperplasia.

2. External manifestations, such as hirsutism, acne vulgaris, virilization and sometimes also as acanthosis nigricans.

**EFFECT OF ANDROGEN EXCESS ON OVULATION/REPRODUCTIVE PERFORMANCE**

The ovarian follicle, from the stage of the preantral follicle starts producing androgens from cholesterol precursors, in the theca interna by the action of the pituitary LH. This physiologic level of the androgens produced by the follicular cohort functions as the substrate for estrogen synthesis (mainly estradiol) by the ovarian granulosa cell layer. Theca cell layer is separated from the granulosa cell layer by lamina basalis or basal membrane. These androgens seep into the granulosa cells from the theca cell layer across the basal membrane. Pituitary follicle-stimulating hormone (FSH) promotes aromatase enzyme activity in the granulosa compartment, which in turn promotes conversion of androgens into estrogen. Thus, a synchronized pattern of LH and FSH action in the period of folliculogenesis promotes increased estrogen production and an optimal estrogenic microenvironment in the follicle. This is referred to as two cells two-gonadotropin theory (Flow chart 2).

3. **DISORDERS LEADING TO ANDROGEN EXCESS IN REPRODUCTIVE AGE GROUP FEMALE**

- Polycystic ovarian syndrome (PCOS) (90% of cases)
- Congenital adrenal hyperplasia (2–5%)
- Cushing’s syndrome
- Masculinizing tumors of ovary
- Androgen-secreting adrenal tumors
- Hyperprolactinemia

4. **POLYCYSTIC OVARIAN SYNDROME**

**Morphology (Fig. 2)**

Polycystic ovarian syndrome (PCOS) constitutes more than 90% of cases with androgen excess in reproductive females. This is a heterogeneous disorder which may present at one end of spectrum with just polycystic ovaries on ultrasound and ovulatory dysfunction and at the other end of spectrum with symptoms such as obesity, menstrual cycle disturbance, hirsutism, acne and infertility. Metabolic disturbances such as elevated serum concentrations of LH, testosterone, insulin and prolactin are common and may have profound implications on the long-term health of women with PCOS. It appears to be a familial condition and a number of candidate genes have been implicated. It has its origins during adolescence.

**Pathophysiology**

In PCOS the theca androgen production is excessive, as observed in thecal hyperplasia of PCOS, and FSH levels are low due to peripheral estrone negative feedback on pituitary, then this leads to suboptimal aromatase activity. This ultimately creates an androgenic microenvironment with suppressed aromatase action, reduced estrogen production and finally follicular atresia, arrest of oocyte growth and maturation. In addition, it also compromises the oocyte and endometrial quality.

**Sources of Excess Androgen in Polycystic Ovarian Syndrome**

Hypothalamic-pituitary-ovarian axis: Increase in LH pulse frequency and amplitude stimulates theca cells of ovary to produce more androgens.

**Abbreviations:** LH, luteinizing hormone; FSH, follicle-stimulating hormone

**Flow chart 2:** Two cells two-gonadotropin theory

- Pituitary LH
- Pituitary FSH
- Theca interna
- Granulosa cells
- Androgens
- Estrogens
- Physiological levels of androgens act as substrate for estrogens
- Estrogen microenvironment of follicle for oocyte growth

Fig. 2: Morphology of normal and polycystic ovary
Hyperandrogenism

Ovary: It is not only as a result of LH hypersecretion that thecal androgen production increases but an intrinsic abnormality in ovarian theca cells and stroma also exists. There is abnormal steroidogenesis due to up regulation of cytochrome P450.6

Hypothalamic-pituitary-adrenal axis: Another pituitary hormone has been found to specifically control the synthesis of androgenic steroids, known as CASH or AASH. This is seen to increase in 15% of cases which specifically increases the secretion of DHEA and DHEAS.1

Hyperinsulinemia promotes hyperandrogenism through an enhanced effect of LH on the production of androgens by the theca cell because insulin and insulin-like growth factor 1 (IGF-1) receptors are similar in structure. In addition free testosterone is elevated because insulin decreases levels of SHBG.1,7,8

Diagnosis
Polycystic ovarian syndrome was redefined at a joint consensus meeting of the American Society of Reproductive Medicine (ASRM) and the European Society of Human Reproduction and Embryology (ESHRE) held in Rotterdam in May 2003. This included the presence of two out of the following three criteria: (1) oligo and/or anovulation; (2) polycystic ovaries on ultrasound and (3) hyperandrogenism (clinical and/or biochemical) with the exclusion of other etiologies. The morphology of the polycystic ovaries has been redefined as an ovary with 12 or more follicles measuring 2–9 mm in diameter and/or increased ovarian volume (> 10 cm3).9

Hyperinsulinemia: An elevated insulin level or even better, a glucose-to-insulin ratio less than 4.5 indicates insulin resistance. Glucose values that fall within the reference range can be obtained in the face of elevated levels of insulin.1

Luteinizing hormone, follicle-stimulating hormone: An elevated luteinizing hormone-to-follicle-stimulating hormone (LH/FSH) ratio greater than two or certainly three has been used frequently to diagnose PCOS. However, only 40% patients with PCOS have an abnormal LH/FSH ratio.1

Testosterone: Levels higher than 2 ng/mL (8.92 nmol/L, 200 ng/dL) or 2.5 times the upper range are consistent with PCOS.1 Hyperthecosis can have testosterone levels in the tumor range.1

Management is Directed Toward Two Aspects10

Correction of Metabolic Disturbance
This involves correcting hormonal or biochemical disturbances, such as of LH hypersecretion, hyperinsulinemia, ovarian or adrenal androgen preponderance and hyperprolactinemia.

- Luteinizing hormone hypersecretion can be suppressed with the use of two to three cycles pretreatment with oral contraceptive pills (OCP). Gonadotropin-releasing hormone (GnRH) analogs can be used in gonadotropin-stimulated cycle for the same before undertaking ovulation induction
- Hyperinsulinemia is managed by treatment with insulin sensitizers for 2–3 months such as metformin or pioglitazone before induction of ovulation
- Ovarian androgen excess is managed by cyproterone containing OCP for two to three cycles and adrenal androgen excess by a small dose of steroid such as dexamethasone 0.5 mg every night
- Five percent cases of PCOS have simultaneous hyperprolactinemia and may require treatment with bromocriptine or cabergoline
- Ovarian drilling by either laser or fulguration may be beneficial to some patients with PCOS, particularly those patients wishing to conceive.

Induction of Ovulation
Ovulation of induction can be done by antiestrogens such as clomiphene citrate, peripheral aromatase inhibitors like letrozole or by gonadotropins with or without GnRH agonist or antagonist.

HAIR-AN SYNDROME
HAIR-AN syndrome is an acronym for an unusual multisystem disorder in women that consists of hyperandrogenism (HA), insulin resistance (IR) and acanthosis nigricans (AN). The precipitating abnormality is thought to be insulin resistance with a secondary increase in insulin levels and subsequent overproduction of androgens in the ovaries.11

CONGENITAL ADRENAL HYPERPLASIA
Multiple enzyme deficiencies are associated with this condition.12 The most frequent enzyme deficiency noted is 21-hydroxylase in congenital adrenal hyperplasia (CAH) and manifests itself with elevated levels of 17-hydroxyprogesterone and the condition is inherited as autosomal recessive mode.

Less frequently, 11-hydroxylase deficiency is present and is characterized by elevated levels of 11-deoxy-cortisol and results in elevated levels of deoxycorticosterone (DOC), a mineralocorticoid. Hypertension and hypokalemia can be prominent features of 11-hydroxylase deficiency.

Another form of CAH, 3-hydroxy-steroid dehydrogenase deficiency results in elevated levels of pregnenolone, 17-hydroxy-pregnenolone and DHEA. This condition is lethal if not detected because no corticosteroids are synthesized.
In females, CAH when presents in its most severe forms, is almost always detected at birth when the presence of ambiguous genitalia makes one suspect the diagnosis. A partial defect of 21-hydroxylase enzyme results in acquired, delayed-onset or attenuated adrenal hyperplasia which manifests at puberty. Hirsutism, irregular bleeding or amenorrhea and virilization (including clitoromegaly) are its characteristic features. The underlying enzyme defect leads to low levels of cortisol which stimulates ACTH release which further leads to stimulation of adrenal glucocorticoid precursors and accumulation of adrenal androgens. The elevations are not as marked as they are with the congenital condition and this condition is also referred to as maturity-onset CAH.

**Diagnosis**

The diagnosis depends on the level of 17-α-hydroxyprogesterone, a steroid substrate which spills over to the androgen pathway and causes increased production of adrenal androgen. If the patient is menstruating then this test should be performed in the follicular phase because 17-OH-progesterone is elevated in the luteal phase. All measurements should be obtained in the morning because of the diurnal rhythm of adrenal steroids. CAH can be screened by measuring 17-OH-progesterone because 21-hydroxylase is the most common defect. Tests revealing levels above 2 ng/mL (6.05 nmol/L) need to be repeated and, if elevated, an ACTH stimulation test (short synacthen test) with 250 µg intravenously of ACTH must be performed. Levels above 10 ng/mL (30.02 nmol/L) at 1 hour are diagnostic.

**Treatment**

Reduction of ACTH levels by substituting cortisol in the form of dexamethasone in the dose of 0.5 mg/day reduces hyperandrogenism. This reverts the reproductive function to normal, facilitating normal ovulation and conception.

**CUSHING’S SYNDROME**

This is due to overproduction of cortisol and may occur due to following conditions:
- Sixty percent cases are due to the excessive pituitary secretion of ACTH (Cushing’s disease). Cushing’s disease has a predilection for younger women (age 20–30 years) and is eight times more common in women
- Primary adrenal disease—adenoma/carcinoma accounts for 25% of cases
- Ectopic secretion of ACTH which is very rare and occurs in the remaining cases. This is 10 times more commonly seen in men than women
- Secretion of corticotropin-releasing hormone (CRH) by a tumor is rarely found.

Androgen excess in Cushing’s syndrome is caused by increased production of adrenal androgens that accompanies increased production of cortisol. Onset is not at menarche unlike PCO and late onset CAH. In addition to frank hirsutism, which is a result of excessive production of adrenal androgen, increased growth in lanugo hair may occur due to increased cortisol levels. Other common findings include obesity (85%), menstrual/ovulatory disorders (75%) and acne (35%).

**Diagnosis**

- Single-dose overnight dexamethasone suppression test: cortisol levels less than 5 µg/dL at 8 am after 1 mg dexamethasone administered at 11 pm the night before the test rules out Cushing’s syndrome. Obese patients have a false positive rate of 13%
- Twenty-four hours urinary free cortisol less than 110 µg excludes Cushing’s syndrome. Levels more than 250 µg are virtually diagnostic
- Low-dose, 2-day suppression test: For final confirmation. Dexamethasone (0.5 mg every 6 hours) is given for 2 consecutive days. Patients with Cushing’s syndrome will not lower their urinary 17-hydroxyl-steroids below 2.5 mg/day and the free cortisol levels below 10 µg on the second day of dexamethasone suppression.

**Treatment**

Treatment is directed in treating the cause and suppressing androgen and cortisol levels by substituting dexamethasone 0.25–0.5 mg or prednisolone 5–10 mg.

**VIRILIZING OVARIAN TUMORS**

Most androgen-secreting ovarian neoplasms are benign, present in women under 30 years of age and are rare. Hirsutism and amenorrhea are typical presenting complaints of reproductive age women with a virilizing ovarian tumor. These women commonly have a history of cyclical menses until the abrupt cessation of menses and the first appearance of hirsutism simultaneously. The rate of progression of androgenic signs is proportional to the amount of testosterone secreted by these tumors.

**Young and Scully Classification:**

**Virilizing Ovarian Tumors**

- Sex cord stromal cell tumors (androblastomas, arrhenoblastomas):
  - Pure Leydig
  - Sertoli-Leydig
  - Gynandroblastomas
• Steroid cell tumors:
  – Stromal luteoma
  – Hypernephromas
  – Leydig cell tumor
  – Hilar cell and lipoid cell tumors
  – Adrenocortical type: Associated with cushingoid-like features in 50% cases.
• Nonfunctioning ovarian tumors:
  – Sertoli-Leydig cell tumors reach palpable size at the time of clinical diagnosis, whereas hilar cell and lipoid cell tumors are very difficult to detect by any means because of their small size.

At all ages, women with a virilizing ovarian tumor have endometrial hyperplasia or adenocarcinoma more frequently than women without such a tumor. Increased aromatization of androgens to estrogens accounts for increased estrogen in these women. Aromatization of androgens occurs in extraglandular sites and involves predominantly the formation of estrone from androstenedione secreted by the tumor.

**ANDROGEN-SECRETING ADRENAL TUMOR**

Pure virilizing adrenal neoplasms are rare. Adrenal tumors are divided into the benign adenoma and the malignant adenocarcinoma. Typically, these are small, impalpable and in half the reported cases occur in premenopausal women.

**Pathogenesis of Anovulation in Androgen-Secreting Tumors**

This is due to increased androgen load from adrenal or ovarian tumors, which, increases peripheral conversion into estrone, which, in turn suppresses pituitary FSH. This leads to lack of aromatase activity in granulosa cells and androgen excess in the intrafollicular environment, eventually leading to follicular atresia. Stimulation of ovarian stromal hyperplasia adjacent to the tumor and induction of the histologic changes of polycystic ovary disease in the contralateral ovary are two mechanisms reported by which nonfunctioning ovarian tumors also can cause increased androgen secretion.

**Diagnosis of Ovarian and Adrenal Tumors**

**Serum Testosterone**

Elevated serum testosterone levels usually higher than 2 ng/mL (8.92 nmol/L, 200 ng/dL) suggest a tumor, usually of the ovary. Further workup is necessary to rule out an ovarian or adrenal tumor. Virilization, together with serum testosterone in the male range (>10 nmol/L) are particularly ominous signs. Suspect an ovarian etiology with elevated testosterone and an adrenal source with elevated DHEAS levels higher than 7 ng/mL (>20 nmol/L).

**Imaging Studies**

Ultrasound is used mainly to determine the location of the tumor (ovarian or adrenal). Ultrasound can locate most ovarian tumors but small hilar cell tumors are not located. Color-flow Doppler is a helpful adjunct for tumor detection and localization.

Computed tomography (CT) scans are not useful for ovarian tumors. Adrenal androgen-secreting tumors usually can be detected with CT scans, particularly with newer machines and 1–2 mm cuts.

**Magnetic resonance imaging (MRI):** Adrenal and some ovarian tumors can be detected with MRI; however, it is more useful for adrenal lesions.

**Radionuclide studies:** Iodomethyl-norcholesterol (NP-59) can light up steroid-secreting areas of the adrenal gland or ovary and, if available, is helpful to differentiate and locate a tumor when other radiographic studies fail to show a tumor.

**Ovarian and adrenal vein sampling:** In cases where the laboratory values indicate a tumor but none can be determined by imaging studies, then sampling of the ovarian and adrenal veins should determine the source of elevated androgens and whether one or both glands are involved.

Selective venous sampling is technically very difficult and must be performed by an experienced invasive radiologist. The left adrenal and ovarian veins drain into the left renal vein at approximately the same junction and, therefore, admixture is possible. The right ovarian vein empties into the vena cava and can be difficult to locate. The right adrenal vein empties into the right renal vein. Also, the danger of thrombosing the adrenal veins exists. Keeping duplicate samples is recommended because many laboratories do not dilute the sample and report values as greater than a particular value. If an error occurs, call the laboratory, alerting personnel to the origin of the samples so that they can run dilutions.

**Treatment**

Unilateral oophorectomy or salpingo-oophorectomy is the treatment of choice for ovarian tumors. Adrenal tumors also must be removed surgically.

**HYPERPROLACTINEMIA**

Prolactin affects androgen synthesis in three ways:
1. It stimulates production of adrenal androgen such as DHEAS. In hyperprolactinemic women, either dexamethasone or bromocriptine reverses the androgen abnormalities, suggesting that a synergistic effect exists between prolactin and ACTH.
2. Sex hormone-binding globulin is low due to direct effect on liver production of this globulin.
3. Hypoestrogenism, which is associated with hyperprolactinemia, also reduces the SHBG levels. However, there is a protective effect against hirsutism by decrease in the 5α-reductase activity in hyperprolactinemic women. Treatment is to reduce prolactin levels with or without adding gonadotropins to promote follicular selection and growth. The available drugs for treatment of hyperprolactinemia are bromocriptine and cabergoline.

**REFERENCES**

**DISORDERS OF THYROID FUNCTION**

**Introduction**

Thyroid disorders are 10 times more common in women than men. Thyroid disorders can affect all aspects of reproductive functions in females that may produce menstrual abnormalities, infertility, abortions, stillbirths and failure of lactation. About 25% female infertility and 15% menstrual cycle disorders may result from thyroid dysfunction. Subclinical hypothyroidism has a high prevalence in the population; therefore, thyroid function abnormalities may be associated with unclear infertility or menstrual disturbances. The next overlap of thyroid disorders and gynecology represents iodine-131 use for differentiated thyroid carcinoma in fertile age with aspects to ovarian failure and gestational risk.

**Thyroid Hormone Synthesis: Metabolism and Action**

Normal thyroid secretion depends on thyrotropin [thyroid stimulating hormone (TSH)]. Secretion of TSH is, in turn, inhibited by thyroid hormones and stimulated by thyrotropin-releasing hormone (TRH). Iodide in serum is trapped by thyroid cells, after which it is oxidized and incorporated into some of the tyrosine residues of thyroglobulin, which then couple to form thyroxine (T4) and triiodothyronine (T3).

The thyroid gland normally contains large stores of thyroglobulin, most of which are in the lumen of the thyroid follicles. When thyroglobulin is resorbed into the follicular cells of the thyroid and hydrolyzed, T4 and T3 are secreted into the circulation. There they are bound to specific serum-binding proteins, so that very little circulates as free T4 (FT4) or T3. In extrathyroidal tissues, T4 is converted to T3 by the action of several T4 5’-deiodinases; this process generates about 80% of the circulating T3. About 80% of T4 and T3 are metabolized by deiodination and 20% by non-deiodinative pathways that include conjugation with glucuronides and sulfates, decarboxylation, and deamination. In tissues, T3 and to a much smaller extent T4 are bound to specific nuclear receptor proteins that interact with regulatory regions of genes, influencing their expression.

**Interpretation of Thyroid Function Tests**

There is a wide array of thyroid function tests, which are available like serum TSH, total T4, total T3, FT4, free T3, anti-thyroid peroxidase antibodies (anti-TPO Ab), anti-thyroglobulin antibody (anti-Tg Ab), thyroglobulin, calcitonin.

**Screening**

According to Indian consensus by Unnikrishnan AG, serum TSH examination is the best way to screen patients with thyroid disease. Serum FT4 estimations are needed for screening only when there is a suspicion of pituitary or hypothalamic disease. Routine screening for all subjects is not necessary. However, screening can be considered in certain special situations (e.g. menstrual irregularities, infertility, depression) as well as in the presence of clinical signs and symptoms of hypothyroidism.
Diagnosis (Flow Chart 1)

The Indian Consensus by Unnikrishnan AG states that the actual diagnosis of primary hypothyroidism must be made on the basis of a high TSH in association with a low FT4. The normal reference values for TSH are 0.5–5.5 mU/L. The linear relationship between TSH and FT4 dictates that serum TSH is more important test, since only TSH can detect mild (subclinical) degrees of thyroid hormone excess or deficiency. Serum total T4 and T3 values reflect not only hormone production but also the serum concentrations of thyroid binding proteins. In the presence of elevated levels of binding proteins serum total T4 and total T3 concentrations are usually increased but serum FT4 and free T3 concentrations remain normal. The reverse occurs when thyroid binding protein levels fall. The main purpose of FT4 and T3 assays is to distinguish reliably between thyrotoxicosis, hypothyroidism, and the euthyroid state.

THYROID DISORDERS AND INFERTILITY

Hypothyroidism and Infertility

The prevalence of hypothyroidism in women in the reproductive age (20–40 years) varies between 2% and 4%. In this age group, autoimmune thyroid disease (AITD) is the most common cause of hypothyroidism. Severe hypothyroidism is commonly associated with ovulatory dysfunction due to numerous interactions of thyroid hormones with the female reproductive system. Both hyperprolactinemia, due to increased TRH production, and altered GnRH pulsatile secretion, leading to a delay in luteinizing hormone (LH) response and inadequate corpus luteum, have been reported. Thyroid responsivity by the ovaries could be explained by the presence of thyroid hormone receptors in human oocytes. Thyroid hormones also synergize with the follicle-stimulating hormone (FSH)-mediated LH/hCG receptor to exert direct stimulatory effects on granulosa cell function (progesterone production). Recently, Cramer et al. showed that serum TSH levels were a significant predictor of failure of in vitro fertilization, as TSH levels were significantly higher among women who produced oocytes that failed to be fertilized. Another pathway through which hypothyroidism may impact on fertility is by altering the peripheral metabolism of estrogen and by decreasing sex hormone-binding globulin production. Both pathways may result in an abnormal feedback at the pituitary level.

Subclinical Hypothyroidism and Infertility

Subclinical hypothyroidism (SCH) has recently been challenged as data have indicated that physiological FT4 variations are narrower in one individual than those observed within the reference range of a population. These data might reflect an abnormally low FT4 value for patients who present with a mildly increased serum TSH. Some authors have proposed restricting the upper normality limit of serum TSH to 2.5 mU/L. Today, however, there is no agreement among endocrinologists about the most appropriate (i.e. physiologically relevant) upper limit of normality for serum TSH.
The studies investigating the association between SCH and infertility were poorly controlled. Considering the largest cohorts published the prevalence of SCH in infertile women ranged from 1% to 4% and most cases with SCH were associated with ovulatory dysfunction.

**Subclinical, Overt Hyperthyroidism and Infertility**

The precise impact of hyperthyroidism on fertility remains ill-defined. As was the case for hypothyroidism, most studies on the prevalence of hyperthyroidism in infertility are derived from uncontrolled and retrospective cohort studies. In only one small study in 53 hyperthyroid patients it was shown that 5.8% of them were infertile. Women with increased thyroid hormones, suggestive of hyperthyroidism and infertility, should undergo a complete laboratory work-up and receive appropriate treatment (avoiding radioactive iodine). Thyroid function should be corrected, especially before an assisted reproductive technology (ART) procedure is planned.

**Autoimmune Thyroid Disease and Infertility**

The prevalence of AITD is 5–10 times higher in women than in men, which might be explained by genetic factors, the effects of estrogens and perhaps chromosome X abnormalities. The importance of AITD is two-fold. First, it is the most common autoimmune disease in women, affecting 5–10% in the childbearing period; second, it is the most frequent cause of thyroid dysfunction, although AITD can also be present without thyroid dysfunction and therefore remain undiagnosed. Numerous studies have investigated the prevalence of AITD in women with infertility. The interpretation of these data is difficult because of selection bias (women with different causes of infertility or a selected cause such as ovulatory dysfunction), the retrospective setting and the different types of control population. There were differences in sample size as well as in the assays used for detecting thyroid antibodies. However, pooling the results of these studies favors a significantly increased incidence of AITD in women with infertility compared to controls, with an overall estimated relative risk of 2.1 ($P < 0.0001$). The underlying pathogenic mechanisms associated with infertility remain largely speculative, as neither animal models nor in vitro data on this issue are available.

**Management in Clinical Practice**

It should be noted that there is no consensus of opinion regarding routine screening of thyroid function in pregnancy however there is agreement in screening of thyroid function as part of the work-up of infertility. Screening and treatment in women of infertile couples, as proposed are summarized in Flow chart 2 in algorithmic format. The major reasons to perform a screening in the setting of infertility are: the increased prevalence of AITD in infertile women compared with fertile women, the beneficial effects of L-thyroxine treatment (in case hypothyroidism) on surrogate endpoints (menstrual cycle, LH pulsatility and hyperprolactinemia), potentially avoiding an ART procedure and the prevention of an evolution to overt thyroid dysfunction after controlled ovarian hyperstimulation (COH) in women with AITD. When thyroid dysfunction is detected, L-thyroxine treatment is able to restore normal fertility and reduce the likelihood of an ART procedure.

**THYROID DISORDERS AND MENSTRUAL IRREGULARITIES**

Menstrual abnormality is known to occur in overt hypo/hyperthyroidism. Most authors have described the clinical picture in established hypo/hyperthyroidism. However, some workers have reported the occurrence of premenstrual syndrome (PMS) and menorrhagia in women with early and subclinical hypothyroidism.

**Hypothyroidism and Menstrual Abnormalities**

Menorrhagia is reported to occur in 32–56% cases of myxedema. There are multiple mechanisms through which reproductive dysfunction occurs, e.g. altered TRH response, altered LH response, peripheral conversion of androgens to estrogens, change in androstenedione metabolism, catecholeostrogens, altered sex hormone binding globulin levels. It has been stated that menorrhagia is more common in hypothyroidism or myxedema, whilst anovulation or oligomenorrhea is common in hyperthyroidism. The relative frequency and type of menstrual disorders and the chronology of the onset of reproductive dysfunction with respect to the onset and type of thyroid disorder have not been well defined. It is common practice to investigate for thyroid functions when goiter or clinical symptoms and signs are present. In hypothyroidism polymenorrhea (increased frequency of menstrual bleeding) is also common. Defects in hemostasis may contribute to this. It is believed that a hypothyroid state leads to decreased levels of factors VII, VIII, IX and XI. Anovulation may also be present. It is of interest that in juvenile hypothyroidism, puberty is usually delayed but precocious puberty has also been described. This is probably due to a “spillover” effect of the glycoprotein hormones: TSH, which is markedly increased in hypothyroidism, has a small FSH- and LH-like effect. Galactorrhoea may also be present in hypothyroidism, possibly because TRH, the hypothysal THS-releasing hormone, increases the secretion of both TSH and prolactin (PRL). Since hypothyroidism slows down virtually every process of the body, its symptoms often mimic those of PMS, including bloating, weight gain, mood changes (depression, irritability), changes in libido, sleep...
disorders, fatigue, malaise, and constipation. Women with hypothyroidism may notice improvement in their symptoms of PMS with thyroid hormone treatment. It is important to note that thyroid hormone medication only improves PMS in women with hypothyroidism because the decreased thyroid hormone levels exacerbate the existing PMS, it does not help most women with PMS only. Women who suffer from PMS should report their symptoms to their physician so that the thyroid function can be evaluated.

Subclinical Hypothyroidism and Menstrual Abnormalities

In subclinical hypothyroidism, when TSH is elevated but T4 is normal, menstrual abnormalities may precede clinically evident hypothyroidism. It is also common after treatment of hyperthyroidism by surgery or iodine-131 and may result from the use of drugs such as lithium carbonate. The patient will respond if treated with synthetic thyroxin. Brayshaw and Brayshaw reported that out of 54 women of PMS, 35 had subclinical hypothyroidism which was relieved by thyroxin.

Hyperthyroidism and Menstrual Abnormalities

In hyperthyroidism, amenorrhea was described as early as 1840 by von Basedow. The most common manifestation is simple oligomenorrhea. Anovulatory cycles are very common. Increased bleeding may occur, but is rare in hyperthyroidism. Nowadays, hyperthyroidism is diagnosed earlier than it once was, and so the clinical picture is generally milder. So, menstrual disorders are less common than before. In a recent paper, 21.5% of 214 patients had disturbances in their cycle, compared to 50% in some older series. In cases of amenorrhea, pregnancy should be ruled out. If hyperthyroidism occurs during childhood, before puberty, the first menstrual period is usually delayed. However, when hyperthyroidism occurs during the early years of puberty, the first menses may begin early. McCune-Albright syndrome is a rare disease affecting the bone and ovaries, which may occur when there is a combination of hyperthyroidism and precocious puberty. Often symptoms of hyperthyroidism, such as irregular or absent menses, heat intolerance, “hot flashes,” insomnia, and mood swings may overlap with and be confused with symptoms of menopause and once the hyperthyroidism is controlled these symptoms may resolve, with the resumption of normal menstrual cycles and normal onset of menopause. This restoration of the menses results in a normal level of estrogen that is important for maintaining the body’s bone mass and decreasing the risk of osteoporosis.

THYROID DISORDERS IN RELATION TO GYNECOLOGICAL SURGERY

The pathophysiologic effects of hypothyroidism involve almost every organ. In the past, hypothyroidism was considered a contraindication of surgery in all situations except emergency surgery. However, several series have now shown that elective surgery can be carried out safely in patients with mild to moderate hypothyroidism. Patients with hypothyroidism have the same rate of postoperative complications when compared with euthyroid patients. When elective surgery is planned, thyroid replacement
therapy should be started and TSH levels will determine the daily dose. Despite the presence of normal thyroid function study results, physiologic abnormalities take months to resolve. In patients with mild to moderate hypothyroidism who undergo emergency surgery, thyroid replacement can begin in postoperative period as soon as patient is able to eat. Close postoperative observation should be performed routinely.

Because all patients of hyperthyroidism are at risk of thyroid storm, elective surgery should be delayed until the patient has been adequately treated with antithyroid agents. In completely elective situations, the euthyroid state should be maintained for approximately three months before a surgical procedure is undertaken. If the patient’s condition has been slowly controlled over several months, surgery can be performed safely and no special perioperative monitoring is necessary. When surgery is urgent, betablockers can be used to control sympathomimetic symptoms such as palpitation, and anxiety. Anti-thyroid medications or radioactive iodine do not render patients euthyroid quickly enough for urgent or emergency surgery. In urgent but not emergency situations, propylthiouracil along with a betablocker can be started 2 weeks before surgery and the patient is carefully monitored for signs of increasing hyperthyroidism. When performing surgery under urgent or emergency situation, patient should be carefully monitored for tachycardia, arrhythmias and hypertension.

**DISORDERS OF ADRENAL FUNCTION**

**Introduction**

The adrenal cortex produces glucocorticoids (primarily cortisol), mineralocorticoids (primarily aldosterone), and androgens (primarily dehydroepiandrosterone and androstenedione). The adrenal medulla is composed of chromaffin cells, which synthesize and secrete catecholamines (mainly epinephrine and lesser amounts of norepinephrine). Most deficiency syndromes affect output of all adrenocortical hormones. Hypofunction may be primary (malfuction of the adrenal gland itself, as in Addison's disease) or secondary (due to lack of adrenal stimulation by the pituitary or hypothalamus, although some experts refer to hypothalamic malfunction as tertiary).

Hyperfunction produces distinct clinical syndromes. Hypersecretion of androgens results in adrenal virilism; of glucocorticoids, Cushing's syndrome; and of aldosterone, hyperaldosteronism (aldosteronism). These syndromes frequently have overlapping features. Hyperfunction may be compensatory, as in congenital adrenal hyperplasia, or due to acquired hyperplasia, adenomas, or adenocarcinomas. Excess quantities of epinephrine and norepinephrine are produced in pheochromocytoma. Adrenal disorders that are commonly encountered in relation with gynecology are discussed here.

**Adrenogenital Syndrome or Adrenal Virilism**

Adrenogenital syndrome or adrenal virilism is caused by an androgen-secreting adrenal tumor or by adrenal hyperplasia. Sometimes, the tumor secretes both excess androgens and cortisol, resulting in Cushing’s syndrome. Adrenal hyperplasia is usually congenital; delayed virilizing adrenal hyperplasia is a variant of congenital adrenal hyperplasia.

**Symptoms and Signs**

Effects depend on the patient’s age at onset. Symptoms and signs include ambiguous genitalia at birth, hirsutism (sometimes the only sign in mild cases), baldness, acne, and deepening of the voice. Libido may increase. In prepubertal children, growth may accelerate. If untreated, premature epiphyseal closure and short stature occur. Adolescent girls may have amenorrhea, atrophy of the uterus, clitoral hypertrophy, decreased breast size, and increased muscularity. In adult men, the excess adrenal androgens may suppress gonadal function and cause infertility.

**Diagnosis**

Adrenal virilism is suspected clinically, although mild hirsutism and virilization with hypomenorrhea and elevated plasma testosterone may also occur in polycystic ovary (Stein-Leventhal) syndrome. Adrenal virilism is confirmed by demonstrating elevated levels of adrenal androgens. In adrenal hyperplasia, urinary dehydroepiandrosterone (DHEA) and its sulfate (DHEAS) are elevated, pregnanetriol excretion is often increased, and urinary free cortisol is diminished. Plasma DHEA, DHEAS, 17-hydroxyprogesterone, and androstenedione may be elevated. A level of greater than 30 nmol/L of 17-hydroxyprogesterone 30 min after administration of cosyntropin 0.25 mg IM, strongly suggests the most common form of adrenal hyperplasia. Virilizing tumors are excluded if dexamethasone 0.5 mg orally is given 6 hourly for 48 hours which suppresses production of excess androgens. If excessive androgen excretion is not suppressed, CT or MRI of the adrenals and ultrasound of the ovaries are performed to search for a tumor.

**Treatment**

Recommended treatment for adrenal hyperplasia is dexamethasone 0.5 to 1 mg at bedtime. For genital ambiguity external genital reconstructive surgery may be required. Adrenal tumors require adrenalectomy.
Anovulation, Infertility, Abnormal Menstruation in Adrenal Disorders

Another way of presentation of adrenal disorders in gynecology is of abnormal menstrual pattern, anovulation and infertility.

Cushing’s Syndrome

Cushing’s syndrome is characterized by hypercortisolism. Whereas the term Cushing’s syndrome denotes the clinical picture resulting from cortisol excess from any cause, Cushing’s disease refers to hyperfunction of the adrenal cortex from pituitary adrenocorticotropic hormone (ACTH) excess. Patients with Cushing’s disease usually have a small adenoma of the pituitary gland. Its clinical manifestations encompass a spectrum of symptoms, the severity of which is often influenced by the presence or absence of androgen excess. Progressive obesity and abnormal waist/hip ratio are not uncommon, although the limbs are often spared. Frequently, patients experience proximal muscle weakness and cannot rise from a sitting position. Patients can also be hypertensive as a result of mineralocorticoid excess. Women usually have excess hair growth on their faces, necks, chests, abdomens, and thighs. Their menstrual cycle may become irregular or stop. Men have decreased fertility with diminished or absent desire for sex. Diagnosis is usually suspected based on the characteristic symptoms and signs. Confirmation, and investigation of the underlying cause, generally requires hormonal and imaging tests.

In Cushing’s disease, the increased plasma ACTH concentrations stimulate increased adrenocorticoid secretion, thus inhibiting hypothalamic corticotropin-releasing hormone (CRH) secretion and other factors from the pituitary. These aberrations in the cycle, as well as changes in secretory patterns, are thought to influence the mechanisms involved in ovulatory function. Although the exact mechanisms have not been elucidated, it is believed that hypercortisolism and adrenal hyperandrogenism suppress gonadotropin secretion with impaired LH response to GnRH.

Adrenal Insufficiency

Adrenal insufficiency can be due to a variety of causes, including deficient hypothalamic secretion of CRH, deficient pituitary secretion of ACTH, or destruction of the adrenal cortex (Addison’s disease, primary adrenal insufficiency). Adrenal androgen deficiency results in loss of axillary and pubic hair in women and decreased libido. Women with autoimmune adrenal insufficiency are at increased risk of premature ovarian failure and anovulation.

Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia (CAH) encompasses a group of autosomal recessive disorders caused by an inherited deficiency of enzymes involved in cortisol synthesis in the adrenal cortex.

These disorders, listed in decreasing order of frequency, include a deficiency of 21-hydroxylase, 11-alpha-hydroxylase, and 3-beta-hydroxysteroid dehydrogenase. Hyperandrogenism induces a disruption of the HPO axis and consequently leads to menstrual irregularities or anovulatory cycles.

Treatment

Apart from the definitive treatment of adrenal disorders, following measures can be taken for ovulatory dysfunction and infertility:

- Ovulation induction with clomiphene citrate 50–200 mg/d for 5 days, commencing on day 2 or 3 of the menstrual cycle is first-line treatment. Of anovulatory women, 25% do not respond to clomiphene and can be treated with gonadotropins. Clinicians expert in assisted reproduction techniques must supervise the treatment because hyperstimulation syndrome and multiple pregnancy rates of up to 25% are recognized complications.
- A short course of dexamethasone can be added to clomiphene to restore ovulation.
- Metformin has been shown to increase both spontaneous and clomiphene-induced ovulation rates.

Adrenal Androgens and Hirsutism

Adrenal glands and ovaries are main sources of androgen production in women apart from peripheral tissues such as fat and skin. Liver and gut play a minor role in androgen production, particularly in the peripheral conversion of testosterone to the most active form dihydrotestosterone.

The endocrine glands secrete 5 androgens through a similar pathway including, DHEAS, DHEA, androstenedione, testosterone, and androstenedioli (has both androgenic and estrogenic activity). Testosterone is the only androgen with direct androgenic activity, while DHEAS, DHEA, and androstenedione are all precursors of testosterone.

The adrenal glands produce all the DHEAS and 80% of the DHEA. The adrenals also secrete 50% of androstenedione and 25% of the circulating levels of testosterone. DHEAS and 11-androstenedione are not secreted by the ovaries and, therefore, are used as markers of adrenal androgen secretion. Their secretion depends on ACTH; prolactin and estrogen can affect adrenal androgen production. Androgen excess affects mainly the pilosebaceous unit (PSU) and the reproductive systems.

The pilosebaceous unit secretes sebum and is the unit from which hair grows. As androgen levels rise, more vellus hairs in the androgen-sensitive areas are converted into terminal hairs. This results in hirsutism. Androgens prolong the growth phase of hair and promote their conversion from vellus type to terminal. Lesions of the pilosebaceous unit are
called acne. Acne can be aggravated or initiated by increased androgen levels as the excess sebum production and the shedding of hyperkeratinized epithelium may occlude the hair follicle.

**Causes of Adrenal Androgen Excess Resulting in Hirsutism**

- Tumors of the adrenal glands (adenomas, carcinomas), which secrete elevated levels of androgens, are known, but rare. They are suspected when DHEAS exceeds 7 μg/mL (18 μmol/L).
- Classical and non-classical (late-onset) CAH.
- Cushing’s syndrome: Patients with Cushing’s syndrome secrete elevated androgens, but diagnosing this disease by hyperandrogenic manifestations without the other signs and symptoms of Cushing’s syndrome would be unusual.

**Laboratory Studies**

The purpose of laboratory tests is to detect the specific androgens involved, the degree of hypersecretion, and the origin of the androgens. The following are markers of adrenal androgen production:

- **DHEAS levels:** Virtually all DHEAS is produced by the adrenal glands. Elevated DHEAS levels indicate an adrenal cause for androgen excess. An adrenal tumor should be suspected if the value is greater than 7 μg/mL (18 μmol/L), and radiographic studies should be undertaken. If no tumor is suspected, then Cushing’s syndrome should be ruled out, if clinically indicated.
- **Cortisol studies:** They are indicated if the physical examination is consistent with Cushing’s syndrome and no other explanation can be found for hirsutism in the patient. A 24-hour urinary free cortisol level or an overnight dexamethasone suppression test should be completed.
- **17-OH-progesterone levels:** This is elevated in the luteal phase, hence the rationale of testing in early follicular phase. CAH due to 21-hydroxylase defect can be screened by measuring 17-OH-progesterone. Tests revealing levels above 2 ng/mL (6.05 nmol/L) need to be repeated and, if elevated, an ACTH stimulation test with 0.25 mg of ACTH (Cortrosyn) must be performed. Levels above 10 ng/mL (30.02 nmol/L) at 1 hour are diagnostic.

**Treatment**

Hirsutism is a sign and not a specific disease. Options for treatment include medical therapy and cosmetic-based temporary and permanent hair removal. Temporary methods of hair removal do not alter the rate of hair growth. Once an androgen-producing tumor, Cushing’s syndrome, and CAH have been diagnosed, treatment should focus on the cause. The patient should be told at the outset that successful treatment will take several months.

**BIBLIOGRAPHY**

There are five basic factors involved in the onset and continuation of normal menstruation. These are: anatomical patency of the genital tract; normal female chromosomal pattern; co-ordinated hypothalamic-pituitary-ovarian axis; active support by two other endocrine glands, namely thyroid and adrenal cortex and responsive endometrium. Defect in one or more of these factors will therefore be responsible for amenorrhea, either primary or secondary.\(^1\)

**PATHOLOGICAL AMENORRHEA**

It is defined as the absence of menstruation for at least 6 months, not due to pregnancy, in a woman of child-bearing age. The usual age limits of menarche and menopause are 16 and 44 years respectively.

**Primary Amenorrhea**

Absence of menarche by age 14 in the absence of development of secondary sexual characteristics, or absence of menarche by age 16, regardless of the presence of normal growth, development and presence of secondary sexual characteristics.

**Physiological Amenorrhea**

Before menarche, after menopause and during pregnancy.

The causes of primary amenorrhea are related to defects in any of the four compartments as described in Figure 1. These compartments are:

1. **Compartment I**: Defect at the level of outflow tract and the uterus.
2. **Compartment II**: Defect in ovulation.
3. **Compartment III**: Defect at the level of pituitary gland.
4. **Compartment IV**: Defect at the level of hypothalamus and central nervous system.

**Disorders of Hypothalamic-Pituitary-Ovarian Axis\(^3\)**

**Hypothalamic**

- **Primary failures**: Compression by tumors (Kallman’s syndrome)
- **Functional disorders**: Psychological disturbances, weight loss, extreme exercise pseudocyesis.

**Pituitary**

- **Primary failures**: Compression by tumors. Damage by surgery, radiotherapy. Infarction (e.g. Sheehan’s syndrome), hyperprolactinemia
- **Functional failure secondary to hypothalamic failure or disorder**.
**Flow chart 1: Etiology of individuals with primary amenorrhea and virilization**

- **Primary amenorrhea**
  - Female appearance with breast development

- **Imaging of pelvis**

- **Uterus absent**
  - **Karyotype**
    - 46, XX
      - Axillary and pubic hair normal
      - MRKH syndrome
    - 46, XY
      - Axillary and pubic hair absent
      - Complete androgen insensitivity syndrome

- **Uterus present**
  - **Outflow obstruction**
    - Hematocolpos
    - Hematometra
    - LF, FSH Normal/decreased
    - Hypothalamic-pituitary failure secondary to an acquired disease
    - PCOD
    - High TSH
    - Hypothyroidism
  - **Normal anatomy**
    - LF, FSH ratio increased
    - Prolactin increased
    - LH, FSH decreased
    - TSH estimation
    - Normal TSH
    - MRI/CT to look for prolactinoma

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**Ovarian**

*Primary failures:* Dysgenesis (genetic/chromosomal), damage by surgery, radiotherapy, chemotherapy.

*Autoimmune disease:*
- Premature menopause
- Resistant ovary syndrome.

**Anatomical Causes of Amenorrhea**

*Simple developmental defects:*
- Absent ovaries (extremely rare)
- Absent uterus/severely hypoplastic, with or without absent vagina—Müllerian anomalies
- Imperforate hymen (lower vaginal aplasia).

**Developmental Defects of Endocrine Origin**

- Androgen-resistant syndrome (testicular feminization), pseudohermaphrodites (genetic and gonadal males) including inhibition of uterovaginal development.
- Causes of delayed onset of puberty are listed in Table 1.
- Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome
- Asherman syndrome.

**Summary of Primary Investigations**

*Flow Chart 2*

**History**

- Previous weight loss (history of rigorous exercises—athletes), or weight gain
Endocrinology

**Fig. 1:** Causes of primary amenorrhea related to defects in either of four compartments

**Table 1: Causes of delayed onset of puberty**

<table>
<thead>
<tr>
<th>Type of Delay</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypergonadotrophic:</strong></td>
<td>Abnormal chromosome, e.g. 45X, mosaic cell lines (27%)</td>
</tr>
<tr>
<td></td>
<td>Normal chromosome but ovarian failure (includes 46 XY, gonadal failure) (16%)</td>
</tr>
<tr>
<td></td>
<td>Testicular feminizing syndrome</td>
</tr>
</tbody>
</table>

| **Hypogonadotrophic:** | Reversible causes: Constitutional delay, weight loss, adrenal disease, thyroid disorder (19%) |
|                       | Irreversible causes: Pituitary deficiency, cerebral tumors, congenital central nervous system defects (12%) |

**Intact gonadal function**

- Anatomical causes, e.g. Müllerian agenesis (18%)
- Genital tract obstruction (12%)
- Inappropriate feedback (8%)
- Anovulation (8%)
- Androgen insensitivity (8%)

Special investigations which must be done to corroborate with clinical diagnosis are shown in Table 4.

- Laboratory investigations
  - Routine blood, urine, and stool
  - Special for tuberculosis
- Hormonal evaluation
- Follicle-stimulating hormone (FSH)/luteinizing hormone (LH)
  - Serum prolactin
  - Plasma testosterone
  - Dehydroepiandrosterone
  - Thyroid-stimulating hormone (TSH) and T3, T4
  - Serum progesterone
  - Estradiol.
  - The hormonal tests must be done at an appropriate time of the menstrual cycle.

**Examination (Table 2)**

- General hirsutism
  - Thyroid swelling
  - Secondary sex characters: Breast development, axillary/ pubic hair (See Tanner staging of breast and pubic hair in Table 3).
- Abdominal: Lumps, tumors, hematometra, enlarged uterus
- Local perineal region
  - Clitoris, vulva, hymen: Bulge or partially imperforate
  - Vagina absent/dimple
  - Pelvic examination (PV) in secondary amenorrhea.

**X-ray**

Chest and bone age.

**Ultrasoundography**

The availability of ultrasonography (USG) has become the most important diagnostic tool, especially in young girls where Pap smears (PS)/PV examination is difficult. Also in obese patients where assessment of uterus and adnexae are difficult. It also helps in assessing tumors in pelvic region.
Flow chart 2: Investigations of primary amenorrhea

Primary amenorrhea

- Normal secondary sex characteristics
  - Pelvic ultrasonography
    - Uterus absent
      - Karyotype
        - 46, XX: Müllerian agenesis
        - 46, XY: Androgen insensitivity syndrome
    - Uterus present
      - Outflow tract obstruction
      - Normal anatomy
        - FSH/LH/Prolactin estimation
          - Normal
            - Hyperthalmic
            - PCOS
            - Resistant ovary
            - Hyperprolactinemia
          - Elevated LH:FSH
          - FSH↑, LH↑
          - Prolactin↑
          - Normal
          - FSH/LH
            - Low
              - Hypogonadotropic hypogonadism
            - High
              - Karyotype
                - 46, XX
                  - Primary ovarian failure
                  - Resistant ovary
                  - Gonadal agenesis
                - 46, XY
                  - Androgen insensitivity, testicular feminization syndrome
              - Karyotype
                - 45, XO
                - 45, XO/46, XX
                - 45, XO/46 XY
              - Hypothalamo-pituitary dysfunction—intracranial lesion
            - Short
              - FSH/LH

- Poor or absent secondary sex characteristics
  - Height

46
### Table 2: Diagnosis based on clinical examination

<table>
<thead>
<tr>
<th>Physical appearance</th>
<th>External genitalia</th>
<th>Internal genitalia</th>
<th>Probable diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Secondary sex characters—present</td>
<td>Normal</td>
<td>Absence of vagina</td>
<td>Müllerian agenesis</td>
</tr>
<tr>
<td>– Normal breast development</td>
<td>Normal</td>
<td>Absence of uterus</td>
<td></td>
</tr>
<tr>
<td>– Normal sexual hair</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Average stature</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Secondary sex characters present</td>
<td>Normal</td>
<td>Normal</td>
<td>• Unresponsive endometrium (rare)</td>
</tr>
<tr>
<td>– Normal breast development</td>
<td>Normal</td>
<td>Normal</td>
<td>• Uterine synechiae (rare)</td>
</tr>
<tr>
<td>– Normal sexual hair</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Average stature</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Poor breast development</td>
<td>Underdeveloped</td>
<td>Underdeveloped</td>
<td>Hypogonadotropic hypogonadism</td>
</tr>
<tr>
<td>– Scanty pubic hair</td>
<td>(vaginal rugosity absent)</td>
<td>(vaginal rugosity absent)</td>
<td></td>
</tr>
<tr>
<td>– Average stature</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Tall and lanky</td>
<td>Underdeveloped</td>
<td>Underdeveloped</td>
<td>Primary ovarian failure</td>
</tr>
<tr>
<td>– Poor secondary sex characters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Stature-short</td>
<td>Underdeveloped</td>
<td>Underdeveloped</td>
<td>Turner’s syndrome</td>
</tr>
<tr>
<td>– Webbing of the neck and cubitus valgus present</td>
<td>‘Streak’ gonads</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Phenotypically female</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average height</td>
<td>Normal</td>
<td>Bilateral ‘streak’ gonads</td>
<td>Pure gonadal dysgenesis</td>
</tr>
<tr>
<td>Delayed secondary sex characters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Normal breast development without areolar pigmentation</td>
<td>Labial or inguinal gonads</td>
<td>Short blind vagina</td>
<td>Androgen insensitivity syndrome (testicular feminization)</td>
</tr>
<tr>
<td>– Scanty pubic and axillary hair</td>
<td></td>
<td>Absence of uterus</td>
<td></td>
</tr>
<tr>
<td>Average stature</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Normal phenotypically female</td>
<td>Labial fusion</td>
<td>Normal</td>
<td>Androgen genital syndrome (late onset)</td>
</tr>
<tr>
<td>– Average stature</td>
<td>Enlargement of clitoris</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Features of hypogonadism</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Dwarf</td>
<td>Underdeveloped</td>
<td>Underdeveloped</td>
<td>• Cretinism due to hypothyroidism</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Hypothalamo-pituitary dysfunction (rare)</td>
</tr>
<tr>
<td>– Mental retardation</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Progesterone Challenge Test

Progesterone tablets are given after blood is given for hormonal evaluation and USG is done. Usually, 5 mg tablet is given twice a day for 5 days in a patient who has amenorrhea for more than 6–8 weeks. Withdrawal bleeding will occur within 7 days if patient has enough estrogen. Then again it must be repeated from day 20th of the cycle for a period of 10 days. This should be carried out at least for a minimum period of 6 months. An obese patient must be encouraged to lose weight. If following progesterone there is no withdrawal and patient has enough estrogen then look for a cause in end organ, namely endometrium. Progesterone challenge test per se has not much value. This is because USG gives much more information. Whenever patient has tuberculosis, full anti-Koch’s treatment must be given. It is preferred that this should be done in consultation with a physician.

### E + P Challenge Test

The following are given: Ethinyl estradiol 0.02 mg (lynoral 0.01/0.05 mg) or conjugated estrogen 1.25 mg (premarin 0.625/1.25 mg tabs) daily for 25 days. T medroxyprogesterone acetate (10 mg) daily to be added from day 15 to day 25.
### Table 3: Tanner staging among females

<table>
<thead>
<tr>
<th>Tanner stage</th>
<th>Breast staging</th>
<th>Pubic hair staging</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Prepubertal</td>
<td>Papilla only elevated</td>
<td>Prepubertal; fine, downy hair over the mons</td>
</tr>
<tr>
<td>2. Small mound centered beneath the papilla which is palpable. Increased areolar diameter</td>
<td>Initial growth of sexual hair which is long, straight or slightly curly and somewhat pigmented; often first on the labia</td>
<td></td>
</tr>
<tr>
<td>3. Intermediate-sized breast tissue with further enlargement of breast and areola</td>
<td>Coarser, more pigmented, curly hair spread over the mons</td>
<td></td>
</tr>
<tr>
<td>4. Further growth, often with projection of areola and papilla forming a secondary mound</td>
<td>Hair is adult in type but with smaller distribution than the inverted triangle characteristic of adult females; generally in shape of inverted triangle</td>
<td></td>
</tr>
<tr>
<td>5. Mature, adult breasts</td>
<td>Adult in quantity and type, with extension onto the thighs; generally in shape of inverted triangle</td>
<td></td>
</tr>
<tr>
<td>6. Figures 2A to E describes the Tanner staging for breast development, which is as follows:</td>
<td>Figures 3A to E describes the Tanner staging for development of pubic hair in females, which is as follows:</td>
<td></td>
</tr>
<tr>
<td>A: Prepubertal</td>
<td>A: Prepubertal stage</td>
<td></td>
</tr>
<tr>
<td>B: Development of breast bud</td>
<td>B: Sparse growth of long slightly pigmented hair usually slightly curly mainly along the labia</td>
<td></td>
</tr>
<tr>
<td>C: Enlargement of breast and areola with no separation of the breast contour</td>
<td>C: The hair becomes darker, coarser and curlier and spreads over the junction of the pubes</td>
<td></td>
</tr>
<tr>
<td>D: Projection of areola and papilla to form a secondary mound above the level of the breast</td>
<td>D: The hair spreads covering the pubes</td>
<td></td>
</tr>
<tr>
<td>E: Reccession of the areola to the general contour of the breast with projection of the papilla only.</td>
<td>E: The hair extends to the medial surface of the thighs and is distributed as an inverse triangle.</td>
<td></td>
</tr>
</tbody>
</table>

### Table 4: Special investigations to corroborate clinical diagnosis

<table>
<thead>
<tr>
<th>Probable diagnosis</th>
<th>Investigations</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Müllerian agenesis</td>
<td>• USG</td>
<td>Uterus: absent</td>
</tr>
<tr>
<td></td>
<td>• Laparoscopy</td>
<td>Tubes: present</td>
</tr>
<tr>
<td></td>
<td>• Karyotype</td>
<td>Ovaries: normal</td>
</tr>
<tr>
<td></td>
<td>• IVP</td>
<td>46, XX</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Urinary tract abnormalities (30%)</td>
</tr>
<tr>
<td>Unresponsive endometrium</td>
<td>• Progesterone challenge test</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td>• HSG</td>
<td>Normal uterine cavity</td>
</tr>
<tr>
<td>Uterine synechiai</td>
<td>• Progesterone challenge test</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td>• HSG</td>
<td>Honeycomb appearance</td>
</tr>
<tr>
<td></td>
<td>• Hysteroscopy</td>
<td>Direct visualization</td>
</tr>
<tr>
<td>Tubercular</td>
<td>• Blood: ESR</td>
<td>Raised</td>
</tr>
<tr>
<td></td>
<td>• X-ray: chest</td>
<td>May have positive finding</td>
</tr>
<tr>
<td></td>
<td>• Mantoux test</td>
<td>Positive (usually)</td>
</tr>
<tr>
<td></td>
<td>• Endometrial biopsy</td>
<td>Positive lesion may be detected</td>
</tr>
<tr>
<td>Hypogonadotropic hypogonadism</td>
<td>• Progesterone challenge test</td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td>• Serum gonadotropins</td>
<td>Low &lt; 5 mIU/mL</td>
</tr>
<tr>
<td>Primary ovarian failure</td>
<td>• Karyotype</td>
<td>46, XX</td>
</tr>
<tr>
<td></td>
<td>• Serum gonadotropins</td>
<td>Elevated &gt; 40 mIU/mL</td>
</tr>
<tr>
<td></td>
<td>• Ovarian biopsy (ovaries: small)</td>
<td>Follicle (−) or Follicle (+)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>– Resistant ovarian syndrome</td>
</tr>
<tr>
<td>Turner</td>
<td>• Karyotype</td>
<td>45, XO or 45, XO/46, XX</td>
</tr>
<tr>
<td></td>
<td>• Laparoscopy</td>
<td>‘Streak’ gonads</td>
</tr>
<tr>
<td>Androgen insensitivity syndrome</td>
<td>• Karyotype</td>
<td>46, XY</td>
</tr>
<tr>
<td>Androgenital syndrome</td>
<td>• Gonadal biopsy</td>
<td>Testicular structure</td>
</tr>
<tr>
<td></td>
<td>• Karyotype</td>
<td>46, XX</td>
</tr>
<tr>
<td></td>
<td>• Serum hydroxy-progesterone</td>
<td>Elevated (&gt; 8 ng/mL)</td>
</tr>
<tr>
<td></td>
<td>• Urinary pregnanetriol</td>
<td>Elevated</td>
</tr>
<tr>
<td>Thyroid dysfunction (hypo)</td>
<td>• Serum TSH</td>
<td>Elevated</td>
</tr>
<tr>
<td></td>
<td>• T3, T4</td>
<td>Lowered</td>
</tr>
<tr>
<td>Diabetes</td>
<td>• Blood sugar</td>
<td>Elevated</td>
</tr>
</tbody>
</table>

Abbreviations: TSH, thyroid-stimulating hormone; USG, ultrasonography; IVP, intravenous pyelogram; HSG, hysterosalpingogram; ESR, erythrocyte sedimentation rate
Hormonal Assessment

- Serum FSH, LH, estradiol—if low then the cause lies in the pituitary
- If FSH and LH are low but estrogen is normal then it is delayed puberty
- If FSH, LH are high and estrogen is low then:
  - Go for the bone age. If bone age is lower than chronological age, then wait and watch
  - Do karyotyping to rule out Turner’s syndrome (TS), etc.

Practical Aspects of Management of Primary Amenorrhea

- Firstly, it is important to assess whether it is primary amenorrhea or delayed puberty
  - Ultrasonography must be done to see the pelvic organs. This way one can rule out Müllerian anomalies and absence of ovaries.
  - If the USG is normal then go for general examination to rule out chronic conditions causing delayed puberty (e.g. Koch’s, anemia, worm infestations, thalassemia, renal failure, etc.)

Role of Laparoscopy

Laparoscopy for pubertal problems has a definite place. Mainly to correlate the USG findings confirming the diagnosis.

Many times, young adolescent girls are brought by parents to find out why periods have not started. They do not like to wait and get various tests done, especially karyotyping which takes weeks to get reported. And if they are from out of town, they like to know soon. Thus, we find laparoscopy gives maximum immediate information. Reassurance is an integral part of management, especially to the parents.

MANAGEMENT

The common principles in the management are:

- Identification of underlying diseases like systemic, nutritional, endocrine and cytogenetic. Serious space occupying central nervous system lesions should also be ruled out or diagnosed and treated. Treatment of the primary disease may reverse the process and allow progression of puberty in some of these, for example, bromocriptine therapy for hyperprolactinemia or adequate nutritional management in nutritionally deprived/imbalanced girls. Specialty referrals for specific underlying diseases are advocated.
- Reassurance to the child and her parents regarding anticipated normal pubertal development in cases of combination delay of growth and puberty (CDGP)
• **Short-term therapy** with sex steroids (estrogens) may be needed in girls with CDGP to trigger the onset of puberty
• **Induction and maintenance of puberty**: Late initiation is beneficial in prevention of early epiphyseal closure and thus not compromising final adult height (FAH). However, to avoid psychological embarrassment vis-à-vis their peers, the therapy should be initiated at 13 years of age. The starting dose of ethinyl estradiol is 1–2 mg/day, which is gradually increased every 2–3 months. The addition of progestin should be either on full breast development or when breakthrough bleeding occurs. Girls with permanent hypogonadism will need this sex-steroid therapy till they reach average age of menopause in the population.
• **Growth promoting, potentiating strategies**: Abnormal physical growth like short stature in TS and Prader-Willi syndrome (PWS) or tall stature of Kallmann’s syndrome (KS) and Swyer’s syndrome (SS) can be appropriately managed. Girls with TS and PWS are known to respond to growth-hormone therapy and achieve an increase in FAH. In order to assure maximum height gain, estrogen replacement can be timely added for achieving optimum synergistic action and preventing early epiphyseal closure. In patients of KS and SS, it is important to start estrogen replacement therapy (ERT) well in time to prevent eunuchoid tall stature. Growth-hormone therapy in girls with PWS is not only beneficial for improving stature but also for reducing obesity and increasing lean body mass and exercise capacity.
• **Prevention of osteoporosis**: Adolescence is critical period for bone acquisition, which is dependent upon nutrition, estrogen and lifestyle. Low bone mineral density-osteopenia/osteoporosis can result from either estrogen deprivation (nutritional, systemic cause) or permanent estrogen deficiency due to hypogonadism. Therefore, girls with permanent gonadal failure need ERT not only for maintenance of puberty but also for prevention of osteoporosis.
• **Future fertility**: With current advances in reproductive medicine, the majority of cases of pubertal disorders can be assured of future fertility. Induction of ovulation by gonadotropins in hypogonadotropic hypogonadism, advanced reproductive technology with donor eggs in hypergonadotropic hypogonadism and bromocriptine/transphenoidal surgery in cases of hyperprolactinemia, pituitary adenoma, etc. provide fertility potentiation. Even in girls with Müllerian agenesis, in vitro fertilization programs employing the woman’s own eggs and husband’s sperm can utilize surrogate motherhood.
• **Surgical therapy**: Gonadectomy is indicated in cases of pure (SS) or mixed gonadal dysgenesis as well as in girls with testicular feminization syndrome (TFS). In TFS, it should be done after achieving full breast development. Creation of neovagina is required in cases of TFS and Müllerian agenesis.

**CONCLUSION**

Primary amenorrhea is a symptom of some underlying disease or disorder. In majority of cases, diagnosis of the specific disorder is possible by its clinical expression. Cyto genetic, biochemical, biophysical and interventional diagnostic procedures are necessary only to corroborate the clinical diagnosis and in few cases where the clinical diagnosis remains disputed. Hence, the indications of special investigations should be oriented on the basis of clinical approach. So far as the results of treatment are concerned, only a few of the disorders are curable, majority are crippling in nature, while some may appear life-threatening. Primary amenorrhea due to polycystic ovarian disease, congenital adrenal hyperplasia or transverse septum of vagina with hematocolpos and hematometra (cryptomenorrhea) are curable disorders. Chromosomal anomaly leading to primary amenorrhea is a crippling disease. Intracranial space occupying lesion associated with primary amenorrhea is a life-threatening condition. Hence, early diagnosis and correct counseling may save these young girls from unnecessary expensive investigations and injudicious treatment. Every possible effort must be done to restore menstrual, coital and reproductive functions in such cases.

**REFERENCES**

INTRODUCTION

Puberty is the transition period between childhood and adulthood during which secondary sexual characteristics start developing, menstruation begins and psychosexual outlook of the individual changes.

PUBERTY

Puberty is the rendering of the Latin word *pubertas* meaning, “grown up”.

The Oxford Dictionary defines puberty as—the state of being functionally capable of procreation.\(^1\)

Puberty is the stage of physical maturation in which an individual becomes physiologically capable of sexual reproduction and is defined by WHO as the age between 10 years and 19 years.

Normal puberty starts at 8–12 years in Indian girls and it takes 3–4 years for the completion of the secondary sexual characteristics. The sequence of pubertal events and normal changes are shown in Table 1 and Figure 1 respectively.

FACTORS AFFECTING THE ONSET OF PUBERTY

- Genetic, a major influence
- Nutritional state
- General health
- Geographic location
- Exposure to light
- Psychological state.

Menstruation usually commences after the maximum growth spurt (6–11 cm/year). There is also a relationship between skeletal maturity and onset of menstruation; it is unusual for menstruation to begin before bone age of 12.5 years or after 14.5 years (Sheil and Turner 1997). Typically, the age of menarche is earlier in girls with moderate obesity (up to 30% above ideal body weight), while it is delayed in those with severe malnutrition.\(^2\) However, the increase in body fat to 23.5% from prepubertal 16% is thought to be an important factor influenced by nutrition (Sternlieb and Munan 1972). High level of leptin, a peptide secreted in adipose tissue that circulates in blood and acts on the central nervous system (CNS) regulatory neurons that regulate eating behavior and energy balance, is associated with earlier age of menarche (Matkovic et al. 1997).

Evidence also suggests that pubertal growth acceleration is due to estrogen and concomitant increase in growth hormone production and secondary stimulation of insulin-like growth factor-I levels. The neuroendocrine regulation of puberty is shown in the Flow chart 1.

---

Table 1: Pubertal events

<table>
<thead>
<tr>
<th>Physical feature</th>
<th>Age range (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thelarche</td>
<td>8–13</td>
</tr>
<tr>
<td>Adrenarche</td>
<td>9–13</td>
</tr>
<tr>
<td>Axillary hair</td>
<td>10–14</td>
</tr>
<tr>
<td>Peak height</td>
<td>10–14</td>
</tr>
<tr>
<td>Menarche</td>
<td>11–15 (mean 12.9)</td>
</tr>
<tr>
<td>Mature sexual hair and breasts</td>
<td>14–15</td>
</tr>
</tbody>
</table>

**PREOCIOUS PUBERTY**

If one accepts the mean ±2.5 standard deviations as encompassing the normal range, then pubertal changes before the age of 8 years in girls and 9 years in boys are regarded as precocious. Increased growth is often the first change in precocious puberty. Occasionally, adrenarche, thelarche, and linear growth occur simultaneously and sometimes menarche may be the first sign. The occurrence of menarche is considered precocious when it occurs prior to 10 years of age.

**Classification**

Precocious puberty can be divided into three categories:

1. **Gonadotropin-dependent precocious puberty (GDPP)/isosexual/central precocious puberty (CPP) or true precocious puberty:** This refers to premature awakening and early activation of the hypothalamic-pituitary-gonadal (HPG) axis.

2. **Gonadotropin-independent precocious puberty (GIPP)/heterosexual/peripheral or pseudoprecocious puberty:** Sexual maturation and development of secondary sexual characteristics without maturation of the HPG axis, under the influence of sex steroids, secreted either from the gonads or adrenals and sometimes exogenous steroid ingestion.

3. **Intermediate type of precocious puberty:** It includes tumors that secrete gonadotropin-like substances [human chorionic gonadotropin (hCG)], e.g., dysgerminomas, teratomas, hepatoblastomas, etc. and does not cause activation of HPG axis.

Precocity occurs five times more frequently in girls than boys, and almost three-quarters (80%) of these are idiopathic or constitutional precocity (true sexual precocity); this must be a diagnosis by exclusion with prolonged follow-up in an effort to detect slowly developing lesions of the brain, ovary or adrenal gland.

**Etiological Factors**

1. **Gonadotropin-dependent precocious puberty:**
   a. **Idiopathic or constitutional:**
      i. Familial
      ii. Sporadic
   b. **Central nervous system lesions:**
      i. Hypothalamic tumors—hamartomas, astrocytomas, ependymomas, gliomas, neuroblastomas, craniopharyngioma
      ii. Infection—encephalitis, brain abscess, meningitis, tuberculous or pyogenic
      iii. Head trauma—at birth or accidental
   iv. Congenital defects—hydrocephalus, craniostenosis, third ventricular cysts
   v. Irradiation

2. **Gonadotropin-independent precocious puberty:**
   a. Gonadal tumors or cysts
   b. Adrenal tumors
   c. Endocrinopathies—congenital adrenal hyperplasia (CAH), primary hypothyroidism
   d. McCune-Albright syndrome (MAS)
   e. Accidental ingestion of oral or topical estrogen creams, estrogen-containing cosmetics, anabolic drugs, sex steroids
   f. Aromatase excess syndrome
   g. Peutz-Jeghers syndrome

**Flow chart 1:** Neuroendocrine regulation of puberty

- Pulsatile secretion of GnRH from the hypothalamus
- Nocturnal pulsatile secretion of FSH and LH from the pituitary
- Progressive increase in gonadotropin pulse frequency and amplitude throughout 24 hours
- Follicular development
- Estrogen secretion
- Breast development
- Endometrial stimulation
- Menarche

**Abbreviations:** LH, luteinizing hormone; FSH, follicle-stimulating hormone; GnRH.gonadotropin-releasing hormone; EGF, epidermal growth factor; TGF-α, transforming growth factor-alpha; GABA, gamma-aminobutyric acid; HPG, hypothalamic-pituitary-gonadal.
3. **Intermediate type of precocious puberty:**

Gonadotropin-secreting tumors—teratomas, hepatoblastomas, dysgerminomas, ovarian granulosa cell tumor, arrhenoblastoma, lipid cell tumor, thecoma, etc.

**Pathogenesis and Clinical Features**

**Gonadotropin-dependent precocious puberty:** The exact trigger that causes premature activation of the HPG axis is unknown but the mechanism is believed to be similar to normal puberty viz. reactivation of hypothalamic gonadostat, either idiopathic in nature or caused by CNS lesions or their treatment. History of head injury, tuberculous meningitis or any other CNS lesions or their treatment and/or presence of neurological, visual or behavioral changes may suggest a possible triggering cause.

**Gonadotropin-independent precocious puberty:** Congenital adrenal hyperplasia or tumors of the adrenals secreting androgens can cause heterosexual development in girls. Persistent intermittently recurring ovarian cysts occurring autonomously or secondary to activation of HPG axis can cause GIPP.

McCune-Albright syndrome usually occurs sporadically in the population and is the result of gene mutations and is characterized by pathognomonic hyperpigmented skin lesions (café-au-lait spots) and the bony changes of polyostotic fibrous dysplasia. Unlike GDPP, vaginal bleeding is often the first sign of precocity occurring due to repeated estrogen exposure and withdrawal with ovarian cyst appearance and regression. Primary hypothyroidism leading to increased secretion of follicle-stimulating hormone (FSH) and prolactin besides thyroid-stimulating hormone (TSH) is also known to cause GIPP.

**Diagnosis (Flow chart 2)**

A careful history and thorough physical examination is mandatory, along with the required laboratory work-up which will aid in arriving at a proper diagnosis.

History should include the chronology of pubertal events, associated behavioral changes, drug usage or incidental drug ingestion, symptoms suggestive of or past history of intracranial lesions and symptoms of hypothyroidism. The growth velocity should be plotted on appropriate growth charts (cm/year) to determine growth spurt. A complete systematic examination including palpation for abdominal masses, neurological and endocrinological examination, estimation of visual fields and optic fundi would help...
in diagnosis of the cause. The clinical stage and type of pubertal development by Tanner’s method, the height of the patient, buccal smear (pyknotic nuclei), karyotyping and bone age are the basic investigations. Serum levels of FSH, luteinizing hormone (LH), estradiol, testosterone, TSH, thyroxine will distinguish complete and incomplete types. High-resolution ultrasonography (USG) of the ovaries and computed tomographic images of the adrenal glands will be required if peripheral cause is suspected. In CNS disease, magnetic resonance imaging (MRI) of the brain for imaging the hypothalamo-hypophyseal area is indicated.

Management

Treatment depends on the underlying cause. Objectives for management include:

- To identify a correctable cause, CNS or otherwise and offer its specific management
- To arrest pubertal development
- To suppress linear growth and further acceleration of skeletal maturation
- To prevent sexual abuse and pregnancy
- To offer multidisciplinary care for associated conditions like behavioral problems, obesity, hyperandrogenism, etc.
- Reassurance and counseling to the parents.

Gonadal, adrenal, liver or CNS tumors require surgery and/or subsequent chemo/radiotherapy.

For CAH, glucocorticoid replacement will suppress production leading to precocity.

Thyroid replacement therapy will suppress precocity by suppressing HPG axis in cases of primary hypothyroidism.

McCune-Albright syndrome is independent of gonadotropins and does not respond to gonadotropin-releasing hormone (GnRH) therapy. The syndrome may be associated with hyperthyroidism or Cushing’s syndrome. Treatment includes medical administration of testolactone (40 mg/kg/day) to suppress conversion of testosterone to estrogen and orthopedic management.

Central precocious puberty is gonadotropin-dependent and therapy is directed to suppress its secretion. Treatment includes giving medroxyprogesterone acetate (MPA) (Provera®) in doses of 100–200 mg intramuscular (IM) every 2–4 weeks. Alternatively, cyproterone acetate, a drug with antiandrogenic and antigonadotropic properties, is also used and appears superior to MPA in the treatment of precocious puberty. However, nowadays the mainstay of treatment is the use of LH-releasing hormone (LHRH) analogs. These are administered 0.2–0.3 mg/kg (maximum 7.5 mg) IM every 4 weeks. They downregulate receptors, cause regression of secondary sexual characteristics, cessation of menses, delay short stature by delaying the closure of epiphyses and normalize growth. Dosage given is triptorelin IM every 28 days or buserelin with cyproterone acetate to improve height.

Isolated Manifestations of Precocious Sexual Development

Occasionally, a young patient may be seen with only one manifestation of precocious sexual development. This may be pubic hair only (premature pubarche or adrenarche), breast development only (precocious thelarche) or menstruation only (precocious menarche). The etiology of such changes though not properly understood, represent unusual sensitivity of one end organ to the very low levels of circulating estrogens (and in case of premature pubarche, androgens) in a young girl. Their importance lies in the fact that they may be the first manifestation of true precocious puberty or even of the estrogenic activity of a feminizing ovarian tumor. Full examination and investigation are therefore essential and hormonal assay will usually demonstrate levels appropriate for the chronological age of the child; bone age will similarly correspond to chronological age in most cases. Of these isolated manifestations of secondary sexual development, the most difficult to assess and most potentially serious is vaginal bleeding. A patient with vaginal bleeding during childhood may have:

- Malignant (or rarely benign) genital tract tumor
- A vaginal foreign body
- Precocious puberty of any etiology
- Precocious menarche
- Other vulval or vaginal lesions, e.g. prolapsed urethra, lichen sclerosis or trauma.

Only when all other causes have been excluded and the bleeding is period-like, although not necessarily regular, it can be accepted as being due to premature menarche.

Incomplete forms (isolated thelarche and adrenarche) are usually self-limited and do not require therapy. Periodic follow-up is mandatory to allow early diagnosis of a progressive condition.

RECENT ADVANCES AND CONTROVERSIES

- Lawson Wilkins Pediatric Endocrine Society suggested that the limit for investigations of girls and boys should be lowered to 7 years and 8 years respectively. Girls with either breast development or pubic hair should be evaluated if this occurs before age 7 in white girls and before age 6 in African-American girls.
- Girls with premature adrenarche/pubarche are at risk for polycystic ovary syndrome (PCOS) and its long-term sequelae. The prevalence of overweight and obesity in children in the United States has dramatically increased during the past 20 years and there has been a rise in the incidence of type 2 diabetes in youth.
- Girls with premature pubarche are more likely to develop functional ovarian and adrenal hyperandrogenism.
- Long-acting GnRH therapy is effective in improving the auxological outcome of patients with central isosexual
precocious puberty (CIPP). Maximum benefit is observed in girls with greater bone age advancement treated at a younger age and for a longer duration of treatment.

REFERENCES


Infertility
INTRODUCTION

Infertility is generally defined as the inability of a couple to conceive after 1 year of sexual intercourse without using any contraception. The term infertility is generally used to denote that a couple has reduced chances to conceive as compared to the general population. Fecundity is the rate of conception in the population in a given time period, usually 1 month, and is around 20%. Infertile couples would fall in one of the two following categories:

1. **Subfertile or hypofertile**: Those who have low fecundity, and can conceive without treatment, e.g. idiopathic infertility, oligospermia, mild endometriosis.
2. **Sterile**: Those who can never conceive without treatment, e.g. bilateral tubal block, azoospermia, ovarian failure.

INCIDENCE

The exact incidence of infertility and the distribution of different factors causing it vary among different populations. In general, the incidence is around 8–9%, i.e. one out of every 12 couples will be infertile. The rough distribution of various factors is as follows: male factor (30–40%), ovulatory factor (20–25%), peritoneal factor (15–20%), cervical and immunological factor (5% each) and unexplained infertility (15–20%). The more detailed the investigations higher will be the chances the finding a definite cause and therefore lesser the incidence of unexplained infertility (Figs 1 and 2).

Figs 1A and B: Female causes of infertility
Infertility evaluation is a stressful experience. When a couple visits a clinician, they have a lot of anxiety and many a times hope for a miracle to occur at the very first visit. It is important that the clinician spends enough time with the couple. Infertility treatment is often long-term and hence a good rapport between the couple and clinician is essential. The help of an infertility counselor should be taken if found necessary.

Initiation of an infertility evaluation should be undertaken after 12 menstrual cycles or 1 year of unprotected intercourse, or after 6 menstrual cycles or 6 months of unprotected intercourse for women 35 years old or older. Evaluation should be considered earlier in situations with significant historical factors that could compromise fertility, such as irregular cycles, pelvic inflammatory disease (PID) or previous infertility.

The First Visit (Flow Chart 1)

The clinician should view the couple as a unit and should see them together at least initially. During the first visit, a detailed history of the couple should be elicited. It is helpful if a questionnaire is prepared which includes all the important points. During this visit, all information regarding previous infertility investigations and treatment should be reviewed. The couple should be provided information about the fertile period and should be specifically asked whether they are able to perform intercourse adequately during the fertile period. A careful and complete clinical examination of both the partners should be performed. Many lifestyle factors can be identified in the history and physical examination that can affect fertility (Box 1). These include but are not limited to smoking, alcohol and street drug use, caffeine use, calcium channel blocker use, excess travel limiting optimal coital timing, use of lubricants or douching with coitus, excess hot tub use, and excess exercise. At the first visit, the various investigations that are needed and the reasons why they are needed, should be explained. The sequence of performing the tests, the discomfort, cost and time involved should be discussed. The available therapies and the prognosis should also be discussed.

At the end of the first visit, the clinician should convey to the patient the following:
- A clinical diagnosis, if possible
- Investigation and treatment
- Rough prognosis
- Estimated time and cost involved.

Primary Evaluation

The four primary diagnostic tests to be performed are:
1. Semen analysis
2. Documentation of ovulation
3. Postcoital test
4. Tests for tubal patency.

These should be performed in about 3 months' time and should not be delayed unnecessarily. If the history or clinical examination is suggestive of a specific abnormality, specific tests for that should be carried out earlier, e.g. serum prolactin assay if galactorrhea is present. If any abnormality is found
in a noninvasive diagnostic procedure, that abnormality should be treated before proceeding with the more costly and invasive procedures.

**Semen Analysis**

Semen analysis is a simple but vital investigation for evaluation of the male partner. If performed skillfully and interpreted intelligently, it provides a wide spectrum of information (Flow chart 2).

**Collection and Transport**

The male partner should be provided with clearly written instructions regarding collection and transport. Ideally, the sample should be collected in the privacy of a room near the laboratory. If not, it should be delivered to the laboratory within 30 minutes of collection. The sample should be obtained by masturbation and ejaculated into a properly labeled, clean, wide-mouthed, glass or plastic container. Semen should not be exposed to extremes of temperature before analysis.

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**Box 1: Clinical examination**

- **General examination:**
  - Height, weight, BMI
  - Thyroid-enlargement
  - Breast-tanner stage, galactorrhea
  - Hyperandrogenism-hirsutism, frontal baldness, acne
- **Abdominal examination:**
  - Abdominal mass
  - Hirsutism
- **Gynecological examination:**
  - Pubic hair
  - Vulva clitoromegaly
  - Speculum examination—Müllerian anomalies of vagina and cervix
- **Vaginal infections**
- **Cervicitis:**
  - Bluish nodules (endometriosis)
  - **Bimanual examination:** Size and mobility of uterus, nodules in the pouch of Douglas, adnexal masses.

**Abbreviation:** BMI, body mass index

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**Flow chart 2: Assessment of a male factor through semen analysis**
**Abstinence**

The sample should be collected after a minimum of 48 hours and not longer than 7 days of sexual abstinence. The period of abstinence should be recorded. The period of abstinence has a remarkable influence on spermatozoa concentration and a lesser effect on motility and morphology. Schwartz et al. have found that each day of abstinence increases the sperm count in healthy donors by 13 mill/mL. Motility seems to be much less dependent on abstinence and remains relatively stable, at least within a 5 day period. However, prolonged abstinence will result in the output of aging sperms with resultant decreased motility.

**Number of Tests**

Two semen samples, at least a week apart, should be evaluated initially. If the two results are remarkably different, additional samples should be tested, because marked variation in sperm count may occur within one individual.

**Initial Macroscopic Examination**

This should include appearance, volume, liquefaction, viscosity or consistency and pH.

**Microscopic Examination**

During the initial microscopic investigations of the sample, estimates of motility and concentration of spermatozoa are performed and the presence of cells other than spermatozoa and of agglutination of spermatozoa is determined.

**Sperm Morphology**

Various stains (Papanicolaou’s, Wright’s, etc.) are used to stain smears. 100–200 sperm are examined and clarified according to numerous systems.

**Normal Values**

Assessment of sperm morphology may vary from one laboratory to another. Most andrology laboratories follow the “strict” or the Tygerberg criteria which has been mentioned in the latest World Health Organization (WHO) recommendations. Though it classifies even minor abnormalities as “abnormal sperms”, it has a better correlation with fertilization and pregnancy rates at in vitro fertilization (IVF) and other assisted reproductive technology (ART) procedures (Table 1).

The WHO in 2010 has published revised lower reference limits for semen analyses as described in Table 2.

**Interpretations of Semen Analysis (Table 3)**

Before giving a definite diagnosis, one must remember that:
- Semen analysis does not measure all the functional properties of spermatozoa.
- There is a wide fluctuation in semen quality over a period of time.
- Fertility is a function of both partners.

**Documentation of Ovulation (Flow chart 3)**

The following tests can be used to document the occurrence of ovulation.

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**Table 1: Semen analysis: Normal reference values (WHO, 2000)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal reference values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume</td>
<td>≥ 2.0 mL</td>
</tr>
<tr>
<td>Liquefaction time</td>
<td>Within 60 minutes</td>
</tr>
<tr>
<td>pH</td>
<td>≥ 7.2</td>
</tr>
<tr>
<td>Sperm concentration</td>
<td>≥ 20 million/mL</td>
</tr>
<tr>
<td>Total sperm number</td>
<td>≥ 40 million/jaculate</td>
</tr>
<tr>
<td>Percent motility</td>
<td>≥ 50% (grade A and B) or ≥ 25% grade A (within 60 minutes of ejaculation)</td>
</tr>
<tr>
<td>Normal morphology</td>
<td>15% or 30%</td>
</tr>
<tr>
<td>Vitality</td>
<td>75% or more live sperms</td>
</tr>
<tr>
<td>White blood cells</td>
<td>&lt; 1 million/mL</td>
</tr>
</tbody>
</table>

**Note:** Grade A: Rapid progressive motility; Grade B: Slow or sluggish progressive motility; 30% or 15%, if based on strict morphological criteria.

**Table 2: Revised lower reference limits for semen analyses (WHO, 2010)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Older WHO criteria for being normal</th>
<th>Newer WHO criteria (2010) for being normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume</td>
<td>2–5 mL</td>
<td>1.5 mL</td>
</tr>
<tr>
<td>Sperm concentration</td>
<td>20 million spermatozoa/mL</td>
<td>15 million spermatozoa/mL</td>
</tr>
<tr>
<td>Total sperm number</td>
<td>40 million spermatozoa per ejaculate</td>
<td>39 million spermatozoa per ejaculate</td>
</tr>
<tr>
<td>Morphology</td>
<td>≥ 4%</td>
<td>≥ 4% normal forms (using “strict” Tygerberg method)</td>
</tr>
<tr>
<td>Vitality</td>
<td>75% of more live</td>
<td>58% of more live</td>
</tr>
<tr>
<td>Progressive motility</td>
<td>50%, forward progression</td>
<td>32%</td>
</tr>
</tbody>
</table>

Flow chart 3: Assessment of ovulation

- Basal Body Temperature

Basal body temperature (BBT) recording is a simple and practical method of monitoring the occurrence and timing of ovulation. Temperature is measured every morning (immediately upon awakening and before any activity) for 5 minutes with the regular thermometer or with special thermometers (expensive and not absolutely necessary).

A significant rise in temperature is not noted until 2 days after the luteinizing hormone (LH) peak, coinciding with a rise in peripheral levels of progesterone to greater than 4 ng/mL. Actual ovulation probably occurs on the day prior to the day of temperature elevation. The temperature rise should be sustained for 11–16 days. The temperature ascent is usually preceded by a slight lowering of temperature called "basal temperature nadir". A distinctly biphasic BBT with sustained high phase of approximately 14 days is indicative of ovulation. A flat, monophasic pattern suggests lack of ovulation (Fig. 3).

The advantages of BBT are its simplicity and the possibility of continuous application for many cycles. Its drawbacks are that some women who ovulate have monophasic charts. The time of ovulation predicted by BBT does not always correlate well with LH measurements. Patients also should not become fixated on taking their temperatures. The most significant drawback of BBT is that it conclusively tells you about ovulation only after it has occurred and hence is not always useful during treatment cycles.

Endometrial Biopsy

A reliable assessment of ovulation can be obtained by an endometrial biopsy. Biopsy is usually performed 1 or 2 days before the expected period to document ovulation and also to assess the adequacy of the luteal phase. A single, long, steady aspiration technique should be used, beginning from the top of the uterine fundus, where the hormonal response is the highest. If only a single piece of tissue is removed from the anterior uterine fundal wall, there is little risk of damage to a recently implanted blastocyst. The histology is ready by the criteria outlined by Noyes et al. Using these criteria, experienced pathologists will agree on the same day 25% of the time, and within 2 days, 80% of the time.

The disadvantage of the procedure is that it is invasive and hence cannot be used repetitively. However, when local endometrial pathology (e.g. tuberculosis) is suspected, if provides additional information about the endometrium.
Hormonal Measurements

**Progesterone**: A single serum progesterone level provides indirect evidence of ovulation. The progesterone measurement must be obtained approximately 7 days before menses begin or 7 days after the suspected day of ovulation. A level of 3 ng/mL or more suggests occurrence of ovulation, but the midluteal phase progesterone should preferably be 10 ng/mL. The progesterone level is subject to the variation associated with pulsatile secretion, but more importantly, there is often poor correlation with the histologic state of the endometrium. The consensus of opinion is that a single midluteal phase progesterone level is insufficient evidence upon which to judge the adequacy of the luteal phase (Fig. 4).

**Urinary LH excretion**: LH kits detects midcycle LH surge. To reliably detect the LH surge, testing must be done on a daily basis, generally beginning 2 or 3 days before the surge is expected based on the overall length of the cycle. The first positive test provides all relevant information; there is no value in continued testing. Test should be performed in the late afternoon or early evening (4–10 PM) because LH surge often begins in the early morning hours and are not detected in urine until several hours later. Ovulation generally follows within 14–26 hours after detection of urinary LH surge and almost always within 48 hours. The day after first positive test is generally the one best day for timed intercourse and artificial insemination, when indicated.

**Serial Sonography (Table 4)**

Serial transvaginal sonography is very commonly used to monitor ovulation. Being a simple, noninvasive and relatively inexpensive investigation, it can be used repetitively. It provides information about both the growing follicle and the endometrium. It is also extensively used to monitor the response of ovulation inducing drugs. Documentation of ovulation by sonography is divided into three parts.

<table>
<thead>
<tr>
<th>Table 4: Ultrasonogram versus midluteal progesterone estimation in detecting ovulation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ultrasonogram</strong></td>
</tr>
<tr>
<td>• Number of follicles can be ascertained, hence, USS is a must during ovulation induction</td>
</tr>
<tr>
<td>• Endometrial evaluation and assessment of other pelvic pathologies possible</td>
</tr>
<tr>
<td>• Noninvasive</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

**Abbreviation**: USS, ultrasound scan

1. **Ovary**: Normally several follicles of less than 5 mm are present. By serial sonography ovarian follicular growth is monitored. The recruited follicle grows at a rate of 2 mm/day and ruptures at around 20 mm diameter (14–29 mm). After ovulation dominant follicle regresses in size in 90% cases, but becomes larger in 5–10% cases and sometimes it may become filled with internal echoes. Figure 5 shows laparoscopic view of an ovary with a developing follicle.

2. **Endometrium**: Proliferation of mucosa is observed by serial sonography. In midcycle endometrium is triple lined which is caused by two apposed layers of hypoechoic mucosa. Endometrium of more than 8 mm thickness is satisfactory. In postovulation period stromal edema leads to thicker echogenic endometrium.

3. **Pelvis**: After ovulation a small amount of fluid visible in cul-de-sac.
Tests to Assess Ovarian Reserve

Tests used to assess ovarian reserve are:

- **Day 3 follicle-stimulating hormone (FSH):** Before the rise in FSH levels to menopausal range there will be a rise in the basal FSH at day 3 as an initial event which could give a clue as to whether the woman is reaching the end of ovarian reserve. Basal FSH estimation gives a better prediction of success with IVF, than the age of the woman. Women with day 3 FSH levels more than 15 IU/L is 3.9 times more likely to have an unsuccessful IVF, the specificity being 96% and positive predictive value being 26%.

- **Serum inhibin B:** Inhibin is normally secreted by the granulosa cells of preantral follicles. Inhibin B levels usually rise during the transition from luteal to follicular phase. This increase depends on the number of follicles recruited during the cycle. In one study, it was found that patients with serum inhibin B levels less than 400 pg/mL had significantly less number of follicles than others.

- **Müllerian inhibiting substance (MIS):** It is produced by granulosa cells as well as by the antral and preantral follicles. MIS levels decline with age and becomes undetectable after menopause. As ovarian reserve decreases serum MIS concentration decreases. Hence, serum MIS can also be used as a measure of ovarian reserve.

- **Clomiphene citrate challenge test (CCCT):** It is worthwhile to screen all women who are 30 years and above, women of any age with unexplained infertility and poor responders to ovulation induction with CCCT and day-3 estradiol. 100 mg clomiphene citrate is given for 5 days from day-5 to day-9. Serum FSH and estradiol are measured on day-3 and day-9. The test need to be done only for women with day-3 FSH value more than 10–15 IU/L or estradiol level more than 65 pg/mL. An increase in FSH to 15 IU/L or more can be assumed to be associated with failure to achieve pregnancy. It is important to remember that values of FSH can vary between different laboratories. In women with poor ovarian reserve there is a high incidence of an exaggerated response. This exaggerated response is a better predictor of ovarian reserve than basal FSH.

- In women over 40 years, even a normal test does not ensure adequate ovarian reserve. An abnormal test can definitely be taken as a reason for considering ovum donation. Although an abnormal test indicates poor prognosis it should not be taken as an absolute inability to achieve pregnancy.

- **Antral follicle count:** Antral follicle count and anti-Müllerian hormone estimation were found to be the most significant predictors of poor response to ovarian stimulation during ART.

WHO has classified anovulation into three types:
1. **WHO type I:** Hypothalamic-pituitary failure. Gonadotropins are in the normal or near normal range.
2. **WHO type II:** Hypothalamic-pituitary dysfunction.
3. **WHO type III:** Ovarian failure.

Ovarian hormones regulate the secretion of cervical mucus. Estradiol stimulates the production of copious amounts of watery mucus and progesterone inhibits the secretory activity of epithelial cells. The sperm penetrability of cervical mucus begins at approximately the 9th day of a normal cycle and peaks at ovulation. Sperm penetrability is inhibited within a day or two of ovulation.

The interaction of spermatozoa with the secretions of the female reproductive tract is of critical importance for the survival and functional ability of spermatozoa. Cervical mucus is the only secretion from the female reproductive tract that is readily available for sampling and study. Postcoital test (PCT) gives vital information about coital technique, cervical factor and sperm function.

**Timing**

Postcoital test should be performed as closely as possible to the time of ovulation. The couple should be advised to abstain from sexual intercourse for about 2 days prior to the test. The test should be performed preferably about 6–10 hours after intercourse.

**Technique**

A nonlubricated speculum is inserted into the vagina and a sample of posterior vaginal fornix pool is aspirated with a 1 mL syringe or pipette. With different syringes, samples are obtained from exocervix and endocervix.

**Evaluation of Cervical Mucus**

Five properties of cervical mucus are studied (volume, consistency, ferning, spinnbarkeit, cellularity) and scored from 0 to 3. A score of greater than 10 is indicative of good cervical mucus favoring sperm penetration (Fig. 6).

**Evaluation for Sperms**

- **Vaginal pool sample:** Spermatozoa are usually killed in the vagina within two hours. The purpose of examining the vaginal pool is to ensure that semen has actually been deposited in the vagina.

- **Exocervical sample:** The number of spermatozoa in the exocervix decreases with time elapsed after intercourse. In a normal woman after coitus with a man with good semen quality more than 25 motile sperms per histopathological examination (HPE) are observed. 10 or more sperms/h high power field (HPF) with good motility is considered satisfactory.

- **Endocervical sample:** The number of sperms near internal os increases gradually and reaches a peak approximately 2–3 hours after intercourse. Thereafter, the number
remains relatively constant for up to 24 hours. Presence of more than 10 spermatozoa/HPF with adequate motility is considered normal.

- **Interpretation:** A normal PCT excludes cervical factor and coital problems. However, a negative test may be due to a number of reasons like incorrect timing, ejaculatory or coital problems, etc.

**Tests for Tubal-Pelvic Factor (Flow Chart 4)**

Indications for early testing for tubal patency:
- Secondary infertility
- Previous ectopic
- Previous septic abortion
- History of tubal surgery
- History suggestive of PID or endometriosis.

**Hysterosalpingography**

Hysterosalpingography (HSG) is a radiographic examination of the endocervical canal, endometrial cavity and the lumen of the fallopian tubes using a radiopaque contrast medium.

HSG is performed after cessation of menstruation and prior to the time of expected ovulation, to avoid the possibility of irradiating an unsuspected pregnancy. A mild analgesic-antispasmodic and injection atropine should be given prior to the procedure. Many types of uterine cannula are available; however, no single cannulation technique will be successful in all patients. The examination is performed using image-intensified fluoroscopy to determine injection of appropriate amount of contrast medium. Spot radiographs should be obtained with early filling of uterine cavity and later on after peritoneal spill has occurred (Figs 7 and 8).

Doxycycline or similar antibiotic should be given following the procedure for prophylaxis against infection.

**Sonohysterosalpingography:** It is the natural extension of the technique saline sonography (SSG). It relies on the observation of fluid accumulation in the cul-de-sac as an indication of tubal patency. It provides very good information about intrauterine pathology but provides no information regarding tubal anatomy and may not determine whether one or both tubes are patent. Even with the use of new sonographic contrast media and 3-D sonography in SSG, its results have not equated with the results of HSG.
Endoscopy, laparoscopy and hysteroscopy are the final diagnostic procedures of the primary infertility evaluation. If the HSG is normal, it is usually performed 6 months after the X-ray. It should be performed before the HSG if pelvic pathology is suspected or diagnosed on sonography or in older women who have no time to wait. The findings of laparoscopy agree with those of HSG in about two-thirds of the cases. The advantage of endoscopy is the ability to perform corrective surgery at the same sitting and the patient should be properly counseled about this preoperatively (Fig. 9).

Laparoscopy-hysteroscopy is performed in the mid-proliferative phase of the cycles. A general anesthetic is administered and equipment for operative endoscopy is kept ready. The uterine cavity is systematically examined with the hysteroscope. The cavity size, endometrium, tubal ostia and cervical canal are observed. Any abnormality, e.g. polyp, septum can be removed at the same time. Laparoscopy is performed through a sub-umbilical incision for the optics and at least one additional puncture either in the suprapubic region or in one of the iliac fossa. Systematic evaluation of pelvic viscera is carried out. The ovaries are flipped with an atraumatic forceps and the undersurface examined. Tube testing is carried out by injecting methylene blue through the cervix. Any pelvic pathology that is found and is likely to interfere with fertility is corrected.

**HSG versus laparohysteroscopy:** It is important to understand that both the procedures are not competitive, but complementary to each other. Both have their advantages and disadvantages. Which of the two procedures is to be performed first would depend on:
- Findings of clinical examination
- Suspicion of pelvic pathology
- Clinician’s experience
- Age of patient and duration of infertility
- Availability of operative endoscopy.

**SECONDARY EVALUATION**

If the results of all the four initial tests are normal, following additional tests may be performed.

**Hormonal Profile**

If the history or clinical examination suggests an endocranial problem, e.g. galactorrhea, appropriate hormonal estimation should be done early in the evaluation. As a routine, serum FSH, LH, prolactin and thyroid stimulating hormone (TSH) should be assayed. Serum FSH and LH should be measured on the 2nd or 3rd day of the period. Additional hormonal measurement—testosterone, dehydroepiandrosterone (DHEAS), should be performed if needed.

**Bacteriological Cultures**

Bacteriological cultures are performed if infection is suspected. Samples can be obtained from semen, cervical mucus, endometrial cavity or peritoneal flushings. These are commonly tested for tuberculosis and *Chlamydia*. In many instances it is cheaper to give an empirical course of antibiotics than to resort to expensive bacteriological testing.

**Immunological Tests**

The two commonly performed immunological tests are: (1) MAR test and (2) immunobead fluorescence.

**BASIC TREATMENT OF INFERTILITY**

There is a wide variation in the initial treatment offered to an infertile couple. Quite a few couples conceive when the initial infertility work up is being carried out. If during the
course of evaluation, a specific abnormality is discovered, specific treatment should be offered. A few basic treatment options are:

**Nonspecific Drugs**

A wide variety of drugs are being used empirically, e.g. vitamins, antioxidants, antibiotics, thyroid extract, etc. There are no controlled trials proving their efficacy. Because some pregnancies will always occur in subfertile period during any treatment or for that matter even without treatment, all these drugs are very frequently administered.

**Timed Intercourse**

This forms the first line of basic infertility treatment. Once an approximate time of ovulation has been determined, the couple should be advised to have coitus every 36–48 hours in a period encompassed by 3–4 days prior to and 2 days after expected ovulation. However, rigid adherence to a schedule should not be demanded as this may produce psychological reactions sufficient to inhibit sexual relations. The couple should be properly counseled about the fertilizable life of the sperm and the egg. The sperms retain their ability to fertilize for 24–48 hours and the egg is fertilizable for 12–24 hours. However, the information on human gametes is speculative (Flow chart 5).

**Controlled Ovarian Stimulation**

When properly timed intercourse fails to achieve a pregnancy, mild form of ovarian stimulation is carried out. This increases the number of eggs released in a month, thereby improving the chances of pregnancy. The most common drug used for this is clomiphene citrate.

Clomiphene citrate is a nonsteroidal estrogen capable of interacting with estrogen-receptor-binding proteins in a manner similar to native estrogen. Clomiphene citrate increases gonadotropin-releasing hormone (GnRH) pulse frequency by this action on the hypothalamus. It results in an increase in LH and, to a lesser extent, in FSH. Increased gonadotropins (in effect, FSH) stimulate multiple follicular developments with a consequent rise in serum estrogen concentrations.

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**Flow chart 5: Management algorithm of anovulatory infertility**

Serum FSH, LH, prolactin, TSH

- Decreased FSH and LH
  - Hypothalamic-pituitary causes
    - Y-chromosome component
      - Gonadectomy
      - Premature ovarian failure
        - Look for other autoimmune disorders and treat if other endocrine failures are identified
        - Usually premature ovarian failure is irreversible but rarely spontaneous ovulation can occur
      - Ovum donation to be considered
    - Ovulation induction with pulsatile GnRH/FSH and LH
- Increased FSH and LH (menopausal range)
  - Karyotyping
  - Pituitary imaging MRI
- Increased prolactin
  - Increased TSH
  - Signs of hyperandrogenism
- Normal FSH, normal or raised LH but not in the menopausal range
  - Pituitary adenoma
  - Bromocriptine
  - Exclude other causes of hyperandrogenism like ovarian/adrenal tumor
  - PCOD
  - Ovarian/adrenal tumor
  - Ovulation induction
  - Treat accordingly
Clomiphene citrate is available as scored 50 mg or 25 mg tablets. The recommended starting dose is 50 mg daily for a total of 5 days. When administering clomiphene, three aspects have to be considered: (1) the dosage, (2) onset and (3) duration of treatment.

**Dosage**

There is at the present time no well-defined clinical or laboratory measure to predict clomiphene citrate responsiveness or dose requirement. However, there are certain factors, which guide the clinician in choosing the dose, i.e. the age of patient, body weight, indication for use [anovulation/polycystic ovarian disease (PCOD)/controlled ovarian hyperstimulation] and past history of response to clomiphene.

In general, clomiphene is started at a dose of 50 mg for 5 days. The clomiphene citrate dosage is increased as soon as it becomes apparent that the current dose is ineffective. The dose is then increased in a stepwise manner, 50 mg at a time.

**Onset of Treatment**

Generally, clomiphene citrate is started on the 2nd or 3rd day of the menstrual cycle. However, one can start clomiphene on a particular day depending on various factors: length of the menstrual cycle, indication, past history.

**Duration of Treatment**

A 4–6 month trial to conceive should be allowed without any intervention. Most clomiphene citrate induced conceptions are likely to occur within the first six ovulatory cycles. Long-term use of clomiphene citrate has been linked to the occurrence of ovarian tumor.

When adequate folliculogenesis is achieved with clomiphene, but the midcycle LH surge does not occur, human chorionic gonadotropin (hCG) can be administered in doses varying from 2,000 IU to 10,000 IU. When determining the time of administering hCG, both the follicular size and endometrial thickness should be taken into consideration.

**Results with Clomiphene**

In properly selected patients, 60–70% ovulate and approximately 35–40% become pregnant. The discrepancy between ovulation and pregnancy rate is due to multiple factors: selection of patients, regimen used, monitoring of treatment, presence of associated infertility factors, antiestrogenic action of clomiphene, early pregnancy loss, etc.

Gonadotropin therapy carries remarkable success rate in patients with hypogonadotropic hypogonadism.

In the present ART protocols, the endogenous gonadotropins are suppressed by giving either GnRH agonists or antagonists. The ovary is thus exclusively under the control of exogenous gonadotropins. GnRH analog is administered in a non-pulsatile fashion to cause an initial flare up followed by downregulation of GnRH receptors, thus suppressing the pituitary. In ART, GnRH downregulation is done as a long or luteal downregulation protocol.

GnRH analog is started on day 21 of the previous cycle. GnRH antagonists are administered subcutaneously starting from day 7. The incidence of ovarian hyperstimulation syndrome (OHSS) is less when antagonists are used compared to long protocol.

**Intrauterine Insemination**

Intrauterine insemination (IUI) involves the placement of a prepared fraction of highly motile sperms directly into the uterine cavity. The rationale for the use of IUI is to reduce the effect of factors that may impede the progress of spermatozoa such as vaginal acidity and cervical hostility and to benefit from the deposition of a bolus of concentrated, motile sperm as close as possible to the oocytes. The procedure is being routinely used in management of infertility when 3–6 stimulated cycles with timed intercourse fail to achieve a pregnancy. The procedure is simple, relatively inexpensive and can be used repetitively.

**Steps in Intrauterine Insemination**

- Ovarian stimulation
- Monitoring of follicular growth and endometrial development
- Timing of insemination
- Sperm preparation
- IUI with prepared sperm.

**Results of Intrauterine Insemination**

The results of IUI in terms of pregnancy rates per treatment cycle vary considerably due to heterogeneity of patient population and different ovarian stimulation protocols. The clinical pregnancy rates vary from 10% to 20% per treatment cycle.

**ASSISTED REPRODUCTIVE TECHNOLOGIES**

ARTs include:

- Oocyte retrieval
- In vitro fertilization and embryo transfer (IVF-ET)
- Gamete intrafallopian transfer (GIFT)
- Zygote intrafallopian transfer (ZIFT)
- Tubal embryo transfer (TET)
- Intracytoplasmic sperm injection (ICSI)
- Cryopreserved embryo transfer

GIFT, ZIFT and TET are not practiced at present because of the high success rates of IVF and ICSI.
In Vitro Fertilization (Fig. 10)

In vitro fertilization is one of the most commonly used assisted reproductive technique (ART). It consists of retrieving a preovulatory oocyte from the ovary; fertilizing it with sperm in the laboratory and subsequently transferring the embryo within the endometrial cavity.

CONCLUSION

When a couple unsuccessful in having a desired child seeks medical advice, the role of the physician is to diagnose the cause of infertility and to try to correct the dysfunction. Primary evaluation of the couple should be performed in the shortest possible time, keeping in mind the couples’ anxieties, expectations and finances. A presumptive diagnosis should be arrived at and appropriate treatment initiated. However, if a successful outcome is not achieved over a period of time, generally 6 months to 1 year, the help of an infertility specialist should be sought for, and advanced treatment initiated.

REFERENCES

Induction of Ovulation

INTRODUCTION

Coordinated effects of hypothalamic gonadotropin-releasing hormones (GnRHs), pituitary gonadotropins, ovarian estrogens and follicular response to these effects result in ovulation. Any derangement of the above factors can result in ovarian dysfunction. Today, nearly 30–40% of infertile patients suffer from ovulatory dysfunction. In the past, a woman with an ovulatory dysfunction had little hope of achieving a pregnancy. However, today, if lack of ovulation is the only problem causing infertility, an infertile couple can expect their chances of conceiving to be close to the rate found in the general population.

CLOMIPHENE CITRATE

The principal mechanism of action of clomiphene citrate (CC) is an increase in the release of GnRH from the hypothalamus with a resultant increase in the pituitary follicle-stimulating hormone (FSH) and the luteinizing hormone (LH) secretion. It has been suggested that CC has an antiestrogenic effect at the level of the hypothalamus and an estrogenic effect at the level of the pituitary and ovary, and this results in an increase in fertility.

Patient Selection

Patients with polycystic ovaries, hypothalamic dysfunction, adrenal androgen hyperfunction and post-pill amenorrhea are ideal candidates for clomiphene therapy. Patients with polycystic ovaries are usually extremely sensitive to CC and very often, ovulation induction occurs with less than the usual starting dose. CC therapy has also been used in certain cases of luteal phase defect and in patients who are unable to conceive due to infrequent ovulation. In cases of associated galactorrhea, prolactin which acts as an inhibitor of ovulation would need to be treated with bromocriptine. Clomiphene has not been found to be effective in women who are deficient in estrogens, due to a low pituitary reserve of gonadotropins, and administration of clomiphene is definitely contraindicated in normally ovulating women because of the high risk of ovarian hyperstimulation. The initial rise in FSH is critical for the development of follicles. Once follicular development is initiated, declining levels of FSH will not impede its progress. CC treatment is usually begun on the 2nd day of the menstrual period, as a 50 mg daily dose and continued for 5 days. Basal body temperature charts and transvaginal sonography allow monitoring of follicular growth. Ovulation usually occurs 5–10 days following the last dose of CC. If ovulation does not occur at the 50 mg level, the dose is increased by 50 mg increments up to the 150 mg level. Human chrorionic gonadotropin (hCG), 10,000 IU, is given as a single intramuscular injection to improve the midcycle LH surge and induce ovulation when follicular maturation is maximum as detected by serum estradiol (E2) levels or estimation of follicular size (18–20 mm) by ultrasonography.

Failure of CC may be of two types: (1) a failure to induce ovulation and (2) induction of ovulation but failure to conceive. This may be due to a nonreceptive endometrium, poor cervical mucus or a deficient luteal phase. Extended therapy is recommended for those patients who fail to ovulate. If conception does not occur even after six ovulatory cycles, re-evaluation should be carried out and patients counseled regarding other treatment modalities.
CLOMIPHENE CITRATE-HUMAN MENOPAUSAL GONADOTROPIN (CC-hMG) THERAPY

In this regimen, CC acts at the hypothalamic and pituitary levels and invokes a mild hypersecretion of pituitary gonadotropins. If administered shortly after menstruation begins, CC will stimulate the recruitment of a number of small follicles. The administration of exogenous gonadotropins will then sustain the growth of these follicles. CC is usually given in the dose of 100 mg from D2 to D6 and 150 IU of human menopausal gonadotropin (hMG) added from D5 on alternate days, i.e. D7 and D9. Human chorionic gonadotropin is administered when the follicle size is 18 mm. The best results using this combination are achieved with extensive monitoring of endogenous LH secretion in the late follicular phase. The LH surge is not predictable by follicle size once the leading follicle exceeds 15 mm in diameter, or by the absolute level of estrogen or the rate of estrogen rise. If undetected, this LH surge can lead to ovulation prior to administration of hCG for timing of intercourse or insemination. This untimely LH surge along with relatively low pregnancy rates are the reasons for the lack of popularity of this regimen.

Apart from hMG, CC has also been used in conjunction with bromocriptine or tamoxifen. Though clinical response is sometimes impressive, the effectiveness of these methods has not been established by controlled studies.

GONADOTROPIN THERAPY

Gonadotropins may be selected for therapy in cases of pituitary amenorrhea after remedial causes of pituitary failure have been treated or ruled out. Patients with severe hypothalamic dysfunction or failure, with primary or secondary amenorrhea, anovulation and low or normal levels of endogenous gonadotropins are ideally suitable for gonadotropin therapy.

Content in Gonadotropin

- Purified FSH—less than 1% LH contamination but still 95% protein impurity
- Highly purified FSH—less than 0.1% LH contamination 4% impurity
- Highly purified hMG—mixture of FSH, LH
- Recombinant gonadotropin—high purity and specific activity
- Unlimited supply with batch consistency complete
- Absence of contamination by the other gonadotropin.

Administration and Dosages

Human menopausal gonadotropin is administered as a daily intramuscular dose of 130–225 IU. The response to gonadotropin therapy depends on the number of antral follicles that are ready. There is however considerable variation in the response of the ovaries to exogenous gonadotropins and it is therefore illogical to set a uniform dose regimen. The dose is always adjusted to suit individual needs and therefore thorough monitoring with ultrasonography and measurement of E2, LH and progesterone levels is essential.

In cases of polycystic ovarian disease (PCOD), the starting dose should be 75 IU of purified FSH and increase in dosage should not be more than 37.5 IU. In other cases, larger doses up to 150 IU may be used. Some studies show that an excess of LH in the follicular phase decreases the chances of conception. It has been suggested that a high concentration of LH through the follicular phase allows a developing oocyte to mature prematurely producing at ovulation an oocyte that is physiologically aged. Such oocytes may have a decreased capacity to fertilize, if they fertilize the embryo it is unlikely to implant, and if it implants, the survival rate is decreased and early abortion may result.

An excess of LH has also been known to increase the chances of ovarian hyperstimulation syndrome (OHSS). It is believed that there is no necessity for exogenous LH to help obtain ovulation since endogenous LH levels seem to suffice. Hence, administration of exogenous pure FSH may help correct any LH:FSH imbalance and bring about ovulation. At our center, the use of pure FSH is always preferred over hMG in women with PCOD, though most studies have found no benefit over hMG from the use of FSH alone, in ovulation induction.

Highly Purified FSH

Recent technical advances have led to the production of highly purified FSH (Metrodin HP) leading to redesigning of ovulation inducing protocols. The advent of this highly purified FSH (9,000 IU FSH/mg protein) has led to more efficient protocols resulting in fewer multiple pregnancies, a lower abortion rate and an even lower risk of OHSS.

Monitoring of Gonadotropin Administration

As mentioned earlier, it is impossible to set a uniform dose regimen since response to therapy varies from one individual to another. Hence, the need for stringent monitoring of the ovarian cycle is a must.

- Ultrasonography: Monitoring by ultrasonography may be started by the 5th day after start of therapy and continued on alternate days till day 9 after which it is performed daily to ensure the growth of follicles and to avoid OHSS. If by the 6th day, no growing follicles are seen, the dosage may be increased. When the dominant follicles reach a size of about 16–18 mm and the endometrial thickness is at least 8 mm, hCG may be administered to induce ovulation. Depending on the number (> 8) of smaller follicles (10–14 mm), it may be necessary to decide whether hCG is required or not, barring which the patient may go into hyperstimulation.

- Estradiol secretion: Follicular function can be gauged by monitoring serum E2 levels along with ultrasound. When
gonadotropin therapy is effective, baseline E2 is enhanced
and this can be seen through E2 assays.

- **Luteinizing hormone**: High LH levels around day 7 and 8
  are a strong predictor of reduced chances of conception.
- **Progesterone**: Serum progesterone levels are raised in the
  midluteal phase and give an indication of the ovulatory
  response. The contribution of smaller follicles stimulated
  by gonadotropin administration should also be taken
  into account. In assisted reproductive technology (ART),
  gonadotropin therapy should only be employed by
  trained gynecologists with experience in dealing with
  ovarian hyperstimulation. A combination of transvaginal
  sonography and hormonal monitoring helps in improving
  the safety and efficacy of ovulation induction.

### GONADOTROPIN-RELEASING HORMONE AGONISTS

A hypothalamic factor which controls the release of LH and
FSH from the pituitary gland was first postulated in 1955.
The natural peptide LH-releasing hormone (LHRH) was
isolated and chemically characterized many years later.
Modification of the native GnRH molecule produced analogs
which were protected from rapid enzymatic degradation
without loss of biological activity, thus imparting them with
longer half-life. Initial exposure to gonadotropin-releasing
hormone agonist (GnRHa) leads to a massive release of
pituitary gonadotropins. Continuous administration leads to
a decrease in pituitary gonadotropin receptor numbers and
consequently a decrease in pituitary sensitivity to further
stimulation leading to a fall in circulating gonadotropin levels.
The LH surge is thus suppressed. After cessation of GnRHa
administration, normal pituitary function is only recovered as
de novo receptor synthesis occurs.

### GnRHa Protocols

To prevent the premature or unpredictable LH surge
associated with the earlier stimulation protocols, routine
gonadotropin suppression by GnRHa has been advocated by
most ART teams.\(^{11}\)

Currently, three types of protocols are followed for
ovulation induction:

1. **Ultrashort regime**: In this regime, GnRHa treatment is
   restricted to the first 3–7 days of the ovarian stimulation
   cycle. Exposure to GnRHa from D2 to D4 of the menstrual
   cycle is followed by exposure to high doses of exogenous
   gonadotropins.

2. **Short regime**: In this regime, GnRHa and gonadotropins
   are administered simultaneously from the early follicular
   phase (D2 or D3) until the administration of hCG.

3. **Long regime**: GnRHa is started from the midluteal phase
   of the cycle prior to the treatment cycle for pituitary desensi-
   tization (downregulation) before initiating gonadotropin
   stimulation. Once desensitization is achieved a mainte-
   nance dose of GnRHa is continued preventing an LH
   surge resulting in ovarian quiescence and suppression of
   circulating hormones. Monitoring of endocrine levels
   and regular ultrasound examination should be carried
   out to assess the degree of downregulation. Adequate
   superovulation can be achieved by the daily administration
   of 150–250 IU of gonadotropins, once downregulation is
   achieved.

Most investigators advocate the superiority of the
long regime over other shorter regimes in spite of higher
requirement of exogenous gonadotropins and the longer
duration of treatment.\(^{12-14}\) At our center as well, we have
a better ongoing pregnancy rate with the long regime and it is
therefore currently the protocol of choice.

Some studies have shown that controlled ovarian
hyperstimulation (COH) with CC/hMG followed by a single
administration of GnRHa instead of hCG results in sufficient
increase in serum LH and FSH to complete follicular
maturation and induce ovulation. Thus, GnRHa has been
advocated by some investigators as an alternative to hCG for
triggering ovulation.\(^{15,16}\)

#### Advantages of GnRHa

- Prevents premature or unpredictable LH surge
- Reduced cycle cancelation
- Decrease in the incidence of OHSS
- Number of poor responders reduced
- Better oocyte recovery
- Higher pregnancy rates.

#### Disadvantages of GnRHa

- Greater total requirement of exogenous gonadotropins
- Increased cost of treatment
- Longer treatment time
- More inconvenience.

Studies also show that stimulation with CC+ recombinant
FSH (rFSH) + recombinant LH leads to comparable pregnancy
rates versus the long protocol. With this new stimulation,
less gonadotropins are used and there are less need for
monitoring (lower cost for patient and clinic). The risk of
OHSS is reduced as well. Therefore, this protocol can also be
recommended as the first-line treatment before resorting to
routine gonadotropin suppression.\(^{17}\)

However, the benefits of pituitary desensitization in COH
far outweigh the disadvantages due to additional costs and
inconvenience and hence it has become one of the most
widely used methods for COH.

### New Frontiers in Superovulation

Certain new drugs have become available in recent years
opening up new vistas in the field of ART.
GnRH Antagonists

In recent times, there has been the development of potential 3rd generation GnRH antagonists which will possibly allow greater degree of flexibility in patient scheduling and therefore provide a viable alternative method of stimulation. GnRH antagonists act as suppressors of gonadotropins, particularly LH, and have all the distinct advantages of GnRHs without the disadvantage of the initial flare up phase prior to suppression. The antagonists bind competitively with GnRH receptors, thereby preventing the native GnRH from exerting its stimulatory effect on the pituitary cells and so avoiding any flare up. Though GnRH antagonist activity was discovered quite some time back, their use was hindered due to a short biological life, low potency and marked histamine release effects. However, new, potent and safer 3rd generation antagonists have now become available. Nal-Lys (antide), cetrorelix and ganirelix are GnRH antagonists which have been found to be effective in instantaneously suppressing gonadotropin secretion. Studies show that GnRH antagonists could replace GnRHs in controlled ovarian stimulation without their side effects and their long desensitization period. Comparison between the mechanism of action of GnRHs and antagonists is shown in Table 1.

The advantage of long protocol are as follows:
1. Better pregnancy rate
2. Premature LH surge is prevented; stimulation is under physician’s control.

The disadvantage of long protocol are as follows:
1. Extended treatment period for pituitary suppression
2. Higher dose of gonadotropin needed
3. Suppression of gonadotropin persists for 10–12 days even after stopping agonist so corpus luteum function is impaired; luteal phase support is mandatory
4. GnRHs may be associated with side effects related to hormonal depletion.

Advantages of Antagonist

In long protocol, normal cycle is switched off – but in antagonist cycle endogenous gonadotropin is maximally used. So, lower number of gonadotropin ampules are needed
1. With antagonist at least with cetrorelix OHSS is reduced
2. No flare effect
3. Cyst formation is lower
4. Mainly used to prevent premature LH surge
5. Ovulation triggering with GnRHa is possible in patients at risk of OHSS.

Disadvantages of Antagonist

Pregnancy rate is reduced especially in ganirelix
Although no effect on oocyte, embryo but direct effect on endometrium cannot be excluded
Timing of oocyte retrieval is not in clinical control.

There are two protocols:
1. Fixed protocol in which antagonist is started on 6th day.
2. Flexible protocol—antagonist started when follicle reaches 14 mm.

Recent meta-analysis has confirmed that fixed protocol yields better pregnancy rate.

Two protocols for administration have been described:
1. Protocol I or multidose protocol: This is also called the Lubeck protocol. COH is carried out with hMG starting on D2 of the menstrual cycle. Antagonist in the form of a daily injection of 0.25 mg/day is started from D6 or D7 or after the follicle size reaches 14 mm until the day prior to ovulation. The amount of hMG needed is comparable to ultrashort protocol of GnRHa which is the least expensive treatment.
2. Protocol II or single dose protocol: This is also called the French protocol. In this, a single dose of 2 or 3 mg of antagonist is administered on D8 or D9 of the cycle or when the serum E2 level is around 550–750 pmol/L and the follicular size greater than 14 mm.

GnRH antagonists and GnRHas provide comparable results in unselected patients, while GnRH antagonists allow a higher flexibility in treatment. The use of GnRH antagonists will prove to have extremely beneficial effects—reduced requirement of exogenous gonadotropins, greater degree of flexibility in stimulation protocols, less time consuming, reduced risk of OHSS and decreased cost of IVF are some of the advantages of GnRH antagonists. However, as yet, the use of antagonists is restricted to a few clinics, since their efficacy and safety have to be proved in long-term studies.

Recombinant FSH

Recombinant FSH is highly purified FSH without any trace of LH activity. It has the same biological property as natural FSH and does not contain any protein contamination as present in FSH isolated from urine of menopausal women. There are two types of rFSH available: (1) follitropin alpha (Gonal F) and (2) follitropin beta (Puregon), but there is no evidence as yet of the superiority of one over the other. However, there are significant advantages of rFSH over Metrodin (pure

<table>
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<th>Table 1: Mechanism of action</th>
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<td><strong>GnRH antagonist</strong></td>
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<tr>
<td>• Receptor blockade without receptor activation</td>
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<tr>
<td>• Competitive inhibition</td>
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<tr>
<td>• Immediate and dose dependent suppression</td>
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<td>• Rapid reversibility</td>
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Following a logical ovulation induction protocol. In some cases, a cost-effective therapy can only be achieved if this decision is correct. Although empirical use of ovulation-inducing regimens has yielded positive results in safe only if this decision is correct. Although empirical use of ovulation-inducing regimens has yielded positive results in

A wide range of cycle regulating and ovulation-inducing drugs are available these days, requiring decisions as to the type of therapy each patient should receive, based on safety, efficacy and cost. Treatment will be reasonably successful and safe only if this decision is correct. Although empirical use of ovulation-inducing regimens has yielded positive results in

### Biosynthetic Human Growth Hormone

Biosynthetic human growth hormone (hGH or GH) acts by stimulating the production of insulin-like growth factor 1 (IGF-1) thus amplifying gonadotropin action. The quantity of exogenous gonadotropins required is therefore considerably reduced. Its use has been suggested in poor responders, however more controlled studies are required to prove its efficacy in terms of pregnancy rates and given the expense of GH, available data does not support the routine use of GH for ovulation induction.

### What is the Optimal Protocol?

A meta-analysis of all randomized controlled trials from 1985 to 1999 concluded that FSH only protocols yielded better pregnancy rate than hMG when GnRH agonists are used. After thorough review of the current literature, it has been concluded that urinary and recombinant gonadotropins are probably equally safe and effective with the respect to the value of adding LH to FSH in the stimulation regimens; data is conflicting in the current literature. The use of GnRH of varying potency and antagonist account for different degrees of LH suppression and probably explains the need for LH in severely suppressed endogenous LH situation as with the use of potent GnRH before gonadotropin stimulation or when GnRH antagonists are introduced during the course of stimulation. The potential benefit of hCG/LH on implantation is intriguing and worthy of further investigation.

In conclusion, the optimal stimulation protocol is one that maximizes the recruitment of fertilizable oocytes and minimizes the risks and is administered and monitored in an acceptable and friendly manner to the patient.

### CONCLUSION

A wide range of cycle regulating and ovulation-inducing drugs are available these days, requiring decisions as to the type of therapy each patient should receive, based on safety, efficacy and cost. Treatment will be reasonably successful and safe only if this decision is correct. Although empirical use of ovulation-inducing regimens has yielded positive results in some cases, a cost-effective therapy can only be achieved following a logical ovulation induction protocol.

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INTRODUCTION

For most women, the occurrence of regular menses is something that is often taken for granted. The absence of the same has profound physiological and psychological ramifications, which include effects of the estrogen depleted state.

At 4 weeks germ cells arise from the yolk sac and migrate along the hind gut to genital ridge. Oogonia are able to move by pseudopodial ameboid movement. Once they reach the genital ridge, they become associated with cortical cords and lose their motility.

Till 28 weeks oogonia undergo mitotic division, some oogonia are lost by atresia. Primary oocyte enters into meiosis. Meiosis starts at 9 weeks but first meiotic division arrested in the diplotene stage of prophase.

Meiosis is regulated by two substances, meiosis inducing substance and meiosis inhibiting substance secreted by granulose cells. So final stage of oocyte number is determined by three factors:
1. Maximum number achieved by mitotic division
2. The time at which they enter meiosis thereby preventing further increase in number
3. Rate of atresia

At 5 weeks: 2,000 germ cells migrate to gonadal ridge
Maximum number of follicles at 20 weeks is 7 million and at birth it is 2 million. Around 14 years the number of follicles in the ovary is reduced to quarter million.

When women reaches above the age of 50 years there is almost no oocyte in ovaries. Menopause occurs when there are approximately 1,000 follicles left in the ovary.

A woman usually reaches menopause somewhere between the ages of 45 years and 55 years. Currently, the average age at menopause is said to be around 51 years, a fact that may be attributed to the improving quality of life over the last few decades.1,2 The loss of ovarian function is characterized by elevated serum gonadotropin levels and low serum estrogen levels. Menopause is said to be premature when the ovarian failure occurs before 40 years of age.2 The fine discrimination between premature menopause and premature ovarian failure (POF) must be acknowledged, as this will be important in diagnosis and management of the patient.

MENOPAUSE

Literally means the cessation of menses. It is defined as the permanent absence of menses resulting from the loss of ovarian function—characterized by depletion of follicles in the ovary, elevated serum gonadotropins and low serum estradiol levels. This may occur anywhere between 45 years and 55 years of age. Premature menopause is when the menopause occurs between 41 years and 45 years of age, while POF is when the ovarian failure occurs before 40 years of age (Table 1).

INCIDENCE

Amenorrhea in the reproductive age groups is very common, varying between 1.8% and 3%,4 and occurring in up to 20% of women complaining of infertility.5 Primary ovarian insufficiency (POI)/POF occurs in approximately 1% of women.6,7 The estimated incidence in the United States in 1 case per 1,000 women by age 30, 1 case per 250 women by age 35 and 1 case per 100 women by age 40. Approximately, 10–28% of women with primary amenorrhea and 4–18% with secondary amenorrhea have POI/POF.

DEFINITION

As defined by the World Health Organization (WHO), ovarian insufficiency can be caused by a primary disorder in the ovary or it can occur as a result of secondary causes. Ovarian insufficiency is considered primary, if the ovary
fails to function normally in response to appropriate gonadotropin stimulation provided by the hypothalamus and pituitary. Ovarian insufficiency is considered secondary, if the hypothalamus and pituitary fail to provide appropriate gonadotropin stimulation. POI (POF, premature menopause or early menopause) is condition characterized by amenorrhea, hypoestrogenism, and elevated serum gonadotropin levels in women younger than 40 years. Although often used as synonyms, POI and menopause are not equivalent. Most women with POI retain intermittent ovarian function for many years, and unlike women who are menopausal pregnancies may occur.

**CLASSIFICATION**

The classification of POF (Table 2) is based upon the chromosomal status or on the degree of development of the secondary sexual characteristics.

Chromosomally, competent ovarian failure is a condition where the chromosomal status is essentially normal, i.e. an euploid state, while a chromosomally incompetent ovarian failure is characterized by an aneuploid state, some degree of chromosomal aberration will always be seen. Depending on the degree of development of the secondary sexual characteristics, POF may be associated with a complete absence, which is associated usually with primary amenorrhea or in the presence of some degree of development of secondary sexual characteristics associated with secondary amenorrhea (Tables 3 and 4).

**ETIOLOGY**

The etiology of POF encompasses a variety of clinical conditions. Though, in a majority of women the cause is usually unknown or is more often genetic, some of the causes of POF are listed in the Table 5. Another fairly common cause of POF is autoimmunity. Studies show that almost 80–92% of women with POF have tested positive for autoantibodies, though only about 20% have actually been found to have symptoms and signs of immunological dysfunction, usually thyroid disorders.

Autosomal recessive disorders associated with POI/POF:
- Cockayne syndrome
- Nijmegen breakage syndrome
- Werner syndrome
- Bloom syndrome.

**PATHOGENESIS**

Premature ovarian failure is a unique example of isolated organ senescence. Absence of or the presence of defective oocytes results in the failure of the ovary as an endocrine organ, leading to the various sequelae associated with this condition. The mechanisms of pathogenesis have been listed in the Table 6. In addition, there are certain conditions where the process has been described clearly. For example, in galactosemia, characterized by the deficiency of galactose-1-uridyltransferase, the resultant defect in carbohydrate metabolism produces gonadotropins with abnormal structures. Also, galactose metabolites can cause premature destruction of ovarian follicles.
Premature Ovarian Failure

Mumps

Effect is maximal during fetal or pubertal periods when even a subclinical infection can result in ovarian failure.

Resistant Ovary Syndrome

Patients with resistant ovary syndrome manifest with primary amenorrhea, and normal secondary sexual characters.

Reason may be the following:
- Gonadotropins is not bioactive
- Receptor/postreceptor defect
- Antibodies preventing binding of follicle-stimulating hormone (FSH)

Genetic Causes of POF

Turner’s Syndrome

Two active X chromosomes are needed during fetal life to maintain normal follicular store. Ninety-nine percent of conception with 45 XO ends up in abortion. One percent account for Turner’s syndrome. Incidence of Turner’s syndrome is 1 in 5,000 live born girls. Spontaneous puberty is possible in 10–20% of Turner’s mosaics. Spontaneous menstruation is possible in 5% of Turner’s mosaics. Children born to a Turner have increased incidence of Down’s syndrome, spina bifida, congenital heart disease, etc. Even if a Turner conceives with donor egg program, there is increased risk of dissection, and rupture of aorta.

Fragile X Syndrome

This is due to mutation in a gene on the long arm of X chromosome. It is X-linked dominant disorder with decreased penetrance.

Autoimmune Causes of POF

Autosomal recessive disorder associated with polyglandular autoimmune syndrome.

Type 1 associated with hypoparathyroidism, celiac disease, Addison’s disease. It is due to mutation in a gene located in chromosome 21q22.

Type 2 associated with thyroid disease, type 1 DM, Addison’s disease.

Premature ovarian failure is irreversible except autoimmune causes of POF, gonadotropin-releasing hormone (GnRH).

CLINICAL MANIFESTATIONS

A woman with POF may present with different symptoms, including those due to the underlying cause.

The first and most common symptom is the acute onset of hot flashes, followed by other symptoms of estrogen deficiency including night sweats, depression, anxiety, mood swings, decreased libido and dyspareunia. She may also present with amenorrhea, primary or secondary. More recent studies have however shown that disturbance of menstrual function is by far the most common and one of the earliest indications of an incipient ovarian failure.

The presence or absence of secondary sexual characteristics depends upon the time of onset of the gonadal failure. Onset early in life may not allow for the development of secondary sexual characteristics, while if the ovarian failure is of a relatively later onset, the secondary sexual characteristics would have already been developed by them.
Other positive findings which would basically indicate estrogen deficiency include, dry vagina/vaginitis, vulvar dystrophy, stress incontinence, etc.

**LONG-TERM CONSEQUENCES**

Women with premature loss of ovarian function, have been found to be at an increased risk of developing the adverse sequelae of estrogen deficiency, cardiovascular disease and osteoporosis (Table 7).

**INVESTIGATIONS**

Investigations in a patient with suspected POF must be aimed at not only confirming/establishing the diagnosis, but also at detecting the underlying cause.

Elevated serum gonadotropins and low serum estradiol form the basis of identifying the presence of POF (Table 8). However, they must be measured on at least two occasions before a definitive diagnosis. Other tests include a chromosomal karyotyping and a pelvic ultrasound (Table 9).

Though ovarian biopsy had been advocated a few decades ago, the current thinking is that since the diagnosis may be established by blood tests, it is better to give empirical therapy than to subject the woman to surgery/anesthesia and their complications.

As autoimmunity is an important cause, tests to identify various autoimmune disorders have been listed in Table 10.

**REDUCED OVARIAN RESERVE**

By definition, a reduced ovarian reserve is the difficulty to produce oocytes with a capacity of becoming living embryos after fertilization.

This is especially important as today more women are voluntarily opting to delay childbirth. Early identification of a failing ovarian reserve will help these women plan their pregnancies and, hopefully reduce the number of women with POF.

The ovarian reserve is identified by measuring serum gonadotropins, along with serum estradiol in the early follicular phase of the menstrual cycle (day 3). Basal inhibin B levels may also be measured. An ovarian volume of less than 3 is also indicative of a failing ovarian reserve even when the serum gonadotropin values are within normal limits (Table 11).

It has been suggested that every woman over the age of 35 years should have S FSH done at least once a year, for the early identification of a diminishing ovarian reserve.

**DIFFERENTIAL DIAGNOSIS OF POF**

Conditions that may mimic POF are those that are associated with an increased level of gonadotropin, pituitary tumors, small cell carcinoma of the lungs, etc. (Table 12).

**TREATMENT**

Treatment of POF basically involves restoration, preservation or substitution of ovarian function.
To date, there has been no method to restore ovarian function. Preservation of ovarian function has been gaining importance and should be freely available in the near future. Along with this, will come the procedures of ovarian transplantation both auto and xeno.

Today, the foundation for the management of POF is to substitute ovarian function with drugs, hormone replacement therapy.

A healthy lifestyle and a diet rich in calcium are essential.

Hormone Replacement Therapy

The most important hormone used is estrogen, with the addition of a progestogen. The usual regime is 3 weeks of estrogen with 2 weeks of added progestogen. The common drugs used and their dosages are listed in Table 13.

Cyclic administration of estrogen and progesterone (Table 14) will restore to some extent the hormonal milieu in the body. Addition of progesterone will prevent the complications associated with exogenous estrogen administration, mainly endometrial hyperplasia. These women, however may require higher doses of estrogens when compared to the usual post-menopausal women.

Spontaneous pregnancy rates while the patient is on hormone replacement therapy (HRT) is up to 5–10%. This is because estrogens may activate receptor formation in the follicles, and the high gonadotropin levels may stimulate follicular growth and ovulation.

Androgens

Women with ovarian failure have lower levels of free testosterone compared with normally ovulating age-matched controls, but only 13% have level below the lower limit of normal.

Androgen replacement could be carefully considered for women who have persistant fatigue, low libido, and poor well-being despite adequate estrogen replacement and when depression has been ruled out or adequately treated.

This should be performed with great caution and for relatively short periods until more data are available.

Available medications include oral methyltestosterone 1.25–2.5 mg/d injectable testosterone esters 50 mg every 6 weeks intramuscularly and subcutaneously testosterone pellet implants 50 mg every 3–6 months.

Ovarian Tissue Cryopreservation

While it has been proved that cryopreserved ovarian tissue has the potential to restore fertility, no pregnancies have been reported to date. Current methods of ovarian tissue cryopreservation involve the slow cooling techniques with the use of DMSO and sucrose as cryoprotectants. Today the accepted indications for ovarian tissue cryopreservation include both time-related damage (natural menopause) as well as autogenic ovarian damage (radio/chemotherapy or surgery) and ovarian tissue transplantation.

Pregnancy in POF

Though these women may have attained menopause at an early age, their desire to carry a pregnancy and have a baby is just like any other. Advances in assisted reproduction have proved to be a boon, as more women with this so-called “problem” become pregnant, thus fulfilling their “birthright” for procreation.

Ovulation Induction

The ideal/most successful protocol for controlled ovarian hyperstimulation in women with POF would be to start down regulation with GnRH agonists, followed by stimulation with human menopausal gonadotropin/rFSH and human chorionic gonadotropin. Usually about three cycles of ovulation induction are tried. The maximum success rates are seen in the first and second cycles. If there is no evidence of follicular growth in these three cycles, the patient is then advised to try ovum donation. The prognostic factors for ovulation induction in women with POF are listed in Table 15.

Role of Corticosteroids in POF

Steroids have been proven to be effective in autoimmune ovarian failure, but have no role in idiopathic or any other type of ovarian failure. The success of ovulation induction in autoimmune ovarian failure treated with corticosteroids is about 40%.
Snowdon et al. have shown increased all-cause mortality in POI/POF. In a survey of 19,000 women aged 25–100 years, POI/POF on the mortality rate at older age have not been long-term follow-up studies to evaluate the impact of and they too can lead perfectly normal lives. Let us not write off women with POF. On the other hand, significantly from this.

Apart from these modes of therapy, psychological support is extremely essential and most of these women will benefit significantly from this. Let us not write off women with POF. On the other hand, we should reassure them that their life is by no means over and they too can lead perfectly normal lives.

**MORTALITY/MORBIDITY**

Long-term follow-up studies to evaluate the impact of POI/POF on the mortality rate at older age have not been conducted. In a survey of 19,000 women aged 25–100 years, Snowdon et al. have shown increased all-cause mortality in women who had ovarian failure before age 40 years (age-adjusted odds ratio of death 2.14 [95% CI, 1.15–3.99]) and stroke mortality (odds ratio 3.07 [95% CI, 1.34–7.03]) several points concerning morbidity and mortality of patients with POI/POF are worth considering as follows:

- A long-lasting hypoestrogenic state at a young age may prevent women from achieving and maintaining adequate bone density. This may put them at increased risk for osteoporosis and fractures later in life.
- Women with POI/POF may be at higher risk for cardiovascular disease, again due to low estrogen levels.
- Patients with POI/POF may be more inclined to undertake unproven treatments to restore fertility and, in this way, may be exposed to iatrogenic damage. The authors recently have observed two cases of bone necrosis due to prolonged treatment with corticosteroids in women with POI/POF and presumed but unconfirmed ovarian autoimmunity.
- POI/POF can coexist with other endocrine and nonendocrine disease (e.g. hypothryoidism, Addison disease, type 1 diabetes, pernicious anemia, lupus).
- The diagnosis of POI/POF may have a deleterious psychological impact and may lead to depression in a young otherwise healthy woman.

**REFERENCES**

INTRODUCTION
Infertility is the inability to conceive (reproduce) after at least 1 year of unprotected intercourse. Society has always placed the burden of infertility or “Barrenness” on women, when in reality male factor is now emerging to be the single most contributing factor in more than 50% of couples referred for infertility investigation and treatment in our clinic. Our observations are no different from those reported worldwide. In man, fertility depends upon his ability to deposit adequate number of healthy, mature, functioning sperm into the female reproductive tract, at the time of ovulation. Any hormone disorders, illness, reproductive tract anomaly and obstruction, and sexual dysfunction can temporarily or permanently affect the sperms and prevent conception. In addition, some disorders including immune system and genetic disorders become harder to treat when they persist without treatment. In 15% of male, genetic abnormalities present include chromosome aberrations and single gene mutation. Yet the most common cause of the male infertility is spermatozoa defects and includes, low sperm count, poor motility or lack of linear progression, poor morphology of sperm that lack the ability to attach and penetrate an egg in order to fertilize it.

Palermo introduced an advanced reproductive technique, intracytoplasmic sperm injection (ICSI), in which a single spermatozoa or spermatid is injected into the cytoplasm of an oocyte. This technique has revolutionized the treatment options for male factor infertility. This method bypasses all the biological selectivity and overcomes not only the issue of poor sperm motility and low count, but it has been successful with sperms that were considered less than ideal for an in vitro fertilization (IVF) process. Round-head sperm, those collected directly from the epididymis, testes and those previously cryopreserved, have also been used. For the very first time, men who in the past have been considered hopelessly infertile now have a reasonable chance to be a biological father with the help of ICSI. The impact of this technique has been so profound that many clinics worldwide have abandoned evidence-based medical treatment in favor of ICSI.

PHYSIOLOGY
The male reproductive organs (Fig. 1) are influenced by hormones secreted in the hypothalamus and the pituitary. Gonadotropin releasing hormone (GnRH) is released from the medial basal hypothalamus in a pulsatile pattern, approximately every 70–90 minutes. The half-life of GnRH is 2–5 minutes. GnRH release is inhibited by testosterone and inhibin. Its secretion is also decreased by corticotropin-releasing hormone (CRH) and opiates. This is clinically evident at times of illness and stress, when there is a decreased production of gonadotropins.

Follicle stimulating hormone (FSH) and luteinizing hormone (LH) are glycopeptides secreted by the gonadotrops in the anterior pituitary in response to GnRH secretion. LH acts on the interstitial cells of Leydig to increase steroidogenesis (synthesis and secretion of testosterone and other androgens). LH release is controlled by the feedback of steroids from the testicle. FSH participates in protein synthesis and the initiation of spermatogenesis at the level of the seminiferous tubules in conjunction with testosterone. It stimulates the sertoli cells to secrete inhibin. FSH release is controlled by the feedback of inhibin from the testicle. Androgens at physiological levels do not suppress FSH secretion. LH and FSH also control their own release by negative feedback to the hypothalamus. FSH binds to Leydig cells and increase the number of LH receptors on the cells.

Spermatogenesis (Fig. 2) occurs in the testes at the seminiferous tubules, which form most of the testis. Sertoli cells, which rest on the basement membrane of the
The prostate contributes acid phosphatase, zinc and citric acid. Qualitative fructose is useful for verifying the presence of the vas deferens.

**MALE FERTILITY EVALUATION**

Initial evaluation should be rapid, noninvasive and cost-effective in order to offer evidence-based medical treatment. There is currently no single test to determine whether a man is fertile or infertile, so several tests to examine different aspects of sperm function are usually required. For most men, a detailed medical history, a complete physical examination and a semen analysis will form the major part of the fertility screening and should take into consideration the major male diagnostic categories (Table 1). Men, who feel uncomfortable about the fertility evaluation, should discuss these feelings with their partner and physician. Talking about the anxiety beforehand may make the actual examination much easier. Systemic diseases associated with male infertility have been extensively documented (Table 2).

**Semen Analysis**

The assessment of the conventional semen analysis parameters remains the main laboratory investigation of the male partner of an infertile couple. Because of the natural variation in sperm numbers, a minimum of three samples have to be examined over an interval of 1–3 months according to the procedures described by the World Health Organization and
report based on Kruger’s strict criteria. The results should be interpreted in conjunction with the personal background information of the involved individual. Patients should have an abstinence of 3 days between samples. The normal values established by the World Health Organization, in 2000, have recently been revised and are presented in Table 3. When abnormal semen analysis results are reported in one or more of the 12 categories, the terms used to describe are listed in Table 4.

In addition to the basic semen analysis, many functions of the sperm can be evaluated in the laboratory. The results of these tests are sometimes helpful in determining the likelihood of pregnancy or in selecting treatments (Table 5). Table 6 summarizes the causes of abnormal semen parameters.

**Biochemical Tests of Seminal Plasma**

Contributions to seminal plasma are made in part by secretions from the sexual accessory glands, each with their distinct biochemical constitution, which include acid phosphate, carnitine, citric acid, fructose, glucosidase and zinc. Therefore, these substances can be used as markers for abnormality of the glands and overall effect on the sperm.

**Biochemical Test of Spermatozoa**

These tests can be considered as indirect functional tests of the spermatozoa as they measure substances derived from spermatozoa. These includes acrosin, adenosine triphosphate, chromatin condensation, creatine kinase, hyaluronidase and reactive oxygen species.

### Table 1: Male diagnostic categories

<table>
<thead>
<tr>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sexual and low ejaculatory dysfunction</td>
</tr>
<tr>
<td>Immunological cause</td>
</tr>
<tr>
<td>No demonstrable abnormalities</td>
</tr>
<tr>
<td>Isolated seminal plasma abnormalities</td>
</tr>
<tr>
<td>Iatrogenic cause</td>
</tr>
<tr>
<td>Systemic cause</td>
</tr>
<tr>
<td>Congenital abnormalities</td>
</tr>
<tr>
<td>Testicular maldescent/acquired testicular damage</td>
</tr>
<tr>
<td>Karyotype abnormalities</td>
</tr>
<tr>
<td>Congenital agenesis of the seminal vesicles and low vas deferens (a cause of obstructive azoospermia)</td>
</tr>
</tbody>
</table>

*Other congenital diseases*

- Varicocele (may be acquired)
- Male accessory gland infection (may be acquired)
- Endocrine cause
- Idiopathic oligozoospermia
- Idiopathic asthenozoospermia
- Idiopathic teratozoospermia
- Idiopathic cryptozoospermia
- Obstructive azoospermia
- Idiopathic azoospermia

### Table 2: Diseases associated with male infertility

<table>
<thead>
<tr>
<th>Disease</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Congenital disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Kartagener’s syndrome</td>
<td>Immotile sperm</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>Associated with agenesis of vas deferens and also with secretory disturbance in epididymis</td>
</tr>
<tr>
<td>Androgen receptor deficiency</td>
<td>Lack of development of genitalia</td>
</tr>
<tr>
<td>Prune Belly syndrome</td>
<td>Testicular maldescent</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>Testicular damage</td>
</tr>
<tr>
<td>Testicular maldescent</td>
<td>Testicular damage</td>
</tr>
<tr>
<td>Von-Hippel-Lindau syndrome</td>
<td>Cystadenoma of epididymis</td>
</tr>
</tbody>
</table>

*Acquired disorders*

- Infections
  - Infectious parotitis (mumps)
  - Tuberculosis
  - Bilharziasis
  - Gonorrhea
  - Chlamydial epididymitis
  - Filarialis
  - Typhoid
  - Influenza
  - Undulant fever (Brucellosis)
  - Syphilis
  - Pemphigus foliaceus in South America

- Endocrine disease
  - Hormonal abnormality
    - Testicular failure and ejaculatory disturbance
  - Hormonal abnormality
    - Testicular failure and loss of libido

- Secondary testicular failure
  - Pituitary failure; usually there will also be androgen deficiency

- Chromophobe adenoma
  - Astrocytoma
  - Hamartoma
  - Teratoma
  - Sarcoidosis

*Neurological disease*

- Paraplegia
  - Erectile impotence and disorders of ejaculation; damage to spermatogenesis; damage to accessory sex glands

*Chronic respiratory tract disease*

- Bronchiectasis
  - May be associated with abnormal sperm cilia in the chronic sinusitis immotile cilia syndrome, situs inversus or secretory

- Chronic bronchitis
  - Disturbance in the epididymis such as in Young’s syndrome
In view of the weak association between the usual semen parameters and fertilization potential of given semen sample, biological tests have been developed which evaluate the ability of the spermatozoon to penetrate the oocyte and assess its characteristics in a biological context. These include post coital testing, determination of leukocytospermia, acrosome reaction, hyposmotic swelling test (HOST), hamster ovum penetration test (HOPT), hemizona assay (HZA), immunological investigation and genetic investigation.

Medications associated with infertility: Certain medications and chemicals have been associated with affecting sperm function, including spironolactone, drugs used for high blood pressure, colchicine for gout, caffeine, nicotine, alcohol, marijuana, other street drugs and anabolic steroids (Table 7).

**History Taking and Examination**

A careful history might be useful in pointing out the cause for infertility. The duration of infertility and details regarding prior workup and treatment should be asked for. Enquiries regarding previous medical and surgical problems, chemotherapy, radiation, use of therapeutic and recreational drugs, smoking and alcohol intake should be made. Ask for any history of trauma or surgery to the testes and testicular involvement during mumps. It is also important to enquire about the sexual habits of the couple. The frequency of sexual intercourse and problems related to erection and ejaculation should be specifically asked or they are likely to be missed. Following a general and systemic examination, local examination of the genitals should be performed. Look for anatomical abnormalities of the penis; presence, size, and consistency of the testicles; and palpate the epididymis, vas deferens and the spermatic cord. To check for the presence of a varicocele, the patient should perform a Valsalva maneuver in the sitting and standing positions in a warm room. Grade 1 varicocele is defined as one palpable only with Valsalva, while grade 2 is palpable at standing, and grade 3 is visible at rest.

**TREATMENT PROCEDURES**

**Stimulation of Spermatogenesis and Sperm Function**

**Medical Treatment**

Treatment of disorders diagnosed during evaluation should be undertaken. This would include correction of endocrine

---

**Table 5: Sperm function tests**

<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPA or zona-free hamster oocyte test</td>
<td>Tests the ability of sperm to penetrate the egg. Patients with a poor SPA should proceed directly to ICSI</td>
</tr>
<tr>
<td>Human zona binding assay</td>
<td>Tests zona penetrating or zona binding ability of human sperm.</td>
</tr>
<tr>
<td>Hypo-osmotic swelling test</td>
<td>Assessment of functional disturbance of the tail membrane to differentiate between viable but immotile sperm and dead sperm. Used clinically to select viable (but nonmotile) sperm for ICSI</td>
</tr>
<tr>
<td>Capacitation assay</td>
<td>To evaluate the ability to sperm to undergo capacitation, Sperm that do not undergo capacitation portend a poor response to IVF, and ICSI should be considered</td>
</tr>
<tr>
<td>Acrosome reaction</td>
<td>Tests the ability of the sperm to undergo the acrosome reaction when exposed to inducing substances. Results correlate with IVF success; abnormal test require ICSI</td>
</tr>
<tr>
<td>Postcoital test</td>
<td>Effect of cervical mucus on sperm viability and function</td>
</tr>
<tr>
<td>Test for sperm antibodies</td>
<td>Immunobead test</td>
</tr>
<tr>
<td></td>
<td>Mixed agglutination test (SpermMar)</td>
</tr>
</tbody>
</table>

**Table 3: Semen analysis: normal reference values (WHO, 2000)**

<table>
<thead>
<tr>
<th>Test</th>
<th>Reference Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume</td>
<td>2.0 mL</td>
</tr>
<tr>
<td>Liquefaction time</td>
<td>Within 60 minutes</td>
</tr>
<tr>
<td>pH</td>
<td>7.2</td>
</tr>
<tr>
<td>Sperm concentration</td>
<td>20 million/mL</td>
</tr>
<tr>
<td>Total sperm number</td>
<td>40 million/ejaculate</td>
</tr>
<tr>
<td>Percent motility</td>
<td>50% (grade A and B) or 25% grade A (within 60 minutes of ejaculation)</td>
</tr>
<tr>
<td>Normal morphology</td>
<td>15% or 30%</td>
</tr>
<tr>
<td>Vitality</td>
<td>75% or more live sperms</td>
</tr>
<tr>
<td>White blood cells</td>
<td>&lt; 1 million/mL</td>
</tr>
</tbody>
</table>

**Table 4: Some of the terms used to describe abnormal semen analysis results**

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teratozoospermia</td>
<td>Morphology &lt; 30% normal head forms</td>
</tr>
<tr>
<td>Asthenozoospermia</td>
<td>Motility &lt; 25% grade A</td>
</tr>
<tr>
<td>Necrozoospermia</td>
<td>Motility = 0%</td>
</tr>
<tr>
<td>Oligozoospermia</td>
<td>Concentration: &lt; 20.0 million/mL</td>
</tr>
<tr>
<td>Cryptozoospermia</td>
<td>Concentration: = 0 million/mL during routine analysis. Only few seen after centrifugation</td>
</tr>
<tr>
<td>Azoospermia</td>
<td>Volume &gt; 0.0 mL, Concentration = 0 million/mL</td>
</tr>
<tr>
<td>Aspermia</td>
<td>Volume = 0 mL</td>
</tr>
</tbody>
</table>

**Note:** Grade A: Rapid progressive motility  
Grade B: Slow or sluggish progressive motility  
30% or 15%, if based on strict morphological criteria
disorders like hyperprolactinemia, thyroid disorders, etc. Infections should be treated with antibiotics (Ib). Counseling and medications like sildenafil may be required for patients with erectile dysfunction (Ib). Retrograde ejaculation may be treated with imipramine or alpha-sympathomimetics, such as pseudoephedrine. If medical treatment of retrograde ejaculation fails, the use of penile electrovibration stimulation and sperm recovery from the urine can be considered.

A variety of empirical treatments have been used in an attempt to improve semen characteristics and fertility. The use of such medications for improving semen parameters is controversial. Clomiphene citrate which increases serum levels of FSH, LH and testosterone may improve the total sperm count but has not yet been proven to increase pregnancy rates when compared with those who receive no treatment (Ia). The use of androgens like mesterolone and testosterone undecanoate has no difference when compared to placebo in the treatment of patients with oligoasthenospermia (Ia). Human chorionic gonadotropin has been used in a dose of 2,500 IU twice weekly for 6–8 weeks in men with hypogonadism (II) and those with isolated Leydig cell dysfunction. Its use in normogonadotropic oligozoospermia though is not effective (Ib). Antioxidants like vitamin C and E, selenium and glutathione have shown some

<table>
<thead>
<tr>
<th>Table 6: Abnormalities in semen parameters</th>
<th>Causes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced semen volume</td>
<td>• Short period of abstinence &lt;br&gt;• Spillage of sample &lt;br&gt;• Retrograde ejaculation &lt;br&gt;• Absence of the vas deferens or seminal vesicles &lt;br&gt;• Ductal obstruction &lt;br&gt;• Hypogonadotropism</td>
<td>• Postejaculation urine microscopy &lt;br&gt;• Transrectal USG &lt;br&gt;• Hormonal evaluation</td>
</tr>
<tr>
<td>Increased semen volume</td>
<td>• Prolonged abstinence &lt;br&gt;• Accessory gland inflammation &lt;br&gt;• Contamination with urine</td>
<td>• Semen culture &lt;br&gt;• Antibiotics</td>
</tr>
<tr>
<td>Semen that does not coagulate</td>
<td>• Ejaculatory duct obstruction &lt;br&gt;• Absence of seminal vesicles</td>
<td>• Transrectal USG &lt;br&gt;• Semen fructose</td>
</tr>
<tr>
<td>Reduced sperm concentration (oligospermia)</td>
<td>• Idiopathic (most common) &lt;br&gt;• Accessory gland infection &lt;br&gt;• Chemotherapy &lt;br&gt;• Cryptorchidism</td>
<td>• Physical examination for varicocele &lt;br&gt;• Antisperm antibody evaluation &lt;br&gt;• Hormonal analysis &lt;br&gt;• Transrectal USG</td>
</tr>
<tr>
<td>Decreased motility (asthenospermia)</td>
<td>• Drugs &lt;br&gt;• Endocrine &lt;br&gt;• Environmental toxins</td>
<td>Toxins include pesticides, lead, carbon disulfide</td>
</tr>
<tr>
<td>Increased morphologically abnormal sperms (teratospermia)</td>
<td>• Epididymal causes &lt;br&gt;• Increased scrotal temperature &lt;br&gt;• Occupational &lt;br&gt;• Radiation &lt;br&gt;• Smoking &lt;br&gt;• Systemic illnesses &lt;br&gt;• Varicocele</td>
<td>Drugs which may affect semen parameters include spironolactone, cyproterone, ketoconazole, cimetidine, tetracycline, nitrofurantoin, sulfasalazine, colchicine, methadone, methotrexate, phenytoin, thioridazine and calcium channel blockers</td>
</tr>
<tr>
<td>Azoospermia</td>
<td>• Obstructive azoospermia &lt;br&gt;• CBAVD &lt;br&gt;• Vasectomy &lt;br&gt;• Infective causes nonobstructive azoospermia &lt;br&gt;• Klinefelter’s syndrome &lt;br&gt;• Young’s syndrome &lt;br&gt;• Cryptorchidism &lt;br&gt;• Chemotherapy &lt;br&gt;• Radiatio</td>
<td>• Examination &lt;br&gt;• Serum FSH levels &lt;br&gt;• Semen fructose &lt;br&gt;• Karyotyping &lt;br&gt;• Sperm centrifuged to verify azoospermia &lt;br&gt;• Postejaculation urine (retrograde ejaculation) &lt;br&gt;• Hormonal evaluation &lt;br&gt;• Testicular biopsy (testicular failure) &lt;br&gt;• Transrectal USG (ejaculatory duct obstruction) &lt;br&gt;• CBAVD—evaluate for cystic fibrosis mutations and renal tract abnormality</td>
</tr>
<tr>
<td>Increased in WBCs</td>
<td>• Prostatitis &lt;br&gt;• May be mistaken for immature sperm cells</td>
<td>Increased round cells may reflect poor prognosis of fertilization</td>
</tr>
</tbody>
</table>

Abbreviations: USG, ultrasonography; CBAVD, congenital bilateral absence of vas deferens; FSH, follicle stimulating hormone, WBCs, white blood cells
promise in improving semen parameters but further studies are required (Ib). Other commonly prescribed drugs like L-carnitine, co-enzyme Q derivatives, N-acetyl cysteine and arginine may have shown improvement in semen parameters in some studies but good evidence regarding improvement in pregnancy rates is lacking.

Surgical Treatment

Treatment of varicocele: The etiology of impaired spermatogenesis in men with varicocele remains to be elucidated. Moreover, men with varicocele may be fully fertile. A prospective randomized study showed that high ligation of the left spermatic vein prevented impaired testicular development and impaired spermatogenesis in adolescent boys. Therapeutically, the effectiveness of an obstruction of the spermatic veins in subfertile men with varicocele, as a treatment of their infertility has been investigated in three (pseudo) randomized studies. None showed an increased pregnancy rate in the treatment group. These results challenge the current treatment approach to the management of subfertile varicocele patients.

Other Treatments

Intrauterine insemination: This involves placement of processed semen into the uterine cavity. Intrauterine insemination (IUI) allows the sperm to be placed past the inhospitable cervical mucus and increases the chance of natural fertilization. IUI involves placement of 0.3–0.5 mL of semen which is processed by various techniques using a very thin flexible catheter via the transcervical route into the uterine cavity. IUI is indicated in male factor infertility, in those with antisymp antibodies, infertility due to cervical factors and in cases of unexplained infertility. Placement of unprocessed semen into the uterine cavity is not practiced as prostaglandins and proteins in semen can cause uterine cramping and occasionally allergic reactions.

Processing of semen aims to obtain a sperm population of uniform morphology and good motility, devoid of dead sperm, miscellaneous cellular elements and seminal plasma which is re-suspended in a medium. The commonly used methods are described. In conventional washing, semen is washed and centrifuged in commercial media, the supernatant discarded and the pellet overlaid with media again. This process may be repeated 2–3 times. After the final wash, the pellet is re-suspended in media and used for IUI. Such a technique is used with near normal samples. Alternatively, in the swim up technique, following sperm preparation by the conventional method, the tube is incubated and sperm/s “swim-up” from the pellet to the overlaying media, which is the used for insemination. Such inseminates have lesser levels of contamination from dead sperms and cellular debris. The gradient method involves centrifugation through a dense liquid phase (density gradient). Commercially available gradient media are overlaid with semen and subjected to centrifugation. Motile sperm cells migrate to the bottom of the tube, which are used for IUI after further washing. The swim up and gradient density techniques have better results than the conventional method, the gradient density technique being used when the sperm concentration is lower and the number of dead and abnormal cells are high.

Intrauterine insemination is usually combined with superovulation of the female partner (Ib). Follicular monitoring with transvaginal sonography is followed by an ovulation trigger with hCG. Some centers time IUI after a natural LH surge identified by a urinary LH kit.

Protocols regarding timing and number of IUIs performed vary. When a single IUI is performed, it may be performed 36 hours following the administration of hCG. Those centers which advocate two IUIs usually space them at least 12 hours apart, between 24 hours and 48 hours after the administration of hCG. Both protocols have their advocates, with studies showing either no difference in pregnancy rates or a significant increase. The Cochrane review states that double IUI showed no significant benefit over single IUI in the treatment of sub-fertile couples with husband semen (Ia).

Success rates per cycle in different studies vary from 8–30%. Variables which determine success rates depend on semen parameters (total number of sperms per inseminate and morphology), method of preparation, age and presence of uterine, tubal or ovarian pathology in the female partner and the use of medications for superovulation. IUI is more successful in unexplained infertility than in pure male factor infertility. A couple may be offered 3–6 cycles of superovulation with IUI before moving to assisted reproductive
technologies. Generally, IUls are performed if the total inseminate contains more than 1 million sperms. If this is not achieved, an early recourse to ICSI should be made.

**Donor insemination:** Therapeutic donor insemination (TDI) is useful in patients with azoospermia or severe oligospermia, when ICSI is not possible or desired. This may be in cases of non-obstructive azoospermia; when there is a possibility of a disease being transmitted from the male partner (inherited, sexually transmitted) or due to financial reasons.

Donor semen available from sperm banks should be collected from healthy young donors after screening by history and appropriate laboratory test for transmissible diseases (HIV, hepatitis B, hepatitis C, syphilis, gonorrhea, *Chlamydia*, and cytomegalovirus (IV)). Sperm thus obtained is cryopreserved. Tests which may become positive after incubation period should be repeated and only then semen should be made available for TDI (e.g. HIV, which should be tested after 6 months). A freeze and thaw cycle results in sperms which are of an inferior quality compared to a fresh sample (lb). Success rates up to 30% per cycle have been reported. TDI may be performed for 6–12 months (III). If conception does not occur, the female partner should be assessed.

**Assisted reproductive techniques:** Since the birth of the world’s first IVF baby, in 1978, IVF has become an integral part of infertility therapy for male. Pregnancy rates from IVF vary widely from program to program and are affected by the woman’s age, her hormonal status and uterine environment, and the man’s sperm quality. Introduction of ICSI is now considered as the method of choice and would replace ineffective conventional therapies. Using microsurgical sperm aspiration (MESA) technique; spermatozoa can be collected from the epididymis and used for assisted reproduction techniques. The application of MESA and ICSI yields a high rate of ongoing pregnancies (30%). Supernumerary spermatozoa aspirated during a fresh MESA procedure can be frozen and thawed for a subsequent treatment cycle. In case no sperm is aspirated from the epididymis, spermatozoa can be retrieved from the testis. The combination of ICSI and testicular sperm extraction (TESA) yields high fertilization and ongoing pregnancy rates. Nevertheless, in the case of bilateral absence of the vas deferens, specific counseling and screening for cystic fibrosis is necessary.

Genetic risks for couples undergoing IVF and ICSI are related to transmission of constitutional genetic abnormalities, genetic alterations present only in sperm, or de-novo generated genetic disorders. Besides known genetic causes of male infertility, recent studies analyzed the possible involvement of genetic polymorphisms as risk factors for spermatogenic impairment. Although initial reports of birth defects in children born after ICSI have been reassuring, the results of a recent study indicate that ICSI may be associated with increased incidence of both major and minor congenital anomalies. ICSI also carries an increased risk of transmitting infertility to the male offspring through the transmission of Y-linked micro deletions. Therefore, the identification of genetic factors should be considered as good practice for appropriate management of the infertile couple.

**Azoospermia and its management:** Absence of sperm in the ejaculate is seen in 1% of all men. Azoospermia has been traditionally classified into “obstructive” and “nonobstructive”. Because of overlapping and confusion with respect to certain etiologies, azoospermia is currently divided into causes due to deficient hormonal stimulation of the testis, testicular dysfunction, and seminal ducts obstruction or dysfunction—pretesticular, testicular, and post-testicular causes respectively (Table 8).

Management of azoospermia depends on the cause. In pretesticular azoospermia, low levels of gonadotropins (LH and FSH) and testosterone are seen. Treatment involves pulsatile GnRH therapy or sequential therapy with hCG (1,000–2,500 IU twice a week) followed by hMG (150 IU three times weekly) after serum testosterone and estradiol levels are back in the normal range. In testicular azoospermia, LH and FSH levels are elevated and serum levels of testosterone are low. Testicular biopsy and karyotyping are indicated. Testicular azoospermia can be treated if spermatozoa are obtained from the tests for ICSI. ICSI is also indicated in post-testicular azoospermia. Exceptions include patients who have undergone vasectomy who can initially opt for a reversal surgical procedure; and in retrograde ejaculation, where sperms obtained from urine can be used for IUI or ART depending on the yield.

Truly azoospermic patients should be evaluated for ejaculatory duct obstruction by TRUS (transrectal ultrasound). TRUS is indicated in patients with azoospermia or severe oligospermia to rule out a complete or partial ejaculatory duct obstruction. TRUS is also useful to evaluate the presence of seminal vesicles. Those patients with ejaculatory duct obstruction are candidates for transurethral resection of the ejaculatory ducts.

### Table 8: Causes of azoospermia

<table>
<thead>
<tr>
<th>Type</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretesticular</td>
<td>• Hypogonadotropic hypogonadism</td>
</tr>
<tr>
<td></td>
<td>• Congenital (Kallmann’s syndrome, Noonan syndrome)</td>
</tr>
<tr>
<td></td>
<td>• Acquired (trauma, tumor)</td>
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<td></td>
<td>• Idiopathic</td>
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<tr>
<td></td>
<td>• Congenital (Klinefelter’s syndrome, Y-deletion)</td>
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<tr>
<td>Testicular</td>
<td>• Acquired (radiotherapy, chemotherapy, torsion, mumps, orchitis)</td>
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<td>• Developmental (testicular maldescent)</td>
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<td>• Ductal obstruction</td>
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<tr>
<td>Post-testicular</td>
<td>• Dysfunction (retrograde ejaculation)</td>
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Flow chart 1: Summary of evidence-based male factor treatment options

WHAT IS IN FUTURE?
An exciting breakthrough in the field of male factor infertility and micromanipulation is a process called round spermatid nucleus injection (ROSNI) that specifically targets men who are not manufacturing sperm and have zero sperm count. ROSNI process involves taking immature cells (round spermitids) directly from testicle, removing the nucleus containing the genetic material and injecting the nucleus into the female partner’s eggs. While this process has yet to produce a livebirth, researchers believe it will eventually become a successful technique that will allow men, who previously had no hope, to father a biological child.

CONCLUSION
Flow chart 1 summarizes possible options available for treating male factor infertility based on evidence gathered through various investigations. Given the high success rates now being achieved using ICSI, there is an increasingly common trend for ICSI to be used as the treatment of choice. More disturbingly, there is a trend for infertile couples to be referred directly for ICSI treatment after an initial infertility consultation.

The source of sperm is no longer a barrier in achieving fertilization and subsequently, an ongoing pregnancy. Epididymal or testicular sperm, which may be fresh or frozen, can be used to achieve pregnancy. Preimplantation diagnosis of embryos should be performed in all patients with genetic or chromosomal abnormality. Due to high cost implications for an ICSI cycle, it is possible that not all patient requiring ICSI will be offered this treatment. They may then have to resort to donor sperm use.

BIBLIOGRAPHY


INTRODUCTION

Human fertilization is a complex process. Out of millions of sperms deposited in the vagina during normal sexual intercourse, only a few thousand sperms actually reach the site of potential fertilization. This high loss is thought to be due to a variety of factors. Intrauterine insemination overcomes some of the barriers responsible for prevention of migration of sperms to the distal part of the fallopian tube.

Intrauterine insemination (IUI) is the direct placement of processed, highly motile, concentrated sperm, washed free of seminal plasma and other cells, into the uterus, adjacent to the medial ends of the fallopian tubes, as close to the ovulated oocytes as possible. This procedure greatly reduces the distance that the sperm must travel and increases the amount of spermatozoa available to the oocytes. The number of sperm that reach the fallopian tubes is increased as much as 25% with IUI. Technical refinements in sperm preparation have led to a significant decrease in side effects and to an increase in the quality of sperm selection. IUI is recommended for those couples where there is insufficiency of good quality sperm reaching the upper reproductive tract of the female partner.

The rationale for use of IUI is to reduce the effect of factors such as vaginal acidity and cervical mucus hostility and to benefit from the deposition of a bolus of concentrated motile morphologically normal sperm as close as possible to the oocytes. Sperm preparation methods developed for in vitro fertilization-embryo transfer (IVF-ET), such as the wash and swim-up technique and the use of Percoll® substitutes like PureSperm® (Nidacon Laboratories, Sweden) and SupraSperm® (Medicult, Denmark), have led to a resurgence of interest in IUI.

Intrauterine insemination, both in spontaneous and preferably, in superovulated cycles, is recommended as the first choice option of assisted conception techniques, since the procedure is noninvasive and also much more cost-effective.

INDICATIONS FOR TREATMENT

Couples seeking IUI should be fully evaluated, including a complete medical history, a clinical examination and investigation for the presence of any abnormality such as tubal damage or ovulatory disorder.

Ejaculatory failure is the classical indication for IUI using husband’s semen, because of the inability of the partner to ejaculate into the vagina, while cervical mucus hostility is a logical indication as the insemination method bypasses the cervical canal. It is also essential that couples receive adequate counseling prior to starting treatment, especially when donor sperm is to be used.

In the Male Partner

- Anatomic defects of penis (hypospadias)
- Sexual or ejaculatory dysfunction where semen is collected using vibrator or electroejaculator
- Retrograde ejaculation
- Impotency
- Immunological factor like autoantibodies and sperm agglutination
Infertility

- High and prolonged viscosity, which results in a firm coagulum inhibiting transport of active sperms near the oocyte
- Oligoasthenoteratozoospermia which reports a low profile semenogram as low sperm count, less motility, poor grade motility and/or high percentage of abnormal sperms.

DONOR SPERM INSEMINATION

The main indications for donor insemination are gross male subfertility (azoospermia or severe oligoasthenozoospermia), familial or genetic disease such as Huntington’s disease, hemophilia and also severe rhesus isoimmunization. The use of cryopreserved semen in donor insemination programs is now mandatory in most countries to minimize the possibility of transmission of the human immunodeficiency virus (HIV) to the recipients.

In the Female Partner

- Anatomic defects of the reproductive tract where direct coitus is not possible
- Psychological and psychogenic sexual dysfunction, e.g. vaginismus
- Cervical factors
- Poor sperm—mucus interaction/failed post coital test/ cervical stenosis
- Destruction of endocervical glands as a result of conization, laser surgery or cryosurgery
- Ovulatory dysfunctions responsive to clomiphene citrate (CC)
- Unexplained infertility where pregnancy is not achieved with other medical intervention
- Minimal endometriosis
- Antisperm antibodies in the cervix
- Women with altered tubal function or with bilaterally blocked fallopian tubes (both) should not be taken for IUI treatment.

The Initial Work-up

Before beginning IUI, couples should be informed of the expected course, the technique aspects of the procedures, the risk of complications and expected outcomes. The following minimal investigations are to be carried out on the:

Husband

- Physical examination—both systemic and local
- Semen analysis
- Morphology and sperm function tests
- Culture and antibiotic sensitivity
- Antisperm antibody
- Screening for infection including syphilis, hepatitis B and HIV
- If needed, appropriate endocrinological investigations and therapy

- The investigations should be carried out within span of 2 months before collection of semen for IUI.

Wife

- History and physical examination both systemic and local
- Detection and timing of ovulation by basal body temperature (BBT), cervical mucus study, USG, monitoring of follicular growth
- Assessment of tubal patency—hysterosalpingogram (HSG)/laparoscopy, hysteroscopy
- Premenstrual D and C and histopathological examination of endometrium
- Screening for local factor including cervical mucus
- Screening for reproductive tract infections including syphilis, Chlamydia, tuberculosis, hepatitis B and HIV
- Appropriate endocrinological investigation:
  - Follicle-stimulating hormone (FSH) day 2/3 of cycle
  - Luteinizing hormone (LH) day 2/3 of cycle
  - Progesterone day 21
  - Thyroid stimulating hormone (TSH)
  - Prolactin
- Antisperm antibody in both cervical mucus and serum
- Women with evidence of vaginitis or presence of pelvic inflammatory diseases should not be taken for IUI. In case it is present procedure should be postponed and condition should be treated by appropriate local and systemic chemotherapeutic agents.

STIMULATION PROTOCOLS AND MONITORING OF THE CYCLE

Intrauterine insemination can be performed in natural (nonstimulated) or stimulated cycles. In natural cycle, ovulation is monitored carefully by either serial ultrasound examination of dominant ovarian follicle or by urinary, plasma or dipstick methods of LH assay. IUI is performed 24 and 36 hours after the onset of LH surge.

When in a women who has ovulatory cycles but fails to become pregnant after 4–6 cycles of IUI, superovulation may provide an effective adjunct to therapy. In stimulated cycles, different protocols are used to activate the ovary to produce more than one mature oocyte, thus increasing the chances of fertilization and thereby pregnancy. The regimens may vary depending upon patient’s response to the drugs.

Different ovarian stimulation protocols used are:

- CC
- CC + human chorionic gonadotropin (hCG)
- CC + FSH/human menopausal gonadotropin (hMG) + hCG
- FSH/ hMG + hCG
- Recombinant follicle-stimulating hormone (recFSH) + hCG
- Gonadotropin releasing hormone agonists [GnRHa (long or short protocol)] + FSH/hMG or recFSH + hCG.
Combination of IUI with ovarian stimulation has several potential advantages over simply awaiting the infrequent spontaneous conception. These include an increase in the number of oocytes available for fertilization, and increasing the levels of follicular and luteal phase gonadal steroids. This approach also optimizes the likelihood of gamete interaction with viable oocytes and sperm being simultaneously present in the genital tract and also provides large numbers of capacitated sperm at the site of fertilization in the distal fallopian tubes. Many of these features are common for technologies such as IVF-ET, gamete intrafallopian transfer and zygote intrafallopian transfer. The major difference with controlled ovarian hyperstimulation and intrauterine insemination (COH-IUI) is that normal fallopian tubes can be anticipated to function appropriately and no surgical procedures are required to collect oocytes. In fact, a number of recent studies comparing IVF and COH-IUI in treatment of infertility with patent fallopian tubes, have highlighted the fact that in many indications, IUI is more cost-effective and the routine use of IVF as a first approach should not be done.4-10

Despite the increased costs of hMG cycles due to medication and cycle monitoring, higher pregnancy rates (PRs) reduced the cost per delivery of hMG-IUI cycles to the rates seen in IUI and CC-IUI cycles.11 Although general recommendations may be made regarding a cost-effective approach to treating infertility, there are factors present in individual patients that would change the efficacy and therefore influence the cost-effectiveness of certain treatments.12

**TIMING OF INTRAUTERINE INSEMINATION**

A well-timed IUI is mandatory and is a “critical key” to success because spermatozoa survive for a limited period in the female reproductive tract and oocytes are fertilizable for only 12–16 hours. Timing of IUI becomes more important when indications include oligospermia.

It is recommended that only one or two insemination should be performed per cycle depending upon clinical, USG monitoring and day/time of hCG administration.

Silverberg et al.13 has shown that two IUIs performed 18 and 42 hours after hCG were superior to a single IUI performed 34 hours after hCG administration. However, many clinics14-18 prefer to perform only one IUI per treatment cycle. When a single insemination is used, it is typically advised 34–36 hours after the hCG dose that initiates ovulation. One prospective randomized trial by Ransom et al.18 compared PRs per treatment cycle of controlled ovarian hyperstimulation (COH) patients receiving a single IUI with COH patients receiving two IUIs. They found that increasing the frequency of insemination does not provide a significant increase in cycle PR.18

**Laboratory Set-up**

A room should be provided for the production and collection of semen. The room should be comfortable, large enough to accommodate two people, and furnished with any materials thought necessary to aid production of semen such as magazines and video films. Trained laboratory personnel and basic equipment requirements should be fulfilled including outpatient clinic facilities and insemination room.

**EQUIPMENT FOR THE INTRAUTERINE INSEMINATION UNIT**

- Centrifuge capable of operating at 300 × g
- CO2 incubator
- CO2 cylinders
- Light microscope
- Laminar airflow hood (Class 2 cabinet)
- Makler sperm counting chamber/hemocytometer
- Pasteur pipettes
- Pipette controller
- Refrigerator
- Test-tube rack
- Culture medium/sperm washing kit/SupraSperm®/PureSperm® or isolate gradient
- Sterile sperm semen specimen container
- 1 mL syringe (disposable)
- Insemination catheter

**GUIDELINES FOR SPERM PREPARATION**

Male partner who has been physically examined and investigated for semen count, culture, antisperm antibodies, HIV, hepatitis B surface antigen (HBsAg) and Venereal Disease Research Laboratory (VDRL) test status should have an abstinence of 3–4 days. Collection of semen by masturbation in sterile container provided by the laboratory, after properly cleaning and drying the penis and hands. The aim of the sperm preparation is to remove cellular debris, abnormal and immotile spermatozoa, seminal fluid (containing prostaglandins) and WBCs from the ejaculate. And while doing sperm washing, the spermatozoa gets capacitated (activated) to penetrate the zona pellucida of the oocyte, which has been released by the ovary.

Particular attention is to be given to the sample collection room which should be isolated, neat and clean, should include a urinal, a washbasin, a bed and a clean and disinfected platform to keep the bottles. Provision of vibrator and erotic-stimulating pictures, is of tremendous help to the tense male partner.

Containers in which sample is collected should be of nontoxic material like polypropylene. If it is made up of glass, it should be borosilicate glass, should be tissue culture washed and heat sterilized. Patient should collect sample
by masturbation rather than direct coitus method, which encourages contamination.

Patient should be asked to collect sample by split ejaculation, which separates prostatic fluid and sperm fraction from seminal plasma. This separation is helpful particularly in oligospermia and those with autoantibodies.

Sperms need to be carefully washed before direct placement into the uterus. Semen is not sterile but does contain nonmotile, morphologically abnormal sperm and nonsperm cells in addition to the normal, motile sperm. Washing is necessary because sperm placed directly into the uterus by passes the protective effects of the cervical mucus. During washing, sperm selection, hyperactivation and partial capacitation occur, events thought to normally occur in the mucus. Washing is important because the seminal plasma contains prostaglandins that can cause intrauterine contractions and therefore must be removed.

For IUI to be successful, adequate sperm must be present. The final washed sperm count should be preferably 3–5 million motile sperms. If there are fewer than 3 million total motile sperms present, the woman should be referred for IVF or intracytoplasmic sperm injection (ICSI).

Media

Although sperms are resistant to many adverse conditions and can survive even in normal saline, it is better to process semen sample in a biochemically defined medium to maintain sperm integrity and promote acrosome reaction and capacitation. Bicarbonate buffered media should be equilibrated with 5% CO₂, 5% oxygen and 90% nitrogen at 37°C, in at least 95% humidity for 8 hours. A pH of 7.2 and osmolality of 285 mOsm/kg is recommended. 10% heat inactivated serum or HSA or synthetic serum can be added so the medium has protein supplement. In case where motility of sperms is adversely affected due to mid-piece defects, methylxanthine derivatives like pentoxifylline and caffeine can be added to medium.¹

Catheters

Many types of catheters are available. Those used for IVF can be tissue culture medium-washed, gas sterilized and reused. Local catheters should be checked for toxicity. A simple method to check toxicity is to pass processed sample through the catheters and check its survival for 24 hours and 48 hours. If 80% sperms are surviving after 48 hours, these catheters can be used. It is better to mark uterocervical length on the catheter before insemination. The mark on the catheter should be 0.5 cm less than the actual uterocervical length to avoid touching the fundus, which may result in contraction of muscles and thus expulsion of inseminated fluid.

Steps of Semen Preparation

- Let the semen sample liquefy at room temperature for 15–30 minutes
- Use of labeled—fresh, presterilized pipettes and conical tubes
- Semen analysis for count and motility is performed and recorded before and after the sperm washing procedure. This is an important part of quality assurance
- The medium to be used should be at 37°C or room temperature and equilibrated in CO₂ incubator before use.

Technique

- Wash and swim-up or Percoll®, PureSperm® or isolate gradient
- Harvest semen analysis for sperm count motility and morphology should be at least 3 million (ideal 3–5 million).

The Principles that Need to be Adhered during the Washing and Insemination Process

- Although the semen is not sterile, sterility should be maintained through the sperm washing procedure
- Protective eye wear and gloves should be used when handling the specimen
- The same pipette should not be used to enter more than one bottle
- If many WBCs are present in the ejaculate, IUI should not be performed. The problem must be diagnosed and treated. Remember, immature sperm can look similar to WBCs
- The total volume of the nongravid uterus is around 0.5 mL; therefore, not more than 0.5 mL should be injected or else the specimen may be displaced from the uterus
- Properly label all tubes and syringes containing the specimen.

Methods of Sperm Preparations

The following procedures are commonly used for semen preparation:

Sperm-wash Procedure

The liquefied sample is first diluted with a culture medium or with buffered physiological saline in the ratio of between 1:1 and 1:3. The suspension is then centrifuged for 10 minutes at 150–200 × g or for 3–5 minutes at 500 × g. The supernatant is discarded, and the resultant pellet is rediluted in a smaller volume of fresh medium. This wash procedure is repeated one to two times. The final pellet is resuspended in 0.3–0.5 mL medium.
Swim-up Technique

After washing and concentrating sperm, 0.3–0.5 mL of prepared medium is carefully layered over the final pellet and the sample is incubated for 30–60 minutes at 30°C in 5% CO₂. It is recommended that the tube be held at an angle of 30° so that a larger interface is created. The supernatant (swim-up specimen) is then collected with care, not disturbing the pellet at the bottom.

Density Gradient Separation

With the density gradient separation method motile spermatozoa are isolated by layering liquefied neat semen over an isotonic gradient solution and centrifuging it for 10–20 minutes at about 200–600 × g. The supernatant is discarded, and after one to two wash runs, pellet is resuspended for insemination in 0.3–0.4 mL medium.

The sperm manipulation method used for sperm preparation for IUI also has an important effect on the outcome, and ideally is chosen according to the characteristics of the semen sample obtained. Huang et al. studied 335 IUI cycles, comparing the different sperm preparation methods in normal and abnormal semen analysis groups. Their results showed that in the abnormal semen samples, the density gradient separation method was superior to the swim-up and swim-down methods on the recovery of a higher number of total, motile, and actively motile spermatozoa (P < 0.05) even though the sperm quality before preparation was somewhat poorer that the samples prepared by the other two methods.

Number of Attempts

The clinician needs to discuss the number of expected cycles. Treatment in a couple with cervical or male factor infertility and the woman who is anovulatory before treatment, should be continued longer than in the woman who is ovulatory or diagnosed with unexplained infertility. If no results are seen then the plan needs to be changed and alternative options discussed. In a woman with documented ovulatory cycle who has failed to become pregnant after four to six cycles of IUI, ovulation induction may provide an effective adjunct to therapy. The combination is thought to increase the number of sperm and oocytes available, resulting in an increased chance of fertilization and PRs in stimulated cycles. Since cumulative PRs after four to six cycles have been good, depending on the indications and other factors, most clinics would suggest continuing IUI for several cycles before proceeding to more advanced assisted reproductive technology procedures. An analysis of 650 treatment cycles by Ferraro et al. including spontaneous cycles and cycles with controlled ovarian hyperstimulation shows a mean monthly PR of 8.9% and cumulative PR of 39% at the end of six IUI cycles. In particular for hMG + hCG cycles, a mean PR equal to 10.9% and a cumulative PR up to 46% at the end of six cycles were obtained.

A randomized longitudinal study of hMG/IUI therapy found cumulative PRs after seven cycles of treatment to be 80%, 53% and 48% for unexplained infertility, endometriosis and male factor, respectively. This study also suggested that cycle fecundity remains relatively constant for the first five cycles and then declines. The patients need to be appropriately counseled that pregnancies may be achieved with further attempts at IUI, but at a significantly lower success rate.

TECHNIQUES OF INTRAUTERINE INSEMINATION

There are variations from laboratory to laboratory, not only with regards to the method of sperm preparation selected, but also as to the final concentration of sperm for insemination. The volume of inseminate may vary from 0.2 mL to 1.0 mL. The volume of material injected may affect the delivery site of the sperm. One study showed that intrauterine injection of volumes greater than or equal to 0.4 mL reached the uterus and tubes. Different types of insemination techniques have been described including a bolus technique, pulsatile intrauterine insemination using an automatic pump and slow release IUI. The latter procedures are believed to mimic the prolonged slow release of small numbers of spermatozoa from the endocervix into the upper genital tract following natural intercourse. However, in practise, the bolus technique is most commonly used.

Bolus Technique

Where the entire inseminate is injected into the uterine cavity over 1–3 minutes. Bolus IUI is performed without changing the count from the swim-up portion of the washed spermatozoa. An important disadvantage of the bolus technique is the single nonphysiological deposition of a very large number of spermatozoa into the uterine cavity in contrast to the prolonged slow release of small numbers of spermatozoa from the endocervix into the upper genital tract following natural intercourse.

Pulsatile Intrauterine Insemination

This uses an automated pump attached to a 1.0 mL syringe and delivers sperms in pulses of 15 minutes over 4–6 hours. The disadvantage of this technique is that the patient’s activity has to be restricted for 4–6 hours, and the patient has to be kept lying down in a supine posture.

Slow Release Intrauterine Insemination

This technique uses an external slow release auto-syringe to inject small numbers of prepared motile spermatozoa in a continuous slow release pattern into the uterine cavity.
Steps of the Intrauterine Insemination Technique

- Well-lighted room with gynecological examination table
- Women to lie in dorsal lithotomy position after emptying the bladder (table may have slight degree of Trendelenburg)
- Under strict aseptic conditions and precautions, the semen sample washed and prepared for insemination be loaded in IUI catheter
- Perform bimanual examination to assess uterine size and position
- Insert speculum into vagina and visualize the cervix
- Clean the os if any discharge is present with dry sterile swab or swab dipped in normal saline
- Thread the preloaded catheter through the cervix. Do not use force
  - A tenaculum does not usually need to be used, except with a marked degree of ante- or retroflexion
  - A stiffer catheter may be necessary in the presence of cervical stenosis
  - Bring prepared specimen into the room in sterile wrapper. The name should be on the wrapper
  - Slowly inject the specimen over 30–60 seconds to avoid flushing the uterus too fast and causing retrograde flow. Be careful that the catheter does not act as an outflow wick. Injecting the solution too rapidly can force semen through the tubes into the peritoneum and cause considerable pain
  - Remove the catheter with slight twist to avoid any spillage
  - Inject 0.5 cc of air to clear the catheter of any remaining specimen; be careful not to inject air into the uterus. Leave the woman in a comfortable reclining position for 15–20 minutes
  - Instruct the woman to call if any abdominal pain, cramps or fever develops; with the onset of menses, or if menses is 2–3 days late, she should call to arrange for a pregnancy test and further instructions
  - If the catheter traumatizes the lining of the uterus and bleeding occurs, the chance of fertilization is reduced because immunoglobulins may be secreted from the endometrium.

Complications of Intrauterine Insemination

- There are fortunately very few and rarely severe
- Uterine cramping (pain—5%)
- Spotting (1%)
- Infection (0.2%)
  - Risks of controlled ovarian stimulation—severe ovarian hyperstimulation syndrome (OHSS) (1%), multiple gestation and ectopic gestation. There are very few complications reported related to the procedure of IUI itself. The estimated risk of infection is 1.8 per 1,000 women. Occasionally spotting or bleeding may occur, especially if a tenaculum or Allis forceps had been used to hold the cervix, or if there was difficulty accessing the uterine cavity. In stimulated cycles, the main risks that worry the clinician are the OHSS and multiple pregnancies.

RESULTS

The results of IUI in terms of PRs per treatment cycle vary considerably between clinics and evaluation of the results is difficult because of the heterogeneity of the patient population and the different ovarian stimulation protocols used in the studies. Usually pregnancy occurs in the first four to six attempts and thereafter the PR is hardly increased by continuing for longer. Careful selection of patients is important.

Those who will benefit most are young women with patent fallopian tubes, with no ovulatory disorder, no endometriosis of moderate or severe degree and no severe degree of male factor infertility in their partner. The generally accepted fecundity of normal couples approaches 15–20%, but the cycle fecundity of couples who do not conceive in 12 months without contraception, is as low as 1–2%.36,27 Intrauterine with or without COH is thus often used in most couples with subfertility or relative infertility, in the absence of mechanical obstruction within the genital tract.

Enhanced cycle fecundity has been demonstrated with homologous IUI in various studies,3,14,28 varying from 9% to 23% and may be higher in individual cases.

CONCLUSION

With a woman having “functional patent tubes” and male partner having “adequate sperm count,” IUI is “reliable and cost-effective treatment option”. In such couples, IUI may “maximize fertility” with “minimum patient risk and less expense”. The average PR of IUI is 10%, but depending on the indications and patient characterization, it can be much more. Addition of superovulation, especially COH is preferable to natural cycle treatment, both for improving success rates, and for ease of regulation and planning of treatment. The prepared semen sample should have certain minimal characteristics, which can prognosticate the outcome. The majority of pregnancies occur in the first three to four cycles. After a trial of four to six cycles, the patient should be counseled appropriately to move on to more advanced forms of assisted reproduction.

REFERENCES


**INTRODUCTION**

The oviduct that runs from the cornual region of the uterus, ending near the vicinity of the ovary, has gained its name as “fallopian tube” since this was first described in the year 1561 by “Gabriele Fallopio”. He called it “the seminal duct that originating from the cornu uteri and looking like a nerve, after a short distance begins to broaden and coil like a tendril. It shows an extremitas of the nature of skin and color of flesh, the utmost end being very jagged and crushed like the fringe of worn out clothes. Further it has a great hole which is held closed by the fimbriae which overlap one another.”

**INCIDENCE**

One in six couples presenting to health practitioner is complaining of infertility and of these, 14% have tubal factor. Tubal disease is responsible for 25–35% of female infertility. It may involve the proximal, distal, or the entire tube and may be transient (obstruction) or permanent (occlusion).

The assessment of patency of the fallopian tubes is an essential part of any infertility workup. Presently, laparoscopic chromopertubation and hysterosalpingography (HSG) are the most commonly used techniques.

**PATHOPHYSIOLOGY**

The peristaltic movements of the fallopian tube are under the influence of estrogen, progesterone and prostaglandins and synchronized movements help in propulsion of sperms and fertilized egg in either direction. The ovarian fimbriae spread over the ovary at ovulation and bring the ovum into fimbrial end. The loss of any of these functions could prevent conception.

**Factors Affecting Fertility**

- Degree of tubal obstruction
- Presence of endosalpingeal destruction
- Presence of peritubal adhesions.

**CAUSES**

Current studies show that the most common causes are:

- Sexually transmitted “nonspecific” infections
  - Chlamydia
  - Gonorrhea, etc.
- Postabortal and postpartal salpingitis.

**Chlamydia/Gonorrhea**

Both ascend from lower genital tract via the mucosal surface of the endocervix or endometrium to the endosalpinx. These microorganisms cause epithelial damage with loss of ciliated cells and produce an inflammatory exudate which may cause adhesions between the mucosal folds.

Streptococci, staphylococci and gram-negative bacteria which mainly cause puerperal, postabortal and traumatic infections probably reach the tube via the lymphatic and vascular channels.

The injury appears to be caused mainly by the endotoxins released from the cell walls of the bacteria.
Salpingitis can also occur as a result of adjacent or distant inflammatory process and may be associated with infection in the bowel such as appendicitis or diverticulitis.

**Tuberculosis**

About 60-98% of patients with genital tuberculosis (TB) are infertile.

*Incidence:* 20% of infertile women from developing countries.

*Pathogenesis:* Genital TB occurs almost always secondary to a focus in another organ, usually the lung from which it spreads via blood stream, lymph channels or directly from peritoneal cavity, urinary tract or bowel, while infection in genital tract may spread to peritoneal cavity.

The fallopian tubes are the most common site of initial infection in genital TB and it is probable that infection of endometrium, myometrium, cervix and vagina is due to spread from the focus in the tubes.

**Hydrosalpinx**

There is distal blockage and dilatation of the fallopian tube which is filled with clear, sterile serous fluid.

- Etiology is controversial
- Chronic infection—end result of pyosalpinx
- Abnormality in muscular part of wall.

**Types**

- Thin-walled hydrosalpinx
- Thick-walled hydrosalpinx (Fig. 1).

A meta-analysis of 15 published retrospective studies comprising 5,592 patients by E-camus et al. (1999) showed negative consequences on pregnancy rate, implantation rate and live birth rate in women with tubal infertility with hydrosalpinx undergoing in vitro fertilization (IVF) than tubal infertility without hydrosalpinx undergoing IVF.

The mechanism by which the presence of hydrosalpinx may exert negative effect on IVF outcome are flushing the embryos into a damaged fallopian tube at the time of embryo transfer and leakage of hydrosalpinx fluid into the uterine cavity rendering environment toxic to embryo.

**Proximal Tubal Pathology**

Proximal lesions of the fallopian tubes occur less often than distal end. Apart from surgical division of the tube, there are however a number of conditions affecting the intramural segment and the isthmus which can cause infertility without necessarily producing complete obstruction of the lumen.

The most common of these are obliterative fibrosis, salpingitis isthmica nodosa, chronic tubal inflammation and endometriosis, less common being polyp, TB, remnant of chronic tubal pregnancy.

**Tubal Pregnancy**

Ectopic pregnancy occurs as often as 1 in 300 live births and the incidence appears to be increasing.

Approximately, one-third of the patients are nulliparous and subsequently more than 50% of them will be infertile.

An increased awareness of the condition by both patients and doctors, together with the use of newer diagnostic methods, means that the diagnosis can often be made before the tube has ruptured and the conservative tubal surgery can be performed preferably with laparoscopic surgery.

**Poststerilization**

The increasing number of sterilization being performed on relatively younger women of low parity together with widespread availability of tubal microsurgery has led to a greatly increased demand for reversal during past 10 years.

Histopathological changes: Flattening and fibrosis of the mucosal folds, deciliation, polyp formation, tuboperitoneal fistulae and tubal endometriosis.

**Congenital Tubal Anomalies**

Not common and their clinical significance is not always clear.

- Convoluted or tortuous tubes
- Accessory tubes and accessory ostia
- Segmental obstruction
- The immotile cilia syndrome.

**Endometriosis**

The association between endometriosis and infertility has been largely based on the high incidence of the condition...
in women undergoing infertility investigation in whom laparoscopy has revealed its presence in 20–50% of cases.

Although the cause of infertility is obvious when endometriosis results in extensive tubo-ovarian adhesions or tubal distortion which interfere with ovulation or ovum release and pickup, recent studies support the view that endometriosis is associated with lower fecundity even when mechanical factors are absent and monthly probability of conception in women with endometriosis is 70–80% less than in normal women.

**INVESTIGATION**

The tubal investigation must start from the simplest and end up in the most sophisticated method if required and from the least invasive to the most invasive keeping in mind the cost, efficacy, safety and practical utility of the information obtained from the procedure.

**Hysterosalpingography**

Hysterosalpingography should be the first test for investigation of tubes. It provides information about the anatomy of the uterine cavity and proximal and distal fallopian tubes, patency and adhesions.

Hysterosalpingography can delineate synechiae and septae in uterine cavity and also delineate fistulation and sinus formation through the myometrium. It can also show direct infiltration of dye in the parametrium.

**Hysteroscopy**

Hysteroscopy may be performed as an office procedure but is probably better combined with other endoscopic investigations.

Hysteroscopy enables inspection of the uterine cavity in detail and also the visualization of the internal ostia and proximal intramural segments of the fallopian tubes.

Pathological condition produces characteristic changes in the hysteroscopic view of endometrium and fallopian tube, like in case of TB, endometrium is seen as pale, yellowish, patchy and there may be fibrosis at some places.

Other findings can be acute endometritis, fibrosis, partial obstruction of ostia, acute salpingitis, salpingitis isthmica nodosa and uterine anomalies.

**Laparoscopy**

It is a well-established technique in the routine investigation and treatment of infertility. It allows a complete and detailed examination of the pelvic organs.

Certain pathological conditions give very characteristic view, e.g. adhesions at the peritubal as well on the liver surface usually suggest chlamydial infection. Tubo-ovarian adhesions involving bowel with tubercles on the surface of tube and ovary may suggest tubercular infection, fallopian tube shows intravasation of dye, fimbrial agglutination and beaded appearance of tube.

Adhesions interfere with ovum pick-up and limit tubal mobility.

**Advantages**

- Simultaneous therapeutic procedure can be performed at the same sitting
- Also identifies nature of pathology that has affected the tubes
- Pathologies commonly diagnosed by laparoscopy are hydrosalpinx, adhesions, fimbrial cyst, disturbed tubo-ovarian relationship.

**Salpingoscopy**

Salpingoscopy should be performed at the time of laparoscopy. The small endoscope (2.0 mm or 2.9 mm) is inserted through an abdominal ostium. Tube is distended with normal saline or glycine.

Following five patterns are identified:

1. Normal mucosal fold.
2. Major and minor folds are preserved but there is slight flattening of variable degree.
3. Major or minor folds are preserved but there are focal lesions like adhesions or agglutination.
4. Extensive lesion of major or minor folds like adhesions, stricture of lumen and formation of pseudospaces.
5. Fold pattern totally lost, lumen is dilated with rigid walls.

**MANAGEMENT**

**Prevention**

Timely detection of tubal infection and proper antibiotic treatment to prevent damage to the tubes.

**Therapeutic**

Management of tubal factor for infertility depends on the type and degree of tubal dysfunction. Various approaches are available. The treatment of choice is also determined by other factors like:

- Age and the ovarian reserve of the patient
- Presence or absence of a male factor
- Socioeconomic considerations.

In addition to less invasive techniques such as transcervical tubal cannulation and selective salpingography, and various surgical approaches, in vitro fertilization and embryo transfer (IVF-ET) is a viable alternative for all types of tubal dysfunction.
**Proximal Tubal Occlusion**

Proximal tubal obstruction and occlusion account for 10–25% of tubal factor.

Therapeutic approaches for proximal tubal occlusion include:
- Transcervical tubal cannulation (Fig. 2)
- Tubocornual anastomosis (TCA)
- In vitro fertilization and embryo transfer.

**Transcervical Tubal Cannulation**

Transcervical tubal cannulation for the reversal of proximal tubal occlusion can be performed under fluoroscopic, falloposcopic, sonographic, or hysteroscopic guidance. Tubal recanalization by hysteroscopic control offers a number of advantages over other techniques. First the guidance of the tubal catheter into the tubal ostia is simple because it is done under direct vision. While 85% of occlusions can be overcome in this way, there is a 30% reocclusion rate and tubal perforations occur in 3–11% of cases. Hysteroscopic transcervical tubal cannulation gives an average ongoing pregnancy rate of 30–40%.

Laparotomy with microsurgical TCA gives pregnancy rates from 38–56%. Thus in selected patients, namely those without coexisting tubal pathology, hysteroscopic transcervical tubal cannulation may be as effective, but less invasive and less costly than the microsurgical approach.

**Tubal Reanastomosis**

Microsurgical tubal anastomosis is the gold standard for reversal of sterilization. It gives an intrauterine pregnancy rate of 60–80% and very low ectopic pregnancy rate of 1–6%. The results obtained by laparoscopic microsurgical anastomosis (Figs 3A and B) look promising with good intrauterine pregnancy rates of 60–80% and a very low ectopic pregnancy rate of 1–6%.

**Distal Tubal Occlusion**

**Operative Techniques**

The three important surgical techniques are usually performed in distal tubal occlusion:
1. Adhesiolysis
2. Fimbrioplasty

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**Distal Tubal Occlusion**

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1. Adhesiolysis
2. Fimbrioplasty
Adhesiolysis

The first part is to inspect the pelvic cavity and abdominal cavity for any inflammatory lesions, TB, adhesions and endometriosis. Liver bed must be evaluated for presence of adhesions (Fitz-Hugh-Curtis syndrome) suggesting chronic infective process. Whether fimbrioplasty or salpingostomy is required, they are usually associated with adhesiolysis. Certain general principles of adhesiolysis should be kept in mind.
- Adhesions should be placed under tension before lysis
- Proceed from midline to laterally (toward adnexa)
- Lysis should be done layer wise cutting superficial adhesions first
- Simple adhesions should be freed first
- Round ligament insertion is an important anatomical landmark in case of difficult adhesiolysis
- Avoid injury to peritoneum as far as possible
- The aim of adhesiolysis is to restore pelvic anatomy to normal and to have free fallopian tube and ovary maintaining their relationship.

Hemostasis is vital and frequent irrigation with suction is essential. One can use monopolar or bipolar electrical currents or use light amplification by stimulated emission of radiation (LASER) depending upon individual choice and availability.

Fimbrioplasty

The principle of fimbrioplasty is to restore the original anatomy of infundibulum by treating phimosis and agglutination.
- Where the fimbriae are encapsulated and hidden by fibrotic bands, the antimesentric border is incised to remove fibrotic bands and expose the fimbriae
- In case of agglutination where the folds are stuck together, a small incision is put at the center of agglutination. Now dilate the opening by introducing atraumatic forceps in closed position and opening it in different directions. Any small fibrotic bands can be lysed as mentioned earlier
- In tubal phimosis, atrumatic forceps are introduced inside the infundibulum. By opening the jaws, the adhesion bands in the infundibulum can be seen. They are incised with mono/bipolar or CO\textsubscript{2} laser.

At the end of operation hemostasis is to be confirmed. Any small oozers are controlled by submerging the infundibular portion of tube in warm (37°C) normal saline for few minutes. Any residual oozers are controlled by bipolar fine coagulation. Care is taken to avoid damage to the mucosa. Severe phimosis is treated by salpingostomy.

Laparoscopic Salpingostomy

There are two types of salpingostomy:
1. Cuff salpingostomy for thin-wall hydrosalpinx
2. Flap salpingostomy for thick-wall hydrosalpinx.

Latter procedure is usually not done as the results are not convincing as compared to assisted reproductive techniques for thick-walled hydrosalpinx.

Cuff Salpingostomy

This operation is usually subdivided into three parts:
1. Opening (incising) the tube
2. Eversion of mucosa
3. Stabilizing the eversion.

Opening the tube (Fig. 4A): Initially, the methylene blue dye is injected to see the end of tube. The central whitish fibrotic area is now exposed. This point is now incised with monopolar current or laser. Once the lumen is opened the dye comes out and soils the field. Operative field is made clear and incision is extended in a cruciate manner. If possible incision should be placed in between mucosal folds to avoid bleeding and if bleeding occurs it has to be controlled with minimum fine bipolar coagulation.

Everting the mucosa (Fig. 4B): After opening the tube infundibulum is assessed for presence of adhesions. If present, they are lysed as mentioned earlier.

Now through the ipsilateral port, the tubal serosa is caught hold of and with contralateral port, Babcock’s grasping forceps is introduced in the lumen of tube. By gradually exerting pressure in opposing direction with each grasper, the mucosa of infundibulum is everted making lumen fairly prominent in the center.

If incision put is too small, eversion will be difficult producing more damage to mucosa and if incision is too large, eversion will not be maintained properly.

Stabilizing the eversion (Fig. 4C): There are different techniques.
- Coagulation of serosa with bipolar forceps, lowest power setting should be used to coagulate only serosa and prevent damage to everted mucosa
- Vaporization of the tubal serosa with focused shot from laser beam
- Suturing with three to four interrupted sutures with 6/0 nonabsorbable material. The results are mostly equal, but suturing is usually preferred in our setup to avoid any lateral thermal damage to mucosa.

The end result of the surgery can be seen in Figure 4D.

Salpingectomy

In the patients who are to undergo IVFs for thick-walled hydrosalpinx or any other reasons, salpingectomy is advisable for improving embryo implantation and reducing the chances of ectopic pregnancy. The mesosalpinx is cauterized very close to tube to avoid damage to ovaries.
HYDROSALPINGES AND ASSISTED REPRODUCTIVE TECHNIQUES

Meta-analyses of large retrospective series have shown that compared with patients with tubal infertility of other causes, women with hydrosalpinx have about half the pregnancy, implantation, and delivery rates, and up to twice the incidence of spontaneous abortion after IVF-ET.

Treatment options for hydrosalpinx include drainage, salpingostomy, proximal tubal ligation, and salpingectomy. A meta-analysis concluded that laparoscopic salpingectomy should be considered for all women with hydrosalpinges due to undergoing IVF-ET.

TUBAL AND OVARIAN MICROSCOPY

Microsurgery involves the use of magnification to enable delicate surgery to be performed with minimal tissue trauma and accurate reconstruction of the different organs. Adequate training in the techniques involved is vitally important.

NEW TECHNIQUES OF IN VITRO FERTILIZATION AND EMBRYO TRANSFER

The success rate of microsurgery for tubal obstruction depends on pre-existing tubal disease.
A large hydrosalpinx will give a poor outcome while fimbrial phimosis can be treated successfully by laparoscopic microsurgery.

Thus, today IVF and tubal microsurgery must be considered as complementary rather than competitive procedures.

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Reconstructive Surgery in Infertility

CHAPTER 90

CHANGING CONCEPT IN RECONSTRUCTIVE SURGERY

Over the past 20 years, there has been considerable change in approach toward surgical management of infertile female. Change of attitude in surgical approach consists of finer technologies like microsurgery by laparotomy or minimal invasive surgery through laparoscopy and hysteroscopy.

Endoscopic approach has gained popularity due to extensive proliferation of endoscopic instruments, use of various energy sources and mastering the technique of endosuturing.

Various newer technologies and devices for prevention of postoperative adhesion have further contributed to significant advancement in endoscopic reconstructive surgery.

But self-assessment of surgical skill must be made before embarking on this form of endoscopic approach. Success rates reported by accomplished surgeons may not be attainable by all without significant rigorous training.

However, in certain areas of anatomic defects like tubal occlusion or tubal adhesion, assisted reproductive technique (ART) has proved to be a better alternative than tubal reconstruction, either by microsurgical technique or by laparoscopy.

Pregnancy rate after surgical treatment in moderate pelvic adhesion compared to those in ART are comparable. But, rate of ectopic pregnancy (13%) following surgical treatment is higher compared to those following in vitro fertilization-embryo transfers (IVF-ET) (5%).

Interestingly, ART has so overwhelmed the field of reproductive medicine that well-established microsurgical procedures are not frequently offered to many patients—even when women are candidates for either procedure. Two most important reasons for such deviation are:

1. High level of skill is essential for efficient performance of reconstructive surgery.
2. Large number of patients are required to maintain this skill.

Inspite of this, simple ART procedure may not be successful or even possible in many infertile women presenting with gross pelvic pathology like dense pelvic adhesions, endometrioma, fibromyoma or hydrosalpinges. Majority of them will require surgical correction prior to ART. Collaborative approach between reproductive surgeon and ART practitioner is essential for a sensible approach of infertility treatment in these desperate cases. Moreover, apart from intra-abdominal pathology, certain anatomic defects, though rare, may exist in the uterine, vaginal and vestibular areas. They require reconstructive surgery for restoration of fertility potential. There is no scope of primary ART treatment for these problems. Therefore, interest in reconstructive surgery will remain alive no matter whether this is performed by conventional method, by open laparotomy, operative hysteroscopy or closed laparoscopy.

INDICATIONS OF RECONSTRUCTIVE SURGERY

- Vestibular and vaginal malformation
- Cervical defect
- Uterine anomalies
- Tubal occlusion or distortion
- Ovarian enlargement or adhesion.

Vestibular or Vaginal Malformations

One of the rare varieties of vestibular dystrophy consists of congenitally stenotic and anteriorly displaced vaginal

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(Chapter updated by Poonam Yadav)
orifice associated with bladder extrophy. Exstrophy of the urinary bladder and epispadias are the anomalies caused by incomplete fusion of the lateral mesodermal elements making up the genital tubercle, the anterior urethral and the bladder walls, the symphysis pubis and the infraumbilical abdominal wall.2

In these anomalies the urethra and vagina are short, the vaginal orifice is frequently stenotic and displaced anteriorly, the clitoris is bifid and the labia, mons pubis and clitoris are divergent. The uterus, fallopian tubes and ovaries are normal except for occasional uterine duplication. The defective pelvic floor may predispose mature females to uterine prolapse, making uterine suspension necessary. Uterine prolapse does not appear to occur when osteotomy and closure of the anterior defect are performed early in life.

Coital problem due to stenotic and anteriorly displaced introitus is the cause of infertility. The introitus can be widened by simple introitoplasty or episiotomy. But if the introitus is situated far anteriorly, the vaginal tube has to be dissected upward and after dividing the perineum in the midline, the vaginal canal can be pulled down and fixed in nearly normal anatomical position. This was performed in one of our cases who was about to marry and her bladder extrophy and deficiency of anterior abdominal wall were repaired at an earlier age with colonic transplantation of both the ureters. Approximation of the clitoral halves in the hair bearing skin of the mons pubis provided satisfactory restoration of the external genitalia. Subsequently she married and delivered a viable child.

The other variety of vestibular defect consists of tough hymen usually associated with rigid perineum leading to dyspareunia or apareunia. Not that all women with tough hymen require surgical correction because at least some of them may have frigidity. These two conditions may be differentiated by gentle internal examination and creating confidence in the female partner. At the initial stage, regular self-dilatation with some lubricant may help.

For the other variety having tough hymen and rigid perineum, surgical reconstruction is essential. The conventional operation of hymenectomy with introitoplasty is performed, which is commonly referred to as Fenton’s operation.

A transverse incision at the mucocutaneous junction on the lower end of posterior vaginal wall is made. The posterior vaginal mucous membrane is lifted by sharp and blunt dissection as in perineorrhaphy up to the junction of lower third and upper two-thirds of vagina. A double-gloved finger is placed inside the rectum. The skin, perineal muscles and some fibers of pubococcygeus muscle are incised vertically in the midline short of outer coat of rectum. Bleeding points are secured. The reflected posterior vaginal mucous membrane is occasionally incised vertically half way through its length, if the hymen is too tough. The apex of this incised mucous membrane is fixed to the central point of the perineal skin which has also been incised vertically. Rest of the vaginal mucous membrane is fixed to raw edges of the perineal skin by interrupted 2/0 catgut or vicryl stitches. A light vaginal pack with Vaseline gauze is left inside for 24 hours.

Reconstructive Surgery for Other Types of Vaginal Malformations

Other types of nonobstructive vaginal malformations do not require reconstructive surgery to improve fertility potential. Complete vertical vaginal septum often associated with uterus didelphys may occasionally cause dyspareunia and under such circumstances, excision of the septum may be indicated. Often the septum may be thick and may contain few blood vessels which have to be secured and ligated.

Reconstructive Surgery for Cervical Defect

Cervical defect is not a specific cause of primary infertility, but is a significant etiological factor of mid-trimester abortion and preterm labor. The common cervical defect associated with reproductive failure is incompetent cervix. Indications, steps and limitations of cervical cerclage have been described elsewhere in this book and is beyond the scope of this chapter.

Reconstructive Surgery for Uterine Defects

The specific situations for reconstructive surgery for fertility restoration in women with uterine defects consist of:

- Congenital uterine anomalies
- Uterine myomas
- Uterine synechiae
- Adenomyoma and adenomyosis.

Some of these defects may prove difficult for surgical correction while others have to be judiciously evaluated whether or not they are contributory factors for infertility. For example, some of the nonobstructive congenital uterine anomalies and asymptomatic subserous or intramural fibroids may not be responsible for infertility and a reconstructive surgery is not essential. Similarly the extent of benefit, which may be achieved following reconstructive surgery for severe grades of uterine synechiae as well as for adenomyosis, has to be evaluated and explained to the couple before a definite surgical approach is planned.

Congenital Uterine Anomalies

Types of Uterine Anomalies and their Impact on Reproductive Failure

American Society of Reproductive Medicine (1988) has classified Müllerian anomalies into seven grades, viz.:

1. Hypoplasia and agenesis
2. Unicornuate
3. Didelphys
4. Bicornuate
5. Septate
6. Arcuate

Based on our observation and from therapeutic effectivity point of view, Müllerian anomalies have been broadly classified into two groups: (1) Müllerian anomalies with a nonfunctioning uterus and (2) Müllerian anomalies with a functioning uterus. Women in group-A belong to the classical Mayer-Rokitansky-Küster-Hauser syndrome and are beyond the scope of discussion in this chapter. Women in group-B (those with functioning uterus) may be further subdivided into three subgroups:

1. Totally obstructive (outflow obstruction)
2. Partially obstructive (one side is obstructed and other side is nonobstructed)
3. Nonobstructive. The question of reconstructive surgery for infertility treatment arises only in the nonobstructive group of Müllerian anomalies.

Women with total or partial outflow obstruction usually present with the problem of hematometra. Infertility is not the primary concern. The nonobstructive group of Müllerian anomalies with a functioning uterus are classically those women who have failure of lateral fusion (didelphic, bicornuate, arcuate uterus), nondevelopment of one Müllerian duct (unicornuate uterus) or complete or partial failure of dissolution of partition formed by fusion of two Müllerian ducts (septate or subseptate uteri). While some women in this category may have a normal reproductive career, others have the problem of either infertility or repeated pregnancy loss. Though it is difficult to establish that these Müllerian anomalies are specifically responsible for infertility and/or pregnancy wastage, yet when all other relevant causes have been excluded, reconstructive surgery is indicated.

Reconstructive Surgery in Different Types of Nonobstructive Müllerian Anomalies

**Didelphic and Unicornuate Uterus**

Overall reproduction is moderately compromised in patients with didelphic uterus. Reproduction is compromised not only due to infertility but by repeated pregnancy wastage and preterm labor. Cerclage has been favorably reported in cases of repeated miscarriage and premature labor. Unification of two uteri is not indicated.

The reproductive history of a patient with unicornuate uterus is not different from those with didelphic uteri. This is because didelphic uterus is a symmetrically increased duplication of unicornuate uterus. Women with history of repeated miscarriage with unicornuate uterus also do well with cerclage operation.

**Bicornuate and Septate Uterus**

Abicornuate uterus is usually not associated with reproductive problems hence surgical intervention is not essential. But a septate uterus may lead to reproductive failures. Infertility may not be the major problem, but reproduction failure is often due to repeated miscarriage or preterm labor. Diagnosis of septate uterus has to be confirmed by clinical examination, hysterosalpingogram (HSG), hysteroscopy and laparoscopy. Diagnosis is essential because, other two similar types of uterine anomalies simulating septate uterus, namely bicornuate and didelphic uteri do not usually require any specific surgical intervention. Moreover, before planning surgery even for septate uterus, other recognized causes of infertility and recurrent miscarriage are to be excluded.

**Surgical Treatment for Septate Uterus**

There are two routes of approach:
1. Abdominal metroplasty and
2. Hysteroscopic resection of septum and metroplasty. At present, abdominal metroplasty is not routinely performed except for a very broad septum. Hysteroscopic resection has been the treatment of choice.

**Abdominal Metroplasty**

There are three approaches
1. Strassman
2. Tompkins and

**Strassman’s Operation**

The original Strassman’s operation is unsuitable for correction of a septate uterus. Strassman used to perform the surgery only on “bicornuate” uterus. The incision line was horizontal and the unification line was longitudinal (Figs 1A and B).

**Tompkins Procedure**

The incision should be made precisely in the groove that can be palpated on the anterior fundal portion. The incision is then carried downward approximately 5 cm and at this point the knife enters into endometrial cavity (Figs 2A and B). The uterine horns now separate spontaneously or by gentle pressure on the incision itself, beginning at the point at which the endometrial cavity was first entered. The uterus is now ready to be sutured into a complete single body. It is important to avoid traumatizing myometrium and including endometrium with the myometrial suture.
Figs 1A and B: (A) Strassman procedure of abdominal metroplasty: Transverse incision on the nonunified area at the fundus; (B) Longitudinal unification of the nonunified area. Originally designed for bicornuate but not suitable for septate uterus. At present, unification of bicornuate uterus is seldom performed.

Figs 2A and B: (A) Tompkins valve metroplasty: Longitudinal incision on the groove starting at fundus for 5 cm till the endometrial cavity is reached; (B) The horns now separate spontaneously or by gentle finger pressure on incision line. Unification of the incision margins.

**Jones Wedge Metroplasty**

The wedge-shaped area to be removed is initially outlined by a suitable dye such as brilliant green. The fundal incision should be approximately 1 cm away from tubal insertion (Figs 3A and B). Cut margins are then approximated in three layers. Care should be taken to avoid tensions on suture lines.

The final size of the reconstructed uterine cavity seems to be unimportant. Many times it appears to be quite small compared to a normal uterus. Symmetry of uterine cavity is more important.

In some cases of complete septum of uterus, cervix is also duplicated. However, resection of cervical septum is never indicated, because, not only is the procedure difficult but this may also lead to postoperative cervical incompetence.
Reconstructive Surgery in Infertility

Hysteroscopic Metroplasty

Septate uterus may be more conveniently corrected by operating hystroscope or by resectoscope. It is desirable that the endometrium is suppressed with Danazol or gonadotropin-releasing hormone (GnRH)-analog for 2 months prior to surgery.

A simple uterine septum without involving the cervix may be incised with scissors or the loop with cutting current under direct vision. The Nd-YAG laser may also be used. The procedure should be performed under laparoscopic visualization of uterine fundus to limit the risk of perforation.

Usually, minimal bleeding results from the incision as the walls of the septum separate and retract. A balloon or a Foley catheter with the bulb distended may be inserted if substantial bleeding is encountered.

There may be some problem when there are two cervices, two uterine cavities and a single fundus. In these cases, the septum should be removed above internal os. This is done by placing a foley catheter in one uterine cavity and the hystroscope in the other (Fig. 4). The septum is incised and the Foley is identified in the other cavity. The excision of the septum is then continued till fundus is reached.

Fedele et al. reported that there is quick re-epithelialization of the cut margins of the septum and hence there is no need to place an intrauterine contraceptive device (IUCD) in the postoperative period. Estrogen supplementation has been suggested to promote epithelial regeneration following hysteroscopic septum resection.

Reconstructive Surgery for Uterine Fibromyoma (Myomectomy)

Except submucous variety, fibromyoma in general cannot be directly held responsible for infertility. By mechanical pressure there could be distortion of the uterine cavity or...
occlusion of the tubal ostium at the cornual end. Cervical or broad ligament fibroids may also be responsible for infertility due to mechanical distortion of the uterocervical canal. Hence, the indication of surgical treatment for fibroid in infertile women are:

- Submucous fibroid
- Intramural fibroid distorting uterine cavity
- Big fibroid, palpable per abdomen
- Symptom producing fibroid, like menorrhagia—whether big or small.

## Approach for Myomectomy

### Submucous Fibroids

Hysteroscopic resection is the treatment of choice.

Contraindications are:

- Uterine cavity more than 10 cm in size
- Suspicion of malignancy (which is rare)
- Coexisting adnexal lump
- When the tumor is sessile and a considerable portion of the tumor is still remaining intramural. This of course will depend on the expertise and experience of the operating surgeon because such tumors may also be removed transcervically if not in one operating session, may be completed in subsequent session after an interval of 6 weeks. Hysteroscopic resection of big submucous fibroid should always be performed under laparoscopic guidance.

The results vary depending on the size and location of myoma, the type of myoma (pedunculated or sessile) and the experience and skill of the surgeon.

### Intramural, Subserous, Cervical or Broad Ligament Fibroids

The conventional approach for removal of these tumors is by open laparotomy. With increasing skill of endoscopic surgeons, availability of specialized and improvised instruments, it is now possible to remove fibroids as big as 16 weeks gravid uterus size through laparoscopy either by morcellation or through colpotomy incision.

The principles of abdominal myomectomy whether by open laparotomy or through laparoscopy should be to minimize the blood loss and to avoid the risk of postoperative adhesion.

### Limiting the Blood Loss

The method suggested and not universally used are:

- Injection of vasopressin
- Bonney’s myomectomy clamp
- Use of tourniquet around the cervix below round ligament.

The correct approach is to make a small incision on the pseudocapsule, not more than 2 cm initially till the pearly white surface of the tumor is identified and the plane between pseudocapsule and the tumor is defined. Either with a single toothed volsellum or a traction suture passed through the substance of the tumor, traction is applied on the tumor. The incision on the pseudocapsule is extended. While the tumor is on traction, the pseudocapsule is dissected with sharp scissor snips and never by blunt finger dissection. In this way the tumor may be shelled out with minimum bleeding. At the final stage of enucleation, the tissue connecting the tumor with its bed may be clamped because these tissues may contain the feeding vessels. Immediately after removal of tumor, raw areas of the tumor bed should be approximated by rows of mattress or interrupted chromic catgut stitches.

### Avoidance of Risk of Postoperative Adhesion

- In case of multiple fibroids, incision on the largest tumor should be made in such a way that through the same incision, few other tumors may be removed.
- Incision at the cornual end should be avoided as this will increase the risk of postoperative tubal adhesion.
- Serosal stitch should be meticulous with less reactive fine suture material (2-0 or 3-0 vicryl). Mattress stitches should be much as much as possible.
- On occasions, an excised piece of parietal peritonuem may be used as a graft on the raw serous stitches of the united capsule. Omental graft is to be avoided.
- Use of barrier antiadhesives like intercede and a second look laparoscope.

Results of myomectomy will depend on age of the patient, duration of infertility, size and number of tumors removed. Berkley et al. observed pregnancy rate of 33% over the age of 30 years, whereas in women under 30 years, pregnancy rate was around 60%. Butram and Reiter reported recurrence rate of myomas after myomectomy as 15%, but 11% of them would require surgery for persistence or reappearance of symptoms.

### Intrauterine Synechiae

Intrauterine synechiae has been defined as the adherence between anterior and posterior uterine wall resulting in complete or partial obliteration of the uterine cavity. The most common cause is puerperal or postabortal curettage. Tuberculosis of genital organs is a significant etiology in our country. Incidence has been variously reported, ranging from 1.5% to 20–25%. There are three grades of intrauterine synechiae:

1. **Mild**: Endometrial adhesions are filmy, avascular and easily disrupted
2. **Moderate**: Fibromuscular adhesions are characteristically thick, but may be covered by endometrium and can bleed when divided
3. **Severe**: Connective or fibrous tissue adhesions lack any endometrial lining and do not bleed when divided.
Therapy

The objective of treatment of uterine synechiae is restoration of menstrual and reproductive function. While hysteroscopic lysis is the accepted form of therapy, there is some controversy regarding use of postlysis prosthesis and postoperative hormonal therapy.

Hysteroscopic Lysis

After the hysteroscope has been introduced into the endocervix, the adhesions, once identified, should be separated at their midpoint. Extensive adhesions should be removed by several separate procedures.

As synechiae are separated with conventional hysteroscopy, blood may obscure vision, and orientation within the cavity is lost. This problem, to some extent, may be solved with an operating resectoscope with a flushing system or with a suction canula through the dual channel hysteroscope. Simultaneous laparoscopy is advised to avoid the risk of perforation.

Adjunctive Therapy

Certain types of prosthesis have been suggested to prevent readhesion. These are polyethylene tubing, catheters, balloons and intrauterine devices. Broad-spectrum antibiotics reduce the risk of infection on the traumatized tissues. Estrogen therapy is also recommended for endometrial proliferation and coverage of the raw area as quickly as possible.

Pregnancy success rates following hysteroscopic lysis with or without adjunctive therapy vary between 40% and 90%. Oelsner and coauthors reported 39% pregnancy rate, 30% of which did not result in viable delivery. Our experience suggests that only in mild and moderate grades of uterine synechiae, some positive outcome may be expected. In severe grades, however, results are absolutely disappointing.

Adenomyoma and Adenomyosis

Adenomyectomy and myolysis have been suggested but the results are not very encouraging.

Reconstructive Surgery for Tubal and Tuboperitoneal Defect

In recent years, several developments have made significant impact on the role of reconstructive surgery on fallopian tubes. ART have radically changed our concept of the “appropriate” candidate for surgical reconstruction for diseased oviduct. Moreover, operative laparoscopy for salpingolysis and neosalpingostomy has become an increasingly popular alternative to traditional microsurgical laparotomy. It appears that pregnancy rates are quite similar following laparoscopic surgery to those achieved by laparotomy. Postoperative adhesion development also occurs frequently after operative laparoscopy. However, still it is likely that microsurgical tuboplasty by laparotomy, especially neosalpingostomy and tubal anastomosis will continue to be used.

Different Types of Tubal Microsurgical Techniques

In general, tubal surgery deals with four major areas of disease that will dictate the type of surgery to be performed. These are:

1. Peritubal adhesion: The operation performed is salpingolysis. Quite frequently, the ovaries may be adhered to the sidewall, fixed to the fallopian tube or enveloped in adhesions and ovariolysis is performed as well.

2. Distal tubal obstruction with or without hydrosalpinx: Reconstructive surgery performed are tuboplasty or salpingoplasty. Depending on the degree of distal obstruction and tubal distortion, two types of operations are performed, viz. fimbrioplasty and neosalpingostomy.

3. Segmental obstruction: Most commonly but not exclusively secondary to previously ligated tubes is treated with end-to-end anastomosis.

4. Proximal tubal obstruction: It is generally treated with tubocornual anastomosis. However, before tubocornual anastomosis, the less invasive therapy of hysteroscopic or fluoroscopic cannulation should be attempted. Uterotubal implantation is rarely performed now as pregnancy rates are much lower than with tubocornual anastomosis.

Salpingolysis or Salpingo-Ovariolysis

Lysis of peritubal or periovarian adhesions is now performed through laparoscopy rather than by open laparotomy. The objective is to restore the normal anatomical positions of distorted adnexa by releasing adhesions with minimum blood loss and damage to surrounding structures and at the same time to prevent future risk of adhesion formation. Pregnancy rate following salpingo-ovariolysis has been reported as 30–60% by open laparotomy approach and 60–70% through laparoscopy.

Salpingoplasty

The procedure includes fimbrioplasty as well as neosalpingostomy.

Fimbrioplasty

Lysis of fimbrial adhesion or dilatation of fimbrial phimosis is known as fimbrioplasty. Sometimes a constricting peritoneal (serosal) ring exists proximal to the site of obstruction. Simple lysis of this constricting band will uncover the normal appearing fimbriae.
If agglutination is found, a fine delicate mosquito forceps can be introduced into the phimotic opening of the tube and gently opened. With the forceps in open position, they are gently withdrawn causing dilatation of ostia. If fimbrioplasty is performed through laparoscope, dilatation may be performed by forceps or tongs. It is needless to mention that gentleness is necessary to avoid excessive trauma or bleeding. Long-term patency may be aided by using fine sutures to maintain established eversion of fimbria in some cases.

**Results**

The reported results following microsurgical as well as laparoscopic fimbrioplasty are between 20% and 70%\(^\text{11,14}\) Risk of ectopic pregnancy following both the approaches is 5%.

**Neosalpingostomy**

Neosalpingostomy is the creation of a new tubal ostium where the fimbrial end is totally occluded.

The following points are worth considering before neosalpingostomy is attempted:

- Neosalpingostomy can be performed for occluded fimbrial end with or without terminal hydrosalpinx
- The procedure will not be useful if the size of hydrosalpinx is more than 2.5 cm. Similarly prognosis of the operation is unsatisfactory if no healthy fimbria is identified following neosalpingostomy
- The procedure will not be useful if on HSG or on salpingoscopy following salpingostomy, the longitudinal mucous folds are not visible (Fig. 5)
- Neosalpingostomy at the ampullary or isthmial region is never rewarding. Only terminal neosalpingostomy is worth attempting
- Fimbria ovarica, which is almost always present at the distal fallopian tube, should be identified before neosalpingostomy is attempted.

Depending on the severity of adhesion, the results in terms of viable pregnancy after fimbrioplasty and neosalpingostomy range between 12% and 70%. Incidence of ectopic is between 4% and 10%\(^\text{15}\).

**Types of Tubal Anastomosis**

Depending on the site of obstruction or segment occluded/resected during previous sterilization, following types of tubal anastomosis are performed:

- **Interstitial-isthmic (Tubocornual)**
- **Isthmic-isthmic**
- **Isthmic-ampullary**
- **Ampullary-ampullary**
- **Interstitial-ampullary**

**Principles of Microsurgical Tubal Anastomosis**

The significant steps of both micro- and microsurgical techniques are described below:

- A loupe (magnification—1.5–6x) or an operating microscope (magnification—30–40x) may be used. Pregnancy
rates are not different when either loupe or microscope is used.¹⁶

• Micro instruments, as used by ophthalmic surgeons, are essential.

• Fine suture materials (vicryl 6-0 to 8-0) on a 3/8” circle taper are to be used for closure of mesosalpinx as well as the tubal wall. Alternatively fine nylon threads may also be used. It is possible to use 6-0 suture material without magnification, but for 7-0 or 8-0 material, loupe or microscope is essential.

• Tension at the site of tubal anastomosis should be minimum. For this, mesosalpinx is to be repaired before repair of tubal lumen.

• Except for reversal of tubectomy procedure, occlusion of cervix by an occlusion clamp (Buxton–Hick’s) may be helpful for distending the uterine cavity with dye and identifying the occluded distal end of the proximal blocked tube (interstitial or isthmic portion). The dye is injected into the uterine cavity through anterior uterine wall by a lumbar puncture needle.

• The incised raw edges of the proximal and distal segment are approximated in two layers by interrupted stitches. Two layer stitches are applied in one of the two ways; either deep muscular and seromuscular or mucosal and seromuscular.

• When microscope or loupe is used, the sutures are usually mucosal and seromuscular, but when microscope or loupe is not used, mucous membrane is avoided and the sutures are muscular and seromuscular. Approximately two to four 6-0 to 8-0 vicryl sutures are used for each layer. For mucosal stitch, the needle is passed from inside to outside the lumen of proximal cut edge and then from outside to inside the lumen of the distal segment (Fig. 6A). The knots will be obviously intraluminal which help to evert the cut edges of the proximal and distal tube thereby minimizing the risk of intraluminary narrowing. Two interrupted stitches are enough. For seromuscular stitch, the sutures are placed through the serosa and muscularis of the distal cut edge and then through the muscular and serosal coat of the proximal tube (Fig. 6B). Initially, the mesosalpinx is approximated to reduce tension on the anastomatic site.

• When there is disparity in the diameter of the opposing lumen to be united, as in isthmic-ampullary or ampullary-interstitial anastomosis, mucosal stitch is avoided and the opposing lumens are united with deep muscular and seromuscular stitches.

• To prevent too large opening in the ampulla, a needle technique for opening the ampulla has been practised. An obturator of an intravenous unit teflon (number 16) is introduced through the fimbriated end of the ampullary segment of the tube and advanced to the obstructed site. The needle is inserted through the teflon obturator and the obstructed end is perforated by the needle and then by the teflon sheath. After the needle is removed the 2-0 nylon (temporary splint) is passed in retrograde manner through the teflon obturator. The other end of the nylon splint is negotiated into the uterine cavity through the opened up distal end of the proximal blocked tube (isthmial or interstitial segment). The sutures are then passed in the manner already described. As the knots are being tied, the tip of the obturator is gradually withdrawn into the lumen and then taken out. If the nylon has been negotiated into the uterine cavity, this may be left behind and removed transcervically after 4–6 days in the postoperative period. Otherwise, the temporary nylon splint should be removed at the end of the anastomosis.

• In the case of cornual block (distal interstitial obstruction), circular incision with stab knife is made at the cornu to identify the dye distended proximal interstitial portion of the tube. The uterus is already distended with methylene blue after cervix has been occluded by an occlusion clamp. The proximal interstitial portion of the tube is rarely occluded. The cornu with the distal blocked interstitial segment is to be scooped out when the patent proximal interstitial portion will be exposed. Some bleeding is inevitable and the bleeding points are coagulated with unipolar cautery. This crater in the cornu is created for interstitial-isthmial or interstitial-ampullary

Figs 6A and B: (A) End-to-end anastomosis of tubal lumen with equal diameter (isthmic-isthmic). Mucosal stitch: The needle passes from inside to outside the lumen of the proximal segment and then from outside to inside the lumen of distal segment. The knots will be intraluminal, the raw edges are everted; this prevents intraluminary narrowing. Mucosal stitch is possible only with magnification; (B) Seromuscular stitch in tubal end-to-end anastomosis: The needle passes through serous and muscular coat of the distal segment and then through muscular and serous coat of the proximal segment. The mesosalpinx is initially united to prevent tension on the suture line of the reconstructed tube.
anastomosis. For interstitial-ampullary anastomosis, the luminar discrepancy may be minimized following the procedure already described for creating an ampullary opening. For cornual block, anastomotic procedures are better alternatives than previously practised uterotubal implantation.

**Alternative Procedure Other than Tubal Anastomosis for Tubal Occlusion**

- **Uterotubal implantation:** This procedure is now practically obsolete. Preparation of distal oviduct for implantation consists of either slitting its antimesenteric border or performing bilateral “fish-mouth” incisions on the cut end of distal tube to help preserve patency. Various incisions have been used to create an opening in the uterus. These include a sharp cornual wedge excision, a reamer and the posterior fundal technique. The cut end of distal fallopian tube is then inserted into the uterine cavity and a nonreactive absorbable suture is brought out through the uterus, superior and inferior to the incision and tied securely. The myometrium is then closed in two layers.

- **Transcervical cannulation of proximal tubal occlusion** (Fig. 7): If the obstruction is restricted to the proximal fallopian tube (interstitial portion of the tube) cannulation should always be attempted before an anastomosis is planned. Placement of catheter may be performed under fluoroscopic guidance or under hysteroscopic control and laparoscopic guidance. The catheter set consists of 9F, 5.5F and 0.035 straight wire. Cannulation is performed as shown in (Fig. 7). The catheters are introduced into the uterine cavity through a hysteroscope or a vacuum adapter. The 5.5F catheter is wedged into the cornu, the 3F catheter with the wire guide is introduced, and the wire guide is advanced through the obstruction. The 3F soft tube is then advanced over the wire. Balloon tipped catheters have also been developed which dilate the proximal portion of the oviduct, once cannulation is achieved. Hysteroscopic cannulation should always be performed under laparoscopic guidance to avoid tubal damage. Patency of proximal oviduct with cannulation can be accomplished in nearly 60% of cases.

**Results**

Success rate with tubal reanastomosis following tubectomy has been recorded as 60–80% live births with the risk of 3–4% ectopic pregnancies (Judd et al. 1976). Success rate following reversal operation will depend on different variables viz; tubal length after anastomosis, site of anastomosis, sterilization procedure performed, interval from sterilization procedure and subsequent recanalization and lysis of postoperative adhesions by second look laparoscopy. Tubal length following anastomosis is the most vital factor for prediction of outcome. Residual length of fallopian tube less than 5 cm is associated with poor pregnancy rate.

**Second Look Laparoscopy after Tubal Anastomosis**

Second look laparoscopy (1–2 weeks) after tubal reconstructive surgery aims at lysis of postoperative adhesions if there are any.

Swolin introduced the concept of second look laparoscopy to evaluate the results of reproductive surgery. Daniell and Pittaway suggested that early second look laparoscopy is safe and effective in reducing adhesion formation. Late second look laparoscopy (after 1 year) and second tuboplasty either by open laparotomy or through laparoscopy do not significantly improve subsequent pregnancy rates.

**Reconstructive Surgery for Congenital Anomalies for Fallopian Tube**

Congenital anomalies of fallopian tubes which may result in infertility are accessory ostium, elongated fimbria ovarica and distal tubal distortion caused by intervening paratubal cysts. These anomalies are not always responsible for infertility and microsurgical correction is not ordinarily indicated except for large paratubal cysts; rather such procedure may lead to further tubal distortion.

Another rare variety of congenital tubal anomaly which has been observed by the author is segmental absence of a portion of fallopian tube (a part of the ampullary portion) with a blind fimbria at the terminal end of mesosalpinx with intervening portion of mesosalpinx remaining vacant. Both the tubes are usually affected. HSG delineates the tubes in the shape of hydrosalpinx. Diagnosis can be made only by laparoscopy.
Usually more than 5 cm of tube remains available for surgical reconstruction. The distal blind end of the proximal segment is resected in an oblique fashion which is then converted into fish-mouth opening by longitudinal slit on the cut margins. Two stay sutures are anchored on the lips of this fish-mouth opening.

An opening on the blind fimbria is made with a stab knife. A fine mosquito forceps is introduced through this opening. The anchoring stitches grasped by the mosquito forceps are brought out through the opening created on the blind fimbria. The lips of the fish-mouth opening are everted and fixed with 6-0 vicryl suture to the external surface of the fimbria (Figs 8A to D). Out of three such cases operated by the author, one became pregnant.

**Reconstructive Surgery of the Ovary**

There are two types of ovarian pathology for which reconstructive surgery may be necessary for improvement of fertility potential. These are:

1. Benign ovarian cysts or tumors and

Current approach of surgical reconstruction is almost always through laparoscopy though under exceptional circumstances like a huge endometrioma, open laparotomy and microsurgery may be an alternative procedure.

**Principles of Ovarian Reconstructive Surgery**

**Cystectomy by Open Laparotomy**

- Effort should be made to make the incision in the axis of the ovary and in its most dependent portion so that normal anatomy may be re-established and normal tubo-ovarian relationship can be maintained.
- Conservation of ovarian cortex as much as possible where primordial follicles are present is of maximum importance. Even if it is possible to preserve one-fourth of healthy ovary, oophorectomy should be avoided.
- Cyst cavity should be obliterated by tiers of string sutures using 2-0 catgut but the cortex should be approximated with 3-0 to 4-0 vicryl by fine surgical procedure. A subcapsular suture is less adhesiogenic than the continuous suture through the ovarian capsule.

**Important Steps of Laparoscopic Cystectomy**

- An incision is made on the axis of the cyst and in its most dependent part. The cyst wall is opened and the cavity is inspected. If it is not suspicious for malignancy—dissection proceeds.
- With the use of atraumatic grasping forceps—one holding the cyst wall and the other one holding the capsule, the cyst wall may be dissected with scissors or bluntly. The blunt dissection is performed by holding the cyst wall with grasping forceps and rotating the cyst wall which will help to peel it off from the healthy ovarian tissue. Extreme care must be taken not to injure the hilar tissues which contain the blood vessels.
- Alternative method involves coagulation or vaporization of the lining rather than resection of the cyst wall.
- Though laparoscopic suturing can be performed on the ovary, it is rarely done unless the cyst removed is quite large or the anatomy distorted.

**Surgery in Dense Tubo-Ovarian Adhesion with or without Uterine Distortion**

Only tuboperitoneal adhesion:

- If the tubes and ovaries are not grossly damaged—adhesiolysis may be attempted. They may require ART as complimentary treatment
- If tubes and/or ovaries are grossly damaged, as in big hydrosalpinx or large chocolate cyst with dense pelvic adhesion, we try to conserve as much ovarian tissue as possible otherwise salpingo-oophorectomy will be the ideal treatment. Subsequently they may be benefited by IVF or IVF with oocyte donation
- In addition to tubo-ovarian pathology, uterus is enlarged and distorted by fibroids or adenomyosis with symptoms

![Figs 8A to D: (A) Congenital absence of ampullary part of fallopian tube. Blocked but normal looking fimbria is seen near ovary. Dotted line at the terminal end of blocked tube indicates the area to be excised followed by longitudinal slitting of the opening to make it fish-mouth in appearance; (B) Two anchoring stitches are placed on either lip of fish-mouth opening. An opening is made at the central region of the blind fimbria with a stab knife. The tips of a mosquito artery forceps are inserted through this newly created opening on the fimbria to grasp the anchoring stitches; (C and D) with traction on the anchoring stitches, the lips of the fish-mouth opening are pulled outside the fimbria. The lips of the opened up tube are everted and fixed to fimbria with 4/0 vicryl]
Ovarian Surgery for Induction of Ovulation in Polycystic Ovarian Syndrome

Bilateral wedge resection of the ovaries by laparotomy was the method which was practised in the past. This has recently been replaced by laparoscopic approach.

Wedge Resection of Ovaries by Laparotomy

The mechanism by which ovarian wedge resection can induce ovulation is not very clear. However, following wedge resection, dramatic changes are seen in androgen, estrogen and gonadotropin level which result in ovulation. Microsurgical procedures followed for wedge resection could not significantly prevent adhesion formation. Moreover, bilateral ovarian atrophy following wedge resection has been reported. For these reasons, this operation at present is very rarely performed.

Laparoscopic Surgery for Ovulation Induction in Polycystic Ovarian Syndrome

Laparoscopic techniques include ovarian biopsy, resection, drilling and cautery. Gjonnaess reported first laparoscopic ovarian cautery for the induction of ovulation in women with PCOS. The mechanism by which laparoscopic surgery may induce ovulation is similar to those observed following wedge resection. Postoperative adhesion formation cannot be totally prevented by laparoscopic ovarian cautery.

Prevention of Adhesion Formation following Reconstructive Surgery with either Laparoscopy or Open Laparotomy

Various surgical adjuvants are used in order to reduce postoperative adhesion formation and reformation. Conventional methods include:

- Avoidance of tissue trauma
- Meticulous attention to hemostasis
- Use of minimally reactive or nonreactive suture material
- More liberal use of laparoscopic and laser surgery.

In addition to these, various adjuvants are being tried to prevent adhesion formation in the following ways:

- By preventing the liberation of proteinaceous material from the site of peritoneal injury
- By preventing formation of a coagulum from the material
- By stimulating fibrinolytic activity
- By keeping peritoneal surfaces from abutting and re-approximating and
- By reducing proliferative activity of fibroblasts.

SUMMARY

There is no doubt that in female infertility requiring surgical intervention, the ideal approach is endoscopic surgery and whenever only surgery appears to be ineffective, this has to be combined with ART procedure. The areas of defect in female reproductive tract likely to be corrected by surgical intervention either by conventional or by endoscopic approach are summarized below.

In the vulvovaginal area, reconstruction is indicated for stenotic introitus due to tough or rigid hymen or rarely associated with bladder extrophy or pseudo-exstrophy. Correction of the defect by introitoplasty will help to resolve dyspareunia or apareunia and may restore fertility.

Uterine anomalies are more frequently responsible for recurrent pregnancy wastage and less for infertility. Of all varieties of uterine anomalies, surgical correction of septate uterus through hysteroscopic septum resection may be beneficial. Uterine anomalies may be associated with congenital cervical incompetence and therefore cervical cerclage may be considered to prevent recurrent miscarriage. Other causes of infertility or recurrent miscarriage must be excluded before surgical intervention is undertaken.

Other types of uterine defects which may be responsible for infertility are uterine myomas, synechiae and adenomyosis. Apart from myomectomy and synchiotomy in selected cases, surgical reconstruction of uterus to a normal shape and size do not bear a favorable prognosis for fertility enhancement.

Four types of surgery are performed for anatomically distorted or occluded tube. These are: salpingolysis for peritubal adhesion, salpingoplasty for fimbrial occlusion or terminal hydrosalpinx, end to end anastomosis for segmental obstruction and tubo-cornual anastomosis for proximal tubal obstruction or so-called cornual block.

In proximal tubal obstruction, before tubocornual anastomosis is planned, fluoroscopic or hysteroscopic cannulation should be attempted. Uterotubal implantation is rarely performed nowadays.

Ovarian reconstructive surgery for fertility restoration consists of excision of benign ovarian cysts or tumors including endometriomas and surgical manipulation of ovaries for induction of ovulation in women with polycystic ovaries. Except for large ovarian cysts, ovarian reconstructive surgery is almost always performed through laparoscopic approach. In all reproductive surgical procedures, meticulous care should be taken to prevent postoperative adhesion formation.

In majority of women with extensive pelvic adhesions with uterine distortion it is no use of performing reconstructive or reproductive surgery. Hysterectomy with conservation of
ovaries with future thought for surrogacy could be a better alternative. Of course, thorough counseling is essential.

REFERENCES

INTRODUCTION

Since time immemorial, there has been a compelling urge and necessity to propagate one’s own species. Reproduction is a basic fundamental right irrespective of caste, creed, religion, race, social, economic and educational status.

Failure to conceive after attempting to do so after 1 or more years is termed as infertility. Most infertile couples experience deep despair and despondency due to lot of social pressures coupled with physical, mental and financial stress involved in attempts to find a solution. Before the era of assisted reproductive technology (ART), treatment options were limited in terms of techniques, medications, skills, efficacy, and were associated with very low success rates in relation to the etiologic factors.

The field of ARTs has progressed rapidly over the past three decades to an extent that 80–90% of couples can be expected to have a healthy child. Louise Brown, the world’s first in vitro fertilization and embryo transfer (IVF-ET) baby was born on July 25, 1978; this was a landmark heralding the revolutionary future of the treatment of human infertility. Indeed we are indebted to Patrick Steptoe and Robert Edwards for this marvelous breakthrough. More than 2 million babies have been born to date with the application of ART in almost all forms of infertility.

HISTORY

Several milestones followed the birth of Louise Brown in 1978. In vitro fertilization (IVF) babies were born in several parts of the world. Oocyte retrieval was done laparoscopically for nearly a decade until first sonography-guided oocyte aspiration was reported in 1981 by Lenz et al. With the advent of vaginal transducers the transvesical transabdominal oocyte pickup was replaced by transvaginal oocyte retrieval.

Gamete intrafallopian transfer (GIFT) was reported by Asch et al. This was followed by zygote intrafallopian transfer (ZIFT) in 1986. In 1992, another path breaking technique was reported by the group from Brussels namely intracytoplasmic sperm injection (ICSI). Subsequently, pregnancies were reported with the use of testicular or epididymal sperm and even spermatids. Embryo transfer (ET) graduated from the four-cell stage to six- to eight-cell stage and eventually progressed to the blastocyst stage transfer with increasing advances in the production of culture media and the introduction of sequential media which could sustain human life in vitro for 5–6 days.

Natural cycle treatments gave way to stimulated cycles with the advent and widespread use of gonadotropins. Urinary derived products are today available in highly purified form and recombinant technology has led to the availability of recombinant follicle-stimulating hormone (FSH), luteinizing hormone (LH) and human chorionic gonadotropin (hCG). The use of gonadotropin-releasing hormone (GnRH) analogs for hormone suppression during a stimulated cycle was another major event which resulted in the establishment of the long protocol as a benchmark protocol. Further research led to the development of the GnRH antagonists which are currently being used in an endeavor to minimize the cost and duration of therapy.

Methods of avoiding excessive, costly and cumbersome ovarian stimulation have resulted in vitro maturation (IVM) of oocytes obtained from antral follicles and this approach
promises to minimize disadvantages of controlled ovarian hyperstimulation.

Pregnancy following human embryo freezing was announced in 1983 by Trounson et al. Later on human oocytes could be successfully cryopreserved. Cryopreservation techniques applied to sperms, oocytes and embryos have been streamlined to yield better success rates. Alternative methods such as vitrification of oocytes and embryos have emerged as an alternative to slow freezing methods.

Identifying a healthy genetically normal embryo for transfer has led to the development and application of preimplantation genetic diagnosis (PGD) and blastomere biopsy.

Laser has also found its utility in the application of several techniques of ART including assisted hatching. Barriers of advanced maternal age and declining fertility have been broken with oocyte donation; also surrogacy has come into vogue for cases with uterine problems and medical contraindications to pregnancy.

**ASSESSMENT OF OVARIAN RESERVE**

Patient response to treatment is directly linked to subsequent chance of conception. Hence, prediction of ovarian reserve assumes importance as a predictor of the response to stimulation as well as the subsequent chance of pregnancy. Women with low ovarian reserve are more prone to abortions and have a higher incidence of birth defects.

- Maternal age is by far one of the most important indicators of reproductive potential, with increasing age especially after 35 years and more so after 37 years signaling a lower chance of pregnancy irrespective of the treatment technique. The quantity and quality of oocytes determine the reproductive potential and both decline with advancing age. Also risks of abnormal progeny increases with increasing maternal age along with pregnancy related complications. Occasionally, a young woman may have a low ovarian reserve, but oocyte quality may not be compromised and hence she may have a better chance of pregnancy.

- Day 3 FSH levels were shown to correlate with ovarian response and pregnancy outcome in IVF cycles by Muasher and Oehninger. High basal FSH levels correlate with a higher cycle cancellation rate and also denote lower chances of pregnancy. FSH levels may show intercycle variation in women with borderline ovarian reserve ranging from normal to high levels; however, finding a single raised FSH level also carries the same importance and the maximal FSH reading is the best predictor of ovarian reserve. Usually a cutoff value of 10 mIU/mL is considered. In general, basal FSH correlates more with ovarian response to stimulation, the number of follicles obtained, number of oocytes retrieved and cycle cancellation rates rather than with distal events of implantation and pregnancy where maternal age assumes greater significance.

- **Basal antral count on sonography evaluation:** Noting the number of antral follicles on day 3–4 of a cycle is also a reliable indicator of the response to be expected from that ovary. Fewer follicles indicate a loss of ovarian reserve and higher cycle cancellation. Antral follicle count is a better predictor compared to the ovarian volume. A multivariate analysis found antral follicle count to be a single best predictor of ovarian response.

- Day 3 estradiol (E2) levels more than 80 pg/mL are thought to be an adverse signal. However, young women may exhibit both high as well as low E2 levels. High E2 may denote low ovarian reserve in women with a hurried follicular phase or may represent a high reserve in women with polycystic ovary syndrome (PCOS). Interpretation is more accurate if combined with FSH levels.

- Clomiphene challenge test was first described by Navot et al. A day 3 FSH level is done and clomiphene citrate 100 mg given from day 5 to 9. Day 10 FSH is estimated and if it is raised more than 10–12, it indicates a low reserve.

- **Day 3 inhibin levels:** A low inhibin level is associated with high FSH levels and vice versa. This test is expensive and not routinely available.

**OVARIAN STIMULATION**

The oocyte that ultimately resulted in the world’s first IVF conception was retrieved from a natural cycle. It was soon discovered that this method had a low efficiency and success rates as everything depended on retrieving a solitary mature oocyte. The natural cycle was also susceptible to untimely hormonal changes which would affect the oocyte quality. When clomiphene and gonadotropins were used in combination, retrieval of several oocytes resulted with concomitant improved pregnancy rates. Efforts to obtain many oocytes from hormonally controlled cycles led to the further development and widespread usage of gonadotropins and later on GnRH analogs and GnRH antagonists.

**Clomiphene**

Clomiphene alone is rarely used in ART cycles mainly due to the low level of response obtained. Advantages of cost and simplicity are offset by a major disadvantage of the occurrence of premature LH surges in up to 20–30% of cycles. Minimal stimulation protocols generally combine clomiphene along with small doses of gonadotropins.

**Gonadotropins**

These are very potent stimulators of the ovary. When started in the early follicular phase, they help in recruiting a large cohort of follicles, and sustain their growth resulting in multiple follicles and subsequent retrieval of a large number of oocytes. However, the disadvantage of premature LH surge with subsequent premature luteinization of the growing
cohort and subsequent low pregnancy rates remains a major disadvantage when used alone.

Gonadotropins currently available are of three types:

1. Urinary: These are derived from pooled urine samples of postmenopausal women and may have impurities and undesirable proteins—generally a combination of FSH and LH 75/150 IU is available.

2. Urinary highly purified: Here impurity levels are lower and selectively FSH alone is also available as 75/150 IU injections which can be administered subcutaneously in view of high purity levels.

3. Recombinant: These are genetically derived and offer advantages:
   - Highly pure with negligible contamination
   - Consistency of preparation—no batch to batch variation
   - No dependence on availability as in urinary.

   Currently, two preparations are available: Gonal-f® (Serono) and Recagon (Organon). Recombinant FSH, LH (leuprolide) and hCG (Ovidrel®) are available.

   Conceptually, recombinant preparations are better than urinary products with advantages of better follicular dynamics, better oocyte competence, shorter treatment duration with lower threshold and total dosage, clinical pregnancy rates appear to be higher though some have reported no significant differences as compared to urinary products. High cost is a factor to be considered.

   In PCOS patients, FSH alone is usually better suited for ovarian stimulation as compared to combined FSH due to the following reasons:
   - Deficient FSH activation is important in the pathophysiology of PCOS
   - FSH prevents increased follicular apoptosis in hyperandrogenic ovaries
   - LH action can increase undesirable androgen production
   - Granulosa cells lack LH receptors at the start of the cycle.

   The stimulation protocols in PCOS are individualized in order to obtain optimal response at a low risk of ovarian hyperstimulation syndrome (OHSS). Protocols used include:
   - Chronic low dose step-up protocol 75 IU FSH daily for 5–7 days increase by 37.5/75 IU if follicles less than 10 mm every 5 days
   - Step-down protocol
     - Initial 150–225 IU/day FSH
     - Later decrease to 75/37.5 IU/day once follicles greater than or equal to 10 mm
   - Sequential protocol
     - Initial step-up followed by step-down once follicle greater than or equal to 14 mm.

**Gonadotropin-releasing Hormone Analogs (Agonists)**

These are obtained by minor modifications of the GnRH molecule which result in significant prolongation of the half-life. When used initially there is a GnRH like action, resulting in release of FSH and LH from the pituitary; however, continuous use results in suppression of the pituitary with downregulation. This dual action has been utilized in various protocols:

**Ultrashort Protocol**

The GnRH analog is given on day 2, 3, 4 of the cycle and the gonadotropins are started on the day following the first GnRH analog dose. This minimizes the use of gonadotropins by utilizing the initial flare-up effect of the analog. However later on, down-regulatory effect can be lost as the effect wanes away especially with longer duration of gonadotropin stimulation.

**Short Protocol**

Here the analog is started from day 2 of cycle and continued up to the day of hCG. Again the initial flare-up is used to recruit a cohort of follicles and subsequent gonadotropin requirements may be reduced.

**Long Protocol**

This is the most commonly used protocol. It offers advantages of better cycle control and also facilitates scheduling of patients. In PCOS, it helps in reducing the tonic LH elevation and helps in obtaining uniform follicular growth. The analog is started either in the midluteal phase on day 21 or on day 2 in the follicular phase. The late luteal start is preferred though there is potential risk of pregnancy; however, studies have shown no deleterious effects. A follicular start can also rescue the corpus luteum and lead to unwanted cysts. All active cysts need to be aspirated prior to starting gonadotropins.

Various molecules are available including leuprolide, triptorelin, buserelin and nafarelin.

**Gonadotropin-releasing Hormone Antagonists**

These are GnRH molecules with aminoacid modifications which compete and block the GnRH receptors resulting in a decrease of FSH and more notably LH from the pituitary. In the follicular phase they prevent or interrupt the LH surge. Two molecules Cetrotide® (Serono) and ganirelix (Organon) have been studied and are in clinical use today.

Two different protocols have been tried:

1. Single 3 mg dose in late follicular phase
2. Daily injections of 0.25 mg from day 7 of stimulation or from the time the leading follicle reaches 14 mm. The antagonist suppresses both FSH and LH within a few hours; there is also a concomitant reduction in E2. This is however not thought to be detrimental to subsequent
implantation and embryo growth. The advantages of the antagonist protocol include:
- Shorter cycle duration
- Fewer injections
- Lower gonadotropin requirement, reduction in cost
- Lower risks of OHSS.

A few studies indicate slightly lower pregnancy rates in the antagonist cycles. This needs to be further evaluated in the light of paucity of data, lack of standardization and initial errors due to learning curve in the application of protocols. The best way to use antagonists needs further evaluation.²⁰

**MAIN TREATMENTS**

Besides intrauterine insemination (IUI), which is the simplest and most basic treatment involving semen processing and deposition of sperms into the uterine cavity in a natural or stimulated cycle, the currently widely practised treatment modalities are IVF-ET and ICSI. Despite several individual center variations in the practise of these treatments, the basic protocols are identical and involve gamete handling (both oocytes as well as sperms) in vitro. IVF relies on natural oocyte fertilization by a motile sperm and is thus suited for cases with normal seminal parameters. Presence of other female factors such as advanced age and other considerations may however lead to ICSI as the procedure of choice despite normal semen characteristics. Micromanipulation is more invasive and involves manual gamete fusion by direct injection of the sperm into the oocyte cytoplasm. Since ICSI is able to achieve fertilization and embryo development in the presence of considerable sperm hypofunction, there are natural concerns regarding the future progeny and their genetic status and fertility potential. Though fertilization and embryo numbers are higher with ICSI there is no significant difference in the pregnancy rates between IVF and ICSI in cases with normal semen characteristics. There is no evidence favoring replacement of all IVF cases by ICSI.

**IN VITRO FERTILIZATION AND EMBRYO TRANSFER**

In vitro fertilization and embryo transfer was initially considered a treatment of choice for tubal factor infertility. Thus cases of tubal disease, occlusion, adhesions or surgery were considered as other treatments could not offer comparable success. Subsequently IVF indications expanded to include PCOS wherein better follicular growth and fertilization rates were obtained. Today the indications cover unexplained infertility, advancing maternal age, repeated trials of conservative treatments, ovarian failure and antisperm antibodies. IVF offers a possibility of diagnosis of gamete dysfunction. With the advent of ICSI, indications have expanded to encompass almost all cases of male infertility.

**Ovarian Stimulation: Oocyte Retrieval**

A couple is recruited into the IVF-ET program after proper selection and investigations. An appropriate ovarian stimulation protocol is selected and follicular growth is observed with serial sonography. Hormone tests (FSH, LH, E₂ and progesterone) are selectively done as per the clinical situation and when three or more follicles attain a size of 17 mm or more, hCG is administered in the dose of 5,000–10,000 IU. The oocyte retrieval is carried out 36 hours later. The hCG injection is a crucial component that initiates the changes required to prepare the oocyte to resume meiosis from the diplotene stage of prophase I in which the oocyte has arrested. The aim is to obtain oocytes in metaphase II after the polar body has been expelled. Oocytes are ready for fertilization at this stage and earlier stage oocytes need to undergo maturation before they can be fertilized. A delay in oocyte retrieval more than 36 hours may result in ovulation and subsequent loss of oocytes in the peritoneal cavity. Very often aspirating the periovian fluid in the pouch of Douglas yields oocytes.

**Oocyte Screening**

On aspirating the follicles, the follicular fluid contents are emptied into Petri dishes and screened for the presence of oocyte-cumulus complexes (OCCs). These are then transferred into flushing medium which is usually hydroxyethyl piperazineethanesulfonic acid (HEPES) buffered so that pH changes are minimal as this procedure is done under the laminar airflow system on a 37°C heated table top outside the CO₂ incubator. The OCC are rinsed with flushing medium and transferred into IVF culture medium in four-well dishes which are placed in the CO₂ incubator for incubation for 2–6 hours.

**Sperm Preparation**

Semen sample is processed by layering or swim-up or density gradient techniques so that a final motile sperm suspension is obtained for insemination.

**Oocyte Insemination**

This is generally done after 2–6 hours of oocyte retrieval. About 5,000–100,000 sperms are gently released around the OCC in the four-well dish and the dishes are returned to the incubator.

**Fertilization Check: Day 1**

Sixteen to eighteen hours postinsemination, fertilization can be noted by the appearance of the second polar body and the presence of two pronuclei with aligned nucleolar bodies—the two-pronuclear (2 PN) stage. Anomalies of fertilization like 3 PN, 1 PN are apparent at this stage. This stage requires
dissection of the cumulus cells away from the oocyte which is usually done with the help of flexible micropipettes of 140–170 µm diameter. At this stage, further incubation can be done in microdroplets of culture medium placed in single-well dishes overlaid with paraffin oil. Usually zygotes are incubated in groups of two or three in each microdroplet of 40–50 µL. Release of paracrine factors by embryos aids in growth. This requires small volumes of culture medium which is provided by the microdroplet. Oil overlay acts as a physical barrier between the medium and the surrounding air. It reduces evaporative loss and slows the rate of gas diffusion, thus buffering the medium from rapid temperature, pH and osmolality changes, especially outside the CO₂ incubator.

**Cleavage: Day 2**

Twenty-six hours after insemination, cleavage begins and a two-cell stage can be observed with two equal sized cells. At 44–48 hours, the four-cell stage is visualized. Embryos are graded based on the number, size, shape of the blastomeres and the degree of fragmentation. Embryos can be transferred at this stage or incubated further and transferred at the six- to eight-cell stage on day 3. Further incubation requires a change in the culture medium and growth can be observed until the blastocyst stage when transfer can be done. There are several advantages of transferring blastocysts as follows:

- More physiological synchronization between the embryo and the uterus
- True assessment of embryo viability post-genome activation
- Avoids exposure to a hyperstimulated setting
- Time available for diagnosis if embryo biopsy done
- Reduced uterine contractions on day 5
- Reduced possibility of cryodamage
- Reduced pregnancy loss
- Applications in genetic diagnosis
- Assessment of development and viability.

Not all embryos may grow until the blastocyst stage and some patients may not have any ET.

**INTRACYTOPLASMIC SPERM INJECTION**

Male infertility treatment has been revolutionized with the advent of micromanipulation. Till then recourse to medication. Operative procedures like varicocele ligation, vasoepididymal anastomosis, etc. and of course IUI, IVF-ET with pooling of semen samples was the only alternative available. This however could not yield desired results especially in cases with severe oligoasthenoteratospermia. Azoospermic cases with no sperm production could not benefit. IVF also could not offer a solution in cases with failed fertilization. ICSI was first reported in 1992 by the group from Brussels. ²³

The evolution of ICSI can be traced to attempts at gamete manipulation. Partial zona dissection (PZD) was first tried out to enhance probability of sperm penetration. ²⁴ This was followed by subzonal insemination (SUZI) wherein sperms were injected into the perivitelline space with a micropipette. ²⁵ Subsequently, ICSI was tried wherein a single sperm was directly injected into the ooplasm resulting in a healthy live birth. ICSI proved to be superior to SUZI. ²⁶

**Indications**

- Male subfertility: Oligospermia, asthenospermia, teratospermia
- Azoospermia: Obstructive/nonobstructive. Techniques such as percutaneous epididymal sperm aspiration (PESA), microsurgical epididymal sperm aspiration (MESA), testicular sperm extraction (TESE) and testicular sperm aspiration (TESA) are used to obtain sperms from the testes or epididymis
- Ejaculatory dysfunction: Retrograde ejaculation, anejaculation
- Poor post-thaw sperm sample
- Poor semen sample on day of oocyte retrieval
- Fertilization failure in IVF cycles
- Unexplained infertility
- High antisperm antibodies
- IVM cycle.

Injection of immotile sperms lowers the fertilization rate. Other factors such as sperm count, morphology (except globozoospermia) and high antisperm antibodies do not affect success rates.

Important laboratory steps which affect the success rates include:

- Concentration and duration of exposure to hyaluronidase for oocyte denudation
- Time of denudation after oocyte retrieval
- Selection of proper sperm—motile
- Position of polar body while injecting
- Aspiration of ooplasm before injection.

An appropriate stimulation protocol (long agonist or antagonist) is used and oocytes are retrieved 36 hours after hCG injection as in IVF cycle. After a short incubation of the OCC, denudation of oocytes in hyaluronidase along with mechanical aspiration is carried out and metaphase II/metaphase I/germinal vesicle oocytes are differentiated. Only metaphase II oocytes are ready for injection. Some metaphase I oocytes may undergo in vitro maturation after incubation and can be injected later. These have lower fertilization rates but similar embryos. Denuded oocytes are incubated till injection.

Sperm preparation is carried out using various techniques depending on the source:
- Ejaculated sperms are prepared by either washing and centrifuging with medium or by density gradient method
• MESA samples are collected and pooled and later centrifuged in density gradient media.
• Testicular sperms are obtained by testicular aspiration or from microbiopsy and the tissue is teased under a microscope to identify sperms. The tissue is then centrifuged with medium and sperms are obtained.

Sperms are placed in a central polyvinylpyrrolidone (PVP) droplet placed in a Petri dish; PVP helps in reducing sperm motility, facilitates better fluid control in the micromanipulators as well as prevents sperm from sticking to the surfaces. The micromanipulator has a high magnification inverted microscope along with a central heated stage for maintaining temperature at 37°C in order to prevent damage to the meiotic spindle. The oocytes are placed in droplets around the central sperm containing PVP droplet under oil overlay. The micromanipulator has holding and injection pipettes which are either air or oil filled. Fine 3D movements are made through micrometers. The oocyte is held in position by gentle suction through a holding pipette. The sperm injection pipette is filled with PVP and a single motile sperm is selected. This is then immobilized by gently rubbing the pipette against the base of the dish resulting in breakage of the tail. This step is important as the break in the sperm plasma membrane is important for release of sperm factors into the ooplasm resulting in oocyte activation. The immobilized sperm is then aspirated into the pipette, the oocyte held with its polar body in 6 o’clock position in order to minimize damage to the spindle body. The oolemma is pierced and ooplasm slightly aspirated into the pipette followed by injection of sperm into the ooplasm. The injected oocytes are rinsed and placed in culture medium droplets in order to ensure proper retrieval of the cumulus oocyte complex without any trauma. Some centers routinely flush the follicles until an oocyte is retrieved using double lumen aspiration needles. In a randomized study Tan et al. reported flushing report more than 70% retrieval rates.

Complications

Though a simple procedure complications can arise during and after oocyte retrieval. The most common is vaginal bleeding at the puncture sites. Occasionally, a large vaginal vessel may be lacerated. Bleeding generally stops with pressure, rarely a vaginal suture is required. Intra-abdominal bleeding following injury to iliac or ovarian vessels may occur and manifests as hemorrhagic shock. Retroperitoneal bleeding can occur which may not be detectable until much later. Pelvic infection can also complicate with formation of tuboovarian abscess. Cases with endometriotic cysts, hydrosalpinges and previous pelvic infections are more susceptible. A single intraoperative dose of antibiotic is given at the time of oocyte retrieval in many centers. Bowel injury and bladder injury can also occur if proper visualization before puncture is not done. Rare complications include adnexal torsion, rupture of endometriomas and even vertebral osteomyelitis.

Procedure

The patient is placed in a lithotomy position and a short general anesthesia is administered. The vagina is irrigated with normal saline and vigorously rinsed. The needle set is then connected to a tube containing some flushing medium and to the suction pump. The ovary is fixed between the probe and pelvic wall. The follicle is visualized in its maximal diameter and the needle is inserted through the needle guide into the follicle with a short jab. Suction is started and the follicle is seen to collapse completely; at the same time, follicular fluid is seen in the tubing as well as the collection tube confirming aspiration. The needle is then advanced into the adjacent follicle and the procedure repeated until all follicles are completely aspirated in both ovaries. This was done transabdominally and transvesically. Later on vaginal transducers arrived on the scene and transvaginal oocyte retrieval became established as a simple, easy and convenient procedure which could be carried out as an outpatient procedure under sedation and local anesthesia. However, many centers use short general anesthesia and the patient frequently is discharged within a few hours of the procedure. A long vaginal transducer of 3–5 MHz frequency to ensure adequate depth of visualization is preferred. A needle biopsy guide is used along with the probe. A 17–18 gauge sharp Echotip® needle is generally used. Follicle aspiration sets with needle, Teflon® tubing and adaptors are readily available. These are tested for mouse embryo toxicity. Suction is generated by a suction pump in the range of 90–120 mm Hg in order to ensure proper retrieval of the cumulus oocyte complex without any trauma. Some centers routinely flush the follicles until an oocyte is retrieved using double lumen aspiration needles. In a randomized study Tan et al. reported flushing report more than 70% retrieval rates.
EMBRYO TRANSFER

This is an important step in the entire treatment which can indeed limit the success rate of the cycle. All efforts prior to this step can go in vain if embryos are not carefully and properly transferred into the uterus. Some studies have demonstrated significant differences in pregnancy rates depending on the individual performing the ET.\(^{31}\) Whilst standardization of the procedure may eliminate this variability.\(^{32}\) Routinely transcervical deposition of embryos is done which is essentially a blind method based on clinical feel. Thus absolute confirmation of embryo placement in the uterus is lacking. Several factors affect ET:

- **Cervical mucus:** This may plug the catheter tip leading to retention of the embryos or damage or improper placement of the embryos. Further, embryos may get stuck to the mucus and get dragged out along with the catheter. Mucus pushed into the uterus may interfere with implantation as well as may lead to contamination.
- **Failed negotiation of the cervical canal:** Commonly acute flexion and version of the uterus hinders the passage of the catheter which if soft may undergo unnoticed coiling or kinking within the cervical canal.
- **Irritation of the uterus and initiation of uterine contractions can lead to embryo expulsion in up to 15% of cases.**\(^{33}\) Higher rates of expulsion and lower pregnancy rates were noted with increasing frequency of uterine contractions.\(^{34}\)

Several methods have been demonstrated to improve the success rates after ET:

- **Dummy transfer:** This is a mock transfer done prior to the actual transfer in the same or previous cycle. This helps in noting the length and direction of the uterus as well as ease of negotiation.

- **Ultrasonography (USG) guided transfer:** Abdominal probe placed above a filled bladder during the actual procedure helps in visualization of the passage of the catheter into the uterus and confirming the release of medium or air bubbles at the time of injection. Also USG evaluation of the direction and length of the uterus helps.

- **Avoiding initiation of uterine contractions:** Avoiding touching the fundus helps in preventing the initiation of uterine contractions. A midfundal deposition 0.5–1 cm below the fundus is ideal.

- **Using a soft malleable catheter to avoid trauma as far as possible is recommended.**

- **As far as possible the cervix must not be held with any instrument in order to avoid irritation to the uterus.**

- **Blood or mucus at the catheter tip is associated with increased embryo retention in the catheter.**\(^{35}\)

- **Cervical infection at the time of transfer also reduces the pregnancy rates.**

- **Use of nonsteroidal anti-inflammatory drug, prostaglandin inhibitors, sedation at the time of transfer is practised in some centers.**

- **Loading of the embryos into the catheter should be done carefully with a small volume of 30–40 µL containing the embryos.** Injection of large volumes of culture medium results in flushing of embryos into the tubes or back through the cervical canal. An ectopic pregnancy rate of nearly 5% has been reported in IVF cycles.

LUTEAL PHASE SUPPORT

Progesterone is commonly used to support the luteal phase in most ART cycles. Down-regulation protocols result in low output of hormones from the corpora lutea due to suppression of FSH and LH. Also during oocyte retrieval a lot of cumulus cells and granulose cells are sucked out leading to concerns about the adequacy of the luteal phase.

Clinical pregnancy rates were shown to improve significantly with luteal supplementation with hCG or progesterone.\(^{36}\) Various formulations of progesterone have been used:

- **Intramuscular progesterone injections 50–100 mg daily** are administered up to the day of beta-hCG estimation and continued thereafter if pregnancy ensues. Disadvantages are pain, discomfort and occasional pruritic rashes. The oily vehicle base is responsible for the pain and formation of nodules at the site of injection.

- **Vaginal progesterone cream in prefilled tube (Crinone®—Serono) is also available and can be used twice daily**

- **Dydrogesterone oral tablets 10 mg twice daily can also be added**

- **Some centers also favor addition of E2 valerate in doses of 2–4 mg daily**

- **Low-dose aspirin 75 mg/day, multivitamin tablets—folicate, anti-oxidants are also recommended in addition by some centers.**

Supplementation is continued up to the day of beta-hCG estimation and thereafter for 11–12 weeks if conception occurs.

LABORATORY ASPECTS

**Equipment**

Any ART setup warrants use of proper equipment placed appropriately in a proper environment. Periodic checks of equipment function and calibration, disinfection of the laboratory, standardization of protocols, monitoring the air quality and periodic assessment of the results are an integral part of any ART setup. Quality assurance and quality control is essential for obtaining standardized results on a consistent basis. Since a single variable is capable of effecting adverse outcome, stringent laboratory monitoring is vital. Some of the basic equipment includes:

- **CO₂ incubator**

- **Laminar airflow**
- Micromanipulator
- **Microscopes**: Stereo zoom microscope, binocular microscope, inverted microscope
- Centrifuge
- Heating blocks
- Standard incubator
- Refrigerator
- Liquid N₂ canisters
- Sperm counting chamber.

*Laboratory disposables*: These include Petri dishes, single-well dishes, four-well dishes, conical round bottom tubes, pipettes, oocyte pickup single or double lumen needles, ET sets, Flexipets, inspection and handling sets, micropipettes amongst others.

**Media and Environment**

Various readymade media are available for use in ART including simple, complex and sequential media. In general gametes must be shifted to fresh media within 48 hours. All media need to be properly equilibrated as per their composition. Proper maintenance of temperature at 37°C and a pH of 7.2–7.4 are vital. Also media have a shelf life and need to be used within this period. Opening a media bottle several times over a long period is not recommended as this alters the composition of the medium. Various antibiotics are often added to the media in order to help avoid infection.

Common media constituents include glucose and amino acids. These are as per the requirements of the gametes and the growing embryo. As the embryo progresses from two-cell to four-cell to morula to blastocyst stage, its requirements change necessitating the use of media of different constitution. Thus sequential media cater to these requirements and assist the growing embryos in fulfilling its needs. Media available include those used for flushing, oocyte handling for a limited time, culture media for incubation within the incubator, sperm preparation media, extended culture media for growth up to blastocyst stage, special ET media, and various other preparations including paraffin oil, hyaluronidase and polyvinylpyrrolidone.

**Embryo Culture**

Maintaining a near-physiological environment in vitro is vital for the growth of embryos. Advances in the development of embryo culture systems including media, equipment and techniques have improved embryo viability significantly resulting in better pregnancy and live birth rates.

Media are vital ingredients as the gametes or embryos develop within them. Media may be of different types such as simple salt solutions with added nutrients or complex fortified media, simple optimized media or sequential media. Media use is governed by the requirements of the growing embryo and changing needs from pronucleate to cleavage stage to blastocyst stage. The chances of culture media induced trauma or damage to the embryo should be minimal. Birth defects attributable to improper media composition have been described.

Generally media are composed of the following:
- **Water**: Highly purified and endotoxin free water is a must for any medium as 99% of the medium contains water.
- **Ions**: Extracellular ionic compositions alter intracellular ions and hence affect the growth. Proper concentrations of Na, Cl, K, phosphate, Ca, Mg is important for maintaining viability. Osmolarity also has to be maintained in the range of 275–295 mOsm/L.
- **Carbohydrates**: Differential needs of the embryo mandates the use of different carbohydrates at various growth stages. The zygote and cleavage cell embryo needs pyruvate and lactate as the major energy metabolite in contrast to glucose which is needed by the morula and blastocyst.
- **Proteins**: Including amino acids affects the growth of the developing embryo significantly as these are readily used for development. Also addition of amino acids results in a greater capacity to withstand stress. Nonessential amino acids and glutamine are useful as energy substrates besides helping in maintenance of pH and osmosis. There is a differential need for amino acids pre- and post-compaction and the sequential media are designed to provide this switch. Glutamine significantly affects the development of the embryo.
- Ammonium accumulation as a result of amino acid metabolism adversely affects growth hence storage of amino acid containing media at 37°C should be avoided and renewal of culture medium within 48 hours is mandatory. Increasing concentration of ammonia in the culture medium has been shown to have a negative impact on human blastocyst development.
- Ethylenediaminetetraacetic acid (EDTA) is a chelator of heavy ion and addition of EDTA in the early stages enhances embryo development while it is detrimental at later stages including postcompaction.
- Antibiotics such as penicillin, gentamicin and streptomycin are generally added to minimize chances of infection.
- Human serum albumin (HSA) is added to alter the solvent properties of the medium. It also negates the effect of toxins. Synthetic serum substitute containing 84% HSA and 16% alpha and beta globulins is also available as an alternative. Recombinant albumin with advantages of elimination of risks of blood products and batch variability has also been found to be equally effective.
- **Buffers**: For 6 hours postfertilization oocytes and embryos are more susceptible to pH related damage as they lack the necessary systems to buffer the acidic/alkaline pH. To a certain extent cumulus cells help in the buffering mechanism. Various buffers have been used to protect gametes and embryos from rapid pH changes:
  - Commonly a CO₂-bicarbonate buffer system is used to maintain a pH of 7.2–7.4. Most media available contain bicarbonate hence a CO₂ incubator is required with a
**Oxygen:** It is important to check the calibration of the incubator with Fyrite® fluid or high accuracy CO₂ infrared sensors periodically. The main disadvantage of this system is a rapid change in pH on exposure to air.

- Alternatively, phosphate based buffers are available but are toxic to embryos in vitro and have limited buffering capacity in cryopreservation.
- Hydroxyethyl piperazinieethanesulfonic acid based systems are commonly used along with some bicarbonate for gamete handling during oocyte pickup in order to maintain pH when the incubator cannot be used.
- Morpholinepropanesulfonic acid (MOPs) is another buffer recently being used with an advantage of less temperature sensitivity as compared to HEPES.

- **Oxygen:** It has been found that lower O₂ concentration promotes growth as compared to 20% O₂ saturation.
- **Temperature:** Maintaining the culture medium at 37°C at all times is vital as fluctuations in temperature result in damage to the meiotic spindle. Ambient light of high intensity is damaging and low illumination is preferable while handling gametes and embryos.
- **Air:** It is important to have pure air in the laboratory. Presence of volatile organic compounds and chemical airborne contaminants significantly affects the culture process. Use of special air filtration units and positive pressure systems improves the success rates.

**OOCYTE DONATION**

Women of menopausal age, those with poor egg reserve or premature ovarian failure can also conceive and deliver a child with this method of using oocytes from a young donor and fertilizing them with husband’s sperms to get embryos which are then transferred to the uterus of the wife.

**Indications for Oocyte Donation**

- Premature ovarian failure congenital
  - Gonadal dysgenesis, Turner’s syndrome post surgery, infections, severe endometriosis, chemotherapy and irradiation.
- Advanced maternal age
- Poor ovarian reserve
- Repeated failed IVF/ICSI cycles
- Prevention of passage of inheritable genetic disorders.

Oocyte donation using in vitro techniques was first described by Trounson in 1983. Donor screening with proper medical, surgical, family, genetic history as well as tests for infections of human immunodeficiency virus (HIV), hepatitis B and hepatitis C need to be done. Matching of donor and recipient characteristics is preferable.

Donors undergo stimulation as in any other ART cycle. However, IVM may be offered as an option to reluctant donors with advantages of minimal or no stimulation, fewer hospital visits and less monitoring.

Cycle synchronization between the donor and recipient is essential as oocyte retrieval and subsequent ET has to be done at an appropriate stage of endometrial development in the recipient. Generally oral contraceptive pills along with GnRH analogs (long protocol) facilitate synchronizing both cycles. In cases of amenorrheic recipients, there is no need to use the agonists. Estradiol valerate 2 mg two-three times a day is generally used for a minimum of 8–10 days for endometrial growth. Sonography monitoring is done to confirm endometrial thickness greater than or equal to 7 mm. Estradiol may be continued for 4–5 weeks if required prior to ET. In cases where the uterus is hypoplastic, several E₂ cycles with cyclical progesterone withdrawal are administered before the recipient is enrolled for ET in order to stimulate uterine and endometrial growth. Once the oocyte retrieval is scheduled for the donor, the recipient is started on progesterone a day before or on the day of oocyte retrieval. The E₂ dose may be increased to 2 mg four times a day along with daily progesterone injection 100 mg/day until the ET and up to the beta-hCG estimation day. Postconception, both E₂ and progesterone are continued up to 12 weeks of gestation.

**SURROGACY**

Women with severe defects or damage to the uterus cannot conceive. However, they can have their biological child by undergoing ovarian stimulation, harvesting their eggs, fertilizing them with their husband’s sperms and transferring the resulting embryos into another woman’s uterus. This person carries the pregnancy till term and delivers a child biologically belonging to the infertile couple. The child is then legally adopted by the couple as their heir. Indications for surrogacy are:

- **Uterine anomalies:** Severe congenital hypoplasia, rudimentary uterus.
- **Uterine damage:** Severe Asherman’s syndrome post-infections, post-trauma.
- Medical conditions precluding pregnancy.

Medicolegal and social issues need to be resolved before surrogacy is considered. Maternal child bonding may complicate the outcome. The surrogate mother is medically evaluated and undergoes the same preparatory procedures as in oocyte donation as a recipient of ET.

**CRYOPRESERVATION**

Cryopreservation aims at preserving living cells at subzero temperatures for extended periods of time with complete recovery of cellular function after thawing. Sperms, oocytes, zygotes, embryos as well as blastocysts have been frozen...
successfully. Currently, either slow freezing or rapid vitrification methods are being used.\(^{41}\)

Cells undergo a lot of chemical, physical and thermal stress during freezing as well as thawing and depending on the cell type different methods are used so that there is minimal damage to cellular function. Cooling results in intracellular ice formation which is detrimental to cellular function. Special molecules called as cryoprotectants are used to facilitate the journey of the cell from 37°C to –196°C where they eventually remain in liquid N\(_2\) until thawing. Osmotic fluxes and changes in solute concentrations need to be minimized.\(^{32}\) Cryoprotectants can be intracellular permeating type or extracellular nonpermeating. Glycerol, propanediol and dimethyl sulfoxide (DMSO) permeate into the cell across the cell membrane and replace intracellular water whereas sucrose is extracellular cryoprotectants which increases the osmotic pressure around the cell. Gradually these molecules help in achieving cell shrinkage with equilibrium maintained across the cell membrane. Cryoprotectant is cell specific with cell membrane permeability and cellular water content being important determinants.

Human sperms were one of the first to be successfully cryopreserved, and thawed semen was found to be capable of fertilization and induction of embryonic development. Sperms can be frozen by the ultrarapid method. Generally after processing the semen, the sperm wash solution is diluted with the freezing medium containing glycerol in the ratio 1:1. It is cooled up to 2°C by placing it above liquid N\(_2\) for 25 minutes and then plunged into liquid N\(_2\). For oocytes or embryos initially DMSO was used but due to its disadvantages propanediol is preferred as the cryoprotectant. Blastocysts are frozen using serial concentrations of glycerol.

Vitrification is a process wherein there is rapid cooling of cells in the presence of high concentrations of cryoprotectants resulting in solidification without intracellular ice formation. The liquid cellular state is converted into a solidified state with the same molecular and ionic distribution and behaves like a viscous supercooled liquid.\(^{30}\) The cells are dehydrated by exposure to a high concentration of cryoprotectant and plunged directly into liquid N\(_2\). Ethylene glycol is commonly used due to its rapid diffusion and equilibration properties. Oocytes, zygotes, embryos\(^{43}\) and blastocysts\(^{44}\) have been vitrified.

Results of cryopreservation vary and are generally lower than fresh cycle rates. Besides procedural damage, the initial cell quality influences future post-thaw function.

**IN VITRO MATURATION**

Stimulating the ovaries in order to obtain several oocytes has its own disadvantages and risks. These include daily injections, long duration of treatment, necessity of monitoring with repeated sonography, blood hormonal tests besides risks of OHSS and long-term associations with malignancy. PCOS patients especially are at a high-risk of OHSS due to recruitment and growth of several follicles. In vitro maturation was initially proposed in this group of patients with a high basal antral count as an alternative method of obtaining oocytes without stimulating the ovaries.\(^{45}\) Earlier Cha et al. had reported in vitro maturation of oocytes collected during gynecologic surgery, fertilization and transfer to a case of premature ovarian failure with healthy livebirths.\(^{46}\) The basic principle is to retrieve oocytes at an early stage without stimulating the ovary, maturing these in vitro, fertilizing them with IVF or ICSI and transferring the resulting embryos into the uterus. It has been demonstrated that OCC can be made to mature in vitro. In fact cumulus cells are thought to modulate and mediate a number of beneficial cellular functions beneficial to the oocyte. They may have autocrine and paracrine effects. The culture medium is generally supplemented with small amounts of FSH, LH. Estradiol and proteins have also been added to the medium in order to mimic in vivo conditions.

With the rising success rates of IVM its application has been extended to various other conditions besides PCOS. High responders with exaggerated responses to small amount of gonadotropins, poor responders who need very large doses of gonadotropins and still have very few follicles, oocyte donors can avoid the long, multiple injection schedules. Recently PGD has also been combined with IVM resulting in a healthy livebirth.\(^{57}\) Malignancy patients requiring chemotherapy can also undergo IVM with shorter treatment duration and avoidance of hormonal stimulation.

**Technique**

Baseline scans are done on day 3–5 and repeated at day 7–10. hCG is administered and oocyte retrieval scheduled 36 hours later. hCG priming has been reported to increase the rates of IVM of oocytes.\(^{48}\) Oocyte retrieval is done using a low suction pressure up to 50 mm Hg. Follicular fluid is collected in 0.9% normal saline and heparin. Follicular flushing, curettage of the follicular wall and several punctures may be required in order to obtain to cumulus-oocyte complexes. The oocytes are incubated for 24–48 hours and denuded. Metaphase II oocytes are identified and either cryopreserved or subject to ICSI. Embryos thus formed are either transferred or cryopreserved.

**PREIMPLANTATION GENETIC DIAGNOSIS**

Initially an experimental genetic screening tool for human embryos,\(^{49}\) now it is well-established clinically and used in several thousand cycles worldwide. It is used for the diagnosis of single gene defects as well as chromosomal disorders e.g. aneuploidy and translocations. Genetically normal embryos are identified and selectively transferred thereby preventing transmission of genetic disorders. Polar bodies, blastomeres or blastocyst trophectoderm cells can be analyzed. The cells
to be biopsied are obtained by PZD done through chemical, mechanical or laser methods.

Either pre- or postfertilization polar body may be biopsied. The advantages include extraembryonic handling as well as time duration available between biopsy and subsequent ET. However, information about sex of the embryo and the paternal genome is not available. Also fragmentation and incomplete biopsy hinders the diagnosis.

Embryos are usually biopsied at the six- to eight-cell stage on day 3 where one to two blastomeres are selectively obtained. The disadvantages are reduction of implantation rates if the embryo is damaged; also time between biopsy and transfer is limited hence rapid diagnosis is essential. Further, the trophectoderm may be at variance with the inner cell mass.

Various autosomal conditions like cystic fibrosis, histiocytosis as well as X-linked fragile X syndrome can be diagnosed on PGD.

Polymerase chain reaction (PCR) is the most commonly used technique with its quick and highly sensitive diagnosis. Multiplex PCR and real time PCR are also being used. Contamination from cumulus cells may cause an erroneous diagnosis, also DNA amplification failure can occur.

Fluorescence in situ hybridization is commonly used for the diagnosis of chromosomal disorders with 9–10 chromosomes being currently studied as well as for translocations. Thus fluorescent DNA probes for sex chromosomes as well as chromosomes 13, 14, 15, 16, 18, 21 and 22 are available.

Target population includes high maternal age, cases of recurrent abortions, repeated IVF cycle failures and genetically abnormal couples with translocations and inversions.

Preimplantation genetic diagnosis is a safe and effective means of identifying genetically abnormal embryos with pregnancy and implantation rates comparable to conventional IVF cycles. With further advances, the scope of PGD will widen to encompass more and more genetic disorders.

**LASER-ASSISTED HATCHING**

Lasers are widely used in medicine. Applications of laser in ART have evolved in recent years and apart from use in research, clinical use is growing as technology and instrumentation are simplifying laser availability and practical utility.

Lasers may be of contact type or noncontact type. In the latter, laser energy at the focal point is absorbed by the tissue water and macromolecules resulting in disruption of the matrix and ablation. The diode noncontact infrared lasers appear to be most appropriate for zona cutting applications. Indium-gallium-arsenic-phosphorus laser is popular with a wavelength of 1.48 µ being rapid, safe and effective.

The zona pellucida post sperm entry undergoes a series of mechanical and chemical changes in order to prevent polyspermy and protect the developing embryo. In some cases, the zona becomes extremely hard and impairs embryo hatching. A mean zona thickness of 18 µm or more is considered significant. Lysine is important and deficiencies in action or function are important for failure to hatch. This deficiency could arise as a result of in vitro culture conditions. Zona thinning or drilling have shown improvement in implantation rates in selected cases wherein it optimizes the implantation window and promotes earlier implantation.

Indications of laser-assisted hatching are:
- Thick zona pellucida
- Elderly patient
- Elevated basal FSH
- Failed implantation cycles
- Poor responders
- Unexplained infertility
- Slow cleaving fragmented embryos
- Very few embryos
- IVM cycles.

Laser can also be used during ICSI for sperm injection where it prevents excessive cell deformation during injection or for carrying out biopsy procedures for PGD. Zona thinning is advantageous with no loss of blastomeres or exposure to contamination with bacteria or WBC or toxins as compared to zona drilling.

Generally assisted hatching is done on day 3 at six- to eight-cell stage. It can be done at the blastocyst stage also. A laser mounted micromanipulator is used. The embryo is held at one end and single or multiple small 30–40 µ holes are drilled by the laser. A large hole can result in loss of blastomeres and can increase the fragility of the embryo as well as increase its susceptibility to bacterial contamination or immune cell invasion.

**COMPLICATIONS OF ASSISTED REPRODUCTIVE TECHNOLOGY**

**Multiple Gestation**

There has been a dramatic rise in the incidence of multiple gestation largely due to the practise of ART. The rate has nearly doubled in the last few years with 90% of the contribution coming from ART techniques and the rest from rising maternal age in the developed world. Multiple gestation has implications for the mother, risks for the children as well as financial and other concerns for the family and health providers. The practise of transferring large number of embryos is largely responsible for this outcome. Triplet gestations and higher warrant embryo reduction procedures to ensure fetal survival. Indeed current practice of ART is focused on reduction in multiple gestation by various techniques including blastocyst transfer and limitation of
the number of embryos transferred. The long-term sequelae of premature births and high order births and the costs of managing these prove to be an enormous burden and drain on the health system.

**Pregnancy Complications**

Assisted reproductive technology pregnancies are at increased risk of preterm delivery, intrauterine growth restriction, low birth weight, perinatal mortality and neonatal intensive care unit (NICU) admissions. Pregnancy-induced hypertension, abrupton placentae, gestational diabetes complicate pregnancies more often and cesarean section rates are very high.

**Congenital Anomalies**

There is an increased risk of malformations in IVF or ICSI children and though the rise in risk is modest, large studies are needed to address this issue. Anomalies of the genitourinary system in particular are increased in ICSI children. Part of the risk is inherent with its basis traceable to the genetic abnormalities linked to infertility and advanced maternal and paternal age. The genetic abnormalities associated with male infertility are now well-known and transmission of DNA defects of sperms into the progeny is not unexpected. However issues of in vitro culture conditions, culture media, blastomere biopsy procedures as well as drug induced abnormalities are a matter of concern.

Concerns regarding fertility of the children born as a result of IVF or ICSI need to be addressed.

In a meta-analysis, Hansen et al. noted an increased risk of anomalies (odds ratio 2) compared to the natural conceptions after correcting for various parameters. However, ethnicity and duration of infertility were not factored in. In a multicentric cohort study, Bonduelle et al. noted an odds ratio for major malformations of 2.77 for ICSI children and 1.8 for IVF as compared to the natural conceptions. There were no differences in developmental milestones in IVF or ICSI children as compared to natural conception children in studies by Sutcliffe. One of the largest studies evaluating ICSI: Child and Family Outcome (ICSI-CFO) study noted no effect of conception status on neurodevelopment, but highlighted increased usage and requirements of health resources by ICSI or IVF children as compared to natural conceptions.

The risk of childhood malignancy is not found to be increased in ART children.

There seems to be an association between ART and some genomic imprintable disorders like Beckwith-Wiedemann syndrome. This has been associated with a loss of methylation at a maternal allele site. Whether this is due to inherent susceptibility of genome alterations in infertility or induced due to in vitro culture conditions need to be evaluated further.

With increasing children being born after ART these would constitute a significant proportion of the population in times to come. It is imperative to simultaneously follow-up ART children diligently and thoroughly so as to detect significant markers of deviations from normalcy.

**Ovarian Stimulation and Cancer**

Studies by Rossing et al. indicated a higher risk of ovarian cancer associated with clomiphene citrate use for more than 1 year. A large study by Venn et al. showed no significant increase in the risk of ovarian and breast cancer in women treated with gonadotropins. Large studies are needed to evaluate the risks of prolonged usage of ovary stimulating agents and current recommendations are to use these for as short duration as possible in the smallest effective dose.

**OVARIAN HYPERSTIMULATION SYNDROME**

One of the most dreaded complications of ART is OHSS which may be seen in various forms in up to 30% of all cases. Severe manifestations are associated with considerable morbidity and occasionally even mortality. Generally OHSS is classified as:

- **Mild:** Ovaries enlarged up to 5 cm with abdominal distension.
- **Moderate:** Ovaries enlarged up to 12 cm with ascites, gastrointestinal symptoms of nausea, vomiting, diarrhea, abdominal pain and weight gain.
- **Severe:** Ovaries enlarged more than 12 cm, massive ascites, pleural effusions, hemoconcentration, oliguria, electrolyte imbalance and disseminated intravascular coagulation (DIC).

It is an iatrogenic condition related to natural or exogenous hCG administration (presence of massive numbers of luteinized follicular cells).

Women at highest risk are young, thin and PCOS with typical necklace sign. Very high levels of E2 >4,000 pg/mL or 1,700 pg/mL in IUI cycles, more than 20 follicles or more than 6 follicles in IUI cycles, luteal phase support with hCG, conception in the treatment cycle and the long GnRH agonist protocol, all increase the risk of developing OHSS.

Pathologically, there is ovarian enlargement with hyperproduction of ovarian hormones and vasoactive substances resulting in a hyperpermeability state with fluid shift to extravascular spaces with hemoconcentration, renal impairment and thromboembolic phenomena. The exact mechanism is not clearly known, but is thought to be related to hCG stimulated ovarian overproduction of vasoactive endothelial growth factor (VEGF) associated with angiotensin II and interleukins.
Precautions can be taken to avoid development of severe OHSS by various means:
- Low-dose cautious FSH use
- Proper, continuous monitoring of follicular growth, E2 levels
- Coasting of FSH— withholding FSH and hCG doses until E2 levels reduce
- Reducing the dose of hCG to 5,000 IU; replacement of hCG with GnRH agonist for ovulation induction in antagonist cycles is being studied
- Usage of GnRH antagonists/insulin sensitizers
- Thorough follicular aspiration
- 20% albumin has been administered at the time of oocyte retrieval with contrasting results
- Cryopreservation of embryos and ET in a later cycle to prevent conception in the treatment cycle
- Avoiding hCG for luteal phase support
- Finally withholding hCG and canceling the cycle.

Treatment of mild and moderate OHSS is conservative with bed rest, symptomatic treatment with antiemetics, anti-inflammatory, anticoagulant agents and administering intravenous fluids to replenish extra cellular losses.
Severe OHSS mandates hospitalization and may even require ICU management. Principles of management are:
- Replace: Crystalloids—glucose saline vigorously and colloids—20% HSA/fresh frozen plasma.
- Aspirate: Ascitic tap is a very simple therapeutic procedure.
- Operate only if: Hemoperitoneum/torsion of ovaries/life-threatening OHSS mandating medical termination of pregnancy (MTP).

REFERENCES
Cloning literally means duplication. A process by with an exact copy or a duplicate is produced is defined as cloning.

There are basically three types of cloning technologies:
1. Recombinant deoxyribonucleic acid (DNA) technology or DNA cloning
2. Reproductive cloning
3. Therapeutic cloning.

Cloning is an umbrella term traditionally used by scientist to describe different processes for duplicating biological material.

INTRODUCTION (FIG. 1)
The current century is destined to bring a tremendous change to science and the practice of medicine. It has been already acclaimed as the century of Biology, as the fusion of molecular genetics and experimental embryology has pushed science beyond the unknown.

The major breakthrough of pioneering works of Ian Wilmut and Campbell with the birth of first ever cloned mammal “Dolly the sheep” (July 5, 1996) has ushered in a new era of science. “A line has been crossed and now reproduction will never be the same.”

What Professor Ian Wilmot did in creating Dolly was that he made a differentiated cell of the skin of the ewe go back to being a totipotent cell by applying some electrical voltages in vitro and then he put back “this” cell into an empty follicle and let it grow and cleave in vitro. The “embryo” so formed was implanted into a surrogate sheep. “This” embryo had chromosomes from only one parent (an absolute duplicate of the parent). After a normal gestational period, the first ever cloned mammal Dolly was born. History was created with the scientific possibilities running as far as your and our imagination can think of. Think of duplicate or triplicate or even eight of you, think of human photostats, think of human spare parts, think of organ factories, whatever, just let your imagination run wild.

Scientists who have focused their cloning efforts on more forgiving embryonic tissue have met with greater success. A simple approach, called embryo twinning (literally splitting embryos in half), is commonly practiced in the cattle industry. Coaxing surrogate cells to accept foreign DNA is a bit trickier. In 1952, researchers in Pennsylvania successfully cloned a live frog from an embryonic cell. Three decades later, researchers were learning to do the same with such mammals as sheep and calves. “What’s new”, observes University of Wisconsin animal scientist Neal First, “is not cloning mammals, it’s cloning mammals from cells that are not embryonic.”

Embryo cells are infinitely easier to work with because they are, in the jargon of cell biologists, largely “undifferentiated”. That is, they have not yet undergone the progressive changes that turn cells into skin, muscles, hair, brain and so on. An undifferentiated cell can give rise to all the other cells in the body, say scientists, because it is capable of activating any gene on any chromosome. But as development progresses, differentiation alters the way DNA, the double-stranded molecule that makes up genes—folds-up inside the nucleus of a cell. Along with other structural changes, folding helps make vast stretches of DNA inaccessible, ensuring that genes in adult cells do not turn on at the wrong time or in the wrong tissue.

The disadvantage of embryonic cloning is that you do not know what you are getting. With adult-cell cloning, you can wait to see how well an individual turns out before deciding to clone it. Cloning also has the potential to make genetic engineering more efficient. Once you produce an animal with a desired trait—“a pig with a human immune system”, perhaps—you could make many copies.
....a line has been crossed, and reproductive biology will now never be the same for people or for sheep. This exotic form of reproduction could be an extremely useful tool if used properly, there is no doubt about the exciting possibilities it opens up in the field of agriculture, champion cows, top wool producing sheep, etc. square tomatoes and potatoes so we can pack them better and easier in square cartons and boxes. The misuse of this technology goes to resurrecting the dead and possibilities of virgin births and women giving birth to their own twins. Men are not required, but we still need the women.

Science is not stopping here and if you have read “Chromosome 6” by Robin Cook you are going to be frightened by the possibilities of using animals as your spare parts. Animal lovers wake up and protest as the human civilization is not ready to die of heart failure, liver failure and kidney failures and we are going to use genetically tinkered apes, monkeys, chimps, baboons or even pigs for providing human race with spare hearts, spare livers and spare kidneys and all this is possible because science has managed to locate the genes responsible for organ rejection and science has further managed to translocate these genes from short arms of chromosome 6 and reimplant them in animal embryos to give you “spare parts animal” a “stepney” you can use when your original tire (heart, liver, kidney, eyes, etc.) gets “punctured”. The only risk is that, we will or may be creating cave men again and human civilization can be seen as they evolved. You might see your very own ancestor ape with your genes 100 million years ago in 2000 AD: scary is not it.

Clinton bans cloning; no funding for such research in the United Kingdom, other countries are not sure what to say. Today the United Nations has taken a bold step to ban human cloning in the whole world.

Science is not resting and in 1997, the Japanese have come out with artificial wombs and a step further was achieved by scientists in October 1997 as producing headless embryos. So in case you had some ethical feelings of killing your clone for spare kidneys or even killing your genetically engineered
Cloning: Current Research

Cloning: Current Research

Like most scientists who score major breakthroughs, Wilmut and his colleagues have raised more questions than they have answered. Among the most pressing are questions about Dolly's health. She is 10 months old and appears to be perfectly fine, but no one knows if she will develop problems later on. For one thing, it is possible that Dolly may not live as long as other sheep. After all, observes NCI's Stewart, "she came from a 6-year-old cell. Will she exhibit signs of aging prematurely?" In addition, as the high rate of spontaneous abortion suggests, cloning sometimes damages DNA. As a result, Dolly could have developed any number of diseases that could shorten her life and it did... Dolly died.

January 21, 1998, George and Charlie the first cloned calves were born in a Texas ranch and this may be the future of pharmaceutical industry. These genetically engineered calves will be able to produce medicines for us humans in their milk. Unfortunately George and Charlie are males the real threat to the pharma industry will be when cows (females) will be born. Cow milk will now act as human albumin (human blood).

Nobody at Roslin or PPL is talking about cloning humans. Even if they were, their procedure is obviously not practical—not as long as dozens of surrogates need to be impregnated for each successful birth. And that is probably a good thing, because it gives the public time to digest the news—and policymakers time to find ways to prevent abuses without blocking scientific progress. If the policymakers succeed, and if their guidelines win international acceptance, it may take a lot longer than the editorial writers and talk-show hosts think before a human clone emerges—even from the shadows of some offshore renegade lab. "How long?" Asks PPL's James. "Hopefully, an eternity."

Mr Seed has created new waves of very high frequency and has once again brought out the controversy of human cloning. Richard Seed who is a physicist doctor from Howard University USA and has worked in biology has stated that he wishes to produce 500 human clones a year and according to him this will eventually extend human life and enhance civilization. So what if USA bans this and 90% of Americans are against the idea of cloning there are other labs around the world—yes Mr Seed there are—but have you given it a second thought...? Is "create a child for a price" or are we going to see a situation of "which one of us is me?" and the question is "1[w]o be or not to be?" and this has to be answered by our society before the likes of Mr Seed are unleashed in our beautiful world of normal humans.

Today cloning has taken a new dimension of resurrecting the dead; an extinct Indian wild ox (Gaur) is born in USA to an American cow (January 2001) "Bessie" in a farm near Sioux City, Iowa. The DNA from this extinct buffalo “Gaur” skin cells was extracted and introduced in 690 empty cow’s eggs. Only 81 grew up to blastocyst and then out of these 81 cleaving embryos (blastocyst) 42 were implanted in 32 cows, only 8 implanted (became pregnant), 5 aborted, 2 were terminated for experiments and 1 is still growing in the cow to be born in February 2001. Only Bessie is left with Noah. This experiment is being carried out by Advanced Cell Technology Company of USA. This imminent birth of a cloned gaur signals a new approach to species preservation (Noah’s New Ark—says the Time magazine°). The other animal candidates for cloning in near future are the Giant Panda, White Rhinoceros and the Bactrian Deer.

The first human cloning from tissue of a dead 2-year-old girl is also under way. The only daughter of a rich couple of the UK died a year back and her DNA is now going to be introduced in empty human follicles and female volunteers trying to resurrect the dead girl.

Mr Lee of New York (www.malepregnancy.com) will be the first male to give birth to a child. He is already midway pregnant by these techniques. But this has proved to be a Hoax website.

The human genome finally revealed a day before the valentine day of 2001 and the latest valentine gift devised by Japanese is a heart-shaped pendant containing a little of your DNA. You can present this to your beloved who could probably use it to clone another you.

It is estimated that in 50 years from today man will alter his own genetic architecture completely and will be in full control of evolution.

There seems to be a positive side to cloning and these optimists say that there is more to cloning than the Narcissist who think the neo-Nazi dreams of a pure human race is about to come true.

Imagine for a moment that your daughter needs a bone marrow transplant and no one can provide a match, or that your wife’s early ovarian failure has made her infertile or your only 3-year-old has drowned in the river or run by a way ward bus or hit by a freak lightning and the grief is unbearable and impossible. Here is where cloning technology might help in giving you a child. Researchers also hope to clone adult human cells that will make it possible to grow new hearts, new livers and kidneys and new nerve cells, or we could just be curing Alzheimer’s, Parkinson’s, diabetes and cancer. Blocking cloning research at this stage might just stop all these dream cures.

But again the other side of misuse is very evident and Mr Wicker a gay man of New York is about to go in for cloning only for the reason that “I can thumb my nose at Mr Death and say, “you might get me, but you’re not going to get all of me”. It (cloning) is a partial triumph over death.

The ethical questions are many:

- What if ....a child dies and one parent wants to clone but other does not? Who owns the rights to a dead person’s DNA?
- What if ....people do not want to be cloned after they die? Will they be able to insert a do-not-clone clause in their will?
Current and emerging technologies in reproductive biology, including assisted reproductive technologies and animal cloning, are discussed in the context of the impact of genomics era biology. The discussion focuses on endocrinology associated with establishment and maintenance of pregnancy, fetal-placental development, lactation, and neonatal survival. Various aspects of uterine biology, including development during the neonatal period and function in adult females, are discussed with respect to reproductive efficiency. It is clear that combining strategies for use of conventional animal models for studying the reproductive system with new genomics technologies will provide exceptional opportunities in discovery and research involving data integration and application of functional genomics to benefit animal agriculture and the biomedical community. New and emerging biotechnologies and comparative genomics approaches will greatly advance our understanding of genes that are critical to development of the reproductive system and to key events at each stage of the reproductive cycle of females and males.

Some interesting facts about cloning:

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Transgenic animal technology is one of the most fascinating technologies developed in the last two decades. It allows us to address questions in life sciences that no other methods have achieved. The impacts on biomedical and biological research, as well as commercial interests are overwhelming. The questions accompanying this fast growing technology and its diversified applications attract the attention from a variety of entities. Still, one of the most fundamental problems remaining is the search for an efficient and reliable gene delivery system for creating transgenic animals. The traditional method of pronuclear microinjection has displayed great variability in success among species. While an acceptable efficiency in the production of transgenic mice has been attained, the relative low efficiency (1%) in creating transgenic livestock has become one of the barriers for its application. In the past decades, improvements in producing transgenic livestock have made a slow progression, however, the recent advancement in cloning technology and the ability to create transgenic livestock in a highly efficient manner, have opened the gate to a new era in transgenic technology. Discoveries of new gene delivery systems have created an enthusiastic atmosphere that has made this technology so unique. This review focuses on gene delivery strategies as well as various approaches that may assist the advancement of transgenic efficiency in large animals.

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Current and emerging technologies in reproductive biology, including assisted reproductive technologies and animal cloning, are discussed in the context of the impact of genomics era biology. The discussion focuses on the endocrinology associated with establishment and maintenance of pregnancy, fetal-placental development, lactation, and neonatal survival. Various aspects of uterine biology, including development during the neonatal period and function in adult females, are discussed with respect to reproductive efficiency. It is clear that combining strategies for use of conventional animal models for studying the reproductive system with new genomics technologies will provide exceptional opportunities in discovery and research involving data integration and application of functional genomics to benefit animal agriculture and the biomedical community. New and emerging biotechnologies and comparative genomics approaches will greatly advance our understanding of genes that are critical to development of the reproductive system and to key events at each stage of the reproductive cycle of females and males.

- Juvenile Diabetes Research Foundation International, 120 Wall Street, 19th Floor, New York, NY 10005, USA. cnierras@jdrf.org.
The Juvenile Diabetes Research Foundation International (JDRF) was founded in 1970 by parents of children with juvenile diabetes to find a cure for diabetes and its complications through the support of research. The foundation was an early supporter of stem cell research, recognizing the promise of stem cells to quicken the pace of discovery for a cure for juvenile diabetes. The JDRF has committed considerable resources to supporting stem cell research in both the United States and abroad. In the United States, the organization has been an advocate on the state and national level for increased funding and for expansion of current federal policy restricting embryonic stem (ES) cell research.


- The Fels Institute for Cancer Research and Molecular Biology and Department of Biochemistry, Temple University School of Medicine, Philadelphia, PA 19140, USA.

Cloning by somatic cell nuclear transfer (SCNT) in mammals has revealed the remarkable ability of an oocyte to reprogram somatic cell nuclei and induce them to recapitulate the development program. Despite the success, cloning remains very inefficient. This review summarizes recent observations from cloning in mice that reveal some of the likely causes for the present inefficiency. One cause appears to be the slow pace of reprogramming combined with the early onset of genome transcription, which together cause cloned embryos to elaborate many somatic cell characteristics even before the first cleavage division. The altered phenotypes of cloned embryos render standard embryo culture conditions grossly sub-optimum. Another cause appears to be a hitherto unappreciated contribution of spindle-associated factors to early embryo development. As current procedures remove the spindle and associated factors, cloned embryos lack these factors. These observations are providing new insight into basic mammalian embryology. They also reveal possible changes to protocols that could improve the overall success of cloning. Copyright 2004 S. Karger AG, Basel.


- Reproductive BioMedicine Online, Duck End Farm, Dry Drayton, Cambridge CB3 8DB, UK. rge@fbmonline.com.

Numerous biomedical scientists have contributed to the wide knowledge on the growth of preimplantation human embryos in vitro, now improving every aspect of the form of clinical care. These data were gained ethically in many countries, to open new vistas including the alleviation of infertility, preimplantation genetic diagnosis and stem cells, combined with some recent reports on human reproductive cloning. After detailed consultations with scientists, clinicians, ethicists and lawyers, many governments passed legislation permitting research under their own particular socially defined conditions. Virtually all of them rejected reproductive cloning; a few have accepted therapeutic cloning. These legislatures saluted the many biomedical scientists striving to improve IVF and its derivatives, recognizing their immense medical potential. A motion recently placed before the United Nations then recommended a worldwide ban on all forms of human cloning. Proponents included the Vatican and many Roman Catholic countries, the USA and others. Opponents included Belgium, China, Japan, Brazil, UK, Germany and France. Mediation was achieved by Iran and other Muslim nations, and led to a motion passed by single vote for a 2-year delay. This may be the first-ever proposal to ban worldwide a particular form of research. It sounds the alarm bells for further research. It raises questions about the UN being an appropriate forum for ethical decisions affecting the entire world and its future medicine. Large blocs of nations committed to particular religions and outlooks confronted each other, a situation in total contrast to the detailed and widespread consultations made by individual governments when deciding their own individual ethics. This event was clearly a narrow escape for free research as defined by each country’s own jurisprudence. It also places research on human embryology and reproductive biomedicine into a more critical situation than before. Current liberalism...
Gene transfer technologies in mammals are the focus of recent research and development. These technologies, including chromosome engineering, gene targeting and nuclear transfer or animal cloning, have enhanced our ability to analyze gene function at the level of the whole organism and have provided the means to modify gene expression. This review discusses the origins and current status of transgenic technologies. Various applications and technologies including chromosome engineering, stem cells, gene traps and modification of livestock are presented. The impact of mouse technologies and genomics on functional analyses is also discussed.


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Despite its long history, the cloning of animals by nuclear transplantation is going through a “renaissance” after the birth of Dolly. The amount of work and achievements obtained in the last 7 years are probably greater than those obtained in half a century of research. However, the principal obstacles outlined years ago with the work on somatic cell cloning in amphibia, are all still there in mammals. The importance of somatic cell nuclear transfer is, without any doubt, beyond the scope of replicating superior animal genotypes. It is an invaluable experimental tool to address fundamental scientific issues such as nuclear potency, cell de-differentiation, chromatin structure and function, epigenetics, and genome manipulation. For these reasons the importance of cloning is not for what it can achieve but for the technical support it can provide to biomedical research and in particular to the study of epigenetics, cancer and stem cell biology, cell therapy and regenerative medicine. In this introductory paper, we will summarize the intellectual and technical framework of cloning animals by nuclear transfer that still remains the only absolute way of judging the success of the procedure. Together with the achievements of the recent past we will mention the very last developments and the many questions that still remain open. Current research efforts are expected to provide some answers and certainly new questions.


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Gene transfer technologies in mammals are the focus of renewed interest owing to the recent emphasis on analyzing gene function in the postgenomic era. Three important developments in this area include transgenics, gene targeting and nuclear transfer or animal cloning. These technological innovations have enhanced our ability to analyze gene function at the level of the whole organism and have provided the means to modify gene expression. This review discusses the origins and current status of transgenic technologies. Various applications and technologies including chromosome engineering, stem cells, gene traps and modification of livestock are presented. The impact of mouse technologies and genomics on functional analyses is also discussed.


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As the demand for cloned embryos and offspring increases, the need arises for the development of nuclear transfer procedures that are improved in both efficiency and ease of operation. Here, we describe a novel zona-free cloning method that doubles the throughput in cloned bovine embryo production over current procedures and generates viable offspring with the same efficiency. Elements of the procedure include zona-free enucleation without a holding pipette, automated fusion of 5–10 oocyte-donor cell pairs and microdrop in vitro culture. Using this system, zona-free embryos were reconstructed from five independent primary cell lines and cultured either singularly (single-IVC) or as aggregates of three (triple-IVC). Blastocysts of transferable quality were obtained at similar rates from zona-free single-IVC, triple-IVC and control zona-intact embryos (33%, 25% and 29%, respectively). In a direct comparison, there was no significant difference in development to live calves at term between single-IVC, triple-IVC and zona-intact embryos derived from the same adult fibroblast line (10%, 13% and 15%, respectively). This zona-free cloning method could be straightforward for users of conventional cloning procedures to adopt and may prove a simple, fast and efficient alternative for nuclear cloning of other species as well.


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Adequate answers to moral questions about cloning require a working knowledge of the science and technology involved, both present and anticipated. This essay presents an overview of the current state of somatic cell nuclear transfer technology (SCNT), the type of cloning that now permits whole organism reproduction from adult DNA. This essay explains the basic science and technology of SCNT and explores its potential uses. Next, this essay notes remaining scientific obstacles and unanswered moral questions that must be resolved before SCNT can be used for human reproduction. Attention is given to aspects related to cloning for therapeutic and research purposes.


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Discussing the ethical issues involved in topics such as cloning and stem cell research in a large introductory biology course. Cell Biol Educ. 2002;1(4):132-44.
Despite the fact that cloned animals derived from somatic cells have been successfully generated in a variety of mammalian species, there are still many unsolved problems with current cloning technology. Somatic cell nuclear transfer has shown several development aberrancies, including a high rate of abortion during early gestation and increased perinatal death. One cause of these developmental failures of cloned embryos may reside in the epigenetic reprogramming of somatic donor genome. In mammals, DNA methylation is an essential process in the regulation of transcription during embryonic development and is generally associated with gene silencing. A genome-wide demethylation may be a prerequisite for the formation of pluripotent stem cells that are important for later development. We analyzed methylation patterns in cloned bovine embryos to monitor the epigenetic reprogramming process of donor genomic DNA. Aberrant methylation profiles of cloned bovine embryos were observed in various genomic regions, except in single-copy gene sequences. The overall genomic methylation status of cloned embryos was quite different from that of normal embryos produced in vitro or in vivo. These results suggest that the developmental failures of cloned embryos may be due to incomplete epigenetic reprogramming of donor genomic DNA. We expect that advances in understanding the molecular events for reprogramming of donor genome will contribute to clarify the development defects of cloned embryos. Copyright 2002 Elsevier Science Inc.


The German constitution contains no easy answers to the question of whether and under what circumstances an altering of the current embryo protection law might lead to the therapeutic or even reproductive cloning of human beings being allowed. Due to the fact that guiding fundamental research does not exist, the time for a decision has surely not yet come. But should concrete opportunities for therapy based on therapeutic cloning begin to emerge or it become clear that reproducitively cloned humans are not genetically disadvantaged when compared with human beings engendered through impregnation (an unrealistic prospect from a present day perspective), then the legislator himself will have to come to a decision, openly and by taking a balanced account of his social responsibilities. Hiding behind the constitution by, for instance, simply alluding to human dignity will then no longer be an option.

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This review article summarizes the historical development of mammalian cloning, presents current advances and presumed risk factors in the field of reproductive cloning, discusses possible clinical applications of therapeutic and diagnostic cloning and outlines prospective commercial trends in pharmaceutical cloning. Predictable progress in biotechnology and stem cell engineering should prove to be advantageous for patients’ health and for novel benefits in reproductive and regenerative medicine.


The cloning of mammals using adult cells as nuclear donors has been achieved and the same procedure can be, at least theoretically, used to clone humans. Another recent technological advance, the derivation of human embryonic stem cells, opens up new possibilities in cell and tissue replacement therapy and heralds significant improvements in gene therapy. Besides suggesting new and potentially valuable medical applications, the insights gained through the use of these techniques could significantly enrich our understanding of basic biology course is often difficult. Teachers may be wary of presenting material biased by personal beliefs, and students often feel inhibited speaking about moral issues in a large group. Yet, to ignore what is happening “out there” beyond the textbooks and lab work is to do a disservice to students. This essay describes a semester-long project in which upper class student presented some of the most complex and controversial ideas imaginable to introductory students by staging a mock debate and acting as members of the then newly appointed President’s Council on Bioethics. Because the upper class students were presenting the ideas of real people who play an important role in shaping national policy, no student’s personal beliefs were put on the line, and many ideas were articulated. The introductory audience could accept or reject what they were hearing and learn information important for making up their own minds on these issues. This project is presented as an example of how current events can be used to put basic cell biology into context and of how exciting it can be when students teach students.

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Despite the fact that cloned animals derived from somatic cells have been successfully generated in a variety of mammalian species, there are still many unsolved problems with current cloning technology. Somatic cell nuclear transfer has shown several development aberrancies, including a high rate of abortion during early gestation and increased perinatal death. One cause of these developmental failures of cloned embryos may reside in the epigenetic reprogramming of somatic donor genome. In mammals, DNA methylation is an essential process in the regulation of transcription during embryonic development and is generally associated with gene silencing. A genome-wide demethylation may be a prerequisite for the formation of pluripotent stem cells that are important for later development. We analyzed methylation patterns in cloned bovine embryos to monitor the epigenetic reprogramming process of donor genomic DNA. Aberrant methylation profiles of cloned bovine embryos were observed in various genomic regions, except in single-copy gene sequences. The overall genomic methylation status of cloned embryos was quite different from that of normal embryos produced in vitro or in vivo. These results suggest that the developmental failures of cloned embryos may be due to incomplete epigenetic reprogramming of donor genomic DNA. We expect that advances in understanding the molecular events for reprogramming of donor genome will contribute to clarify the development defects of cloned embryos. Copyright 2002 Elsevier Science Inc.

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mechanisms regulating human development. On the other hand, these preliminary results are viewed by many as the opening of the Pandora's box and there are loud voices clamouring that research in these areas be forbidden in perpetuity. I suggest in the following article that at present we do not know enough to make anything but an entirely emotional decision about future applications of these techniques. I try to summarize the current state of the research in the field and indicate how much further research is necessary if benefits and drawbacks are to be properly understood.


This paper explores the legal ramifications of human reproductive cloning in response to "Dolly"—the first animal cloned from an adult cell. No attempt is made to address the complex moral and ethical dilemmas that will inevitably be consequential on future successes in human reproductive cloning. Some of the potential benefits of cloning are briefly summarized but discussion is focused primarily on the current state of the law in the UK and some other European jurisdictions. Attempts to legislate on human cloning in the US, the emerging role of the EU and amendments to the European Convention on Human Rights are outlined. The potential problems likely to be encountered in the enforcement of any global treaties or international regulations are highlighted. It is argued that attempting to control human cloning by imposing legal prohibition is futile and a pragmatic solution to this impending problem is required forthwith.

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**CLONING IN NEWS**

**News Items on Cloning**

Here is the chronology of events which followed:

- **February 11, 1997 (USA: Federal legislation):** A bill was brought before the US Senate which would criminalize human cloning. Scripps Howard news service reported that "widespread protests from the scientific community coupled with concern about the Republican leadership’s haste in bringing the bill forward" killed the bill.

- **January 1997 (USA: Southern Baptist Resolution):** Messengers (delegates) to the annual meeting of the Southern Baptist Convention passed a resolution supporting a US government ban on funding human embryo research. They also asked that human cloning be prohibited.

- **November 1998 (USA: Advisory Committee):** Harold Shapiro, chairman of the National Bioethics Advisory Committee, said that human cloning may be "impossible to stop". Research is being done with "stunning speed".

- **February 20, 1998 (Korea: Calf clone):** The Korean Times reported that researchers at the Seoul National University had successfully cloned a calf using methods identical to those which produced "Dolly". "Researchers said that Korea became the fifth country in the world to clone an adult animal after the United Kingdom, Japan, New Zealand and the United States."

- **April 20, 1999 (Japan: Calf clones: Approx. date):** Japanese researchers at the Snow Band dairy in Hokkaido produced twin calves. They used a mammary cell extracted from colostrum: the milk produced by a cow shortly after having given birth.

- **April 27, 1999 (Canada: Goats):** Nexia Biotechnologies Inc. of Montreal, Quebec have produced the world’s first cloned goats. The triplets are named Arnold, Danny and Clint. The company’s eventual goal is to produce transgenic animals—goats with a human gene—which will produce milk containing spider-silk proteins. The proteins would be extracted and "used for artificial tendons or ligaments, tissue repair, wound healing and sutures".

- **May 1999 (Scotland: Aging problem):** The Scottish researchers who cloned Dolly, the first cloned mammal, have discovered that her cells are 6 years older than her chronological age. The cell that was used to fertilize the sheep ovum that became Dolly came from an adult female sheep, aged 6 years. Apparently, cells have an internal mechanism, which keeps track of its age. This mechanism was not reset to 0 when Dolly was conceived. She was, in essence, over 6 years old when she is born. Dolly will probably have a lower life expectancy as a result.

- **June 16, 1999 (USA: Southern Baptist Resolution):** The Southern Baptist Convention passed a resolution which calls once more for the US government to continue its ban on federal funding for human embryo research. They also asked that privately-funded researchers voluntarily stop this research as well.

- **October 17, 1999 (Russia: Woolly mammoth):** A team of French, American, Dutch and Russian paleontologists successfully airlifted a male, 23 tonne (25 ton) woolly mammoth from its grave in Siberia where it had been frozen for 20,000 years. It was almost complete except for its head, which had been exposed to air in the past. Since the species has been extinct for over 10,000 years, some scientists have proposed that attempts be made to breed a living mammoth from DNA, sperm or cell nucleus retrieved from the carcass. A modern elephant ovum would be used, because it is the closest living relative to the mammoth. Some suggestions are:
  - Retrieve some mammoth DNA from its bones or tissue and insert it into a living elephant cell. If successful, this would produce an elephant-mammoth hybrid with mammoth DNA pieces in some of the elephant chromosomes. If successful, the result would be an elephant with some mammoth features.
  - Perform artificial insemination between a mammoth sperm and unfertilized ovum of a living elephant. If
Cloning: Current Research

They then measured the telomeres of sample cells from the animals. These are structures at the ends of the cells chromosomes. The telomeres shorten as cells divide and age. Once they are frayed beyond repair, the cell dies. The researchers found that the telomeres in the cloned cows were much longer than those in normal cows of the same age, and in many cases they were longer than telomeres in newborn calves. The cow’s cells appeared younger than the cow’s chronological age!

Clone the mammoth by inserting the nucleus from a female mammoth into an egg cell from a female elephant. Thus, cloning may not be possible.

- January 13, 2000 (USA: Monkey clone): According to Day Watch: “Scientists announced on Thursday that they had cloned a monkey. The researchers at the Oregon Regional Primate Research Center said the rhesus monkey named "Tetra" was cloned by splitting a very early embryo into four parts. The cloning process is different from the one that created Dolly the sheep. Researchers hope the experiment will result in the production of identical lab animals for testing.” This procedure is actually "embryo cloning".

- April 27, 2000 (USA: Aging problem of clones solved?): Scientists at Advanced Cell Technology, Inc. of Worcester, MA, successfully cloned six cows. They grew cells from a 45-day fetus “until they neared the end of their life span, then put those cells back into eggs, which they allowed to develop into calves”. They then measured the telomeres of sample cells from the animals. These are structures at the ends of the cells chromosomes. The telomeres shorten as cells divide and age. Once they are frayed beyond repair, the cell dies. The researchers found that the telomeres in the cloned cows were much longer than those in normal cows of the same age, and in many cases they were longer than telomeres in newborn calves”.

- August 17, 2000 (Britain: Human cloning may proceed): An advisory group in Britain has recommended that the ban be lifted on human “therapeutic cloning”. The goal is to create organ transplants, which bear the DNA of the recipient patient. “At present embryo research is allowed only for treating infertility and preventing disability in children. Government ministers have already indicated that they support Professor Donaldson’s proposals. Members of Parliament will vote on the issue later this year. At the same time, the law will be strengthened to prevent cloning with the aim of producing a baby.”

- September 25, 2000 (Scotland: Gay conception may be possible): Catholic World News reported the comments of Dr Calum Mackellar, a lecturer in bioethics and biochemistry at the University of Edinburgh. He speculated that future developments in cloning research might make it possible to obtain a human ovum from a woman, remove its DNA, and replace it with the DNA from a male. Theoretically, the ovum could then be fertilized with the sperm from a second male—perhaps a spouse of the first male. The fertilized “male egg” could then be implanted in the womb of a surrogate mother. This could produce a child whose DNA was derived from both of the newborn’s fathers, with no female DNA involved. He recommends that the new cloning bill to be introduced into the British Parliament later in 2000 include a section, which would deal with the creation of a male egg. Dr MacKellar said: “The ethical, philosophical and theological issues surrounding the creation of children with two genetic fathers and a surrogate mother are extensive, and they need to be thoroughly thought through before any legislation is considered in parliament... If the government does not take careful notice of the issues surrounding the male egg, another report will need to be written by another Chief Medical Officer just because no-one believed this could happen”.

- October 9, 2000 (USA: Endangered species cloning): Robert Lanza of Advanced Cell Technology reported that scientists have impregnated a cow with a cell cloned from an Asian gaur—a large, rare wild ox. They removed the DNA from a cow’s ovum, fused it with DNA taken from a skin cell of a gaur, and produced a gaur embryo that is accepted by the cow’s immune system. The embryo was implanted in the cow’s uterus. They hope that “Bessie” will deliver a gaur calf in November. If the technique works, then a new method will have been found to save endangered or recently extinct animals. Many species are becoming extinct in the wild; in some cases, the species do not readily mate in zoos. Cloning may be their only hope of survival.

- October 11, 2000 (Bahamas: Religious group will try to clone human): An unnamed American couple has paid £300,000 to a religious group, the Raelians, to clone their dead daughter. She had died at the age of 10 months as a result of a medical accident. Her parents had some cells from her body saved in the hope of producing an identical twin of her in the future. At a September press conference in Canada, Dr Brigitte Boisselier, Scientific Director of the Raelians, said: “We’ve got the funding. We anticipate being able to start in October”. She announced that up to 50 women had volunteered to act as surrogate mothers. The lab will be set up in a third world country, which has no laws against cloning. Reaction was varied:

- Professor Ian Wilmut, the scientist who created Dolly the sheep, said: “It sounds to me like a very misguided exercise. Clearly everybody feels very sorry for any couple who loses a child but you cannot get that child back. People should realize that as a biological truth. Quite apart from that, it is absolutely criminal to try this in a human.”
- Michael West, chief executive of Advanced Cell Technology, in Massachusetts, said: “People with experience in vitro fertilization would probably be able to do it. The directions are all in the scientific literature. They’re not top secret”.
- Dr Vivienne Nathanson, head of ethics at the British Medical Association speculated: “They may succeed and if they do it will be very interesting... But rather than winning a Nobel Prize these people may have to face almost universal condemnation. There is fairly broad consensus worldwide that this is undesirable. It is too risky and underpinning the scientific risk there are tremendous moral and ethical problems. I am not convinced that people understand how unsafe the science is”.
- Professor Robert Winston, the test tube baby pioneer, was more pessimistic: “As they are so extremely unlikely to succeed I hardly feel the need to raise my voice to condemn them”.

Bans on Cloning

Following the January 2001 announcement by Severino Antinori, Panos Zavos and others with plans to begin human cloning, the world leaders reacted by calling for global bans.
- **February 2 (Japan issues warning to scientists on human cloning project):** Tokyo (AP)—Prime Minister Yoshiro Mori instructed his science minister to take steps to prevent Japanese researchers and doctors from participating in an international project to clone human beings.
- **February 4 (Australian scientist horrified at human clone plan):** Two international medical scientists tried to lure Victoria's top reproductive scientist, Alan Trounson, into a taboo-busting project aimed at cloning the first human being. Trounson’s reply: “I am sure they would like anybody who would add credibility to the team to go on it. No way. No way!”
- **February 8 (Romania bans human cloning):** (Monitorul Online) Deputies decided to forbid human cloning in Romania, by passing a draft bill, which ratified the European Convention concerning the protection of the human rights and that of the human being’s dignity.
- **February 10 (French President calls for ban on human cloning):** French President Jacques Chirac criticized Britain’s decision last month to let scientists clone human embryos for medical research, and called for an international ban on the practice. Research cloning, Chirac said, “leads to the creation of embryos for the purposes of research and the production of cells and, in spite of the ban, makes reproductive cloning practically possible...”
- **February 21:** Takashi Sasagawa, minister in-charge of Japan’s science and technology policy, said that Japan should revise its law banning human cloning to prohibit Japanese from cloning humans abroad.

- **March 1 (Council of Europe ban on human cloning takes effect):** The Council of Europe’s protocol against human cloning, the first binding international ban, took effect on March 1 when a fifth nation ratified it. Twenty-four of the 41 Council of Europe states have signed the protocol.
- **March 8 (Human cloning illegal in China):** The Xinhua News Agency reported that a member of the Chinese People’s Political Consultative Conference National Committee stated that human cloning is not allowed in China.
- **March 10 (Prominent Italians against human cloning):** Rome (AP)—A day after researchers meeting in Rome vowed to clone babies, an Italian lawmaker condemned them as “Frankenstein doctors” and urged parliament to ratify an international pact banning human cloning. A prominent cardinal also condemned the project, as did the head of Italy’s national committee on bioethics.
- **March 12 (British, Australian, and Italian medical authorities condemn human cloning):** Antinori and Zavos were condemned by Britain’s Human Fertilisation and Embryology Authority and by the Australian Medical Association. The Italian medical association warned that any member who tries to clone a human risks expulsion and loss of the right to practice medicine.
- **March 13:** The Cypriot government said it would not permit human cloning after Antinori identified Cyprus as a possible locale for his project.
- **March 13 (Kenyans join condemnation of human cloning):** Archbishop Ndingi Mwana’a Nzeki of Nairobi, the vice chancellor of Kenyatta University, and Muslim leaders also joined criticism of human cloning.
- **March 13 (German and Filipino bishops oppose human cloning):** Roman Catholic bishops in both Germany and the Philippines have condemned all forms of human cloning, either for reproductive or so-called therapeutic purposes.
- **March 30 (Prominent scientists oppose cloning):** Rudolph Jaenisch and Ian Wilmut, head of the team that created the first mammal cloned from an adult, opposed human cloning in a letter to Science magazine.
- **April 12 (Schroeder speaks against human genetic modification):** German Chancellor Gerhard Schroeder recently said, “We agree on what we do not want: the cloned, optimized, genetically selected human being.” (New York Times, “Horror Expressed in Germany Over Dutch Euthanasia”).
- **April 19 (Britain to ban human cloning):** The government announced that it would introduce a legislative ban on human cloning, which was already disallowed under the British regulatory framework.
- **May 3 (Canada introduces legislation on genetic and reproductive technologies):** The Canadian Health Minister submitted to the House of Commons legislation that would ban human cloning; germline modification; and commercialization of human eggs, sperm, embryos or surrogate arrangements. The proposed legislation would
also set up a regulatory framework to control other uses of reproductive technology.

- November 30 (Lagos, Nigeria, University VC calls for measures against human cloning): University of Post Harcourt vice-chancellor, professor Nimi Briggs, has called for urgent measures to regulate research on human cloning.

**TEN MYTHS ABOUT HUMAN CLONING (GREGORY E PENCE 1998)**

**Who is Afraid of Human Cloning?**

*Cloning Xeroxes a Person*

Cloning merely recreates the genes of the ancestor, not what he has learned or experiences. Technically, it recreates the genotype, not the phenotype (Even at that, only 99% of those genes get recreated because 1% of such a child’s genes would come from those in the egg—mitochondrial DNA). Conventional wisdom holds that about half of who we are comes from our genes, the other half, from the environment. Cloning cannot recreate what in us came from the environment; it also cannot recreate memories. The false belief that cloning recreates a person stems in part from the common, current false belief in simplistic, genetic reductionism, i.e. that a person really is just determined by his genes. No reputable geneticist or psychologist believes this.

*Human Cloning is Replication or Making Children into Commodities*

Opponents of cloning often use these words to beg the question; to assume that children created by parents by a new method would not be loved. Similar things were said about “test tube” babies, who turned out to be some of the most-wanted, most-loved babies ever-created in human history. Indeed, the opposite is true: evolution has created us with sex drives such that, if we do not carefully use contraception, children occur. Because children get created this way without being wanted, sexual reproduction is more likely to create unwanted, and hence possibly unloved, children than human cloning. Lawyers opposing cloning have a special reason for using these pejorative words. If cloning is just a new form of human reproduction, then it is constitutionally protected from interference by the state. Several Supreme Court decisions declare that all forms of human reproduction, including the right not to reproduce, cannot be abridged by government. Use of words such as “replication” and “commodification” also assumes artificial wombs or commercial motives; about these fallacies, see below.

*Human Cloning Reduces Biological Diversity*

Population genetics says otherwise. Six billion people now exist, soon to be eight billion, and most of them reproduce. Cloning requires in vitro fertilization, which is expensive and
inefficient, with only a 20% success rate. Since 1978, at most a half million babies have been produced this way, or at most, one out of 12,000 babies.

Over decades and with such great numbers, populations follow the Law of Regression to the Mean. This means that, even if someone tried to create a superior race by cloning, it would fail, because cloned people would have children with noncloned people, and resulting genetic hybrids would soon be normalized. Cloning is simply a tool. It could be used with the motive of creating uniformity (but would fail, because of above), or it be used for the opposite reason, to try to increase diversity (which would also fail, for the same reason).

**People Created by Cloning Would be Less Ensouled than Normal Humans, or Would be Subhuman**

A human who had the same number of chromosomes as a child created sexually, who was gestated by a woman, and who talked, felt and spoke as any other human, would ethically be human and a person. It is by now a principle of ethics that the origins of a person, be it from mixed-race parents, unmarried parents, in vitro fertilization, or a gay male couple hiring a surrogate mother, do not affect the personhood of the child born. The same would be true of a child created by cloning (who, of course, has to be gestated for 9 months by a woman).

Every deviation from normal reproduction has always been faced with this year. Children greeted by sperm donation, in vitro fertilization, and surrogate motherhood were predicted to be less-than-human, but were not.

A variation predicts that while, in fact, they will not be less-than-human, people will treat them this way and hence, such children will harmed. This objection refines prejudice and makes it an ethical justification, which it is wrong to do. The correct response to prejudice is to expose it for what it is, combat it with reason and with evidence, not validate it as an ethical reason.

**People Created by Cloning Could be Used for Spare Organs for Normal Humans**

Nothing could be done to a person created by cloning that right now could not be done to your brother or to a person’s twin. The US constitution strongly implies that once a human fetus is outside the womb and alive, he has rights. Decisions backing this up give him rights to inherit property, rights not to suffer discrimination because of disability, and rights to US citizenship. A variation of this myth assumes that a dictator could make cloned humans into special SWAT teams or suicidal bombers. But nothing about originating people this way gives anyone any special power over the resulting humans, who would have free will. Besides, if a dictator wants to create such assassins, he need not wait for cloning but can take orphans and try to indoctrinate them now in isolated camps.

**All People Created from the Same Genotype Would be Raised in Batches and Share Secret Empathy or Communication**

Pure Science fiction. If I wanted to recreate the genotype of my funny Uncle Harry, why would my wife want to gestate five or six other babies at the same time? Indeed, we now know that the womb cannot support more than two to three fetuses without creating a likely disability in one. Guidelines now call for no more than two embryos to be introduced by in vitro fertilization, which of course is required to use cloning. Such assumptions about cloned humans being created in batches are linked to nightmarish science fiction scenarios where human society has been destroyed and where industrialized machines have taken over human reproduction. But this is just someone’s nightmare, not facts upon which to base state and federal laws.

**Scientists Who Work on Human Cloning are Evil or Motivated by Bad Motives**

The stuff of Hollywood and scary writers. Scientists are just people. Most of them have kids of their own and care a lot for kids. No one wants to bring a handicapped child into the world. Movies and novels never portray life scientists with sympathy. This antiscience prejudice started with Mary Shelley’s Frankenstein and continues with nefarious scientists working for the government on The X Files. People who call themselves scientists and grandstand for television, such as Richard Seed and Brigitte Boisselier of the Raelians, are not real scientists but people who use the aura of science to gain attention. Real scientists do not spend all their time flying around the world to be on television but stay at home in their clinics doing their work.

**Babies Created by Cloning Could be Grown in Artificial Wombs**

Nope, sorry. Medicine has been trying for 50 years to create an artificial womb, but has never come close to succeeding. Indeed, controversial experiments in 1973 on live-born fetuses in studying artificial wombs effectively shut down such research. Finally, if anything like such wombs existed, we could save premature babies who have not developed lung function, but unfortunately, we still cannot—premature babies who cannot breathe at all die. Thus, any human baby still needs a human woman to gestate him for at least 6 months, and to be healthy, 9 months. This puts the lie to many science fiction stories and to many predictions about cloning and industrial reproduction.
Only Selfish People Want to Create a Child by Cloning

First, this assumes that ordinary people do not create children for selfish reasons, such as a desire to have someone take care of them in old age, a desire to see part of themselves continue after death, and/or the desire to leave their estate to someone. Many people are hypocritical or deceived about why they came to have children. Very few people just decide that they want to bring more joy into the world, and hence create a child to raise and support for life as an end-in-himself. Let’s be honest here. Second, a couple using cloning need not create a copy of one of them. As said above, Uncle Harry could be a prime candidate. On the other hand, if a couple chooses a famous person, critics accuse them of creating designer babies. Either way, they cannot win: if they recreate one of their genotypes, they are narcissistic; if they choose someone else’s genes, they are guilty of creating designer babies. In general, why should a couple using cloning have a higher justification required of them than a couple using sexual reproduction? If we ask: what counts as a good reason for creating a child, then why should cloning have any special test that is not required for sexual reproduction? Indeed, and more generally, what right does government has to require, or judge, any couple’s reasons for having a child, even if they are seen by others to be selfish? Couple desiring to use cloning should not bear an undue burden of justification.

Human Cloning is Inherently Evil: It can Only be Used for Bad Purposes by Bad People

No, it is just a tool, just another way to create a family. A long legacy in science fiction novels and movies make the word “cloning” so fraught with bad connotations that it can hardly be used in any discussion that purports to be impartial. It is like discussing equal rights for women by starting to discuss whether “the chicks” would fare better with equal rights. To most people, “cloning” implies selfish parents, crazy scientists, and out-of-control technology, so a fair discussion using this word is not possible. Perhaps the phrase, “somatic cell nuclear transplantation” is better, even if it is a scientific mouthful. So if we should not call a person created by cloning, a “clone”, what should we call him? Answer: a person.

HUMAN REPRODUCTIVE CLONING FROM THE PERSPECTIVE OF THE FUTURE

Imagine that you are one of the human clones that will be born (There is no doubt that this will happen sooner or later even if Clonaid’s announcement turns out to be a hoax). And imagine yourself listening into the current arguments for making cloning illegal. You hear people opinion that cloning threatens human dignity, that it would be playing God, that it represents a slippery slope toward a dehumanized future, that everybody has a right to a unique genome (except identical twins?) or to an unknown genome, and so forth. How would it make you feel? To hear all these dignified people talking about you as if your very existence were a crime against humanity?

Such an imaginary point-of-view helps us put things in perspective. There is one argument that, as a future clone, you might understand and agree with: concerns about the safety of the procedure. The argument that we ought to wait to try it on humans until we have perfected the method on animals makes some degree of sense. But even so, suppose you were a slightly deformed human clone—would you agree that it was a terrible moral offense to have caused you to come into existence?

Historically, we find that many a great medical breakthrough, now seen as a blessing, was in its own time ferociously condemned by bioconservative moralists. This was the case with anesthesia during surgery and childbirth—people argued that it was unnatural and that it would weaken our moral fibers. It was also the case with heart transplantations—how yucky to take a living heart of one person and put it in the chest of another! And it was the case with in vitro fertilization—these “test tube babies” would be dehumanized and would be subject to grave psychological abuse. Now of course, anesthesia is taken for granted, heart transplantation is seen as one of medicine’s greatest triumphs, and the public approval rate of in vitro fertilization is up from 15% in the early seventies to over 70% today.

What can we learn from these historical episodes? We can learn that our immediate emotional reactions to medical developments are not a reliable guide to their morality. We can learn that we are prone to prejudice and to narrow-minded failure to appreciate the long-term benefits of technological development. We can learn that the “yuck factor” should be profoundly distrusted and that it should definitely not be glorified (pace Leon Kass, chair of the President’s Council on Bioethics) as a “Wisdom of Repugnance”.

We all have a moral responsibility to recognize the clone for what she is a unique human person, with just as much human dignity as those of us who were conceived in other ways.

By the time the first human clone becomes an adult, the moral debates over cloning may already be long forgotten. The present opponents of cloning may have retired or moved on to being outraged about other things. The clone may be spared having witness being referred to by pundits in such derogatory language as we hear today.

In the big scheme of things, cloning will not significantly change the world. Some people will owe their lives to this technology, and some infertile couples will be grateful for having had the chance to raise a child of their own that they would otherwise have lacked. Some people may misguidedly use cloning to try to bring back a lost child or a loved one,
not realizing that personal identity is not reducible to genetic identity. Some people may choose to have a child that is a clone of a stranger they admire, perhaps a great scientist, athlete or religious leader; yet if the current level of demand for elite sperm or elite eggs is any indication, the class of people who will choose to do this will be a tiny minority.

Meanwhile, other areas of technology will be advancing fast and furiously, leading to developments that will overshadow cloning. Some of these developments will be frightening genetically engineered biowarfare agents, for example, new weapons based on molecular nanotechnology. Those prospects deserve our serious attention and concern. Other developments will open up unprecedented opportunities for human growth and flourishing. One day we will find ways of halting and reversing the aging process. We will have the option of extending our intellectual, physical, emotional and spiritual capacities far beyond the levels that are possible today. This will be the end of humanity’s childhood, and the beginning of a post-human era. Our descendants, or even you and I if we manage to stay alive until then, will look back on today and today’s primitive condition in much the way we look back on our humanoid ancestors before they developed language, learned to use fire and took up agriculture. Few of us would want to go back to that stage, and in the future few will want to return to the present day.

We have a choice. We can work against the developments that will make us posthuman and join the reactionary forces that decry each new technological breakthrough that changes human nature. Or we can stand by the sidelines and passively watch the future unfold. Or we can actively participate in creating the future that will enable us to reach almost unimaginable levels of human flourishing and well-being through the use of advanced technology to defeat disease and aging and to increase our human capacities to entirely new levels. For those who choose this third option, the World Transhumanist Association offers an opportunity to join others in the effort to make our worthiest dreams come true. Your help is needed.

CONCLUSION

Despite the fact that cloned animals derived from somatic cells have been successfully generated in a variety of mammalian species, there are still many unsolved problems with the current cloning technology. The developmental failure of cloned embryo may be due to incomplete epigenetic reprogramming of the donor genome DNA. Future is promising in understanding the genomic DNA reprogramming and future may see a successful generation of human clones and cloned animals. When is the world going to change to cloned human race cannot be predicted today.

Until recently, there were few ethical, social or legal discussions about human cloning via nuclear transplantation, since the scientific consensus was that such a procedure was not biologically possible. With the appearance of Dolly, the situation has changed. But although it now seems more likely that human cloning will become feasible, we may doubt that the practice will come into widespread use.

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INTRODUCTION

Stem cells are primal cells found in all multicellular organisms that retain the ability to renew themselves through mitotic cell division and can differentiate into a diverse range of specialized cell types. All stem cells regardless of their source have three general properties:
1. They are capable of dividing and renewing themselves for long periods
2. They are unspecialized
3. They can give rise to specialized cell types.

HISTORY AND PERSPECTIVE OF STEM CELL RESEARCH

In the early 1960s, Ernest McCulloch and James Till started a series of experiments that involved injecting bone marrow cells into irradiated mice. Visible nodules were observed in the spleens of the mice, in proportion to the number of bone marrow cells injected. Till and McCulloch called the nodules “spleen colonies”, and speculated that each nodule arose from a single marrow cell: a stem cell.

Several types of stem cell have been discovered from germ cells, the embryo, fetus and adult. Each of these has promised to revolutionize the future of regenerative medicine through the provision of cell-replacement therapies to treat a variety of debilitating diseases.

HUMAN EMBRYONIC STEM CELLS

Human embryonic stem cells were discovered in 1998. The donated spare embryos in in vitro fertilization (IVF) were used in these studies. Reliance Life Sciences, Mumbai, has to its credit the first South East Asia’s embryonic stem cell line.

Embryonic Stem Cell Culture

Human embryonic stem cells are isolated by transferring the inner cell mass of the blastocyst into the culture medium. The cells divide and spread over the surface of the dish. The inner surface of the culture dish is typically coated with mouse embryonic skin cells that have been treated so they do not divide. This coating layer of cells is called a feeder layer. This feeder layer not only gives the inner cell mass cells a sticky surface to attach itself, but also releases nutrients into the culture medium. Recently, research is carried to devise ways of growing embryonic stem cells without the mouse feeder cells because of the risk that viruses or other macromolecules in the mouse cells may be transmitted to the human cells. Over the course of several days, the cells of the inner cell mass proliferate and begin to crowd the culture dish. When this occurs, they are removed gently and plated into several fresh culture dishes. The process of replating the cells is repeated many times and for many months, and is called subculturing. Each cycle of subculturing the cells is referred to as a passage. After 6 months or more, the original 30 cells of the inner cell mass yield millions of embryonic stem cells. Embryonic stem cells that have proliferated in cell culture for 6 or more months without differentiating are pluripotent, and appear genetically normal are referred to as an embryonic stem cell line.

Characterization of Embryonic Stem Cells

The process in which tests the carried out to see whether the stem cell line exhibits the fundamental properties that make them embryonic stem cells is called as characterization.
These tests include:

- Growing and subculturing the stem cells for many months
- To determine the presence of surface markers those are found only on undifferentiated cells
- Test for the presence of a protein called octamer-binding protein 4 (Oct-4), which undifferentiated cells typically make
- Karyotyping
- Determining whether the cells can be subcultured after freezing, thawing and replating
- Testing whether the human embryonic stem cells are pluripotent.

**Differentiation of Embryonic Stem Cells**

To generate cultures of specific types of differentiated cells, the chemical composition of the culture medium or the surface of the culture dish is altered, or the cells are modified by inserting specific genes.

**ADULT STEM CELL/SOMATIC STEM CELL**

An adult stem cell is an undifferentiated cell found among differentiated cells in a tissue or organ. It can renew itself, and can differentiate to yield the major specialized cell types of the tissue or organ.

The primary role of adult stem cells is to maintain and repair the tissue in which they are found. Unlike embryonic stem cells, which are defined by their origin (the inner cell mass of the blastocyst), the origin of adult stem cells in mature tissues is unknown.

It is now known that adult stem cells are found in many more tissues than they once thought possible. Thus, adult stem cells could be used for transplants. In fact, adult blood forming stem cells from bone marrow have been used in transplants for 30 years.

In the 1960s, researchers discovered that the bone marrow contains at least two kinds of stem cells. One population, called hematopoietic stem cells, forms all the types of blood cells in the body. A second population, called bone marrow stromal cells, generates bone, cartilage, fat and fibrous connective tissue.

In the 1960s, scientists who were studying rats discovered two regions of the brain that contained dividing cells, which become nerve cells. However, it was not until the 1990s that the scientists agreed that the adult brain does contain stem cells that are able to generate the brain’s three major cell types: 1. The astrocytes 2. Oligodendrocytes 3. Neurons.

**Location of Adult Stem Cell**

Stem cells are thought to reside in a specific area of each tissue where they may remain quiescent (nondividing) for many years until they are activated by disease or tissue injury. The adult tissues reported to contain stem cells include brain, bone marrow, peripheral blood, blood vessels, skeletal muscle, skin and liver.

**Adult Stem Cell Differentiation**

Adult stem cells enter normal differentiation pathways to form the specialized cell types of the tissue in which they reside. They may also exhibit the ability to form specialized cell types of other tissues, which is known as transdifferentiation or plasticity.

**Normal Differentiation Pathways of Adult Stem Cells**

In a living animal, adult stem cells can divide for a long period and can give rise to mature cell types that have characteristic shapes and specialized structures and functions of a particular tissue. The following are examples of differentiation pathways of adult stem cells:

- Hematopoietic stem cells give rise to all the types of blood cells
- Epithelial stem cells in the lining of the gastrointestinal tract occur in deep crypts and give rise to several cell types: absorptive cells, goblet cells, Paneth cells and enteroendocrine cells
- Skin stem cells occur in the basal layer of the epidermis and at the base of hair follicles. The epidermal stem cells give rise to keratinocytes while the follicular stem cells can give rise to both the hair follicle and to the epidermis.

**Adult Stem Cell Plasticity and Transdifferentiation**

Certain adult stem cell types are pluripotent. This ability to differentiate into multiple cell types is called plasticity or transdifferentiation.

- Hematopoietic stem cells may differentiate into: brain cells—neurons, oligodendrocytes and astrocytes; skeletal muscle cells; cardiac muscle cells and liver cells
- Bone marrow stromal cells may differentiate into: cardiac muscle cells and skeletal muscle cells
- Brain stem cells may differentiate into: blood cells and skeletal muscle cells.

**Uterine Stem Cells**

The endometrium of the human uterus undergoes cyclical processes of regeneration, differentiation and shedding as part of the menstrual cycle. Endometrial regeneration also follows parturition, almost complete resection and in postmenopausal women taking estrogen replacement therapy. In nonmenstruating species, there are cycles of endometrial growth and apoptosis rather than physical shedding. Attempts to isolate, characterize and locate
endometrial stem cells have only been undertaken in the last few years. Evidence for the existence of adult stem/progenitor cells in human and mouse endometrium is now emerging because functional stem cell assays are being applied to uterine cells and tissues. These fundamental studies on endometrial stem/progenitor cells will provide new insights into the pathophysiology of various gynecological disorders associated with abnormal endometrial proliferation, including endometrial cancer, endometrial hyperplasia, endometriosis and adenomyosis.

**Fetal Stem Cells**

Fetal stem cells can be isolated not only from fetal blood and hematopoietic organs in early pregnancy, but from a variety of somatic organs as well as amniotic fluid and placenta throughout gestation. Fetal blood is a rich source of hematopoietic stem cells, which proliferate more rapidly than those in cord blood or adult bone marrow. First-trimester fetal blood, liver and bone marrow also contain a population of mesenchymal stem cells, which appear to be more primitive with greater multipotentiality than their adult counterparts. Fetal stem cells may thus represent an intermediate cell type in the current debate focusing on dichotomized adult versus embryonic stem cells, and thus prove advantageous as a source for downstream cell therapy applications.

**Umbilical Cord Blood Stem Cells and Cord Blood Banking**

These are obtained from the umbilical cord immediately after birth. Like bone marrow, umbilical cord blood (UCB) is another rich source of hematopoietic stem cells. These hematopoietic stem cells are usually referred to as neonatal stem cells and are less mature than those stem cells found in the bone marrow of adults or children.

In 1972, Norman Ende showed the utility of cord blood in treating leukemia while the first transplant was done in 1988 by French researcher Eliane Gluckman when UCB was given from the newborn to his 5-year-old sibling suffering from Fanconi’s anemia.

**Advantages**

The advantages of using cord blood as a source of stem cells are its noninvasive procurement and its vast abundance. Until recently, UCB was discarded after birth, along with the placenta. Now, in several countries around the world including India, cord blood is collected and either banked in public banks for general use or stored by private companies for private use, in private cord blood banks (e.g. ReliCord in India).

Cord blood has recently emerged as an alternative source of hematopoietic stem cells for treatment of leukemia and other blood disorders. In these applications, UCB has the notable advantage that despite its high content of immune cells, it does not produce strong graft-versus-host disease (GVHD). Therefore, cord blood grafts do not need to be as rigorously matched to a recipient as bone marrow grafts. This expands the available donor pool for hematopoietic stem cell transplants considerably.

The use of UCB stem cells for other uses, such as organ and tissue repair, is under investigation.

**Cord Blood Transplant versus Bone Marrow Transplant**

The advantages over bone marrow transplant can be summarized as follows (Fig. 1):

- Cord blood has a high rate of engraftment
- It is more tolerant of tissue mismatches
- Results in a lower rate of severe GVHD

In 143 cord blood transplants (fully to two-thirds matched), done by Ms Eliane Gluckman, risk of GVHD was just 5% in related transplants and 20% in unrelated transplants. One percent (related) and 6% (unrelated) deaths were reported. In contrast, large studies with fully matched bone marrow transplants had shown risk of GVHD at 47%. Seventy percent deaths were reported. Cord blood is far safer than bone marrow when used in transplants.

- It is unexposed to most diseases. Virtually free from virus as less than 1% of infants contract cytomegalovirus (CMV) in womb
- Cord blood is a perfect match for the donor child itself
- 1-in-4 chance of human leukocyte antigen (HLA) matching in a current or future sibling
- HLA match can be done speedily
- 3/6 HLA match transplants are feasible
- Size of donor pool is very large
- Easy to collect as compared to bone marrow

**Fig. 1: Advantages of using umbilical cord blood (UCB)**

Abbreviations: CMV, cytomegalovirus; GVHD, graft-versus-host disease; HLA, human leukocyte antigen
Infertility

- Readily available (with HLA and infectious disease testing is completed)
- Better immune acceptance
- Safer than bone marrow transplants
- Lowers cost of therapy—one time cost
- Lower remission rates.

Disadvantage

A disadvantage of UCB, and an argument against generalized use, is the limited number of stem cells in any given cord. This increases the risk of graft failure once transplanted into an adult (Fig. 2).

Collection of Umbilical Cord Blood

Umbilical cord blood is easily collected using special collection kits. The umbilical cord is clamped and cut in the same manner, as it would be for normal delivery of the baby. Using a blood collection bag, cord blood is drawn from the umbilical cord. Between 60 mL and 120 mL of cord blood can be collected per birth. At the same time, maternal blood is also collected for infectious disease testing.

Need for Cord Blood Banking

Cord blood stem cells are an allergenic source and must be HLA matched for transplantation. Since it is difficult to find matched stem cells in a general population, a repository consisting of large number of samples is needed. The cord blood transplants are shown worldwide in Figure 3.

Cord Blood Processing

- HLA and infectious disease testing
- Removal of red blood cells (RBCs)
- Addition of dimethyl sulfoxide (DMSO) and dextran
- Enrichment and reduction of volume to 25 mL
- Controlled rate freezing
- Cryogenic storage.

Amniotic and Placental Stem Cells

Amniotic epithelial cells develop from the epiblast by 8 days after fertilization and prior to gastrulation opening the possibility that they might maintain the plasticity of pre-gastrulation embryo cells. Amniotic epithelial cells isolated from human term placentas express surface makers normally present on embryonic stem and germ cells. In addition, amniotic epithelial cells express the pluripotent stem cell-specific transcription factors Oct-4 and nanog. Under certain culture conditions, amniotic epithelial cells form spheroid structures which retain stem cell characteristics. Based on immunohistochemical and genetic analysis, amniotic epithelial cells have the potential to differentiate to all three germ layers:
1. Endoderm (liver, pancreas)
2. Mesoderm (cardiomyocyte)

Amnion derived from term placenta following livebirth may be a useful and noncontroversial source of stem cells for cell transplantation and regenerative medicine.\(^6\)

**POTENTIAL USES AND OBSTACLES IN THE USES OF HUMAN STEM CELLS**

There are many technical hurdles between the promise of stem cells (Fig. 4) and the realization of these uses, which will only be overcome by continued intensive stem cell research.\(^1,3,5\)

Cell-Based Therapies

Stem cells, directed to differentiate into specific cell types, offer the possibility of a renewable source of replacement cells and tissues to treat diseases including Parkinson’s and Alzheimer’s diseases, spinal cord injury, stroke, burns, heart disease, diabetes, osteoarthritis and rheumatoid arthritis.

Preliminary research in mice and other animals indicates that bone marrow stem cells, transplanted into a damaged heart, can generate heart muscle cells and successfully repopulate the heart tissue.
To be useful for transplant purposes, stem cells must:

- Proliferate extensively and generate sufficient quantities of tissue
- Differentiate into the desired cell type(s)
- Survive in the recipient after transplant
- Integrate into the surrounding tissue after transplant
- Function appropriately for the duration of the recipient’s life
- Avoid harming the recipient in any way.

**On and Off Signals for the Genes**

Turning genes on and off is central to differentiation process. Some of the most serious medical conditions, such as cancer and birth defects, are due to abnormal cell division and differentiation. A better understanding of the genetic and molecular controls of these processes may yield information about how such diseases arise and suggest new strategies for therapy. A significant hurdle to this use and most uses of stem cells is to understand the signals that turn specific genes on and off to influence the differentiation of the stem cell.

**Test New Drugs**

Human stem cells could also be used to test new drugs. For example, new medications could be tested for safety on differentiated cells generated from human pluripotent cell lines. Other kinds of cell lines are already used in this way. Cancer cell lines, for example, are used to screen potential antitumor drugs. But, the availability of pluripotent stem cells would allow drug testing in a wider range of cell types.

**Nuclear Transfer for Stem Cells or Somatic Cell Nuclear Transfer**

The major problem facing widespread use of embryonic stem cells in cell therapies and organ replacement is their anticipated rejection by the patient’s immune system, which will recognize them as foreign. One way around this problem would be to produce “custom” embryonic cells, matching the patient’s immunologic profile.

The approach, known as “nuclear transfer for stem cells” or somatic cell nuclear transfer (SCNT), would lead to the production of cells and tissue matching one’s self that would not elicit rejection when the cells are transplanted into the patient.

For nuclear transfer—stem cells, the deoxyribonucleic acid (DNA) from any one cell in the body of a patient (usually a skin or muscle cell) could be removed and transferred into an unfertilized egg that previously had its own DNA removed.

In a culture dish, the egg is coaxed into developing as if it had been fertilized. The one egg cell divides rapidly and generates a ball of cells, called the blastocyst, in only 5–6 days. The inner cell mass is then removed and embryonic stem cells are harvested.
cells grown out of it. These embryonic stem cells, containing the patient’s DNA, now match the patient’s immunological profile and will not be rejected by the patient’s immune system. These embryonic stem cells can now be used to generate cells and tissues for the patient.

In the nearer future, therapies would probably be restricted to injection of tissue-specific progenitors that have been generated from the “custom” embryonic stem cells, which then will contribute to the repair of damaged organs in the patient.\(^1\,\text{,}\,\text{3}\)

**Embryonic Stem Cell Bank**

Embryonic stem cell bank is an alternative approach to finding compatible stem cells for a given patient from a wide array of donors, as is done for blood banks. However, this approach will have the same limitations as organ donor and bone marrow registries, i.e. the problem of limited availability of compatible donors. This problem particularly affects ethnic minorities who are of rarer type and are severely under-represented in the organ and bone marrow registries.\(^1\,\text{,}\,\text{3}\,\text{,}\,\text{4}\)

**Human Embryonic Stem Cells as a Model for Early Human Development**

The availability of human pluripotent stem cells allows us to study previously inaccessible basic processes that occur during human embryogenesis such as gastrulation and organogenesis.

Recently, a team led by Golos and colleagues at the Wisconsin National Primate Research Center, Madison, has reported the development of a stem cell model that mimics the formation of the placenta during the earliest stages of human development. The work could one day help us better understand and treat diseases of pregnancy such as pre-eclampsia.

It is possible to develop trophoblastic cells from the embryoid bodies—the clumps of cells that arise when undifferentiated stem cells are removed from flat culture plates and grown in a suspended culture of proteins and hormones. These trophoblastic cells are the building blocks that lead to the formation of the placenta, which orchestrates a maternal environment that protects and nurtures a fetus during pregnancy. By using embryonic stem cells to create a window to these very early stages of human development, scientists now can gain access to the cellular and chemical secrets of how such critical features as extraembryonic membranes, especially the placenta, grow and develop during pregnancy. A better basic understanding of the events that occur during human pregnancy will ultimately lead to advances in maternal and fetal health.\(^7\)

**In Utero Stem Cell Transplantation**

In utero hematopoietic stem cell transplantation is a promising approach for the treatment of selected congenital immunodeficiency disorders [i.e. severe combined immunodeficiencies (SCIDs), chronic granulomatous disease, hyperimmunoglobulin M (hyper-IgM) syndrome and others] and hemoglobinopathies [i.e. sickle cell disease and thalassemia].\(^8\)

**Fetomaternal Cell Traffic, Pregnancy-Associated Progenitor Cells and Autoimmune Disease**

Fetal cells in maternal blood are a potential source of fetal genetic material that can be obtained noninvasively. Efforts to isolate these cells from maternal peripheral blood are limited by their low circulating numbers (approximately 1 per mL of maternal blood in euploid pregnancies). Expansion of these cells by culture would provide more cells for diagnosis and give an opportunity to study fetal metaphase chromosomes. Despite extensive optimization of culture conditions, many groups have failed reproducibly to grow fetal cells from preprocedural maternal samples. An unexpected benefit of this research has been the discovery of a novel population of fetal cells, the pregnancy-associated progenitor cell (PAPC), which remains in maternal blood and tissue for decades following delivery. These cells might play a role in some autoimmune diseases such as scleroderma. PAPCs appear to have stem cell characteristics such as the ability to proliferate and differentiate. Recently, developed animal models will help to ascertain whether these cells cause disease, respond to disease, or have therapeutic applications.\(^9\)

**THE ETHICS OF HUMAN EMBRYONIC STEM CELL RESEARCH**

The status of the human embryo and human embryonic stem cell research is a controversial issue as, with the present state of technology, the creation of a human embryonic stem cell line requires the destruction of a human embryo. Stem cell debates have motivated and reinvigorated the “prolife” movement, whose members are concerned with the rights and status of the embryo as an early-aged human life. They believe that embryonic stem cell research instrumentizes and violates the sanctity of life and constitutes murder.\(^10\) Fundamental assertion of those who oppose embryonic stem cell research is the belief that human life is inviolable, combined with the opinion that human life begins with the moment a sperm cell fertilizes an egg cell to form a single cell.

Most stem cell researchers use embryos that were created but not used in in vitro fertility treatments to derive new stem cell lines. Most of these embryos are slated to be destroyed, or stored indefinitely, long past their viable storage life. In the United States alone, there have been estimates of at least 400,000 such embryos.\(^11\)

Recently, researchers at Advanced Cell Technology of Worcester, Massachusetts, succeeded in obtaining stem cells from mouse embryos without killing them (Lanza technique).
If this technique and its reliability are improved, it would alleviate many of the ethical problems related to embryonic stem cell research.12

**Stem Cells without Embryonic Destruction**

Notably, a fundamental impediment to the widespread acceptance of embryonic stem cell research is the destruction of the embryo. Consequently, some stem cell researchers are working to develop techniques of isolating stem cells that are as potent as embryonic stem cells, but do not require the destruction of a human embryo. Some believe that human somatic cells can be coaxed to “dedifferentiate” and revert to an embryonic state. Researchers at Harvard University, led by Kevin Eggan, have attempted to transfer the nucleus of a somatic cell into an existing embryonic stem cell, thus creating a new stem cell line. Another study published in August 2006 also indicates that differentiated cells can be reprogrammed to an embryonic-like state by introducing four specific factors.

Researchers at Advanced Cell Technology, led by Robert Lanza, reported the successful derivation of a stem cell line using a process similar to preimplantation genetic diagnosis, in which a single blastomere is extracted from a blastocyst. It should be noted that this process has not yet demonstrated the ability of donor blastocysts to survive to term as well after blastomere harvesting. Nevertheless, this technique may in future allow for the creation of stem cells without embryonic destruction.

**POLICY ON STEM CELL RESEARCH**

**International Policy**

Embryonic stem cell research has divided the international community. In the European Union, stem cell research using the human embryo is permitted in Sweden, Finland, Belgium, Greece, the United Kingdom, Denmark and the Netherlands; however, it is illegal in Germany, Austria, Ireland, Italy and Portugal. The issue has similarly divided the United States, with several states enforcing a complete ban and others giving financial support. The countries in Asia—China, Japan, Korea, Taiwan—all have supportive policies toward stem cell research. India still has no policies (apart from the guidelines) covering stem cell research but is currently formulating them. The Middle East is largely restrictive with the exception of Israel and Iran. Australia is partially supportive (exempting reproductive cloning yet allowing research on embryonic stem cells that are derived from the process of IVF); however, New Zealand, most of Africa (excepting South Africa) and most of South America (excepting Brazil) are restrictive.

**Indian Policy**

The Indian government had set up a committee comprising of the experts from the Indian Council of Medical Research (ICMR) and the Department of Biotechnology in 2005 to frame National Guidelines for Stem Cell Research and Therapy in a bid to regulate the research activity in this emerging sector. These guidelines were submitted to the health ministry in 2006 and are available on the ICMR website for interested readers—www.icmr.nic.in/stem_cell/stem_cell_guidelines.pdf. However, ICMR has not listed penalty in the guidelines, which would act as a rule book for the future research.

**KEY EVENTS IN STEM CELL RESEARCH**

- 1960s—Joseph Altman and Gopal Das present evidence of adult neurogenesis, ongoing stem cell activity in the brain; their reports contradict Cajal’s “no new neurons” dogma and are largely ignored.
- 1963—McCulloch and Till illustrate the presence of self-renewing cells in mouse bone marrow.
- 1968—Bone marrow transplant between two siblings successfully treats SCID.
- 1978—Hematopoietic stem cells are discovered in human cord blood.
- 1981—Mouse embryonic stem cells are derived from the inner cell mass.
- 1992—Neural stem cells are cultured in vitro as neurospheres.
- 1995—US President Bill Clinton signs into law the Dickey Amendment which prohibited federally appropriated funds to be used for research where human embryos would be either created or destroyed.
- 1997—Leukemia is shown to originate from a hematopoietic stem cell, the first direct evidence for cancer stem cells.
- 1998—James Thomson and coworkers derive the first human embryonic stem cell line at the University of Wisconsin, Madison.
- 2000s—Several reports of adult stem cell plasticity are published.
- 2003—Dr Songtao Shi of NIH discovers new source of adult stem cells in children’s primary teeth.
- November 02, 2004—California voters approve Proposition 71, which provides $3 billion in state funds over 10 years to human embryonic stem cell research.
- 2004–2005—Korean researcher Hwang Woo-Suk claims to have created several human embryonic stem cell lines from unfertilized human oocytes. The lines are later shown to be fabricated.
- 2005—Researchers at Kingston University in England claim to have discovered a third category of stem cell, dubbed cord-blood-derived embryonic-like stem cells (CBEs), derived from UCB. The group claims these cells are able to differentiate into more types of tissue than adult stem cells.
- 2001–2006—US President George W Bush endorses the Congress in providing federal funding for embryonic stem
cell research of approximately $100 million as well as $250 million dollars for research on adult and animal stem cells. He also enacts laws that restrict federally-funded stem cell research on embryonic stem cells to the already derived cell lines.

- May 05, 2006—Senator Rick Santorum introduces bill number S. 2754, or the Alternative Pluripotent Stem Cell Therapies Enhancement Act into the US Senate.
- July 18, 2006—The US Senate passes the Stem Cell Research Enhancement Act HR 810, and votes down Senator Santorum’s S. 2754.
- July 19, 2006—President George W Bush vetoes HR 810 (Stem Cell Research Enhancement Act), a bill that would have reversed the Clinton-era law which made it illegal for Federal money to be used for research where stem cells are derived from the destruction of an embryo.
- November 07, 2006—The people of the US state of Missouri passed Amendment, which allows usage of any stem cell research and therapy allowed under federal law, but prohibits human reproductive cloning.
- January 07, 2007—Scientists at Wake Forest University led by Dr Anthony Atala and Harvard University report discovery of a new type of stem cell in amniotic fluid. This may potentially provide an alternative to embryonic stem cells for use in research and therapy.
- February 16, 2007—The California Institute for Regenerative Medicine became the biggest financial backer of human embryonic stem cell research in the United States when they awarded nearly $45 million in research grants.
- June 6, 2007—Research reported this week by three different groups shows that normal skin cells can be reprogramed to an embryonic state in mice. The race is now on to apply the surprisingly straightforward procedure to human cells.

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Lasers in Human Reproduction

**INTRODUCTION**

The term LASER is an acronym for “light amplification by stimulated emission of radiation”. Professor Bruhat first reported the use of the carbon dioxide (CO₂) laser at laparoscopy in 1979, and since then there have been several advances made in the use of lasers in endoscopic surgeries. In 1985, the lasers were also used in enhancing results in assisted reproductive technologies (ARTs), with the help of the new technique of “assisted laser hatching”.

**LASERS IN ENDOscopy**

Gynecological laparoscopy which at one time was a purely diagnostic entity has now been revolutionized to first line operative intervention and this has been greatly facilitated by the application of lasers. The laser as a surgical tool has been at the forefront of minimally invasive surgery. The control and precision of lasers has allowed the performance of advanced operative laparoscopy with relative safety and ease. Laparoscopic surgeries not only reduce the length of stay in hospital, which is a crucial factor in today’s economic climate, but also reduces postoperative morbidity and the length of convalescence and allow the woman to return to their normal routine much earlier compared to open surgeries.

**LASER PHYSICS**

A laser device strengthens or amplifies light, producing a highly directional, powerful light beam—much like focusing sunlight through a magnifying glass to produce a beam concentrated enough to light a fire. LASER contains what is referred as an active lasing medium, a collection of atoms or molecules that are housed in an optical resonant cavity. They are named according to the media contained in their optical cavity. The typical laser, such as the carbon dioxide type, is a tube filled with gas, which is electrically excited (other lasers may use different gases, liquids or solids as their medium). As an electric current passes through the tube, the gas molecules become charged or excited and emit absorbed or excess energy as photons—tiny “packages of light”. The light is reflected back and forth by mirrors at either end of the tube, a process that amplifies the energy, producing an intense light beam of a single wavelength or color. The beam comes out through a partially silvered mirror at one end of the device as an ultrafine, very strong light beam that can deliver extreme heat. In producing light beams with different properties, laser technology takes advantage of the special characteristics of a whole range of gases, solids and liquids, some of them exotic elements—including argon, krypton, neodymium, titanium and holmium. Depending on the substance used, the laser beam has a longer or shorter wavelength. Each laser has its own unique properties and is used for different procedures: photo ablation (vaporizing or melting tissue), photo disruption (breaking chemical bonds) or photocoagulation (sealing, shutting).

**LASER TISSUE INTERACTION**

Primary tissue effects of laser are produced by heat energy. Water content of soft tissue is about 80% by volume. If latent heat of vaporization is delivered by the laser beam, the tissue crater reflects the intensity profile of incident energy. When temperature rises to more than 57°C, irregular damage occurs and cell dies. Between 57°C and 100°C, cell death without vaporization occurs. Additional damage occurs due to lateral conduction which is proportional to the amount of time spent in lasing. Depending on the type of laser, its beam can...
Infertility

Carbon Dioxide Lasers

Carbon dioxide is almost completely absorbed by thin layer of water. The infrared beam of the CO₂ laser cuts tissue by vaporizing it. Cells absorb laser light to the boiling point of water and then explode in a puff of steam and cellular detritus called a "laser plume". In the hands of a skillful operator, the focused beam of the CO₂ laser performs better than the finest surgical knife, avoiding the mechanical damage of conventional surgery, reducing postoperative bleeding, scarring and swelling. Furthermore, laser seals the cut surfaces of tiny blood vessels, thereby making surgery almost bloodless in some cases. However, while a knife cuts deeply and swiftly, a carbon dioxide laser proceeds layer by layer, finding maximum effectiveness in delicate operations and such procedures as removing genital warts or excising small skin cysts. One major disadvantage of the CO₂ laser is its relative inflexibility and superficial range. It cannot reach far into the body for deep internal procedures, nor can it be attached to a fibreoptic viewing tube or endoscope. Another limitation is the need for elaborate safety precautions. The eyes must be protected, and the smoke, spray and stench from carbon dioxide laser can be considerable and so the operating staff needs to wear masks to minimize throat irritation and reduce the risk of contamination from breathing in the plume.

Neodymium: Yttrium-Aluminum-Garnet Lasers

The neodymium: yttrium-aluminum-garnet laser (Nd:YAG) operates in the near infrared range. Having a shorter wavelength than the CO₂ laser, the YAG beam can penetrate deeper into tissues—as deep as 2-6 mm. Another advantage of the Nd:YAG is that unlike the more cumbersome CO₂ laser, its light can be transmitted through long, flexible fibreoptic cables enabling it to reach inaccessible parts of the body. According to wave duration (power), the Nd:YAG does different things. At low power it destroys cells by denaturing protein (disrupting molecular structure), rather as egg white solidifies and turns opaque when heated, so that the cells die and slough off. At higher power, it vaporizes tissue and because it scatters heat widely is ideal for "debulking" or shrinking cancerous growths (shriveling them up, much like a grape loses water to become a raisin).

In gynecological surgeries CO₂ and YAG lasers are used most commonly. Although new lasers are continually being developed, those most prevalent in medicine today are: the carbon dioxide (CO₂) laser, the neodymium: yttrium-aluminum-garnet (Nd:YAG) solid state laser and the argon laser. Lasers recently introduced for medical uses include the excimer laser and the tunable dye laser.

Laser Laparoscopic Procedures

Almost all the gynecological procedures can now be performed laparoscopically with the aid of lasers, thereby avoiding all the sequelae associated with open surgeries.

The common procedures that have been aided by the use of laser during laparoscopy are:
- Fulguration or excision of endometriosis
- Lysis of adhesions
- Myomectomy
- Removal of ectopic pregnancy
- Ovarian cystectomy
- Ovarian drilling in polycystic ovary syndrome (PCOS)
- Tuboplasty or Neosalpingostomy
- Salpingo-oophorectomy
- Division of uterosacral ligaments
- Presacral neurectomy
- Laparoscopic-assisted vaginal hysterectomy (LAVH)
- Retropubic urethropexy
- Sacral colpopexy

Advantages of Lasers Over Laparotomy

- Surgical time is short
- Bleeding is minimal
- Very little scarring
- Requires short or no hospitalization
- Fast recovery.

LASER IN MANAGEMENT OF FIBROID

Magnetic resonance (MR) image-guided percutaneous laser ablation is used to treat uterine fibroids. Under MR-image guidance needles are inserted, through an area of skin that has been locally anesthetized, into the center of the targeted uterine fibroid. Bare laser fibers are inserted down the center of each of the needles into the targeted fibroid. Laser energy is then used to destroy the fibroid.

LASER HYSTEROSCOPIC PROCEDURES

The common procedures that can be carried out with the aid of a hysteroscope are:
- Endometrial ablation
- Metroplasty
- Adhesiolysis
- Ablation of submucous myoma and adenomatous polyps.

LASERS IN ASSISTED REPRODUCTION

Assisted hatching has been defined as a “method of breaching or weakening the zona pellucida of a viable embryo” either with the use of a thin microneedle to slice through the zona, or with the use of various acidified solutions, or with the creation of an opening with a laser beam, thus enabling or assisting embryo to hatch, with resultant implantation into
the endometrium. Cohen and his coworkers initially carried out this path-breaking work in 1990. They postulated that if the zona was opened mechanically, the hatching of the embryo would be facilitated. Since then, assisted hatching has been used in many in vitro fertilization (IVF) centers for infertile patients to increase their chance of successful outcome.

Indications of Assisted Laser Hatching

Although conceptually very appealing, numerous studies have shown that uniform application of assisted hatching may not necessarily improve pregnancy rates. However, assisted hatching may be useful for a particular subset of patients, which includes:

- Women within the ages of 35–38 years
- Women with elevated day 2 follicle stimulating hormone (FSH) levels of more than 15 mIU/mL
- Women with repeated ART failures
- Women having embryos with zona thickness of more than 15 microns.

Physiology of Hatching

The hatching site in humans develops in close proximity to the inner cell mass. In human blastocyst, small blebs or vesicles are seen to project through the zona prior to hatching. These may not represent the final site in which the blastocyst may hatch. Small trophoectoderm projections are also visualized in "in vitro" grown blastocyst prior to their hatching. These projections with a measurement of 27 µm in humans, are supposed to serve as the first contact point between the blastocyst and the uterine endometrium. This region of the blastocyst will ultimately attach to the uterine endometrium.

The blastocyst undergoes repeated cycles of expansion and collapse prior to the accomplishment of hatching. Blastocyst collapse is a rapid procedure lasting less than 5 minutes. On the other hand, re-expansion takes place over many hours. Just prior to the complete extrusion of the blastocyst during hatching, blastocyst collapse may take place. It should be noted that mechanical, chemical, osmotic, or temperature related stress factors could trigger blastocyst collapse. The blastocyst normally hatchs on day 6 or day 7 of culture or by day 5 in patients who have undergone zona micromanipulation, such as intracytoplasmic sperm injection (ICSI) or assisted hatching.

Impairment of Hatching Process

Many blastocysts demonstrate problems, such as the failure to hatch. This may be accompanied by an over expanded blastocyst, leading to blastocyst death. This is mainly due to hardened zona. Excessive hardening of the zona can occur in vitro cultured embryos, especially those that have undergone extended culture or cryopreservation. The hardening can also be caused by premature discharge of cortical granules during oocyte maturation, or through release of oximes or free radicals by the cumulus, or granulose cells. The overexposure of sperms during IVF culture conditions can also cause zona hardening in human blastocyst. It has also been observed that embryos with variable zona thickness hatch more easily than those with a uniformly thick zona. Age of the patient and the cause of infertility can also influence zona thickness.

Deficient quality and quantity of embryonic and uterine secretions can also impair hatching. The embryo deficiencies can be due to improper culture conditions, fragmented embryos, embryos with damaged blastomeres following cryopreservation, or elderly patients. Abnormal intrauterine environment can also give rise to deficient secretion of uterine lysins.

Factors Promoting Hatching

Ideal culture conditions with more extensive use of sequential media, has improved the rates of blastocyst development and hatching. Usage of supplements like human serum, albumin, or macromolecules such as the glycosaminoglycan hyaluronate may lead to zona softening. Growth factors, such as heparin binding epidermal growth factor, have resulted in increasing the rate of blastocyst hatching. Blastocyst that have resulted following ICSI procedure have a higher incidence of getting trapped as the breach in zona is not big enough for the blastocyst to completely hatch. ICSI, as well as other techniques of assisted hatching which cause smaller openings, such as partial zona dissection (PZD), can undergo this abnormal trapping with resultant increase in the incidence of monozygotic twinning.

Various techniques of assisted hatching performed on day 3 or day 5 embryos, have facilitated the hatching process. Proper hatching of adequate size (20–25 microns) would result in accelerated hatching process, where the embryo may hatch through a thick zona on day 5 instead of day 6. In these types of blastocysts, there is no expansion of the blastocyst, which decreases the chance of zona thinning. There is a possibility of earlier implantation as compared to non-hatched embryos.

General Principles of Assisted Hatching

Hatching is normally carried out on day 3 after the oocyte retrieval when the embryos are at the 6–8 cell stage. It is generally recommended to hatch the embryo after the blastomere adherence has increased. This prevents blastomere loss occurring through the hatched zona due to postembryo transfer uterine contractions. Hatching is generally carried out on an inverted microscope fitted with either a micromanipulator and/or diode laser.

The embryos are placed in 20–50 L droplets of HEPES-buffered media and covered with oil. In case of laser hatching, one can place the embryos in bicarbonate based culture
media droplets due to the speed of the process. During the hatching process, the microscope stage is maintained at a temperature of 37°C. It is essential to minimize pH and temperature fluctuations. The size of the hole should be between 30 microns and 40 microns. A smaller hole can cause embryo trapping, while a larger hole will cause blastomere loss. The incidence of monozygotic twinning is increased following improper hatching. Many groups have bypassed this problem by using the technique of laser zona thinning, rather than full thickness zona hatching. Following hatching the embryos are placed back into the incubator. The embryo transfer is done 30 minutes to 4 hours later. This delay in embryo transfer helps in establishing fibrinous bridges over the open zona, thus protecting the embryo from macrophage invasion and infections. Many groups, including the author, believe in treating the patient with broad spectrum antibiotics and methylprednisolone or dexamethasone (personal preference) for 4 days, postembryo transfer. This may reduce the incidence of macrophage invasion and infection.

Various methods of assisted hatching are:
- Mechanical hatching (PZD)
- Chemical assisted hatching using acid Tyrode's solution
- Assisted laser hatching.

**Assisted Laser Hatching**

Laser hatching was first introduced by Tadir, using beams of light varying in their wavelength. This technique was initially used for zona pellucida drilling by Palankar in 1991, using excimer laser beams. The technique of assisted laser hatching is very simple to execute. However, before going into the actual mechanism of action, it is necessary, to discuss the general principle of laser vis-a-vis embryo.

**Types of Laser**

There are mainly two types of lasers that are used in the field of embryology.

In the “contact laser systems”, the laser beam is directed through a microscopic glass laser fiber that has to be in direct contact with the zona pellucida. Numerous systems such as the ArF excimer laser (Ultraviolet, 193 nm wavelength) or the erbium-yttrium: aluminum-garnet (Er:YAG, wavelength 2.940 nm) have been tested. Although uncommon, the Er:YAG laser has been shown to be very safe and efficacious.

The “noncontact laser systems” are being widely accepted all over the world. Although the infrared InGaSp diode laser is the most popular laser, other systems have been tested such as the KrF excimer (wavelength 248 nm), Holmium: yttrium-scandium-gallium-garnet (Ho:YSGG; wavelength 2.1 µm), and the ultraviolet laser which are used in association with petri dishes with membranous bottom (wavelength 337 nm).

In the “nonobjective base lasers”, the laser source is independent. The beam is reflected and refocused through a collimator onto the special laser objective. The beam then passes through the glass bottom of the petri dish, the culture media, and finally through the properly positioned zona pellucida. In this system, the laser beam has to be aligned using a pilot laser every time one starts the laser. The majority of the systems are based on this configuration (Fertilase, research instruments).

In the “objective based laser systems”, the laser generator is fitted to the special laser objective (ZILOS-TK® laser by Hamilton Thorne). Hence, there is no need to realign the beam every time one uses the laser. The rest of the mechanism is similar to the nonobjective base laser previously described.

Once the laser beam exits the objective, it enters the petri dish and then the culture media. Both of these minimally absorb the laser energy. Thus, there is hardly any dissipation because the water content of the culture media absorbs the ultraviolet peak spectrum of the beam. This results in the virtual elimination of the mutagenic effect of the laser on the gametes. The beam then passes tangentially through the zona of the targeted embryo where the focused beam dissipates laser energy to the zona. The water molecules, as well as some zona pellucida macromolecules, absorb laser energy at about 200°C (on the beam axis). The majority of the heat is dissipated into the surrounding culture media. This, in turn, causes zona pellucida thermolysis. As the beam passes tangentially through the zona, the hole created has a cylindrical appearance. The cuts can be made with great precision without disturbing the blastomeres. It can be easily used on oocytes, day 2, day 3, or day 5 embryos.

The size of the holes is based on two parameters: the intensity (energy) of the beam and the exposure time. In most diode lasers, the beam intensity is constant. Thus, the size of the hole can be increased by increasing the exposure time. Generally the laser power is about 100 MW where the exposure time should not exceed 10–20 msec. Generally, two pulses of 15–20 msec will drill a hole of 30–40 microns.

**Standard Assisted Laser Hatching**

In the standard assisted laser hatching procedure, the embryo is placed in culture droplets. The area of the zona is identified where the largest underlying perivitelline space may be identified. The laser target is placed on the zona. Normally 2–3 pulses suffice in creating a 30–40 microns hole in the zona. In embryos with thicker zona, more pulses may have to be used to achieve the same effect. The hatched embryos are then replaced back into the incubator.

**Assisted Laser Hatching with Zona Pellucida Thinning**

Assisted laser hatching with zona pellucida thinning is a modification of the standard full thickness assisted laser hatching procedure. The initial studies were carried out with acid Tyrode’s solution. However, presently this technique...
is practiced using diode laser which places the embryo in droplets. The laser target is then placed on the zona where it is thinned by 50% of its original thickness. This is carried out for one-fourth circumference of the embryo. Some authors have demonstrated improved results with YAG laser with 50% thinning of the zona done over a distance of 20 microns diameter. Once the thinning is done, the embryos are replaced back into the incubator. Zona thinning reduces the risk of blastomere loss and embryo infection, compared to the standard full thickness hatching.

**Blastocyst Assisted Hatching**

Blastocyst assisted hatching can also be performed in various ways to improve pregnancy rates. In mechanical hatching, the zona is hatched by rubbing it with a microneedle mounted on a micromanipulator. In chemical hatching, the blastocyst is exposed to pronase whereas, in laser hatching, the zona is exposed to two or three short 3-5 msec exposures. In pronase hatching droplets of pronase at a concentration of 10 IU/mL are made. Early and expanding blastocysts are placed in pronase for 1 minute at 37°C. The blastocysts are removed from pronase within a minute, prior to the complete disappearance of the zona. After thorough washing in culture media, they are put back into the incubator. Embryo transfer is later carried out hours after incubation.

In blastocyst laser hatching, the embryos are transferred to culture media droplets under oil. The laser is targeted on the zona where short pulses of laser lasting 3-5 msec are fired. The blastocysts are then transferred back into the incubator. Both techniques have yielded improved pregnancy rates as compared to non-drilled blastocysts.

**Assisted Hatching with Removal of Anucleate Fragments**

Anucleate cytoplasmic fragments are frequently seen in cleaving embryos. Embryo fragments are generally seen in elderly women and those with a poor cycle response. Embryos with excessive fragmentation are known to have lower implantation rates due to reduced cytoplasm available for normal cell division. It can also be due to obstructed gap junctions which hamper intracellular communication. Alikani et al. demonstrated an increase in implantation rate, following removal of fragments from poor grade embryos.

In this procedure, the embryo is placed in HEPES-buffered media droplets under oil and held in place with a holding pipette. Assisted hatching is carried out either with acid Tyrode’s or diode laser. Fragments are gently aspirated using a 12-micron outer diameter micropipette attached to a mouth or a syringe assembly. The inner diameter is between 5 microns and 10 microns. The fragments are removed gently, without damaging the proximal blastomeres. The embryo is given multiple washes and then placed in culture media. Typically, embryo transfer is executed 4-24 hours after the hatching.

**Applications of Assisted Hatching**

Assisted zona hatching has come a long way since its introduction in 1989. Among the various methods like mechanical dissection, Acid Tyrode’s hatching, and laser assisted hatching techniques, laser hatching has become the most popular because of its advantages like hole size control, less time of exposure of embryos, and reproducible results. However, other methods are still employed by few units. Assisted zona hatching has been utilized for a number of purposes. Zona hatching of oocytes can be done to increase chances of fertilization in oligospermic patients undergoing IVF. Sometimes, in oocytes with thick zonae, ICSI may cause increased degeneration. To overcome this, zona may be thinned, with the help of diode laser to a certain length prior to ICSI, and ICSI performed along that thinned section of zona. This reduces the mechanical stress during subsequent hatching.

The hatching of zonae is done to improve implantation rate. Assisted hatching is repeatedly proven to be helpful in patients with multiple implantation failure.

In cryopreserved-thawed embryos, the zonae get thick and become difficult to hatch while some groups have shown better implantation rate when assisted hatching was performed in frozen-thawed embryos. Assisted hatching can be applied to the zona thickening caused as a result of increased patient age. Zona thickening can also be caused due to medication or inappropriate culture conditions. Such embryos may also qualify as candidates for assisted hatching.

Fragmentation in “in vitro” cultured embryos may hamper proper division of embryos by reducing the availability of cytoplasm or by special contortion of blastomeres. Research has indicated that fragment removal following zona hatching (in embryos with 10–20% fragmentation) result in further development and implantation rate similar to grade 1 embryos.

Assisted hatching may facilitate embryo aspirations. Alikani et al. proved that a degenerated blastomere in an embryo may release toxic compounds to affect the proper division and development of the other blastomeres. As a result, it is beneficial to aspirate and remove the degenerated blastomere, which can be done with a micropipette following zona hatching.

Assisted hatching of zona is also helpful preceding biopsies of polar bodies (I and II), blastomeres, and blastocysts for preimplantation genetic diagnosis (PGD) to screen for any genetic anomalies in oocytes or embryos. In the field of stem cell research, assisted hatching of blastocyst zona can be followed by aspiration of inner cell mass for embryonic stem cell culture.
LASER SAFETY

The use of lasers has helped in expanding the indications for laparoscopic treatment of disease, but at the same time has increased the risk of complications from the operation of the laser and injury to pelvic structures due to the treatment of more advanced disease. This risk can be minimized by following the particular guidelines for safety for each laser.

One of the most susceptible areas of the body to serious laser injuries is the eye. The wavelengths in and near the visible spectrum are most dangerous. The Nd:YAG, argon, and potassium titanyl phosphate (KTP) lasers (visible and near-visible laser energy) can burn the retina, whereas the CO₂ laser (far-infrared energy) can cause corneal burns. Nd:YAG laser particularly is known to cause retinal burns because this light is invisible and so there is no protective blink response to it. Wearing a protective tinted eyewear can prevent these burns. These should be worn by everyone in the operating room; including the patient. The tinted eyewear filters the wavelength of the specific laser for which it is designed while allowing as many of the other wavelengths to pass in order to maximize visibility. Sometimes, inadvertent laser burns can occur to the operator, assistant, or the patient. It can occur due to redirection of laser energy from reflective surfaces like the surgical instruments. The primary risk of injury during laparoscopy is to the patient’s intra-abdominal structures due to the closed nature of surgery and short separation distances of the neighboring sites. Several methods have been developed which attempt to minimize reflection by scattering the laser beam or absorbing stray energy and thereby preventing these injuries. This is accomplished by instruments that are finely wire-brushed, sand-blasted, or glass-beaded. When used as backstops, titanium metal is preferred to stainless steel or instruments with ebonized coatings. Stainless steel does not handle heat well and there is a tendency to break down over time. Moreover, localized heating can occur, thereby creating potential for thermal burns on contact. Ebonized coatings absorb the incident laser energy thereby reducing reflections, but it causes the instrument to heat up, predisposing the tissue to secondary burns. Moreover, these coatings degrade with each laser impact over time.

Another cause of inadvertent laser burns is due to human error, the incidence of which depends upon teamwork, operator experience, and eye-hand-foot coordination. To prevent such burns, aiming beam should always be visualized prior to firing the laser. For contact lasers, the tip should always be visualized, especially immediately after firing the laser since the tip remains hot and can burn the surroundings.

Injuries can rarely occur due to accidental activation of the laser when not in use, like what may happen on pressing the laser pedal unintentionally. Placing the laser on standby mode when not in use will reduce the risk of injury by this mechanism.

The liberal use of irrigating solutions to moisten lap packs, gauze bandages, and drapes in the surgical areas reduces the risk of accidental ignition of the materials within the surgical field. Flame-retardant surgical drapes for laser surgery are also available. These two precautions, however, may not completely eliminate the risk of ignition. Liberal use of irrigating fluids adds extra protection. The use of alcohol and ether solutions should be avoided due to their flammable nature. Anesthesiologists should be informed that flammable anesthetic gases are to be avoided as well.

Even if one adheres to the appropriate precautions as mentioned, complications can still arise especially while working in anatomically difficult areas or when severe disease is distorting the anatomy. As for example, ureteral injuries have been reported despite prior hydrodissection of the peritoneum. This, however, is rare with most injuries involving the use of electrocautery. Identifying the exact course of the ureter helps minimizing these injuries. Bladder perforation and loss of the sapphire Nd:YAG laser tip are other laser-related complications that have been previously reported. These injuries are a “calculated risk” of operating with lasers and are dependent to a large extent upon operator experience.

A less direct, but more common, source of injury associated with lasers involves inadvertent bumping into laser arms (for example, with the head) and tripping over power lines to lasers and other instruments in the operating rooms. Such injuries have been reported and can be serious. Attention to detail with respect to positioning of equipment is important, as is care in moving around an operating room full of numerous additional pieces of equipment.

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Lasers in Human Reproduction

CHAPTER 94


SECTION 11

Imaging in Obstetrics and Gynecology
INTRODUCTION

High-resolution transvaginal sonography (TVS) has been widely available since mid-1980 and has gained acceptance as an integral part of gynecologic and easily obstetric sonographic examinations. In many ultrasound laboratories, the standard examination of female pelvis consists of transvesical-transabdominal sonography (TAS) combined with TVS and in some cases, transvaginal color flow Doppler (TVCFD) (Figs 1 and 2).

Patient need not be fasting unless an upper abdomen scan is also asked for. TAS is performed first which provides a wider field for view and overview of pelvic organs. For a TVS, patient is asked to void immediately before examination. The transvaginal approach by passes attenuating tissue and allows a high frequency probe to be placed close to “target organs”. Scanning is performed with patient supine, thighs abducted and knees flexed. Probe is covered with a condom or sheath containing small amount of gel. Probe is inserted gently with slight push toward rectum. Four types of probe movements are required (i) pushing and pulling, (ii) rotation, (iii) rocking or upwards and downwards and (iv) side to side or “Panning” (Figs 3 to 5).

TVS probe may be disinfected by cidex.

NORMAL FEMALE PELVIS

Female pelvis consists of true and false pelvis. Female genital organs lie within true pelvis (Fig. 6).

Uterus

It is a pear like organ between urinary bladder anteriorly and rectosigmoid posteriorly. It consists of two major parts: The body or corpus and the cervix. Isthmus separates the body
Figs 3A to C: Probe movements

Fig. 4: Probe movements; nowadays fingertip and finger cap probes are also available
and cervix. Fundus of the uterus is the superior portion of the uterus between the insertion of the tubes.

The ratio of the length of body and cervix varies with age. Before menarche, the corpus is approximately one half the length of cervix; in nulliparous women, the corpus and cervix are of approximately equal length, and in multiparous women, the corpus is about twice the length of the cervix.

Uterus measures about $8 \times 4 \times 4$ cm in childbearing age, which increases by about 1 cm in multiparous women. After menopause uterus atrophies (Table 1).

Uterus consists of (i) myometrium: It is homogeneous in echotexture with smooth margins (ii) endometrium: It is seen as a hyperechoic band in the center of the uterus. The total thickness of endometrium represents the anterior and posterior opposed layers. Normal endometrial thickness and appearance varies with phase of menstrual cycle. Endometrial fluid when present should not be included in the measurement (Fig. 7).

**Evaluation of Endometrium**

The thickness of the endometrium varies depending on the different phases of the menstrual cycle. The thickness of the broadest portion is measured in the midsagittal plane of the uterus. The anterior and posterior portions are measured together.
**Table 1: Measurements of uterus and volume of ovaries in different age groups**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Size of uterus</th>
<th>Cervix uterine-body ratio</th>
<th>Mean ovarian volume (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prepubertal</td>
<td>(1–3.3) × (0.5–1) cm</td>
<td>2:1</td>
<td>3</td>
</tr>
<tr>
<td>Nulliparous</td>
<td>7 × 4 × 4 cm</td>
<td>1:3</td>
<td>9.8</td>
</tr>
<tr>
<td>Parous</td>
<td>8.2 × 5.2 × 5.2 cm</td>
<td>1:3</td>
<td>9.8</td>
</tr>
<tr>
<td>Menopausal</td>
<td>(3.5–6.5) × (1.2–1.8) cm</td>
<td>Cervix shorter</td>
<td>5.8</td>
</tr>
</tbody>
</table>

Proliferative phase: Immediately after menses, the endometrium is constituted by the basal layer and will be thin, measuring less than 4 mm in width. As proliferative phase progresses, the endometrium increases in thickness. The fully grown proliferative endometrium measures 6–10 mm in thickness. The appearance is typically described as trilaminar. The central cavity line will be echogenic. On either side of the central cavity line the hypoechoic functional layer will be seen. The endometrial-myometrial interface will be hyperechoic. These three lines form the trilaminar pattern.

Secretory phase: The endometrium thickens further in the secretory phase. The hypoechoic functional layer of the endometrium will become hyperechoic due to the presence of stromal edema. The change to hyperechoic appearance starts at the endometrium. In the mid-secretory phase, the full thickness of the endometrium will be echogenic. Thus, the trilaminar pattern will be lost in the secretory phase. The thickness of the secretory endometrium ranges from 7 mm to 14 mm. An endometrial thickness of more than 15 mm in the childbearing age group should be taken as abnormal and has to be sampled to exclude hyperplasia/malignancy.

Postmenopausal phase: The mean endometrial thickness in asymptomatic postmenopausal women is 3.4 ± 2.5 mm. A thickness greater than 4 mm is considered abnormal and is an indication to sample the endometrium. A meta-analysis of 35 studies found that an endometrial thickness less than 5 mm will exclude endometrial pathology in the majority of women. It is not unusual to find fluid in the endometrial cavity in postmenopausal women. Even though it does not always signify an abnormal endometrium, there is a high-risk for pathology in such women. The presence of irregularity in the endometrial surface and the thickness of the endometrium excepting the fluid region will give a clue as to the presence of pathology. If the thickness including the fluid is 5 mm or less the presence of pathology is unlikely. Normally there will be a hypoechogenic area between the endometrium and the myometrium—the subendometrial halo. This should not be included in the measurement of the endometrium. This halo will be lost when there is malignancy invading the myometrium. In a postmenopausal woman the arcuate vessels will be calcified and multiple echogenic areas will be seen distributed in the myometrium. In the presence of extensive calcification it will be difficult to measure the endometrial thickness due to poor visualization.

**Evaluation of the Cervix**

The probe should be withdrawn 2–3 cm in order to visualize the cervix. The endocervical canal which is a continuation of the endometrial cavity will be seen as an echogenic line. Polyps and growths in the endocervix can be delineated. In preovulatory periods mucus will be seen as a hypoechogenic linear shadow. Nabothon cysts may appear as anechoic cystic areas in the cervix.

**Ovaries**

Ovaries are ellipsoidal; position is variable especially in multiparous women. In nulliparous female, ovaries are situated in the ovaries fossa (also known as fossa of Waldeyer). The ovarian fossa is situated on the lateral pelvic wall and is bounded anteriorly by the obliterated umbilical artery, ureter and internal iliac artery posteriorly and the external iliac vein superiorly (Fig. 8).

Ovaries in girls younger than 2 years of age are typically less than 1 mL in volume. After menarche, ovaries generally measure 30 × 20 × 20 mm (Fig. 8).

**Folliculogenesis**

In proliferative phase of menstrual cycle, multiple small follicles, 10 mm in diameter are seen. A dominant follicle develops in midcycle which measures up to 20 mm in diameter. After ovulation corpus luteum develops (Figs 9A to E).
These include:
- **Uterus didelphys**: Two uteri, two cervix and may be a septated vagina (Figs 13A and B).
- **Bicornis bicornis**: Two uteri and two cervix (Figs 14A to C).
- **Bicornuate (unicollis) uterus**: Two uteri with partially fused lower segment (Figs 15A and B).
- **Septate uterus**: Thick or thin fibrous septa divides the myometrial component (Figs 16A to D).
- **Arcuate uterus**: Fundal dimpling is seen (Fig. 17A).
- **Unicornis uterus with rudimentary horn** (Fig. 17B).
- **T-shapes uterus** (Fig. 17C).

**Diseases of the Myometrium**

**Benign conditions**:
- **Adenomyosis** (Figs 18 to 20)
- **Myometritis**
- **Myometrial calcification**

**Benign tumors**:
- **Leiomyoma** (Figs 21 to 23)
- **Arteriovenous malformation** (Fig. 24)

**Malignant tumor**: Sarcomatous change in leiomyoma (Fig. 25).

**Adenomyosis**

It is defined as ectopic endometrial glands and stroma within myometrium.

Ultrasoundographic appearance (Figs 18 to 20):
- Diffuse uterine enlargement with no alteration in echotexture or uterine contour.
- **Focal adenomyosis**: Poorly defined area of abnormal echotexture within myometrium.
- Focal or diffuse speckled appearance of the myometrium (salt and pepper appearance)
- Cystic areas at endometrial-myometrial interface (Fig. 26)
- Increased thickness of posterior myometrium as compared to anterior myometrium.
- Ill-defined, focal abnormal texture lesion defined as adenomyoma
- Scattered vascularity on color flow imaging
- Additional ovaries lesions (Endometriotic cysts) may be seen (Fig. 27).

**Myometritis**

Ultrasoundographic findings include (Fig. 28):
- Multiple bright spots within myometrium
- Fluid in endometrial cavity
- Fluid within pouch of Douglas
- Probe tenderness
- Blood flow pooling.

**Myometrial Calcifications**

- Most common cause—calcified myoma
- Less common cause—arcuate artery calcification (Fig. 29).
Figs 9A to E: Follicular phase, dominant follicle and controlled ovarian hyperstimulation
Fig. 10: Fallopian tube—3D picture

Fig. 11: Polycystic ovarian disease with fluid

Figs 12A to D: Hypoplastic, normal, menopausal uterus
Figs 13A and B: Bicornuate (septate) uterus

Figs 14A to C: Double vaginal double cervix

Figs 15A and B: Two uteri fused in lower end 3D picture
Leiomyoma
These may be submucosal (5–10%) which displace/distort the endometrium. Most common type is intramural (within the wall of uterus) myomas which distort the uterine cavity. Panmural myomas extend through and through from the outer surface to the endometrial cavity. Few myomas may have a pedicle.

- Ultrasonography (USG) appearance depends on age, site, size and composition of the tumor.\(^6\)
- When muscular component predominates, lesion is a well-defined, concentric mass with poor sound through transmission (Isoechoic fibroids—difficult to see by USG).
- Increasing echogenicity marks the start of fibrous degeneration. With further aging, myomas undergo cystic degeneration (e.g. hemorrhagic, proteolytic) seen as an anechoic mass with posterior enhancement.
- Highly echogenic portions with acoustic shadowing is seen from areas of calcification or from myxomatous and lipomatous change.

Arteriovenous Malformation
These may appear on gray scale imaging as subtle myometrial inhomogeneity, tubular spaces within the myometrium, intramural uterine mass, endometrial or cervical mass or
sometimes as prominent parametrial vessels. Their appearance is nonspecific. These anechoic, tubular spaces fill with color on color flow imaging and show low resistance flow with high peak systolic velocities on spectral analysis. Venous flow also shows high flow velocities and systolic velocity peaks similar to an arterial pattern, which suggests arteriovenous shunting (Fig. 24).

Sarcomatous change within leiomyoma:
- Rare condition
- Ultrasound appearance is identical to that of benign tumors.

Figs 17A to C: (A) Fundal dimpling (arcuate uterus) 3D picture; (B) Unicornuate uterus and (C) T-shaped uterus

Figs 18A and B: Adenomyosis

Fig. 19: Adenomyosis color
Diseases of the Endometrium

**Benign condition:** Endometritis (Figs 30A and B)

**Benign tumors:**
- Endometrial hyperplasia (Figs 31A and B)
- Endometrial polyps (Figs 32 and 33)

**Malignant tumor:** Endometrial tumors (Fig. 34).

**Endometritis**
- Occurs with pelvic inflammatory disease (PID) and in postpartum patients.
- Sonographically, endometrium is echogenic or irregular with small amount of endometrial fluid.
Fig. 25A and B: Malignant changes in fibroid

Fig. 26: Adenomyosis (endometrial-myometrial cystic areas)

Fig. 27: Ovarian lesions of endometriosis

Fig. 28: Myometritis

Fig. 29: Myometrial and endometrial calcification
Figs 30A and B: Endometritis and cervicitis

Figs 31A and B: Endometrial hyperplasia

Fig. 32: Polyp

Fig. 33: Polyp on sonohysterography
Endometrial Hyperplasia

It is the most common cause of vaginal bleeding in both premenopausal and postmenopausal women, results from unopposed estrogen stimulation. Sonographically the endometrium is diffusely or focally thickened. Diagnosis is confirmed by endometrial biopsy (Fig. 31).

Endometrial Polyp (Figs 32 and 33)

- These represent areas of overgrowth of endometrial glands and stroma covered by endometrial epithelium.
- They usually arise from the fundus and are multiple in 20% cases.
- Presents with vaginal bleeding or mucus discharge.
- Appear sonographically as areas of increased endometrial thickening. TVS shows focal irregularity of the endometrial stripe, endometrial myometrial interface, however, is preserved.
- Sonohysterography confirms the diagnosis.

Endometrial Carcinoma

- Seen in postmenopausal women with postmenopausal bleeding.
- The telltale sign of endometrial carcinoma on ultrasound is not simply thickening of the endometrium but rather focal irregularity and myometrial distortion.
- Most of endometrial carcinoma are either diffusely or partially echogenic, 10–15% may be isoechoic.
- Sonography is helpful in assessing superficial or deep invasion and in follow-up management.

Diseases of the Uterine Cavity

- Endometrial fluid (Fig. 35)
- Intrauterine contraceptive devices (IUCD) (Fig. 36)
- Synechiae (Asherman’s syndrome) (Figs 37 and 38).
Endometrial Fluid
- Physiological (menstrual phase, normal early pregnancy)
- Pathological (abnormal pregnancy—missed abortion, ectopic pregnancy, molar pregnancy).
  - Infection
  - Obstruction
    - Malignant
    - Cervical stenosis

Intrauterine Contraceptive Devices (Fig. 39)
- Ultrasound helps to locate the position of IUCD when string is not felt.
- Seen as bright reflector within the uterus.
- Synechiae (Asherman’s syndrome).
- Intrauterine fibrous adhesions across the endometrial cavity.
- Synechiae form a mesh or spider’s web within the uterine lumen, may cause infertility, hypomenorrhea or amenorrhea, better seen with sonohysterography.

Sonohysterography (Figs 32, 33, 37, 38)
This is done by using saline contrast, which is pushed through the cervix by a pediatric Foley’s or feeding tube under
transvaginal scan visualization. This is an excellent, easy, noninvasive, quick and reliable method to evaluate uterine cavity for Asherman’s disease, polyps, submucous fibroids, focal lesions or even malignancy.

**ULTRASOUND AND Puerperium**

- Postpartum uterus should return to near normal size within 6–8 weeks after delivery.
- Postpartum ultrasound is visually requested if there is clinical concern about retained product or endometritis.

**Ultrasonography**

- The cavity may look normal.
- Echogenic mass within cavity—suggestive of retained products.
- Heterogeneous mass may be due to retained bits, blood clot, necrotic or injected material in the absence of placental tissue.9
- Fluid within endometrial cavity—blood or infection (Figs 40A and B).
- *Gas within cavity*10: It may be a normal finding in puerperium, at least until the end of third postpartum weeks.
- May indicate infection.

**DISEASES OF CERVIX**

1. *Nabothian cysts*: These are obstructed and hence dilated inclusion cysts, of no clinical relevance. May be seen at the interval os level and in the stroma, could indicate cervicitis (Fig. 30).
2. *Cervical fibroids*: Are well-defined, hypoechoic masses (Fig. 41A).
3. *Cervical cancer*: Ultrasound is not especially useful in the diagnosis of cervical malignancy. USG serves to document the complications of advanced cervical disease and its treatment. For example, ultrasound can document cervical stenosis and intrauterine fluid retention or hydronephrosis (Fig. 41B).
4. Ultrasound also can calculate volume of mass, staging and 5-year survival.

**VAGINA**

The most common lesion visualized with sonography is Gartner’s duct cysts. Transverse vaginal septums may present as amenorrhea with hematocolpos (Fig. 41C).

**OVARIAN SONOGRAPHY**

**Benign Cystic Lesion of Ovarian and Parovarian Structures**

**Functional Cysts**

- Follicular cysts
- Corpus luteum cysts
- Corpus luteum of pregnancy
- Theca luteum cysts
  - Surface epithelial inclusion cysts
  - Rete cysts
  - Hyperreactis luteinalis
  - Ovarian hyperstimulation syndrome (OHSS)
  - Polycystic ovarian syndrome
  - Ovarian Remnant syndrome
  - Neonatal ovarian cysts
  - Paratubal, parovarian cysts
  - Endometriosis and endometriomas
  - Pelvic inflammatory disease
  - Peritoneal inclusion cysts
Ovarian Neoplasms

- Surface epithelial stromal tumors
  - Serous tumors
  - Mucinous tumors
  - Epidermoid
  - Clear cell tumors
  - Transitional cell (Brenner) tumors
- Germ cell tumors
  - Mature cystic teratomas (Ovarian dermoid cysts)
  - Mature solid teratoma
  - Immature teratoma
  - Dysgerminoma
  - Yolk sac tumors
- Sex Cord—stromal tumors
  - Fibroma
  - Thecoma
  - Granuloma cell tumors
  - Sertoli-Leydig cell tumors
- Metastatic tumors.

Functional Cysts

- Follicular cysts: Thin-walled, unilocular 3–8 cm in size. Usually regress spontaneously\(^1\) (Fig. 42).
- Corpus luteum cysts: Commonly complicated by hemorrhage. Thick-walled with echogenic contents (Fig. 43).
- Corpus luteum of pregnancy: Corpus luteum of pregnancy may become enlarged and cystic. Needs follow-up ultrasound and monitoring (Figs 44A and B).
- Theca lutein cysts: Usually multilocular results from over-stimulation by high levels of circulating human chorionic gonadotropin (hCG) in trophoblastic disease (Fig. 45).

Surface Epithelial Inclusion Cysts

These result from cortical invaginations of ovarian surface epithelium. Mostly seen in postmenopausal women, usually multiple (Fig. 46).

Rete Cysts

Rare origin, located within ovarian hilus. Indistinguishable from other simple cysts\(^1\) (Fig. 47).

Hyperreactis Luteinalis

Ovarian enlargement resulting from the presence of multiple luteinized follicle cysts, secondary to hCG stimulation.\(^1\) Self-limiting condition USG shows bilaterally enlarged ovaries containing multiple cysts. Cysts may be simple or have hemorrhagic contents (Fig. 48).

Ovarian Hyperstimulation Syndrome

Seen in women undergoing ovulation induction, after administration of gonadotropins followed by hCG or rarely clomiphene alone (Figs 49A and B).
Fig. 42: Thin wall follicular cysts

Fig. 43: Corpus luteum cyst

Figs 44A and B: Functioning corpus luteum blood flow

Fig. 45: Theca lutein cysts

Fig. 46: Menopausal cystic ovaries
Ultrasonography in Gynecology

**CHAPTER 95**

**Ultrasonography:** Mild to moderate OHSS is characterized by cystic ovarian enlargement (greater than 5 cm in diameter) and a small amount of pelvic fluid. Severe OHSS is characterized by cystic ovarian enlargement with abdominal distension and discomfort or pain with or without nausea and vomiting or diarrhea. Ascites, pleural effusion seen\(^{13}\) (Figs 50A and B).

**Polycystic Ovarian Syndrome**

Seen in 16–22% of women in their reproductive years and in up to 50% of women presenting to infertility clinics.

**Ultrasonography:** Typical polycystic pattern is defined by the presence of 10 or more cysts measuring 2–18 mm in diameter in a single plane arranged peripherally around an increased amount of central stroma (Garland sign) (Necklace sign)\(^{14}\) (Fig. 51).

Greater ovarian stromal blood flow velocity and lower impedance have been demonstrated in women with PCO. The impedance of uterine arteries has been demonstrated to be increased (Fig. 52).

**Ovarian Remnant Syndrome**

It is a complication of oophorectomy in patients with distorted anatomy resulting from adhesions and endometriosis, making surgical dissection difficult; residual ovarian tissue may form a cystic or complex mass (Fig. 53).

**Paratubal, Paraovarian Cysts**

These arise from the mesonephric and parameso-nephric structures. Most common in 3rd and 4th decade and may be multiple. Morphologically, these cysts are indistinguishable from simple functional cysts. They may be complicated by hemorrhage, torsion or rupture (Figs 54A and B).
It is the presence of endometrial tissue outside the endometrium and myometrium. Ovaries, uterine ligaments, rectovaginal septum, cul-de-sac and pelvic peritoneum are the most common sites.

**Endometriosis**

It is the presence of endometrial tissue outside the endometrium and myometrium. Ovaries, uterine ligaments, rectovaginal septum, cul-de-sac and pelvic peritoneum are the most common sites.

**Ultrasonography:** Endometriomas have a variety of appearances ranging from an anechoic cyst to a cyst containing diffuse low level echoes with or without solid components to a solid appearing mass. Presence of a fluid-fluid level, punctate or linear bright echogenic foci in the wall of the cyst favors the diagnosis of endometrioma. TVS does not detect endometriotic implants.

**Pelvic Inflammatory Disease (PID)**

Ovarian involvement in PID is almost always secondary to salpingitis.
Sonographic findings may be normal early in the disease course. Timor-Tritsch et al. described the sonographic findings as\(^1\) (Figs 55A to E):

- Thickening of tube wall greater than or equal to 5 mm
- "Cogwheel sign"—Cogwheel shaped structure seen in cross-section of tube in acute salpingitis.
- Incomplete septa correlating with folds or kinks in dilated tube.
- "Beads-on-a-string" sign: Hyperechoic mural nodules within fluid tube representing flattened and fibrotic endosalpingeal folds.
- Tubo-ovarian complex: Ovary cannot be separated from the tube by pushing with the vaginal probe.
- Tubo-ovarian abscess: Conglomerate mass or fluid collection.
- Cul-de-sac fluid.\(^1\)
Peritoneal Inclusion Cysts

These are formed by trapping of fluid (which is normally produced by active ovaries) within peritoneal adhesions. A history of trauma, abdominal surgery, PID or endometriosis is common. USG shows the ovary surrounded by septations and fluid and lies inside or in the wall of a large ovoid or irregular anechoic cyst.

Ovarian Vascular Lesions

Ovarian Torsion

Usually caused by ovarian (particularly dermoid) and parovarian cysts. Sonographic appearance depends on the duration, degree of torsion and any associated intraovarian mass. USG shows a cystic, solid or complex mass with or without pelvic fluid, thickening of wall. These findings however are nonspecific. Enlargement of ovary with absent or markedly diminished ovarian flow is a specific finding (Figs 56A and B).

Massive Ovarian Edema

Accumulation of edema fluid within ovarian stroma is most likely due to torsion of the ovary. A definitive diagnosis of massive ovarian edema cannot be made on preoperative imaging but should be considered in the differential diagnosis of a solid extrauterine mass in the appropriate clinical setting.

Ovarian Venous Thrombosis

Occurs most often postpartum, may also follow pelvic operations, pelvic trauma—sonographically thrombosed vein appears as an anechoic to hypoechoic tubular mass extending superiorly from the adnexa with absence flow on Doppler. A perivenous phlegmon with increased vascularity may be seen.

Masses of the Ovary

Ovarian Neoplasms

Surface Epithelial Stromal Tumors

Serous tumors: Benign serous cystadenomas appear as sharply margined, anechoic masses that may be large and are usually unilocular. Internal thin-walled septations and papillary projections may be seen (in borderline tumors) (Fig. 57).

Serous cystadenocarcinomas are usually multilocular, containing multiple papillary projections and septations, echogenic material is occasionally seen within the loculi.

Mucinous tumors: Sonographically, mucinous cystadenomas have thicker and more numerous septations and frequently contain fine, gravity-dependent echoes produced by thick contents.

Mucinous cystadenocarcinomas usually appear as large, multiloculated cystic lesions containing echogenic material and papillary excrescences (Fig. 58).

Pseudomyxoma peritonei is by far the most common manifestation of atypically proliferating mucinous tumors.

Endometrioid tumors: Ultrasonography: These tumors are seen as cystic masses containing papillary projections (Fig. 59).

Clear cell tumors: Sonographic features of clear cell tumors are nonspecific, usually seen as complex, predominantly cystic masses (Fig. 60).

Transitional cell tumors (Brenner’s tumor): These are usually small (1–2 cm), hypoechoic and solid. Extensive calcification may be seen cystic areas are unusual.

Germ Cell Tumors

- Mature cystic teratomas (Ovarian dermoid): Ultrasonography features include the presence of regional diffuse bright echoes with or without posterior acoustic
shadowing, hyperechoic lines or dots, shadowing echodensity and a fluid-fluid level\textsuperscript{21} (Figs 61 and 62).

- **Immature teratomas**: These are rare malignant tumors, usually large and predominantly solid.
- **Struma ovari**: This term is used for tumors (mature cystic teratomas) containing thyroid tissue.
- **Dysgerminoma**: Sonographically, the presence of a solid ovarian mass with a multilobulated appearance, separated by fibrovascular septa, is highly suggestive.
- **Yolk-sac tumors**: Similar in appearance to that of dysgerminomas.

**Sex Cord-Stromal Tumors**

- **Fibromas**: Meig’s syndrome complicates about 1% of ovarian fibromas and is defined as ascites and pleural effusion accompanying a fibrous ovarian tumor usually a fibroma. Two typical appearances have been described sonographically.\textsuperscript{21} The first has features similar to that of uterine fibroid. Second appearance is that of a hypoechoic mass with substantial attenuation.
- **Thecoma**: Sonographically, these tumors are similar in appearance to fibromas.
- **Granulosa cell tumors**: Sonographically small tumors are predominantly solid, having an echogenicity similar to that of fibroids. Large ones resemble cyst adenomas and are multiloculated and cystic.
- **Sertoli-Leydig cell tumors**: Similar in appearance to granulosa cell tumors.

**Metastatic Tumors**

Tumor spread to ovaries is by several routes:

- **Direct spread**: Carcinomas of fallopian tube and uterus colonic carcinomas and retroperitoneal sarcomas.
Through the lumen of fallopian tube onto the surface of ovary. Uterine corpus carcinoma.
- Distant site metastatic deposits via blood and lymphatics.
- Transcoelomic dissemination with surface implantation.\textsuperscript{11}

\textit{Ultrasonography}: Bilateral ovarian enlargement by solid masses is highly suggestive. These masses may contain hypoechoic areas that represent cystic degeneration or necrosis.

\textit{Ovarian lymphoma}: Solid hypoechoic masses.

\section*{EVALUATION OF AN OVARIAN MASS}

\textit{Morphologic parameters}: Benign tumors are usually unilocular, well-defined borders, thin walls or septa.

Malignant tumors are multilocular, have thick or irregular walls or septa, poorly defined borders, mural nodules, solid components and echogenic elements.\textsuperscript{22}

\textit{Doppler parameters}: Neovascularity is a feature of malignant tumors and is characterized by 1,000 impedance, high velocity flow. Most authors used a cut off for malignancy of less than 0.4 for RI and 1.0 for PI (Table 2).

\textit{Color flow mapping}: Peripheral vascularization appears to be more common in benign tumors, whereas malignant tumors tend to have more centrally located vessels.

Arrangement of vessels is also a helpful discriminator because benign masses tend to have regularly spaced vessels, whereas malignant tumors demonstrate random distribution of vessels.\textsuperscript{23}
**Table 2: Scoring system for endometriosis based on transvaginal color and pulsed Doppler sonography**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reproductive age</td>
<td>2</td>
</tr>
<tr>
<td>Chronic pain (premenstrual or menstrual)</td>
<td>1</td>
</tr>
<tr>
<td>Infertility</td>
<td>1</td>
</tr>
<tr>
<td><strong>B-mode ultrasonography</strong></td>
<td></td>
</tr>
<tr>
<td>Position (medial, retrouterine)</td>
<td>2</td>
</tr>
<tr>
<td>Bilaterality</td>
<td>1</td>
</tr>
<tr>
<td>Serial sonography positive</td>
<td>2</td>
</tr>
<tr>
<td>Thick walls</td>
<td>2</td>
</tr>
<tr>
<td>Homogeneous echogenicity</td>
<td>2</td>
</tr>
<tr>
<td>Clear demarcation form the ovary</td>
<td>1</td>
</tr>
<tr>
<td><strong>Transvaginal color Doppler</strong></td>
<td></td>
</tr>
<tr>
<td>Vascularization</td>
<td>2</td>
</tr>
<tr>
<td>Pericystic/hilar location</td>
<td>2</td>
</tr>
<tr>
<td>Regularly separated vessels</td>
<td>2</td>
</tr>
<tr>
<td>Existence of notching</td>
<td>1</td>
</tr>
<tr>
<td>RI &lt; 0.40 (menstrual phase)</td>
<td>2</td>
</tr>
<tr>
<td>RI = 0.41 to 0.60 (late follicular/corpus luteum phase)</td>
<td>2</td>
</tr>
<tr>
<td>CA-125 &gt; 35 IU/mL</td>
<td>2</td>
</tr>
</tbody>
</table>

*Abbreviations: RI, resistance index; CA-125, carcinoembryonic antigen 125*


Absence of diastolic notch has been associated with malignant tumors.

**Gestational Trophoblastic Disorders**

**Complete Hydatidiform Mole**

Snowstorm appearance on sonography without associated embryonic or fetal structure; large sonoluent areas result from stasis of maternal blood between the molar villi. Theca lutein cysts are seen. High serum β-hCG levels combined with sonographic appearance is highly indicative of the disease. Doppler shows high velocities and low resistance flow in uterine arteries24 (Fig. 63).

A complete mole may co-exist with a normal fetus and placenta in cases of molar transformation of one ovum in a dizygotic twin pregnancy.25

**Partial Hydatidiform Mole**26

Refers to the combination of a fetus with localized placental molar degeneration. In 90% of cases, partial moles are triploid, having inherited two sets of chromosomes from the father and one from the mother. Partial mole presents on ultrasound as an enlarged placenta containing multicystic, avascular sonoluent spaces. (Swiss Cheese Appearance). Fetus show symmetric IUGR and malformations.

**Invasive Hydatidiform Mole**

It is defined as the penetration of molar villi from a complete hydatidiform mole (CHM) or partial hydatidiform mole (PHM) into the myometrium or the uterine vasculature. Sonographically it appears as focal areas of increase echogenicity within the myometrium. The lesion is heterogeneous, often containing fluid filled cavities.

**Placental Site Trophoblastic Tumor**

It is the rarest form of GTD. Sonographically it is similar in appearance to invasive mole.

**Choriocarcinoma**

It is a highly malignant tumor that metastasizes to lungs, liver and brain. Sonographically, it appears as a solid, echogenic mass with cystic areas suggestive of hemorrhage.27

**Pelvic Kidney (Fig. 64)**

Rarely ectopic kidney is visualized in the pelvis and may mimic abnormal T-O masses.

**SUMMARY**

Pelvic sonographic imaging is the technique of choice for evaluation of pelvic organs and is a very commonly performed
examination. For vaginal bleeding and pelvic pain, the main roles are to determine the presence of lesion, its origin and whether surgery is required. Where there is difficulty, a tailored MRI examination can be helpful.

CONCLUSION

Transvaginal ultrasound is a very good, reliable, reproducible, easy, safe method to evaluate the female pelvis and very accurate for gynecological diagnosis.

REFERENCES

INTRODUCTION

Ultrasound in obstetrics is the most important investigation in all stages; rather it may now be included as a routine examination rather than a specialized investigation. This does trigger off a debate of whether all pregnancies should be scanned and at what gestation and how many times. In India, to do obstetric scan a prenatal diagnostic technique (PNDT) registration is required.

FIRST-TRIMESTER ULTRASOUND

During the first trimester, the conceptus progresses from a single-celled zygote to fetus (Fig. 1). Major changes occur in the intervening period; during which time the corresponding sonographic appearances depend on the stage of development and size of the conceptus. The goals of a sonographic examination should be clinically relevant and appropriate to the development stage (Fig. 2).¹

Fig. 1: Journey of life
Early in the first trimester, the major clinical concerns of a referring physician are:

- What is the site of implantation? (Is the pregnancy intrauterine or ectopic?)
- Is the embryo-fetus alive?
- What is the likelihood of subsequent demise of a live embryo-fetus?

Endovaginal sonography (Fig. 3) has been widely available since the mid-1980s and has radically altered transvaginal sonographic (TVS) practice in the first trimester. Transvaginal color flow Doppler (TVCFD) became available in the early 1990s. Other important goals of first trimester diagnosis include the following:

- Assessment of gestational age
- Determination of the number of embryo and assessment of chorionicity and amnionicity of multiembryonic pregnancy
- Detection of embryonic-fetal anomalies
- Assessment of uterine or adnexal masses
- Assessment of cervix (Fig. 4).

NORMAL SONOGRAPHIC APPEARANCE (TABLE 1)

Gestational Sac

Implantation of the blastocyst is complete by day 23 menstrual age. At that time conceptus measures 0.1 mm and is beyond the resolution of current ultrasound equipment (Figs 5A to H). The earliest sonographic sign of intrauterine pregnancy was described by Yeh and colleagues, who identified a focal echogenic zone of decidual thickening at the site of implantation at 3.5–4 weeks’ menstrual age. This sign may be difficult to appreciate. TVCFD may provide the first reliable evidence of the presence of an intrauterine pregnancy. Peritrophoblastic flow characterized by high-velocity, low impedance signal is seen.

In the series of Emerson and coworkers, the sensitivity of diagnosis of intrauterine pregnancy was improved from 90% of TVS alone to 99% using TVCFD. The specificity of diagnosis of intrauterine pregnancy with TVCFD was 99–100%.

The first reliable gray-scale sonographic evidence of intrauterine pregnancy (Fig. 3) is visualization of the gestational sac within the thickened decidua. This sign first described by Yeh and colleagues, is referred to as the intradecidual sign. Using TVS is usually possible to identify the gestational sac within the decidua by approximately 4.5 weeks menstrual age, when the mean gestational sac diameter (MSD) should be approximately 2.5 mm (Figs 6A to D).
### Table 1: Normal transvaginal sonographic (TVS) findings: 3.5–6.5 weeks' menstrual age

<table>
<thead>
<tr>
<th>Approximate menstrual age (week)</th>
<th>Sonographic signs</th>
<th>Sonographic features</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.5–4</td>
<td>Decidual thickening</td>
<td>Focal thickening of the echogenic decidua at the site of implantation</td>
<td>Sign difficult to appreciate</td>
</tr>
<tr>
<td>After 4.5</td>
<td>Trophoblastic flow</td>
<td>High-velocity, low-impedance signal at the implantation site prior to visualization of the gestational sac</td>
<td>Peak velocity of 8–30 cm/s</td>
</tr>
<tr>
<td>4.5–5.5</td>
<td>Intradecidual sign</td>
<td>Gestational sac within the decidua abutting the endometrial canal</td>
<td>Should always be seen when maternal serum β-hCG is 1,700–2,000 mIU/mL (First International Reference Preparation)</td>
</tr>
<tr>
<td>After 5.5</td>
<td>Double-decidual sign</td>
<td>Echogenic ring formed by decidua capsularis/chorion leave surrounded by echogenic decidua vera</td>
<td>Vague sign nondiagnostic</td>
</tr>
<tr>
<td>After 4.5</td>
<td>Yolk sac (YS) sign</td>
<td>Visualization of the YS within the gestational sac</td>
<td>Yolk sac often seen when MSD is 5–6 mm and always seen when MSD is 8 mm</td>
</tr>
<tr>
<td>5.5</td>
<td>Double-bleb sign</td>
<td>Visualization of the amnion as a 2 mm bleb adjacent to the YS</td>
<td>Transient finding; after this stage, visualization of the amnion in the absence of a visible embryo is abnormal</td>
</tr>
<tr>
<td>5.5–6.5</td>
<td>Visualization of the embryo</td>
<td>Visualization of the embryo adjacent to the YS</td>
<td>Embryo should always be seen when the MSD is 16 mm</td>
</tr>
<tr>
<td>After 6.5</td>
<td>Cardiac activity</td>
<td>Cardiac activity within embryo immediately adjacent to the YS</td>
<td>Nonvisualization of cardiac activity may be completely normal in embryos 4–5 mm CRL</td>
</tr>
</tbody>
</table>

Abbreviations: hCG, human chorionic gonadotropin; MSD, mean gestational sac diameter; CRL, crown rump length

Figs 5A to H: Sonoembryology
The double-decidual sign (Figs 5A to H) is based on visualization of an echogenic ring formed by the decidua capsularis and chorion leave eccentrically located within the echogenic deciduas vera. Originally described by Nyberg and associates and can often be identified by about 5.5–6 weeks menstrual age at approximately the same time that the yolk sac (YS) becomes visible with TVS.

**Yolk Sac**

The YS is involved in transfer of nutrients to the embryo, in hematopoiesis, and in formation of the primitive gut. It is normally round or oval and has a uniformly thick, echogenic wall, can often be demonstrated by TVS when the MSD is 5–6 mm and it is often seen before visualization of the embryo or amnion (Fig. 7).

Using TVS, the YS should always be visualized when the MSD is at least 8 mm. The YS grows at a rate of 0.1 mm per millimeter of growth of the MSD before 15 mm MSD, after which it grows at a rate of 0.03 mm per millimeter of growth of the MSD.

**Embryo and Amnion**

At approximately 5.5 weeks’ menstrual age, the amnion may normally be visualized before the embryo as a 2-mm bleb adjacent to the YS. This transient finding was originally described by Yeh and Rabi Nowitz and is referred to as the double-bleb sign. Visualization of the amnion without an embryo after the double-bleb stage is abnormal (Fig. 8).

Chorionic fluid is often more echogenic than the anechoic amniotic fluid. Sonographic differentiation between the amnion and the chorion is usually not difficult in first trimester and allows for reliable determination of amnionicity and chorionicity in multifetal pregnancies (Fig. 9).

Using TVS, embryos as small as 1–2 mm in crown rump length (CRL) can be identified routinely. The embryo should reliably be identified when the MSD is 16 mm or large with optimal scanning parameters using high-resolution TVS. Cardiac activity may be identified immediately adjacent to the YS and is indicative of a live embryo. The absence of cardiac activity however, does not necessarily indicate embryonic demise (ED). Using TVS, absent cardiac activity may be normal in embryos up to 9 mm in CRL (Figs 10 to 12).
ECTOPIC PREGNANCY

Ectopic pregnancy account for 1.4% of all pregnancies and for approximately 15% of maternal deaths.

Specific Sonographic Findings

The intradecidual sign\(^2\) can be used to demonstrate the presence of an intrauterine pregnancy before visualization of the YS or embryo. Using TVS, the double-decidual sign is usually demonstrated at approximately the same time that the YS is visualized. In patients with ectopic pregnancies, the decidua may slough, resulting in a fluid collection within the endometrial canal referred to as a “decidual cast of pseudogestational sac”. A pseudogestational sac (Figs 13A to C) is a fluid collection within the endometrial canal (intradecidual sign) or the two concentric rings of the double decidual sign.
Small cysts within the decidua may appear as sac-like structures in patients with ectopic pregnancy. These decidual cysts may be distinguished from gestational sacs in that the cysts do not about the endometrial canal and do not have an echogenic trophoblastic ring (Figs 14 and 15).

**Live Embryo in the Adnexa**

The sonographic demonstration of a live embryo in the adnexa is specific for the diagnosis of ectopic pregnancy.

**Nonspecific Findings**

- *Adnexal mass*: An adnexal mass can be found in conditions other than ectopic pregnancy and is therefore not diagnostic. The presence of an adnexal mass in patients with a positive beta human chorionic gonadotropin (β-hCG) who have no sonographic evidence of intrauterine pregnancy, however, has a positive predictive value of 70–75% for ectopic pregnancy (Fig. 16).
- *Tubal ring*: A tubal ring is an echogenic adnexal ring separate from the ovary created by the trophoblast of the ectopic pregnancy surrounding the gestational sac. In the series of Nyberg and colleagues, the positive predictive value of a tubal ring for ectopic pregnancy was 100%.
Embryonic Cardiac Activity

Using transabdominal scanning (TAS), normal embryos less than 9 mm in CRL may have absent cardiac activity. Using TVS, normal embryos less than 4 mm or 5 mm in CRL may have absent cardiac activity. The absence of cardiac activity (Fig. 18) in larger embryos is diagnostic of ED (Flow chart 1).

Gestational Sac Characteristics

The most reliable indicator of abnormal outcome based on gestational sac characteristics is abnormal gestational sac size.

EARLY PREGNANCY FAILURE

The most accurate indicator of a live embryo or of ED is sonography. The sonographic diagnosis of early pregnancy failure depends on the stage of development.

- **Loss within the first 2 weeks after conception (3–4 weeks menstrual age):** This type of pregnancy failure is called “subclinical or preclinical loss” or loss before the patient has missed a menstrual period. Often, the patient has no sonographic evidence of pregnancy at this stage.
- **Loss at 5 and 6 weeks menstrual age:** The sonographic diagnosis of pregnancy failure is usually based on gestational sac findings.
- **Loss at 7–8 weeks menstrual age:** The sonographic diagnosis of ED is usually based on demonstration of an abnormal embryo or gestational sac.
- **Loss within 9–12 weeks menstrual age:** The sonographic diagnosis of ED is usually based on demonstration of an abnormal embryo. Structural embryonic abnormalities (head, heart) can sometimes be demonstrated with ultrasound.

Ultrasound Diagnosis

**Embryonic Cardiac Activity**

Using transabdominal scanning (TAS), normal embryos less than 9 mm in CRL may have absent cardiac activity. Using TVS, normal embryos less than 4 mm or 5 mm in CRL may have absent cardiac activity. The absence of cardiac activity (Fig. 18) in larger embryos is diagnostic of ED (Flow chart 1).

**Follow-up**

**Gestational Sac Characteristics**

The most reliable indicator of abnormal outcome based on gestational sac characteristics is abnormal gestational sac size.
In 1986 using TAS, Nyberg and colleagues defined an abnormally large gestational sac as a gestational sac of at least 25 mm MSD lacking an embryo, or a gestational sac of at least 20 mm MSD lacking a YS. These criteria were re-evaluated for TVS. Using TVS, if the MSD is 8 mm or larger without a demonstrable YS, or 16 mm or larger without a demonstrable embryo, the gestational sac is abnormally large, indicating pregnancy failure.

Other gestational sac criteria to be less reliable in the diagnosis of demise include: a distorted gestational sac shape, a thin decidual reaction (< 2 mm), weak decidual amplitude, an absent double-decidual sign, or an abnormally low position of the gestational sac within the endometrial cavity.

Normal gestational sac growth is at 1.1 mm/day. Nyberg and associates found that patients with early pregnancy failure had MSD growth rates of less than 0.7 mm/day.

**Amniion and Yolk Sac Characteristics**

Visualization of the amnion in the absence of a sonographically demonstrable embryo is abnormal and is diagnostic of an anembryonic gestation or ED with resorption of the embryo.

Other findings include: a collapsing irregularly marginated amnion, visualization of the amnion in the absence of a visible embryo, and YS calcification.

**Embryonic Bradycardia (Fig. 19)**

In a study by Doubilet and Benson, a heart rate of less than 80 bpm in embryos with a CRL less than 5 mm was universally associated with subsequent ED, a heart rate of 80–90 bpm was associated with a 64% risk of demise, a heart rate of 90–99 bpm was associated with a 32% risk, and a heart rate of 100 bpm or more was associated with an 11% risk. In embryos under 5 mm in CRL, 100 bpm represented a plateau above which increase in heart rate were not associated with decreased risk of subsequent ED, a finding indicating that heart rates of 100 bpm or higher are normal in these embryos.

In embryos 5–9 mm in CRL, a heart rate lower than 100 bpm was always associated with abnormal outcome, with the normal heart rate plateau identified at 120 bpm. In embryos 10–15 mm in CRL, a heart rate of less than 110 bpm appears to be associated with a poor prognosis.

**Mean Gestational Sac Diameter in Relation to the Crown Rump Length**

The measurement of the MSD should be 5 mm greater than the CRL.

**Yolk Sac: Size and Shape**

Yolk sac diameters of at least 5.6 mm between 5 weeks and 10 weeks menstrual age are always associated with abnormal outcome. A persistently abnormal YS shape is also a predictor of abnormal outcome.

**Relation of β-hCG to Mean Gestational Sac Diameter**

Nyberg and colleagues found that 63% of abnormal pregnancies had a disproportionately low serum β-hCG for gestational sac size.

**Subchorionic Hemorrhage**

In a group of patients presenting with vaginal bleeding between 10 weeks and 20 weeks menstrual age, identification
of a subchorionic hemorrhage was associated with a 50% fetal loss rate. When the volume of the hematoma was less than 40% the volume of the gestational sac, the outcome tended to be favorable.

**TVCFD Predictors of Pregnancy Failure**

Inadequate trophoblastic invasion of the spiral arteries may be seen in early pregnancy failure and may be associated with increased resistance to flow in the spiral arteries. One study suggests that an abnormal resistive index (> 0.55) in the decidual spiral arteries and active arterial blood flow in the intervillous space may be associated with an increased incidence of early pregnancy failure.

**FETAL ANOMALIES (FIGS 20 TO 26 VARIOUS ANOMALIES IN FIRST TRIMESTER)**

Diagnosis of gross anomalies such as cystic hygomas and large cranial cyst can be made in the first trimester with TVS. Many severe anomalies may have a normal sonographic appearance in the first trimester. The most dramatic example is anencephaly, which may only become obvious after ossification of the calvarium occurs at 12 weeks’ menstrual age.

In the first trimester, normal embryologic anatomy may mimic the sonographic appearances of fetal anomalies of developmental stage. The fetal rhombencephalon appears as a cystic structure in the posterior fossa beginning at 7 weeks menstrual age and should not be mistaken for an intracranial cyst or hydrocephalus.

Physiologic midgut hernia is often demonstrated as a small (6–9 mm) echogenic mass protruding into the umbilical cord at approximately 8 weeks menstrual age and is still present in 20% of normal fetuses at 12 weeks.

**FIRST TRIMESTER MASSES**

**Ovarian Masses**

The most common mass seen in the first trimester of pregnancy is the corpus luteum cyst. Corpus luteum cysts may be occasionally more than 10 cm in diameter. Internal septations and echogenic debris may be seen. Corpus luteum
cysts usually regress or have decreased in size on follow-up sonographic examination at 16–18 weeks’ menstrual age.

Other cystic masses may appear initially in the first trimester of pregnancy because of displacement by the enlarged uterus. Although malignant ovarian neoplasm associated with pregnancy is rare, torsion, rupture, or dystocia is not. Dermoid cysts may present a characteristic appearance of a cystic mass with focal calcification and a fluid-fluid level (Fig. 27).

**Uterine Masses**

Uterine fibroids are common pelvic masses often identified during pregnancy. Most fibroids do not change in size during pregnancy. Some fibroids, however, may enlarge rapidly because of stimulation by estrogen.

Fibroids may be differentiated from focal myometrial contraction by the transient nature of myometrial contractions. A repeat examination 20–30 minutes after the initial examination reveals the absence of a focal myometrial contraction, whereas fibroids are still present. Fibroids also may distort the uterine contour (serosal surface), whereas focal myometrial contractions usually do not (Fig. 28).

**ULTRASOUND IN SECOND AND THIRD TRIMESTER**

Second and third trimester of pregnancy are the vital periods for growth. Where routine scanning is advocated, it is normally done in the second trimester for an accurate analysis of growth, placenta, liquor, congenital anomalies.
and color flow of uterine artery for prediction of intrauterine growth retardation.

Following need to be evaluated and documented during a routine second and third trimester scanning:
- Fetal number, presentation and activity.
- Assessment of gestational age and weight.
- Placental location, appearance, its relationships to the internal cervical os.
- Umbilical cord.
- Estimation of amniotic fluid volume.
- Biophysical profile.
- Color Doppler study of uterine artery, umbilical artery, middle cerebral artery (MCA), descending thoracic aorta, ductus venosus.
- Evaluation of congenital anomalies.

**Fetal Number**

In multiple pregnancies chorionicity and amnionicity should be documented. Number of placentas, comparison of fetal sizes and amniotic fluid volumes, gender of twins (if visible) needs evaluation (Figs 29A and B).

The amniotic cavity increases in size during the late first trimester and second trimester. In dichorionic twin gestation the intertwin membrane consists of two layers of amnion and two layers of chorion. A potential space exists in the inter membrane which may be filled by proliferating placental villi giving rise to twin peak sign.

In monochorionic diamniotic twins, the membrane consists of only two layers. Twin peak sign is not seen.

**Gender of the Twins**

Twins of different gender originate from two separate ova (dizygotic) and are always dichorionic and diamniotic. When twins are of same gender or gender is not identified chorionicity cannot be determined.

**Number of Placenta**

Sonographic identification of two separate placental masses in a twin gestation confirms dichorionicity. A single placental mass does not differentiate between a monochorionic and dichorionic gestation.

A potential pitfall for falsely diagnosing two placentas is the presence of large succenturiate lobe with a shared single placenta, however by following the cord insertion back to a single shared placenta, this can be resolved.

Four chamber view of heart cardiac activity rate and rhythm require mention.

**Estimation of Gestational Age**

Basic fetal measurements used to estimate age are the biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC) and femur length (FL).

**Biparietal diameter**: It is appropriately measured through any plane of section that traverses the third ventricle and thalami. Calvaria should be smooth and symmetrical. Cursors are positioned in one of the three following ways: outer edge of near calvarial wall to inner edge of far calvarial wall, inner edge of near calvarial wall to outer edge of far calvarial wall or middle of near calvarial wall to middle of far calvarial wall (Fig. 30).

**Head circumference**: The plane of section is through the third ventricle and thalami in central position of brain, cavum septum pellucidi in the anterior portion and tentorial hiatus in the posterior portion of brain. Cursors are positioned at the outer edge of the near calvarial wall to outer edge of far calvarial wall (Fig. 31).

**Femur length**: The transducer need to be aligned to the long axis of the bone to obtain a proper plane section. Only the ossified portions of the diaphysis and metaphysis are measured. Cartilaginous ends of the femur are excluded (Fig. 31).

**Abdominal circumference**: We measure fetal AC at the position where the transverse diameter of the liver is the greatest. This
can be determined sonographically as the position where the right and left portal veins are continuous with one another. Section should be spherical, lower ribs symmetrical and shortest length of the umbilical segment of the left portal vein is depicted. Measurement is taken to the skin edge (Fig. 32).

Most authors show a variability of ± 1 week (2SD) in patient with optional menstrual histories between 14 weeks and 20 weeks. Virtually all studies demonstrated a progressive increase in variability from 20 weeks to term, but the degree to which the variability increases in the late third trimester of pregnancy has been a subject of some disagreement in literature. Most authors concluded a variability of approximately 3½ weeks (2SD). In cases of shape changes of the skull (ruptured membranes, breech presentations, multiple gestation, dolichocephaly or brachycephaly) may lead to errors in BPD measurement. To assess the shape change, cephalic index needs to be evaluated.

CI = BPD/FOD × 100
(CI, cephalic index, FOD, fronto-occipital diameter).

HC is one of the most reliable individual parameters for estimation of menstrual age. Of the four basic ultrasound measurements, AC has generally had the largest reported variability. This is partly attributed to the fact that AC is more accurately affected by growth disturbances than other parameters.
Other Biometric Parameters
- When head is in direct occiput posterior position—interorbital and intraorbital diameter.
- When head is in direct occiput anterior position—transverse diameter of cerebellum and cisterna magna.
- Measurement of ventricular dimensions.
- All long bones of arms and legs, fetal foot length, fetal clavicle length.

Placental Sonography
The placenta is visible as early as 10 weeks as a thickening of the hyperechoic rim of tissue around gestational sac. At 12–13 weeks, intervillous blood flow is seen. At 14–15 weeks, placenta is well established and a prominent hypoechoic area, the "retroplacental complex" composed of the decidua, myometrium and uterine vessels is seen. It should not be more than 1–2 cm in thickness (Fig. 33).

Third trimester placenta is a highly vascular structure. As a rule of thumb, placenta should be approximately equal in thickness (in mm) to the gestational age in weeks ± 10 mm. Term placenta should generally not be thicker than 4.0 cm.\(^\text{17}\)

Thrombi and Hematomas (Figs 34A and B)
- Retroplacental hematomas: Separation of basal plate and uterine wall. Incidence—5%, increases threefold in pre-eclampsia. More than or equal to 30–40% placental detachment is associated with grave prognosis.
- Subchorionic or marginal hematoma: At the lateral margin of the placenta. Incidence is 2%.
- Acute (0–48 hours) hematomas sonographically appear echogenic becoming isoechoic at 3–7 days followed by hypoechoic echotexture at 1–2 weeks. After 2 weeks portions may be anechoic.

Placenta Previa (Fig. 35)
Primary cause of third trimester bleeding type:
- Complete: When internal os is completely covered by placenta.
- Incomplete: When placental tissue reaches the edge or partially covers the cervical os.
- Low lying placenta: Where the placental edge is within 2 cm of the internal cervical os.

Umbilical Cord
It consists of two umbilical arteries and one umbilical vein (UV) (Figs 36A to C). There is a 30–60% increased incidence of other fetal anomalies in presence of single umbilical artery.\(^\text{18}\) Multivessel cords are rare and have been reported in association with congenital anomalies and conjoined twins.
Figs 34A and B: Placental hemorrhages

Grading | Placenta | Location
--- | --- | ---
0 | | Low lying
1 | | Marginal
2 | | Complete
3 | | Complete

Fig. 35: Placenta grading and location

**Nuchal Cord**

It is seen in 25% of pregnancies. Seen sonographically as two adjacent loops of cord in cross section posterior to the neck on sagittal images and by visualizing cord circumferentially around the fetal neck on axial images. A single loop of cord near fetal neck is most often an incidental finding and is not associated with fetal mortality or morbidity (Fig. 37).

**Ultrasound and Amniotic Fluid**

- Scanning the uterus to select the single deepest pocket of amniotic fluid free of umbilical cord and fetal parts. The greatest vertical dimension is measured with probe perpendicular to the floor. This is referred to as maximum vertical pocket (MVP). 2–8 cm was taken as a normal range. 19
- A semiquantitative sonographic assessment of the amniotic fluid volume was developed, known as amniotic fluid index (AFI) (Fig. 38). Patient lies supine and maternal abdomen is divided into four quadrants using maternal sagittal midline vertical and arbitrary transverse line approximately halfway between pubic symphysis and the upper edge of uterine fundus. Transducer is kept parallel to maternal sagittal plane and perpendicular to coronal plane. Deepest pocket of amniotic fluid free of cord or fetal structures is measured in all four quadrants (Fig. 38). Values greater than 5 cm and less than 18–20 cm are considered normal by most examiners. 20

These two methods of fluid estimation have their own inherent limitation, therefore a subjective evaluation by a trained Sonologist is a better option.

**Evaluation of the Cervix (Fig. 4)**

Uterine cervix can be evaluated sonographically by three ways: (1) transabdominal, (2) transvaginal and (3) translabial (transperineal). 21

**Cervical Length**

It is the distance between the internal os and external os. 22
- Transabdominal sonography: Mean 3.2–5.3 cm
- Transvaginal sonography: Mean 3.2–4.8 cm
- Transperineal sonography: Mean 2.9–3.5 cm.

**Cervical Width**

It is the anteroposterior diameter at the midpoint of cervix. The width increases with advancing gestational age, and its 50th percentile value is 3.52 cm.
Effacement

It is the change from a closed cervix to a wedge-shaped-opening of the internal os followed by progressive shortening of the cervix craniocaudally. The process of complete effacement described as U- or V-shape is dependent on the descent of the fetal head.

Funneling

Dilatation of the internal os as amniotic sac protrudes into the cervical canal.

Cervical incompetence: Short cervix (< 2 cm TVS), wide internal os diameter, funneling of internal os and the definitive hourglass herniation of membranes.

Fetal Biophysical Profile

Fetal heart rate reactivity, fetal breathing movement, fetal movement and fetal tone are the acute markers. Amniotic fluid volume and placental grading have been considered chronic markers.

Data have demonstrated that in fetal acidemia the first biophysical activities to become compromised are fetal heart rate reactivity and fetal breathing movements. In advanced fetal acidemia, fetal body movements and fetal tone are also absent. The chronic markers of the fetal condition (amniotic fluid volume and placenta grading) are not altered by acute acid base changes. The presence of oligohydramnios is considered to the result of chronic fetal distress and reflects fetal hypoxia of long duration.23

Some include placental grading as a part of biophysical profile as grade 3 placentas have been associated with an increased incidence of abnormal fetal heart rate pattern (44.4%) and abruptio placentae (14.8%) during labor.

Ultrasound in Congenital Malformations

Fetal major abnormalities occur in about 1 in 50 pregnancies and result in spontaneous abortions, perinatal morbidity and postnatal mental and physical disabilities. The detection of anatomic congenital anomalies is one of the primary goals of prenatal care.
Clinical high-risk groups for a detailed anomalies scan are shown in:
- Advanced maternal age
- Previous birth of a malformed fetus
- Family history of a malformed fetus
- Consanguinity
- Exposure to drugs or radiation
- Maternal diabetes mellitus
- Bad obstetric history
- Bleeding in early pregnancy.

Sonographic findings indicative of detailed anomalies scan:
- **First trimester:**
  - Oligoamniotic sac
  - Embryonic bradycardia
  - Abnormal YS
  - Increased nuchal translucency
  - One identified anomaly.
- **Second and third trimester:**
  - Increased nuchal fold thickness
  - Symmetric intrauterine growth restriction (IUGR)
  - Polyhydramnios
  - Oligohydramnios
  - Breech presentation
  - Twins
  - One identified anomaly.
- **Nonsonographic investigation:**
  - Abnormal results from a chorionic villus sampling (CVS) or amniocentesis
  - Abnormal immunoglobin profile
  - Abnormal triple test/increased alfa-fetoprotein/abnormal pregnancy-associated plasma protein (PAPP).

A detailed anatomic evaluation of the fetus and its environment is essential. The optimal time to visualize fetal anatomy is 18–22 weeks.

**DOPPLER ULTRASONOGRAPHY IN OBSTETRICS (FIGS 39A AND B)**

**Fetal Arterial Circulation (Fig. 40)**

**Uterine Arteries**

In pregnant uterus, a progressive transition occurs from a low volume high resistance to a high volume low resistance circulation. Diastolic notch usually disappears by 24 weeks. Resistance index (RI) drops from 0.84 to 0.56 at 24 weeks. The presence of notch, elevated RI or pulsatility index (PI) with advancing gestation are the indicators of increased vascular resistance and impaired uterine flow (Fig. 41).

**Umbilical Arteries**

It provides information on blood perfusion of the fetoplacental unit. High vascular impedance detected in first trimester gradually decreases with advancing gestation. Diastolic flow usually appears at 20 weeks. RI normally is less than 0.7. An increase in RI values, systolic/diastolic ratio or absent/reversal of diastole are associated with IUGR (Figs 42A to C).
Ductus Venosus

It is a trumpet like small vein with a narrow entrance that connects umbilical sinus to the hepatic veins and inferior vena cava (IVC). FVW of DV displays a continuous forward flow throughout the cycle. Biphasic FVW consists of two surges of velocity peaks, first corresponding to ventricular systole (S wave), second to ventricular diastole (D wave). These are followed by a reduction in velocity during the atrial systole (A wave).

During fetal hypoxia, there is an increased blood flow to DV from UV. In addition, there is a reduction of the A wave and an absent or even reversed flow during atrial contraction can be seen.

3D AND 4D ULTRASOUND

Three-dimensional (3D) and four-dimensional (4D) ultrasound in obstetrics provides sculpture like pictures of the fetus with a more accurate study of fetal surface anatomy for assessing fetal congenital anomalies. 4D scanning provides live 3D pictures which will go a long way in improving maternal fetal bonding and even fetal family bonding if the father and siblings are allowed to see the 4D scanning of a pregnant woman.

Advantages and Possibilities of 3D and 4D Imaging

Three-dimensional and 4D ultrasound as raw methods in ultrasound diagnostic have numerous advantages in comparison to classical gray scale imaging. Reduced study time, faster examination procedure, and increased perspective form volume data provides between qualitative and quantitative information about selected area.

Applications of 3D and 4D Imaging

Obstetrics (Figs 45 and 46)

- Fetal morphology, malformation, agenesis
- **Bone shape abnormalities**: Spina bifida, dwarfism, cleft palate, cleft lip
- **Skeletal dysplasia**
- **Fetal heart**: Better correlation between valves, chambers and vessels volume calculation of heart cavities; atrial and ventricular communication; assessment of valvular function
- **Variety of fetal volume evaluation**: Urinary bladder, stomach, cyst

- **Fetal biopsy**: Umbilical blood sampling punctures with precision, amniocentesis, kidney dilatation, uropathy
- **Fetal movement and mimic**: Normal and abnormal fetal gestures; evaluation of fetal sleep and awakening, hand and feet motion, eyelid limbs and mouth motion
- **Fetal neuromyopathy genetic diseases**: fetal reactivity or tonicity
- **Cord insertion using power-Doppler and 3D**
- **Frontal bones.**
ULTRASONOGRAPHY AND PRENATAL DIAGNOSIS

Amniocentesis

Amniocentesis for diagnostic purpose must be carried out under concurrent ultrasonography guidance so that tip of operator needle is visible all the time to prevent the damage to the fetus. The use of ultrasonography control can also reduce the number of needle insertions and incidence of bloody taps and patient’s anxiety (Fig. 47).

Chorionic Villus Sampling (Figs 48 and 49)

In the first trimester, CVS is the common sampling method for cytogenetic studies. CVS can be performed either transcervically or transabdominally. The type of procedure is determined by the location of the implantation site and the position of the uterus.

Cordocentesis (Percutaneous Umbilical Blood Sampling)

An ultrasonography-guided cordocentesis is a major advancement as it opened up many newer diagnostic possibilities, e.g. to diagnose hemoglobinopathies and fetal injection, for obtaining rapid chromosome analysis. It evaluates fetal hydrops and fetal acid-base status in growth restriction and for diagnosis and management of isoimmunization (Fig. 50).

INDIAN LAW (PCPNDT ACT) AND OBSTETRIC ULTRASOUND

To practice obstetric ultrasound and even to refer an obstetric case for ultrasound, the Indian Law requires the obstetrician to register a genetic counseling center and the ultrasound clinic to register as genetic clinic and the laboratory to register...
as a genetic laboratory. All records of obstetric ultrasound have to be kept for 2 years and Preconception and Prenatal Diagnostic Techniques (PCPNDT) Act of Government of India prohibits any preconception sex selection technique or divulgence of gender of fetus in any manner to anyone. An obstetric ultrasound can be requested for or done only for one of the 23 approved indications under the law.

**CONCLUSION**

Ultrasound today offers the only noninvasive reproducible, accurate and cheap test for monitoring fetal growth (2D and 3D ultrasound). A pregnancy should be ideally screened at each trimester for accurate assessment; routine obstetric ultrasound will help to improve health care delivery to pregnant women.

**REFERENCES**

Color Doppler in Decision-making for Delivery

Narendra Malhotra, Kuldeep Singh, Jaideep Malhotra
(Chapter updated by Ruchika Garg)

Certain fetuses die due to sudden unexplained event, which cannot be predicted. Certain pregnancy deaths occur due to placental insufficiency. This is a slow process and can be predicted by tests for fetal well-being.

**INTRODUCTION**
To make decision for delivery of a fetus who is at distress (acute or chronic) is probably the most difficult decision that an obstetrician has to make. An obstetrician has to decide that the distressed baby should not be delivered too prematurely as that may be subsequently requiring a prolonged neonatal intensive care unit (NICU) care with long-term morbidity and problems, on the other hand if the delivery is delayed and the fetus develops acidosis, intrauterine, this will have its own major problems leading to severe neonatal morbidity and mortality. The tests for fetal wellness include Manning’s Score, Vintzeł’s modification and color Doppler. These have to be understood and used to the best to deliver a healthy and nondistressed baby.

**PATHOPHYSIOLOGY OF FETAL DISTRESS**
Fetal growth restriction previously defined as intrauterine growth retardation or intrauterine growth restriction (IUGR), is a pathological decrease in the rate of fetal growth. It means that the fetus is not growing properly; it does not imply hypoxia or acidosis. It is possible to assess fetal growth accurately by B mode, 2D, gray scale ultrasound. Addition of color Doppler gives information about fetal oxygenation, hypoxia and acidosis and 3D or 4D ultrasound picks up subtle soft tissue markers for growth restriction. Fetal compromise is defined as a hypoxemic, hypoxic, or acidic fetus; this is a pathophysiological deterioration of many of the fetal growth restriction (FGR) fetuses, Hence, color Doppler is an important tool for timing of delivery and termination of pregnancy.

**INDICATORS FOR FETAL WELLNESS**
Fetus will gain control with gestational age as follows:
- **Tone**: Control from 8 weeks onward
- **Movements**: From 9 weeks onward
- **Breathing**: From 22 weeks onward
- **Fetal cardiac sympathetic and parasympathetic control**: From 24 weeks onward (Nonstress test). Fetus loses its control with hypoxia as follows at an umbilical cord pH of:
  - 7.20: Abnormal NST
  - Less than 7.20: Loss of fetal breathing
  - 7.10–7.20: Loss of fetal movements
  - Less than 7.10: Loss of fetal tone
This should be kept in mind for interpretation of hypoxia and acidosis.

**TESTS FOR FETAL WELL-BEING**
- Ultrasound B Mode (Tells pathological decrease in fetal growth)
- Color Doppler (Tells hypoxemia, hypoxia or acidosis)
- Nonstress test (Tells fetal hypoxia or acidosis)
- Manning’s score is a combination of one chronic (amniotic fluid) marker and four acute markers (Tone, movement, NST, fetal breathing) of distress.
• Vintzello’s modification is used to cut short the test duration of Manning score and to reduce the false predictive values because of oligohydramnios and in this test only NST (VAST) and amniotic fluid index is taken.

**Duplex Evaluation in Normal and High-risk Pregnancy**

Fetal growth depends on a steady supply of nutrients and oxygen from the mother, and a normal uteroplacental and fetoplacental circulation is necessary for this to occur. In recent years, however, Doppler ultrasound has given us a noninvasive method of evaluation of blood flow in the fetoplacental and uteroplacental circulation in normal and complicated pregnancies.

During pregnancy there is a hyperplasia and hypertrophy of the uterine wall and the arteries elongate and become coiled. At the base of the placenta, the endometrium is progressively thinned as it is invaded by the trophoblast. The trophoblast migrates along the entire length of spiral arterioles and strips it of its muscular elastic coat by the 20th postmenstrual week. This has the effect of reducing resistance to blood flow at this level.

**ASSESSMENT OF MATERNAL-PLACENTAL UNIT (FLOW CHART 1)**

The fetomaternal exchange unit is shown in Flow chart 2. Whenever there is a less supply of nutrition and oxygen to the fetus, the fetus cardiac dynamics get altered and a redistribution of blood to cerebral vessels and cardiac vessels occur, shutting down the aortic blood flow and splanchnic blood flow. This causes less nutrients and oxygen to go to the fetal organs and hence restricts the growth of muscles and bones, making the fetus small. Finally, the renal blood flow and blood flow to intestines is also affected leading to oligohydramnios and also may lead to necrotizing enterocolitis and/or mucous aspiration, while the brain receives compensatory blood flow and leads to a brain sparing effect in the growth. Finally the cerebral vessels get constricted due to cerebral edema and due to not receiving oxygen and nutrients and this is the end stage FGR which will lead to cardiac failure and fetal death.

**COLOR DOPPLER ASSESSMENT**

Color Doppler assessment (Flow chart 3) will give us information of maternal unit, placental unit and fetal unit. Color Doppler tells us the amount of blood reaching the target organ or area.

Evaluation of the three compartments of blood supply, the uterine, the placental and the fetal gives a good idea of utero-placental-fetal perfusion and gives an idea of developing hypoxia much before other tests for fetal well-being become positive. Color Doppler in pregnancy should evaluate.
• **Uterine:** Both sides
  
  • **Placental:** Umbilical artery
  
  • **Fetal:**
    - Middle cerebral
    - Fetal aorta
    - Fetal venous circulation.

### Uterine Artery

Color flow mapping and pulsed wave Doppler evaluation of the uterine arteries is now an accepted, reliable method of evaluating the low-risk mother for prediction of a hypertensive disorder in pregnancy\(^1\) and a high-risk mother\(^2\) for prediction of perinatal morbidity and mortality.\(^3\) It is imperative to obtain right and left uterine artery flow velocity waveforms in the terminal portion of the arterial course, distal to the origin of the tubal branch and proximal to the “fanning” out of arcuate arteries. Indices used to predict adverse outcome should be deployed after 24–36 weeks of pregnancy. The variables includes a resistive index of greater than 0.55, a systolic/diastolic ratio of greater than 2.60, a notch in early diastole, a systolic notch and a large difference of the right and left sides of the uterine circulation.\(^2\) Normal and abnormal waveform on uterine artery Doppler assessment is shown in Flow chart 1 and Figures 1 and 2 respectively.

### Fetoplacental Circulation

The fetal circulation (Fig. 3) is characterized by a high blood flow and a low vascular resistance. Umbilical blood flow of perinatal morbidity and mortality.\(^3\) It is imperative to obtain right and left uterine artery flow velocity waveforms in the terminal portion of the arterial course, distal to the origin of the tubal branch and proximal to the “fanning” out of arcuate arteries. Indices used to predict adverse outcome should be deployed after 24–36 weeks of pregnancy. The variables includes a resistive index of greater than 0.55, a systolic/diastolic ratio of greater than 2.60, a notch in early diastole, a systolic notch and a large difference of the right and left sides of the uterine circulation.\(^2\) Normal and abnormal waveform on uterine artery Doppler assessment is shown in Flow chart 1 and Figures 1 and 2 respectively.

![Flow chart 3: Assessment of maternoplacental fetal unit by color Doppler](image)

![Fig. 1: Normal waveform](image)

![Fig. 2: Abnormal waveform](image)
increases with gestational age and pressure gradient driving the blood from the descending aorta through the placenta and back to the inferior vena cava.

**Doppler Sampling Sites in the Fetus**

- Umbilical arteries
- Middle cerebral artery
- Ductus venosus
- Descending abdominal aorta.

**Umbilical Arteries (Figs 4 and 5)**

With increasing placental resistance, the diastolic flow decreases. The absence of diastolic flow and especially reversal of flow in diastole indicates that the fetus is at risk for intrauterine death. These changes are most likely due to increased placental villous vasoconstriction and placental villous infarction.

The NST along with the fetal biophysical profile are presently used to assess fetal well-being. The umbilical artery waveform analysis detects fetal compromise more accurately than does fetal heart rate monitoring. As mentioned, if the Doppler waveform from the umbilical artery shows no flow in diastole, then this has a grave prognostic significance for the fetus. This is especially so if there is retrograde flow in diastole.

**Middle Cerebral Artery (Figs 6 and 7)**

The fetal middle cerebral artery is easy to locate with Doppler ultrasound. As hypoxemia supervenes within the fetus, dilatation of the cerebral vessels leads to a lowered resistance to blood flow, and it is this low resistance which
such that the reverse flow in atrial systole in the inferior vena cava is transmitted to the ductus flow also. Preliminary data from the ductus venosus would suggest that retrograde flow at any point of the cycle (most commonly during arterial contraction) is indicative of a extremely high chance of perinatal morbidity in terms of metabolic acidemia and a greater than 50% mortality within 3 days. The advantage of the ductus venosus, unlike the umbilical artery and middle cerebral flows, is that the measurement appears not to be altered by gestation and therefore is useful throughout pregnancy.

**OXYGENATION OF FETUS (FLOW CHART 4)**

### Hypoxemia

This condition is produced when circulating oxygen is reduced and tissue perfusion of oxygen is normal. Fetal PO₂ falls to critical level of 19 mm Hg, fetal pH ranges between 7.25 and 7.20. This leads to some compensatory saving mechanisms by increase of left heart cardiac output leading to increased and preferential perfusion of brain and heart. These will show as:

- Altered cardiac velocities (Fetal echocardiography)
- Low resistance cerebral flow (MCA ↓ RI)
- High resistance umbilical flow (↑ RI of UA).

NST changes do not occur at this stage.
Flow chart 4: Oxygenation of fetus

Pathophysiology

Less oxygen to fetus

Fetal reserve up to 50%

Fetal cardiac dynamics altered

Redistribution

Hypoxia pH 7.10–7.20

pH ≤ 7.10

Acidemia Acidosis

Terminal stage pH 7.10

Ultrasound finding

No signs on USG and color Doppler

Fetal echocardiography

UAPI (Umbilical API)
Diastolic in MCA (RI)
UARI (Umbilical ARI)
NST normal

AC (Abdominal circumference)
Slowing of FL (Femur length diameter)
Slowing of BPD (Biparietal)

Mild oligohydramnios
BPP normal (Near normal)

- AEDF in UA
- Aorta, renal (RI)
- Oligohydramnios
- RI of MCA
- Forward flow in ductus
- Fetal tachycardia
- BPP affected
- REDF in UA, aorta, renal
- MCA decompensation
- Severe oligohydramnios
- REDF in ductus venous
- Loss of variability of FHR
- Loss of fetal tone
Hypoxia

Hypoxia is produced when fetal oxygen supply drops to surpass the oxygen reserve. Fetal PO₂ drops to 16-17 mm Hg and this leads to tissue hypoxia. The metabolism changes to anaerobic and the scalp pH falls to 7.20 and below.

These changes will show as:
- Absent end diastolic flow (AEDF) in umbilical artery
- Increased blood flow in middle cerebral artery
- Abnormal NST
- May be reduced fetal movements
- Amniotic fluid slightly reduced or even normal
- Fetal heart variability still maintained
- Reduced blood flow in fetal aorta.

Asphyxia or Acidosis

If fetal oxygenation further deteriorates there is severe tissue hypoxia. Fetal PO₂ falls to 16 or even less and pH 7.10–7.20. Fetal lactic acidosis and acidemia occurs.

These changes will show as:
- AEDF/REDF in umbilical artery
- AEDF in fetal aorta
- High resistance in MCA (cerebral decomposition)
- Altered ductus venosus and fetal inferior vena cava flows
- Marked oligohydramnios (AFI < 5)
- Abnormal NST (Flat, nonreactive pattern)
- Loss of fetal heart variability
- No fetal movements
- Reduced fetal tone (fetus lying limp).

These changes in color Doppler have been described by Bilardo CM et al.18

SUMMARY

The use of color Doppler to measure flow velocity waveforms within the fetoplacental circulation to predict increased perinatal morbidity and mortality should be undertaken in a step-wise manner. Pregnancies that are identified as being at risk can be investigated by the use of umbilical artery waveforms. In the absence of an acute maternal illness, a pregnancy with a fetus with growth parameters above the 2.5 percentile and normal umbilical artery flows should be managed expectantly.

In a pregnancy with a fetus with abnormal umbilical artery flows, a repeat assessment of the placental resistance should be made twice per week to determine the trend of the systolic/diastolic ratio. An assessment of middle cerebral artery flow should also be made. Normal middle cerebral artery flow and a slow improvement in the umbilical artery flow, requires no intervention. In the presence of abnormal middle cerebral artery flows, delivery should be considered. If prolongation of the pregnancy is desirable, flow in the ductus venosus should be determined. If the ductus venous flows are normal then reassessment of fetal condition with color Doppler and cardiotocography should be undertaken twice a week. Should the ductus venosus flows become abnormal, then consideration for delivery should be made at any gestation.

CONCLUSION

Fetal and maternal Doppler examination gives an early and reliable warning of the fetal perfusion status and hypoxemia. Hypoxia and acidosis can be diagnosed by Color Doppler examination. Uterine A Doppler is different. It is a screening kept to distinguish women at risk to develop PIH and IUUGR. Uterine A study in low-risk cases amounts to preventative obstetrics. Doppler ultrasound is a noninvasive technique used in obstetrics to improve perinatal outcome in high-risk situations. There are accepted tools in diagnosis and management of EGR fetuses and help in reducing perinatal mortality. It is important to remember that obstetric management should not be solely based on abnormal Doppler. All possible clinical, biochemical and Doppler information should be put together along with the "ART" of obstetrics to get the best possible outcome.

REFERENCES


INTRODUCTION

Invent of three-dimensional (3D) and four-dimensional (4D) ultrasound (US) has made a dramatic improvement in fetal imaging. On 3D US multiple 2D US sections are taken very closely placed to each other and they are all put together to construct a 3D image. That means we have a whole block of tissues instead of just a thin slice of a 2D US. Four-dimensional US is a live 3D, where 3D reconstruction is so fast, 16–32 frames/minute, that it appears real-time. 3D, 4D US is therefore a volume ultrasound.

The volume data can be viewed as a 3D object and in multiplanar mode in three orthogonal planes—sagittal, coronal and axial (Fig. 1). All can be correlated to each other by the reference point which is represented as a dot on all three images. This dot is actually an intersecting point of two lines seen on all three images. This dot represents the same structure on all three planes.

The volume can be seen as rendered image. Rendered image means watching the whole volume as a whole block of tissue. The rendering direction can also be selected, which means one can select to see the volume from above, below, right, left, front or back.

Various modes of rendering (Fig. 2) can be selected singularly or combined to optimize the visualization of soft tissues, bony structures or vessels. We all know about face watching on volume US. This is surface rendering.

It is used to see the face and limbs of the fetus. Rendering by transparent modes (Fig. 3) shows the internal organs of the fetus and bones in the same acquired volume depending on selection of rendering mode transparent minimum, X-ray or transparent maximum.

Angiome mode can be applied on a volume acquired with power/color Doppler which shows the vasculature in the given volume like angiography. One can select to see the blood vessels in reference with the surrounding tissues by glass body rendering or only the blood vessels by angiome mode (Fig. 4). This is like doing an angiography, where only the contrast enhanced blood vessels will be seen. The advantage here is that no contrast or invasive procedure is required.

Magicut (Fig. 5) is an electronic scalpel. This is used to cut off the extra tissue shadows from the rendered image. Tissues can be cut off in whole thickness or up to variable depth.

Tomographic US imaging (TUI)—allows simultaneous visualization of multiple parallel slices in one of three orthogonal planes like CT or MRI. This is very important for the understanding of fetal anatomy and diagnosing abnormalities like posterior urethral valve, tracheoesophageal fistula, diaphragmatic hernia, cleft palate, fetal mass lesions, cranial and spinal abnormalities, etc.

Volume contrast imaging (VCI) allows thicker slices to be examined in real-time. These slicing can be done in A plane—the plane of acquisition and in C plane—coronal plane. It is very useful again for spine and corpus callosal defects, etc.
Volume calculations by 3D using virtual organ computer-aided analysis (VOCAL) II software are much more accurate than 2D volume calculations for lung, liver, cerebellum, ventricles, follicles, endometrium, etc.

Spatial temporal imaging correlation (STIC) is offline 4D US and has proved to be extremely useful for evaluation of the heart.

All these together, ultimately help to understand the complex anatomy better with surface analysis of minor defects, volume measurements and vascular studies.

In gynecology, it has a major role in diagnosis of congenital uterine anomalies, diseases of the endometrium and evaluation of adnexal masses and also for assessment of follicle and endometrium in infertility cases.

In early pregnancy 3D sonography is absolutely superior to the standard 2D sonography in assessment of first trimester of pregnancy. It has moved the embryology from postmortem studies to in vivo. Development of the embryo can be studied in detail by transvaginal 6–9 MHz volume probe (Figs 6 and 7). This is known as sonoembryology.
Using 3D power Doppler hemodynamic changes occurring during early placentation can be studied. Moreover, this accuracy can be achieved with even a shorter examination time. Three-dimensional orientation and multiplanar imaging gives unlimited tomograms, with only limited probe manipulation and minimizes the fetal exposure to US waves. Acquire a single sweep of the complete fetus in up to 5 seconds maximum. Using surface rendering and maximum mode multiplanar mode and TUI shows a complete detailed anatomy of the embryo at least till 12 weeks. It is especially useful with unfavorable fetal position.

**GENETIC SCAN**

Genetic scan or the nuchal scan (Fig. 8) is done between 11 weeks and 14 weeks of pregnancy to exclude chromosomal malformations. This includes measuring nuchal translucency, nasal bone, ductus venosus flow, looking for tricuspid regurge, measuring facial angle, looking for omphalocele, renal pyelectasis, etc. Assessing for nuchal translucency, nasal bone and facial angle require a true midsagittal section. This may always not be easy whether abdominal or vaginal route is selected. A study by Kurjak et al. has shown that using 3D US, midsagittal plane of the fetus can be visualized successfully 100% of the times versus 80% of the times with 2D technique. A study by Eppel et al. shows that 3D transvaginal technique offers a shorter examination time and higher success rate for measuring nuchal translucency though it results in slight but significant underestimation of the measurement. This probably may be due to the transvaginal approach instead of transabdominal.
When the starting section is transverse or coronal, it is very difficult to find out nasal bone in midsagittal plane by 2D US, 3D US can be a useful tool to find out and measure the nasal bone. But if the angle between US transducer and imaginary line passing through fetal face profile is less than 30° or more than 60°, that is if fetal head is hyperextended or flexed, 3D cannot help over 2D technique to see the nasal bone. Using multiplanar mode Peralta et al. have described a gap between the nasal bones on axial plane in 20% of fetuses and in about 40% of these fetuses in midsagittal plane, nasal bone may be erroneously considered absent on 2D US. So, 3D US can demonstrate absent nasal bone in axial plane, reducing the false positives. In second trimester screening maximum transparent mode is preferred to multiplanar to show unilateral or bilateral absence of nasal bone.

Genetic syndromes are often diagnosed by craniofacial dysmorphism. Three-dimensional US has remarkably improved the detection rate of facial anomalies and thus helped in diagnosis of genetic syndromes.

**Facial Abnormalities**

Three-dimensional US has improved the detection rate of facial anomalies. In 90% of cases correct and reproducible face images can be produced in second trimester (Fig. 9). Best time is between 23 weeks and 30 weeks, but proper fetal position is essential. To get a proper position pressing mother’s abdomen repeatedly, turning mother to one or another side or re-examining after a few minutes would help when fetus is not in a favorable position to see the fetal face.

Though this reduces to only 30% after 34 weeks due to the obligatory position that the fetus has to attain with its growing size.

Merz et al. have reported well-defined facial images as early as 9th week of pregnancy. Three-dimensional US has an important role in diagnosis of facial cleft, micrognathia, nasal abnormalities and eye abnormalities.

Diagnosis of cleft lip and palate (Fig. 10) is almost 100%, including the cleft of soft palate also. Cleft palate can be diagnosed by tomographic ultrasound imaging (TUI) (Fig. 11), by mixture of light and surface rendering and by reverse face view where the viewing direction of the 3D rendered image is from posterior to anterior.

Three-dimensional US can also pick up isolated soft palate defects as shown by studies by Pilu et al. Another technique to detect the cleft palate is the 3D “reverse face” view. After acquiring the face volume the viewing direction is changed to back, so that you see the facial bones from inside the skull. Maxilla and palate can be reliably studied as early as 11 weeks. Early diagnosis of median cleft syndrome is possible in which the frontal bones and nasal bones are largely separated with hypertelorism, flat nasal bridge, rudimentary nostrils and other facial abnormalities.

Size, morphology and placement of the ear are important for diagnosis of chromosomal abnormalities (Fig. 12). Seventy percent of trisomy 21 babies have helix-lobe lengths more than two standard deviation from mean. Detection of ear appendices may be a marker of renal malformation.
The important features of fetal dysmorphism diagnosed by 3D US are:
- Flattening or prominence of occipital bones
- Early closure of sutures
- Hypo/hypertelorism/microphthalmia
- Retro or micrognathia and jaw index: anteroposterior (AP) diameter of mandible/biparietal diameter (BPD) (< 0.23 is micrognathia)\(^\text{10}\)
- Low placed or abnormal shape of ears, ear appendices
- Asymmetry of face
- Altered facial angles—superior or inferior
- Cleft lip/palate
Apart from the defects or anatomical variations, 3D 4D US can also show the fetal expressions (Fig. 13) which express the fetal behavior. The expressions recorded so far are:
- Yawning
- Smiling
- Swallowing
- Sucking
- Blinking
- Grimacing
- Mouthing
- Tongue expulsion.

**Cranial Abnormalities**

Skull bones and sutures (Fig. 14) can be identified by 3D US, which is difficult with 2D US due to natural curve of the skull. Maximum transparency mode is used for this. Excessive diastasis of the sutures can be seen in cranium bifidum occultum and premature closure can diagnose
craniostenosis and microcephaly early. By 3D multiplanar display diagnosis of acrania and exencephaly can be rather easy depicting correct sagittal and coronal sections.

**Central Nervous System**

Development of diencephalon, mesencephalon and rhombencephalon can be studied from 9 weeks of gestation. Diagnosis of alobar holoprosencephaly is possible as early as 10 weeks by absence of central cleft.

In late second and third trimester, if fetus is in cephalic presentation, transvaginal approach can be a better approach to study fetal brain. Placenta and thick skull bones may be obstructing the vision on transabdominal approach. Once the fetal brain has been scanned, it is then possible to navigate in the stored volume. By multiplanar display, the brain anatomy can be studied in detail (Fig. 15).

Using TUI in all the three orthogonal planes all the coronal, sagittal and axial sections required for a detailed neurosonogram can be achieved by one single sweep of the fetal head.

Development of brain in second trimester has three developmental landmarks:

1. Development of lateral ventricle into frontal, occipital and temporal horns
2. Development of corpus callosum
3. Development of cerebellar vermis.

Virtual organ computer-aided analysis (VOCAL) may be used for volume calculation of cerebellar hemispheres, vermis and intracranial lesions. Volume contrast imaging in coronal plane depicts the midline structures like corpus callosum (Fig. 16), optic chiasma and cerebellar vermis.

Agenesis of corpus callosum and cerebellar vermian hypoplasias—Dandy-Walker syndrome can be diagnosed by 3D US. Normal corpus callosum and cerebellar vermis with ventriculomegaly is most likely due to aqueduct stenosis.

Paladini and Volpe have suggested tentorovermian angle, tentoroclivus angle, clivovermian angle, etc. to diagnose vermian abnormalities. Skull base development can be studied by measurement of anterior skull base length and posterior cranial fossa length and skull base angle. Brain growth leads to higher increment in posterior cranial fossa length leading to 6° flexion in the skull base angle. Craniofacial variability index can assist in fetal facial anatomy to study craniofacial development. These can be measured on TUI and multiplanar mode. This technique has proved to be almost as sensitive as CT scan or MRI for study of expansive brain lesions. Three-dimensional US may be applied to every CNS abnormality diagnosed with traditional 2D technique and may offer further information useful to correct diagnosis. It can delineate the exact nature and anatomic level of anomaly.

Three-dimensional power Doppler also delineates the cerebral vasculature and its abnormalities (Fig. 17).

Study of fetal motorial and behavioral pattern is essential for complete evaluation or functional integrity of fetal central
nervous system (CNS) (Figs 18A and B). Four-dimensional US allows the evaluation of fetal motorial and behavioral patterns. With 4D US it is possible to better define the degree of normality and pathology of fetal neurological functions in utero and to find out which fetuses are at risk of bad neurological outcome. Kurjak et al. have described patterns of neurodevelopmental behavior during the three trimesters of pregnancy using 4D US.\textsuperscript{15} The changes in the motorial pattern expresses the evolution of the maturative process of CNS during intrauterine life. These fetal behavior and movements can help diagnosis of motoric development failure at the end of the first trimester. Delayed motoric development is seen in fetuses of diabetic mothers.

Fetuses with arthrogryposis show early disturbances in motoric development with absent limb movement and joint contractures.

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Figs 18A and B: (A) Movements of hand; (B) Fetus scratching the ear
Spinal Abnormalities

Evaluation of spine in sagittal, coronal and axial, all three planes are essential to diagnose spinal abnormalities correctly. All the three views cannot be achieved in one fetal position on 2D US. Three-dimensional US saves examination time and clearly can show all the three views at a time on multiplanar view along with the overlying skin surface by using maximum mode transparent rendering and surface rendering (Fig. 19). Using 4D VCI-C can also show coronal view even when on 2D US only axial section is seen.

Using magicut and 3D rotation, it is also possible to see each vertebrae separately (Fig. 21B) and to define the extent of lesion especially in cases of open spinal canal defects (Fig. 20). 3D-4D US have almost 100% sensitivity and very high specificity for diagnosis of spinal abnormalities (Fig. 21A). Longitudinal scan of the fetus is used with maximum mode to evaluate the thoracic cage, clavicle and scapulae. Absent 12th rib is a marker for trisomy 21.

Chest

Multiplanar mode and TUI allows to study the spatial relationship between lungs, heart, esophagus and diaphragm\(^\text{17}\) (Fig. 22). Trachea and esophagus morphology can be studied thus helping to diagnose tracheoesophageal fistulae early and decide the type in utero. VOCAL and 3D-4D multiplanar mode is useful for assessment of fetal lung volume and thymus volume.

Diaphragmatic hernia can be easily diagnosed by 2D ultrasonography (USG) also but the role of 3D USG here is to assess the amount of lung compression and calculate the exact lung volume which is very important for deciding the prognosis.

Ruano et al. have evaluated the potential of 3D power Doppler to predict neonatal outcome and pulmonary arterial hypertension in fetuses with congenital diaphragmatic hernia. Severity of pulmonary arterial hypertension was associated with progressive reduction in prenatal vascular indices.
Abdomen

Using transparent mode and multiplanar mode the abdominal organs can be very well defined with definition of all tissue planes. Three-dimensional US is an effective tool for diagnosis of gastrointestinal malformations and gives additional information over 2D US for pediatric surgeons for surgical planning and for counseling with parents. All abdominal masses may be better evaluated by multiplanar mode to evaluate the origin and extension. Inversion mode helps to define cystic lesions and can be best used to confirm the diagnosis of pyloric stenosis, duodenal atresia, posterior urethral valves, obstructive uropathy, etc. Surface rendering allows clear visualization of genitals. Hypospadias is seen as “Tulip sign” and clitoral hypertrophy can be diagnosed in third trimester.

Anterior abdominal wall defects are well demonstrated on volume USG. 3D is very useful to differentiate the bowel containing from the liver containing omphalocele. Use of 3D multiplanar display is more accurate than the use of 2D US for measuring the size of omphalocele. Congenital anomalies of the abdomen like omphalocele and gastrochisis can be clearly evaluated through 3D US.

Role of 3D-4D US in fetal echocardiography is discussed in the chapter of fetal echocardiography.

Limb Abnormalities

Accurate analysis of majority of bony structures can be done by using maximum mode rendering of 3D US. Phocomelia and Sirenomelia like abnormalities can be diagnosed as early as 11–12 weeks (Fig. 23). 3D-4D US enables detailed examination of fingers and toes with almost 100% certainty of detecting agenesis and extra digits. Motor abnormalities and abnormal attitude of fingers, toes or hands and legs like club feet, overriding of fingers or thumb in the fist may be a manifestation of chromosomal or neurological abnormality (Figs 24 and 25).

Placenta

It is known that pregnancy induced hypertension occurs only after at least 70% of the placental vasculature is obliterated. Three-dimensional power Doppler with angiomode of the placental vasculature may show obliteration of the placental vessels and help to predict pregnancy induced hypertension much earlier.

Benacerraf et al. has described a novel use of 3D US in offline fetal evaluation. According to her study five volume sweeps should be taken of every fetus, and they are examined offline. This method has proved to be successful in detailed evaluation of fetal anatomy and very sensitive for diagnosing fetal anomalies. These sweeps are axial section of fetal head, axial section of fetal thorax, axial section of fetal abdomen, longitudinal sweep of lower limbs and longitudinal section of head.
Conjoined Twins

In conjoined twins (Fig. 26), practicability and the consequent morbidity of the fetuses after separation depend on the degree of codivision of organs and vascular structures. Therefore, detailed and accurate anatomic and vascular map is fundamental for evaluation of joined organs in conjoined fetuses is of fundamental importance to decide the line of treatment. Moreover, defects like orofacial cleft, diaphragmatic hernia, imperforate anus and neural tube defects are also common. Bega et al. have reported that combining multiplanar display and surface rendering can assess these fetuses fairly reliably, as early as 10 weeks. Three-dimensional US can be of great help in classifying more accurately the type of conjoined twins and color Doppler may be of further help.
Ectopic Pregnancy

Three-dimensional US with rendered image in coronal plane plays an important role for the diagnosis of cornual (Fig. 27) or interstitial pregnancy. We have used 3D power Doppler for monitoring the vascularity of ectopic pregnancy which is treated conservatively. Decreasing vascularity indicates a regressing pregnancy.

LIMITATIONS OF 3D-4D US

As for 2D US, factors like maternal obesity, maternal scar, maternal movements, excessive fetal movements, which come in way of sound propagation are obstacles for 3D US also. Oligohydramnios does not permit sufficient fluid interface for rendering and so is not a favorable factor for reconstruction and surface rendering.

GYNECOLOGY

Three-dimensional US in gynecology has one great advantage and that is it gives coronal view of the uterus. This has made 3D US as effective as magnetic resonance (MR) for diagnosis of uterine abnormalities. Most commonly used tools in gynecology are surface texture rendering, at times mixed with smooth surface mode, multiplanar mode, TUI in coronal section. The rendering direction is most commonly from above, as if you are looking at the uterus from the top. Transvaginal is the approach always selected.

CONGENITAL UTERINE ABNORMALITIES

They are seen in 1–5% of females. They result from incomplete fusion of the Müllerian ducts in the intrauterine life. Three-dimensional US is a very sensitive tool for the diagnosis of congenital uterine anomalies (Fig. 28). It is known as virtual hysteroscopy.

Sensitivity of the volume USG for the detection of congenital uterine abnormalities is above 98% (Table 1).

Septate uterus is most commonly associated with complications of pregnancy including premature deliveries and dystocias, abortions, ectopic pregnancies and infertility. Frequency of ectopic with septate uteri is 27.34% as compared to 13.3% otherwise. Incidence of first trimester abortions is 28–45% and second trimester abortions is 5%.

Bicornuate versus Septate Uterus on 3D US

- Dimple on the fundus
- Highest point of the endometrial cavity is at least 5 mm higher than the fundal top
- Dipping of the myometrium.

ACQUIRED UTERINE ABNORMALITIES

Fibroids

Fibroids are easily and reliably diagnosed by 2D and color Doppler. Three-dimensional US is done to precisely assess the relationship between submucous fibroid and uterine cavity. 3D is done in fibroids for follow-up in pregnancy, menopause and when under gonadotropin-releasing hormone-agonist (GnRH-A) treatment for volume measurement by VOCAL. These are the conditions which may show remarkable increase or decrease in size of the fibroid. In difficult cases, 3D power Doppler angiomode can be used to differentiate between fibroids and adenomyomas. Circumferential vascular pattern suggests fibroid, whereas radiating/penetrating vascular pattern suggests adenomyoma (Fig. 29).
Polyp

Endometrial polyps (Fig. 30) are projectile lesions from the endometrial walls into the endometrial cavity and are best seen on 2D US in periovulatory phase as solid isoechoic lesions in the endometrial cavity. They are difficult to differentiate from other endometrial lesions like hyperplasia, malignancy or synechiae. Single feeding vessel in pedicle on color Doppler may be seen, but with thick pedicles it may be more than one vessel supplying the lesion. Three-dimensional US is the diagnostic tool for diagnosis of polyp. The TUI in coronal plane shows the pedicle also and exact site of origin. It, thus, differentiates polyp from hyperplasia and malignancy.

Table 1: Sensitivity of various types of ultrasound examinations

<table>
<thead>
<tr>
<th>Ultrasound</th>
<th>Sensitivity</th>
<th>Specificity</th>
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<tbody>
<tr>
<td>TVS</td>
<td>95.21%</td>
<td>92.21%</td>
</tr>
<tr>
<td>TVCD PD</td>
<td>99.29%</td>
<td>97.23%</td>
</tr>
<tr>
<td>Volume USG</td>
<td>98.38%</td>
<td>100%</td>
</tr>
<tr>
<td>Sonohysterography</td>
<td>98.18%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Abbreviations: TVS, transvaginal sonogram; TVCD PD, transvaginal color Doppler; power Doppler; USG, ultrasonography.

Source: Richman TS et al. Radiology 1984
**Synechiae**

These are the most commonly missed lesions on 2D US. Three-dimensional US delineates and localizes the adhesions and helps surgical planning. In cases of bridging adhesions 3D gives exact assessment of extent of obliteration of cavity. Sonohysterography is a better tool to assess the capacity of the cavity.

**SONOHYSTEROGRAPHY**

It is done for definition of intracavitary lesions like polyps, synechiae, submucosal fibroids, hyperplasia, etc. (Fig. 31). Sonohysterography also can be used for better definition of uterine shape in congenital uterine anomalies. It can be further extended into sonosalpingography (SSG) for checking the tubal patency.

**Technique**

With the patient in lithotomy position, cervix is exposed by the help of Sim’s Speculum and anterior retractor. Catheter 6 Fr. (ext. diam. 1.6 mm, int. diam. 1.1 mm) is inserted into the external os. Distend the balloon in the cervix with 1–2 mL of fluid. This fixes the bulb in the cervical canal. Slowly inject 5–10 mL of normal saline with 20 mL syringe under transvaginal US monitoring. The speculum and retractor are removed once the catheter is fixed and probe is introduced. Negative contrast-normal saline may be used and shows intracavitary lesions better than with Positive contrast-Echovist. Echovist has a disadvantage of high reflectivity giving posterior shadowing and obscuring the solid endometrial cavitory lesions, though it may define the shape of the cavity better. Once the cavity is filled with saline a single 3D sweep is taken to include the whole uterine volume and is rendered with mixture of smooth surface and texture. Thicker slice and low thresholds will show the texture of the endometrial wall also.

When tubes also are to be delineated the fluid instilled is 10–20 cc. The field of vision is aimed in such a way that the uterus and ovary will be seen together. Using a full size color box and a sudden gush of color with injection of saline will prove the patency of the tube on that side.

**Comparison of Sonosalpingography, Hysterosalpingography and Laparoscopy**

- Sensitivity of SSG is 97.3% for open tubes and specificity of 92% and of laparoscopy is 94.6%, whereas sensitivity of hysterosalpingography(HSG) is 94.5% but with a specificity of only 84%.21
- Results of SSG correlated positively with laparoscopy in 97% whereas SSG and HSG showed 93% correlation.22
Advantages of Sonohysterosalpingography

- Outpatient department procedure, less time consuming, cost-effective
- Noninvasive
- No anesthesia
- Diagnoses uterine anomalies and pelvic pathologies
- No radiation, no iodinated contrast
- Reproducible and reliable for assessment of tubal patency
- Can be demonstrated in real-time.

Disadvantages of Sonosalpingography

- Tubal spasm misinterpreted for occlusion
- Hydrosalpinx gives tubal flow–false positive for patency
- Technical competence required
- Site of block cannot be located exactly
- Intratubal pathology cannot be detected
- Peritubal adhesions and tubal motility cannot be assessed
- Findings are subjective.

In cervical or uterine malignancies 3D USG helps to detect the invasion of surrounding organs and tissues. Three-dimensional power Doppler shows typical chaotic vascular pattern of malignancy due to microaneurysms and arteriovenous fistulae (Figs 32A and B).

In cervical or uterine malignancies 3D USG helps to detect the invasion of surrounding organs and tissues. Three-dimensional power Doppler shows typical chaotic vascular pattern of malignancy due to microaneurysms and arteriovenous fistulae (Figs 32A and B).

OVARIAN LESIONS

Ovarian Cysts

Three-dimensional ultrasound is essential for any complex cyst of the ovary to define the wall thickness and wall characteristics. Solid projections and septae may sometimes only be defined by 3D US. As 3D may show all three orthogonal planes, sometimes the cystic lesions considered to be ovarian cysts on 2D US may discover themselves as hydrosalpinx on 3D multiplanar or surface rendered mode by incomplete septae and sausage shape. Three-dimensional power Doppler is absolutely essential for any large or suspicious cyst or cyst in high risk group females as even simple looking cysts may show tumor vascularity.

Dermoids (Fig. 33)

They are most likely of ovarian origin.

On US they show thick wall with echogenic material in lumen. Regional diffuse bright echoes with or without acoustic shadowing may be seen due to hair clumps or fat in Rokitansky’s protuberance. Fluid level due to sebaceous material and hyperechoic lines and dots due to hair may be seen.

These are typical features and have individual positive predictive value for dermoid.

- Eighty percent for shadowing echodensity
- Seventy-five percent for regionally bright echoes
- Fifty percent for hyperechoic lines and dots
- Twenty percent for fluid level.

Positive predictive value for more than two features is 100%. Of these features there are certain which are much better defined by 3D US and they are thickness and characteristics of the cyst wall, and shape of the solid projections.

INFERTILITY

We shall discuss the role of 3D US in infertility under three headings. Its role in baseline scan is to assess the ovarian reserve, in preovulatory assessment of follicle and endometrium and in secretory phase.

Baseline Scan

This scan is done to define the type of ovary and to assess the reserve of the ovary and the down regulation.

Ultrasound features of polycystic ovaries has been described at different times by different people. Enlarged ovaries bigger than 10 cc show good correlation between US diagnosis of polycystic morphology and histopathological criteria for polycystic ovaries. Other features are multiple
immature follicles (2–8 mm), predominant hyperechoic stroma (3D), etc.

The new parameters that have come up are ovarian area (5.3 cm²), stromal area (4.6 cm²) and ratio of the two.

Three-dimensional USG is complementary to 2D USG for the diagnosis of PCOS (Fig. 34), except for assessment of antral follicle count. This is considered as one of the most sensitive parameter for assessment of ovarian response. Ovary is acquired in one volume and VOCAL is done to calculate the ovarian volume. This volume is rendered by minimum mode which will show all the follicles black. Rendering by inversion mode is better which will show all antral follicles as solid balls. But proper threshold adjustment is essential. Rotating this volume slowly can be one method to count the number of these follicles. Another method can be using TUI, but there are chances of over counting the follicles by this method.

Kupesic has shown correlation between the ovarian stromal flow index (FI) and number of mature oocytes retrieved in IVF cycles and pregnancy rates. Vascularity index (VI), FI and vascularity flow index (VFI) are 3D power Doppler histogram indices calculated by the computer from the volumes acquired with power Doppler and defined by VOCAL.

- Vascularity index (abundance) VI
- Flow index (intensity) FI
- Vascularity flow index (perfusion) VFI

**Endometrial Assessment for Downregulation**

- E2 below 60 pg/mL, endo. volume below 1.9 mL—has a sensitivity of 95.2% and specificity of 75%—area under curve (AUC)–0.83
- E2 below 80 pg/mL, endo. volume below 1.9 mL—sensitivity 100%, specificity 93.2%—AUC–0.97%

These assessments are not very useful in clinical practice as E2 levels preferred for adequate downregulation are 30–50 pg/mL. However, these 3D volume assessment by VOCAL for endometrium are highly reliable.

<table>
<thead>
<tr>
<th>Reliability (unstimulated endo)</th>
<th>2D</th>
<th>3D</th>
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<tbody>
<tr>
<td>Interobserver</td>
<td>0.66</td>
<td>0.93</td>
</tr>
<tr>
<td>Intraobserver</td>
<td>0.84</td>
<td>0.95</td>
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**Preovulatory Scan**

**Follicular Assessment**

*Follicular volume* is more reliable than follicular diameter. And volumes calculated by 3D VOCAL are more reliable than volumes calculated by 2D US, three diameter formula (Fig. 35). The limits of agreement between the volume of the follicular aspirate and 3D volume of the follicle were +0.96 to –0.43 with 3D, and +3.47 to –2.42 by 2D volume estimation. But for volumes of follicles of smaller than 10 mm diameter, the limits of agreement are too high.

Follicular volumes of between 3 cc and 7 cc are optimum for oocyte retrieval.

Moreover according to Kurjak et al. on the day of human chorionic gonadotropin (hCG), if cumulus like echoes are not seen in all three planes in the follicle, it is less likely to be mature fertilizable oocyte. It is possible to see the cumulus only in up to 40% of follicles by 2D US but using 3D rendering we have found that cumulus can be seen in more than 90% of the mature follicles.
This study was done to find out if 3D and 3D power Doppler indices for assessment of pre-hCG follicle and endometrium are better than 2D and CD. The 500 superovulation with intrauterine insemination (IUI) cycles were randomly studied for cases of idiopathic infertility. Human chorionic gonadotropin was given for ovulation trigger when follicle and endometrium appeared mature by 2D and CD parameters. 3D and 3D power Doppler of follicle and endometrium was done for all patients. We have found that even when 2D and color Doppler parameters were normal, only a percentage of patients conceived who had following endometrial and follicular parameters:

Follicular volume 3–7–5 cc, follicular VI 6–20, follicular FI above 27.
Endometrial volume above 3, endometrial FI above 20, endometrial VFI above 5.24

Similar values are suggested by different authors. Greater than 2.5 mL endometrial volume before hCG has a significantly higher pregnancy rates. Median values for a favorable endometrium is 4.28 ± 1.9 mL.

Volume USG–VOCAL and color histogram—VI, FI, VFI values (Figs 36A and B) in our experience have proved to be of added value in evaluation of ovarian response, endometrial receptivity and pre-hCG follicular and endometrial evaluation, though larger studies may be needed to standardize the techniques and values.

Ovarian volumes may also be useful in predicting the risk of ovarian hyperstimulation syndrome (OHSS) in the preovulatory phase. Even when the age of the patient and total number of follicles are similar, the ovarian volume was significantly higher in the patients who developed OHSS (271 ± 87 versus 157.30 ± 54.20 mL).25

**Secretory Phase**

Though 3D does not have a significant role to play in the secretory phase assessment, we have done a retrospective assessment of 350 pregnancies after IUI and have derived a few parameters which would be predictive of implantation.

Subjective signs of implantation:
- Echogenicity of the endometrium
- Asymmetrical thickening of the endometrium (better seen on 3D)
- Localized area of increased vascularity in the endometrium.

Vascular parameters for prediction of implantation:
- Endometrial VI : below 20 : 85%
- Endometrial FI : 30 ± 5 : 88%
- Endometrial VFI : below 4 : 91%

Full potential of 3D is yet to be completely developed, though storing volumes and studying predefined sections later on by different specialists is a boon. It is important to think and find out as to what information you want out of the stored volume and how to bring it out.

Sectional plane studies like CT or MR can be done at a much lower cost, noninvasively and are much less troublesome.
to the patient. Initial scanning time may be longer, but with increasing practice, it decreases.

Volume USG is an indispensable tool in any center for prenatal diagnosis. Three-dimensional sonography is a fundamental tool for complete neurosonographic examination of the fetus and can help to a better understanding of complex mechanisms leading to normal or abnormal brain development.

Rendering modes will allow better definition of anatomic spatial relationship between spine and ribs, visualization of clavicles and scapula, evaluation of abdominal masses diagnosed by 2D and anomalies of genitalia. Multiplanar mode is useful for evaluation of thoracic vertebra and sternum.

Three-dimensional US is finding a new role in understanding of normal embryonic and fetal morphology and also for early diagnosis of pathologies.

Three-dimensional and 4D techniques are seen as powerful complement to conventional US, but not a substitute to them. Three-dimensional US is not a substitute for 2D US but is a useful complementary technique. All 3D tools must be used complementary with power Doppler. It must be offered to all high-risk patients.

REFERENCES

INTRODUCTION

“Stop thinking in terms of limitations and start thinking in terms of possibilities.”
—Terry Josephson

True to the saying, had the scientists stopped dead at the limitations of a modality, our world of imaging would never had progressed. There is no denying the fact that ultrasound is the lifeline of obstetrics and gynecology, but what if a sonogram leads us to a question mark? For such instances, we have computed tomography (CT) scan and magnetic resonance imaging (MRI) as a backup.

Computed tomography was discovered independently by a British engineer named Sir Godfrey Hounsfield and Dr Alan Cormack. For their work, Hounsfield and Cormack were jointly awarded the Nobel Prize in 1979.

Because of advances in computer technology, CT scanners have vastly improved patient comfort because they are now much faster. These improvements have also led to higher-resolution images, which improve the diagnostic capabilities of the test.

Computed tomography is essentially a series of X-rays in “slices” through the body, which are then analyzed by a computer, and an image constructed from the data. It can show the precise location of a tumor, its shape, and whether it is solid or hollow. Although it can give clues as to whether or not a tumor is cancerous, only a biopsy can tell for sure. There is a drawback that a CT scan is not reliable in helping to find tumors that are less than 2 cm in size.

Computed tomography has revolutionized medicine because it allows doctors to see diseases that, in the past, could often only be found at surgery or at autopsy. CT is noninvasive, safe and well-tolerated. It provides a highly detailed look at many different parts of the body.

COMPUTED TOMOGRAPHY IMAGING

Benefits

- CT scanning is painless, noninvasive and accurate
- A major advantage of CT is that it is able to image bone, soft tissue and blood vessels all at the same time.
- Unlike conventional X-rays, CT scanning provides very detailed images of many types of tissue as well as the lungs, bones, and blood vessels
- CT examinations are fast and simple; in emergency cases, they can reveal internal injuries and bleeding quickly enough to help save lives
- CT may be less expensive than MRI. In addition, it is less sensitive to patient movement
- CT can be performed if you have an implanted medical device of any kind, unlike MRI
- CT imaging provides real-time imaging, making it a good tool for guiding minimally invasive procedures such as needle biopsies and needle aspirations of many areas of the body, particularly the lungs, abdomen, pelvis and bones.

Risks

- There is always a slight chance of cancer from radiation. However, the benefit of an accurate diagnosis far outweighs the risk
- The effective radiation dose from this procedure is about 10 mSv, which is about the same as the average person receives from background radiation in 3 years
- Women should always inform their physician or X-ray technologist if there is any possibility that they are pregnant
CT scanning is, in general, not recommended for pregnant women because of potential risk to the baby. Nursing mothers should wait for 24 hours after contrast material injection before resuming breast-feeding. The risk of serious allergic reaction to contrast materials that contain iodine is rare. Children should have a CT study only if it is essential for making a diagnosis and should not have repeated CT studies unless absolutely necessary.

**MAGNETIC RESONANCE IMAGING**

It was developed from knowledge gained in the study of nuclear magnetic resonance. In its early years, MRI was referred to as nuclear magnetic resonance imaging (NMRI), but the word nuclear has been associated with ionizing radiation exposure, which is not used in an MRI, so to prevent patients from making a negative association between MRI and ionizing radiation, the word has been almost universally removed.

Medical MRI most frequently relies on the relaxation properties of excited hydrogen nuclei in water and lipids. When the object to be imaged is placed in a powerful, uniform magnetic field, the spins of atomic nuclei with a resulting nonzero spin have to arrange in a particular manner with the applied magnetic field according to quantum mechanics. Nuclei of hydrogen atoms (protons) have a simple spin 1/2 and therefore align either parallel or antiparallel to the magnetic field.

**MAGNETIC RESONANCE IMAGING VERSUS COMPUTED TOMOGRAPHY**

A CT scanner uses X-rays, a type of ionizing radiation, to acquire its images, making it a good tool for examining tissue composed of elements of a relatively higher atomic number than the tissue surrounding them, such as bone and calcifications (calcium based) within the body (carbon based flesh), or of structures (vessels, bowel). MRI, on the other hand, uses nonionizing radiofrequency (RF) signals to acquire its images and is best suited for non-calciﬁed tissue.

Computed tomography may be enhanced by use of contrast agents containing elements of a higher atomic number than the surrounding flesh (iodine, barium). Contrast agents for MRI are those which have paramagnetic properties. One example is gadolinium.

Both CT and MRI scanners can generate multiple two-dimensional (2D) cross-sections (slices) of tissue and three-dimensional (3D) reconstructions. Unlike CT, which uses only X-ray attenuation to generate image contrast, MRI has a long list of properties that may be used to generate image contrast. By variation of scanning parameters, tissue contrast can be altered and enhanced in various ways to detect different features.

Magnetic resonance imaging can generate cross-sectional images in any plane (including oblique planes). CT was limited to acquiring images in the axial (or near axial) plane in the past. The scans used to be called computed axial tomography scans. However, the development of multidetector CT scanners with near-isotropic resolution, allows the CT scanner to produce data that can be retrospectively reconstructed in any plane with minimal loss of image quality.

For purposes of tumor detection and identification, MRI is generally superior. However, CT usually is more widely available, faster, much less expensive, and may be less likely to require the person to be sedated or anesthetized.

**Safety**

Implants and foreign bodies—pacemakers are generally considered an absolute contraindication toward MRI scanning.

Ferromagnetic foreign bodies (e.g. shell fragments) or metallic implants (e.g. surgical prostheses and aneurysm clips) are also potential risks.

**Pregnancy**

No harmful effects of MRI on the fetus have been demonstrated. In particular, MRI avoids the use of ionizing radiation, to which the fetus is particularly sensitive. However, as a precaution, current guidelines recommend that pregnant women undergo MRI only when essential. This is particularly the case during the first trimester of pregnancy, as organogenesis takes place during this period. The concerns in pregnancy are the same as for MRI in general, but the fetus may be more sensitive to the effects—particularly to heating and to noise. However, one additional concern is the use of contrast agents; gadolinium compounds are known to cross the placenta and enter the fetal bloodstream, and it is recommended that their use be avoided.

Despite these concerns, MRI is rapidly growing in importance as a way of diagnosing and monitoring congenital defects of the fetus because it can provide more diagnostic information than ultrasound and it lacks the ionizing radiation of CT.

**MAGNETIC RESONANCE IMAGING TO ASSESS THE FETUS IN UTERO**

It is fraught with technical challenges, including the major problem of artefacts caused by movement of both the mother and the fetus. Until recently clinical MRI consisted mainly of spin echo methods with long duration of imaging (4-10 minutes). Magnetic resonance is sensitive to motion and even minor movements may render the scans unusable. For this reason in utero MRI of the fetus was impossible without other interventions. The first consistently successful attempts at fetal imaging using magnetic resonance were made by paralyzing the fetus with muscular blocking agents given through the umbilical vessels. This introduced an element of risk to the procedure but was often carried out in conjunction with other procedures that required cannulation of the umbilical vessel. Less invasive attempts involved maternal sedation, usually with intravenous benzodiazepines, but
these were not completely without risk, and the adequate monitoring of sedated women in the scanners was a problem. The introduction of ultrafast imaging methods had the most important impact in the field of in utero MRI. Echo planar imaging and single shot fast spin echo techniques allow the acquisition of single, high resolution images in less than 1 second, which effectively freezes physiological movement and allows imaging with no invasive interventions.

The first study using MRI in gestation was done by Smith in 1983. Later, its use grew progressively in obstetrics and fetal medicine, especially in the evaluation of the central nervous system (CNS) of the fetus. This is due to fact that the fetal CNS is not easily evaluated by ultrasound because of the ossification of the calvaria in the third trimester, besides frequent inappropriate fetal position.

Although ultrasound continues to be the most used modality of prenatal exam routine because of its low cost, more equipment availability, safety, high sensibility and good real-time capacity of analysis, MRI is potentially good at the morphological evaluation of those fetuses that are not easily studied by ultrasound.

According to Poutamo et al. (1999), the main inherent problem of ultrasound is:

- Acoustic skull cap shadow, which prejudices mainly the study of the posterior fossa
- Presence of the cephalic pole in the maternal pelvis, especially in the transverse insinuations, prejudicing the sagittal evaluation of the cephalic pole
- In some of these cases, the problem can be solved by the transvaginal ultrasound probe
- Distance enlargement between the ultrasound probe and the cerebral structures in the cases of an important hydrocephaly
- Intracranial hyperechoic images, such as tumors and hemorrhage which can prejudice the rest of the cerebral anatomy evaluation
- Acoustic shadow presence from the jaw and the base of the cranium which hinders a good evaluation of the cervical region
- Slight difference of echogenicity between tissues such as the esophagus and the trachea
- Maternal obesity
- Strong polyhydramnios or oligohydramnios.

**Indications**

Primary indications for MRI (the American College of Radiology and the Society for Pediatric Radiology Recommendations) include:

**Brain and spine:**
- **Brain:**
  - Venticulomegaly
  - Agenesis of the corpus callosum
  - Posterior fossa anomalies
  - Holoprosencephaly
  - Cerebral cortical malformation
- **Vascular abnormalities:**
  - Vascular malformations
  - Hydranencephaly
  - Infarctions
  - Monochorionic twin pregnancy complications
- **Spinal abnormalities:**
  - Neural tube defects (NTDs)
  - Sacrococcygeal teratomas
  - Caudal regression
  - Sirenomelia
  - Vertebral anomalies

**Skull, face and neck masses:**
- Venolymphatic malformations
- Hemangiomas
- Teratomas
- Goiter
- Facial clefts

**Thorax:**
- Masses in thorax
- Volumetric assessment of lung parenchyma
- Abdominal, pelvic and retroperitoneal masses
- Complications of monochorionic
- Fetal surgery assessment.

**Most Recommendations for Fetal MRI are Related to CNS Pathologies**

The cerebral ventricles can be well-defined by MRI. They have a high signal on T2-weighting images. They show morphological and size variations during the pregnancy. There is a physiological relative ventricular enlargement until 25 weeks of gestation which persists at the level of occipital horns until the 30th week. On the ultrasound, the enlargement of the transverse atrial diameter above 10 mm after 25 weeks is considered to be pathological. The cerebral parenchyma can be well studied (Fig. 1).

**Fig. 1:** Sagittal view on T2-weighting showing the corpus callosum (dark arrow)
Figure 2 shows cerebellar hemispheres, ventricular atrium and cingulate gyrus on MRI.

Although the main indication of fetal MRI are related to CNS pathologies, MRI has shown a large utility in the detection of other fetal anomalies, such as diaphragmatic hernia, urinary and abdominal wall defects. The naso-oropharynx and trachea present as a bright structure on T2-weighted because they are filled with amniotic fluid. The thyroid gland is difficult to be identified on T2-weighted, but can be detected on T1-weighted as a moderate hyperintense structure compared with surrounding tissues (Fig. 3).

The fetal lungs are well-demonstrated by MRI thanks to the presence of water in their constitution (Fig. 4). Maturation of the lung commences around 24 weeks’ gestation. As the lung develops there is an increase in water content and a rise in the phospholipid concentrations that relate to surfactant production. Therefore, the method allows the evaluation of pulmonary maturity after the 26th week of gestation because the MRI signal intensity could vary in both proteins and lipids concentrations (Fig. 5).

The fetal heart can also be viewed by MRI (Fig. 6). A central low intensity area on T2-weighted represents the fetal heart, which can be seen from the early second trimester. Nevertheless, the architecture of the heart and the major vessels of the fetus are also seen as low intensity areas on T2-weighted sequences. These low intensity signals are related to the effect of blood flow on the MRI signal which are not well-identified given its movement.
Fig. 6: Sagittal view of the whole male fetus (33 weeks) showing the aorta in hyposignal on T2-weighting (blue arrow) and the heal (white arrows). Note the fetal bladder in hypersignal (red arrow) and the umbilical cord insertion.

Fig. 7: Coronal view on T2-weighting showing the fetal thorax and the abdomen. The lungs (black arrow) are well seen as a hypersignal and the low signal of the liver (white arrow) and the spleen (red arrow). Note a cyst (blue arrow) close to the liver with the same aspect of the bladder (green arrow).

The fetal liver is the most readily visible abdominal organ by MRI, which in part relates to its size and to its position below the high signal intensity of the fetal lungs (Fig. 7). It possesses a homogeneous intermediate intensity signal on T2-weighted. The hepatocyte chemical composition varies with gestational age. This is due to glycogen augmentation which occurs at the end of pregnancy. So, the signals emitted by the liver will significantly change within the 24th and 40th week of gestation. The portal and hepatic vein can also be visible at the end of the pregnancy. The gallbladder is detected as a bright and cystic structure on T2-weighted. The structures of the upper digestive apparatus can be viewed by MRI because of the ingested amniotic fluid.

The signal intensity of proximal small bowel is different from that of distal small bowel and colon. The bowel loops are identified as serpiginous structures in high signal on T2 and low signal on T1. The spleen is frequently depicted with signal intensity similar to that of the liver.

The kidneys are easily evaluated by MRI (Fig. 8), but their visualization is more difficult before 20th week of gestation due to their small size and low contrast with retroperitoneal fat. The bladder is easily visualized by MRI due to its degree of repletion (Fig. 9).

The musculoskeletal system can be well-detailed in the third trimester. The upper and lower extremities can be easily identified (Figs 10 and 11). Obviously, the quality of image will depend on the degree of movement occurring during the scan.

Fig. 9: Sagittal view of the fetus on T1-weighting showing the low signal of the bladder (arrow). Note also the hyposignal of the amniotic fluid.
Magnetic resonance imaging has been used also in the evaluation of the placenta, especially in the cases of placenta previa and placental masses such as chorioangioma (Fig. 12). The maternal sagittal view offered by MRI shows with a good definition the cervix and the placental margin. The placenta has a high signal on T2, which we can see easily the myometrial-placental interface (Fig. 13). The MRI can also help the ultrasound in the evaluation of the placenta accreta, increta and percreta, which is very important to define the intrapartum morbidity and mortality.

In obstetrics, MRI is an attractive alternative to X-ray pelvimetry.

**Advantages and Disadvantages of In Utero Magnetic Resonance Imaging**

**Advantages**

*Improved diagnostic accuracy:* Better contrast between different tissues allows improved visualization of anatomy.

*No adverse effects from physical factors:* In utero MRI is not affected by physical factors that can degrade ultrasonography, such as the lie of the fetus, the habitus of the mother and reduced volume of liquor.

**Disadvantages**

*Cost and limited resources:* In utero MRI is more expensive than ultrasonography, is not as widely available, and at present lacks experienced staff for reporting on the scans.
**Limited research:** Most research and clinical work has concentrated on fetal abnormalities in the second trimester, but controlled, large studies are required to evaluate the role of in utero MRI in acquired problems later in pregnancy, such as the effects of in utero growth restriction on the fetus’s brain.

**Potential effects on hearing:** High auditory noise during the procedure may affect a child’s hearing.

### CT-MRI in Obstetrics and Gynecology

**Computed Tomography and Magnetic Resonance Imaging in Gynecology**

While CT provides good spatial resolution (the ability to distinguish two structures at an arbitrarily small distance from each other as separate), MRI provides comparable resolution with far better contrast resolution (the ability to distinguish the differences between two arbitrarily similar but not identical tissues).

It makes management decisions in a number of benign conditions including uterine anomalies, adenomyosis, leiomyomas of the uterus and endometriosis, especially in the context of infertility; it facilitates identification and characterization of adnexal masses. In uterine malignancy, the multiplanar capability and excellent soft tissue contrast permits accurate assessment of depth of tumor invasion, tumor volume, and extension to adjacent structures.

**Fibroids**

Computed tomography has a limited role in the diagnosis of uterine fibroids. On CT scans, fibroids are usually indistinguishable from healthy myometrium unless they are calcified or necrotic. Calcifications may be more visible on CT scans than on conventional radiographs because of the superior contrast differentiation with CT.

Magnetic resonance imaging has an important role in defining the anatomy of the uterus and ovaries and in assessing disease in patients in whom ultrasound findings are confusing. MRI also may be helpful in planning myomectomy, or selective surgical removal of a fibroid. Fibroids are sharply marginated areas of low-to-intermediate signal intensity on both T1- and T2-weighted MRIs (Fig. 14). One-third of fibroids have a hyperintense rim on T2 images.

**Endometriosis**

Computed tomography scanning typically is not performed in the radiologic evaluation of endometriosis because the appearance of endometriosis and endometriomas on CT scans is nonspecific. If CT scanning is performed, endometriomas appear as cystic masses. A slightly high attenuation crescent lying dependently within the cyst has been described as a more specific feature. Complications of endometriosis, such as bowel obstruction, are evident on CT scans. Urinary obstruction may cause hydronephrosis.

The appearance of endometriomas on magnetic resonance images is variable and depends on the concentration of iron and protein in the fluid, products of blood degradation. Most endometriomas have the gross appearance of chocolate cysts, representing highly concentrated blood products. MRI demonstrates these endometriomas as cystic masses with very high signal intensity on T1-weighted images and very low signal intensity on T2-weighted images (Figs 15 and 16).

This low signal intensity on the T2-weighted images is termed shading. This pattern of signal intensities results from the high iron concentration in the endometrioma and is rarely seen in other masses of any type.
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Fig. 16: T1-weighted magnetic resonance image of an endometrioma. Note the characteristic high signal intensity (similar to that of fat) of this right-sided adnexal endometrioma (arrow)

Ovarian Cysts

- MRI images have better soft tissue contrast compared to CT scan images, particularly for identifying fat and blood products, and can give a better idea of the organ of origin of gynecologic masses
- CT scan allows examination of the abdominal contents and retroperitoneum in cases of malignant ovarian disease
- MRI can be safely used during pregnancy to further evaluate adnexal masses after ultrasonography
- The advantages of MRI include the capacity to develop 3D planar images, delineate tissue planes, and characterize tissue composition.

Fig. 17: Complex echogenic mass posterior to bladder

Fig. 18: Lobulated pelvic mass with fat and a calcified mural nodule

Dermoid

Ultrasound appearances are often characteristic because of the presence of a highly echogenic dermoid plug (Rokitansky nodule), which is the solid element within the cyst that contains hair follicles, sebaceous glands, fat and calcified elements (Fig. 17). Fluid-fluid levels can also be seen. Ovarian dermoids are the most commonly missed ovarian neoplasms on sonography, often due to the “tip of the iceberg” sign, in which the back wall of the cyst is obscured by acoustic shadowing.

The diagnosis of ovarian dermoid cysts using CT and MRI is fairly straightforward, as these imaging modalities are better able to identify and distinguish the multiple specific densities within the masses (Fig. 18). On a CT scan, fat attenuation within a cyst, with or without calcification in the wall, is diagnostic for ovarian dermoid cysts. A floating mass of hair can also sometimes be identified at the fat-fluid interface. Using MRI, the sebaceous component of dermoid cysts can be identified with very high signal intensity on T1-weighted images. The signal intensity of the sebaceous component on T2-weighted images is variable, usually approximating that of fat. Chemical-shift artifacts in the frequency-encoding direction can also be used to detect fat and distinguish it from a hemorrhage.

Uterine Anomalies

Magnetic resonance imaging is considered the criterion standard for imaging uterine anomalies. MRI provides high-resolution images of the uterine body, fundus and internal structure. In addition, it can help evaluate the urinary tract for concomitant anomalies. In the past, intravenous urography was used for this purpose. Most types of uterine anomalies can be diagnosed confidently using pelvic MRI (Figs 19 and 20).
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Fig. 19: MRI image of septate uterus. The patient has a thin, fibrous septum that cannot be resolved distally at the fundus. More importantly, the outer fundal contour remains convex, thus excluding a bicornuate uterus.

Fig. 20: Bicornuate uterus. The midline uterine external fundal cleft (superior border) has a depression greater than 1 cm, excluding septate uterus from the differential diagnosis. This image is of bicornuate bicollis, since two cervices are present. Bicornuate uterus is distinguished from didelphys uterus because some degree of fusion has occurred between the lower uterine segments (i.e. they are fused, although the cavities are not communicating).

Magnetic resonance imaging provides high-resolution images of the uterine cavity, the configuration of the uterus (body and fundus) and the ovaries.

Malignancies

The uses of MRI in gynecological malignancies include tumor detection, lesion characterization, staging, treatment planning, assessing treatment response, monitoring complications and surveillance after treatment. Due to its excellent tissue contrast resolution, MRI has an established role in identifying deep myometrial invasion (Fig. 21) and

this can help in making a preoperative decision regarding the need for lymphadenectomy. It has sensitivity and specificity of 87% and 91%, respectively, a positive predictive value (PPV) of 87% and a negative predictive value (NPV) of 91% for the identification of myometrial invasion greater than 50%. MRI also performs particularly well in the detection of cervical invasion (Fig. 22); sensitivity, specificity, PPV and NPV are 80%, 96%, 89% and 3%, respectively. Extrauterine disease is also readily detected on MRI.

Magnetic resonance imaging has also been advocated in the surveillance and detection of recurrent disease. Recurrent endometrial cancer can present as a pelvic mass or as pelvic or retroperitoneal lymphadenopathy.

Less frequently, it can manifest as peritoneal carcinomatosis and distant metastases are usually associated with high grade tumors or advanced disease at presentation.
Cervical Cancer (Figs 23 and 24)

Magnetic resonance imaging has the widest application in cervical carcinoma, out of all the gynecological malignancies. It plays an important role in staging, surgical and radiotherapy planning, monitoring treatment and detecting recurrence.

Ovarian Cancer

As for ultrasound, contrast-enhanced CT has an accuracy of 95% in the detection of adnexal masses. CT has an overall accuracy of 66-93% in distinguishing between benign and malignant disease but a low specificity (Fig. 25). For staging ovarian cancer, surveillance following treatment and detecting recurrent ovarian cancer, contrast enhanced abdominal and pelvic CT is the most widely used imaging technique. CT has the advantage of rapidly assessing upper abdominal, pulmonary and pleural disease.

In our experience, MRI has a sensitivity equivalent to that of ultrasound in identifying malignancy. However, its specificity is substantially higher than that of ultrasound. This improved specificity of MRI is due to its superior ability to detect blood products in endometriotic cysts, fat in dermoids (Fig. 26) and fibrous tissue in leiomyomas, which can appear malignant on ultrasound.
SUMMARY

Though it was hitherto considered that CT-MRI are expensive tools, there are instances where we find they are indispensible too.

BIBLIOGRAPHY

Oncology
INTRODUCTION
Problems around the vulvar region are common and can lead to severe discomfort and embarrassment for women. They generally suffer in silence, ignore the problem until it gets very severe or use home remedies, which worsen the situation. Conditions commonly seen are boils, abscesses, Bartholin’s cysts, growths like warts, rashes like lichen simplex/psoriasis/lichen planus/lichen sclerosis as well as cancerous and precancer lesions.

SOLID BENIGN TUMORS OF VULVA
The incidence of solid benign tumors in the vulva is low; but a variety of benign tumors including fibromas, fibromyomas, lipomas, hemangiomas, neurofibromas and endometriomas have all been reported. These tumors can originate from any of the three germinal layers that constitute the anogenital area. Most solid tumors should be excised, both to ascertain the diagnosis and to relieve the patient’s discomfort.

Condyloma Acuminatum
This is one type of morphologic manifestation of HPV infection in the lower genital tract. They are frequently associated with cervical, vaginal and anal human papilloma virus (HPV) infection. Careful clinical evaluation, Pap smear and colposcopy are essential in patients presenting with vulvar warts. This is necessary not only to exclude cervical and vaginal dysplasia but also to define the extent of condylomatous involvement. The most common approach to vulvar condylomata is the local application of 25% podophyllum resin. Multiple applications may be necessary. Use is restricted to the vulva in nonpregnant patients. Vaginal application may lead to undesirable absorption and neurotoxicity. Surgical excision/cautery/laser ablation are indicated in: (1) extensive lesions, (2) multicentric HPV infections, particularly with involvement of the vagina, urethra or anus, (3) failure of topical chemical agents, and (4) additional presence of significant intraepithelial neoplasia, etc.

Hidradenoma of Vulva
These are small, firm to soft tumors of vulva. Most are found in the interlabial folds, in the labia majora or in the perineum. Because these tumors are apocrine in origin, the labia minora location is unusual. Hidradenomas are classically asymptomatic and most lesions are discovered during a routine pelvic examination. Curative treatment consists of local excision.

Vulvar Intraepithelial Neoplasm
The first two cases were described by Bowen, in 1912. The vulvar intraepithelial lesions are subdivided into vulvar epithelial neoplasia (VIN) I corresponding to mild dysplasia, VIN II similar to moderate dysplasia and VIN III, which corresponds to severe dysplasia or carcinoma in situ (CIS). VIN in young women is commonly associated with HPV. However, HPV is less frequently identified in VIN lesions of older women suggesting some other etiology. Itching is the
primary symptom in 50% of patients with in situ cancer. Other presenting complaints are the presence of a lump, bleeding and pain. Careful inspection of the external genitalia, including perianal areas, thighs and buttocks under a bright light and magnification is always helpful. Colposcopy is preferred any day.

Although, surgical excision of VIN is favored, patients typically do not require total vulvectomy. Wide local excision is usually successful, but an attempt should be made to obtain clear margins. The carbon dioxide (CO₂) laser has also been successfully used. It is used particularly in areas where excision hampers presentation of anatomy, such as in the clitoral/perianal region. Simple vulvectomy is recommended in patients with extensive Paget’s disease of the vulva or widespread VIN where it is difficult to rule out invasive cancer, even with multiple biopsies. Procedures performed for extensive VIN III or Paget’s disease includes total or partial vulvectomy, skinning vulvectomy and multiple wide excisions. These may result in large denuded areas requiring vulvar reconstruction.

**CANCER OF THE VULVA**

Carcinoma vulva is the fourth most common female genital tract malignancy. There has been an increase in the incidence in the past few decades. This can be attributed to the increased life expectancy of the female population and the increased incidence of HPV infection. Deoxyribonucleic acid (DNA) of HPV has been identified from preinvasive as well as invasive lesions of the vulva. Chronic immunosupression, systemic hypertension, diabetes mellitus and obesity are seen associated with vulvar cancer but no definite etiological link has been proved yet. It is reported that 13% of cases are associated with cancer in other sites like cervix, vagina and anal canal. This may be due to the common etiological factor, HPV infection. With better understanding of the lymphatic drainage of vulva, the surgical approach to vulvar cancer has drastically changed. The present surgical approach is more conservative. The advances in radiotherapy and chemotherapy have also contributed to the less radical surgical approach.

Most often it affects the inner edges of the *labia majora* or the *labia minora*. Less often, cancer occurs on the clitoris or in Bartholin’s glands. In the United States, vulvar cancer accounts for about 4% of cancers in the female reproductive organs and 0.6% of all cancers in women. Over 90% of cancers of the vulva are squamous cell carcinomas. The second most common type of vulvar cancer (about 2–4%) is melanoma. A small percentage of vulvar cancers develop from glands and are called adenocarcinomas. Adenocarcinomas can also form in the sweat glands of the vulvar skin. Paget disease of the vulva is a condition in which adenocarcinoma cells are found in the vulvar skin. Between 20% and 25% of patients with vulvar Paget disease also have an invasive adenocarcinoma of a Bartholin gland or sweat gland. In the remaining 75–80%, the malignant cells are found only in the skin’s top layer. Less than 2% of vulvar cancers are sarcomas, tumors of the connective tissues under the skin that tend to grow rapidly. Unlike other cancers of the vulva, vulvar sarcomas can occur at any age, including childhood.

Almost 85% of women with vulvar cancer are over 50 years of age and half are over 70 years of age, at the time their cancer is first diagnosed. However, 15% of new patients are under age 40. The average age of women diagnosed with invasive cancer is 70 years, whereas women diagnosed with noninvasive vulvar cancer are on average about 20 years younger. In general, vulvar cancer in younger women tends to be associated with infection with the high-risk HPV types. In elderly women, HPV is less likely to be a risk factor. Women who are infected with a high-risk HPV have a much higher risk of developing vulvar cancer if they smoke. The risk of vulvar cancer appears to be slightly increased by lichen sclerosus et atrophicus (LSA), with about 4% of women with LSA later developing vulvar cancer. Women with a family history of melanoma or dysplastic nevi (atypical moles) elsewhere on the body are at risk for developing a melanoma on the vulva.

Recent studies suggest that squamous cell vulvar cancer (the most common type) can develop in at least two ways. In about one-third to half of cases, HPV infection appears to have an important role. Vulvar cancers associated with HPV infection seem to have certain distinctive features. In addition to being younger, women with these cancers often have multiple areas of VIN elsewhere on their vulvas and are usually smokers.

The second process by which vulvar cancers develop does not involve HPV infection. Vulvar cancers not linked to HPV infection usually are diagnosed in older women (age 55–85) who rarely have VIN but often have LSA. DNA tests from vulvar cancers in older women not infected by HPV often show mutations of the p53 tumor suppressor gene.

The most common symptom of VIN is persistent itching that does not improve. However, many patients do not have symptoms. Areas of VIN are usually thicker and lighter in color than the surrounding skin. However, some cases of VIN can appear red, pink, or darker than the surrounding skin. The signs and symptoms of early invasive vulvar cancer are similar to those of symptomatic VIN. As invasion and growth progress, a distinct tumor is more likely to be recognized. The most common symptoms are a red, pink or white bump or bumps with a wart-like or raw surface. An area of the vulva may appear white and feel rough. About half of the women with vulvar cancer complain of persistent itching and a growth. Some also complain of pain, burning, painful urination, bleeding, and discharge not associated with the normal menstrual period. An ulcer that persists for more than a month is another sign.
The revised FIGO staging of carcinoma of the vulva is presented in Table 1.

Table 1: Revised FIGO staging of carcinoma of the vulva

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tumor confined to the vulva</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>Lesions ≤ 2 cm in size, confined to the vulva or perineum and with stromal invasion ≤ 1.0 mm*, no nodal metastasis</td>
</tr>
<tr>
<td>IB</td>
<td>Lesions &gt;2 cm in size or with stromal invasion &gt;1.0 mm*, confined to the vulva or perineum, with negative nodes</td>
</tr>
<tr>
<td>Stage II</td>
<td>Tumor of any size with extension to adjacent perineal structures (1/3 lower urethra, 1/3 lower vagina, anus) with negative nodes</td>
</tr>
<tr>
<td>Stage III</td>
<td>Tumor of any size with or without extension to adjacent perineal structures (1/3 lower urethra, 1/3 lower vagina, anus) with positive inguinal or femoral lymph nodes</td>
</tr>
<tr>
<td>IIIA</td>
<td>With 1 lymph node metastasis (≥ 5 mm), or 1-2 lymph node metastases(es) (&lt; 5 mm)</td>
</tr>
<tr>
<td>IIIB</td>
<td>With 2 or more lymph node metastases (≥ 5 mm), or 3 or more lymph node metastases (&lt; 5 mm)</td>
</tr>
<tr>
<td>IIIC</td>
<td>With positive nodes with extracapsular spread</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Tumor invades other regional (2/3 upper urethra, 2/3 upper vagina), or distant structures</td>
</tr>
<tr>
<td>IVA</td>
<td>Tumor invades any of the following: Upper urethral and/or vaginal mucosa, bladder mucosa, rectal mucosa, or fixed to pelvic bone, or Fixed or ulcerated inguinal or femoral lymph nodes</td>
</tr>
<tr>
<td>IVB</td>
<td>Any distant metastasis including pelvic lymph nodes</td>
</tr>
</tbody>
</table>

*The depth of invasion is defined as the measurement of the tumor from the epithelial stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion.

Table 2: 5-year surgical stages for cancer of vulva

<table>
<thead>
<tr>
<th>Stage</th>
<th>Relative 5-year survival rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>93</td>
</tr>
<tr>
<td>II</td>
<td>87</td>
</tr>
<tr>
<td>III/IVA</td>
<td>43</td>
</tr>
</tbody>
</table>

Staging of Cancer Vulva

The revised FIGO staging of carcinoma of the vulva is presented in Table 1.

Survival (Table 2)

A recent report from the Mayo clinic, divided patients into two groups—those with or without lymph node spread of the cancer. Women who had no lymph node spread had a 5-year survival of 96%. Those with spread to the lymph nodes had a 5-year survival of 64%.

Standard treatment in vulvar cancer is surgery with or without adjuvant radiation therapy.1,2 Because of the psychosexual consequences and significant morbidity associated with standard radical vulvectomy, there is a definite trend toward vulvar conservation and individualized management of patients with early vulvar cancer.

Differential Diagnosis

The differential diagnoses of vulvar carcinoma are unilocular cyst, Bartholin’s cyst, hemangioma, seborrhea, keratoma, hydradenoma and wart. Lichen sclerosus is one of the common conditions which presents with pruritus vulva. Since, there can be associated keratinizing squamous cell carcinoma, the vulva should be examined preferably with colposcopy and multiple biopsies should be taken. If there is a lesion the biopsy should be taken from the center of the lesion as well as from the periphery. Patients who have tumor with no distinct boundary, the biopsy can be directed after painting with acetic acid or toluidine blue. The abnormal area will be acetowhite when painted with acetic acid and bluish when painted with toluidine blue. In the case of Bartholin’s gland adenocarcinoma FNAC may be preferred. Positron emission tomography (PET) scan is evolving as an imaging technique which provides information about depth of invasion which is important in staging.

Management of Vulvar Carcinoma

Carcinoma In Situ

Vulvar intraepithelial neoplasia occupying nonhairly areas can be considered an epithelial disease; however, VIN occupying hairy sites usually involves the pilosebaceous apparatus and requires a greater depth of destruction or excision.

Standard treatment options:

- Wide local excision or laser beam therapy or a combination of both.
- Skinning vulvectomy with or without grafting.
- Use of 5% fluorouracil (5-FU) cream (response rate of 50–60%).3 The use of topical 5-FU is not a reliable first choice for treatment.

Stage I

Treatment options depend on the size and depth of the cancer and whether the patient also has VIN. For microinvasive lesions (< 1 mm invasion) with no associated severe vulvar dystrophy, a wide (5–10 mm) excision is indicated. For all other stage I lesions, if well lateralized, without diffuse severe dystrophy, and with clinically negative nodes, a radical local excision with complete unilateral lymphadenectomy should be performed.4 Candidates for this procedure should have lesions 2 cm or less in diameter with 5 mm or less invasion, no capillary lymphatic space invasion and clinically uninvolved nodes.5 A literature review suggests that the local recurrence rate is 7.2% after radical local excision compared with 6.3% after radical vulvectomy.6
If the cancer is larger and quite extensive, another option is a radical vulvectomy with bilateral inguinal node dissection. The definition of radical vulvectomy is being extended with the realization that the effect of radical surgery is limited by the closest resection margin rather than the achievement of total organ ablation. One study suggested that the margin of clearance of the tumor is the best predictor of local recurrence. All of the recurrences were with surgically free margins less than 8 mm.

**Stage II**

The treatment for most stage II vulvar cancers is partial radical vulvectomy and bilateral inguinal node dissection. Adjuvant local radiation therapy may be indicated for surgical margins less than 8 mm, capillary-lymphatic space invasion and thickness greater than 5 mm, particularly if the patient also has positive nodes.

**Stage III**

Some of these bulky cancers can be cured by radical operations—modified radical vulvectomy with inguinal and femoral node dissection. Radiation therapy of 45–50 Gy to the pelvis and groin is indicated when there is capillary-lymphatic space invasion and a thickness of greater than 5 mm, particularly if the nodes are involved.

For those patients unable to tolerate radical vulvectomy or who are deemed unsuitable for surgery because of site or extent of disease, radical radiation therapy may result in long-term survival. Where radiation therapy is being tested for primary definitive treatment of vulvar cancer, some prefer to add concurrent 5-FU or 5-FU and cisplatin.

**Stage IV**

- Radical vulvectomy and pelvic exenteration
- Surgery followed by radiation therapy to the vulva for large resected lesions with narrow margins. Localized adjuvant radiation therapy consisting of 45–50 Gy may also be indicated when there is capillary-lymphatic space invasion and thickness greater than 5 mm, particularly if the nodes are involved. Radiation therapy to the pelvis and groin should be performed if two or more groin nodes are involved.
- Radiation therapy of large primary lesions to improve operability followed by radical surgery. A radiation dose of up to 55 Gy with concomitant 5-FU has been suggested.

**Management of Early Vulvar Carcinoma (Flow charts 1 to 4)**

The management of vulvar carcinoma depends upon the site and size of the tumor, the depth of invasion and presence or absence of clinical node involvement.

As previously emphasized, radical vulvectomy (Whey’s method) is no longer advised for early vulvar cancer. Recent studies have proved that radical local excision irrespective of depth of invasion gives a cure rate which is comparable to radical vulvectomy with much less psychosocial sequelae.

Management of stage I lesion should be individualized. For patients with no clinically suspicious groin nodes, the preferred surgical management is conservative.

**Management of Stage IA**

If the tumor is < 2 cm in size and the depth of invasion is < 1 mm, wide radical excision should be preferred. Inguino-femoral lymphadenectomy is not advised for such a patient as the incidence of node involvement is negligible.

**Management of Stage 1B**

A lateral lesion which is defined as a lesion 1 cm lateral to the midline is less likely to metastasize to contralateral inguino-femoral lymph nodes (< 1%). If the lesion is < 2 cm in size and the depth of invasion is > 1 mm, lateral lesions are treated with radical local excision and unilateral inguino-femoral lymphadenectomy done through a separate
groin incision. This is based on the fact that metastasis rarely occurs in the skin bridge in patients without clinically involved groin needs. Both superficial and deep nodes should be removed. If only superficial groin dissection is done, there is a high incidence of groin recurrence. This was proved in a randomized controlled study among 143 patients by Frederick Stehman et al.

When radical local excision is done for lateral lesions of the vulva, at least a 1 cm grossly negative margin should be obtained. The depth of excision should be up to the level of the inferior fascia of the urogenital diaphragm. For lesions involving the lateral or posterior aspects of vulva, radical local excision is ideal. For anterior lesions, clitoris-savings surgeries with tumor free margin of minimum 8 mm should be preferred. In a younger patient, if the lesion involves the clitoris, chemoradiation is an alternative.

If ipsilateral lymph glands are positive for malignant cells chances of contralateral glandular involvement are 15%. Hence, if ipsilateral lymph nodes are found to be positive for malignant cells, bilateral lymphadenectomy should be done. Midline lesions are likely to metastasize to bilateral inguinofemoral lymph nodes and hence need bilateral lymphadenectomy.

If groin recurrence occurs, mortality is reported to be 90%. Patients who have 3 or more microscopically involved groin lymph nodes should undergo pelvic lymphadenectomy. An alternative is to give external radiation to pelvis and inguinofemoral lymph nodes. A randomized control trial by GOG group with surgery and radiotherapy for the inguinofemoral lymph nodes showed that, patients receiving radiotherapy had decreased groin recurrence. Hence it is better to give adjuvant radiation if the unilateral groin nodes are found to be positive.

Patients who have associated non-neoplastic lesion like lichen sclerosus should be treated based on their age. In younger women, a conservative approach with radical local
excision of the malignant lesion and topical steroids can be advised for lichen sclerosus or squamous hyperplasia. But if they have vulvar intraepithelial neoplasia (VIN), it requires superficial local excision of the lesion.

**Recurrent Vulvar Cancer**

Treatment options will depend on how soon the cancer comes back and whether it is local, regional, or distant. If the recurrence is local, it may still be possible to remove the cancer by surgery or by using combinations of chemotherapy, radiation therapy and surgery. When local recurrence occurs more than 2 years after the initial treatment, the prognosis is better than if the cancer had recurred sooner. When the cancer is unresectable, chemotherapy and/or radiation therapy may be used to help relieve symptoms such as pain caused by the cancer, or to shrink the tumor so that surgery may become an option.

**Case 1**

A 62-year-old postmenopausal multiparous female patient came with a large ulcer in vulvar region since few months. On examination, an ulcerative growth involving bilateral labia majora in lower two-thirds was seen. Upper one-third of labia majora had hypopigmented patches with thickening. Foul smelling discharge was present. Biopsy confirmed the diagnosis of invasive squamous cell carcinoma of vulva. Sonography of abdomen and pelvis was normal and magnetic resonance imaging (MRI) of pelvis revealed mass arising from labia majora bilaterally extending into lower one-third of vagina. Bilateral inguinal and external iliac lymph nodes were enlarged. Total vulvectomy with partial vaginectomy with perineal reconstruction and diversion colostomy was done on December 3, 2004 (margins were sent for histopathology, were found free of tumor on frozen section. Left iliac fossa sigmoid loop colostomy was done. Perineum was reconstructed with bilateral rotation flaps taken from medial side of thighs). Histopathology revealed invasive squamous cell carcinoma of vulva. The patient received radiotherapy (teletherapy 37 sittings and brachytherapy three sittings) till May, 2005. Computed tomography of abdomen and pelvis done in August, 2005 revealed multiple enlarged lymph nodes along the right external iliac and both obturator vessels. Received three cycles of chemotherapy (CPL, 5FU and taxol). Patient developed vulvar ulcers and swelling of right lower limb in October, 2005 and died after 6 months (Figs 1A to E).

**Case 2**

A 57-year-old postmenopausal lady, presented with a fungating mass in the vulvar region of 3 months duration, was operated for vulvar cancer 2 years prior in an outside hospital. After investigations, she underwent a radical vulvectomy with bilateral groin dissection. The urethra was spared since on frozen section, it was found to be uninvolved by tumor. Postoperatively she received radiation treatment. Eighteen months later, the patient had a second recurrence in the perineal region. After counseling, she was taken up for an anterior exenteration with ileal conduit with wide local resection of vulva (Figs 2A to F).

**OTHER TYPES OF VULVAR MALIGNANCIES**

**Melanoma**

Melanoma is the second most common vulvar cancer. It usually presents as a raised pigmented lesion. The most
Fig. 1C: Perineal reconstruction with bilateral rotation flaps from medial side of thighs

Fig. 1D: End result after surgery

Fig. 1E: Excised specimen from vulva, perineum and lower vagina

Fig. 2A: Fungating recurrent mass

Fig. 2B: After wide excision, urethra intact (confirmed to be free of tumor on frozen section)
common site of the lesion is the labia minora and clitoris. FIGO staging applicable to squamous cell carcinoma is not applicable to melanoma. The lesion is staged based on the vertical thickness of the lesion measured from the tip of the granular layer to the deepest point of invasion. Melanoma is a very small lesion and the prognosis depends on the depth of invasion rather than the diameter. Incidence of lymph node metastasis correlates with the vertical thickness of the lesion.

Several microstaging systems have been described for vulvar melanoma (Table 3).

### Management

Wide radical excision with a 2 cm margin is the preferred mode of treatment. Lymphadenectomy can be deferred for lesions

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**Table 3: Microstaging systems of vulvar melanoma**

<table>
<thead>
<tr>
<th>Clark-level</th>
<th>Chung-depth of invasion</th>
</tr>
</thead>
<tbody>
<tr>
<td>I Intraepithelial</td>
<td>Intraepithelial</td>
</tr>
<tr>
<td>II Into papillary dermis</td>
<td>&lt; 1 mm from granular layer</td>
</tr>
<tr>
<td>III Filling dermal papillae</td>
<td>1.1–2.0 mm from granular layer</td>
</tr>
<tr>
<td>IV Into reticular dermis</td>
<td>&gt; 2 mm from granular layer</td>
</tr>
<tr>
<td>V Into subcutaneous fat</td>
<td>Into subcutaneous fat</td>
</tr>
</tbody>
</table>

Source:
< 0.76 mm thick with no lymph vascular space invasion. For patients with lesions larger than this, groin dissection is recommended. Patients who have deeply invasive lesion with more than 4 mm tumor thickness have high-risk of systemic metastasis. Hence, they may not benefit from regional lymphadenectomy. Palliative radiation can be given for brain and bone metastases. The prognosis is not as good as squamous cell carcinoma and the overall 5 years survival rate is only 25–50%. Patients who have lesions invading 1 mm or less will have good prognosis but for patients who have greater invasion, prognosis is worse. Additional prognostic factors are age, presence of multiple lesions, tumor ulceration, midline location of tumor, histological growth pattern, aneuploidy and lymph vascular space involvement.

**Bartholin’s Gland Carcinoma**

It is a very rare form of vulvar cancer. Primary tumor is very rare occurring in 2–7% of vulvar malignancies. It usually occurs in postmenopausal women. The Bartholin’s gland are situated posterolateral to the labia minora. The duct opens into the introitus at junction between the anterior two-third and posterior one-third of the labia minora. The duct is line by stratified squamous epithelium and it changes to transitional epithelium at the distal end. Malignant tumors can arise either from the gland or the duct. Because there are several types of cells in the duct and the gland, several types of malignancies can arise. This can be adenocarcinoma, squamous carcinoma, transitional cell carcinoma, adenosquamous carcinoma or adenoid cystic carcinoma.

**Signs and Symptoms**

The initial symptoms is usually a mass in the vulva and pain. Malignancies can be mistaken for benign cysts or abscesses which are more common.

**Treatment**

As in squamous carcinoma of the vulva, the management can be conservative. Wide local excision is advised for the primary tumor as the gland is situated deep in the vulva which entails deep dissection. Since it is difficult to maintain tumor-free margin during the dissection, postoperative radiotherapy is advised. Prognosis is similar to that of squamous cell carcinoma.

**Paget’s Disease**

Paget’s disease of the vulva is usually an intraepithelial lesion. Rarely, it is found to be invasive. Usually it presents as an erythematous well-defined lesion with irregular borders. Microscopically, it is characterized by the presence of Paget’s cells which are large eosinophilic cells. These cells are seen spread in the dermis or in the dermal appendages. Four clinical entities of Paget’s disease are identified.

**Noninvasive Paget’s Disease**

This is an adenocarcinoma in situ. It can be treated by wide local excision. The final diagnosis is by examination of the excised lesion.

**Invasive Paget’s Disease**

In invasive Paget’s disease, there will be invasion into the surrounding dermis and subcutaneous fat. Since there is invasion, groin nodes are involved in about 50% of cases. Hence groin lymphadenectomy is advised if the lesion is found to be invasive after excision.

**Third Type**

The third type of the lesion is found to be associated with underlying adenocarcinoma of sweat glands or Bartholin’s gland.

**Fourth Type**

The fourth type is characterized by associated extragenital Paget’s disease, usually of the breat or rectum.

Local recurrence is common after excision. This may be due to the associated malignancy of underlying sweat glands.

**Basal Cell Carcinoma**

These are rare tumors arising from skin or hair follicles of the vulva. They are invasive but rarely metastatic. Management is by wide local excision.

**Sarcoma**

Sarcoma of the vulva is a heterogeneous group of tumors, the most common of which is leiomyosarcoma. This is usually seen in the labium majus as a large tender mass. Lymphatic involvement is rare. Treatment option is wide local excision.

Other rare sarcomas are epitheloid sarcoma and rhabdomyosarcoma. Epitheloid sarcoma may mimic Bartholin’s cyst. They behave more aggressively than other sarcoma. Wide excision is the treatment for early disease. Rhabdomyosarcoma is usually found in children. Radical surgery was the standard approach previously but presently they are managed with wide local excision followed by chemoradiation. With this multi-model approach, 5-year survival rates have improved.

**REFERENCES**

INTRODUCTION
Cervical intraepithelial neoplasia (CIN) includes a group of different intraepithelial lesions, which cytologically and histologically differ from normal but which do not possess all criteria of malignancy. It includes all grades of dysplasia and carcinoma in situ (CIS).

CURRENT CONCEPT OF DEVELOPMENT OF CERVICAL CANCER
Cervical cancer does not develop suddenly from normal tissue but it is preceded by inflammatory pattern, which progresses through various grades of dysplasia and then CIS and finally invasion occurs. Hence, CIN is considered as precancerous lesion. This has been confirmed by various experimental studies and clinical studies (retrospective and prospective).

Experimental Studies
Effect of different oncogenic agents was studied on animals by different authors. Wentz applied methylchloranthrene to cervix of young female mice. Patten used young adult female mice and inoculated them with trichomonas organism; Christopherson used podophyllin in mice.

It was noted that first reaction was inflammation followed by mild and then moderate dysplasia and if application was discontinued at any of these stages, changes reverted back to normal suggesting that process is reversible up to stage of moderate dysplasia, although moderate dysplasia took longer than mild dysplasia to revert to normal. Once the changes of severe dysplasia occurred, even if application of carcinogen was stopped, the disease process did not show regression suggesting that severe dysplasia is an irreversible entity for the rest of the life in that animal; it remains static and does not progress further indicating that it is still dependent on carcinogen for its progression. If application of carcinogen is continued, the lesion progresses to CIS, which is not only irreversible but also liable to progress in absence of carcinogen thus indicating that CIS cell has attained autonomous growth potential.

Clinical Studies Retrospective
Schottlander in 1912 found on histopathology of seven cases of cancer cervix that by the side of cancer growth epithelium showed malignant changes with no involvement beyond basement membrane. He called it cervical growth spreading into epithelium at periphery. It was later confirmed as CIS.

Encouraged by this study, Telinde reviewed slides of patients operated for cancer cervix. He found evidence of dysplasia and CIS adjacent to invasive lesion.

Prospective Studies
Women who refuse to undergo any treatment for dysplasia have shown that CIN is a precancerous lesion, the mean time required to transit from index level dysplasia to CIS is as shown in Table 1.

Relative risk of dysplasia progressing to cancer as compared to control is as follows:
- Mild dysplasia carries nine-fold relative risk
• Moderate dysplasia carries 26.3-fold relative risk
• Severe dysplasia carries 83.3-fold relative risk
• Peterson found that in 10 years, one-third of cases of CIS progressed to invasive cancer.

**Etiology**

Etiology of CIN is same as that of cervical cancer. Cervical carcinogenesis is a very complex process. Basically, it is an interplay between host resistance or immune response and effect of carcinogen. The exact cause is not known. There probably is not a single cause but a combination of contributory factors which ultimately lead to the disease. These factors are all related to social and sexual behavior pattern. There is initially a process of initiation followed by process of acceleration. It is caused by some sexually transmitted agent, may be DNA of sperm (Reid) or viruses like herpes simplex or human papilloma virus (HPV) infection. The other important epidemiological factors are age at sexual initiation, age at first conception, interval between subsequent conceptions, poor obstetric care, multiple pregnancies, multiple sexual partners, unstable sexual relations, cigarette smoking, malnutrition and contraceptive practice.

**Natural History**

Patient may remain asymptomatic or may complain of chronic leukorrhea or contact bleeding.

On clinical examination, cervix may appear absolutely healthy or may show evidence or erosion or endocervicitis. The natural history of cervical cancer is shown in Flow chart 1.

**METHODS OF DIAGNOSIS**

**Cytology Screening**

It is the most simple and economical method. It is not 100% accurate, it is credited with 87% accuracy. It has a certain false-negative rate varying from 1.8% to 20% from laboratory to laboratory. Normal cytological findings are shown in Figures 1A to D.

**Factors Limiting Pap Test Sensitivity**

• Presence of few abnormal cells
• Small size of lesion

**Cytologic Diagnosis of Dysplasia**

There is dissociation between nuclear development and maturation of cytoplasm. There is a malignant looking nucleus surrounded by adequate normal cytoplasm. There is increase in nuclear/cytoplasmic (N/C) ratio, evidence of mitosis, hyperchromasia, variation in size and shape of cells, coarse chromatin clumping, margination of chromatin clumps to the periphery of nuclear border, irregular nuclear border, thickening of nuclear membrane. According to Bethesda classification¹ nuclear abnormality in mature cells represents low-grade squamous intraepithelial lesion.
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(LGSIL) and nuclear abnormality in immature cells represent high-grade squamous intraepithelial lesion (HGSIL).

**Cytologic Grading of Dysplasia**

Richart grades them according to number of parabasal cells with abnormal nuclear pattern (Figs 2A to C)
- Less than 10% parabasal cells—mild dysplasia
- 10–20% parabasal cell—moderate dysplasia
- More than 30% parabasal cells—severe dysplasia.

Reagen grades them according to nuclear size
- Study of 2,500 (normal) cells—average nucleus size 7µ
- Study of 5,000 (dysplastic) cell—average nucleus size 14µ
- Study of 6,500 (CIS) cells—average nucleus size 13µ.

**Argyrophilic Nucleolar Organizer Region**

Argyrophilic nucleolar organizer region (AgNOR) is a new molecular tumor marker, which stands for silver-stained nucleolar organizer regions: DNA is present in dysplastic cells. They appear as black dots, which increase in number but decrease in size with advancing dysplasia. The lesions with low counts often regress, whereas those with high counts progress and need treatment.

**HPV Testing**

Eighty percent ascus and LSIL positive smears are preceded by HPV infection in young women whereas 80% are transitory and self-limited, and disappear over a period of 18 months or so; only 20% persist and form a high-risk group beyond 30 years of age. Incorporating HPV testing in cytology screening improves the predictive value, reduces unnecessary colposcopy referral and overtreatment but justifies follow-up in persistent cases.

The HPV testing is done either by study of cells in liquid-base cytology or endocervical secretion and self-obtained vaginal swab. Combined HPV testing Pap smear yields 96% sensitivity as compared to only 60–70% with Pap smear alone.

**Liquid Based Cytology**

Here the plastic (not wooden) spatula is placed in a liquid fixative (buffered methanol solution) instead of smearing on a slide. This removed the blood, mucus and inflammatory cells. The suspended cells are then gently sucked onto the filter membrane and the filter is pressed onto a glass slide to form a thin monolayer, and then it is stained. The liquid can also be employed to test HPV infection, making it a cost-effective technique. The cells wash off plastic device more than wooden one and the fixation solution contains hemolytic and mucolytic agents.

Automated computerized image processor eliminates 25% most likely negative smears and 75% are selected for cytotechnician screening.

**Colposcopy**

Colposcopy alone is credited with accuracy of 80% combined use of cytology and colposcopy increases the diagnostic accuracy to 98.9%. Both are complementary to each other although both have their failures. Cytology evaluates morphologic changes in exfoliated cells whereas colposcopy evaluates mainly changes in the terminal vascular network of cervix, which reflects biochemical and metabolic changes in tissue. The entire transformation zone should be seen by colposcopist before and after application of 3–5% acetic acid.

In the interpretation of colposcopy findings, occurrence of white epithelium, mosaic or punctuations are significant findings in CIN lesions. If abnormal vasculature or alteration in tone opacity and color is noted, the lesion is most probably already overt cancer. Normal colposcopy findings are shown in Figures 3A and B.

International Federation for Cervical Pathology and Colposcopy has revised the colposcopic terminology since 2002, as follows:

Colposcopic findings suggestive of LSIL includes lesions with indistinct borders, fine punctuations, small size mosaic and absence of atypical vessels (Figs 4A to D).

Colposcopic findings suggestive of HSIL includes lesions with distinct borders, coarse punctuations, large size mosaic and atypical vessels.

Colposcopy can also help to take precise biopsies from most abnormal area on transformation zone to arrive at accurate cyto-histo correlation.
Colposcopy plays a very important role in decision making about conservative management of CIN by ablation or excisional procedure or combination of both technics.

**Visual Inspection after Painting with Acetic Acid**

In countries with low resource setting, where routine colposcopy cannot be practiced, low cost methods for identifying abnormal areas have to be evolved. One such method is visual inspection after painting with acetic acid (VIA). Patients with abnormal findings should have biopsy done. Sensitivity of VIA is comparable to conventional Pap. Specificity of VIA is comparable to colposcopy.

**Endocervical Curettage**

Endocervical curettage is a must along with biopsy taken under colposcopic control. Results of endocervical curettage are controversial. Results are usually negative or unsatisfactory if patient has normal squamous and/or columnar epithelium. If patient has frank invasive cancer, large chunks of tissue are obtained by this technique. If material obtained by this technique consists of small fragments of neoplastic tissue, then it may be impossible to differentiate between dysplasia, CIS or microinvasive cancer (Figs 5A to D) due to poor orientation of tissue fragments or lack of sufficient cervical epithelium or stroma to establish the diagnosis. In such cases, conization is indicated.

**Microcolpohysteroscopy**

In 1984, Soutter and associates\(^2\) reported use of microcolpohysteroscopy to define extent of endocervical involvement of CIN, when upper limit of the lesion could not be seen at colposcopy. They demonstrated good correlation between microcolpohysteroscopy and histological measurement.
Schiller Iodine Test

This test was evolved by Dr. Schiller in 1938. This test has a definite place wherever colposcopic facilities are not available. It is based on the principle that stratified epithelium is rich in glycogen whereas glandular epithelium, metaplastic epithelium, dysplastic and neoplastic epithelium lack glycogen. In this test, cervix is painted with solution of iodine and potassium iodide, which stains glycogen containing epithelium dark brown. Nonstaining areas on cervix are called Schiller positive areas and systemic biopsies from these Schiller positive areas are important to achieve good cyto-histo correlation.

Histology

Cytologic diagnosis has to be validated by histological examination before instituting any kind of therapy. The various types of biopsies that can be taken are:

- Four quadrant biopsy (obsolete in today's practice with colposcopy)
- Colposcopically directed biopsy with endocervical curettage
- Large loop excision of transformation zone (LLETZ) or loop electrosurgical excision procedures (LEEP)
- Cone—indicated in endocervical lesions.

Limitations of Punch Biopsy

- Tissue may be crushed
- Tissue may be of small size. False-negative rate of small biopsy procedure (54%) is of concern, particularly if microinvasion or invasive lesion is missed.
- Tissue may not include stroma.

Low Voltage Diathermy Loop Biopsy

- Produces samples of greater dimensions
- Hemorrhage can be controlled
- Sophisticated equipment required
- Artifactual damage minimum
- Larger biopsies obtained—so diagnoses of micro or invasion easily made
- False-negative rate of biopsy minimized.

Histologically cervical intraepithelial neoplasia is characterized by:

- Disintegration of regular stratification (loss of stratification)
- Depolarization of cells within tissue (loss of polarization)
- Disintegration of differentiation (proliferation of basal cells with crowding and mitosis).

Histological Grading (Novak and Woodruff)

- Mild dysplasia—undifferentiated cells limited to lower one-third of epithelium.
- Moderate dysplasia—50–75% thickness of epithelium composed of undifferentiated cells.
- Severe dysplasia—full thickness of epithelium composed of neoplastic cells except for a thin line of flattened and mature squamous cells at the top.
- Carcinoma in situ—a lesion in which all or most of epithelium shows cellular features of cancer but no invasion in the underlying stroma.

These changes may also be seen in endocervical gland epithelium.

Deoxyribonucleic Acid Analysis

Major difficulty lies in separating CIN lesion that is neoplastic from those which are reparative or metaplastic in character. By light microscopy, it is not easy to distinguish between immature metaplasia or beginning of neoplasia. Deoxyribonucleic acid (DNA) analysis can help in such cases. There are two techniques:

1. Chromosomal karyotyping: It is done on fresh tissues.
2. Spectrophotometric analysis: It is done on preserved cytologic and histologic samples.

Aneuploidy is hallmark of malignant potential, because it is evidence of major mitotic defects with resultant increase and decrease in chromosomal numbers. It indicates that CIN carries neoplastic potential and hence must be eradicated by treatment. Polyploidy or diploidy suggests that CIN changes are due to reparative or metaplastic activity and hence can be left alone.
NEW CERVICAL CANCER SCREENING RECOMMENDATIONS—ACOG GUIDELINES

Today, new recommendations for cervical cancer screening are being released by two separate groups; the US Preventive Services Task Force (USPSTF) and a multidisciplinary partnership among the American Cancer Society (ACS)/American Society for Colposcopy and Cervical Pathology (ASCCP)/American Society for Clinical Pathology (ASCP).

Key recommendations in the guidelines are shown in Table 2. Although the two sets of guidelines were developed independently, they are generally consistent.

### MANAGEMENT OF CERVICAL INTRAEPITHELIAL NEOPLASIA

Prophylactic management involves the following:
- Keeping epidemiological factors in mind, identification of the “high-risk” group from population.
- Annual cytologic screening of the high-risk group.
- Early diagnosis and prompt treatment of inflammation.

#### Management of Patients with Abnormal Cytology (Flow chart 2)

There are three arms of management:
1. Follow-up

#### Table 2: The US Preventive Services Task Force (USPSTF) and American Cancer Society (ACS)/American Society for Colposcopy and Cervical Pathology (ASCCP)/American Society for Clinical Pathology (ASCP) guidelines at a glance

<table>
<thead>
<tr>
<th>Population</th>
<th>USPSTF</th>
<th>ACS/ASCCP/ASCPs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Younger than 21 years</td>
<td>Recommends against screening Grade D recommendation</td>
<td>Women should not be screened regardless of the age of sexual initiation or other risk factors§</td>
</tr>
<tr>
<td>21–29 years</td>
<td>Recommends screening with cytology every 3 years Grade A recommendation</td>
<td>Screening with cytology alone every 3 years is recommended.</td>
</tr>
<tr>
<td>30–65 years</td>
<td>Recommends screening with cytology every 3 years or for women who want to lengthen the screening interval, screening with a combination of cytology and HPV testing every 5 years Grade A recommendation</td>
<td>Screening with cytology and HPV testing (cotesting) every 5 years (preferred) or cytology alone every 3 years (acceptable) is recommended</td>
</tr>
<tr>
<td>Older than 65 years</td>
<td>Recommends against screening women who have had adequate prior screening¹ and are not otherwise at high-risk for cervical cancer Grade D recommendation</td>
<td>Women with evidence of adequate negative prior screening. Screening should not be resumed for any reason, even if a woman reports having a new sexual partner</td>
</tr>
<tr>
<td>After hysterectomy</td>
<td>Recommends against screening in women who have had a hysterectomy with removal of the cervix and who do not have a history of a high-grade precancerous lesion (i.e. CIN 2 or 3) or cervical cancer</td>
<td>Women of any age following a hysterectomy with removal of the cervix who have no history of CIN2+ should not be screened for vaginal cancer. Evidence of adequate negative prior screening is not required. Screening is not required. Screening should not be resumed for any reason, including if a woman reports having a new sexual partner</td>
</tr>
<tr>
<td>HPV vaccinated</td>
<td>Women who have been vaccinated should continue to be screened</td>
<td>Recommended screening practices should not change on the basis of HPV vaccination status</td>
</tr>
</tbody>
</table>

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¹These guidelines were developed to address cervical cancer screening in the general population. These guidelines do not address special, high-risk populations who may need more intensive screening. These special populations include women (1) with a history of cervical cancer; (2) who were exposed in utero to diethylstilboestrol (DES), and (3) who are immune-compromised [e.g. infection with human immunodeficiency virus (HIV)].

²The USPSTF recommendations are based on its assessment of net benefit—identified benefits minus identified harms. Interventions that are deemed to have substantial net benefit receive an A grade; interventions with moderate to substantial net benefit receive a B grade; interventions with small net benefit receive a C grade; interventions that have no or negative net benefit (have harms that exceed the benefits) receive a D grade. If the available evidence does not meet USPSTF standards, an “I statement” is issued. Each letter grade is accompanied by a suggestion for practice. For A and B recommendations, the suggestion is to “offer/provide this service.” For D recommendations, the suggestion is to “recommend against” the use of this service.

§The majority of recommendations are “strong,” meaning that the group is confident that further research would be unlikely to change the recommendation, based on the overall quality of the available evidence, the prospect of obtaining better evidence, and the balance between benefits and harms. The strength of each recommendation is noted in the individual working group reports in an outline supplement.

‡When to begin screening was address at the 2009 Practice Improvement in Cervical Screening and Management (PICSIM) symposium on management of cervical abnormalities in adolescents and young women. This question was not part of the review of the new guidelines.

§Adequate negative prior screening is three consecutive negative cytology results or two consecutive negative cotests within the 10 years before cessation of screening, with the most recent test occurring within the past 5 years.

Abbreviations: HPV, human papilloma virus; CIN, cervical intraepithelial neoplasia; USPSTF, US Preventive Services Task Force; ACS, American Cancer Society; ASCCP, American Society for Colposcopy and Cervical Pathology; ASCP, American Society for Clinical Pathology
2. HPV DNA testing
3. Colposcopy
   Decision is based on:
   - **Age of the patient**: Young patients in 20–30 years age group may be asked to come for follow-up as they are less likely to have invasive disease, whereas patient in age group late 30s and 40s must be subjected to colposcopy and directed biopsy to rule out invasive pathology.
   - **Severity of abnormality**: Low-grade squamous intraepithelial lesion may be asked to undergo repeat smear at 3–6 months follow-up but HGSIL must be subjected to colposcopy and biopsy.
   - Facilities of colposcopy versus HPV DNA testing.
   - HPV DNA testing facilities can decrease the load on colposcopy clinics. Patients with HPV type 16 and 18 positivity call for immediate treatment or follow-up at shorter intervals and patients who are type 6 and 11 positive may be asked to undergo follow-up at longer intervals. Large number of studies on HPV positive patients have shown that it takes as much as 2 years to get null effect on cytology and colposcopy following HPV infection.
   - Patients compliance in terms of follow-up.

**TREATMENT OF LOW GRADE SQUAMOUS INTRAEPITHELIAL LESION**

- Establish accurately type and extent of the lesion by cytology, colposcopy and biopsy
- Improve general health of individual so as to improve host response and immunity
- Treat specific inflammatory agent
- Close observation of lesion for progression or regression
- HPV DNA analysis, if facilities available
- Age and parity
- Use of barrier contraceptives.

**Actual Management of High-grade Squamous Intraepithelial Lesion**

About 20 years ago, only accepted treatment of CIN was hysterectomy with wide vaginal cuff. The reason was impossibility of evaluating extent of lesion. All the tissue that was involved with the pathological process had to be removed.

Increasing use of colposcopy in past decade has revolutionized the management of CIN. It has led to conservatism. Hysterectomy is considered as over treatment and unnecessary. The basic philosophy in treatment of CIN is that CIN is a local disease and has not spread into underlying stroma or lymphatic channels, therefore complete removal of pathological tissue is considered satisfactory. The modalities of tissue removal are:

- **Tissue destruction by ablative techniques**:
  - Electrocautery or diathermy
  - Cryosurgery
  - Laser therapy.
- **Surgical removal or excisional techniques**:
  - LLETZ/LEEP
  - Conization
  - Hysterectomy.
Local Destruction of Cervical Intraepithelial Neoplasia

Most important colposcopy centers now accept this method provided following criteria are strictly met with:

- Patient is seen and assessed by expert colposcopist
- Colposcopist is able to see the lesion in its entirety
- Colposcopically directed target biopsy from most abnormal area rules out invasion
- Destruction of the tissue is carried out under colposcopic control
- Adequate post-treatment cytology and/or colposcopy follow-up is possible.

**TREATMENT MODALITIES (TABLE 3)**

- Local destructive methods—when entire abnormal T zone is visible on colposcopy
- Local excisional procedures—when lesion extends into endocervical canal (unsatisfactory colposcopy)
- Combination of two procedures—when cervical lesion spreads into endocervical canal and extends in upper one-third of the vagina.

**Destructive Methods**

- Cryotherapy
- Electrocoagulation diathermy
- Cold coagulation
- Laser vaporization.
  
  One must aim for depth of destruction or excision of at least 5 mm.

**Cryotherapy**

- Cryonecrosis affected by crystallization of intracellular water

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**Table 3: Comparison of different methods of treatment of dysplasia and cervical intraepithelial neoplasia**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cryotherapy</th>
<th>Coagulation</th>
<th>Laser ablation</th>
<th>Conization knife</th>
<th>Laser conization</th>
<th>LLETZ</th>
<th>LEEP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Place</td>
<td>OPD</td>
<td>OT</td>
<td>OPD</td>
<td>OT</td>
<td>OPD or OT</td>
<td>OPD</td>
<td>OPD</td>
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<td>Anesthesia</td>
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<td>GA</td>
<td>Nil</td>
<td>GA</td>
<td>Local</td>
<td>Local</td>
<td>Local</td>
</tr>
<tr>
<td>Instrument’s cost</td>
<td>Cheap,</td>
<td>Cheap,</td>
<td>Expensive</td>
<td>Cheap not</td>
<td>Expensive, not</td>
<td>Expensive,</td>
<td>Expensive,</td>
</tr>
<tr>
<td>and portability</td>
<td>portable</td>
<td>portable</td>
<td></td>
<td>portable</td>
<td>portable</td>
<td>portable</td>
<td>portable</td>
</tr>
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<td>Risk of equipment</td>
<td>Nil</td>
<td>Nil</td>
<td>Yes</td>
<td>Nil</td>
<td>Yes</td>
<td>Nil</td>
<td>Nil</td>
</tr>
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<td>Complications during</td>
<td>Nil</td>
<td>Nil</td>
<td>Yes</td>
<td>Nil</td>
<td>Yes</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depth of destruction</td>
<td>4–5 mm</td>
<td>8–10 mm</td>
<td>7 mm</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Pain</td>
<td>Nil</td>
<td>Painful</td>
<td>Slight</td>
<td>–</td>
<td>Slight</td>
<td>Nil</td>
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<tr>
<td>Bleeding</td>
<td>Nil</td>
<td>+</td>
<td>Nil</td>
<td>++</td>
<td>Slight</td>
<td>Slight</td>
<td>Slight</td>
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<tr>
<td>Sepsis</td>
<td>Discharge</td>
<td>+</td>
<td>Nil</td>
<td>+</td>
<td>Slight</td>
<td>Slight</td>
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<tr>
<td>Healing</td>
<td>6–8 weeks</td>
<td>6–8 weeks</td>
<td>4 weeks</td>
<td>6–8 weeks</td>
<td>4 weeks</td>
<td>4–6 weeks</td>
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<td>Tissue-for histology</td>
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<td>NA</td>
<td>NA</td>
<td>Available with</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>excision methods</td>
<td>histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cure rate</td>
<td>90%</td>
<td>90–95%</td>
<td>90–97%</td>
<td>90–95%</td>
<td>90–95%</td>
<td>85–90%</td>
<td>90–95%</td>
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<tr>
<td>Pregnancy complications</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>Stenosis</td>
<td>Cervical</td>
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<td>cervix, abortion,</td>
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<td>premature</td>
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<td></td>
<td></td>
<td>labor, cervical</td>
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<td></td>
<td></td>
<td></td>
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<td>dystocia with</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>excisional</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>methods</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postoperative</td>
<td>Indrawn</td>
<td>Indrawn</td>
<td>Seen</td>
<td>Visible</td>
<td></td>
<td></td>
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<tr>
<td>transformation zone</td>
<td></td>
<td></td>
<td></td>
<td>with zone</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>excisional</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**Abbreviations:** NA, not available; GA, general anesthesia; OPD, outpatient department; OT, operation theater
• Freeze-thaw-freeze technique gives best results
• Depth of ablation 4–5 mm
• Cure rate 27–96%.7
• Gases used are carbon dioxide (CO₂) (–60°C), nitrous oxide (N₂O) (–80°C), freon (–60°C).

Electrocoagulation Diathermy8,9
Using needle and ball electrodes with electrosurgical unit
• Destroys tissue by fulguration and coagulation
• Temperature of over 700°C is produced
• Procedure is painful
• General anesthesia is required
• Depth of destruction 7 mm
• Cure rate 88–97%.10

Cold Coagulation
• Destruction of tissue by application of thermosound heated 120°C.
• Treatment for 20 seconds given over 5 lapping areas
• Equipment simple and inexpensive
• Local anesthesia required
• Cure rate 94%.10

Laser Vaporization
• Boils intracellular water—producing steam and exploding the cell
• CO₂ laser is well suited for cervical lesions
• Power density and dwell time may be varied
• Power may be continuous or pulse mode
• Equipment is expensive
• Vaporization technique easy to learn
• Depth of destruction can be controlled
• Local anesthesia required
• Complication—primary or secondary hemorrhage may occur
• It is the mode of choice for CIN that extends into vaginal fornices.

Excisional Methods
Indicated in unsatisfactory colposcopy
• LLETZ or LEEP (Can be used as an alternative to cone biopsy).
• Cone
  – Cold knife cone
  – Laser cone—described by Dorsey and Diggs, in 1979
  – Tissue available for histological evaluation
  – Helps to judge completeness of excision
  – Incomplete excision—indicator of patients at high risk of recurrence.

LLETZ
• Prendiville et al. was the first to describe LLETZ in 1989:11
  – Loops of various dimensions are required
  – Good diathermy machine with steep power versus impedance curve required.
• Procedure under local anesthesia
• Under colposcopic control
• Complications:
  – Vaginal bleeding and discharge for 2–12 weeks12
  – Secondary hemorrhage requiring hospitalization12
  – Cervical stenosis13
  – T zone visible—73–90% of patients12,13
  – Success rate 95–97%.11–13
• Advantages: Tissue available for histopathological evaluation.14

Surgical Procedures

Conization
It can be of two types:
1. Diagnostic (small cone)
2. Therapeutic (large cone).

Indications of Small Cone
If conization is purely done as diagnostic procedure (to rule out invasion) and hysterectomy is the method of choice, then a small cone biopsy or ring biopsy is necessary to arrive at the diagnosis. If conization is used as thera peutic procedure then one has to do a large conization.

If upper limit of the lesion is seen through the colposcope, in other words if normal columnar epithelium is seen above lesion, then it can be assumed that there is no abnormality at higher level and under these circumstances it is unnecessary to remove whole of endocervical canal.15,16 It is desirable to leave intact as much of endocervical canal as possible for following reasons:
• Hemorrhage is rarely a problem with small cone
• Endocervical canal, which is so important for fertility, is retained
• Internal os is left intact.
  If lesion extends beyond colposcopic vision, then whole of endocervical canal must be sacrificed.

Indications of Large Cone
• If lesion extends beyond colposcopic vision
• If cone is being used as the therapeutic procedure in young patient desires fertility or uterus
• If cyto is positive and colpo is negative.
Management of Large Lesion Involving Endocervical Canal, Whole of Ectocervix and Upper Part of the Vagina

If the lesion is involving whole of ectocervix and part of vaginal epithelium, in such a case amputation of cervix with excision of abnormal vaginal epithelium is the line of treatment, or combination of cone and destructive methods may be applied.

Hysterectomy with Vaginal Cuff

Although it is considered as over treatment by promoters of therapeutic conization, it is the line of treatment in following cases:

- Presence of other gynecological problem like dysfunctional uterine bleeding (DUB), prolapse, fibroid.
- Recurrent lesions.
- Residual lesions after conization.
- Multiparous patients who will not be able to come for follow-up.
- High-risk cases on epidemiological basis.
- Patient over 40 years.
- Large lesion involving upper one-third of vagina.

Differences between therapeutic cone and hysterectomy are shown in Table 4.

### TREATMENT OF CERVICAL INTRAEPITHELIAL NEOPLASIA DURING PREGNANCY

- Pregnant woman with abnormal smear should undergo colposcopy.
- Biopsy should be deferred unless one is suspecting micro or invasive lesion on colposcopy, to avoid iatrogenic bleeding.
- Colposcopy should be repeated every 3 months to ensure that the lesion is not progressing.
- Treatment should be avoided as far as possible during pregnancy, even of a lesion of grade CIN III, as antenatal smears may show exaggerated abnormalities and may regress or become negative after delivery.

### FUTURE PROSPECTS

- **Molecular risk assessment for CIN**: Molecular markers may help to decide which patient without lesion are likely to develop invasive cancer and which patient with invasive cancer are likely to develop recurrence or second primary.

- **Genome markers**: General genomic markers described for CIN include numeric alteration of chromosomes I and II. Specific genetic alterations include abnormal expression of ras and myc oncogenes and altered expression of epidermal growth factor in case of CIN.

- **Chemoprophylaxis**: Chemoprevention trial of HGSIL using 5-FU cream, thymopoietin and interferon are under study.

- **Vaccine against HPV for primary prevention of disease**: This is so as major risk factor for cervical cancer is HPV infection.

It is stated that early chapters on cervical cancer control program were written by cytopathologists and final chapters will be written by immunologists and molecular biologists.

### CONCLUSION

There is no single way in which CIN can be treated. Modality of treatment selected depends on factors like age, parity, extent of lesion, location of lesion and expertise in colposcopy. Use of colposcopy has revolutionized the management of CIN. In 1963, WHO made an epoch making statement that "cervical cancer is totally preventable disease." All those who are working towards achieving this goal, it becomes their duty to make use of cytology to detect these lesions, locate with the help of colposcope, arrive at accurate diagnosis by doing colposcopically directed biopsies and eliminate them as early as possible. This approach can go a long way in the prophylactic management of cervical carcinogenesis.

### REFERENCES


### Table 4: Differences between therapeutic cone and hysterectomy

<table>
<thead>
<tr>
<th>Cone</th>
<th>Hysterectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up with cytology and colposcopy is a must</td>
<td>Not that important</td>
</tr>
<tr>
<td>Incidence of subsequent invasive cancer higher</td>
<td>Incidence of subsequent invasive cancer much less</td>
</tr>
</tbody>
</table>


INTRODUCTION
Cancer of uterine cervix is the most common cancer in women in developing world. Eighty percent of all the cases of cancer cervix occur in developing countries. India is a high-risk country for cervical cancer which accounts a quarter (126,000 new cases, 71,000 deaths around the year 2000) of the world’s burden. The age-standardized incidence rates range from 16 to 55 per 100,000 women in different regions with particularly high rates in rural areas. As more than 75% cases are diagnosed in the late stages, no curative treatment is possible leading to high morbidity and mortality. To reduce mortality it is essential to diagnose these cases early.

Cervical cancer prevention efforts worldwide have focused on screening women at risk of disease using Pap smears and treating precancerous lesions. Pap smear screening was developed in the 1930s and named after inventor Dr George Papanicolaou. Pap smear programs, also known as cytological screening programs, have achieved impressive results in reducing cervical cancer incidence and mortality in some developed countries. Cervical cancer incidence can be reduced by as much as 90% where screening quality and coverage are high.¹

In Finland, a National Cervical Cancer Screening Program that was launched in 1963 decreased the cancer cervix rate to 5.5 cases per 100,000 women.² In developing countries, where some 80% of new cases exist, only 5% of women have had a Pap smear in the last 5 years in contrast to 40–50% women in developed countries.

Although Pap smear-based screening efforts have been introduced in several developing countries, many have achieved only limited success. Problems have included:

- Follow-up diagnostic and treatment services are unavailable to most women
- Clients often do not understand that having a Pap smear is important to cancer prevention.
- Control of cervical cancer by early detection and treatment is a priority of the National Cancer Control Program of India. There are no organized cytology screening programs in the country. The technical and financial constraints to organize cytology screening have encouraged the evaluation of visual inspection approaches as potential alternatives to cervical cytology in India.

Downstaging for cervical cancer is defined as “the detection of the disease in an earlier, curable stage, in asymptomatic women, using a simple speculum for visual examination of the cervix.”³

HISTORICAL BACKGROUND
This strategy was proposed by World Health Organization (WHO) in 1985, as an alternative approach in the developing countries where a meaningful coverage of all at risk women by cervical cytology would not be possible for decades to come.⁴

RATIONALE FOR CLINICAL DOWNSTAGING OF CANCER OF THE CERVIX
Organized cytology screening is the mainstay of early detection of cervical cancer. Unfortunately in developing countries, where the load of the disease is heavy and the populations are virtually unscreened, nationwide cytology screening programs are not possible in foreseeable future because of paucity of economic and manpower resources.
At present, in the developing countries, 80–85% of women with cervical cancer present to the treatment centers at advanced stages, when treatment no matter how sophisticated, fails to improve survival time. The objective of the “downstaging” approach is to improve the stage distribution of cervical cancer at the time of diagnosis with the aim of improving prognosis. Several pilot studies have proven that up to 50–70% of cases of cervical cancer can be detected on visual examination, not only overt cases, but also some cases of cervical intraepithelial neoplasia (CIN).

Although visual screening is a suboptimal approach in comparison to the cytological screening, it is relevant in areas where there is a heavy load of prevalent cancer and screening by cytology is not yet feasible but adequate treatment facilities are available. Such a strategy is not expected to decrease the incidence of invasive cancer, but would decrease morbidity and mortality from the disease through early detection.

The downstaging methodology—an attempt to investigate the feasibility of early detection through visual inspection (VI) by paramedical health workers as an alternative approach to cervical cytology has been attempted by various studies (Singh et al. 1992; Bhargava et al. 1993; Sujathan et al. 1995; and Rao et al. 1995).

### APPROACH TO CLINICAL DIAGNOSIS

Approaches to visual screening currently being evaluated include:

- **Unaided VI of the cervix, referred to as “downstaging” by WHO (VI) (Table 1).**

- It involves looking at the cervix during a speculum examination to detect early stage cancer. Downstaging has been shown to be poorly sensitive and specific to detect cervical neoplasia and is no longer considered as a suitable screening test for cervical cancer.³

- **Unaided visual inspection of the acetic acid (VIA) treated cervix:** VIA of cervix treated with 3–5% acetic acid could serve as a “helpful supplement” in aiming to detect CIN. A study of 1,351 women in India found that VIA performed by trained nurses detected 96% of moderate-severe dysplasia and cancer, while Pap smears (obtained by trained nurses and examined by a Cytopathologist) detected 62%. The specificity of VIA for detecting these lesions was 68%.⁸ VIA is less effective for screening postmenopausal women because physiological changes make observation of cervical lesions difficult.

- **Aided VIA treated cervix (VIAM):** This approach involves the use of a small, lightweight, low-powered (2–4X), monocular telescope to view acetic acid treated tissues. This technique is currently being evaluated in several Asian countries, but its sensitivity, specificity and any advantage that it confers in comparison with unaided VI is yet to be determined.

- **Visual inspection after the application of Lugol’s iodine (VILI):** VIA, VIAM and VILI are currently being investigated in multicenter cross-sectional studies (without verification bias), in which cytology and human papillomavirus (HPV) testing are also simultaneously evaluated.⁹

- **Speculoscopy:** In this method, an additional fluorescent light source aids in the detection of white lesions in acetic acid treated cervix. Information regarding its efficacy as a screening tool is limited.

- **Cervicography:** This involves the inspection, by trained personnel, of photographs of the cervix taken at the time of speculum examination. Its sensitivity and specificity in comparison with cervical cytology has not been established. Special cameras are required and special readers have to be available to assess the photographs.

### HEALTH EDUCATION

Health education is a prerequisite of any screening program. Adequate programs of public and professional education to make them aware of the symptoms and signs of the disease and of its potential curability if detected early, should be organized to accompany, and preferably precede, introduction of the screening program. This will encourage the women to willingly (voluntarily) join the screening program, which will go a long way in improving patient compliance. On the other hand, the health personnel involved should possess adequate knowledge about the disease to be able to anticipate a woman’s worries and questions and be prepared to deal with them in a professional and reassuring manner.

### Women to be Screened

As for cervical cytological screening, it is important that the age groups examined are those where the incidence of cervical cancer is high. The aim should be to screen every woman in the target group (age 35–55 years) at least once in her lifetime at about 40 years of age.

### PERSONNEL NEEDED FOR THE EXAMINATION

Female primary health care workers should be employed to do the clinical examination. These health workers should be trained for a period of at least 1 week, in the gynecology department of a district hospital, on how to perform a speculum examination of the cervix. By the end of the training, they should be well acquainted with the symptoms and signs of the disease and be able to distinguish a clinically normal cervix from a cervix with simple erosion or one with a suspected invasive cancer. They should also be trained on how to take a specimen for culture and a cervical smear for diagnostic purposes. During the training an adequate
<table>
<thead>
<tr>
<th>Normal cervix</th>
<th>No medical intervention required. Call for rescreening, if 35 years or above, according to established policy.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postmenopausal cervix</td>
<td>No medical intervention required. Call for rescreening, if 35 years or above, according to established policy.</td>
</tr>
<tr>
<td><em>Ectopy (erythroplasia)</em>: Normal physiological change seen during pregnancy and puerperium</td>
<td>No medical intervention required. Call for rescreening, if 35 years or above, according to established policy.</td>
</tr>
<tr>
<td>Abnormal cervix</td>
<td>Take swab for culture and send to laboratory (if facilities available). Refer the patient to the primary health clinic.</td>
</tr>
<tr>
<td>Cervicitis</td>
<td>Take swab for culture and send to laboratory (if facilities available). Refer the patient to the primary health clinic.</td>
</tr>
<tr>
<td>Condition</td>
<td>Action</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Nabothian follicles (chronic cervicitis)</td>
<td>Take swab for culture and send to laboratory (if facilities available).</td>
</tr>
<tr>
<td></td>
<td>Refer the patient to the primary health clinic.</td>
</tr>
<tr>
<td>Cervical polyp (benign)</td>
<td>No medical intervention required.</td>
</tr>
<tr>
<td></td>
<td>Call for rescreening, if 35 years or above, according to established policy.</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>Refer the patient to the oncology center</td>
</tr>
</tbody>
</table>
exposure of the health worker to women with clinically normal and abnormal findings will have to be ensured by the training gynecologist. Some primary health care workers may already have performed speculum examinations of the cervix as part of family planning program; however, such workers should still be specially trained to recognize the signs of invasive cervical cancer.

**EQUIPMENT REQUIRED**

Visual examination should be preferably performed at the primary health clinics, which are equipped with the following:
- Examination table, preferably with stirrups
- Sterile speculae, preferably Cusco’s
- Sterile rubber gloves
- Source of light, a lamp or a torch
- Stationary.

**EXAMINATION**

The procedure and the reason for it should be carefully explained to the woman to be examined and she should be made as comfortable as possible.
- Privacy of the patient is important, female relative or friend may be of assistance in providing reassurance. Good visualization of the cervix is essential, therefore adequate light is important.
- Speculum should be lubricated with warm water only, prior to insertion.
- Woman should not be using any intravaginal medication at the time of the examination.
- The examination should not be performed during menstrual period.

**REPORTING VISUAL INSPECTION FINDINGS**

Objective of the visual examination is solely, to be able to recognize clinically normal from abnormal cervix and refer abnormal looking cases for further evaluation and diagnosis.

All findings should be carefully recorded in the provided printed forms (Fig. 1).

The gross appearance of the cervix should be classified into:
- Normal
- Abnormal
- Suspicious of malignancy.

**Normal Cervix**

A normal cervix appears smooth, round, pink, lubricated with clear mucoid secretion and has a central hole the “external os”. The shape of the external os varies with parity, being round in a nulliparous woman and slit like or cruciate in a multipara. Cervix in postmenopausal women appears atrophic.

**Abnormal Cervix**

This category will include all benign looking lesions, such as:
- Hypertrophy
- Redness or congestion
- Irregular surface
- Distortion
- Simple erosions (that do not bleed on touch)
- Cervical polyps (with smooth surface)
- Abnormal discharge (foul smelling, dirty/greenish, white/cheesy, blood stained)
- Nabothian follicles
- Prolapsed uterus.

These appearances usually accompany following clinical conditions:
- Infections
- Ectopy (erythroplasia)
- Benign tumors.

**Suspicious of Malignancy**

Malignancy should be suspected when there is:
- An erosion that bleeds on touch
- A growth with an irregular surface.

Both of these lesions may be friable and bleed on touch or may be accompanied with an offensive discharge (Figs 2 and 3).

**FREQUENCY OF EXAMINATION**

WHO (1992) recommended that in low resource settings, the aim should be to screen every woman once in her lifetime—at 40 years. Frequency of screening should be increased to “once every 10 years” and then “once every 5 years” for women 35–55 years of age. The frequency could be increased based on resources. The women should be advised to return to the clinic if symptoms develop between scheduled examinations.

**REFERRAL PROTOCOL**

- A woman with normal findings should be called back for a repeat examination according to the decided policy.
- For women with abnormal findings but not suspected to have cervical cancer, a number of clinical conditions may be relevant, including infections. If necessary facilities are available, a swab should be taken for culture at the time of examination and sent to the laboratory. The patient should be referred to the primary health center (PHC) for further evaluation and treatment by the physician.
VISUAL EXAMINATION REPORTING FORM

PATIENT’S PROFILE
Name Last: ______________________ First: ______________________ Middle: ______________________
Age: ______________________
Address: ______________________________________________________

Date of marriage: ______________________ No. of children: ______________________
Menstrual cycles: REG: ______________________ IRREG: ______________________
Intermenstrual bleeding: YES: ______________________ NO: ______________________
Contact bleeding: YES: ______________________ NO: ______________________
Pregnant: YES: ______________________ NO: ______________________
Last menstrual period: ______________________
Contraceptives: YES: ______________________ NO: ______________________
If yes, specify: ______________________________________________________
Cytological examination: YES: ______________________ NO: ______________________
If yes, date: ______________________ Result: ______________________

HUSBAND’S MEDICAL HISTORY (If ever been treated for STD):

PER-SPECULUM EXAMINATION OF THE CERVIX: ______________________
Discharge: ______________________ Normal: ______________________
Bloody: ______________________________________________________
Dirty/greenish: ______________________
Foul smelling: ______________________________________________________
White/cheesy: ______________________________________________________

Appearance of cervix:
Normal
Abnormal:
• Hypertrophy
• Redness/congestion
• Irregular surface
• Distortion
• Erosion (does not bleed on touch)
• Polyp/growth (with smooth surface)
• Nabothian follicles
• Prolapsed uterus
  Suspicious of malignancy:
  • Erosion (friable or bleeds on touch)
  • Growth (friable/fungating/irregular)
  • Nonspecific appearance

PLAN OF ACTION
1. Swab taken for culture: YES: ______________________ NO: ______________________
2. Smear taken: YES: ______________________ NO: ______________________
3. Advice given:
   1. Rescreen after three to five years
   2. Referred to PHC
   3. Referred to oncology center.

Fig. 1: Visual examination reporting form
Women suspected to have malignant lesions should be directly referred to the oncology center for further assessment.

**ASSESSMENT AND EVALUATION OF THE PROGRAM**

In areas where downstaging programs have been initiated, every measure should be taken to assess the efficiency of the staff and evaluate effectiveness of the approach.

The staff of the gynecology department at the oncology referral center should make field visits to randomly examine the women already been examined by the primary health care workers to assess false positive and false negative rates of VI. Furthermore, the field staff should be given refresher course when and where possible.

With regards to the evaluation of effectiveness of the program, it is important to remember that the program should not be expected to have immediate impact on improving the stage distribution of cases in an area, but only after it has been in operation for several years will it be possible to judge its effectiveness.

Thus, it is advisable to base evaluation of the program on the following measures:

**Short-term Measures**

- Change in background knowledge of the target population. Two random sampling surveys should be performed. The first, prior to the introduction of the health education campaign and the second, 1 year after the campaign has been completed.
- Proportion of women in the target population screened. For this (as well as some of the other evaluation measures), it will be necessary to procure accurate estimates of the numbers of women in the target population.
- Proportion of women screened found to be abnormal.
- Proportion of women screened abnormal who attend for diagnosis and therapy.
- Utilization of treatment services and proportion of cases treated by surgery, radiotherapy and palliative care. It is to be expected that the proportion of cases that can only be treated by palliative care will diminish with time, and thus, this can also be regarded as an additional long-term evaluation measure.
- Rates of detection of CIN (by degree) and invasive cancer.
- Determination of the economic costs of the program.

**Long-term Measures**

- Change in stage distribution of invasive cancers. It is unlikely that a stage shift indicative of true effectiveness would be seen in less than 3 years and possibly would not be seen for 5 years or more. Screening can be expected to bring to light disease that is detectable, but which has not yet been recognized because the symptoms are not intrusive. This will increase the apparent incidence in the areas and indeed the stage distribution may shift as such disease is likely to have a better prognosis than disease that presents between screens or that with more severe symptoms.
- Change in rate of advanced disease. This, if calculated on an annual basis, should begin to fall with effective programs after about 3–4 years, if not before, for a highly effective program with rapid and almost complete screening of the target population.
- Change in mortality from the disease. With an effective program, mortality from the disease will fall. This effect should be detectable within 1 or 2 years of a significant reduction in the rate of advanced disease.

The study by Indian Council of Medical Research (ICMR) showed that using high-risk signs of cervix, with or without bleeding symptoms, VI or “downstaging” can detect 50–60% early-stage cancers. While this strategy can bring about clinical downstaging (from stage III–IV to stage 0–IIA) and thus has a potential for bringing down the case fatality rates, it has limitations in detecting dysplasias. In view of poor specificity, this approach can only help to reduce the mortality and not the morbidity and therefore cannot be recommended as a screening tool for detecting precancerous lesions.3
Regional cancer centers can play a leadership role in teaching/training/treatment of invasive cancers and evaluation activities. Organized screening has to be done at PHC level or its subcenter, i.e. close to the target population, utilizing the services of paramedical workers under the existing circumstances. VIA or VILI would be the only suitable test immediately available. Although “see-and-treatment” approach in the same sitting and at PHC level would avoid unnecessary referral to community health center (CHC) and another visit, there is no evidence that it can reduce incidence and mortality from cervical cancer.

Treatment of all high-grade lesions [moderate and severe dysplasia high-grade squamous intraepithelial lesion (HSIL)] must be carried out using ablative or excisional procedures. Especially targeting the age group of 35–65 years, the program must cover a high proportion of eligible women (> 80%). To begin with, all women should be offered at least one screening test at an age between 40 years and 45 years.12

REFERENCES

INTRODUCTION
Cervical cancer is a disease that results in devastating mortality in third world countries where screening and treatment of the disease are not widely available and is a leading cause of cancer mortality worldwide. It is the second most common gynecological malignancy and in India, around 130,000 new cases are reported annually (compared to 14,000 in USA and 9,000 in UK) and 74,000 deaths occur.\(^1,2\) The estimated incidence is 20–40/100,000 women per year and constitutes 62% of all female genital malignancies. Unfortunately, 80% of cases are detected at later stages.

Cancer cervix remains a disease, which may be treated in the early stage adequately and effectively by either radical radiotherapy or surgery. Evolution has taken place in surgical treatment of cervical cancer since 18th century. The systematic investigations and management began with Wertheim of Vienna and now it is more and more becoming a tailored surgery.

SURGERY FOR CERVICAL CANCER
Surgical treatment has refined over decades to optimize tumor resection and reduce normal tissue injury. Radical abdominal hysterectomy and pelvic lymphadenectomy remain the gold standard procedure for early cervical cancer—stages IA, IA2, IB1, IB2 and IIA.\(^3\) It requires the removal of cervix, corpus with parametria, paracolpos at the level of ureter, one-fourth to one-third of the vagina and pelvic lymphadenectomy. Para-aortic node sampling in selected patients—stages IB2 and IIA. In respect to surgical extensiveness, radical hysterectomy and pelvic node dissection can be divided into five classes, namely class I to class V (Piver, Rutledge and Smith) (Table 1).

Preoperative Evaluation
Clinical staging can be refined preoperatively to determine treatment modality. Apart from usual hematological and biochemical evaluation, chest X-ray, intravenous urogram, lymphangiogram, CAT scan and MRI to assess the extent of the disease, traditional examination under anesthesia, cystoscopy and accurate colposcopic assessment are the

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Extramural hysterectomy, removal of all pericervical tissue</td>
</tr>
<tr>
<td>II</td>
<td>Modified radical hysterectomy, removal of medial 50% of cardinal and uterosac ligaments, uterine vessels are divided medial to ureter</td>
</tr>
<tr>
<td>III</td>
<td>Radical hysterectomy—Wertheim-Meigs operation, wide radial resection of the parametrium and paravaginal tissues, ureter dissected completely to bladder entry, uterosac ligaments divided at origin, cardinals divided at pelvic side wall. Upper one-third of vagina removed</td>
</tr>
<tr>
<td>IV</td>
<td>Extended radical hysterectomy—Ureter divided from pubovesical ligaments, superior vesical artery ligated and upper two-thirds of vagina excised</td>
</tr>
<tr>
<td>V</td>
<td>Extended radical hysterectomy—More radical procedure with possible bowel, bladder or ureteric dissection</td>
</tr>
</tbody>
</table>
basic needs before surgery. Reliability of lymphangiography ranges from 80% to 90%. Recently, MRI has become an excellent modality for the same with overall accuracy of 90% and accuracy of 94% for parametrial involvement (Table 2).5

**Basic Surgical Technique**

After examination of the patient under general anesthesia, the abdomen is opened using a low transverse (Maylard, Cherney, Pfannenstiel) or a low vertical abdominal incision. Careful exploration of abdomen and pelvic peritoneum is done followed by pelvic and para-aortic lymphadenectomy. Approximately 5–10% of patients with stage IB have para-aortic lymph node metastasis. Para-aortic lymph node metastasis in the absence of pelvic node metastasis is uncommon in cervical cancer. Extraperitoneal lymphadenectomy precedes hysterectomy and is beneficial as the bowel handling is overcome and incidence of postoperative ileus is less. If nodes are found unresectable, the procedure is abandoned. Pelvic lymphadenectomy requires the bilateral removal of all visible nodal tissues from the midportion of psoas muscle to the pyriformis space bilaterally to assess resectability and rule out gross parametrial invasion. The uterine artery is transected at its origin from hypogastric artery and the ureter unroofed from its entry into the broad ligament to its intramural portion in the bladder with lateral retraction from cardinal ligament. Table 3 reveals the extension of the resection for surgical procedures. Radical surgery does not necessitate removal of tubes and ovaries because of low prevalence of metastasis to the ovary (from stage IB: 0.5% in squamous cell carcinoma and 1.7% in adenocarcinoma). They are usually removed in premenopausal and postmenopausal women, if grossly abnormal, for ovarian cancer prophylaxis in appropriate candidates.

Recently, by virtue of giant histological sections, it has been shown that in cervical cancer with volume less than 5 mL, medial parametrial involvement is 3.8% and lateral parametrial involvement is 2.2%. Hence, tailoring radicality in smaller cervical cancer by using Type II radical hysterectomy is acceptable as safe with low morbidity. For larger volume cancers, Type III radical hysterectomy removing lateral part of parametrium is necessary.

After the logic of evidence-based medicine, several conclusions are to be reached from the recent prospective, randomized phase III clinical trials.7 In patients in whom the risks of either positive margins or lymph nodes are low, both radical surgery or radiotherapy are equally efficacious options. Recent survey suggested there may be a survival advantage for surgical intent to treat patients for tumors 4 cm or smaller in stage IB and IIA (cervical canal lesions).

**Postoperative Care and Follow-up**

The contributing factors for quicker postoperative recovery are: transverse lower abdominal incision; discontinuation of pelvic drain; practice of retroperitoneal abdominal drain; placement of suprapubic Foley catheter; early oral feeding; admission to hospital on the day of surgery and initiation of critical care pathways. Postoperative irradiation is indicated if high-risk factors such as large tumor size, lymph vascular invasion and or deep stromal invasion are identified. Patients with positive lymph nodes, positive parametrial invasion or positive margins should receive postoperative irradiation with chemotherapy. All other patients with more advanced clinical stages of cervical carcinoma should be treated with external pelvic irradiation, brachytherapy and concurrent chemotherapy. The prognostic factors concerned are tumor volume, gross tumor configuration, vaginal or endometrial cavity extension, histologic grade of tumor, depth of tumor invasion, vascular invasion, regional and distant lymph node metastasis and distant metastasis.

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**Table 2: Staging procedures**

<table>
<thead>
<tr>
<th>Physical examination</th>
<th>Radiologic studies</th>
<th>Procedures</th>
<th>Optional studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palpate lymph nodes</td>
<td>Intravenous pyelogram</td>
<td>Biopsy</td>
<td>Computerized axial tomography</td>
</tr>
<tr>
<td>Examine vagina</td>
<td>Barium enema</td>
<td>Conization</td>
<td>Lymphangiography</td>
</tr>
<tr>
<td>Bimanual rectovaginal examination</td>
<td>Chest X-ray</td>
<td>Hysteroscopy</td>
<td>Ultrasoundography</td>
</tr>
<tr>
<td>(under anesthesia recommended)</td>
<td>Skeletal X-ray</td>
<td>Colposcopy</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>Size of the growth</td>
<td></td>
<td>(for microscopic lesions)</td>
<td>Positron emission tomography</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Colposcopy (for microscopic lesions)</td>
<td>Radionuclide scanning</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cervical smear shows malignant cells, but no growth seen in cervix</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cystoscopy</td>
<td>Laparoscopy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Proctoscopy</td>
<td></td>
</tr>
</tbody>
</table>

* Allowed by FIGO

Information not allowed by FIGO to change the clinical stage
Complications

There are short-term and long-term bladder dysfunctions owing to bladder atony. Ureterovaginal and vesicovaginal fistulae are seen in 2–4% of patients. Decreased defecation urge and constipation are reported; small bowel obstruction in 1.3–5%, vaginal cuff cellulitis 5%, wound infection 2%, pneumonia 2%, thrombosis and pulmonary embolism 1%, obturator nerve transection in 0.6%, peroneal nerve compression 0.6% and chronic lymphedema are few of the complications of radical surgery. Lymphocyst formation after radical hysterectomy and lymphadenectomy is due to interruption of efferent pelvic lymphatics and can result in lymphedema pelvic discomfort and infection as well as an increase in the frequency of deep venous thrombosis and pulmonary embolism. Variation in the incidence of lymphocyst formation depends on the extent of lymphadenectomy, retroperitoneal drain placement and differences in the surgical management used for ligating lymphatic channels. Lymphocysts can be treated with percutaneous ultrasound-guided drainage followed by minocycline sclerotherapy. Laparoscopically directed marsupialization or surgical resection has also been reported. Less than 20% patients suffer reaccumulation of lymphatic fluid.9

Radical Vaginal Hysterectomy

Oncological surgeon familiar with advances of laparoscopic technique and radical vaginal hysterectomy is able to take advantage of the benefits of both routes. Significant advantages to abdominal procedure include: possibility of regional anesthesia especially in patients with medical conditions; reduced surgical trauma because of absence of abdominal incision; applicability in obese patients; shorter surgical time in experienced hands; decreased need for blood transfusion; lower risk for complications; faster recovery and shorter hospitalization. It is contraindicated in the presence of chronic inflammatory disease, previous pelvic reconstructive surgery, endometriosis or ovarian abnormality. Radical vaginal hysterectomy has unique role in situations like microinvasive cervical cancer, stump cancer and younger patients.

Radical Trachelectomy9,10

Novak in 1948 and Amburel in 1967 named the subfundic extended hysterectomy, and devised the radical trachelectomy, especially in stage IB cases. In 1994, Dargent pioneered this procedure and published the first series which was later modified by Shepherd. Seven centers all over the world are performing this procedure for last 20 years. It allows preservation of body of uterus and reproductive function following acceptable oncologic principles.

Bilateral pelvic lymphadenectomy and evaluation is done laparoscopically followed by resection of vaginal portion of cervix, parametrium and upper portion of vagina. Descending cervical branch of uterine arteries is ligated, uterus divided at the isthmus and permanent prophylactic cerclage is placed for prevention of preterm delivery in future. Patient is advised regular follow-up and contraception for 6 months. Radical trachelectomy is ideally suited for stage IB1 small volume tumor, where future fertility is strongly desired. Laparoscopic vaginal approach is definitely superior but requires expertise in this field. Preoperatively frozen section of proximal end of resection is assessed.

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Cervical conization</th>
<th>Total abdominal or vaginal hysterectomy</th>
<th>Modified radical hysterectomy</th>
<th>Meigs radical abdominal hysterectomy</th>
<th>Radical vaginal trachelectomy</th>
<th>Modified Mitra’s/Schauta’s radical vaginal hysterectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervix uteri</td>
<td>Partially removed</td>
<td>Completely removed</td>
<td>Completely removed</td>
<td>Completely removed</td>
<td>Majority removed</td>
<td>Completely removed</td>
</tr>
<tr>
<td>Corpus uteri</td>
<td>Preserved</td>
<td>Completely removed</td>
<td>Completely removed</td>
<td>Completely removed</td>
<td>Preserved</td>
<td>Completely removed</td>
</tr>
<tr>
<td>Ovaries and tubes</td>
<td>Preserved</td>
<td>Preserved</td>
<td>Preserved</td>
<td>Preserved</td>
<td>Preserved</td>
<td>Preserved</td>
</tr>
<tr>
<td>Parametrium and paracolpos</td>
<td>Preserved</td>
<td>Preserved</td>
<td>Removal at level of ureter</td>
<td>Partially removed</td>
<td>Preserved</td>
<td>Removed at level of ureter</td>
</tr>
<tr>
<td>Uterine vessels</td>
<td>Preserved</td>
<td>Ligated at level of cervical internal os</td>
<td>Ligated at level of uter</td>
<td>Ligated at origin from hypogastric vessels</td>
<td>Preserved</td>
<td>Preserved</td>
</tr>
<tr>
<td>Uterosacral ligaments</td>
<td>Preserved</td>
<td>Ligated at uterus</td>
<td>Ligated midway to sacral attachment</td>
<td>Ligated near sacral attachment</td>
<td>Partially removed</td>
<td>Partially removed</td>
</tr>
<tr>
<td>Vaginal cuff</td>
<td>Preserved</td>
<td>Not removed</td>
<td>1–2 cm removed</td>
<td>2 cm removed</td>
<td>1–2 cm removed</td>
<td>&gt;2 cm removed</td>
</tr>
</tbody>
</table>

If nodes are positive, procedure is abandoned and chemoradiation offered. Preoperative workup includes tuboperitoneal factors for infertility, endocervix invasion, lymph node metastasis and parametrial involvement by MRI. In the era of assisted reproductive technologies, the need to learn and practice technique may become inevitable.

Overall survival rate is excellent with 5-year survival of 95% with a recurrence rate of 4.3% and death rate of 1.5%. Pregnancy outcomes are favorable, provided treated at high-risk pregnancy clinic and elective cesarean by classic section where level III neonatal intensive care is available. Delivery of viable pregnancy rate is 52.85 and risk of extreme prematurity is 13.7%.

**Excisional Techniques**

Excisional techniques have been an effective treatment for cervical intraepithelial neoplasia (CIN) for many years; loop electrical excision procedure (LEEP) and large loop excision of the transformation zone (LLETZ) are relatively simple outpatient treatments for CIN and more effective, with low complications rates, 90% success rate in treating carcinoma in situ (CIS) with low recurrence rate of 4–5%. Indications are: unsatisfactory colposcopic examination; treatment of biopsy proved CIN 2, CIN 3 and CIS; suspicion of squamous microinvasive or adenocarcinoma in situ; persistent CIN-1 for 1 year or noncompliant patients; two-grade discrepancy between cytology and colposcopic or histologic diagnosis; symptomatic cervical ectropion. The goal is to remove the transformation zone with the lesion completely and obtain an adequate margin of normal tissue.

**Laparoscopic Surgery**

Laparoscopic radical surgery for early cervical cancer is a safe and effective procedure. Complications and recurrence are quite comparable to abdominal radical hysterectomy. The complications related to surgery were decreased after substantial learning period and improved technology. In future, laparoscopic oncology surgery will gradually replace the conventional surgery and will be the choice of surgical management.

**Surgical and Preoperative Advancements**

Antibiotic prophylaxis with short-term and long-term intravenous cefotaxime is effective. Factors like operating time, weight of the patient, blood loss and replacement are related to febrile morbidity.

Use of surgical hemoclips (modified Magara technique) or endoscopic staplers improve the radicality of lateral parametrial resection. Liposuction-assisted nerve sparing radical surgery or intraoperative electrical stimulation helps to reduce bladder dysfunction. Retroperitoneal pelvic suction drains lead to fewer ureteric and bladder complications and are necessary to assess postoperative blood loss. Currently, nonclosure of peritoneum with vaginal cuff closure is preferred. Preoperative serum squamous cell cancer antigen (SCC) and cancer antigens CA 125, CA 19-9 levels play a role to assess lymph node status, especially double-tumor-marker (DTM) index. Preoperative intramuscular iron injections for 5–10 days offer better visualization of nodes intraoperatively. Rectopexy refixation of the terminal rectum helps to prevent postoperative complications. Port site metastasis after laparoscopic surgery is a new phenomenon.

**Nerve Sparing Radical Hysterectomy**

Major radical hysterectomy morbidities are disturbance in bladder, sexual and rectal function resulting from damage to sympathetic and parasympathetic nervous systems. In an attempt to nullify this, nerve sparing radical hysterectomy was invented. The cardinal ligament is divided into two parts. The superficial vascular part containing uterine, vaginal and inferior vesical vessels is dissected, while the deep neural part is preserved. To retain bladder function, the pelvic splanchnic nerves, pelvic plexus and bladder branches are preserved by meticulous dissection of cardinal ligament, uterosacral ligament and rectovaginal ligament.

**Recurrent Cervical Cancer**

There are limited treatment options for patients with recurrent cervical carcinoma—because of low response and a negligible impact on long-term survival. There are specific criteria for surgical response like small centrally located recurrence in cervix. Pelvic exenteration remains the therapeutic option. Introduction of high-dose rate intraoperative radiation therapy (HDR-IORT) combined with radical surgical resection has widened the scopes of patients who may be offered surgery when disease extends close to pelvic side walls.

New ablative techniques based on developmentally derived surgical anatomy termed total mesovisceral resection and the laterally extended endopelvic resection (LEER) aim at increasing the resection rate even of tumors extending to the pelvic sidewalls.

**Exenterations**

Exenterative surgery should be considered for both advanced primary carcinoma and recurrent disease. There are three types: anterior, posterior and total, the most frequently practiced being the anterior and total. It improves quality of life in spite of distant metastasis or resistant disease. Careful assessment and accurate tissue diagnosis is mandatory. It is not prudent to them as palliative nor is it realistic to expect good survival and to be dealt by experienced gynecological oncologist and his team. Modern postoperative care and
reconstructive surgical possibilities, e.g. neobladder, low rectal anastomosis, neovagina with interdisciplinary involvement have made a higher quality of life for patients. Five-year survival rate of 30–60% has been achieved in specialized centers.

**Cervical Cancer in Pregnancy**\(^{21,22}\)

It is relatively uncommon with incidence of 1 in 1000 pregnancies but remains the most common malignancy diagnosed during pregnancy. Treatment is tailored as per the stage. In stages IA1, IA2, stage IB1, postpartum treatment is considered. In IB2 and IIA stage of tumor, treatment depends on the gestational age. If less than 20 weeks, radical hysterectomy with fetus in situ is carried out. In advanced pregnancy, classical cesarean section is done to deliver the baby before hysterectomy.

**Neoadjuvant Chemotherapy**

Cisplatin-based neoadjuvant chemotherapy (NACT)\(^{23}\) followed by radical hysterectomy proves to be an interesting approach with increased survival compared to radiotherapy alone. Potential advantages being uncompromised blood supply, better tolerance, tumor more chemosensitive, reduction of tumor bulk with more feasible operability and less toxic than radiation and eradication of subclinical metastasis. Large prospective and randomized study by European Organization for Research and Treatment of Cancer (EORTC) comparing NACT followed by radical hysterectomy and concomitant chemoradiation is under trial to explore preoperative chemotherapy again.

**Value of Sentinel Lymph Node Sampling**

The original goal of sentinel lymph node (SLN) mapping in cervical cancer is to identify on frozen section, patients with micrometastasis, to avoid two treatment modalities: by calorimetric method using lymphazurin and radioisotopic method using technetium-99.

**Outcome**

In early cervical cancer, radical surgery offers a 5-year cure rate in stage IB of 85–90% and in stage IIA, 70–75%. The limiting factor is the nodal involvement and the cure rate is reduced to 60%. They also require adjuvant therapy postoperatively.

**Advantages of Primary Surgery over Radiotherapy**

There are important major and minor advantages of primary extensive surgery over irradiation for early stage disease. This allows first and foremost accurate assessment of the extent of cervical cancer and other intra-abdominal incidental conditions and disease. Function of normal ovaries can be preserved in select patients. The vagina remains soft, pliable, moist and functional. Sexual function is not disturbed. Late recurrence is very rare and late complications are uncommon; psychological benefit by removal of tumor needs a mention.

**Robotic Radical Hysterectomy**

Robotic technique appears to provide some patients advantages over laparoscopic and laparotomy approach.
NEWER TREATMENTS IN THE MANAGEMENT

Therapeutic Vaccines

In addition to preventive vaccines such as Gardasil and Cervarix, laboratory research and several human clinical trials are focused on the development of therapeutic human papillomavirus (HPV) vaccines.

These vaccines focus on the main HPV oncogenes E6 and E7. It is hoped that immune responses against the two oncogenes might eradicate established tumors.24

Targeted Therapy

Bevacizumab (Avastin) is a targeted drug that keeps new blood vessels from forming. It has been used alone and with chemotherapy to treat advanced cervical cancer. It is also being studied as a part of the treatment for earlier stage cervical cancer.

Hyperthermia

It is a treatment that raises the temperature around the tumor. Some research suggests that adding hyperthermia to radiation may help keep the cancer from coming back and help patients live longer.25

CONCLUSION

It is the individual surgical technique that offers the highest cure rate and lowest incidence of complications to the patient with invasive carcinoma cervix. From the patient’s point of view, the initial treatment provides the best chance for long-term cure of the disease and secondary treatment for recurrent disease offers only limited long-term cure. In the author’s series over a period of 5 years between 1995 and 1999, 61 patients underwent radical surgery (class III) for stages IA and IB. Incidence of nodal metastasis was 13% in par with other studies. All procedures’ approach through Pfannenstiel incision was feasible with few complications, namely bladder dysfunction 1.7%, thrombophlebitis, wound sepsis 5%, lymph edema 5%, incidence of fistula nil.

To have accuracy of communication internationally, efforts are being taken to redefine the extent of parametrial, paravaginal and paracervical resections. Morbidity and mortality associated with radical hysterectomy can be reduced by innovative modifications of surgical techniques.

ACKNOWLEDGMENTS

I sincerely thank Dr MG Pai, Dr Ramalingam and Dr Suma Natarajan, for the encouragement in this endeavor.

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CHAPTER 104

Ovarian Tumors: Epidemiology and Classification

Richa Singh Chauhan
(Chapter written and updated by Richa Singh Chauhan)

INTRODUCTION

It is important to have an internationally agreed classification of ovarian tumors in order to allow a proper analysis of the trends in their incidence and for proper and meaningful comparisons of treatment. The pathology of ovarian neoplasm is one of the most complex areas of gynecology, because the ovary gives rise to a greater range and variety of tumors than does any other organ. Ovaries consist of sex cells which are totipotent and of mesenchymal cells which are multipotent, so when the ovary becomes neoplastic almost any sort of tumor can result. Certainly ovarian tumors are characterized by an extraordinary and bewildering varieties of histological pattern and grades of malignancy leading to complexity in classification.

Approximately 70–80% of ovarian tumors are benign in nature but the continued poor prognosis of the remaining 20% malignant ovarian neoplasms is the reason for main focus on ovarian cancers.

INCIDENCE

Ovarian cancers account for about 5% of all gynecological cancers in India. In Western countries, ovarian cancer is the most common malignancy of the female genital tract. Incidence is highest in Sweden followed by Norway, the United States of America, Germany and the United Kingdom. It is relatively less prevalent in Latin American, African and Asian countries including India and Japan. In the United States of America annual age adjusted incidence rate is 14 per 100,000 women and lifetime risk is 1.4%. Approximately 19,000 new cases are diagnosed every year and 12,000 women die from this disease in same period. In England and Wales, these numbers are approximately 4,500 and 3,700 respectively. In India, ovarian cancers account for 15–20% of genital tract cancers way behind cancer cervix.

Ovarian cancer is the leading cause of deaths due to malignancies of female genital tract. Of all the cancer deaths in women it is the fourth most common cause (after breast, colon and lung) and only lung cancer has poorer prognosis. The median survival for all stages is about 18 months and 5 years survival is only 25–30% (as against 66% in cancer endometrium and 54% in cancer cervix).

An increasing trend in incidence is being observed in Western countries partly due to increase in aged population and advancements in diagnosis but part of the increase is real. This is associated with very modest improvement in survival over 20 years and has led to an overall increase in mortality due to ovarian cancers in contrast with other cancers of genital tract whose mortality rates have markedly fallen.

EPIDEMIOLOGY

Age

The different types of ovarian tumors do have little different age specific incidence. Epithelial ovarian tumors of benign and low malignant potential generally occur in women between the ages of 20 years and 45 years. Epithelial cancers are rare prior to age of 10 years, incidence gradually rises up to maximum in 5th and 6th decade and then it plateaus up to 8th decade. Average age at diagnosis is about 53 years.
Sex cord and mesenchymal tumors similarly occur maximum between 30 years and 60 years. Germ cell tumors present a different age pattern. Dysgerminomas predominantly occur around 20 years of age while teratomas show bimodal age distribution with peaks before 30 years and after 60 years of age.\textsuperscript{3}

**Geographic and Ethnic Distribution**

Evidences do not support significant ethnic or racial differences in ovarian cancer risk. The large geographic differences in incidence are probably due to environmental factors. Similarly in a particular society, socioeconomic class also makes a very minor difference in the incidence of ovarian cancers.

**Environmental Factors**

No direct relationship between industrial pollution or cigarette smoking and ovarian cancers has been found but asbestos and talc have been suspected to act as carcinogens. High fat diet and increased milk (lactose) intake particularly by women with low tissue levels of galactose-1-phosphate uridyl transferase is reported to increase the risk.\textsuperscript{4}

Ionizing radiation, used earlier to treat metropathia hemorrhagica, was shown to increase risk of ovarian cancers.

**Hormonal, Ovulatory and Reproductive Influence**

Nulliparous women are at higher risk of developing ovarian cancers. The risk declines progressively with the number of children she has had. Pregnancy, irrespective of the outcome, seems to have protective effect. Use of oral contraceptives also reduces the risk. Early menarche and late menopause are also associated with increased risk of ovarian cancers. All these factors indirectly are attributed to ovulatory status of the woman. As suggested by Fathalla, incessant ovulation leading to epithelial inclusions and mutations resulting in oncogene activation is supposed to be the probable explanation of higher incidence of ovarian cancers in women who have ovulated more in their life time.\textsuperscript{5} Sustained elevated levels of gonadotrophins associated with ovulatory cycles may be the other factor.

**Familial and Genetic Factor**

Familial factors are an important determinant of susceptibility to ovarian cancer. Genetic predisposition to ovarian cancers has been observed in 1–3% of epithelial ovarian cancers. A woman can have genetic risk of site-specific familial ovarian cancer, breast-ovarian familial cancer syndrome or Lynch II syndrome. Women with history of ovarian cancer in more than two close relatives have substantially higher risk (up to 40%) of familial ovarian cancer. Breast ovarian familial cancer syndrome related to BRCA1 gene has been more commonly found in Jewish women. In this group women having history of breast or ovarian cancer in close relatives or themselves, besides having breast cancer earlier are also at increased risk of having ovarian cancer. Another type of genetic predisposition described as Lynch II syndrome has been identified in which familial tendency to develop colon, breast, endometrial and ovarian cancer is seen.\textsuperscript{5,7}

Association of gonadoblastoma and dysgerminoma with dysgenetic gonads and presence of Y chromosome, granulosa theca cell tumors with Peutz-Jeghers syndrome of familial polyposis and ovarian fibromas with multiple nevoid basal cell carcinoma has been observed.\textsuperscript{2}

**Other Factors**

Tubal ligation and hysterectomy reduce the risk and removal of beta tubes and ovaries dramatically reduces the risk of developing ovarian cancer.\textsuperscript{8}

**Classification**

It is important to have an internationally agreed classification of ovarian tumors in order to allow a proper analysis of the trends in their incidence and for proper and meaningful comparisons of treatment.

World Health Organization’s classification system based on histogenesis, the cell or tissue of origin is the most explanatory and accepted system of classification of this complex set of tumors.\textsuperscript{9}

According to the nature of malignancy, epithelial ovarian tumors are classified as benign, malignant and intermediate (also designated as borderline tumors or tumors of low malignant potential). The concept of borderline tumors evolved as it was recognized that 10–20% of tumors were intermediate in their histology appearance, were confined to ovaries or showed indolent behavior when disseminated and had an excellent prognosis.

**Borderline Tumors**

Borderline tumors are staged using the same system as per ovarian cancers but these tumors are made of abnormal cells rather than cancer cells.

**Surface Epithelial Tumors (Müllerian Tumors)**

**Serous Tumors**

- Benign—serous cystadenoma, papillary cystadenoma, cystadenofibroma
- Borderline—serous tumors
- Malignant—serous cyst adenocarcinoma, papillary adenocarcinoma.
**Mucinous Tumors**
- Benign—mucinous cystadenoma
- Borderline—mucinous cystadenoma
- Malignant—mucinous adenocarcinoma.

**Endometrioid Tumors**
- Benign—cystic endometrioma
- Borderline—endometrioma
- Malignant—adenocarcinoma, adenosquamous carcinoma.

**Clear Cell Tumors**
- Benign—clear cell cystadenoma
- Borderline—clear cell tumor
- Malignant—clear cell adenocarcinoma.

**Brenner Tumors**
- Benign Brenner tumor
- Borderline—Brenner tumor
- Malignant Brenner tumor.

**Mixed**
- Undifferentiated carcinoma
- Unclassified epithelial tumors

**Sex Cord Stromal Tumors**

**Granulosa: Theca Cell Tumors**
- Granulosa cell tumors
- Theca cell tumor
- Mixed with fibroma.

**Sertoli-Leydig Cell Tumors (Androblastoma, Arrenoblastoma)**
- Well differentiated—Sertoli cell tumors, Leydig cell tumors, Sertoli-Leydig cell
- Poorly differentiated.

**Gynandroblastoma**

**Lipid Cell Tumors**

**Germs Cell Tumors**
- Dysgerminoma
- Endometrial sinus tumor-yolk sac tumor
- Embryonal carcinoma
- Polyembryoma
- Choriocarcinoma
- Teratoma
  - Immature
  - Mature—solid
    i. Cystic—dermoid cyst (mature cystic teratoma)
    - dermoid with malignant transformation
  - Monodermal—specialized
    i. Struma ovarii
    ii. Carcinoid tumor
    iii. Others
- Mixed.

**Gonadoblastoma**

**Nonspecific Soft Tissue Tumors**
- Fibroma, fibrosarcoma
- Leiomyoma, leiomyosarcoma
- Angioma, angiosarcoma
- Lymphoblastoma.

**Unclassified Tumors**
- Secondary (metastatic) tumors

**REFERENCES**

Ovarian Carcinoma: Clinical Features/ Diagnosis/Principles of Treatment

INTRODUCTION

Ovarian cancer is the fifth leading cause of cancer related mortality among American women. The combined 5 years survival rate for all patients with ovarian cancer approximates 40%.

The lifetime risk of ovarian cancer in general population is 1.6%. A woman affected with one family member has 4% lifetime risk and with two family members the risk is increased to 7%. In presence of BRCA1 or BRCA2 gene mutation, the lifetime risk is increased to 7%,1,2 Cancer of the ovary is the second leading site among female cancers in Indian registries. The age adjusted incidence rate varies from 1.9 per 100,000 in Barshi (Rural Maharashtra) to 8.7 per 100,000 in New Delhi. In Trivandrum, ovarian cancer is the fourth leading site among all cancers in women with age adjusted rate at 3.7 per 100,000.3

CLINICAL FEATURES

The lack of clinical symptoms during early stages of disease, absence of easy identifiable and detectable precancerous lesions and paucity of clinical tests make ovarian cancer a killer disease. Most patients usually present when the disease has spread to abdomen or retroperitoneum, hence little chance of cure.

The most common symptoms among women with ovarian cancer were unusual bloating, fullness and pressure over abdomen or pelvis and were reported by 71% of patients. Other symptoms were abdominal pain, back pain, lack of energy, frequent urination, urgency or burning sensation. Symptoms reported in up to 21% of patients include constipation, lack of appetite, diarrhea and nausea.

SCREENING FOR OVARIAN CANCER

Potential techniques include:
- History and bimanual pelvic examination
- Transvaginal ultrasound
- Measurement of serum cancer antigen (CA)-125.

Bimanual Examination

Sensitivity and specificity of bimanual pelvic examination is not known and often the tumors are picked up at late stage by this screening.

Transvaginal Ultrasound

Both MRI and pelvic ultrasound are equally effective to identify the internal architecture of adnexal masses but the cost difference favors ultrasound. The ovaries are closer to the transducer during transvaginal sonography thereby giving a clearer image of the ovaries and small adnexal masses. A clearer image of the ovaries and small adnexal masses is usually obtained with vaginal probes. However, large cystic masses usually require combined transvaginal and transabdominal techniques to totally view the mass. The differences between benign and malignant masses on transvaginal ultrasound are listed in Table 1.
Doppler Flow Studies

Doppler studies are useful to distinguish benign tumors from malignant tumors. Blood vessels caused by angiogenesis have little smooth muscle support resulting in increased flow and low resistivity index. Blood flow spectrum is assessed by putting the cursor in center within septae, heterogenous areas or papillary projections are suspicious of malignancy. Doppler flow studies for prediction of malignancy vary from 37% to 100%, depending on threshold resistivity index, patient population and operator experience. Flow studies are combined with assessment of architectural features to improve overall accuracy. Neovascularization in ovarian tumors results in vessels lacking normal muscular intima resulting in low resistance to blood flow as compared to benign tumors. Large number of false-positives identified by Doppler reflects neovascularization in benign tumors. Thus application of Doppler ultrasound to the characterization of adnexal masses is controversial and its routine use is not recommended.

CT Scan-MRI and PET

The presence of a pelvic mass with ascites on clinical examination suggests advanced gynecologic malignancy. An abdominopelvic CT scan helps to define extent of disease before primary exploration for staging and debulking. Bulky, high, para-aortic nodes, visceral metastasis or bulky mesenteric disease correlates highly with patients who cannot be technically debulked into optimal disease status with less than 1 cm large residual disease implants. Contrast CT scan yields high quality information about retroperitoneal nodes and ureters. Helical spiral CT scans records images during arterial, capillary and venous phases of tissue enhancement during contrast administration allowing improved imaging of small vessels and tissue interfaces within visceral parenchyma. MRI scans can generate sagittal, coronal and transverse images thus giving a true estimate of three dimensional relationships. Positron emission tomography (PET) combines metabolic localized tracers and nuclear medicine scintigraphy techniques to image patterns of metabolic uptake suggestive of malignancy or infection. Most frequently 18F-fluorodeoxyglucose (FDG) is used to localize areas of accelerated rates of glycolysis found in neoplastic cells.

Measurement of CA-125

Cancer antigen-125 is an antigenic determinant on a high molecular weight glycoprotein. The domain of CA-125 includes tissues derived from both celomic epithelium and the Müllerian duct. Accordingly elevated levels are detectable in a wide variety of conditions besides epithelial ovarian cancer including the following:
- Healthy subjects (1%)
- Endometriosis and endometriotic cysts
- Pelvic inflammatory disease
- Leiomyoma
- Adenomyosis
- Ectopic pregnancy
- Ovarian cystadenoma
- Liver disease
- Pancreatitis
- Peritonitis
- Renal failure
- Pregnancy
- Luteal phase of menstrual cycle.

Main Use of CA-125

Indications of Effectiveness of Cancer Therapy
- Decreasing levels indicate good response to treatment and favorable prognosis.
- Persistent levels indicate either a growing tumor or recurrence of previously treated tumor.
- Rising levels show poor response or unfavorable prognosis.

The sensitivity for CA-125 levels greater than 35 µ/mL does not have sufficient sensitivity to be considered as a screening method. CA-125 is used as an adjunct to ultrasonography or as a initial test with ultrasonography being done in only those cases showing a raised serum levels. CA-125 is increased in 85% of nonmucinous ovarian cancers and measurement is a useful way to monitor response to chemotherapy.

Risk Scoring

A widely recognized method of estimating the risk of malignant ovarian cancer based on initial workup is the risk of malignancy index (RMI). It is recommended that women with an RMI score over 200 should be referred to a center with experience in ovarian cancer surgery. The RMI is calculated as follows:

\[
\text{RMI} = \text{Ultrasound score} \times \text{Menopausal score} \times \text{CA-125 level}
\]

where
- Ultrasound score
- Menopausal score
- CA-125 level

There are two methods to determine the ultrasound score and menopausal score, with the resultant RMI being called RMI 1 and RMI 2, respectively, depending on what method is used (Table 2).
Differential Diagnosis
The detection of ovarian cancer in the early stage is often impossible. Patients with advanced ovarian cancer present with a wide variety of nonspecific signs and symptoms such as abdominal, gastrointestinal, pain, constitutional, urinary and pelvic.10

Because these symptoms are associated with large number of unrelated conditions, the diagnosis of advanced stage ovarian cancer is often delayed by months.

Principles of Management
The involvement of gynecologist is strongly recommended to provide the state of art comprehensive surgical and medical care for both primary and recurrent disease.

Surgical Strategies
There is a debate whether optimal surgical debulking is a function of inherent resectability of the tumor and its biological aggressiveness or the skill of the surgeon. It seems clear that when women are looked after in specialized gynecological oncology units, their overall survival is substantially improved.

Treatment of Early Ovarian Cancer
In stage IA unilateral ovarian cancer, unilateral oophorectomy and surgical staging has to be considered when fertility has to be retained. Stage I, grade 1 tumors need no adjuvant therapy but all others require adjuvant chemotherapy. Treatment scheme for patients with advanced stage ovarian cancer is shown in Flow chart 1.

Primary Cyto Reduction (Surgical Staging for Ovarian Cancer)
International Federation of Gynecology and Obstetrics (FIGO) staging is based on findings at surgical exploration (Tables 3 and 4). A preoperative evaluation should exclude the presence of extraperitoneal metastases. The importance of thorough surgical staging cannot be overemphasized because subsequent treatment will be determined by the stage of disease.11

Technique for Surgical Staging
An midline or paramedian abdominal incision is recommended to allow adequate access to the upper abdomen. The ovarian tumor should be removed intact, if possible, and a frozen histologic section should be obtained.12 If ovarian malignancy is present and the tumor is apparently confined to the ovaries or the pelvis, thorough surgical staging should be performed. Staging involves the following steps:

- Any free fluid, especially in the pelvic cul-de-sac, should be submitted for cytologic evaluation.
- If no free fluid is present, peritoneal washings should be performed by instilling and recovering 50–100 mL of saline from the pelvic cul-de-sac, each paracolic gutter and beneath each hemidiaphragm.
- A systematic exploration of all the intraabdominal surfaces and viscera is performed, proceeding in a clockwise fashion from the cecum cephalad along the paracolic gutter, and the ascending colon to the right kidney, the liver and gall bladder, the right hemidiaphragm, the entrance to the lesser sac at the paraaortic area, across the transverse colon to the left hemidiaphragm, down the left gutter and the descending colon to the rectosigmoid colon. The small intestine and its mesentery from the Treitz ligament to the cecum should be inspected.
- Any suspicious areas or adhesions on the peritoneal surfaces should be biopsied. If there is no evidence of disease, multiple intraperitoneal biopsies should be performed.
- The diaphragm should be sampled either by biopsy or by scraping with a tongue depressor and obtaining a sample for cytologic assessment.
- The omentum should be resected from the transverse colon, a procedure called an infracolic omentectomy.

### Table 2: Risk of malignancy index for malignant ovarian cancer

<table>
<thead>
<tr>
<th>Feature</th>
<th>RMI 1</th>
<th>RMI 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrasound abnormalities</td>
<td>0 = No abnormality</td>
<td>0 = None</td>
</tr>
<tr>
<td>• Multilocular cyst</td>
<td>1 = One abnormality</td>
<td>1 = One abnormality</td>
</tr>
<tr>
<td>• Solid areas</td>
<td>3 = Two or more abnormalities</td>
<td>4 = Two or more abnormalities</td>
</tr>
<tr>
<td>• Bilateral lesions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Ascites</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Intra-abdominal metastases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menopausal score</td>
<td>1 = Premenopausal</td>
<td>1 = Premenopausal</td>
</tr>
<tr>
<td></td>
<td>3 = Postmenopausal</td>
<td>4 = Postmenopausal</td>
</tr>
<tr>
<td>CA-125</td>
<td>Quantity in U/mL</td>
<td>Quantity in U/mL</td>
</tr>
</tbody>
</table>

RMI 2 of over 200 has been estimated to have a sensitivity of 74–80%, a specificity of 89–92% and a positive predictive value of around 80% of ovarian cancer9
• The retroperitoneal spaces should be explored to evaluate the pelvic and paraaortic nodes. This surgery involves typically, removal of uterus, tubes and ovaries together with infracolic and gastrocolic omentum and surgical staging. In addition, up to 30% of cases either large bowel or small bowel resection is required to effectively leave the disease less than 1 cm in diameter. The surgical resection of all gross disease, also referred to as optimal debulking is associated with improved disease free internal and overall survival compared to patients where extensive surgery has not been done. When women has ovarian cancer and the surgery is performed by a gynecologist, it is more likely to include appropriate staging and optimal cytoreduction than surgery performed by an obstetrician, gynecologist or general surgeon.\textsuperscript{13}

**Germ Cell Tumors**

Initial evaluation includes a detailed physical examination and investigations like hemogram, ultrasound, X-ray chest,
### Table 3: International Federation of Gynecology and Obstetrics (FIGO) staging for primary carcinoma of the ovary

**Stage I**  
*Growth limited to the ovaries*

- **Ia**  
  Growth limited to one ovary; no ascites containing malignant cells
  No tumor of the external surface; capsule intact

- **Ib**  
  Growth limited to both ovaries; no ascites containing malignant cells
  No tumor on the external surfaces; capsules intact

- **Ic**  
  Tumor either stage Ia or Ib but with tumor on the surface of one or both ovaries; or with capsule ruptured; or with ascites present containing malignant cells or with positive peritoneal washings

**Stage II**  
*Growth involving one or both ovaries with pelvic extension*

- **IIa**  
  Extension and/or metastases to the uterus and/or fallopian tubes

- **IIb**  
  Extension to other pelvic tissues

- **IIc**  
  Tumor stage IIa or IIb but with tumor on the surface of one or both ovaries; or with capsule(s) ruptured; or with ascites present containing malignant cells or with positive peritoneal washings

**Stage III**  
*Tumor involving one or both ovaries with peritoneal implants outside the pelvis and/or positive retroperitoneal or inguinal nodes. Superficial liver metastasis equal stage III. Tumor is limited to the true pelvis, but with histologically proven malignant extension to small bowel or omentum*

- **IIIa**  
  Tumor grossly limited to the true pelvis with negative nodes but with histologically confirmed microscopic seeding of abdominal peritoneal surface

- **IIIb**  
  Tumor of one or both ovaries with histologically confirmed implants of abdominal peritoneal surfaces, none exceeding 2 cm in diameter. Nodes negative

- **IIIc**  
  Abdominal implants greater than 2 cm in diameter or positive retroperitoneal or inguinal nodes or both

**Stage IV**  
*Growth involving one or both ovaries with distant metastasis. If pleural effusion is present, there must be positive cytologic test results to allot a case of stage IV. Parenchymal liver metastasis equals stage IV*

### Table 4: Carcinoma of the ovary—staging

<table>
<thead>
<tr>
<th>International Federation of Gynecology and Obstetrics (FIGO)</th>
<th>TNM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary tumor cannot be assessed</td>
<td>TX</td>
</tr>
<tr>
<td>0 No evidence of primary tumor</td>
<td>T0</td>
</tr>
<tr>
<td>I Tumor confined to ovaries</td>
<td>T1</td>
</tr>
<tr>
<td>IA Tumor limited to one ovary, capsule intact, no tumor on ovarian surface, no malignant cells in the ascites or peritoneal washings</td>
<td>T1a</td>
</tr>
<tr>
<td>IB Tumor limited to both ovaries, capsules intact, no tumor on ovarian surface, no malignant cells in the ascites or peritoneal washings</td>
<td>T1B</td>
</tr>
<tr>
<td>IC Tumor limited to one or both ovaries, with any of the following: Capsule ruptured, tumor on ovarian surface, positive malignant cells in the ascites or positive peritoneal washings</td>
<td>T1c</td>
</tr>
<tr>
<td>II Tumor involves one or both ovaries with pelvic extension</td>
<td>T2</td>
</tr>
<tr>
<td>IIA Extension and/or implants in uterus and/or tubes, no malignant cells in the ascites or peritoneal washings</td>
<td>T2a</td>
</tr>
<tr>
<td>IIB Extension to other pelvic organ, no malignant cells in the ascites or peritoneal washings</td>
<td>T2b</td>
</tr>
<tr>
<td>IIC IIA/B with positive malignant cells in the ascites or positive peritoneal washings</td>
<td>T2c</td>
</tr>
<tr>
<td>III Tumor involves one or both ovaries with microscopically confirmed peritoneal metastasis outside the pelvis and/or regional lymph nodes metastasis</td>
<td>T3 and /or N1</td>
</tr>
<tr>
<td>IIIA Microscopic peritoneal metastasis beyond the pelvis</td>
<td>T3a</td>
</tr>
<tr>
<td>IIIB Macroscopic peritoneal metastasis beyond the pelvis 2 cm or less in greatest dimension</td>
<td>T3b</td>
</tr>
<tr>
<td>IIIC Peritoneal metastasis beyond pelvis more than 2 cm in greatest dimension and/or regional lymph nodes metastasis</td>
<td>T3c and /or N1</td>
</tr>
<tr>
<td>IV Distant metastasis beyond the peritoneal cavity</td>
<td>M1</td>
</tr>
</tbody>
</table>
CT of abdomen and pelvis to determine the extent of disease. Serum markers like AFP, β-hCG and LDH are important in diagnosis and management of germ cell tumors.

Early stages are cured with appropriate surgery and adjuvant BEP CT. Stage 1A dysgerminomas and stage 1A grade 1 immature teratomas can be eradicated with surgery alone. Most patients in whom a contralateral ovary and uterus are preserved, can anticipate normal menstruation and have a reasonable probability of having a healthy offspring.

**Laparoscopic Staging of Ovarian Cancer**

Advances in technology have broadened the indications for laparoscopic surgery and it is now accepted practice in the routine management of benign adnexal masses. Laparotomy remains the gold standard for management of ovarian cancer. The routine use of laparoscopy for surgical staging of early ovarian malignancies, second look surgery, assessment for cytoreductive surgery in advanced disease should not be considered as it is still undergoing evaluation.

Ovarian cancer is treated with a combination of chemotherapy after surgery. An exception would be in carefully selected cases when the tumor is confined to the ovary.

**CHEMOTHERAPY**

Paclitaxel and cisplatin based combinations are the first line of chemotherapy for invasive ovarian tumors. The platin compounds include cisplatin and carboplatin. Cisplatin and carboplatin appear to be comparable in terms of efficacy, but combinations of paclitaxel and carboplatin is preferred because of reduced toxicity. The old standard of cisplatin/cyclophosphamide has been replaced by combinations of cisplatin/paclitaxel which demonstrated high overall response rates (73% vs 60%) and progression free survival (18 months vs 13 months). Complete clinical response (51% vs 31%) and median survival (38 months vs 24 months) has been better with cisplatin/paclitaxel regimen. Paclitaxel 175 mg/m² over 3 hours with carboplatin with an area under the concentration—time curve [AUC of 5 to 7.5 (PC)] is an accepted regimen. This combination has the advantage of being given as outpatients and better toxicity profile. To date there is no data that more than six cycles of chemotherapy are required for induction.

**Response to Chemotherapy**

This is assessed by monitoring serum CA-125 values in patients with an increased preoperative value. A decrease in value is associated with tissue regression and a progression is associated with a serial increase.

After six cycles of paclitaxel-platinum chemotherapy the clinical response rate exceeds 70%. Unfortunately progression occurs in 10–15% of cases.

**Second Look Laparotomy**

To assess response to first line chemotherapy, second look laparotomy is generally reserved for patients participating in clinical research protocols. The rationale for the performance lies in the ability to detect patients with residual disease below the limits of clinical detection. On basis of physical examination, radiographic studies and biochemical testing, patients who meet these requirements undergo second look surgery. Approximately 50% will have no documented evidence of disease, 25% will harbor microscopic residual disease, 25% will have gross residual disease. It is debated whether subsequent management decisions based on information gained by second look procedure leads to improved or longer survival.

**Chemotherapy**

After six cycles of paclitaxel-platin based chemotherapy the clinical response exceeds 70%. Unfortunately, progressive disease occurs in 10–15% of patients. The optional post-treatment surveillance after first line chemotherapy has not been determined. By convention patients are seen at 2–3 month intervals and a CA-125 is performed in addition to physical examination.

**INTERPERITONEAL CHEMOTHERAPY**

The intraperitoneal route of administration for cisplatin and paclitaxel chemotherapy is the primary treatment of optimally resected stage III ovarian cancer and is an acceptable therapeutic alternative to intravenous chemotherapy with carboplatin and paclitaxel. It can be used in patients with optimally resected tumors who have a good performance status and are in overall good health.

**IMMUNOTHERAPY**

Trials of monoclonal antibodies directed towards ovarian cancer associated antigens are being conducted. Monoclonal antibodies directed towards CA-125 (Ovarex) and toward the human milk fat globulin (HMFG) tumor associated antigens have been conducted.

There is currently a great deal of interest in the use of immunotherapies in ovarian cancer. Cytokines have been used extensively in second line therapy, and the activity of interferon-α, interferon-γ and interleukin-2 have been demonstrated.

**GENE THERAPY**

It will not be unrealistic to foresee a time when each patient’s tumor will be assessed for the presence of various suppressor genes and oncogenes depending upon molecular biological
profile and individual gene therapy prescribed. However, as our understanding of the molecular levels becomes clearer, then it can be confidently predicted that gene therapy alone may prove optimal modality to ensure cure for all patients with ovarian cancer.

**MANAGEMENT OF RECURRENT DISEASE**

Many chemotherapy treatment options are currently available with recurrent ovarian cancer. Patients refractory to platinum based chemotherapy have poor prognosis and should be entered into clinical trials and supportive care. Relapse within 6 months of platinum based therapy should be treated with second line agents. Some of the commonly used drugs are topotecan, oral etoposide, altretamine, gemcitabine, ifosfamide, vinorelbine, liposomal doxorubicin and radiation therapy. Although a number of agents are available for recurrent cancer, the response rates are modest ranging from 20% to 35% and duration of response limited ranging from 2 months to 4 months.

**PROGNOSIS**

Ovarian cancer usually has a relatively poor prognosis. It is disproportionately deadly because it lacks any clear early detection or screening test, meaning that most cases are not diagnosed until they have reached advanced stages. More than 60% of women presenting with this cancer have stage III or stage IV cancer, when it has already spread beyond the ovaries.

The 5-year survival rate for all stages of ovarian cancer is 47%. For cases where a diagnosis is made early in the disease, when the cancer is still confined to the primary site, the 5-year survival rate is 92.7%.

**REFERENCES**

21. Surveillance, Epidemiology, and End Results Program. Survival rates based on SEER incidence and NCHS mortality statistics, as cited by the National Cancer Institute in SEER Stat Fact Sheets—Ovarian Cancer.
INTRODUCTION

Trophoblastic tumors are fetal allografts in maternal tissues and present unique biological, immunological and pathological problems. The screening programs for persistent trophoblastic disease following evacuation of hydatidiform mole have been instrumental in the near elimination of fatalities from sequelae to mole. Most patients with metastatic diseases are now cured and usually retain reproductive function. This is achieved with the development of sensitive assay systems to precisely measure human chorionic gonadotropin (hCG) and the availability of effective chemotherapy.

GESTATIONAL TROPHOBLASTIC DISEASE

Gestational trophoblastic disease (GTD) is the terminology now used to span the spectrum of cellular proliferation ranging from the various forms of hydatidiform mole, through invasive mole (IM) and gestational choriocarcinoma (CC) to placental site trophoblastic tumors (PSTTs). It is now well-recognized that molar pregnancy comprises two distinct entities, complete hydatidiform mole (CHM) and partial hydatidiform mole (PHM), which differ on the basis of chromosomal pattern, gross and microscopic pathology and clinical presentation. PSTT is a rare neoplastic subtype of GTD. Epithelioid trophoblastic tumor (ETT) is the most recently described and rarest of the trophoblastic tumors.

Gestational trophoblastic diseases include:
- Complete hydatidiform mole (Fig. 1)
- Partial hydatidiform mole
- Invasive mole
- Gestational choriocarcinoma (Fig. 2)
- Placental site trophoblastic tumor
- Epithelioid trophoblastic tumor.

Complete hydatidiform mole and PHM differ in their invasive potential and propensity for malignant transformation. Approximately 8–20% of patients with CHM may be expected to develop persistent trophoblastic disease following molar evacuation. PHM gives rise to persistent trophoblastic disease in less than 3% of cases.

GESTATIONAL TROPHOBLASTIC NEOPLASIA

This terminology is now used to include all malignant forms which replaces the terms chorioadenoma destruens, metastasizing mole and choriocarcinoma. The persistent elevation and plateauing of the hCG without any other clinical or radiological evidence of the disease (chemical only) is also a gestational trophoblastic neoplasia (GTN) and it is not
essential to make a histological verification for diagnosis of GTN. PSTT should be classified separately.

**NORMAL TROPHOBLAST**

Trophoblast populations of normal placenta are composed of cytotrophoblast, syncytiotrophoblast and intermediate trophoblast. Cytotrophoblast and syncytiotrophoblast form the villous trophoblast that covers the chorionic villi. The cytotrophoblast is the trophoblastic stem cell. In the villi which are in contact with the placental bed, the cytotrophoblast merges imperceptibly with the trophoblastic columns. They usually express cytokeratins but produce little or no hormones. Syncytiotrophoblast is formed from fusion of cytotrophoblast and is composed of multinucleated cells with abundant dense cytoplasm. It secretes large amounts of hCG, some human placental lactogen (hPL) and placental alkaline phosphatase (PLAP) but has little capacity for further proliferation. After 8 weeks, production of hCG decreases while hPL and PLAP increase as pregnancy advances. Syncytiotrophoblast also synthesizes estrogen and progesterone. Intermediate trophoblast can be further subdivided into villous intermediate trophoblast located in the villous columns, implantation site intermediate trophoblast located in the placental site and chorionic type intermediate trophoblast located in the chorionic laeve of the fetal membranes.

Studies using monoclonal antibodies with high sensitivity and specificity for measuring hCG and its free subunits suggest that trophoblastic cells in complete and partial moles differ significantly in the manner in which they secrete the free subunits of hCG. Complete moles have higher serum levels of free α-hCG whereas partial moles have higher levels of β-hCG.

**GENETICS OF HYDATIDIFORM MOLES**

The male and female gametes are unique in having a haploid set of chromosomes. At fertilization the complete complement of 23 pairs is restored. The fertilized egg before division duplicates its chromosome so that each daughter cell has a complete set of 23 pairs.

Vassilakos P, Suzulman AE, Surti U and Fisher RA have clearly demonstrated that CHM and PHM are separate syndromes with different genetic background.

**Complete Hydatidiform Mole**

Chromosomes in CHM are entirely paternally derived. The ovum loses its maternal haploid set of 23X by an obscure mechanism and is fertilized by a sperm containing paternal haploid set of 23X. Further development takes place by duplication of the 23X to form 46XX without simultaneous cell division (Fig. 3) (monospermic-homozygous). Nearly 95% of complete moles are formed in this manner and rarely 46XY and 46XX moles are found as a result of fertilization of an “empty egg” by two sperms carrying X and Y or X and X chromosomes (dispermic diploidy—heterozygous). The resulting moles are totally androgenetic and therefore total allografts in the mother instead of being hemiallografts, as in normal pregnancy. It has been suggested that heterozygous moles are more prone to develop IM and CC, but this lacks conclusive evidence.
Partial Hydatidiform Mole

Partial hydatidiform mole is a product of a fertilization error. An apparently normal ovum containing 23X haploid set of maternal chromosome is fertilized by two spermatozoa, commonly one with 23X and other with 23Y paternal haploid set of chromosomes, resulting in 69XXY karyotype (Fig. 4). Partial moles are thus diandric triploid. A diploid ovum of 46XX if combined with a paternal haploid set—23X/Y does not result in molar pregnancy. Thus in both complete mole and partial mole, there is a dominance of the zygote by paternally derived chromosomes.

CLINICAL PATHOLOGY OF GESTATIONAL TROPHOBLASTIC DISEASES

All types of GTDs exhibit proliferation of both syncytiotrophoblast and cytotrophoblast cells which maintains secretion of hCG. PSTT arising from the intermediate trophoblast cells produces low levels of hCG and hPL.

Complete Hydatidiform Mole

The classical histologic features of complete mole are generalized diffuse hyperplasia of both cytotrophoblast and syncytiotrophoblast often associated with cytological atypia, generalized edema of chorionic villi which distend to form central cisterns giving the macroscopic appearance of “bunch of grapes,” and absence of an embryo which perishes before 1 mm size, embryonic death and resorption occurring before the formation of fetal erythrocytes (Fig. 5). Fisher and others in 1997 reported the presence of fetal blood cells in seven CHMs by polymerase chain reaction amplification of DNA. Their conclusion was that fetal blood cells may be present in the villi of CHMs and the presence of fetal erythrocytes alone should not be considered indicative of a diagnosis of PHM. Even though hyperplasia of the trophoblast is the important factor in molar disease, this does not give a reliable guide to the subsequent development of persistent disease.

Partial Hydatidiform Mole

Partial hydatidiform mole is formed by diandric triploidy and the placenta is characterized by focal, variable hydropic villi and usually by focal, mild trophoblastic hyperplasia predominantly confined to the syncytiot (Fig. 6). Fetal vessels are usually present and contain nucleated fetal erythrocytes. The embryo usually survives to an average age of 9 weeks. Since, the incidence of triploidy is 1–2% in clinical abortions, the diagnosis of partial mole may be made more frequently if histopathological examination is routinely done. As hydropic degeneration of the villi is not clinically evident in all cases and as evidence of fetal tissues persist, partial moles are often diagnosed as missed abortion. The presence of swollen villi affected only part of the placenta; a fetus, often with congenital malformations, was frequently found and excessive trophoblastic proliferation was either absent or very mild. It is thought that the persistence of the maternal haploid sets of chromosomes in partial moles results in a
milder clinical course. It was thought that partial mole does not transform into choriocarcinoma. Recently, Seckl et al. have reported three cases of choriocarcinoma following partial mole.16 Many other reports of malignant sequelae following PHM was reported by many other authors also subsequently.17-19

**Invasive Mole**

The majority of CHMs remit after evacuation and curettage, but the tendency in some instances to invade the myometrium resulting in uterine perforation and extension to adjacent organs is well-known and approximately 16% of CHMs behaved in this way.20,21 Histologically the appearance of the chorionic villi is similar to that of other CHMs, but swelling of villi is less often seen in deeply implanted IMs and histological diagnosis is based on the excessive trophoblastic proliferation, markedly irregular shape of villi and their invasive nature.

Invasive mole denotes molar villi found in places other than the original implantation site, usually in the myometrium, but it may be harbored in the vagina or lungs. It is a locally invasive, rarely metastatic lesion characterized microscopically by trophoblastic invasion of the myometrium with identifiable villous structures. Most IMs show moderate to marked trophoblastic activity and persistence of villous structures. It behaves like blood-borne deposits of a malignant neoplasm. The histological diagnosis of IM is rarely made, as hysterectomy is seldom done and it is difficult to identify from curettings.22 It is associated with uterine subinvolution, postmolar bleeding and rising hCG level. Deep penetration into the myometrium can lead to perforation of the uterus and massive intraperitoneal hemorrhage. Chemotherapy may be started on the basis of rising hCG level and it is not necessary to confirm the histopathological diagnosis of IM or CC.

**Gestational Choriocarcinoma**

This is a malignant neoplasm in which differentiation toward villous cytотrophoblastic and syncytiotrophoblastic is seen. It can occur after complete mole, partial mole, normal pregnancy, abortion or ectopic pregnancy. In some cases there is no known antecedent pregnancy and it is postulated that CC may develop from a conceptus ab initio.23 The tumor is composed of cytотrophoblastic and syncytiotrophoblastic cells without villous formation. It stimulates virtually no stromal reaction and is therefore essentially a mixture of hemorrhage and necrosis with tumor cells scattered within the mass. On microscopic examination, viable tumor is usually confined to the rim of the neoplasm as CC lacks an intrinsic vasculature, the tumor cells deriving nutrition by invasion of maternal blood vessels. Widespread intravascular dissemination to lungs, brain and other sites is common. The metastatic sites have a tendency to rapidly outgrow their blood supply resulting in necrosis and hemorrhage.

**Placental Site Trophoblastic Tumor**

Placental site trophoblastic tumor is a name proposed by Scully and others, two decades ago to describe a variant of gestational trophoblastic tumor (GTT).24 It is a rare type of GTN and is composed mainly of intermediate cytotrophoblastic cells arising from the placental implantation site. These tumors can result from any type of antecedent pregnancy and are locally invasive and less widely metastatic. PSTT produces more of hPL than hCG as it contains less syncytiotrophoblast and hence hCG may not serve as a reliable tumor marker for follow-up. However, clinically the diagnosis should be suspected when hCG levels are low relative to the tumor burden. Necrosis is more prominent in PSTT as opposed to hemorrhage in GTN and vascular invasion is not as common as in GTN. The tumor invades the myometrium by dissecting between the smooth muscle fibers. Treatment of this condition is primarily surgical with multiagent chemotherapy if indicated. In a series of 13 patients following hysterectomy for PSTT, a 43% recurrence was reported.25 Placental site trophoblastic tumor usually present with amenorrhea or irregular vaginal bleeding months or years after a normal pregnancy, an abortion or rarely, a hydatidiform mole and origin from both moles and normal pregnancy has been demonstrated genetically.27,28 Occasionally, the patient may be pre or postmenopausal.27 The mean interval from the last pregnancy is 3.4 years but ranges from less than 2 years to over 5 years, as was seen in a review of 34 cases at Charing Cross Hospital.29 The uterus in PSTT is usually enlarged and pregnancy proteins such as hCG, hPL and β1-glycoprotein (SP-1) are elevated although hCG is seldom as high as in CC. In rare instances (< 10% of reported cases), PSTT may be associated with nephrotic syndrome, which has remitted after eradication of the tumor.26

**Epithelioid Trophoblastic Tumor**

This is a rare form of trophoblastic tumor described recently. It is composed of chorionic-type intermediate trophoblast and is distinct from choriocarcinoma and PSTT. The tumor is composed of sheets and nests of mononuclear trophoblast with clear, eosinophilic and vacuolated cytoplasm resembling “chorionic-type” intermediate trophoblast. ETT usually presents as a discrete uterine mass and the biological behavior appears similar to PSTT.30

**Epidemiology**

The earlier report of an increased incidence of hydatidiform mole among Asian countries was probably as a result of hospital based rather than population based studies. The incidence of hydatidiform mole is around 1 per 1,000 pregnancies in most parts of the world and perhaps as high as 2 per 1,000 in Japan.31 The hospital based data in the author’s series from Calicut Medical College is 5 per 1,000 deliveries.32
Many studies have documented an increased incidence of hydatidiform mole among women over 35 and an even greater increase over 40 years of age. Some of the studies showed a modest increase in risk in teenagers.

The history of a previous mole imparts nearly 10 times risk for subsequent molar pregnancy. For those with two previous moles, the risk reported by Bagshawe et al. was 1 in 6.5 pregnancies. An increased risk has been observed among women whose partners were above 45 years. The age related differences in the incidence of hydatidiform mole may be due to the defective gametogenesis at the extremes of reproductive life. No maternal or paternal age related risk was seen in partial moles. There is some evidence to suggest that the deficiency of β-carotene and animal fat in diet may increase the risk of hydatidiform mole. Studies from Vietnam suggest a possible link with exposure to the chemical, Agent Orange.

The most important risk factor for choriocarcinoma is a history of hydatidiform mole, accounting for a 1,000–2,000 fold increased risk of subsequent CC. Estimates of proportion of women who develop choriocarcinoma after a molar pregnancy have ranged from 2% to 19%. Persistent trophoblastic disease or GTN may follow complete and partial mole with an incidence of approximately 8% and 0.5% respectively. Nearly 50–60% of CC patients have a history of hydatidiform mole. The risk of developing GTN after a normal delivery is 1 in 40,000–50,000. In a series from Charing Cross Hospital, 13% of the patients treated for choriocarcinoma had developed GTN following normal delivery. GTN following normal delivery tends to be a highly aggressive variant with wide spread metastases. GTN may also follow spontaneous abortion or ectopic pregnancy. Maternal age above 40 is a strong risk factor and there is some evidence to suggest that teenage patients are also at a higher risk.

**PRESENTATION OF MOLAR PREGNANCY**

**Vaginal Bleeding**

Vaginal bleeding is the most common presenting symptom in patients with complete mole, occurring in nearly 95% of cases. Molar chronic villi may disrupt maternal vessels by separating from the decidua resulting in large amounts of retained blood in the endometrial cavity. Retained blood may undergo oxidation and "prune juice" like fluid may leak from the uterine cavity. Sudden and profuse bleeding can also occur in patients with complete mole. Majority of the patients will be anemic.

**Excessive Uterine Enlargement**

The uterine size on palpation tends to be larger than gestational age in nearly 50% of the cases. Excessive uterine size is usually associated with markedly elevated hCG from trophoblastic overgrowth. In the rest of the cases the size may be corresponding to the period of gestation and in some, it may even be small for age.

**Theca Lutein Cysts (Fig. 7)**

Clinically evident theca lutein cyst is seen in 20–25% of cases along with marked elevation of hCG. While theca lutein cysts are generally noted at the time of presentation, they may enlarge substantially after evacuation. The mean regression time for the lutein cyst is 8 weeks. Acute ovarian torsion and rupture needing emergency laparotomy has been noted in patients with large lutein cysts. Ultrasound guided aspiration is recommended to avoid such complications. During hysterectomy, ovaries may be retained, after aspiration of the cyst.

**Preeclampsia**

With the routine use of ultrasound in early pregnancy, especially in patients with first trimester bleeding, the diagnosis of hydatidiform mole is made at an early stage resulting in a dramatic reduction in the incidence of preeclampsia amongst patients with hydatidiform mole. About 10% of molar pregnancies develop preeclampsia and this is associated with hyperemesis and unduly enlarged uterus.

**Hyperemesis Gravidarum**

Hyperemesis requiring antiemetic treatment and hospitalization for correction of electrolyte disturbances may be seen in 15–20% of cases.

**Hyperthyroidism**

Clinically evident hyperthyroidism with elevation of serum free thyroxine (fT4) is seen in about 5% of cases. The thyroid function tests will rapidly return to normal after evacuation of the moles. It is proposed that high levels of hCG has
thyroid-stimulating hormone (TSH) like activity. Patients with uncontrolled hyperthyroidism may develop "thyroid storm" at the time of induction of anesthesia and evacuation. Thyroid storm is characterized by hyperthermia, delirium, atrial arrhythmias including atrial fibrillation, cardiovascular collapse and coma. Administration of β-adrenergic blocking agents prevents or rapidly reverses many of the cardiovascular and metabolic complications of thyroid storm. Antithyroid drugs and high-dose hydrocortisone are also used in treating these patients.

Respiratory Insufficiency

About 2% of patients may develop respiratory insufficiency. Patient may present with tachycardia, tachypnea, anxiety or confusion immediately after evacuation. While embolization of molar tissue to the pulmonary vasculature may contribute to respiratory distress, it may also result from cardiovascular complication of toxemia, thyroid storm or overzealous fluid replacement. Some patients may require intubation and mechanical ventilation.

With the availability and use of ultrasound for the diagnosis and evaluation of early pregnancy now a day, diagnosis of CHM is made before the patients develop the classic signs and symptoms. Investigation of first trimester bleeding by ultrasound is a routine now and it may diagnose an abnormal pregnancy like hydatidiform mole at the earliest. In some cases, routine ultrasound examinations, for the purposes of confirming gestational age or for antenatal screening will lead to the diagnosis of asymptomatic molar pregnancy.

Presentation of Partial Mole

Patients with partial mole usually do not present with the classical features of complete mole. The vaginal bleeding is slight and occurs late. The clinical diagnosis before evacuation is incomplete or missed abortion in more than 90% of cases. The diagnosis of partial mole is made after histological review of products of conception from presumed incomplete or missed abortion.

DIAGNOSIS

Ultrasonography (Figs 8 and 9)

Ultrasonography has proved to be an accurate and sensitive technique for the diagnosis of complete mole. Complete mole produces a characteristic vesicular pattern due to generalized swelling of the chorionic villi. The chorionic villi in first trimester complete moles tend to be smaller and have less cavitation. However, the majority of first trimester complete moles still demonstrate a typical ultrasound appearance of a complex, echogenic intrauterine mass containing multiple small cystic spaces. Ultrasonography may also contribute to the detection of PHM mole. The ultrasound findings observed in these cases are an excessively enlarged placenta, cystic spaces within the placenta, gestational sac which is either empty or containing amorphous echoes or a growth retarded fetus.

Human Chorionic Gonadotropin Measurement

Markedly elevated hCG levels are commonly seen in patients with complete mole. Genest et al. reviewed the clinical and pathological characteristics of 153 cases of complete mole managed at the New England Trophoblastic Disease Center between 1980 and 1990 and suggested that pre-evacuation hCG levels were greater than 100,000 U/L in 46% of the patients. The measurement of a high hCG level (> 100,000 U/L) may therefore suggest the diagnosis of a complete molar pregnancy, particularly when associated with vaginal bleeding and uterine enlargement. In contrast, PHM is less commonly associated with markedly elevated hCG values. Studies using monoclonal antibodies with high sensitivity and specificity for measuring hCG and its free subunits
suggest that trophoblastic cells in complete and partial moles differ significantly in the manner in which they secrete the free subunits of hCG.\(^{43,44}\)

**MANAGEMENT OF HYDATIDIFORM MOLE**

When a diagnosis of complete or partial molar pregnancy is made, the most appropriate method of evacuation should be decided. Assessment of the patient for the presence of medical complications, including anemia, preeclampsia, hyperthyroidism and respiratory insufficiency, is essential. It is appropriate to have a baseline hCG estimation in addition to routine blood and urinalysis.

The primary management of hydatidiform mole is evacuation of the mole. Cross matched blood for transfusion and appropriate fluid resuscitation measures should be kept ready at the time of evacuation. Evacuation is done under anesthesia by suction evacuation and intravenous oxytocin is given to promote uterine contraction. When the uterus is empty, the uterine cavity is gently curetted using a sharp curette to ensure complete evacuation and this specimen is sent for histopathological examination. Big theca lutein cysts if present are managed by ultrasound guided aspiration to avoid torsion. It may take 6–8 weeks for disappearance of the lutein cysts. An ultrasound examination after 1 week of suction curettage will ensure completeness of evacuation. A repeat (check) curettage is done if the pre-evacuation size of the uterus was greater than 16 weeks and if there is evidence of incomplete evacuation on ultrasonography after 1 week.

Hysterectomy with mole in situ (Fig. 10) is an option in patients who are above 40 years and who desire no further childbearing. Hysterectomy reduces the risk of subsequent development of CC\(^{45}\) and completely eliminates the risk of IM. It does not eliminate the potential for malignant sequelae and monitoring with \(\beta\)-hCG levels is mandatory. Theca lutein cysts if present are left alone after reducing the size with multiple needle pricks. Hysterotomy is not to be considered as a method of evacuation of the mole. Patients who are Rh negative should receive Rh immune globulin at the time of evacuation as the Rh D factor is expressed on trophoblast\(^{41}\) and also due to the reported presence of fetal RBCs in complete mole.\(^{17}\)

**Chemoprophylaxis**

The use of chemoprophylaxis during evacuation of hydatidiform mole remains controversial. However, several investigators have reported that chemoprophylaxis can reduce the incidence of postmolar tumor.\(^{46,47}\) In a prospective randomized trial, Kim et al. observed that in patients with high-risk complete mole, prophylactic chemotherapy reduced the incidence of postmolar tumor from 47% to 14% and among patients with low-risk complete mole, prophylactic chemotherapy did not influence the incidence of persistent disease (7.7\% versus 5.6\%).\(^{47}\) However, patients who developed persistent tumor after prophylactic chemotherapy required more courses of chemotherapy. Prophylactic chemotherapy may be useful in patients with high-risk complete mole when hormonal follow-up is either unavailable or unreliable. The main objection for exposing all patients with molar pregnancy to chemotherapeutic agents is that only a small percentage are at risk for developing persistent disease, who are readily identified by proper follow-up.

**Human Chorionic Gonadotropin (hCG) Assays**

A reliable assay for total hCG is the key to the management of patients with trophoblastic disease. The assay must measure all portions of hCG molecule particularly free beta-subunit, hyperglycosylated hCG (hCG-H), nicked hCG and hCG missing the terminal carboxyl segment. These fractions are more common in neoplasia than is total hCG. It is important to ensure that the laboratory provides accurate assay results, as false low values may result in inappropriate management. The most appropriate automated immunometric test for managing GTN presently appears to be the DPC Immulite series of tests.\(^{48}\)

**Follow-up (Flow Chart 1 and Table 1)**

Patients with complete and partial mole should be monitored with serial hCG values after evacuation to assure that they achieve complete and sustained remission. The expected fall in serum \(\beta\)-hCG per week follows a log linear fashion. Patients must be encouraged to use reliable contraception during the period of follow-up. There is no conclusive evidence to suggest that oral contraceptives (OCs) increase the risk of development of CC.\(^{49}\) Present day low-dose OC pills may be safely prescribed without increasing the risk of persistent disease. With the controversy surrounding this issue, it may be prudent to advise them on barrier contraceptives till the hCG is normal and then to start on OC pills.

Fig. 10: Specimen of hysterectomy with mole in situ
devices are avoided due to the risk of perforation. Serum hCG measurement may be done prior to evacuation and one day after evacuation.

On an average, 20% of patients undergoing evacuation of CHM develop postmolar GTD, with a range of 6–36% as reported by various authors. In our own series of 1,569 cases of hydatidiform moles diagnosed and treated over a period of 15 years from June 1990, the incidence of GTN was 20.5%.53

Criteria for the Diagnosis of Postmolar Trophoblastic Neoplasia54

This is shown in Table 2.

Diagnostic Evaluation

The optimal management of GTN requires a thorough evaluation of the extent of the disease prior to the initiation of the chemotherapy. All patients should undergo a careful pretreatment evaluation including physical examination, hCG measurement, hepatic, renal and thyroid function tests and complete blood count. The metastatic workup should include chest X-ray, ultrasonography or computed tomography (CT) scan of abdomen and pelvis and CT or magnetic resonance imaging (MRI) scan of the head. Extensive workup with CT and MRI is not required in cases diagnosed on the basis of serum hCG levels following molar evacuation unless they show resistance to chemotherapy.

Classification of the Malignant Gestational Trophoblastic Disease

This is shown in Table 3.
multiagent chemotherapy. High-risk metastatic disease should always be started on combination chemotherapy.

**FIGO Staging and Risk Factor Scoring for Gestational Trophoblastic Neoplasia 2002 (Table 4)**

Placental site trophoblastic tumor will be categorized separately from other GTN. The criteria for the diagnosis of GTN is shown in Table 1.

Criteria for methods used to diagnose metastases in trophoblastic neoplasia are the following:
- Chest X-ray is appropriate for diagnosing lung metastases and is used to evaluate the risk factor score according to the number and size of lung metastases (CT scanning is preferable)
- Liver metastases may be diagnosed by CT scanning or by ultrasound
- Brain metastases may be diagnosed by MRI or CT scanning
- To diagnose intra-abdominal metastases, CT scanning is preferable.

**FIGO Risk Factor Scoring Values (Table 5)**

In order to stage and allot a risk factor score a patient’s diagnosis is allocated to a stage as represented by Roman numerals I, II, III and IV. This is then separated by a colon from the actual risk factor score expressed in Arabic numerals. For purposes of reporting, patients are divided into low-risk (score 0-6) and high-risk (score > 7) groups. Bagshawe’s risk scoring system, which was modified and adopted by WHO, was further modified in the International Federation of Gynecology and Obstetrics (FIGO) risk scoring system. From the WHO scoring, ABO blood grouping has been omitted and liver metastasis has been given a score of 4. PSTT has been classed separately. There is no intermediate-risk group.

Examples of low-risk and high-risk staging/scoring are as follows:
- A 45-year-old lady has a hydatidiform mole evacuated uneventfully. The hCG decreases from a pre-evacuation value of 80,000 mIU/mL to 1,000 mIU/mL 4 weeks after the D and C, but then persists between 800 and 1,000 mIU/mL for 4 weeks. Clinical examination shows no abnormality or evidence of metastases. Ultrasound of the uterus shows a 2 cm lesion in the myometrium. Chest X-ray is negative. This patient is staged FIGO stage “I: 2”. The two risk factors present are the patient’s age and the hCG of 1,000 mIU/mL, i.e. $10^3$.
- A 41-year-old lady has bleeding after her third successful pregnancy. Histology of curettings is suggestive of CC. Ultrasound shows a 5 cm lesion in the myometrium and chest X-ray shows multiple (more than eight) lung nodules, 1-2 cm in size. Brain MRI shows a 3 cm lesion in the right frontal lobe of the brain. This patient is staged FIGO “IV: 13” as she is aged 41 (1) and is post full-term pregnancy (2), has a brain metastasis (4), has more than six metastases to the lung (4) and has a 5 cm lesion in the uterus (2). The histologic confirmation of CC does not add to the risk score by the FIGO system.

**Low-Risk Gestational Trophoblastic Neoplasia**

Patients in FIGO stage I, II or III with risk score of 0 and below are grouped as low-risk GTN and can be started on single-agent chemotherapy. A sustained remission can be achieved in these patients after primary treatment with single-agent chemotherapy. Methotrexate and actinomycin D are the primary drugs used in the management of non-metastatic disease. 5-fluorouracil and oral etoposide also gives excellent results.

Guidelines for the management of GTN have been shown in Flow charts 2 and 3.

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<th>Table 4: The International Federation of Gynecology and Obstetrics (FIGO) 2002 staging system for gestational trophoblastic neoplasia</th>
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*Abbreviation: GTN, gestational trophoblastic neoplasia*

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<th>Table 5: The International Federation of Gynecology and Obstetrics (FIGO) risk factor scoring system</th>
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<td>Largest tumor size (cm)</td>
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<tr>
<td>Site of metastasis</td>
</tr>
<tr>
<td>Number of metastasis</td>
</tr>
<tr>
<td>Previous failed chemotherapy</td>
</tr>
</tbody>
</table>

*Abbreviations: hCG, human chorionic gonadotropin; GIT, gastrointestinal tract*
Flow chart 2: Guidelines for the management of gestational trophoblastic neoplasia

Abbreviations: GTN, gestational trophoblastic neoplasia; hCG, human chorionic gonadotropin; CBC, complete blood count; BUN, blood urea nitrogen; Act-D, actinomycin D; MTX, methotrexate; TAH, total abdominal hysterectomy

Source: International Federation of Gynecology and Obstetrics (FIGO) with permission

**Methotrexate**

Methotrexate has been used in the management of malignant GTD since 1950s and achieves up to 100% cure rates in nonmetastatic disease. Pretreatment evaluation of liver function and renal function along with complete hemogram should be done. Total WBC count and platelet count are monitored twice a week. Toxicity includes ulceration of the gastrointestinal (GI) tract, bone marrow depression, alopecia and photosensitivity reaction of the skin. Anemia and infections increase the risk of toxicity. Methotrexate should not be given if there is impairment of renal or liver function. Mild to moderate toxicity is experienced by 25–30% of patients.

**Actinomycin D (Table 6)**

Actinomycin D, given as intravenous infusion at a dose of 9–13 µg/kg for 5 days is an equally effective therapy. The cycle can be repeated every 14 days. Nausea, vomiting, alopecia and transient marrow depression is seen in 30–40% of patients. Local extravasation of the drug may cause sloughing of the tissues and extreme care should be taken in administering the drug, preferably as a diluted infusion via
Flow chart 3: Guidelines for the management of gestational trophoblastic neoplasia

Post-hydadiform mole
stage IV or risk factor ≥ 7

Non-molar GTN diagnosed from metastases

Investigation, staging and risk factor scoring

hCG, CBC, platelets, BUN, creatinine, liver function tests, coagulation studies (if indicated), chest X-ray, pelvic ultrasound. If chest X-ray is positive—CT/USG scan abdomen, particularly liver CT or MRI brain as indicated

Stage I, II, III with risk factor ≥ 7 or stage IV

Multiple agent chemotherapy (e.g. EMA-CO) [for cerebral metastases MTX dose is increased to 1 g/m²]

Resolution

Follow with hCG and clinical surveillance for one year

Persistent neoplasia

Consider surgery for isolated resectable lesions (usually lung, brain or liver)

Second-line multiple agent chemotherapy (EP-EMA)

No response

Consider Taxol/5-FU/Ifosfamide

Table 6: Single-agent regimens for low-risk gestational trophoblastic neoplasms

- MTX
- MTX 0.5 mg/kg IV or IM daily for 5 days
- Pulse MTX weekly 50 mg/m² IM weekly
- MTX/FA
- MTX 1 mg/kg IM or IV on days 1, 3, 5, 7
- FA 0.1 mg/kg PO on days 2, 4, 6, 8
- High-dose MTX/FA
- MTX 100 mg/m² IV bolus
- MTX 200 mg/m² 12-hour infusion
- FA 15 mg q 12 hours in four doses IM or PO beginning 24 hours after starting MTX
- Actinomycin regimens
- ACTD 12 mg/kg IV push daily for 5 days
- ACTD 1.25 mg/m² IV push q 2 weeks

Abbreviations: MTX, methotrexate; IV, intravenous; IM, intramuscular; PO, by mouth; FA, folinic acid (calcium leucovorin); ACTD, actinomycin D

Gestational Trophoblastic Disease

a large peripheral vein. In such a situation, local infiltration with hydrocortisone and lignocaine is advised. Actinomycin D can also be given in alternating cycles with methotrexate to improve the remission rate and to reduce the toxicity.

Methotrexate should be avoided, if there is an abnormality in hepatic or renal function. Patients who develop resistance to sequential single-agent chemotherapy are then treated with combination chemotherapy as for high-risk disease. Several studies have demonstrated the high curability of low-risk metastatic GTD when appropriate therapy is administered. Ross and coworkers were the first investigators to identify the highly favorable prognosis in this group of patients (curing 20 of 21 patients—95%) with relatively non-toxic sequential methotrexate and actinomycin D chemotherapy. Subsequent reports by Brewer et al. and Hammond et al. Goldstein and coworkers, Bagshawe, Jones and Lewis and Lurain et al. documented virtually 100% cure rates in low-risk metastatic disease using initial single-agent chemotherapy.

Single-agent chemotherapy is safe, highly effective, and avoids the greater morbidity associated with multiagent chemotherapy. With appropriate initial classification and selection of patients as well as proper administration of treatment, cure rates approach 100%. It is apparent however, that 30–50% of patients in this category will develop resistance to the first chemotherapeutic agent and require alternate treatment. It is therefore very important to carefully monitor patients undergoing treatment for evidence of drug resistance (plateau or rise in hCG level and/or development of new metastases) so that a change to a second agent can be made at the earliest possible time. Approximately 5–15% of patients treated for low-risk metastatic disease with sequential single-agent chemotherapy will require multiagent chemotherapy with or without surgery to achieve complete remission.

Surgery may be necessary to eradicate persistent disease in the uterus, if all evidence of metastatic disease has disappeared and if the hCG remains elevated despite repeated courses of chemotherapy or rarely to excise isolated pulmonary metastases. Hysterectomy may also be incorporated into the initial management of the patient with low-risk metastatic disease resulting in a higher likelihood of single-agent chemotherapy success, fewer courses of chemotherapy and a shorter duration of treatment.

Chemotherapy Alone

Single-agent chemotherapy is the preferred treatment in patients with stage I disease who desire to retain fertility.
When primary single-agent chemotherapy was administered to 495 patients with stage I GTTs. 452 patients (91.3%) attained complete remission. The remaining 43 resistant patients subsequently achieved remission after combination chemotherapy or surgical intervention. When patients are resistant to single-agent chemotherapy and desire to preserve fertility, combination chemotherapy and want to retain fertility, local uterine resection may help to define the site of the resistant tumor. Low-risk GTN is treated with single-agent chemotherapy. Methotrexate is the drug of choice. Vaginal metastases may bleed profusely because they are highly vascular and friable. When bleeding is substantial, it may be controlled arteriographic embolization of the hypogastric arteries may be required to control hemorrhage from vaginal metastases.

Investigations before starting chemotherapy: Complete blood count and platelets, prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen, blood urea nitrogen (BUN), creatinine and liver function tests.

Drug schedules: Single-agent chemotherapy regimens
- Methotrexate 0.4 mg/kg intramuscular (IM) for 5 days, repeated every 2 weeks. The primary failure rate is 10%
- Methotrexate with leucovorin rescue: Methotrexate 1 mg/kg IM on alternate days for four doses with leucovorin 0.1 mg/kg, 24 hours after each dose of methotrexate. The next course is given after an interval of 15-18 days. Primary failure rate is 20–25%. This is most widely adopted regime
- Methotrexate 50 mg/m² IM weekly (pulse regimen): This is associated with 30% primary failure rate. If it fails, methotrexate 0.4 mg/kg for 5 days can be given or the drug can be changed to actinomycin D 12 µg/kg for 5 days
- Actinomycin D 1.25 mg/m² given every 2 weeks (pulse regimen). The failure rate is 20%
- Actinomycin D 12 µg/kg IV daily for 5 days. Respect every 2 weeks. This can be preferred in patients with hepatic dysfunction. Primary failure rate is less—8%
- Methotrexate 250 mg infusion over 12 hours (pulse regimen). It is associated with high failure rate of 30%.

The low-dose methotrexate folic acid regimen is the most widely used regime with very high success rate. This regime is well-tolerated. Side effects like alopecia or myelosuppression are very rare. Serum hCG value should be repeated weekly. After the first course of chemotherapy, the hCG value is expected to fall by one log or more. This could achieve remission in 87.6% of patients. A second course of chemotherapy is administered if the hCG level does not decline by one log within 18 days of completion of the first course.

Before each course, complete blood count, platelet count, creatinine, BUN and serum glutamic oxaloacetic transaminase (SGOT) should be done. After the first negative hCG level, two to three additional courses of chemotherapy should be administered.

The primary failure rate of the pulse regimens is greater than single-agent 5 days course. The pulse regimens are intended to reduce the cost of therapy. If after a course of the pulse regimen, the hCG level plateaus or rise the 5-day regimen should be adopted. The authors of a Cochrane review of randomized controlled trials (RCTs), on this issue concluded that "pulsed" dactinomycin is superior to weekly parenteral methotrexate at the reported doses. However, the authors believe that well-designed, multicentred, randomized double-blind trials are required to evaluate other chemotherapy regimens, most importantly “pulsed” dactinomycin with the widely used 8-day methotrexate-folinic acid (MTX-FA). If the regression of β-hCG after two courses of MTX-FA regime is inadequate, actinomycin D is substituted. If the decline of hCG is not adequate even after changing to actinomycin D, the patient must be treated with combination chemotherapy.

Actinomycin should be given through a free-running IV infusion. Extravasation can cause severe sloughing. Failure of single-agent regimen is an indication to switch to combination chemotherapy. In single-agent chemotherapy, remission is achieved with only one course in 81.5% of patients. The overall success rate of therapy, which sometimes involves more than one line of treatment in low-risk patients, is reported as nearly 100%.

Single-agent regimens for low-risk GTNs have been shown in Table 6.

Management of High-risk Metastatic Gestational Trophoblastic Disease

The association of the prognostic factors (Table 3) places the patient in the high-risk category and will require multiagent chemotherapy for cure.

High-risk Gestational Trophoblastic Neoplasia

International Federation of Gynecology and Obstetrics stages I, II and III with WHO score 7 or greater or stage IV are high-risk GTN and these patients should be treated initially with multiagent chemotherapy with or without adjuvant radiotherapy or surgery. Until the mid-1980s, the primary multiagent regimen used was methotrexate, actinomycin D and cyclophosphamide (MAC) and reported cure rates ranged from 63% to 71%. Bagshawe and colleagues at Charing Cross Hospital, London developed the seven-drug CHAMOCA protocol in mid-1970s employing cyclophosphamide, hydroxyurea, actinomycin D, methotrexate with folic acid, vincristine and doxorubicin, and reported a primary remission rate of 82%.

After the discovery of etoposide in the late 1970s as a very effective chemotherapeutic agent for GTT, Newlands et al. formulated the etoposide, methotrexate, actinomycin D, EMA-CO regimen (Table 7) employing etoposide, high-dose methotrexate with folic acid, actinomycin D, cyclophosphamide and vincristine with a complete clinical response of 80%. 
Bower et al.76 updated the Charing Cross Hospital experience using EMA-CO to treat 272 women with high-risk disease. There were 11 (4%) early deaths, 214 (78%) complete remission and an additional 33 (12%) complete response to subsequent cisplatin-based chemotherapy and surgery with an overall survival rate of 88%. Kim et al.77 from Korea treated 165 high-risk patients with EMA-CO regimen with overall survival rate of 84%.

The high response rates, good long-term survival and the minimal acute and cumulative toxicity associated with EMA-CO protocol make it the current initial treatment of choice for high-risk metastatic GTT. Colony stimulating factors should be used when necessary to avoid treatment delays, as the success of the EMA-CO regimen seems to depend on treatment given at short intervals without interruption. Granulocyte colony stimulating factor (G-CSF) 300 µg subcutaneously may be given on days 9–14 of each subsequent treatment cycles in patients who develops neutropenia. Chemotherapy should be continued until three consecutive weekly normal hCG values are reached. Two to four courses of EMA-CO regimen are given after the first normal hCG level.

The etoposide, methotrexate, dactinomycin with etoposide and cisplatin (EMA-EP) regimen (Table 7), substituting etoposide and cisplatin for cyclophosphamide and vincristine in the EMA-CO regimen seems to be the most appropriate therapy for patients showing incomplete remission. The bleomycin, etoposide and cisplatin (BEP); etoposide, ifosfamide and cisplatin (VIP) and ifosfamide, carboplatin and etoposide (ICE) protocols were also successful in patients who failed to respond to EMA-CO regimen.

When central nervous system (CNS) metastasis is present, whole brain irradiation (3,000 cGy in 200 cGy fractions) is given simultaneously with initiation of chemotherapy. Brain irradiation has the dual purpose of being both tumoricidal and hemostatic. During radiotherapy, the methotrexate infusion dose in the EMA-CO protocol is increased to 1 gm/m² and 30 mg folinic acid is given every 12 hour for 3 days, starting 32 hour after the infusion begins. As an alternative to brain irradiation, the Charring Cross Hospital group recommended intrathecal as well as high dose intravenous methotrexate.

Liver metastases from CC are ominous as they tend to be extensive disease at multiple sites. There is a significant risk of serious hepatic bleeding, especially during the first course of chemotherapy. Whole-liver irradiation with 2,000 cGy over 2 weeks combined with chemotherapy is recommended to reduce the risk of bleeding.

Intensive multimodality therapy with appropriate combination chemotherapy, adjuvant radiotherapy and surgery has resulted in cure rates of 80–90% in patients with high-risk metastatic GTTs.

### Role of Surgery in the Management of Trophoblastic Disease

Surgery has an important role in the management of GTD. Molar pregnancies should be evacuated by suction curettage and medical methods are best avoided. Hysterectomy may be considered as part of primary evacuation if other gynecological morbidity is present. Additional surgical procedures, especially hysterectomy and thoracotomy are of use in removing known foci of chemoresistant cases with persistent or recurrent high-risk metastatic disease.53,78 Prompt hCG regression within 1 or 2 weeks of surgical resection indicates a favorable outcome. In women with excessive vaginal bleeding, arterial embolization should be considered if maintenance of fertility is desirous. Hysterectomy may be required for the management of excessive uterine bleeding either at presentation or after the onset of chemotherapy and in the management of chemoresistant disease localized to the pelvis. Hysterectomy is the treatment of choice for the management of placental site tumors confined to the uterus. In cases of intra-peritoneal...
bleeding as a result of perforation of the uterus by IM, resection and closure or even hysterectomy may be required.

**Pregnancy following Gestational Trophoblastic Disease**

Patients with GTD may be assured that they may expect a normal reproductive outcome. However, patients with GTD are at an increased risk of developing recurrent molar pregnancy, the reported risk being 1%. Some of the series have reported a higher incidence of abortion. Risk of congenital anomalies is not increased by chemotherapy for GTN. An increased risk of placenta accreta was reported by some authors. All patients should have an ultrasound at 8–10 weeks in the subsequent pregnancy to rule out molar changes.

In our own series, out of the 262 pregnancies following hydatidiform mole, 224 had full-term normal delivery, 17 had cesarean section, 16 ended in abortion, two developed ectopic pregnancy and three patients developed recurrent mole.

**Recurrent Molar Pregnancy**

The risk of recurrent molar pregnancy following one molar pregnancy is approximately 1%, which is an increased risk as compared to the risk of molar pregnancy in the general population (1:1000 pregnancies). In a series of 34 patients who had at least two molar pregnancies between 1965 and 2001 at the New England Trophoblastic Disease Centre, four patients with an initial partial mole had a subsequent complete mole, and six patients with initial complete mole had a subsequent partial mole. 10 patients had repeat partial mole and 14 had repeat complete mole.

The risk of recurrent mole after two molar pregnancies was reported as 15% and 28% respectively by Bagshawe et al. and Sand et al. In patients with recurrent mole, there is an increased risk of persistent GTT. Parazzini et al. reported a three-fold increase in persistent GTT in subsequent molar pregnancies in patients with repeat mole. Among 34 patients with repeat mole, reported by Elizabeth et al. four (20%) out of 20 complete mole and none out of 14 partial moles were treated for persistent GTT following their first molar pregnancy. In contrast, persistent GTT developed following the second mole in eight of 18 (44.4%) complete moles and two of 16 (12.5%) partial moles. Therefore, the risk of persistent GTT after one molar pregnancy is reported to be 11.8% and after two molar pregnancies is 29.4%.

**Repeat Molar Pregnancies with Different Partners**

Tuncer et al. reported that six of their patients developed a molar pregnancy with at least two different partners and one patient with three different partners. Similarly, Magili et al. described a patient who had two molar pregnancies with one partner and developed a third mole following donor insemination. Repeat molar pregnancy with different partners suggests that the abnormality of the oocyte may be contributing to the development of molar pregnancy. Ovum donation may be an option for patients with repeat moles. Elizabeth et al. reported a normal term delivery after ovum donation in a patient who had recurrent mole with different partners.

**In Vitro Fertilization and Recurrent Mole**

Recurrent hydatidiform mole following in vitro fertilization and embryo transfer has been reported by Barash et al. and by Tanos et al. In vitro fertilization with embryo selection does not guarantee the prevention of molar pregnancy. As most complete moles develop by monospermic fertilization, with replication of the paternal chromosomes, attempted prevention of triploid embryos by intracytoplasmic sperm injection alone may not be successful in the prevention of molar disease. The use of IVF with fluorescent in situ hybridization for male sex selection or with DNA typing has been described as a technique for identification of those abnormal products.

**Multiple Pregnancies with Mole and Coexisting Fetus**

This is a rare condition estimated to be 1 per 22,000–100,000 pregnancies. Patients present with what appears to be hydatidiform mole or twin gestation with rapid enlargement of uterus. Careful ultrasound examination will reveal a normal fetus, amniotic sac and placenta with separate molar tissue elsewhere. Partial moles may have a fetus, but have diffuse molar changes throughout the single placenta. However, the diagnostic accuracy of this condition is only 70%. These cases are often diagnosed late, are associated with a live birth rate of around 25%, and are at a higher risk of developing preeclampsia and hemorrhage. The subsequent need of chemotherapy for persistent disease is greater than other molar pregnancies. The present policy is to allow the pregnancy to go to term depending on the patient’s choice. Patients are counseled regarding a substantial risk of fetal loss and they are registered for follow-up. Conservative management of these patients allowing the pregnancy to go ahead unless there are clear cut medical grounds for termination such as preeclampsia or hemorrhage appears to be the treatment of choice.

**Management of Placental Site Trophoblastic Tumor**

For patients with disease localized to the uterus, the treatment of choice is hysterectomy followed by adjuvant chemotherapy in selected cases. Women with metastatic PSTT at the time of diagnosis cannot be cured by surgery alone and treatment
with multiagent systemic chemotherapy is required. Initially there were fears that PSTT was unresponsive to chemotherapy. However, more recently there have been a number of reports demonstrating success of various different multiagent chemotherapeutic regimens in treating metastatic PSTT particularly pulmonary metastases. Data from Charing Cross Hospital, London suggest that EMA-EP is the preferred adjuvant chemotherapeutic regimen. However, the effectiveness of newer anticancer agents such as the taxanes (paclitaxel, docetaxel) and camptothecins (topotecan and irinotecan) need to be evaluated for their effectiveness in GTN.

False Positive Human Chorionic Gonadotropin (hCG)

False positive or “phantom hCG” is now recognized as a problem where patients are treated inappropriately by curettage, laparoscopy, single-agent and multiagent chemotherapy, and even hysterectomy assuming they have trophoblastic tumor. These false positive tests are due to heterophilic antibodies in the blood mimicking hCG in hCG tests. In spite of treatment, the hCG will remain high in such cases. To distinguish false positive from true hCG rise, it is necessary to do the following tests:

- The finding that a heterophilic antibody blocking agent [Scantibodies Inc. heterophilic blocking reagent (HBR)] prevented or limited false detection (confirmatory criterion).
- DPC Immulite® assay and Roche Elecsys® hCG assays are reported not to have false positive results.

Quiescent Gestational Trophoblastic Disease

Highly differentiated trophoblastic tissue remains in the body following mole, normal pregnancy or abortion producing low levels of real hCG. This is slow growing tissue and does not respond to chemotherapy. These cases should be followed up as they may become active and metastatic disease may develop later. Presence of hCG-H is an indication to start treatment. Low levels of hCG is seen in PSTT. An increase in free β-subunit is associated with PSTT.

CONCLUSION

The outcome of GTD depends on the early detection of persistent disease by regular follow-up of patients after evacuation of hydatidiform mole. The regional and national referral centers for management of GTN in the UK and the USA have resulted in very high cure rates and elimination of fatality from GTN. In developing countries including India, there is no such program. It is up to the practicing physicians to organize such follow-up clinics in regional tertiary care centers and start a trophoblastic disease registry for scientific analysis. We at Calicut in the northern region of Kerala in South India, have started such a center 15 years ago and so far have followed-up more than 1,500 cases with excellent results.

One of the fascinating aspects of GTN is the ability of the disease to exist in a quiescent form without producing clinical problems for long periods of time. Clearly there must be a small amount of abnormal tissue present but not producing enough hCG to be detected by currently available assays. These rests of GTN are important since they can be reactivated by the hormonal surge of subsequent pregnancies. The dilemma of false positive hCG versus low persistent levels of real hCG has to be addressed by refining the hCG assay methods.

Essential Update: New Guidelines Issued for Management of Gestational Trophoblastic Neoplasia

In September 2013, the European Society of medical Oncology issued clinical practice guidelines for the diagnosis and treatment of GTD. Recommendations include the following:

- Management of GTN requires pathology review, centralization of care and monitoring of hCG.
- After staging with the FIGO scoring system, treatment may include either single-agent methotrexate or single-agent actinomycin D for low-risk disease or multiagent chemotherapy for patients with high-risk disease.
- Low-risk disease requires 6 weeks of maintenance therapy after normalization of hCG, while high-risk disease with liver or brain metastases requires 8 weeks of maintenance therapy.
- In patients with ultra-high-risk GTN, induction with low-dose etoposide and cisplatin may reduce the risk of early mortality.
- Management of PSTT/ETT varies according to disease stage and risk factors for poor outcome which include the interval from last know pregnancy; patient presenting within 4 years of their last known pregnancy may need hysterectomy with pelvic node sampling, while those presenting later may be treated with multiagent and subsequent high-dose chemotherapy.

REFERENCES


INTRODUCTION
Over past few decades, significant advances have been made in our understanding in the prevention, diagnosis and treatment of the diseases of body of uterus (Figs 1 and 2). Today, the disease is staged surgicopathologically as opposed to clinical staging and different risk factors have been identified as the causative factors of endometrial carcinoma (EC). It is found commonly in postmenopausal women. The median age is around 60 years, with less than 5% occurring in women less than 40 years of age. However, in the recent past, there is evidence of increasing incidence in younger age group and an overall increase in developing and developed countries. This may be due to increased screening, improved hysteroscopic diagnosis, increase in geriatric population and estrogen use. Incidence of cancer endometrium varies widely. The highest incidence is in white Americans and the lowest in India and Japan. In India, it ranks third among gynecological malignancies next to cervix and ovary, the incidence being 2/100,000 women and the ratio of endometrial carcinoma to cervical cancer is 1:15 to 1:25. Adenocarcinoma accounts for 95% of all endometrial cancers, while sarcoma accounts for less than 5%. 74.84% cases of endometrial cancer present in surgical stage-I and 2.9% are in stage IV.
ETIOPATHOLOGY

Multiple epidemiological exogenous and endogenous risk factors have been identified in patients of EC.

Exogenous Risk Factors

The million women study\(^4\) showed that women taking unopposed estrogen are at increased risk of EC compared to those who have never taken hormone replacement therapy (HRT), but if progestogen is added this increased risk disappears. The cancer thus induced, most likely progresses from endometrial hyperplasia, tends to be well-differentiated and carries a better prognosis because of increased surveillance and early detection.\(^5\) Tibolone doubles the risk of EC compared with those not on HRT.\(^5\) Association between tamoxifen and development of EC has been reported.\(^6\) So, women with breast cancer on tamoxifen should have annual screening for EC. Association has been noted with typical high fat and high protein western diet.\(^7\)

Endogenous Risk Factors

Menarche before 12 years or menopause after 52 years is associated with high incidence of cancer endometrium.\(^8\) Nulliparity accounts for 2-3 times more risk of developing EC than multipara and also accounts for poor prognosis.\(^9\) Overweight women (more than 200 lbs) have two fold increased risk of cancer endometrium.\(^10\) It is related to reduced serum hormone binding globulin which is found to be depressed in women with EC.\(^11\) Endometrial adenocarcinoma can occur as a component of Lynch type II family cancer syndrome. Other contributing factors are adenomatous hyperplasia, polycystic ovary syndrome (PCOS), diabetes mellitus, granulosa-theca cell tumor of ovary, hypertension, arthritis and myoma uterus.\(^12\)

Full term pregnancy, menarche after 15 years, use of oral contraceptive (OC) pills,\(^13\) raloxifene,\(^14\) smoking\(^15\) and soy consumption\(^16\) are thought to be protective factors. Protective effect of oral contraceptive used for 1 year lasts for even 10 years after cessation.

PATHOLOGY

Cancer endometrium arises from the glandular component of endometrium in the upper portion of corpus as a friable growth. Spread of the disease occurs initially within the endometrium and/or myometrium, as well as to isthmus and cervix (Figs 3 and 4). Progression beyond the uterus occurs through lymphatic pathways into pelvic and abdominal lymph nodes. Vaginal metastases develop in 10–15% of cases. Those in the lower vagina are usually suburethral and represent vascular embolism. It can metastasize to lungs, liver, brain and bone by hematogenous route. Peritoneal spread is common in aggressive papillary serous carcinoma.

Once in the peritoneal cavity, EC behaves similar to ovarian cancer. The rate of extrauterine tumor spread and lymph node metastasis increases with the depth of myometrial invasion, the degree of endocervical extension and the presence of poor prognostic histologic factors.

Histopathology

According to World Health Organization (WHO)/International Society of Gynecological Pathologists (ISGP) classification,\(^17\) all tumors are microscopically verified (Table 1). The histopathological types are:
Endometrial Carcinoma

107

Table 1: World Health Organization Classification of endometrial carcinoma

<table>
<thead>
<tr>
<th>Category</th>
<th>Subcategories</th>
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<tbody>
<tr>
<td>Endometrioid adenocarcinoma</td>
<td>• With squamous differentiation</td>
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<tr>
<td></td>
<td>• Villoglandular</td>
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<td></td>
<td>• Secretory</td>
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<td></td>
<td>• With ciliated cells</td>
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<tr>
<td>Other adenocarcinomas</td>
<td>• Mucinous adenocarcinoma</td>
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<td></td>
<td>• Serous adenocarcinoma</td>
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<td></td>
<td>• Clear-cell adenocarcinoma</td>
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<td>• Mixed adenocarcinoma</td>
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<td></td>
<td>• Squamous cell carcinoma</td>
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<td>• Transitional cell carcinoma</td>
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<td></td>
<td>• Small cell carcinoma</td>
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<tr>
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<td>• Undifferentiated carcinoma</td>
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- Endometrioid adenocarcinoma:
  - Adenocarcinoma
  - Adenoacanthoma (Adenocarcinoma with squamous metaplasia)

- Adenosquamous carcinoma (mixed adenocarcinoma and squamous-cell carcinoma)
- Mucinous adenocarcinoma
- Papillary serous adenocarcinoma
- Clear-cell adenocarcinoma
- Undifferentiated carcinoma
- Mixed carcinoma

Primary sclerosing cholangitis (PSC), clear cell and adenosquamous, are associated with significantly poor prognosis.

CLINICAL PRESENTATION

One to five percent of cases of endometrial cancer are asymptomatic, detected by Pap smear, ultrasonography (USG) (Figs 5A to D), computed tomography (CT) scan or hysterectomy for some other purpose. About 10% of cases of postmenopausal bleeding have endometrial cancer, but over 90% of cases of endometrial cancer present with abnormal bleeding. 10% of patients present with purulent

Figs 5A to D: (A) Doppler ultrasound in a patient with endometrial carcinoma; (B) Transvaginal ultrasound in a 52-year-old menopausal patient with the complaints of irregular bleeding and offensive vaginal discharge since 2–3 months; (C) Doppler ultrasound in the same patient as described in Figure 5C; (D) Color Doppler examination of a 58-year-old postmenopausal patient presenting with irregular bleeding and abdominal pain since 1 month

vaginal discharge, sometimes blood tinged. In few patients, bleeding is not overt because of cervical stenosis and they present with pelvic discomfort and uterine enlargement with eventual associated infection. Pain of an extraordinary character (Simpson’s pain) is noted by 15% of patients. The pain is referred to hypogastrium or to both iliac fossae, not severe, and tends to appear at the same time each day lasting for 1–2 hours. It is probably because of expulsive uterine contraction.

General physical examination is frequently normal. Abdominal mass, ascites, hepatic or omental metastases may be revealed in advanced cases. Examination of vulva, vagina and cervix reveal no abnormality. On bimanual examination, the uterus may be small or enlarged due to pyometra, associated myoma or tumor infiltration. In advanced cases uterus may be irregular and fixed. Rectovaginal examination does evaluate the parametria and cul-de-sac for nodularity or indurations. Adnexal palpation may indicate their involvement.

Screening

As life-time risk of development of EC is only 1.2%,\textsuperscript{18} the routine mass screening for EC by Pap smear/aspiration cytohistology is not cost effective. However, women at risk may be subjected for screening by transvaginal sonography (TVS), hysteroscopy and biopsy.

INVESTIGATIONS AND DIAGNOSIS

Suspicion of EC should be borne in mind in women with postmenopausal bleeding with a healthy cervix, postmenopausal women with pyometra, presence of endometrial cells (normal or abnormal) on Pap smear and in perimenopausal women with abnormal uterine bleeding. Various devices such as Gravlee jet wash; Vabra\textsuperscript{a} aspirator and Pipelle\textsuperscript{b} are used for aspiration cytology. Pipelle\textsuperscript{b} (a soft flexible plastic suction cannula) biopsy is reliable with 97.5% sensitivity.\textsuperscript{19} Negative cytohistology does not rule out EC. The diagnostic accuracy of curettage is high\textsuperscript{20} though there is chance of over staging in 40–50% of stage II cases.\textsuperscript{21}

As a minimum, the pathology report should indicate both the tumor type and the degree of differentiation.

Assessment of endometrial thickness by TVS plays an important role in diagnosis and screening. In postmenopausal women with endometrial thickness greater than 4 mm, 22% have been reported to have EC\textsuperscript{22} and no women with endometrial thickness less than 4 mm had carcinoma endometrium.\textsuperscript{23} However, recurrent bleeding after a negative evaluation is an indication for repeat sonography, hysteroscopy and curettage.

Hysteroscopy is currently regarded as the gold standard for the assessment of any abnormal uterine bleeding. It prevents overlooking small circumscribed EC, which might have been missed by blind curettage alone. It also gives additional information regarding tumor extension, particularly to that of uterine cervix. The risk of dissemination of cancer cells into the peritoneal cavity through fallopian tube during hysteroscopy, the implication of which is uncertain, can be minimized by using carbon dioxide insufflation instead of saline.\textsuperscript{24}

Computed tomography scan has been widely replaced by magnetic resonance imaging (MRI) (Fig. 6) in detecting the depth of myometrial invasion, extraterine spread and involvement of cervix with overall accuracy of 71–97%.\textsuperscript{25} CT and MRI are equivalent in terms of evaluating nodal metastasis, but neither is good enough to replace surgical lymph node assessment. Despite high accuracy, MRI and CT should be reserved for high risk and morbidly obese patients unsuitable for surgical staging.

Elevated values of cancer antigen-125 (CA-125) correlate with extraterine spread of disease. Cystoscopy, sigmoidoscopy, intravenous urography, etc. are reserved for locally advanced disease.

MANAGEMENT

Surgery remains the cornerstone in the management of EC. Since 1988, the Gynecologic Oncology committee of Federation Internationale de Gynecologie et d’Obstetrisme (FIGO) has recommended surgical staging of endometrial cancer, as multiple studies indicated the inaccuracy of clinical staging. Therefore, once the diagnosis of endometrial cancer has been made, routine presurgical evaluation is performed to assess operability. However, clinical staging is useful in advanced cases where surgery is not possible.

Fig. 6: Magnetic resonance imaging scan showing endometrial adenocarcinoma in the same patient as described in Figure 5D

Staging

The clinical and surgical stagings for endometrial cancer are shown in Tables 2 and 3, respectively.

Notes about Staging

Histopathology—Degree of Differentiation

Cases of carcinoma of the corpus should be grouped with regard to the degree of differentiation, as follows:

- **G1** less than equal to 5% of a non-squamous or non-morular solid growth pattern
- **G2** equal to 6–50% of a non-squamous or non-morular solid growth pattern
- **G3** greater than equal to 50% of a non-squamous or non-morular solid growth pattern.

Notes on Pathologic Grading

- Notable nuclear atypia, inappropriate for the architectural grade, raises the grade of a grade I or grade II by one
- In serous and clear cell adenocarcinomas, nuclear grading takes precedence
- Adenocarcinomas with squamous differentiation are graded according to the nuclear grade of the glandular component.

Rules Related to Staging

- Corpus cancer is now surgically staged, therefore procedures previously used for determination of stages are no longer applicable (e.g. the findings of fractional curettage to differentiate between stage I and stage II)
- It is appreciated that there may be small number of patients with corpus cancer who will be treated primarily with radiation therapy. In these cases, the clinical staging adopted by FIGO in 1971 would still apply, but designation of that staging system would be noted
- Ideally, width of the myometrium should be measured along with the depth of tumor invasion
- As a minimum, any enlarged or suspicious lymph node should be removed in all patients. For high-risk patients (grade III, deep myometrial invasion, cervical extension, serous or clear cell histology), complete pelvic lymphadenectomy and resection of any enlarged para-aortic nodes is recommended.

Importance of Surgical Staging

The surgicopathological staging provides more precise information about the extent of the disease and predicts treatment outcome and identifies the need for adjuvant treatment. Creasman et al. in 1987, identified important risk factors like uterus size, tissue differentiation, depth of myometrial invasion, presence of intraperitoneal metastasis and LVI, which correlated with the incidence of lymph node invasion and in turn the prognosis. Cervical, adnexal and vaginal involvement change the stage of disease and hence the prognosis. A decrease in survival rate is observed in presence of cervical spread. A decrease in survival rate is observed in presence of cervical spread. A decrease in survival rate is observed in presence of cervical spread. A decrease in survival rate is observed in presence of cervical spread. A decrease in survival rate is observed in presence of cervical spread. A decrease in survival rate is observed in presence of cervical spread. Wolfson et al. in 1992 reported 25% error in clinical staging as compared to surgical staging. About 12% of clinical stage I had more advanced disease, 59% of clinical stage II was down staged and 37% were upstaged. Positive peritoneal cytology is found in 8–13% of cases and there is no evidence that patient with

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Source: ACOG Technical Bulletin No. 155
positive peritoneal cytology face worse prognosis. Nuclear grade and lymphovascular space invasion (LVSI) have been shown to be independent prognostic variables. The estrogen receptor (ER) and progesterin receptor (PR) levels in the tissue are indicators of survival, lack of which carry poor prognosis. Aneuploid tumors are associated with increased risk of early recurrence and disease-related mortality.

**Prognostic Variables in Carcinoma Endometrial**

The stage of the disease is the most important prognostic factor. A number of other individual prognostic factors for disease recurrence or survival have been identified (Table 4).

**Age**

Age is an independent prognostic variable. Endometrial cancer occurring in women less than 50 years of age has better prognosis than that occurring after 70 years. The lesser survival in the older age group is because of the increased incidence of extraterine invasion and deep myometrial invasion at the time of diagnosis which is due to higher incidence of grade III tumors and unfavorable histological types (papillary serous and clear cell).

**Histologic Type**

Clear cell and papillary serous types of endometrial cancer are associated with increased risk for development of invasive disease and metastasis than endometroid type. The overall survival for patients with these aggressive subtypes is only 33% as against 92% for patients with endometroid type tumors.

**Histologic Grade**

Patients with grade III tumors were more than five times likely to develop recurrence than those with grade I and II.

### Table 4: Prognostic variables in endometrial carcinoma

- Age
- Histological types
- Histological grade
- Myometrial invasion
- Lymph vascular space invasion
- Isthmus cervix extension
- Adnexal involvement
- Lymph node metastasis
- Intraperitoneal tumor
- Tumor size
- Peritoneal cytology
- Hormone receptor status
- DNA ploidy/proliferative index
- Genetic/molecular tumor markers

**Management of Stage I and Stage II**

**Surgical Staging Procedure**

Surgery remains the main modality of treatment in stage I and II cancers. Treatment algorithm for early stage endometrial cancer is shown in Flow chart 1. The minimum surgery required is usually an exploratory laparotomy by suprapubic midline incision. Peritoneal washings are taken from the pelvis and abdomen with 100-150 mL of saline, followed by careful exploration of the intra-abdominal viscera. The omentum, liver, peritoneal cul-de-sac and adnexal surfaces should be examined and palpated for any possible metastases, followed by careful palpation of suspicious or enlarged nodes in the aortic or pelvic areas. The standard surgical procedure is an extraperitoneal hysterectomy and bilateral salpingo-oophorectomy (BSO). Adnexal removal is recommended even if the adnexae appear normal, as they may contain micrometastases. Vaginal cuff removal has neither surgical nor survival benefit. Parametrial tissue removal is not necessary in stage I and IIa.

In stage IIb, modified radical hysterectomy is the standard of treatment. Primary radiotherapy followed by extraperitoneal hysterectomy is an alternative mode of treatment.

Uterus, after hysterectomy, should be sent for immediate frozen section analysis. In case of non-availability of such facility, uterus should be cut open to look for tumor size, depth of myometrial invasion, cervical extension, so that spot decision about lymphadenectomy can be taken. It has been shown that naked eye examination of the fresh surgical specimen accurately predicts the presence and depth of myometrial invasion in approximately 90% of cases.

Although mandated through the staging system, lymphadenectomy of the pelvis and para-aortic areas remains controversial. Selective node sampling is of dubious value as a routine; complete lymphadenectomy being reserved for cases with high-risk features. In the United Kingdom, the Medical Research Council’s (MRC) ASTEC (A Study in the Treatment of Endometrial Cancer) trial, which randomized women to pelvic lymphadenectomy or no lymphadenectomy in stage I endometrial cancer, showed no therapeutic benefit of lymphadenectomy.

Lymphadenectomy is not required in grade I tumor with greater than half invasion or grade II tumor confined to the endometrium, because the chance of nodal metastasis in these cases is less than 4% (Table 5). Tumor size greater than 2 cm has 21% incidence of nodal metastasis whereas tumor less than 2 cm with less than half myometrial invasion rarely has nodal metastasis. Lymphadenectomy in grade II adenocarcinoma is controversial. However, this is indicated in grade II tumor less than 2 cm, radiological and clinical suspicion of lymph node infiltration and in other high-risk cases. When pelvic nodes are negative, para-aortic node involvement is only about 2%. One-third of patients with pelvic node metastasis will have some para-aortic
Patients with suspicious aortic or common iliac node, positive pelvic node and with other high-risk situations are candidates for para-aortic lymphadenectomy. Complete low, i.e. infra-inferior mesenteric para-aortic lymphadenectomy should be done when indicated.

**Vaginal Hysterectomy**

In selected patients with marked obesity, poor medical status or uterovaginal prolapse, vaginal route has a place, particularly in grade 1 disease, but intraperitoneal extension of disease and nodal status cannot be assessed. Moreover, there is chance of intraperitoneal spillage with uterine manipulation.
Laparoscopic Surgical Procedure

Laparoscopic-assisted surgical staging (LASS) in EC is feasible and safe procedure, especially in obese and elderly high-risk women. Surgical approaches utilized in the laparoscopic staging of EC include, recommended surgical staging procedure, laparoscopic-assisted vaginal hysterectomy (LAVH) and retroperitoneal lymphadenectomy, whenever indicated. Lymph node harvest is comparable to that of laparotomy. Moreover, it has definite role in incompletely staged patients to decide for adjuvant treatment. Taking into consideration the benefits of early recovery, mobilization, discharge and less requirement of pain relief, time has come to state that laparoscopy is the procedure of choice for women with EC.

Adjuvant Therapy

Most patients do not need any adjuvant treatment. However in some, depending on surgicopathological features indicating risk of relapse, adjuvant treatment is instituted. The patients are classified into groups at different risk of relapse depending on various factors (Flow chart 2).

Adjuvant therapy is in the form of radiotherapy, chemotherapy and hormone therapy. While vaginal vault recurrence is common in tumor extending to cervix, upper abdomen failure is typical in papillary serous carcinoma. The pattern of failure anticipated plays an important role in selecting type of adjuvant therapy. Radiotherapy would take care of the local recurrence at vault while chemotherapy can exert a systemic effect.

Radiotherapy

In addition to established surgicopathological risk factors deciding adjuvant radiotherapy, another factor that is often ignored is patient’s age. A recent update of Postoperative Radiation Therapy for Endometrial Cancer (PORTEC) shows that age greater than 60 years is an independent predictor of locoregional relapse, hence candidate for adjuvant radiotherapy. Vaginal irradiation: Intravaginal irradiation therapy (IVRT) is given in intermediate risk group by vaginal ovoids. Pelvic irradiation could be teletherapy and brachytherapy given in high-risk group patients. External pelvic radiation reduces the risk of pelvic recurrence, but without any survival benefit. However, cases with superficial cervical invasion can be dealt with IVRT only. The role of extended field radiotherapy is still debated. It is utilized in para-aortic nodal metastasis, multiple pelvic node metastasis and gross serosal or adnexal involvement. The place of whole abdomen radiation (WAR) is not established. It may be of use in high-risk cases.

Vaginal Vault Irradiation

Postoperative Vaginal Irradiation

- Stage I—G1 and G2 with superficial invasion, G3 with no invasion
- Stage II (occult)—G1 and G2 with superficial myometrial invasion.

Dose: High dose rate Iridium or low dose rate Cesium source via colposat to deliver 6,000–7,000 cGy.
**External Pelvic Irradiation**
- Stage I G3 with any degree of myometrial invasion
- Stage I G1 and 2 with deep myometrial invasion
- Large volume tumor
- Any tumor with lymph vascular space invasion.
  *Dose: 4,500–5,040 cGy over 5–6 weeks.*

**External Field Irradiation**
Patients with positive para-aortic nodes as the only evidence of spread outside the pelvis.
*Dose: 4,500–5,000 cGy.*

**Whole Abdomen Irradiation**
- Papillary serous and clear cell tumors which have a propensity for upper abdominal secondaries
- Patients with adnexal and upper abdominal disease which has been surgically excised
- Should not be given for gross residual intraperitoneal disease
  *Dose: 3,000 cGy in 20 fractions.*

**Chemotherapy**
Routine use of chemotherapy is not justified. However, it is used in high-risk tumors to reduce and prevent extrapelvic failure. Cyclophosphamide + adriamycin + cisplatin given for six cycles give 2 years progression-free survival in 79% cases and an overall survival of 83%.44

**Hormone Therapy**
Though widely used in the past, meta-analysis of different trials failed to demonstrate any survival benefit of progesterone as an adjuvant therapy.45
Progestogen therapy (medroxyprogesterone acetate 600 mg/day) may prove a viable alternative to surgery in young women in early stage disease with well-differentiated adenocarcinoma desirous of fertility.46

**Stage III Management**
In operable stage III a disease, the treatment of choice is surgicopathological staging with total abdominal hysterectomy (TAH) and BSO or radical hysterectomy or tumor reductive surgery whichever is feasible. Surgical eradication of all macroscopic disease should be the aim. This is followed by radiotherapy and/or chemotherapy as required. With surgery along with radiotherapy survival rate at 5 years is around 50%.

In stage III b and c, which is usually inoperable, pelvic radiation followed by surgery or external pelvic replacement therapy (RT) or extended field RT followed by intrauterine and intravaginal brachytherapy is the treatment of choice.

**Stage IV Management**
Patients with extrapelvic metastases are managed with surgery, radiotherapy and systemic chemotherapy or hormone therapy. Recent years have seen increased role of aggressive cytoreduction in patients with advanced EC. Optimal cytoreduction is a good indicator of improved survival. Gynecologic Oncology Group (GOG) recently reported that chemotherapy (doxorubicin-cisplatin) significantly improved progression-free survival and overall survival in comparison to whole abdomen irradiation in stage III and IV endometrial cancer having maximum of 2 cm of postoperative residue.47 Local radiation may be beneficial, particularly in brain or bone metastases, and occasionally pelvic radiotherapy may help in providing local tumor control and preventing bleeding or complications from local disease.

**Follow-up**
Patient should be seen every 3–4 months in first 3 years, every 6 months in the third to fifth year, and annually thereafter. At each visit patient should have a complete physical and pelvic examination and a Pap smear taken from vaginal vault. USG and CA-125 measurement, CT scan, MRI may be done when considered appropriate. Chest X-ray should be taken annually. Pelvic and distant recurrences should be confirmed by fine needle aspirate cytology (FNAC) or laparoscopy/ laparotomy.

**Management of Recurrent Disease**
Approximately, 10–15% of patients with early EC relapse; 80% recurrences occur within 2 years of treatment and most of them are detected by physical examination and imaging. In surgery alone, group recurrence mostly occurs in pelvis and treatment is radiotherapy. Pelvic exenteration can be tried in selected cases, but with significant morbidity. Recurrences after surgery with adjuvant RT or RT alone are usually extrapelvic. Local RT can be tried in isolated recurrences outside the previous RT field.

Patients with nonlocalized recurrent tumors may benefit from progestin therapy (medroxyprogesterone acetate 50–100 mg thrice, daily or megestrol acetate 80 mg 2–3 times daily).47 Depo-provera 400 mg intramuscular (IM), weekly and megestrol acetate 80 mg 2–3 times per day, are also used. Hormone therapy is useful in metastatic hormone receptor positive disease and hormone receptor positive tumor with positive peritoneal cytology. The effect of hormone therapy sustains for several years.48 The progestin therapy is continued as long as the disease is static or in remission. Maximum clinical response may not be apparent for 3 or more months after initiating therapy. Chemotherapeutic agents like cisplatin,
adriamycin and traxol has been recommended for patients with advanced or recurrent disease, nonamenable to cure by surgery and/or radiotherapy. Tamoxifen in doses from 10–40 mg/day has been shown to be effective in the management of metastatic and recurrent endometrial cancer.

**Hormone Replacement Therapy**

As 80% of recurrence occur within 2 years, it is worthwhile to withhold HRT during this period. Conjugated estrogen 0.625 mg along with medroxyprogesterone acetate (MPA) 2.5 mg daily can be used thereafter. However, selective ER modulator like raloxifene would be the best choice for women with EC.

**ENDOMETRIAL CANCER-DIAGNOSED POSTHYSTERECTOMY**

Diagnosis of endometrial cancer after hysterectomy presents management dilemma, particularly if adnexae have been retained. If high-risk factors are identified, complete surgical staging with removal of both the adnexae is recommended. Alternately, external beam radiation therapy to the pelvis may be used. Patient with a grade I or II lesion with minimal myometrial invasion and no LVSI generally require no further therapy.

**RESULTS**

The overall 20 years survival rate for all forms of EC is about 80%. The survival is best described in Tables 6 and 7. Long-term survival depends on stage, grade of disease, myometrial invasion and histology. Cure rate in stage I and II uterine carcinomas is good. In stage I cases, inner half myometrial invasion show a 5-year survival of 82–97% as compared to 66–85% survival with more than half myometrial invasion. There is a reported 96%, 5-year survival rate in patients with no residue at surgery as against 65% for those who had residual disease. In high-risk cases, IVRT reduces the recurrence rate from 12% to 4%. The pelvic recurrence in surgery only patients was 32% as compared to 17% in surgery with radiotherapy.

**FERTILITY PRESERVATION IN ENDOMETRIAL CANCER**

The problem of fertility preservation in endometrial cancer occurs when young women develop the disease, which is a possibility among those with chronic anovulation. Conservative management in the form of large doses of progestagens may be thought of in younger patients with well-differentiated endometrial cancer, without evidence of myometrial or cervical involvement made out by MRL.
In a study by Seli E et al. medroxyprogesterone at a dose of 200–800 mg was given continuously for 3 months and endometrial sampling repeated. Resolution was found to occur in 50–80% but recurrence was seen in 30–40%. Progestagens incorporate intrauterine system have also been studied in such situations in small studies. These serve only to delay definitive treatment till pregnancy is completed.

**FUTURE DIRECTIONS**

Endometrial cancer results from multiple genetic events including alterations in proto-oncogenes, tumor suppressor genes and deoxyribonucleic acid (DNA) repair genes. Moreover, there is a strong correlation between local cellular immune response and patient outcome in endometrial cancer. Her-2/neu, p53, ER and PR, cathepsin D, and lamininare immunohistochemically detectable additional prognostic factors; need to move from the laboratory to clinical application. A sensitive molecular marker needs to be identified, though there may be controversies about which molecular marker is useful, there is little doubt that molecular genetic studies of endometrial cancers and precursor lesions will lead to advances in patient care.

**REFERENCES**

INTRODUCTION
Germ cell tumors account for 20–25% of all ovarian tumors. Of these, 95% are benign while less than 5% are malignant. In the first two decades of life, almost 60% of ovarian tumors are of germ cell origin and 30% of these are malignant. However, in girls less than 10 years of age, up to 84% of germ cell tumors are malignant.

Although uncommon, they are aggressive tumors that are generally curable, if found and treated early. Due to their rarity, natural progression of disease into malignant giant cell tumor (GCT) is ill defined. Correlation of histological subtypes with prognosis has led to formulation of individualized treatment plans. Dramatically improved prognosis is seen with the use of combination chemotherapy after initial surgery for many women with these tumors.

Managing these tumors in adolescents pose a dilemma in many cases in trying to meet the objective of cure with radical therapy on one hand and preservation of reproductive function on the other.

HISTOGENESIS (FLOW CHART 1)
Most germ cell tumors develop in the gonads from undifferentiated germ cells. Malignant germ cell tumors can also develop in extragonadal sites such as the retro-peritoneum or the mediastinum.

Biology
Recent studies of germ cell tumors have suggested that cyclin D2 is overexpressed in malignant germ cells and is oncogenic. GCT differentiation may be influenced by several interacting pathways, such as regulators of germ cell totipotentiality, embryonic development, and genomic imprinting. Sensitivity and resistance to chemotherapy may be based in part on a p53-dependent apoptotic pathway.

Cytomorphological studies of tumor revealed that Trisomy 3, 8, 12 and 14 were the most common numerical changes identified. Isochromosome 12p is the only recurrent structural...
rearrangement in ovarian GCT, particularly in dysgerminomas and malignant GCT with a yolk sac component.

Immature teratomas frequently have chromosomal abnormalities (63%), of which gains of chromosomes 3, 8, 12 and 14, losses of chromosomes 4 and 13, and several structural rearrangements including isochromosome 12p are common. It has been proposed that cytogenetically abnormal immature teratomas are more likely to recur than their cytogenetically normal counterparts.

Mature teratomas that have undergone malignant transformation display multiple numerical and structural chromosomal anomalies principally involving chromosomes X, 1, 3, 4, 5, 9, 10 and 11.

From the cytogenetic data available to date, it appears that isochromosome 12p gains of chromosomes 1, 8, 21 and loss of chromosomes 6 and 13 are responsible for tumorigenesis.

**Mechanism of Germ Cell Transformation**

Almost 100% of tumors show increased copy numbers of isochromosome 12p.

Increased isochromosome 12p copy number, cyclin D2 expression, consistent near triploid-tetraploid chromosome numbers, and increased expression of wild-type p53 result in tumorigenesis. Abnormal chromatid exchanges during meiotic crossing over leads to increased isochromosome 12p copy number and cyclin D2 overexpression. In cells containing unrepaired DNA strand breaks, cyclin D2 can block p53-dependent apoptosis and leads to reinitiation of cell cycle and genomic instability. This abnormal cell division and proliferation may be mediated by postnatal and pubertal gonadotropin stimulation.

Recently, models involving other cyclins and inhibitory molecules have also been proposed.

**CELLULAR CLASSIFICATION**

The World Health Organization (WHO) has described the following histologic subtypes.\(^3\)\(^6\)

1. Dysgerminoma
2. Other germ cell tumors
   a. Endodermal sinus tumor (rare subtypes are hepatoid and intestinal)
   b. Embryonal carcinoma
   c. Polyembryoma
   d. Choriocarcinoma
   e. Teratoma:
      - Immature
      - Mature:
        - Solid
        - Cystic:
          - Dermoid cyst (mature cystic teratoma)
          - Dermoid cyst with malignant transformation
      - Monodermal and highly specialized:
        - Struma ovarii

- Carcinoid
- Struma ovarii and carcinoid
- Others (e.g. malignant neuroectodermal and ependymoma)

f. Mixed forms.

**PATHOLOGICAL TYPES**

**Dysgerminoma**

It is the most common germ cell tumor accounting for about 30–40% of all ovarian germ cell tumors. Almost 70–80% of dysgerminomas occur between the age group of 10 years to 30 years. About 70% of dysgerminomas are stage 1 (confined to one or both ovaries) at diagnosis. Bilateral involvement is present in 10–15% cases.\(^7\) Bilateral ovarian spread may also be seen in advanced stage disease and with mixed germ cell tumors. Approximately, 5% of dysgerminomas are found in phenotypic females with abnormal gonads.\(^8\) Dysgerminoma has a predilection for lymphatic dissemination especially to retroperitoneal lymph nodes. Hematogenous spread to lung, liver and bone occurs in advanced stage disease.

Grossly, it is a solid, fleshy and lobulated tumor with rubbery consistency. Histologically, the tumor is composed of large round, polyhedral cells with clear cytoplasm and central prominent vesicular nuclei. The cells are arranged in cords or clumps due to thin fibrous septae that may be infiltrated by lymphocytes, foreign body giant cells and granulomas. Occasionally, dysgerminomas may contain syncytiotrophoblastic giant cells producing elevated serum human chorionic gonadotropin (hCG) levels.\(^9\)

**Endodermal Sinus Tumor**

It is also known as yolk sac tumor, as it is derived from primitive yolk sac. These tumors occur in patients in the second decade of life with a median age of 16–18 years. They frequently present following spontaneous rupture and hemorrhage.

Grossly, these tumors are unilateral, large, smooth, encapsulated with lobulated surface. Histology reveals a wide range of patterns (microcystic, endodermal sinus, solid, alveolar-glandular, papillary, macrocystic, hepatoid, primitive endodermal). The classic pattern contains Schiller-Duval bodies (central capillary surrounded by layers of germ cells) and eosinophilic globules containing alpha-fetoprotein (AFP).\(^10\) Intracellular and extracellular hyaline droplets (periodic acid-Schiff positive) are also seen in endodermal sinus tumor (EST).

These tumors secrete tumor marker AFP that may be useful in diagnosis, monitoring treatment response and prognosis.

**Embryonal Carcinoma**

Pure embryonal carcinoma is extremely rare. It is usually present as part of mixed germ cell tumor. Embryonal carcinoma
secretes estrogens leading to precocious pseudopuberty and irregular bleeding in young girls.

Gross examination of embryonal carcinoma reveals a solid, hemorrhagic, necrotic tumor, resembling a larger form of EST. Embryonal glands, gland-like clefts (embryoid bodies), and syncytiotrophoblastic giant cells are present microscopically. Embryonal carcinoma secrete tumor markers hCG and AFP.

Polyembryoma

Histological analysis of polyembryoma demonstrates erythroid bodies in different stages of presomite development.

Choriocarcinoma

Pure nongestational choriocarcinoma is extremely rare tumor. However, choriocarcinoma commonly develops as part of mixed germ cell tumor. Approximately, 50% of prepubertal girls with nongestational choriocarcinoma are isosexually precocious. Grossly, the tumor is unilateral, solid and is characteristically hemorrhagic. It secretes tumor marker hCG, which is pathognomonic of choriocarcinoma. Human chorionic gonadotropin is used to monitor treatment response and identify persistent disease.

Teratoma

Teratomas are classified into immature (malignant), mature (dermoid cyst) and monodermal (struma ovarii, carcinoid).

Immature teratomas are the second most common GCT and account for approximately 20% of all malignant GCT. They occur mostly (50%) in the second decade of life and rarely after menopause. At diagnosis, 70% cases are stage IA while bilateral involvement indicates diffuse peritoneal spread.

They are classified as Grade I, II or III if they have 0 or 1, 3 or less, or 4 or more low-power fields (X-40) containing immature neuroepithelium per section, respectively. Immature teratomas are solid tumors containing variable amount of immature tissue derived from any of the three germ cell layers. Immature neuroepithelium is the predominant immature tissue found. The degree of immaturity of the three germ cell layers reflects the aggressiveness and potential for recurrence and metastasis.12

Dermoid cysts contain mature tissue, and upon gross examination skin, teeth, bone, hair, sebaceous glands and neural tissue predominate; whilst cartilage, respiratory and intestinal epithelium are also common. They are cystic tumors with a firm capsule. About 1-2% of benign cystic teratomas undergo malignant change, usually in postmenopausal age.13

Monodermal teratoma comprise mainly of one tissue element. The most common type of monodermal teratoma, struma ovarii, is comprised of at least 50% mature thyroid tissue. Argentaffin cells in dermoid cysts are usually the site of origin for ovarian carcinoid, although this is rare.

Mixed Germ Cell Tumor

As the name suggests, mixed germ cell tumors contain more than one histological type. Dysgerminoma with EST, and immature teratomas with EST are frequent combinations.

CLINICAL FEATURES

The most common presentation of most germ cell tumors is abdominal pain with palpable pelvic abdominal mass. The other presentation may include abdominal distension due to tumor or ascites, fever, vaginal bleeding, acute abdomen due to rupture, torsion or hemorrhage.14 In phenotypic females with gonadal dysgenesis dysgerminoma may be present either alone or in combination with other tumors, especially gonadoblastoma (50%). Sometimes isosexual precocious puberty in premenarchal girls and menstrual irregularities in older women may be the presenting symptom.

PREOPERATIVE EVALUATION

Workup in suspected cases of germ cell tumor should include chest radiograph to rule out lung metastasis, ultrasonography (USG) of abdomen and pelvis for spread, serum tumor markers like hCG, AFPs and lactic dehydrogenase isoenzymes. Imaging studies like magnetic resonance imaging (MRI) or computed tomography (CT) scan identify the spread of the tumor.

Karyotype must be done in suspected cases of gonadal dysgenesis as there is a 25% risk of developing malignant germ cell tumor in phenotypic female with Y chromosome.15

Tumor Markers

Role of Tumor Markers

Tumor markers are molecules occurring in blood or tissue that are associated with cancer and whose measurement or identification is useful in cancer diagnosis or clinical management. Germ cell tumors have the unique property of producing oncofetal proteins (tumor markers) like AFP, hCG and lactate dehydrogenase (LDH) that are vital in the evaluation and management of patients with GCTs.

Serial measurement of these tumor markers aids in diagnosis, staging, prognosis and monitoring response to therapy.3 Obtaining levels of AFP, beta-hCG, and LDH in patients in whom GCTs are suspected is mandatory prior to treatment, as is monitoring these levels during and after treatment. The serum tumor markers in various histological types of germ cell tumors are shown in Table 1.

Human Chorionic Gonadotropin

Human chorionic gonadotropin (hCG) is a glycoprotein produced by tumors containing syncytiotrophoblast and is
used as a tumor marker in gestational trophoblastic disease and germ cell tumors. hCG is a valuable marker in these tumors, screening reliably in all cases and indicating poor responses to treatment. The level correlates with tumor mass and thus has prognostic value.

**Alpha-fetoprotein**

Alpha-fetoprotein (AFP) is a normal fetal serum protein synthesized by the liver, yolk sac, and gastrointestinal tract that shares sequence homology with albumin. Normally its concentration in adult serum is less than 20 ng/mL.

The AFP is elevated in germ cell tumors containing embryonal or endodermal sinus elements. The specificity and sensitivity of AFP for endodermal sinus tumor is 78 and 57% respectively. After therapy, reappearance of elevated levels of AFP strongly suggests tumor recurrence. World over AFP is used for screening of germ cell tumors.

Elevated levels of AFP occurs in certain liver diseases, especially acute viral or drug-induced hepatitis and conditions associated with hepatic regeneration. However, elevated levels greater than 500 ng/mL are usually indicative of hepatocellular carcinoma and germ cell tumors.

**PROGNOSIS**

**Dysgerminoma**

For stage 1A tumor (confined to the ovary) of less than 10 cm size, with an intact capsule unattached to other organs and without ascites, the 10-year survival following conservative surgery was 88.6%. Successful pregnancies following unilateral salpingo-oophorectomy (USO) have been documented in number of patients. Even patients with incompletely resected dysgerminoma can be rendered disease free following bleomycin/etoposide/cisplatin (BEP) chemotherapy.

**Nondysgerminomatous Germ Cell Tumors**

Although long-term survival is the rule for mature teratoma, survival for immature teratoma following surgery only is related to the grade of the tumor, especially its neural elements. Before the modern chemotherapeutic era, nondysgerminomatous germ cell tumors had a high rate of recurrence, especially endodermal sinus tumors of the ovary had a 50% mortality rate. However, with modern combination chemotherapy dramatically improved prognosis has been seen.

**Mixed Germ Cell Tumors**

For mixed germ cell tumors, size and histology were the major factors determining prognosis. Prognosis was good when tumor was less than 10 cm diameter, regardless of the composition of the tumor. While prognosis was poor for large tumors when more than one-third of the tumor was composed of endodermal sinus elements, choriocarcinoma or grade 3 immature teratoma.

**PRETREATMENT COUNSELING**

Before initiation of treatment, informed written consent of patient or parents (if patient is minor) should be taken discussing the various treatment options and its long-term implications. In case of conservative treatment, need for close follow-up for long period of time must be emphasized and agreed upon by the patient or parents.

**SURGICAL STAGING**

In the absence of obvious metastatic disease, accurate staging of germ cell tumors of the ovary requires laparotomy with careful examination of the entire diaphragm, both paracolic gutters, pelvic and para-aortic lymph nodes, and the omentum. The contralateral ovary should be carefully examined and biopsied if necessary. Ascitic fluid or peritoneal washings should be examined cytologically.

Frozen section facilities must be kept ready at the time of surgery to understand the type of tumor and to enable right decision taking.

In patients with dysgerminoma, lymphangiography or CT scan is indicated if the pelvic and para-aortic lymph nodes were not carefully examined at surgery. It would seem prudent to obtain baseline serum levels of AFP and hCG as soon as the diagnosis is established since persistence of these markers in the serum after surgery indicates unresected tumor.

**STAGING**

Staging of germ cell tumors follows the International Federation of Gynecology and Obstetrics (FIGO) and the American Joint Committee on Cancer (AJCC).16,17

**Stage I**

Stage I ovarian germ cell cancer is growth limited to the ovaries.
• **Stage IA**: Tumor is limited to one ovary; capsule is intact, and no tumor is present on the ovarian surface. No malignant cells are present in ascites or peritoneal washings.¹

• **Stage IB**: Tumor is limited to both ovaries; capsules are intact, no tumor is present on the ovarian surface. No malignant cells are present in ascites or peritoneal washings.²

• **Stage IC**: Tumor is limited to one or both ovaries with any of the following: capsule is ruptured, tumor is present on the ovarian surface, malignant cells are present in ascites or peritoneal washings. (³Note: Malignant ascites is not classified. The presence of ascites does not affect staging unless malignant cells are present.)

### Stage II

Stage II ovarian germ cell cancer is growth involving one or both ovaries with pelvic extension and/or implants.

- **Stage IIA**: Extension and/or implants are present on the uterus and/or fallopian tubes. No malignant cells are present in ascites or peritoneal washings.
- **Stage IIB**: Extension to and/or implants are present on other pelvic tissues. No malignant cells are present in ascites or peritoneal washings.
- **Stage IIC**: Pelvic extension and/or implants (stage IIA or IIB) with malignant cells are present in ascites or peritoneal washings.

Different criteria for designating cases to stages IC and IIC have an impact on the diagnoses. To evaluate the impact, determine if rupture of the capsule was spontaneous or caused by the surgeon; and if the source of the malignant cells detected was peritoneal washings or ascites.

### Stage III

Stage III ovarian germ cell cancer is growth involving one or both ovaries with microscopically confirmed peritoneal implants outside the pelvis. Superficial liver metastasis equals stage III. Tumor is limited to the true pelvis but with histologically verified malignant extension to the small bowel or omentum.

- **Stage IIIA**: Microscopic peritoneal metastasis is present beyond the pelvis (no macroscopic tumor).
- **Stage IIIB**: Macroscopic peritoneal metastasis is present beyond the pelvis and less than or equal to 2 cm in greatest dimension.
- **Stage IIIC**: Peritoneal metastasis is present beyond the pelvis and is more than 2 cm in greatest dimension, and/or regional lymph node metastasis is present.

### Stage IV

Stage IV ovarian germ cell cancer is growth involving one or both ovaries with distant metastasis. If pleural effusion is present, there must be positive cytological test results to designate a case to stage IV. Parenchymal liver metastasis equals stage IV.

### STAGEWISE TREATMENT PLANS

#### Stage I Tumors Dysgerminoma

In younger patients anxious to preserve fertility, unilateral salpingo-oophorectomy conserving the uterus and opposite ovary with a proper staging laparotomy is accepted treatment. Patients with stage IA tumors, who are completely staged, may be observed after surgery without adjuvant treatment. To identify this small subset of patients, all patients must be subjected to comprehensive surgical staging before taking any treatment decisions. All patients except those with stage IA dysgerminoma require postoperative chemotherapy.

However, if pelvic and para-aortic nodes sampling has not been done then postoperative lymphangiography or CT scan must be done to evaluate the same before managing the patient conservatively.

Recurrence after conservative treatment is seen in 15–25% cases but can be treated successfully with a high likelihood of cure.¹⁸ Incompletely staged tumors or higher stage tumors should receive adjuvant chemotherapy or radiotherapy. Advantage of chemotherapy is to allow recovery of reproductive potential in patients with intact uterus, ovary and tube, while radiation results in loss of fertility due to ovarian failure.

#### Nondysgerminomatous Germ Cell Tumors

For patients with stage IA, low grade (grade 1) immature teratoma, USO should be performed when fertility is to be preserved. All patients except those with stage I, grade I immature teratoma require postoperative chemotherapy.

With platinum-based combination chemotherapy, the prognosis for patients with endodermal sinus tumors, immature teratomas, embryonal carcinomas, choriocarcinomas, and mixed tumors containing one or more of these elements has improved dramatically.¹⁹ Combination chemotherapy of BEP or vincristine, actinomycin-D, and cyclophosphamide (VAC) may be given (Table 2). On comparison, BEP is preferred over VAC because of lower relapse rate and shorter treatment time.³

Also in well-staged patients with completely resected tumors, relapse is essentially unheard of following platinum-based chemotherapy. Even in well-staged patients, there is a recurrence rate of 25% following VAC therapy.²⁰

#### Stage II, III, and IV Ovarian Germ Cell Tumors

For patients with stage II, III and IV, complete staging laparotomy with total abdominal hysterectomy with bilateral salpingo-oophorectomy is recommended with removal of as much gross tumor as can be done safely without resection
of portions of the urinary tract or large segments of small or large bowel. However, for the younger patient anxious to preserve fertility, a USO followed by cisplatin-based adjuvant chemotherapy BEP (3 or 4 courses) should be given. In such cases, chemotherapy with BEP is the preferred treatment as it is less sterilizing than wide-field radiation.

BEP has shown excellent results in all stages of malignant germ cell tumors (sustained remission of 96%). When there is residual disease or elevated levels of AFP or hCG after maximal surgical debulking, 3 or 4 courses of BEP combination chemotherapy are indicated.

Recurrence after 3 courses of BEP as adjuvant therapy is rare. Patients who do not respond to a cisplatin-based combination may still attain a durable remission with VAC as salvage therapy. All patients who do not respond to standard therapy are candidates for clinical trials.

For patients with extensive intra-abdominal disease whose clinical condition precludes debulking surgery, chemotherapy (neo-adjuvant) can be considered prior to surgery.

### ROLE OF SECOND-LOOK LAPAROTOMY

Role of second-look laparotomy (SLL) remains limited and ill defined. Evidence suggests that SLL is not beneficial in patients with initially completely resected tumors who receive cisplatin-based adjuvant treatment. However, second-look surgery may be of benefit for a small subset of patients whose tumor was not completely resected at the initial surgical procedure and who have teratomatous elements in their primary tumor. Surgical resection of residual masses at SLL should be undertaken to avoid further progression of disease.

### FOLLOW-UP

Post-treatment follow-up should be done at 3 monthly intervals for the first year and 6 monthly thereafter. At the follow-up visit, physical examination, X-ray chest, USG or CT scan of abdomen and pelvis, and tumor markers study should be done.

### RECURRENT OVARIAN GERM CELL TUMORS

Recurrence occurs in 15–20% of germ cell tumors. Most recurrence occurs in the first 2 years of treatment. The common sites of recurrence are the pelvis, opposite ovary, retroperitoneal lymph nodes and abdomen.

Recurrence rates after USO alone for stage IA disease are high (17–53%) due to inadequate staging and inclusion of mixed germ cell tumors. Cisplatin-based combination chemotherapy with and without adjuvant radiation therapy has been used effectively to treat recurrent disease. However, adjuvant radiation is not effective in treating recurrence of germ cell tumors other than dysgerminomas. Salvage therapy for recurrence depends on response to previous chemotherapy.

In cisplatin sensitive tumors (relapse) cisplatin-based combination chemotherapy is useful. Nonresponders (persistent or progressive disease) to a cisplatin-based combination chemotherapy may still attain a durable remission with VAC or ifosfamide or cisplatin as salvage therapy. Newer potential treatments include an ifosfamide combination or high-dose chemotherapy and autologous marrow rescue.

Although the role of secondary cytoreductive surgery for patients with recurrent or progressive ovarian germ cell tumors remains controversial, it may have some benefit for a select group of patients, particularly those with immature teratoma. After maximal effort for surgical cytoreduction, chemotherapy should be considered.

### POST-THERAPY FERTILITY

Preservation of reproductive function may be possible after combination chemotherapy. Successful pregnancies have been documented after treatment. Post-surgery adhesions may cause infertility and advances in artificial reproductive technology can play a crucial role in such patients.

### SURVIVAL RATES

- The survival rates for dysgerminomas presenting at early and advanced stages are 95% and more than 80% respectively.
- The survival rates for stage I and II ESTs are reported to be 60–100%, whereas for those with stage III or IV disease the prognosis is less favorable (50–75%).
- Survival rates for embryonal carcinoma are slightly higher than those for ESTs.
- The prognosis of immature teratomas is governed by grade and stage. Grade 1, stage 1 have 100% survival rate,
whereas stage III and grade 1 have only a 50% chance of survival. Most patients with mature teratomas show long survival times.

- The prognosis is better for gestational choriocarcinoma than nongestational carcinoma.
- The prognosis for mixed GCT is dictated by the proportion of the more malignant component and the stage.

REFERENCES

INTRODUCTION
Radiobiology is term applied to the scientific study of the effects of ionizing radiation on cells and tissues, both normal and malignant.

An understanding of the fundamental mechanisms of tumor radiosensitivity and resistance may help to select patients who would benefit from treatment.

It is interaction of X-rays with the cell, which precipitates a chain of molecular events that result in the inhibition of cell division (Fig. 1). Radiation is particularly lethal to cells during cell division (mitosis).

RADIATION EFFECT
There are biological factors influencing radiosensitivity, so effect of treatment varies from patient to patient.

OXYGEN EFFECT
Oxygen has an important effect in modifying the biological response to irradiation. The presence of oxygen enhances the effect of radiation.

METHODS OF OVERCOMING TUMOR HYPOXIA
Correction of Anemia
Patients with cervical cancer undergoing radical pelvic irradiation have a poorer prospect of survival, if their pretreatment hemoglobin level is below 12 g/dL compared with patients with hemoglobin greater than 12 g/dL.
**Principles of Management and Dosage**

Once a diagnosis of malignancy has been reached, some important management decisions must be made:
- To select necessary investigations
- To undertake curative (radical) or palliative therapy
- To choose appropriate palliative or radical treatment
- To choose appropriate support services (e.g. nursing and social services) for patient and family.

**Radical or Palliative Treatment?**

Radical treatment means the attempt to kill or remove all the malignant cells present.

Palliative treatment is aimed at relieving the symptoms of cancer (e.g. pain, dysphagia, dyspnea) or restraining temporarily the growth of the tumor.

**Assessment before Treatment**

The increasing complexity of curative cancer management for many tumors, with different combinations of surgery, radiotherapy and chemotherapy for different stages of disease, requires a coordinated multidisciplinary approach. Information required for a decision on treatment:
- **Age and general medical condition**: The latter includes coincident disease (e.g. diabetes mellitus, chronic respiratory disease, peptic ulceration).
- **Tumor spread**: Local, regional nodes, distant metastases. Staging is the term applied to determine the extent of the disease. Staging may include clinical, radiological or laboratory findings.
- **Histology**: Histological confirmation of the tumor should be obtained.

**Choice of Radical or Palliative Treatment**

The following factors relating to the tumor, the patient and available resources can influence the decision. The importance of each factor will vary from patient to patient.
- **The tumor**:
  - Site
  - Size
  - Spread
  - Operability
  - Radiosensitivity or chemosensitivity
  - Histology
  - Clearance of surgical resection margins.
- **The patient**:
  - Age and general condition
  - Morbidity and mortality
  - Function and cosmesis
  - Reliability of follow-up after treatment
  - Preference of patient.
- Technical resources.

**Palliative Radiotherapy**

Palliative radiotherapy is aimed at relieving local symptoms of advanced disease. The following criteria should be applied to achieve good palliation:
- Prompt relief of symptoms
- Minimal upset from treatment
- Simple treatment technique
- Limited number of fractions.

- Palliative radiotherapy should relieve symptoms with minimal side effects. The amount of upset varies with site, dose and fractionation.

**Technical Factors in Radiotherapy**

In any radiation treatment, the clinician has to define the following parameters:
- Tumor volume
- Target volume
- Treatment volume
- Radiation energy and quality
- Number of fields
- Arrangement of fields
- Use of wedges, tissue compensators or bolus
- Dose
- Total number and frequency of fractions
- Overall treatment time.

**Fractionation**

Fractionation refers to the division of the total dose into a number of separate fractions, conventionally given on a daily basis, usually 5 days a week.

**Follow-up**

**Aims**

The reasons for following up patients are:
- Confirmation of response to treatment and of resolution of its side effects
- Detection of persistent or recurrent disease at a stage when curative “salvage” treatment is possible
- Detection of late complications of treatment
- Reassuring the patient that he or she is free of tumor
- Management of patients with persistent or progressive disease or complications of treatment.

**CANCER OF CERVIX**

**Epidemiology and Etiology**

Cancer of the cervix is the second commonest gynecological malignancy with an incidence of 13 per 100,000 in England and Wales. *Incidence is much higher in India.*
It is more common in women of lower socioeconomic
groups due to the early age of first intercourse.
Other factors may be responsible, upcoming is human
papillomavirus infections.

**Types of Cancer of Cervix**

*Cervical Intraepithelial Neoplasia*

Cervical intraepithelial neoplasia (CIN) is graded according
to the degree of histological abnormality. The features
examined are (a) the degree of differentiation, (b) mitotic
activity and (c) the appearance of cell nucleus.
Cervical intraepithelial neoplasia III is the most abnormal
grade. It corresponds to carcinoma-in-situ and is most likely
to progress to invasive cancer. Minor degrees of CIN (I and II)
may regress or go on to invasion.

**Microinvasive Cancer**

Microinvasive cancer is defined as non confluent invasion less
than 3 mm from the basement membrane of the epithelium
into stroma.
*Treatment:* Cervical intraepithelial neoplasia is treated by
laser therapy or cold coagulation (cryosurgery). Micro-
invasive carcinoma is treated by conization in young patients
and by hysterectomy in those who do not plan to have
children.

**Invasive Carcinoma**

About 90–95% are due to squamous cell carcinoma and about
5% are due to adenocarcinomas.

Local spread is to the adjoining tissue: Vaginal vault,
fornices, upward to the corpus, laterally to the parametria,
anteriorly to the bladder and posteriorly to the rectum.

**Staging and Investigation**

Clinical staging is carried out under general anesthesia. In
order to understand the anatomy properly. Figures 2 and
3 show uterus and vagina in sagittal and coronal sections,
respectively.

Essential investigations are a full blood count, serum urea,
creatinine and electrolytes, chest radiograph and intravenous
urogram (IVU).

**International Federation of Gynecology**
**and Obstetrics (FIGO) Staging of Carcinoma**
**of the Cervix (Figs 4A to L)**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Clinical findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Carcinoma-in-situ</td>
</tr>
<tr>
<td>I</td>
<td>Growth confined to the cervix</td>
</tr>
<tr>
<td>IA</td>
<td>Microinvasive carcinoma</td>
</tr>
<tr>
<td>IB</td>
<td>Clinically invasive carcinoma</td>
</tr>
<tr>
<td>IIA</td>
<td>Spread beyond the cervix</td>
</tr>
<tr>
<td>IIB</td>
<td>Spread to parametrium</td>
</tr>
<tr>
<td>IIIA</td>
<td>Spread to the lower third of the vagina</td>
</tr>
<tr>
<td>IIIB</td>
<td>Spread to the pelvic side wall</td>
</tr>
<tr>
<td>IVA</td>
<td>Spread to the bladder or rectum</td>
</tr>
<tr>
<td>IVB</td>
<td>Spread to distant sites pelvis</td>
</tr>
</tbody>
</table>

**Treatment**

Surgery and radiotherapy alone or in combination are curative in cervical cancer.

**Stage IA**

For young women with non bulky tumors who have a negative
lymphogram or CT scan of the pelvic and para-aortic nodes,
a radical Wertheim’s hysterectomy is the treatment of choice.
For patients who are older or have a positive lymphogram
or are not fit for or refuse surgery, radical radiotherapy with
Figs 4A to L: Stages of carcinoma of cervix
infracavitory therapy with or without pelvic external beam irradiation should be given. External beam is not essential unless the tumor is poorly differentiated or the lymphogram is positive.

Many radiotherapists, however, treat all stage I cases with pelvic external beam in addition to intracavitary therapy.

Stages IB (Bulky), IIA-B

Radical radiotherapy is the treatment of choice for bulky stage IB and IIA-IIIB. This normally requires a combination of uterine and vaginal intracavitary therapy and pelvic external beam irradiation.

In patients with stage III disease, uremia may be advanced at presentation if there is bilateral ureteric obstruction. Radical radiotherapy should only be started if renal function and general condition improve sufficiently.

A combination of surgery and radiotherapy, if carefully combined, can achieve equally satisfactory cure rates in patients with stage IB, IIA and early IIB disease.

Stage IVA

The outlook for this stage is grim and many patients are in poor medical condition. Intracavitary therapy may not be feasible because of fistula formation and treatment is limited to pelvic external beam irradiation alone.

TYPES OF RADIOTHERAPY TREATMENT

The American Brachytherapy Society recommends the use of brachytherapy in all cases of locally advanced cervical cancer (2012 American Brachytherapy Society).

Radiotherapy

Radiotherapy is the other treatment option for stage IB1 and IIA disease. For stage IB2, IIB, III and IV, radiation is the treatment of choice. The cervix can tolerate very high doses of radiation. This fact combined with the convenient position of the uterus in the center of the pelvis, which allows intracavitary sources to be kept in the uterine cavity, makes radiation effective in the treatment of cancer of the cervix.

Advantages of Radiotherapy

Radiotherapy has the following advantages:

- Treats the cervix along with the draining lymphatics and lymph nodes. Radiation to the whole pelvis takes care of all the pelvic nodes, which even the most radical surgery cannot achieve without producing much morbidity.
- Cure can be achieved with preservation of the organs
- Primary mortality is almost nil
- Can be given when surgery is contraindicated due to other reasons
- Cure can be attempted even in advance disease.

After the initiation of radiation therapy in the year 1903, radiation treatment has evolved enormously. The radiation source, which was initially Radium has been changed to Cesium and Iridium. The dose of radiation is presently calculated in Gray (Gy). 1 Gray = 100 rads; 1 cGy = 1 rad. Radiation treatment is given as both intracavitary (ICRT) and external beam radiation therapy (EBRT).

In the radiation treatment of cancer of the cervix, the tumor, parametrium and pelvic side walls (where the lymph nodes are situated) are irradiated by intracavitary source. The radiation to the pelvic side wall will not be enough from the intracavitary source. Hence, the pelvic side wall is irradiated with external beam mega voltage teletherapy using linear accelerator. Patients who have common iliac and para-aortic node involvement need extended field radiation.

Either EBRT or ICRT can be administered first. However, in the following situations, EBRT is preferred first.

- Bulky tumors
- Parametrial involvement (suboptimal dosimetry due to altered geometry if ICRT is administered initially)
- Large necrotic tumors (Practical difficulty in carrying out ICRT)
- Bleeding tumors (intracavitary administration can provoke bleeding).

External Beam Radiotherapy

External beam RT is given using linear accelerator or a Cobalt 60 machine. The entire pelvis is treated by radiation. All tissues that are within the square marked by the green field on the X-ray are treated by EBRT (Figs 5 and 6). The target tissues are the tumor, the parametrium lymphatics and the lymph nodes in the pelvic side wall. However, toxicities to the bladder and the rectum, which are also in the same field, are the major concern. EBRT is given at a total dose of 40–45 Gray, usually in 20 fractions at a rate of 1.8–2 Gy/day for 5 days a week. Treatment is given usually in a four-field technique, one anteroposterior, one posteroanterior and two lateral fields. Treatment can also be given in two fields.

Intracavitary Radiation Therapy (ICRT) Brachytherapy

The success of radiotherapy of cervical cancer lies in the extreme tolerance of the cervical tissue to high doses of radiation; as high as 200 Gy. Since the tumor in the cervix is approachable transvaginally, it can be irradiated by the intracavitary source. The dose of radiation given from the intracavitary source depends on the inverse square law. As the distance from the source increases the dose decreases. Hence, from the sources kept in uterine cavity and lateral vaginal fornix, the maximum radiation is delivered to the tumor and the parametrium. Part of the radiation would be delivered to the pelvic side walls where the lymph nodes are situated (Figs 6 and 7).
In the older method, the tubes which contain the radiation source are preloaded. The disadvantage of this method was the high radiation risk for medical and paramedical personnel.

To overcome this risk, the remote afterloading system was devised.

**Intracavitary Radiotherapy using Afterloading Technique**

Intracavitary radiation therapy is presently administered using high dose rate (HDR) isotopes, i.e. isotopes that produce radiation at high rates of more than 12 Gy/hour. At these rates the biological effects produced by radiation is roughly 1.7 times that produced by the older isotopes. The radiation source used is Iridium 192.

In HDR ICRT, the sources are introduced into the patients’ body through applicators. The applicators are hollow and are
made of metal. They are usually available in a set of three. The one which is inserted into the uterine cavity is called the tandem. The other two are placed in the lateral fornices and are called the colpostats. The tubes are inserted, locked in place and further secured with gauze packing. These metal tubes are connected to flexible plastic tubes which in turn are connected at the other end to the device which houses the radiation source. The operator can load and unload the radiation source from the remote housing by providing signals. Thus, the radiation to the operator is minimized.

Since the sources are kept in the uterine cavity and the lateral vaginal fornices, the primary tumor in the cervix and the parametrium are irradiated to the maximum. The anteriorly located bladder and posteriorly located rectum are comparatively spared of radiation. The pelvic side walls receive only minimal dose from ICRT. It will be taken care of by EBRT.

After securing the connections, a computer program calculates the radiation dose. The prescribed dose is calculated by the radiation given to point A. Point A is defined as a point 2 cm superior to the external os and 2 cm lateral to the middle of the cervical canal. Point A corresponds to the point where the uterine artery crosses the ureter. The usual dose prescribed is about 7 Gy to point A weekly for 3 consecutive weeks. This amounts to a total ICRT dose of 35–40 Gy to the cervix. This, when combined with EBRT of 45 Gy, amounts to a total of 80–100 Gy. This total dose that the cervix receives is a critical dose above which the probability of viable tumor cells remaining is reduced to extremely low levels.

The dose received at point A correlates with the probability of local control because this is the site of the parametrium which is the most common site of invasion beyond the cervix. The dose received at point A helps predict the doses received at various other points within the pelvis. The tumor in the cervix receives approximately three times the dose calculated at point A. Point B is located 5 m lateral to the midline and 2 cm superior to the external cervical os. Point B is described to calculate the dose received by the pelvic lymph nodes.

The computer program when activated directs radiation sources shaped like small balls, through the tubing systems into the metal tubes that are placed within the patient. These pellets are retained till the necessary dosage, prescribed by the radiation oncologist have been administered. Whenever the patient wants to communicate with the medical personnel, she can give signals following which the sources can be retrieved. When the treatment is over, the computer redirects the radiation sources back into the secure housing. The tubes are disconnected. The metal tubes are removed and the patient discharged after a few hours observation.

**Chemoradiation**

In the radiation treatment of stage IB2 and IIA bulky tumors, chemoradiation is (Flow charts 1 and 2). This is confirmed by several studies by Gynecologic Oncology Group (GOG). Here, radiation is administered along with a chemotherapeutic agent usually cisplatin—concurrent chemoradiation.
Cisplatin here acts primarily as a radiation sensitizer, i.e. it makes tumor tissue more sensitive to the destructive action of radiation. Another advantage of chemotherapy is that micrometastases outside the radiation field also will be taken care of. Cisplatin is given is a relatively low dose of 40 mg/m² weekly till the entire course of radiation is completed. Improved overall survival and reduced local and distant recurrence have been reported in a Cochrane review.

Management of stage I B2, IIB and III: Radiation is the treatment of choice, for the treatment of bulky stage IB, IIB and III disease, as attempting surgery will result in leaving positive margins. Concurrent chemoradiation with Cisplatin combined with EBRT and ICRT is the standard treatment. Trials have been conducted with neoadjuvant chemotherapy followed by radical surgery for bulky stage Ib disease. A Cochrane review on the approach reveals that this has a potential to be beneficial in treating more women with surgery especially if they are young. The benefit however has to be proved by proper RCTs.

Management of stage IVa: Invasion of the bladder and rectum is an ominous finding. The curative dose of radiation in the presence of bladder or rectum involvement is well above the tolerance limit for the normal tissues. This dose will subject the patient at risk of developing vesicovaginal or rectovaginal fistulae. Surgery, if considered should be pelvic exenteration where urinary or fecal diversion is mandatory. If the patient presents with fistula, pelvic exenteration with urinary or fecal diversion is the choice. The decision to go for radiation or surgery depends upon the general condition of the patient and her choice. If the patient’s general condition is good enough to withstand exenteration surgery, it should be preferred.

Management of stage IVB: Metastatic disease is practically incurable. Radiation is primarily chosen to provide palliation, reduce pelvic pain and control bleeding. It also aids in relieving ureteric obstruction. In such situations, curative doses are not prescribed. Instead, lower total doses with high dose per fraction are prescribed which provides adequate palliation.

Practical Problems

- Failure to identify the cervical os: If it is impossible to insert a uterine applicator because the cervical os cannot be confidently identified or because of local hemorrhage,
a vaginal applicator alone may be inserted or the whole procedure deferred until more pelvic irradiation has been given to shrink the tumor and/or stop the hemorrhage.

• Perforation of the uterus: Occasionally, in error, the uterus may be perforated by the applicator, particularly if the external os is difficult to identify because the tumor has distorted it. If perforation has occurred the applicator should be withdrawn and the patient started on antibiotics.

• Verification of intracavitary insertion: After the insertion of the uterovaginal applicator, lateral and anteroposterior radiographs of the pelvis are taken to show the exact position of the applicators. This is best done in theater itself, with a portable X-ray machine.

Dosimetry

Rectal Probe

A further possible aid in avoiding rectal overdose in directly loaded systems is a scintillation counter at the end of a narrow probe. This can be inserted at the end of the operation and the maximum dose rate at the rectal mucosa obtained by a series of readings at various distance along the rectal wall.

Dosage

Cancericidal doses, e.g. 75 Gy at point A or to the 60 Gy isodose, from central sources can be safely delivered. This would give point B about one-fifth of the central dose (15 Gy), much too low to deal effectively with secondaries.

External beam pelvic irradiation. For genuine stage I disease, intracavitary cesium alone is adequate, and capable of achieving a cure rate of 90% or more. However, nodal metastases can hardly ever be ruled out with confidence. Most radiotherapists therefore supplement intracavitary therapy with megavoltage irradiation delivered to the lateral parts of the pelvis to bring this dosage to a tumoricidal level.

External beam can precede or follow intracavitary therapy.

Target Volume

This should include the whole of the pelvis. It will encompass the primary and any local spread, and the common, internal and external iliac nodes. The upper border of the field is the junction of the fourth and fifth lumbar vertebrae. The lower border is the bottom of the obturator foramina of the pubic bones. It may need to extend a few centimeters more inferiorly if there is involvement of the lower third of the vagina. The outer margin is 1 cm lateral to the pelvic brim.

Energy and Dose

Megavoltage therapy is advised. The aim is to give the desired dose at point B, additional to the dose already given from intracavitary therapy, while giving a much lower dose to A which is already heavily irradiated. There will be some photon dosage to A, if only from scattered irradiation. The dose to A can be varied while leaving the dose at B unchanged, by using different thicknesses of central filter, and changing them, if need be, during the course. In this way, the doses can be arranged to summate to the required levels. Table 1 summarizes the intracavitary external beam doses from a typical insertion using the Sheffield technique, the intracavitary and external beam doses for different stages of the disease.

Table 1: Treatment of carcinoma of the cervix

<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment</th>
<th>Point (Gy)</th>
<th>Cs (Gy)</th>
<th>External beam (Gy)</th>
<th>Cs + Ext. beam (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Conization/hysterectomy</td>
<td>A</td>
<td>60</td>
<td>15</td>
<td>75</td>
</tr>
<tr>
<td>I</td>
<td>Hysterectomy (Wertheim’s) / Cs + external beam</td>
<td>B</td>
<td>15</td>
<td>35</td>
<td>50</td>
</tr>
<tr>
<td>IIa, b</td>
<td>Cs + external beam or external beam alone</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIIa, b</td>
<td>Defunctioning colostomy (rectovaginal fistula) or urinary diversion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(vesicovaginal fistula) Then radical/palliative external beam</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVa</td>
<td>Palliative external beam +/- chemotheraphy or palliative Cs.</td>
<td></td>
<td>30 Gy in 10 daily fractions (whole pelvis)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVb</td>
<td></td>
<td></td>
<td>20 Gy to point A (one insertion)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: Cs, Cesium

SIDE EFFECTS OF RADIATION

The cervix and body of uterus are unusually tolerant of high dosages. The more vulnerable organs that are potential sources of trouble are the rectum, bladder and any loops of bowel trapped or adherent in the pelvis.
Bowel
During external irradiation diarrhea is often troublesome, occasionally requiring treatment to be suspended for a few days. Treatment is with an antidiarrheal agent (e.g. loperamide), and a high fiber diet, avoiding fruit and vegetables.

Bladder
Irritation of the bladder with dysuria and frequency is both less common and less troublesome. An anticholinergic (e.g. propantheline) often relieves the discomfort.

Skin
Washing the treated area is permitted.

Late Reactions
The probability of developing late major pelvic complications following radical intracavitary and external beam therapy is about 5%. These mainly affect the bladder and bowel.

- Symptoms are of colicky abdominal pain, rectal urgency, tenesmus, constipation and diarrhea.

- The treatment of troublesome proctocolitis is initially conservative, with Predsol enemas. If measures fail, then surgery is required with either a temporary or permanent colostomy.

- Malabsorption is common and often accompanies other evidence of late pelvic morbidity.

Bladder
Up to 25% of patients may have severe symptom of bladder dysfunction. Blood in the urine (hematuria) may result. Cystoscopy is advisable.

- Vesicovaginal fistula is a major complication. Treatment is by transplanting the ureters into the ileum (ileal conduit).

- The results of primary radical surgery or radiotherapy or a combination of preoperative cesium followed by surgery for stage IB are excellent, with a 5-year survival of about 90%. Cure rates from radical radiotherapy decline with advancing stage: 80% (IIA), 65% (IIB), 45% (IIIA) and 35% (IIIB) and 15% (IV).

Follow-up
Most recurrences in the cervix or regional nodes tend to occur in the first 2 years after treatment. A suggested follow-up policy is 1 month after treatment and two monthly for the first year, three monthly in the second year and six monthly from years 3 to 5. The likelihood of relapse beyond 5 years is small and routine follow-up is probably not essential.

Cancer of the Cervical Stump
Carcinoma may develop in the stump after subtotal hysterectomy. A distinction needs to be made between true stump carcinoma, which has arisen on the cervical stump a year or more following surgery and coincidental stump carcinoma which is detected within a year of hysterectomy. In the latter case the cancer can be assumed to have been present but not suspected at the time of surgery. Intracavitary treatment is difficult, as the length of the canal left, about 2 cm, is rarely enough to hold a uterine applicator. Vaginal applications can be made, supplemented, or replaced entirely by external irradiation.

Cervical Cancer in Pregnancy
Carcinoma of the cervix is fortunately rare in pregnancy, about 1% of cases. Management will depend upon the extent of the disease at the time of diagnosis, the age of the pregnancy and the wishes of the patient.

- For stage II or more advanced, radical radiotherapy is given following cesarean section. Treatment is started by external beam 10 days after delivery and completed by intracavitary therapy.

Cancer of the Body of the Uterus
(Carcinoma Corpus Uteri)
Myometrial invasion occurs in less than 5% of well-differentiated tumors and about 30% of poorly differentiated tumors. Blood spread to lungs, liver and bone is relatively common in later stages.

Clinical Features
Irregular bleeding, especially after the menopause, is the cardinal symptom. It is occasionally detected as an incidental finding in the cervical screening program.

FIGO Staging of Endometrial Cancer
(T stages of malignant tumors classification in parentheses).

<table>
<thead>
<tr>
<th>Stage</th>
<th>Clinical finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Carcinoma confined to the corpus (T1)</td>
</tr>
<tr>
<td>IA</td>
<td>Uterine cavity 8 cm or less in length (T1a)</td>
</tr>
<tr>
<td>IB</td>
<td>Uterine cavity greater than 8 cm in length (T1b)</td>
</tr>
<tr>
<td>II</td>
<td>Extension to the cervix (T2)</td>
</tr>
<tr>
<td>III</td>
<td>Extension beyond the uterus but confined to the true pelvis (T3)</td>
</tr>
<tr>
<td>IV</td>
<td>Extension beyond the true pelvis or involvement of the bladder or rectum (T4)</td>
</tr>
</tbody>
</table>

The standard treatment is surgical, i.e. total hysterectomy. Cases technically operable but unsuitable for surgery, are treated by radical radiotherapy, either intracavitary, external beam or a combination of both.
For a well-differentiated adenocarcinoma which is clinically stage I and penetrating less than a third of the myometrium, there is no need for supplementary pelvic irradiation.

The indications for postoperative radical radiotherapy are:
- Moderately or poorly differentiated histology
- Myometrial invasion greater than a third of its thickness
- Stage II or III disease
- Tumor at the surgical resection margins
- Invasion of vascular spaces.

**RADIATION THERAPY**

Three important trials evaluated the role of pelvic radiotherapy in stage I endometrial cancer:
1. Norwegian trial
2. Postoperative radiation therapy for endometrial (PORTEC) trial
3. Gynecological oncology group (GOG) 99 trial.

The GOG 99 trial provided the essential information that helped to finally end the major controversies over the indications for pelvic radiotherapy and the extent of surgery in the treatment of endometrial cancer. Contrary to the other two trials, in the GOG 99 trial, surgery consisted of total abdominal hysterectomy (TAH) with bilateral salpingo-oophorectomy (BSO), peritoneal cytology and pelvic and para-aortic lymphadenectomy. In the 8-year period from 1987 to 1995, 440 patients were randomized, 202 individuals were randomized for neoadjuvant therapy which comprised the low-risk group and 190 were randomized for pelvic radiation. Surgically staged IB, IC and II occult were also included. The 2 year vaginal and pelvic recurrence rate was 12% in NAT group and 3% in RT group. The pelvic failure rate was 8.9% in the surgery alone group, compared with 1.6% in the postoperative pelvic irradiation group. Overall survival rates also were improved in patients receiving postoperative pelvic irradiation compared to those treated with surgery.

This study confirms the substantial reduction in loco-regional recurrence by pelvic RT.

Following surgical staging, hysterectomy and bilateral salpingo-oophorectomy, individualized radiation therapy is planned, tailored to the extent necessary and thus unnecessary radiation is avoided, optimizing survival rates.

Patients with Stage IA, grade I and II have excellent prognosis and do not require postoperative therapy.

Patients with disease other than stage IA, grade I and II require postoperative management which includes:
- Vaginal vault radiation
- External pelvic irradiation
- Extended field (pelvic and para-aortic) irradiation
- Whole abdomen irradiation
- Progestins
- Systemic chemotherapy.

### Vaginal Vault Irradiation

Postoperative vaginal radiation is given as an outpatient treatment using high dose rate iridium source by afterloading technique. Morbidity is less for vaginal vault irradiation. Patients who are most likely to benefit from vaginal irradiation are those who have surgical stage I, grade 1 and 2 with superficial (< 50%) invasion or grade 3 with no invasion and stage IIC (occult), grade 1 and 2 with superficial myometrial invasion.

### Postoperative Vaginal Irradiation

- Stage I—G1 and G2 with superficial invasion, G3 with no invasion
- Stage II (occult)—G1 and G2 with superficial myometrial invasion.

**Dose:** High dose rate Iridium or low dose rate Cesium source via colpostat to deliver 6,000–7,000 cGy.

### External Pelvic Irradiation

Patients who have cervical stromal involvement, positive pelvic nodes, adnexal or parametrial disease and patients with stage I grade 3 with any degree of myometrial invasion and patients with grade 1 and 2 with any myometrial invasion and large tumor (> 2 cm), grade 2 or 3 and superficial myometrial invasion or any grade tumor with lymph vascular space involvement are advised external pelvic irradiation. Irradiation usually involves delivery of 4,500–5,040 cGy in 180 cGy daily fractions over 5–6 weeks to cover the upper half of vagina and pelvis. The vaginal apex is boosted to 6,000–7,000 cGy.

Patients who are at high risk of recurrence due to factors like poor tumor grade, deep myometrial invasion extension to the cervix, parametrical spread, pelvic node involvement, etc. are those who would benefit from whole pelvic irradiation.

**Indication**
- Stage I G3 with any degree of myometrial invasion
- Stage I G1 and 2 with deep myometrial invasion
- Large volume tumor
- Any tumor with lymph vascular space invasion.

**Dose:** 4,500–5,040 cGy over 5–6 weeks.

### Extended Field Irradiation

Some patients who need whole pelvic irradiation may have para-aortic node involvement as well. If they are not found to have disease spread outside the pelvis other than para-aortic nodes, they are treated with extended field irradiation to the para-aortic area. The dose given is 4,500–5,000 cGy, five-year-survival rates of 43–47% have been reported.
The 5-year-survival rates were seen to be better for patients with microscopic nodal disease than those with gross nodal disease.

**Indication:** Patients with positive para-aortic nodes as the only evidence of spread outside the pelvis.

**Dose:** 4,500–5,000 cGy.

### Whole Abdomen Irradiation

Patients who have positive residual upper abdominal disease and those who have papillary serous and clear cell tumors, which have a propensity for upper abdominal recurrence, are treated with whole abdominal irradiation. The recommended dose is 3,000 cGy in 20 daily fractions of 150 cGy. The kidneys are shielded to 1,500–2,000 cGy. Patients who have gross residual intraperitoneal disease cannot be treated with whole abdominal irradiation as 3,000 cGy will not be sufficient to treat gross disease. They have to be treated with progestagens or chemotherapy.

The treatment of patients with positive peritoneal cytology as the only evidence of disease spread outside the uterus is controversial.

**Indications**
- Papillary serous and clear cell tumors, which have a propensity for upper abdominal secondaries
- Patients with adnexal and upper abdominal disease, which has been surgically excised
- Should not be given for gross residual intraperitoneal disease.

**Dose:** 3,000 cGy in 20 fractions.

### Technique and Dosage

**Intracavitary combined with external beam (no surgery):** Two intracavitary uterovaginal insertions are carried out. Dosage of intracavitary therapy and external beam is as for cervical cancer.

The uterine cavity is usually on the large side, and will hold a longer applicator (e.g. 7.5 cm) than most cases of cervical cancer. In the Sheffield system, a typical distribution would be 25 mg uterine and two 20 mg vaginal sources (total 65 mg).

Vaginal applicators are various types, as for the cervix. Some workers apply vaginal cesium at only one of the two insertions. The Manchester and Sheffield techniques are also applicable to the corpus.

In the Stockholm method, the uterine cavity is packed with as many small cesium sources as it will accommodate—Heyman capsules, holding 8–10 mg each. Each capsule has an attached numbered thread, so that they can be removed in the correct sequence.

**External beam alone (postoperative):** A parallel opposed pair of fields is used.

Forty-five Gy in 20 daily fractions over 4 weeks (9–10 MV photons).

External beam alone (no surgery). If the patient is unfit for a general anesthetic or if there is any contraindication to intracavitary insertion, external pelvic irradiation alone is used.

A parallel opposed pair of fields is used.

Fifty Gy in 25 daily fractions over 5 weeks (9–10 MV photons).

### Palliative Radiotherapy

Palliative radiotherapy is indicated for troublesome vaginal bleeding in patients who are not fit for radical surgery or radical radiotherapy. If the patient is fit enough for a general anesthetic, a single uterine intracavitary insertion (20 Gy to point A or reference isodose) may be possible. If not, a simple parallel opposed pair of fields is used.

**Energy and Dose**

Thirty Gy in 10 fractions over 2 weeks or 20 Gy in five daily fractions over a week (9–10 MV photons).

Cervical cancer of the corpus is one of the more favorable cancers, as most are well-differentiated, slowly growing and metastasize late. For stage I disease 5-year survival is up to 90%, for stage II, it is reduced to 50%, and to 20% for stage III and IV.

### Uterine Sarcomas

Uterine sarcomas are rare, representing less than 5% of uterine tumors. They may occur in young or in post-menopausal women. There is a high incidence of distant metastases, especially to lung. Treatment for stage I and II is a total hysterectomy and bilateral oophorectomy followed by postoperative pelvic external beam irradiation (50 Gy in two fractions over 5 weeks) for Mixed Müllerian and endometrial stromal sarcomas.

### Cancer of the Ovary

Cancer of the ovary accounts for 20% of gynecological malignancy and for about 4,000 new cases per year in the UK and for over 2,000 deaths. Overall it represents 2.3% of all cancers and 4.2% of cancer deaths. The average yearly incidence is 15 per 100,000 women and is rising. The peak incidence is between 40 years and 60 years. The etiology is unknown, though oral contraceptive use seems to have a protective role.

### Pathology

There is a wide variety of histological types:
Primary Malignant Tumors

- **Common epithelial tumors:** Most ovarian tumors (90%) arise from the surface epithelium.
  - **Serous tumors:** Serous cystadenocarcinoma, papillary cystadenocarcinoma. This is the most common type, amounting to about 42% of malignant tumors
  - Mucinous tumors (12%)
  - Clear cell carcinoma (6%)
  - Endometrioid carcinoma (15%)
  - Undifferentiated carcinoma (17%).
- **From germ cells (6%)**:
  - Dysgerminoma is a rare malignant tumor of children and young women. It is analogous to seminoma of the testis in males. It is highly sensitive to drugs and radiation.
  - Teratomas differentiate the various embryonic layers and are mostly benign.
  - Choriocarcinoma
  - Yolk sac tumor
- **From specialized hormone-producing cells (2%)**:
  - Granulosa cell tumors
  - Androblastomas.

Secondary Tumors

Uterus, breast and gastrointestinal tract. Krukenberg tumors are metastases from a gastric cancer simulating ovarian cancer.

FIGO Staging of Ovarian Cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>Clinical finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Tumor confined to the ovary</td>
</tr>
<tr>
<td>IA</td>
<td>Tumor confined to the pelvis</td>
</tr>
<tr>
<td>IB</td>
<td>Tumor spread to other pelvic tissues</td>
</tr>
<tr>
<td>II</td>
<td>Tumor of IIA or IIB with tumor on the surface on one or both ovaries</td>
</tr>
<tr>
<td>III</td>
<td>Tumor extending to the abdominal cavity, including peritoneal surfaces of the omentum</td>
</tr>
<tr>
<td>IV</td>
<td>Distant metastases (Fig. 8).</td>
</tr>
</tbody>
</table>

Tumor Markers

There are no tumor markers specific to ovarian cancer. CA-125 is the most helpful tumor marker and is raised in about 80% of patients with advanced disease.

Treatment

The management of ovarian cancer requires a multidisciplinary approach. Surgery, radiotherapy and chemotherapy all have a part to play, although, sadly, more intensive treatment of advanced disease has not produced much improvement in survival.

Surgery

Surgery is central to the treatment of stages I–III ovarian cancer. If possible, a total abdominal hysterectomy and bilateral salpingo-oophorectomy is carried out.

For stages I and IB, where the capsule of the ovary is intact, there is no need for postoperative adjuvant therapy.

Radiotherapy in Ovarian Tumors

The role of radical radiotherapy in epithelial ovarian cancer remains uncertain. The whole of the abdomen is at risk of spread. This probably explains why pelvic irradiation alone for stage I and II disease is ineffective. For stages I–III where there is minimal residual disease, whole abdominal irradiation is advised. Contraindications are multiple abdominal operations (increased risk of late gastrointestinal morbidity or impaired pulmonary function, and risk of late pulmonary fibrosis).

Target Volume

The volume should include the whole abdominal cavity. The upper border should be 2 cm above the diaphragm (in full expiration). The lower margin is the bottom of the obturator foramen of the pubis.

Technique

Anterior and posterior fields are used, stimulated in the supine and prone position.
Dose and Energy

A dose of 22.5 Gy is given in 20 daily fractions over 4 weeks to the whole abdomen (9–10 MV photons).

Monitoring of whole abdominal irradiation. Full blood count is monitored twice weekly. Liver function tests become abnormal since the liver is irradiated. Full pulmonary function tests should be carried out before treatment since part of the lower lobes is included in the volume.

Early reactions: Nausea, anorexia, vomiting and diarrhea are normal during treatment but resolve usually within 3 weeks of the end of treatment.

Late reactions: Late complications are usually related to gastrointestinal toxicity (9%), particularly to small bowel. Stenosis and hemorrhage are the main risks, particularly if more than one abdominal operation has been carried out.

Chemotherapy

Ovarian cancer is moderately sensitive to chemotherapy. Cure is extremely rare. Treatment is therefore essentially palliative. The most active drugs are cisplatin, its analogue carboplatin and the alkylating agents (e.g. chlorambucil and cyclophosphamide).

Results of Treatment

Ovarian cancer has a poor prognosis, largely due to its advanced stage at the time of diagnosis. The overall survival rate is 50%. In patients who have had adequate surgery, 5-year survival is 95% in stage I, 70% in stage II, 20% in stage III and 0–5% in stage IV. Where surgery has been inadequate, the survival for stages I–III is poorer (70%, 60% and 10% respectively).

CANCER OF THE VAGINA

Most cancers in the vagina are secondary deposits from uterus, rectum or ovary. Primary tumors of the vagina are rare with an incidence of less than 1 in 100,000 women. It usually occurs over the age of 60 years. The etiology in most cases is unknown. However, there was an outbreak of adenocarcinoma of the upper third of the vagina in teenage children whose mothers had been treated with very high doses of diethylstilbestrol for threatened abortion.

Stages I and IIA squamous cell carcinomas in the lower third can be treated by interstitial implantation using iridium-192. For stages I–III in the upper third and stage IIB and III in the lower third, vaginal intracavitary and external beam are used (45 Gy in 20 daily fractions over 4 weeks; 9–10 MV photons) using an anterior and two posterior oblique fields. This is followed by vaginal intracavitary therapy delivering a further 25–30 Gy to the vaginal mucosa.

For stage IV, an external beam alone is given (50 Gy in 20 daily fractions over 4 weeks; 9–10 MV photons).

Results of Treatment

Prognosis is less favorable than for cervical cancer: 5-year survival following radical radiotherapy is about 75% for stage I, 60% for stage II and 20% for stage III.

CANCER OF THE VULVA

Cancer of the vulva is rare, one-fifth of frequency of cervical cancer. It mainly occurs in elderly women.

The etiology is unknown. An association with viral infection (herpes simplex virus type 2, human papilloma virus) is suggested (but unproven), and vulvar intraepithelial neoplasia (VIN) has been postulated. Viral vulvar condylomata are also associated with vulvar cancer.

Macroscopic and Microscopic Appearance

Tumors may be exophytic or ulcerative. There is often associated leukoplakia. Virtually, all are squamous cell carcinomas. Adenocarcinoma is rare.

Spread

Local spread is to the surrounding skin, perineum, vagina and urethra. Lymphatic spread commonly occurs to the inguinal and femoral nodes and may be bilateral. Subsequent spread is to the external iliac nodes. Blood-borne spread is late.

Vulvar itching is common (70%), often with a vulvar mass or ulcer. Discharge and bleeding are less common.

Treatment

Surgery

Surgery is the treatment of choice.

Radiotherapy

The role of radiotherapy is in the postoperative radical treatment of the pelvis for involved groin nodes and the palliation of local symptoms of advanced disease.

Target volume: The groin and pelvic nodes bilaterally.

Technique

Parallel opposed anterior and posterior fields.

Dose and energy: 45–50 Gy midplane dose in 20 daily fractions over 4 weeks (9–10 MV photons). Inoperable local disease.

Target volume: The field should cover the tumor with a generous margin.

Direct field with bolus.

Gestational Trophoblastic Tumors

These include hydatidiform mole, choriocarcinoma and its variant, the placental site trophoblastic tumor. They affect
women during and after their reproductive period. The unique feature of these tumors is that they are derived from the trophoblast of the placenta rather than from the patient’s own tissues.

**Diagnosis**

Clinical presentation of GTT is usually with a hydatidiform mole. Typically, there is vaginal bleeding at the end of the first trimester.

The diagnosis of choriocarcinoma should be borne in mind in any woman of reproductive age with disseminated cancer of unknown origin.

A baseline chest radiograph is taken to detect lung metastases.

The initial treatment of a GTT should be suction evacuation of uterus. Serial blood human chorionic gonadotropin (hCG) levels are measured before and after evacuation. In most uncomplicated hydatidiform moles, hCG levels fall to normal as the mole degenerates. Most GTTs are exquisitely chemosensitive, particularly to methotrexate.

The role of radiotherapy is limited.

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4. FIGO staging of Malignancy. 1990.
INTRODUCTION

Cytotoxic chemotherapy is assuming an increasingly important role in the management of gynecologic tumors both in an adjuvant setting and as therapy for clinical disease as well as for palliation. Choriocarcinoma and germ cell tumors (GCTs) of the ovary, which in the prechemotherapy era were nearly always fatal, are now among the most curable of all cancers; moreover, significant prolongation and improvement of quality of life for those with epithelial ovarian carcinomas and uterine malignancies is now a present day reality. Clinical pharmacological principles in gynecological anticancer chemotherapy, such as those concerned with selection of appropriate agents and factors in the decision to treat, response evaluation and the rationale for combination chemotherapy are discussed. Common and frequent toxic effects encountered with chemotherapeutic agents used in gynecology, oncology and chemotherapy are presented and their management that includes strategies to minimize occurrence or reduce their severity is also outlined.

CANCER OF THE CERVIX

Chemotherapy is currently reserved for patients with advanced locoregional or metastatic disease and in those who recur after primary treatment with surgery or radiotherapy. Several single agents such as cyclophosphamide, 5-fluorouracil, hydroxyurea, mitomycin C, vinca alkaloids, bleomycin and cisplatinum have shown to produce response in cervical carcinomas with the rates ranging between 10% and 44%. However, single agents show a very low complete response rate and the response is still poorer in previously irradiated patients. Among all the agents, cisplatin has been reported to produce the highest single agent response rate. As a consequence of poor and inconsistent antitumor activity by the single drugs, combination chemotherapy has evolved in the last one decade or so. Presently the combination chemotherapy is designed to be utilized as an adjunct to surgery, radiotherapy or both. Two approaches are being studied—neoadjuvant or concomitant administration of chemotherapy schedules. In neoadjuvant practice, the tumor is considered to be more sensitive prior to the local treatment and it may be easier to deliver maximal doses of the drugs. The concomitant approach aims at enhancement of tumor cell kill and possible improvement in the sensitivity of the cancer cells to radiation. In recent years, reports on these chemotherapy trials are available and combination regimens appear to provide better response rate than single agents. The patterns of Care Study, USA has reported the rising trends in the use of chemotherapy in patients with stage III and IV disease. Radiotherapy and chemotherapy (without surgery) was utilized in 3.7% and 10.5% in 1984 and 1990 respectively. Sardi and coworkers found success with neoadjuvant chemotherapy (cisplatin, vinblastine and bleomycin) before surgery and radiation, than radiation alone for stage II and III disease. The 2-year disease-free survival for stage II and III disease was 79% and 50% for chemotherapy treated patients as compared to 47% and 26% for the historically matched controls.

In the radiation of stage IB2 and IIA bulky tumors, chemoradiation is preferred. This is confirmed by several studies by the Gynecologic Oncology Group (GOG). Radiation is
administered along with a chemotherapeutic agent usually cisplatin—concurrent chemoradiation. Cisplatin here acts as a radiation sensitizer. Another advantage is that micrometastasis outside the radiation field will also be taken care of. Cisplatin is given in a relatively low dose of 40 mg/m² weekly till the entire course of radiation is completed. Improved overall survival and reduced local and distant recurrence have been updated in the recent most Cochrane review.

Despite significant response to chemotherapy, it has to be understood that the overwhelming majority of patients with advanced disease (stage IIIB, III, IV) will continue to be treated with radiotherapy alone and the combination chemotherapy can be utilized in experimental and research settings. This is because the concomitant chemotherapy has the drawback of adverse toxicity and the sequential combination of radiotherapy and chemotherapy does not improve pelvic control and overall survival of patients.4

**Indications of Chemotherapy in Carcinoma Cervix**
- Advanced locoregional (stage III/IV) as neoadjuvant or concomitant basis
- Metastatic disease especially in lungs/bones/lymph nodes
- Recurrent disease postsurgery or radiotherapy.

**Best Known Protocol**
- Injection cisplatin 30 mg/m² intravenous (IV) weekly during radiotherapy as concomitant
- BIP regimen (bleomycin, ifosfamide and cisplatin) three cycles administered on a monthly basis as neoadjuvant or adjuvant.

**Contraindications**
- Nephropathy
- Cystitis.

**CANCER OF THE ENDOMETRIUM**

**Hormonal Therapy**

Synthetic progestational agents are commonly used as systemic treatment in recurrent endometrial carcinomas. The most important advantage is that few side effects are encountered by this modality of treatment. The response rates range from 15% to 29%.6 Response to hormonal therapy is related to the histologic grade of the tumor, disease-free interval and receptor status. The progestosterone receptor content of endometrial tumors correlates well with subsequent response to progesterone therapy.7 Even though well differentiated tumors tend to have the highest receptor positivity; receptor positivity appears to be a better correlate than grade. The most commonly used progestogens are hydroxyprogesterone or medroxyprogesterone (400 mg intramuscularly weekly). Oral megestrol acetate (Megace 160 mg/day) produces similar results. These progestogens should be continued indefinitely until recurrence or distant metastases develop. Tamoxifen has been shown to bind estrogen receptor (dose of 20 mg daily) and thus increase the number of progesterone receptor in vivo. This fact will enhance the effect of progesterational agents and hence the suggested use of tamoxifen alternating with progesterone is to take advantage of the receptor induction to increase hormonal sensitivity.8 Postmenopausal patients do better with tamoxifen than premenopausal cases due to preponderance of estrogen receptors. A Cochrane review of several large randomized placebo-controlled studies has failed to identify benefit of adjuvant progestin therapy.9

**Chemotherapy**

Patients in whom hormonal treatment fails may be considered for cytotoxic chemotherapy. Detailed study of drugs have demonstrated antimitotic activity as single agent namely, cisplatin, doxorubicin, paclitaxel and carboplatin. Doxorubicin appears to be the most active, with response rates of 10–37% reported, including complete responses in 5–20% patients so treated.10 Cisplatin and carboplatin apparently have a similar activity, with reported response rates ranging from 4% to 42%.11 Paclitaxel appears to be a newer promising agent in endometrial cancer treatment. A phase II trial by the GOG, reported by Ball, noted an overall response rate of 36%.12 There is only modest information on combination chemotherapy for endometrial carcinoma. It must be mentioned that so far there does not appear to be a clear benefit of combination chemotherapy over a single agent in the treatment of women with advanced or recurrent endometrial carcinoma. Finally, chemotherapy is also indicated in patients with serous papillary or clear cell endometrial carcinomas following surgery and radiotherapy.13 Currently, newer regimens combining paclitaxel, ifosfamide and etoposide are being tried to improve results.

**Cancer of the Ovary**

Even though aggressive surgery [total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH-BSO) plus omentectomy and tumor extirpation] remains the cornerstone in the management of ovarian cancer, there is high-risk of relapse following surgery alone. Thus, further therapy is required in all but a small proportion of patients (stage I grade 1).14 In recent years, the role of chemotherapy has been more firmly established in this neoplasm and during the same period, the indications of radiotherapy have become more defined. Anticancer medication can eradicate primary disease and possibly sterilize micrometastasis. Local tumor can serve as an indicator for knowing the chemo sensitivity of the neoplasm. It could be reasonably expected that the
response of micrometastases should be similar to that of the primary. Systemic chemotherapy may be more beneficial to patients with minimal tumor burden. The rationale behind use of chemotherapy in ovarian cancer is to treat gross or micrometastases within or outside the peritoneal cavity. Chemotherapy can be used as single or multidrug therapy. Initially, the single drug melphalan was used postoperatively and showed promising response. A number of anticancer agents have shown both in vitro and in vivo response to the epithelial cancers. These include alkylating agents (melphalan, thiopeta, chlorambucil and cyclophosphamide), doxorubicin, epirubicin, cisplatin, methotrexate, 5-fluorouracil, etoposide, hexamethylmelamine (HEM) and recently paclitaxel.

Combination chemotherapy regimens have replaced single drug therapy. The first study that showed significant benefit of the multidrug chemotherapy as compared to single agent regimen was GOG trial in patients with bulky advanced disease. In subsequent years, the studies have addressed the issue of adjuvant chemotherapy in patients with minimal residual disease and also the use of aggressive chemotherapy in advanced disease. The cisplatinum based chemotherapy (discovered in the late 1970s) either cisplatin plus cyclophosphamide or standard three-drug cyclophosphamide, doxorubicin, cisplatin (CAP) regimen are now considered the ideal schedule in this neoplasm (Table 1). More recently carboplatin has been tested against cisplatin-based regimens and has shown less adverse toxicities. Paclitaxel became available in 1990s and with the introduction of carboplatin, paclitaxel and carboplatin has now become the standard in first-line chemotherapy at many centers.

The International Federation of Gynecology and Obstetrics (FIGO) recommends the following regimens:
- Paclitaxel 175 mg/m² over 3 hours and carboplatin at area under the curve (AUC) 6 over 1 hour
- Docetaxel 75 mg/m² over 1 hour and carboplatin AUC 5 over 1 hour.

The dose of carboplatin is based on Calvert’s formula using creatinine clearance calculated by Cockcroft formula—[(140 – age) × weight in kg × .85/serum creatinine × 72]. POMB-ACE regimen—cisplatin, vincristine, methotrexate, bleomycin, actinomycin D, cyclophosphamide and etoposide.

### Dose Intensity Chemotherapy

The drug dose is unquestionably important in determining the response to chemotherapy. The ideal dose of the drugs, optimal scheduling of the regimen, total numbers of cycles and total effective doses significantly influence the treatment outcome. In the dose intensity (DI) studies of ovarian cancer, a 2-cm nodule represents 10⁶ to 10⁷ cells, so that in an ideal situation, four to five cycles of chemotherapy will be needed to eliminate the cancer cells. The first evidence that cisplatin was effective in the treatment of advanced ovarian carcinoma gave rise to a number of clinical trials incorporating low-dose and high-dose cisplatin with or without cyclophosphamide and doxorubicin. Against this background Levin and Hryniuk (1987) were able to identify the effective dose of cisplatin was 100 mg/m² every 3–4 weeks.

### Drug Resistance

Epithelial ovarian cancer is highly drug sensitive and approximately 60–80% of patients will achieve an objective response to cisplatin-based chemotherapy. Unfortunately, a complete clinical response is not tantamount to cure and approximately, 50% of advanced ovarian cancer will relapse within 1–2 years post-treatment. Even though second-line treatments have clinical responses, survival for these patients is usually less than 12 months (after relapse). A multiplicity of biologic, pharmacologic and biochemical factors are likely to interact to limit the effectiveness of chemotherapeutic agents in this neoplasm.

### Second-line Chemotherapy

In the ovarian cancer patients refractory to cisplatin-based chemotherapy regimens, a number of alternative drugs have been clinically tested. These include hexamethylmelamine, etoposide, ifosfamide and paclitaxel. Some of the new agents, which are also being tried, are gemcitabine, docetaxel, tetraplatin and topotecan.

### Intraperitoneal Chemotherapy

It is a logical approach to a disease process such as ovarian carcinoma that spreads primarily by intraperitoneal seeding.

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**Table 1: Common regimens for ovarian carcinoma**

<table>
<thead>
<tr>
<th>1. Cisplatin-cyclophosphamide:</th>
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</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>75–100 mg/m²</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>750 mg/m²</td>
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<tr>
<td>Repeat every 3 weeks for 6 cycles</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>2. Cyclophosphamide, doxorubicin and cisplatin (CAP):</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>500 mg/m²</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>50 mg/m²</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>50 mg/m²</td>
</tr>
<tr>
<td>Repeat every 3 weeks for 6 cycles</td>
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<table>
<thead>
<tr>
<th>3. Cisplatin-paclitaxel:</th>
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<tbody>
<tr>
<td>Paclitaxel</td>
<td>175 mg/m² (3-hour infusion)</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>75 mg/m²</td>
</tr>
<tr>
<td>Repeat every 3 weeks for 6 cycles</td>
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</table>
and remains confined to the peritoneal cavity for a significant part of the disease course. It is based on the rationale that cytotoxic agents with low solubility and high molecular weight clear from the peritoneal cavity slowly compared to clearance from the systemic circulation. Despite the theoretical appeal, there are certain doubts about actual results. Agents that have been evaluated for safety, pharmacokinetics and possible effectiveness in ovarian cancer when used intraperitoneally include cisplatin, carboplatin, 5-fluorouracil, doxorubicin, mitoxantrone, melphalan, mitomycin C, methotrexate, cytarabine, etoposide and thiotapec. 17

In GOG 172 study, IV cisplatin and paclitaxel were compared with intraperitoneal cisplatin (100 mg/m²) on day 2 and paclitaxel 135 mg/m² IV over 24 hours on day 1 and paclitaxel 60 mg/m² intraperitoneally on day 8. Six such cycles are given every 21 days. There was a 25% reduction in the risk of death in the intraperitoneal group. A Cochrane meta-analysis found an increase in overall survival and progression-free survival in advanced ovarian cancer in IP group.

**GERM CELL TUMORS OF OVARY**

**Dysgerminoma**

It is the female counterpart of testicular seminoma. Recent data of GCTs have shown that dysgerminoma is analogous to other histology subtypes as regards its chemosensitivity. In the GOG, the dysgerminoma patients of stage III or IV disease and those with macroscopic residual disease after surgery are treated with induction bleomycin, etoposide, cisplatin (BEV) chemotherapy. This is followed by consolidation with vincristine, actinomycin, cyclophosphamide (VAC) regimen. The overall response to the chemotherapy regimen was noted in more than 85% of the patients (Table 2). 18

The other GCTs of the ovary include endodermal sinus tumor, embryonal carcinoma, and choriocarcinoma, mixed GCTs and teratomas. Chemotherapy is usually on an adjuvant setting in GCT and the preferred regimens are cisplatin, vincristine, bleomycin (PVB) or BEP. In these tumors, the chemotherapy response is in the range of 50–70%.

**GESTATIONAL TROPHOBLASTIC DISEASE**

Gestational trophoblastic disease is a group of diseases that extends over the range of the relatively benign hydatidiform mole, invasive mole or placental site trophoblastic tumor to the choriocarcinoma with its high potential for widespread metastasis and high mortality without therapy. Fortunately, the tumor is rare and when it occurs is sensitive to many chemotherapeutic agents including methotrexate, d-actinomycin, cisplatin, etoposide, vincristine, cyclophosphamide and chlorambucil. In good prognosis cases, single agent methotrexate or d-actinomycin is usually sufficient. In more aggressive disease, combination chemotherapy is usually effective. Response to therapy can be followed by the fall in the human chorionic gonadotropin level or its beta subunit, which serves as a marker for residual tumor. In experienced hands and with early therapy, the overall rate is 96%. 19

Anatomic staging of choriocarcinoma (I, confined to corpus; II, metastases to pelvis and vagina; III, pulmonary metastases with or without uterine, pelvic or vaginal involvement and IV, other metastases such as brain, liver, kidneys or gastrointestinal tract) is seldom used. Recent therapeutic planning relies on the scoring system that was developed at the Charing Cross Hospital by Bagshawe20 and later adopted by other groups including the World Health Organization (WHO). The importance of this scoring system lies in the identification of a high-risk choriocarcinoma that requires more intensive use of drug combinations to achieve cures and prevent emergence of resistance. The total score for a patient is obtained by adding the individual score for each prognostic factor with a score of 4 being considered low-risk, a sum of 5–7 as intermediate risk and a score greater than 7 as high-risk.

Future fertility following chemotherapy for trophoblastic tumors has been reported since the early 1960s and in general, fertility appears to be well-preserved. A study of 445 long-term survivors treated between 1958 and 1978 showed that 86% of all those who wished for further pregnancies had one or more live births. 21 Women who received three or more drugs were less likely to conceive than those who received methotrexate. 22

**BREAST CANCER**

Although breast cancer management strictly falls under the purview of the surgeons and oncologists but gynecologists are more often than not faced with the predicament of discovering early breast lumps during their routine

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**Table 2: Details of regimen**

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<thead>
<tr>
<th>Regimen</th>
<th>Dosage</th>
<th>Schedules</th>
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<tbody>
<tr>
<td>VAC</td>
<td>Vincristine 1.5 mg/m² (maximum 2.5 mg)</td>
<td>Weekly IV given for 12 weeks</td>
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<tr>
<td></td>
<td>Actinomycin D 0.5 mg/m²</td>
<td>5 days course every 4 weeks</td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide 5–7 mg/kg</td>
<td>5 days course every 4 weeks</td>
</tr>
<tr>
<td>PVB</td>
<td>Cisplatin 20 mg/m²</td>
<td>Daily × 5, IV q 3 weeks for 4 courses</td>
</tr>
<tr>
<td></td>
<td>Vinblastine 12 mg/m²</td>
<td>IV q 3 weeks for 4 courses</td>
</tr>
<tr>
<td></td>
<td>Bleomycin 20 mg/m² (maximum 30 U)</td>
<td>IV weekly for 7 courses (8th course on 10th week)</td>
</tr>
<tr>
<td>BEP</td>
<td>Bleomycin 20 U/m² (maximum 30 U)</td>
<td>IV weekly × 9</td>
</tr>
<tr>
<td></td>
<td>Etoposide 100 mg/m²</td>
<td>IV days 1–5 q 3 weeks × 3</td>
</tr>
<tr>
<td></td>
<td>Cisplatin 20 mg²</td>
<td>IV days 1–5 q 3 weeks × 3</td>
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Role of Chemotherapy in Gynecologic Malignancies 1003


INTRODUCTION

The concepts of development of invasive cervical cancer have undergone a remarkable change in the last 30 years. Although it has been known since centuries that cervical cancer was in some way related to sexual activity no definite carcinogen was implicated.

It was in the 1970s that Zur Hausen\(^1\) in Germany implicated that the human papillomavirus (HPV) was the causative organism, which led to the development of cervical cancer.

The further developments were rapid. Over a 100 different types of HPV were discovered specific to human beings. At least 30 of these affect the genital mucosa and they are further divided into high oncogenic potential and low oncogenic potential. Cervical cancer is the first solid tumor associated with virus infection. It is a DNA virus, spherical with 72 capsomeres and double stranded circular viral genome (Fig. 1).

ETIOPATHOLOGY

The virus enters the genital tract by sexual contact and may affect any part of the lower female genital tract. The incubation period is usually 1–6 months. After that, the first lesions may appear and there is a rapid and active growth of the virus. At the same time, the immune responses occur and the host tries to contain the virus. After about 9 months of this activity, one of the two outcomes is expected. If the immune response is good, there is a sustained clinical remission, which occurs in the majority. However, if the immune response is poor then there is a persistent and recurrent disease. Here the lesions go through the low-grade squamous intraepithelial lesion (SIL) to high-grade SIL and eventually to invasive cervical cancer (Fig. 2).

CLINICAL PRESENTATION

This infection may not cause any symptoms hence diagnosis is difficult. HPV diagnosis is possible by\(^2\)
- Clinical
- Cytology
- Colposcopy
- Histopathology
- Molecular biology.
**Clinical**

Diagnosis is based on the appearance of warts on the external genitalia, which are usually due to low oncogenic potential virus. Warty lesions on cervix and upper vagina, usually indicate infection with high oncogenic virus.

**Cytology**

Smears showing koilocytes, multinucleated cells and cells with orangeophilic cytoplasm, which are called dyskeratocytes, are pathognomonic of HPV infection (Figs 3 to 8).

**Colposcopy**

It is the most important tool to make a clinical diagnosis. The lesions may be exophytic, i.e. rising above the surface epithelium. These are either florid or micropapillary lesions. They may also be flat which are then detected on the application of acetic acid. These may appear also as white punctations (Figs 9 to 12).

**INVESTIGATIONS**

**Histology**

Characteristic change is koilocytosis with or without atypia. Various grades of dysplasia may also be observed. The basement membrane is all-important and contains the lesion for a long time. It is more than just an anatomical barrier. It is also an immunological barrier and it is the zone of host tumor interaction. Virus can cause breaks in the basement membrane, leading to early invasion (Figs 13 and 14).

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**Fig. 2:** Natural course of human papillomavirus (HPV) infection

**Fig. 3:** Human papillomavirus (HPV) induced neoplastic transformation
Molecular Biology

These methods are expensive but are very reliable to detect HPV.

Human papillomavirus-DNA test by Hybrid Capture 2 is a simple test, which will do viral typing also. It can be used for primary screening. Currently, it is expensive but much
Human Papillomavirus Infection and its Role in Cervical Cancer

Fig. 10: Micropapillary lesions

Fig. 11: Flat condyloma

Fig. 12: White punctation

Fig. 13: Koilocytotic changes breaks in the basement membrane

Fig. 14: Basement membrane more than just an anatomical immunological barrier zone of host tumor barrier

Fig. 15: Human papillomavirus-deoxyribonucleic acid (HPV-DNA) test: hybrid capture 2

research is being done to make it available and affordable for women in the developing world (Fig. 15).

Human papillomavirus-DNA detection can also be done by polymerase chain reaction (PCR). Genital swabs and cervical biopsies can be tested.
Human papillomavirus (HPV) testing is available in convenient kit-based systems which make screening possible on a population basis. In a low-resource setting, a single round of HPV testing was compared with cervical cytology and visual inspection with acetic acid. It was found that even a single round of HPV testing was associated with a significant reduction in the numbers of advanced cervical cancers and deaths from cervical cancer.

**IMMUNE RESPONSE TO HUMAN PAPILLOMAVIRUS**

It is the most important factor to clear infection. The response consists of innate and adaptive immunity. The Langerhans cell count and CD4 cell counts are decreased and interferon signaling is inhibited, if the immune response is poor. Molecular and cell biological evidence is convincing that HPV E6 and E7 oncogenes down regulate the cell cycle. The E6 oncogene inactivates the p53 tumor suppressor gene and E7 oncogene suppresses the pRB or the retinoblastoma gene.

**Viral Persistence Implies Ineffective Host Defense**

 Clinically HPV 16–18 may be cleared in 8–16 months whereas HPV 6–11 may be cleared in 4–8 months, if the immune response is adequate and the CD4 count is high.

**MANAGEMENT OF HUMAN PAPILLOMAVIRUS**

There are many modalities of treatment available. Essentially the management is long-term. The ultimate aim being to prevent the development of cervical cancer. The management may be considered as:

**Counseling in Human Papillomavirus**

This is very important. At times, patients are devastated by the news that they have a sexually transmitted disease (STD) and that too something, which may lead to cancer. It is important to allay their fears. Marital relationships can also be greatly disturbed. It is necessary to give very positive messages. Some of these are:

- HPV infection has relevance to cervical cancer screening and regular checkups are a must
- HPV infection is common, about 10% of all women have it sometime in their lives
- Cervical cancer is comparatively rare, only 10–20 women in 100,000 get it
- HPV infection is not a disease. Body immunity can overcome it
- Usually sexually transmitted. Not much is proved yet about other modes of transmission
- Having HPV is not a sign of infidelity
- Both partners need advice, checkup and perhaps treatment.

**Appropriate Management of Cervical Intraepithelial Neoplasia (Flow Chart 1)**

Human papillomavirus (HPV) may be associated with various grades of cervical intraepithelial neoplasia (CIN). If so, the appropriate treatment for CIN has to be carried. In general, low-grade SIL can be kept under observation and treated conservatively. Almost 70% regress and become normal over a period of 6 months to 1 year. However, if the lesion persists, progresses or recurs it needs further treatment.

In high-grade SIL, the treatment is excisional. A cold knife cone or Laser conization are advocated with multiple biopsies of the specimen to exclude invasion.

In developing countries where facilities are limited and follow-up difficult, a simple hysterectomy may be advised to those women who have completed their family and are above the age of 40 years. Many women request for hysterectomy and are reluctant for long-term follow-up.

**Medical Methods**

The use of podophyllin resin for treatment of genital warts is age old. The application of 10% podophyllin in tincture Benzoin should be followed by a soap and water wash after 6–8 hours. Podophyllin induces mitosis in the epithelium. The warts get shriveled and fall off. It is very acceptable to patients. However, it is not suitable for large and multiple lesion and is also contraindicated in pregnancy.
Trichloroacetic acid and 5% fluorouracil cream are other drugs used for local application.

**Surgical Methods**

Excision of vulval and perianal warts is possible by electrocautery. Depending on the size and the number of lesions, it can be done under general or local anesthesia. Tissue should be sent for biopsy and if possible for viral typing. For cervical and vaginal lesions, the best options are CO₂ laser and Cryotherapy. Carbon dioxide laser is an extremely valuable tool in the management of especially multicentric disease. A large surface area of lower genital tract can be treated at a sitting. The lesions are evaporated and there is minimal blood loss and cell debris. Healing occurs well without scarring.

Carbon dioxide laser treatment of the cervix is particularly suitable for young girls desirous of childbirth. It does not interfere with subsequent fertility status and obstetric performance of the cervix.⁵

Cryotherapy is used effectively and is an inexpensive treatment. It can give up to 87% cure rates and may be used in 2–3 sittings.⁶

**Follow-up**

It is necessary on short- and long-term basis. In the short-term follow-up, 3–6 monthly check-up is advised till the lesions have healed and disappeared. During this time, several tests may be needed.

In the regular follow-up, annual gynecological checkup and Pap smears are advised for a lifetime.

The follow-up is more intense for those with 16/18 infection as they are high oncogenic potential viruses. HPV is a multicentric disease. The entire lower genital tract is exposed to the virus and is susceptible to the development of neoplasia. Hence, follow-up has to include a careful inspection of vulva, perineum, vagina, cervix and endocervix.⁷

With good immunity a woman should clear her HPV infection in 6 months. The lesions become smaller and then disappear. During this period, she may be given nutritional supplements of Vitamins C, A, E and folic acid. These improve the immune status and are also effective in cell regeneration.

Genital tract infections also need to be treated. Use of antifungal drugs, antiprotozoal and antibiotics are effective so also local use of vaginal pessaries and ointments.

Contraceptive usage has to be discussed and barrier contraceptive is preferred. Oral contraceptive and intrauterine contraceptive device (IUCD) should be discouraged.

The male partner can also be asked to undergo a checkup. Penile warts and penile hygiene are significant factors.

Since, there is a high prevalence of STDs, checkup with human immunodeficiency virus (HIV) test, Herpes simplex virus (HSV) II, and Chlamydia serology may be suggested for both partners.⁸

### VACCINES AGAINST HUMAN PAPILLOMAVIRUS

There is no drug therapy available as yet against HPV virus unlike the treatment of HIV infection. However, prophylactic vaccines are currently marketed in over 16 countries.

The development of HPV vaccines is a major medical achievement of 21st century.

Finally there is some hope that cervical cancer may be controlled globally.

Human papillomavirus causes cervical cancer, a large portion of anal and other genital cancers, genital warts, recurrent respiratory papillomatosis, and cancers of the head and neck.⁹ A quadrivalent HPV 6/11/16/18 vaccine (Gardasil/Silgard; Merck and Co. Inc., Whitehouse Station, NJ) was licensed in the United States in June 2006 and subsequently in the European Union. The vaccine is a three-dose regimen and is indicated in girls and women 9–26 years of age for the prevention of cervical, vulvar, and vaginal cancer; their respective precancers; and genital warts caused by HPV types 6, 11, 16, and 18. The vaccine is labeled US Food and Drug Administration (FDA) Pregnancy Category B, because animal reproductive toxicology studies revealed no evidence of impaired female fertility or harm to the fetus due to the vaccine. However, because there are no adequate and well-controlled studies in pregnant women, and animal reproduction studies are not always predictive of human response, the vaccine is not recommended for use in pregnant women.

The bivalent vaccine is against 16/18 virus, but also gives cross protection against other oncogenic subtypes. Its trade name is Cervarix¹⁰ and was licensed for use in 2009. The cost of the vaccine is approximately US$ 400, which is going to be a major deterrent for its use in developing countries.¹⁰

### GLOBAL VIEW OF CERVICAL CANCER

The global incidence of cervical cancer is rising. It is predicted that whereas the total incidence in 2002 was 493,000 cases, by the year 2020 it will be 702,500. Out of these only 83,000 cases occurred in the developed countries and as many as 409,000 cases were seen in the developing countries. By the year 2020, this ratio will be worse. There will be only 92,500 cases in the developed countries whereas there will be 639,000 in the developing world. This also has to take into consideration that the total population in the developing world is seven times that of the developed world.

The HPV-DNA prevalence in normal women has been studied in various parts of the world.¹¹ It is found to vary from 7.63 in Asia, which is the lowest to 23.41 in Africa, which is the highest. The reason why the incidence of cervical cancer is high even though the global incidence of HPV is low because of the presence of cofactors, which decrease the immune status. The significant cofactors are high parity, prolonged...
use of oral contraceptive pills, smoking or use of tobacco and concurrent HIV infection. Other significant factors are low socioeconomic status, poor diet and concurrent HSVII and *Chlamydia trachomatis* infection.

In conclusion, the association of HPV and cervical cancer is causal and necessary. HPV-based preventive strategies, screening and vaccination should target all cases. Vaccines may provide a solution for the developing countries.

Finally, Obstetricians and Gynecologists and their professional associations must play a critical role in the introduction of these strategies and must become effective advocates for its use.

**REFERENCES**

Endoscopy
INTRODUCTION
As we ushered in the 21st century, the use of endoscopic techniques for better visualization and diagnosis has become the common practice of gynecologists. Imaging techniques like ultrasonography, computed tomography (CT) scan and magnetic resonance imaging (MRI) all have a role to play in the patient management but there is immense value of seeing directly and on a video monitor in a magnified view. It has had a tremendous impact on the acceptance and popularity of diagnostic laparoscopy and hysteroscopy. So in this chapter we shall highlight the indications, contraindications, basic techniques and instrumentations of diagnostic laparoscopy and hysteroscopy.

Since its evolution in 1930, by Kalk of Germany after the initial attempts by Pantaleoni (1869) and Phillips Bozini (1805), diagnostic laparoscopy blossomed in Europe and spread to the United States where Ruddock (1934) popularized it with the introduction of biopsy forceps and diathermy coagulation. Raoul Palmer of France in 1947 introduced lithotomy Trendelenburg position and created gaseous distension and described manipulation of uterus by a uterine cannula. Introduction of cold light fountain by Hopkins (1953) was a major breakthrough. Laparoscopy spread to various parts of the world but major revival came due to its undisputed role in female sterilization procedure. Kurt Semm (1977) of Germany was the first to introduce operative laparoscopy by publishing report of procedures like salpingectomy, oophorectomy and myomectomy.

Since that time diagnostic and operative laparoscopy have spread, refined and have now become most widely acceptable means of diagnosis and management.

INDICATIONS OF DIAGNOSTIC LAPAROSCOPY

Infertility Evaluation
This is the most common and apt indication of diagnostic laparoscopy. It helps to assess the tuboperitoneal factors, ovarian and uterine morphology and to see the functional capability of the tubes by chromoperturbation (Figs 1A and B). It is a complete evaluation of an infertile female and guides for further management according to the pelvic factor diagnosed.

Endometriosis
As Adamson (1990) rightly said endometriosis is a visual diagnosis. Endometriotic cysts smaller than 1 cm are unlikely to be detected by existing imaging modalities like USG (Figs 2A to F), CT scan and MRI. So a minimal and early grade I and grade II endometriosis (Figs 3A and B) is most likely to be picked up by a laparoscopy only.

Chronic Pelvic Pain
Several patients of chronic pelvic pain remaining undiagnosed by all possible tests are best evaluated by a diagnostic laparoscopy and the technique is known as “conscious pain mapping” where in the operator evaluates the pelvis for any possible focal lesion causative of pelvic pain and then touches several points in the pelvis to which the patient responds if there is a pain. It has proved quite popular in the western world.
Fig. 1A: Normal tubes and ovaries

Fig. 1B: Chromopertubation

Fig. 2A: Dilated hydrosalpinx

Fig. 2B: Polycystic ovaries

Fig. 2C: Bilateral endometriotic cyst

Fig. 2D: Deep intramural myoma
Identification of Adnexal Mass

Laparoscopy identifies the nature of the adnexal mass, such as pelvic inflammatory disease, ovarian tumors (Fig. 4A), tubal pregnancy (Fig. 4B) or tubercular mass (Fig. 4C). Aspiration of fluid (Fig. 4D) for cytology, culture sensitivity of pus and tissue sample for biopsy can be obtained at the time of laparoscopy.

Identification of Congenital Defects

Laparoscopy identifies double (Fig. 5A), unicornuate (Fig. 5B), bicornuate or septate uterus (Fig. 5C). Anomalies like absence of uterus (Fig. 5D) or presence of rudimentary horn can all be diagnosed by laparoscopy.

Evaluation of Cases of Amenorrhea

It can be good for evaluation of cases of primary and secondary amenorrhea. In primary amenorrhea we can find absence of uterus, hematometra and hematosalpinx as a result of obstruction to out flow of menstrual blood (in cases of imperforated hymen or in cicatrized ill-developed cervix). Ovarian status can be seen as streak ovaries (Fig. 6A) or polycystic enlarged ovaries (Fig. 6B) as causes of amenorrhea.

Assistance to Hysteroscopic Procedures

During advanced operative hysteroscopic procedures like septal resection (Fig. 7A) or cases of difficult adhesiolysis in Asherman’s syndrome (Fig. 7B).
Fig. 4A: Bilateral endometriotic cyst
Fig. 4B: Ampullary ectopic pregnancy
Fig. 4C: Encapsulated caseous ball
Fig. 4D: Encysted tubercular fluid collection
Fig. 5A: Double uterus
Fig. 5B: Unicornuate uterus
Fig. 5C: Bicornuate uterus
Fig. 5D: Absent uterus

Fig. 6A: Streak ovary
Fig. 6B: Bilateral polycystic ovaries

Fig. 7A: Thick wide deep septum
Fig. 7B: Asherman's syndrome
Laparoscopic Inspection
May be required after perforation of uterus during medical termination of pregnancy (MTP) to decide the next line of management or during an endometrial resection by hysteroscopy.

Second Look Laparoscopy
Second look laparoscopy is a very important indication in modern times. As a follow-up of major laparoscopic procedure it is performed to assess and break adhesions, following myomectomy and endometriosis surgery. It is advocated as a follow-up surveillance of initial laparoscopy for pelvic inflammatory disease (PID), tuberculosis or at times to evaluate the success of conservative medical management of ectopic pregnancy.

Assistance in ART Procedures
In infertility practice the procedure of gamete intrafallopian transfer is done by laparoscopy wherein the ovum and sperm are inserted in the fallopian tube by specialized catheters. It is a joint diagnostic and operative laparoscopy.

TECHNIQUE AND INSTRUMENTATION OF DIAGNOSTIC LAPAROSCOPY

Pneumoperitoneum Veress Needle (Fig. 8A)
It is first introduced by a vertical intraumbilical incision to create pneumoperitoneum for the safe entry of trocar.

It is available in reusable or disposable models containing a spring-loaded tip that retracts as it pierces the abdominal wall, allowing a blunt tip to engage on entry into the peritoneal cavity. The needle should be held by the shaft and directed toward the center of the pelvic cavity at an angle of 45° to the horizontal. Before connecting to the insufflator, the intra-abdominal position of the needle should be ascertained. This can be done by several methods which are listed below.

- As the needle enters the peritoneal cavity, there would be a hissing sound of air being sucked in.
- About 10 mL of saline can be instilled into the peritoneal cavity through the needle. If the needle is in the peritoneal cavity, the saline cannot be aspirated back as it falls into the dependent portion of the peritoneal cavity.
- In the hanging drop technique, a drop of saline instilled into the needle will be sucked in if the needle is in the peritoneal cavity, whereas it will remain there itself if it is extraperitoneal.

Trocars (Fig. 8B)
The trocar punctures the anterior abdominal wall after appropriate insufflation and carries with it the sleeve, through which the telescope is inserted after the trocar is withdrawn. The trocar tip can be pyramidal or conical. The trocar sizes are 11 mm, 6 mm or 3 mm to accommodate suitable telescopes.

Gas Insufflator (Fig. 8C)
Electronic CO₂ insufflators are used to provide controlled pneumoperitoneum for safe performance of laparoscopy. These insufflators after being connected to the trocars sleeve deliver CO₂ at a desired pressure and flow rate.

A carbon dioxide gas insufflator should provide a continuous flow of gas to maintain an intra-abdominal pressure ranging from 10 mm Hg to 15 mm Hg. Before the introduction of the primary trocar, a higher intra-abdominal pressure of 20 mm Hg can be set to facilitate insertion of trocar as well as to increase the distance between the trocar and the retroperitoneal vessels. Hence, after the insertion of the trocar, the pressure is reduced to 12–15 mm Hg. Flow rate is ideally kept at 1 liter/minute during initial insufflation with Veress needle and increased to higher flow rates when connected to the trocar.

Light Source (Fig. 8D)
High intensity light sources like xenon or halogen are used to give sharp images and hence better diagnosis. Light sources are connected to the telescope by means of fiber optic cables, which should be of superior quality for good images.

Camera (Fig. 8E)
Endoscopic camera is attached at the telescope and converts the electronic image to an optical image to be viewed from the video monitor. They are available as single chip or three chip cameras. Though for diagnostic laparoscopy the surgeon can even view in the pelvis directly from the telescope without a camera and monitor.

Ancillary Instruments
Ancillary instruments are used through a second puncture which can be suprapubic or in the lower abdomen, close to the anterior superior iliac spine. These ports can use either a probe, aspiration needle, biopsy forceps or a grasper. It is always better even during a diagnostic laparoscopy to be able to lift up the adnexa, and expose the full length of the tubes.

TECHNIQUE OF DIAGNOSTIC LAPAROSCOPY

Patient is laid in modified dorsal lithotomy position. General anesthesia (GA) is given. With monitoring of end-tidal (ET) CO₂ after creation of pneumoperitoneum, trocar is inserted, connected to CO₂ insufflator, light source and endovision camera. Uterus is manipulated by a uterine cannula to strongly antevort or retrovert the uterus.
Fig. 8A: Veress needles

Fig. 8B: Trocars 5 mm and 10 mm

Fig. 8C: Electronic CO₂ insufflator

Fig. 8D: Xenon light source

Fig. 8E: High definition three chip camera
Peritoneal Entry

The peritoneal cavity can be entered by an open or a closed technique. In the open, Hasson technique, the peritoneal cavity is entered through a mini-laparotomy incision which may be a transverse or vertical one in the subumbilical region. The cannula is directly introduced without prior insufflation of the peritoneal cavity. Gynecologists usually prefer the closed technique, where the peritoneal cavity is initially distended with CO₂ and the trocar is introduced blindly into the peritoneal cavity.

Entry through Palmer’s Point

The primary trocar can also be introduced through the Palmer’s point, which is about two fingers breadth below the left costal margin in the mid-clavicular line.

Laparoscopes

The light sources currently available are 250–300 watts xenon or mercury halide bulbs.

The ideal illumination required for performing operative procedures is provided by a 10 mm telescope. Types of telescopes are:

- Zero degree straight-forward telescope
- Thirty degree forward-oblique telescope.

Diagnostic laparoscopy is completed in a systematic manner. At first the surgeon confirms that no bowel or omental injury has been caused by needle or trocar insertion. Then he starts with inspection of the upper abdomen—the liver, gallbladder, subdiaphragmatic space and note any adhesion if present. Then it is good to first have panoramic view of the pelvis (Fig. 9A) to note any obvious anomaly and then gradually to bring the scope into focus on particular areas of interest. Normally it is best to retrovert the uterus and inspect the uterovesical pouch (Fig. 9B). Then after strict anteversion posterior surface, cul-de-sac and uterosacral ligament are visualized. Note is made of endometriotic implants or bowel adhesions. Then systematically the right and left adenexa are visualized by always lifting the ovary by another probe or grasper and inspecting all surfaces of the ovary and especially the ovarian fossa (Figs 9C and D) to look for early endometriotic implants as this is the most common site of endometriosis. The tubes are carefully studied. The proximal portion is examined for presence of nodules as can be in salpingitis isthmic nodosa (Fig. 9E). The tube is viewed in its entirety for the presence of sacculations, dilatation or adhesions (Fig. 9F). The fimbriae are manipulated or examined under water to look for perifimbrial phimosis or fine fimbrial adhesions that may impede ovum pickup. Any caseous material or tubercles if present should be noted (Figs 10A and B). Fluid in the pouch of Douglas (Fig. 10C) is aspirated and sent for cytological and bacteriological evaluation. Chromopertubation is performed by injecting dilute methylene blue.

So by above all it appears that diagnostic laparoscopy has an immense value and it should be the endeavor of every gynecologist to be adept with the basic techniques and instrumentation.

Instruments and Energy Sources for Cutting and Hemostasis

Complex laparoscopic surgeries involving division of tissues and maintenance of hemostasis are possible by mechanical means or by the use of different energy sources.

The mechanical means are suturing, stapling and the application of vascular clips.

The energy sources available for cutting tissues are:

- Electrical energy
- Laser
- Ultrasonic energy.

Monopolar and bipolar electrosurgical instruments are used to perform various types of surgeries and to obtain hemostasis.

Current Waveform

Three types of electrical currents are used in electrosurgery:

1. Cutting
2. Coagulating
3. Blended

Monopolar instruments use current that flows from an active electrode, through the tissue, achieving a cutting or coagulating effect. The circuit is completed through the patient’s body.

In bipolar diathermy, the current flows through the tissue between the two electrodes and the patient’s body is not part of the circuit. It is safer compared to monopolar current because current travels only through the tissue held between the jaws.

Surgical lasers available for gynecologic use include CO₂, argon, potassium-titanyl-phosphate (KTP), and neodymium: yttrium-aluminum-garnet (Nd:YAG).

The Harmonic scalpel (Ethicon Endosurgery) uses vibration at the rate of 55,000 cycles per second as an energy source to break hydrogen bonds in tissue, resulting in cutting or coaptation of vessels. Their use is advantageous as they result in minimal lateral thermal spread of energy, and there is no risk of electrical injury.

Staplers

The endoscopic gastrointestinal anastomosis (endo-GIA), originally designed for GIA, is used in gynecologic laparoscopy as a stapling device for securing and dividing tissue.
Fig. 9A: Normal pelvic anatomy

Fig. 9B: Uterovesical pouch adherent by adhesion

Fig. 9C: Right adherent ovary with endometriotic implants

Fig. 9D: Left adherent ovary with endometriotic implants

Fig. 9E: Right fallopian tube salpingitis, isthmic nodosa

Fig. 9F: Right fallopian tube grossly convoluted and sacculated
**COMPLICATIONS OF LAPAROSCOPY**

- **Pneumoperitoneum** extraperitoneal insufflation occurs when the Veress needle fails to enter the peritoneal cavity.
- Rarely pneumothorax can occur when an upper abdominal site is chosen for insufflation.
- Rarely a penetrating injury to major blood vessels can occur at the time of insufflation, especially in lean and thin patients.
- Laceration of abdominal viscera like bowel, omentum and bladder can occur by sharp trocar.
- Gas embolism.

**How to Minimize these Complications?**

- Safety checks of Veress needle placement like syringe test should be carried out just after inserting the needle.
- When the incorrect placement of Veress needle is recognized, then CO₂ is allowed to escape and needle is reinserted.
- Elevating the anterior abdominal wall and directing the needle or trocar toward pelvic area may avoid major vessel injuries.
- If the intubation is difficult, place a nasogastric tube to decompress the stomach before placement of Veress needle. The syringe test usually permits early recognition of stomach or bowel penetration.
- Trendelenburg tilt to be given only after the Veress needle insertion and telescope goes in.
- Very thorough inspection of bowel, omentum and bladder for any inadvertent injury.
- Entry of the trocar to be controlled and gentle avoiding sudden thrust.
- Direction of trocar should not be perpendicular to abdominal wall rather it should be toward the pelvis to avoid injury to major blood vessels.
- All patients should have their bladder drained after anesthesia is induced to prevent bladder injury.
- The Z track method can lessen the risk of trocar hernias.
- Meticulous closure of the rectus sheath to minimize risk of umbilical hernia.

**Limitations**

Laparoscopy cannot be performed in the following situations:

- Increased risk of bowel perforation, ileus and peritonitis in patients with distended bowel.
- Diaphragmatic hernia.
- Cardiorespiratory disease.
- Massive intraperitoneal hemorrhage.
- Extremely obese patient—it may be difficult to insert the instruments into peritoneal cavity.
- Presence of large abdominal mass.
- Advanced intrauterine pregnancy.
DIAGNOSTIC HYSTEROSCOPY

Hysteroscopy simply implies looking inside the uterine cavity by means of a telescope. It has immense value for diagnosing various gynecological conditions.13

Indications

Infertility Evaluation

As a part of endoscopic evaluation of an infertile patient it is combined routinely with laparoscopy to study the uterine cavity. It establishes the normalcy of the cavity by showing normal looking ostia and normal endometrium (Figs 11A to C). If it shows any abnormality then therapeutic hysteroscopy can be taken up.

Congenital Anomalies

Hysteroscopy combined with laparoscopy confirms whether the uterus is septate or bicornuate, enables to assess the capacity of each horn and permits evaluation of the depth and thickness of septum in planning resection of septum.14

Abnormal Uterine Bleeding

This is the most frequent presentation when a diagnostic hysteroscopy is required.15 This helps to diagnose endometrial polyps (Fig. 12A) submucous myomas (Fig. 12B) and occasionally cases of endometrial carcinomas. In postmenopausal women when endometrial thickness is more on transvaginal scan, they can be subjected to diagnostic hysteroscopy and in cases of suspected lesion, a biopsy can be obtained.

Recurrent Pregnancy Loss

Diagnostic hysteroscopy is a very useful adjunct in the array of diagnostic tests outlined for defining causes of recurrent pregnancy loss. Hysteroscopy may help to reveal uterine synechiae (Fig. 12C) septum or unicornuate and bicornuate uterus. So it should now be made a part of work-up of a female with recurrent abortions.

Asherman’s Syndrome

Panoramic visualization of the uterine cavity in suspected cases of uterine synechiae enables the confirmation and assessment of the type and extent of synechiae. It also helps to ascertain the condition known as T-shaped uterus where the uterine cavity becomes long and narrow (Fig. 12D).

Misplaced Intrauterine Contraceptive Device

Hysteroscope helps to locate a misplaced intrauterine device (Fig. 12E) or confirm its absence due to spontaneous expulsion.16
Fig. 12A: Endometrial polyps

Fig. 12B: Submucous myoma

Fig. 12C: Grade III synechiae

Fig. 12D: Narrow uterine cavity

Fig. 12E: Misplaced IUCD

Fig. 12F: Foreign body
Foreign Bodies

Like retained tips of Carman cannula and even fetal bones (Fig. 12F) are quite frequently encountered in diagnostic hysteroscopy in cases where an MTP of gestation age more than 10 weeks has been carried out.

Endometrial Tuberculosis

In India this is the most common cause of infertility. Symptoms includes: pelvic pain, decreased menstrual bleeding and occasionally abnormal uterine bleeding. So when such cases are subjected to hysteroscopy, we often find plaques of caseous material, fibrosis and at time tubercles (Figs 13A to F). This also gives an opportunity to take a targeted biopsy.

Assessment of Cornual Pathology

When hysterosalpingogram (HSG) shows bilateral tubal block hysteroscopy is useful to study the interstitial portion of the fallopian tube and decide a tubo-tubal cannulation (Fig. 14) or tubo-cornual implantation.

**TECHNIQUE AND INSTRUMENTATION**

- Hysteroscope
- Distension media
- Technique of diagnostic hysteroscopy

**Hysteroscope**

The most commonly applied hysteroscope has a 4 mm telescope with 30° oblique view. The diagnostic sheath is of

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**Fig. 13A:** Pseudo-ostia formation

**Fig. 13B:** Criss-cross fibrosis

**Fig. 13C:** Multiple polyposis

**Fig. 13D:** Tubular cavity with caseous material
5 mm which has inflow channel for running the distension medium. Fiberoptic cable is attached to the telescope and xenon light source is connected to give bright illumination. Endoscopic camera is attached and gives optical images on the monitor. Other hysteroscopies available are:

**Microhysteroscope**

This specialized endoscope converts a panoramic hysteroscope into a high powered microscope by switching the lens to 150 × light contact is made with the mucous membrane. This has been described by Hamou (1981)\textsuperscript{17} to perform in vivo cytology.

**Contact Hysteroscope**

It does not require a sheath or a distending medium. This has been described by Baggish.\textsuperscript{16,19} Actual contact is made with the mucosa, so bleeding does not interfere with examination and allow visualization of endocervical canal and endometrium in its natural collapsed state. The view obtained lies between panoramic hysteroscopy and microhysteroscopy. Diagnosis is based on color, architectural pattern, contour and touch. It is quite difficult to interpret, though the images obtained are very good.

**Flexible Hysteroscope**

A 4.8 mm diameter soft and flexible fiberoptic hysteroscope has been introduced by Fujinon. The flexible hysteroscope is somewhat more difficult to handle but offers the particular advantage in aligning the catheter for tubal canalization.

**Bittocchi’s Hysteroscope**

Bittocchi et al.\textsuperscript{20} have devised a 4 mm hysteroscope which has a telescope of 1.7 mm, offers continuous inflow-outflow system and also incorporates an operative channel through which scissors, graspers and biopsy forceps can be introduced. So it is a unique combination of diagnostic hysteroscopy (as outer diameter of total instrument is 4 mm) and facility for simultaneous operative intervention.

**Distension Media**

Commonly used for diagnostic hysteroscopy are saline or Ringer lactate but others which could be used are CO\textsubscript{2}, Hyskon and dextran 70.\textsuperscript{21} Hyskon has the major advantage that it
is immiscible with blood so it allows excellent visualization even during bleeding, but after getting dried Hyskon clogs the hysteroscope channel. CO₂ insufflation requires special insufflator devices so it is not popular in India. Due to above, saline or Ringer lactate are the preferred distension media for diagnostic hysteroscopy. Ringer lactate is available as one and three liter bottles. It can be instilled by gravity method by hanging it high on an IV stand or enclosing in a pressure bag or attaching to an infusion pump.

Diagnostic Hysteroscopy Technique

This can be performed under local anesthesia (LA) with injection of lidocaine 1%, 10–15 mL directly into the cervix. Hardly ever the need of IV sedation or general anesthesia (GA) arises. Premedication of anxiolytic and antispasmodic analgesic can be given. It is best performed in immediate postmenstrual phase as endometrium is the thinnest and allows good visualization. Patient is laid in dorsal lithotomy position and cervix is grasped with single tooth tenaculum. A diagnostic 4 mm or 5 mm sheath is selected, the light generator is switched on, fiberoptic cable attached to the telescope. The distension media is attached to run outside for diagnostic hysteroscopy. Ringer lactate is available as one liter bottles. It can be instilled by gravity method by hanging it high on an IV stand or enclosing in a pressure bag or attaching to an infusion pump.

Routine dilatation of the cervix should be avoided; it should only be gently sounded to see the direction of the uterus. As the scope is inserted the endocervical canal shows longitudinal folds, papillae and clefts. The vascular pattern of normal endocervix shows branching tree-like vessels. These are well observed with a contact or microhysteroscope. The internal os appears as a narrow constriction on top of the endocervical canal. The isthmus is a cylindrical extension above the os. The corpus of uterus is a capacious cavity above the isthmus. The central point of Müllerian duct fusion is above the os. The corpus of uterus is a capacious cavity above the isthmus. The central point of Müllerian duct fusion is seen projecting down from the fundus. The cornua occupy either side of this fused area. The tubal ostia are visible at the upper extremities of the fundus and show great variation in their appearance and angle of entry in the uterine cavity. The endometrium is smooth and pink-white in color during the proliferative phase of the cycle. In the secretory phase the endometrium is lush and velvety; it protrudes in the cavity irregularly and can be easily mistaken for small polyps. The hue of secretory endometrium is magenta. The interior of the cavity, particularly when liquid media are used, first appears cloudy with fine debris floating in the medium. The thickness of the endometrium can be easily appreciated by placing pressure on the telescope and pushing on the posterior wall of the uterus. This maneuver creates a groove in the endometrium. After completion of diagnostic examination the patient can be discharged after some time.

Prevention

- Aseptic precautions
- Cervix and internal os should be negotiated under direct vision
- Hysteroscopy should be avoided in presence of gross cervical infection, uterine infection or salpingitis
- Careful and constant monitoring of fluid input/output is critical to prevent fluid overload.

Limitations

- Cardiorespiratory disease
- Intrauterine pregnancy
- Infection
- Cervical cicatrization.

CONCLUSION

In coming years diagnostic laparoscopy and hysteroscopy will have a decisive role in the diagnosis and further management of gynecological conditions and every gynecologist will have to be well acquainted with the basics of instrumentation and technique.

REFERENCES

INTRODUCTION

A detailed and repeatable visualization of the pelvis has been enabled by way of *Laparoscopy*, which has had a great impact on the management of infertility. The advent of endoscopy and improvement in technique and technology with the addition of *Hysteroscopy* to the endoscopic armamentarium has allowed direct visualization of the endometrial cavity, tubal ostia and cervical canal. This has improved our ability to understand, diagnose and treat the various causes of infertility.

We focus on the efficacy and limitations of some of the important fertility promoting endoscopic procedures, restriction of space precludes detailing of technique. Endoscopy can be used for both diagnosis and therapy.

DIAGNOSTIC

As a diagnostic tool a combined laparoscopic and hysteroscopic examination is the gold standard for the evaluation of infertility.\(^1\) Direct visual examination is superior to hysterosalpingography justifying use of the more invasive procedure.

Laparoscopy allows an assessment of tubal patency and also identifies pelvic pathology while hysteroscopy helps in diagnosis of intracavitary lesions. Chromopertubation demonstrating a free spill at the fimbrial end is reassuring, but distension of the tube with blockage at the fimbrial end indicates hydrosalpinx formation which can be easily detected during chromopertubation.

Development of smaller diameter endoscopies has further simplified the procedure. Microlaparoscopy and mini hysteroscopy, performed under local anesthesia or mild sedation have a high degree of diagnostic accuracy despite a smaller visual field, and have been proposed as the first-line diagnostic procedures.\(^2\)

Salpingoscopy and falloposcopy allow evaluation of the tubal lumen. The former is a transfimbrial approach allowing visualization from the ampullary-isthmic junction to the fimbriae. The latter is a transcervical approach allowing assessment of the tubal lumen from the uterotubal ostium to the fimbria. Falloposcopy has the potential to become a standard investigation for infertility since tubes that look normal externally can have lesions of the endosalpinx.\(^3\) High cost of equipment has been a major deterrent. Transvaginal hydrolaparoscopy was introduced to assess the tubo-ovarian relationship. Since, it can only view the pouch of Douglas its use is limited.

THERAPEUTIC

The decreased morbidity and shortened hospital stay, an opportunity to diagnose and treat at the same time and a reduction in postoperative adhesion formation has led to the immense popularity of operative endoscopy. Surgeries performed include:

**Ovarian factor**
- Polycystic ovary syndrome (PCOS)—ovarian drilling
- Endometriosis—ablation
- Ovarian cysts—excision/cystectomy.

**Tubal factor**
- Distal tubal occlusion—fimbrioplasty, neosalpingostomy.
- Proximal tubal obstruction—transcervical tubal recanalization, reversal of sterilization.

**Uterine factor**
- Asherman’s syndrome—adhesiolysis
- Congenital anomalies—metroplasty, excision of rudimentary horn
- Fibroids—myomectomy
**Peritoneal factor**
- Adnexal adhesions—adhesiolysis.

**POLYCYSTIC OVARY SYNDROME**

Infertility in PCOS is related to anovulation. Surgical induction of ovulation was achieved by wedge resection of the ovary. This fell into disrepute because of increased morbidity and postoperative adhesion formation. Endoscopy revived this surgical option in the form of ovarian drilling. Ovulation occurs presumably because of a decrease in stromal mass or disruption of parenchymal blood flow leading to reduction in ovarian androgen production and luteinizing hormone levels.4

Ovarian drilling can be performed using unipolar needle cautery or laser.5 The ovarian surface is fulgurated at evenly spaced points. Cautery is maintained until the ovarian capsule and cortex is penetrated, 5–6 seconds at each point using a current of 300–400 watts.6 4–8 punctures are enough with the use of the cautery.7 For laser the number of punctures is higher 20–40.8 Restraint must be used as premature ovarian failure has been reported after too generous a drilling of the ovarian cortex. The peritoneal cavity should be lavaged to reduce risk of adhesions.

**Results**

To date there is no standardization of the technique. Ovulation rates ranging between 70% and 90% and pregnancy rates of 70% have been reported.9 The minimum "dose" of diathermy that is required and the modification for each patient needs to be determined.

**Prognostic Factors**
- Duration of infertility less than 3 years
- Use of diathermy rather than laser
- Pretreatment LH levels more than 10 IU/L
- Age.

**Advantages**
- As effective as gonadotropin therapy. One time procedure
- Intensive ultrasound monitoring is not required
- Reduces risk of multiple pregnancy and ovarian hyper-stimulation syndrome (OHSS)
- Increases sensitivity of ovary to stimulation.

**Disadvantages**
- Adhesion formation
- Possibility of inducing premature ovarian failure.

**ENDOMETRIOSIS**

Twenty to forty percent of subfertile women have endometriosis. The cause of infertility in endometriosis is debatable. In severe endometriosis distortion of the tubo-ovarian relationship may lead to infertility. In the absence of a mechanical factor, infertility is attributed to ectopic implants inducing a peritoneal inflammatory reaction, an autoimmune response or to related endocrine abnormalities. Surgical treatment involves:
- Ablation/resection of implants
- Correction of abnormal pelvic anatomy
- Management of endometriomas.

**Ablation of Implants**

Ablation of implants is done by coagulation, vaporization and excision. Coagulation can be achieved by using the unipolar or bipolar electrocautery, the endocoagulator or various surgical lasers. Laser is a more precise delivery system and causes less damage to the adjacent tissues. Results with all the techniques are comparable.

**Correction of Tubo-ovarian Relationship**

The range of adhesions encountered varies from fine avascular adhesions to extremely dense adhesions that completely obliterate tissue planes. Lysis of adhesions must be meticulous, causing minimal tissue trauma and maintaining complete hemostasis. Adhesions may be lysed by delicate pressure with scissors, aqua dissection or blunt and sharp dissection. Vital structures must be clearly identified before dissection.

**Management of Endometrioma**

Cysts smaller than 3 cm are usually vaporized/coagulated. Cysts greater than 3 cm are dealt with by cystectomy or drainage, stripping of the cyst wall and coagulation of the base and any remnant endometriotic tissue. Simple incision and drainage of the cyst leads to increased rate of recurrence.10 Extraovarian endometriotic cysts are formed by invagination of the ovarian cortex therefore ablation should be limited. Drainage of the cyst with eversion of the cyst wall gives good results.11
Results and Recommendation

Meta-analysis of literature suggests that in mild and moderate endometriosis laparoscopic ablation is superior to no treatment or medical treatment for infertility management. Restoration of the tubo-ovarian relationship improves pregnancy rates with a cumulative pregnancy rate of 70%. Pregnancy outcome with laparoscopy or laparotomy for severe endometriosis does not differ significantly therefore choice of technique should be based on surgical expertise.

TUBAL OCCLUSION
Occlusion may be fimbrial or cornual.

Fimbrial Block/Hydrosalpinx
Fimbrial agglutination, fimbrial encapsulation and prefimbrial phimosis are sequelae of infection. Collection of fluid within the tubal lumen leads to the formation of hydrosalpinx. Chronic infection like genital tuberculosis is not uncommon in India. The fallopian tubes are the most common sites of involvement. These may form tubo-ovarian masses.

Fimbrioplasty
Distension of the fallopian tube with methylene blue dye facilitates surgery. The tube is stabilized holding the serosa with an atraumatic forceps. A 3-mm alligator forceps is introduced into the tubal ostium. Deglutination of the fimbria is achieved by opening the jaws of the forceps inside the lumen and gently withdrawing it from the tube a number of times in different directions.

Correction of prefimbrial phimosis is done by incising the fibrous bands constricting the infundibulum using blended current. Radial incisions are made along avascular points starting at the fimbrial end and going beyond the region of the constriction.

Results: Success rates range from 20% to 50%. Ectopic pregnancy rate is seen in 5%.

Limitations: Forced insertion may lead to mucosal trauma. Reformation of adhesions.

Neosalpingostomy
After distending the tube with dye the tube is inspected to locate site of scarring. The tube is stabilized and an incision is made extending from the ostium toward the ovary. Two to three radial incisions may be required to expose the fimbria. Electrocautery, laser or micro scissor can be used. Meticulous hemostasis using bipolar cautery and peritoneal lavage are essential to optimize outcome.

Results of reconstructive surgery are optimal when the tubal mucosa shows minimal damage, varying between 58% and 77%.

Prognostic factors for surgery are:
- Extent of adhesions
- Nature of adhesions
- Diameter of the hydrosalpinx < or > 1 cm
- Macroscopic condition of endosalpinx
- Tubal wall thickness.

Cornual Block
Cornual block occurs in approximately 15% of patients with tubal infertility. The technique of transcervical tubal cannulation was developed by and it transformed the treatment of cornual occlusion.

A coaxial catheter system is used to access the tubal ostia under direct hysteroscopic vision. The block is removed by moving the catheter with the wire guide in and out of the tubal lumen. Laparoscopic control is maintained to avoid risk of tubal perforation and to facilitate passage of the cannula.

Results
Recanalization is achieved in 80–90% of tubes, and pregnancy rates are in the range of 40%. Compared to tubal microsurgery the procedure gives better results and is minimally invasive, the ectopic pregnancy rates are also much lower. Pregnancy rates are poor when the wire guide is required to open the block.

FIBROIDS
Laparoscopy reveals subserous fibroids and bumpy irregularity caused by intramural fibromyomas, whereas hysteroscopy is useful in detecting and treating intracavitary submucous fibromyomatous polyps.

Laparoscopic myomectomy for intramural fibroids in the infertile patient was not encouraged because endoscopic suturing did not give a sound uterine scar. Currently this view is being opposed. Laparoscopic myomectomy for infertility should be attempted by an experienced surgeon.

Hysteroscopic polypectomy and myomectomy enhance fertility and should be the procedures of choice for intrauterine lesions.

ADHESIOLYSIS
An inverse relationship exists between the grade of adhesions and the pregnancy rate. Before commencing dissection a careful identification of intra-abdominal structures is essential. Adhesions should be coagulated before division. Thick adhesions should be divided one layer at a time to prevent trauma to underlying structures.

Intrauterine Adhesions
The incidence of infertility due to uterine structural abnormalities and endometrial pathology is approximately
5–10%. Hysteroscopic surgical procedures for intrauterine pathology became popular as they avoided cutting through uterine musculature to enter the cavity.

**Adhesiolysis for Asherman’s Syndrome**

Asherman’s syndrome is found in approximately 5% of infertile women. The sine qua non for the development of intrauterine adhesions is endometrial trauma, especially to the basalis layer. The simple movement of the hysteroscope can break mild or minimal adhesions. Thicker lesions require use of scissors or electrocautery. Laparoscopic control is advocated. Balloon catheter can be used to provide tamponade. The use of IUD’s and catheters is not recommended. Conjugated estrogen should be administered after surgery.

**CONGENITAL UTERINE ANOMALIES**

Incidence is 0.1–1.5%. Müllerian anomalies due to defective lateral fusion may be associated with infertility or repeated pregnancy loss.

Prevalence in women with recurrent pregnancy loss is significantly higher (10–12%). Among congenital anomalies, septate uterus is associated with the highest incidence of reproductive failure.

**Metroplasty**

The septum can be cut with scissors, electrocautery or a bipolar vaporizer (Versapoint). “Shortening technique (thin septa): Incision starts from the apex. “Thinning technique” (wide septa): Incisions are made along each side of the septum alternately, thinning the septum.

The dissection is complete when the hysteroscope can be moved freely from one cornual recess to the other without intervening obstruction and when both ostia can be visualized simultaneously. A small residual septum of less than 1 cm does not impair reproductive outcome. Incision of cervical septum does not lead to cervical incompetence.

Results of hysteroscopic metroplasty for recurrent pregnancy loss are excellent and superior to those obtained by transabdominal approach. Cumulative pregnancy rate is 80–89% at 36 months and overall miscarriage rate is 15%. Results are not as good when surgery is performed primarily for primary infertility.

**Complications:** Perforation, uterine rupture in subsequent pregnancy though rare has been reported.

**CONCLUSION**

The minimal invasiveness, the reduced morbidity and excellent results have assigned endoscopic surgery the central role in infertility management.

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**REFERENCES**

INTRODUCTION

The symptoms attributable to chronic anovulation are the main reasons that women with polycystic ovary syndrome (PCOS) present themselves to the clinicians. Not surprisingly, a major complaint is the infertility that accompanies PCOS. Historically, PCOS has been described by Stein and Leventhal in 1935, which identified the association of polycystic ovaries with hirsutism, amenorrhea and obesity. Prior to the availability of ovulation inducing agents, laparotomy with bilateral ovarian wedge resection (OWR) rapidly gained popularity. Surgical OWR was the first established treatment for anovulatory PCOS patients but was largely abandoned because of the risk of post-surgical adhesion formation. Ovulation rates obtained with OWR were excellent. But several investigators noted postoperative adhesions that gave suboptimal pregnancy rates. Hence, today OWR is all but obsolete having been replaced by other modalities of treatment.

It was replaced by medical ovulation induction with clomiphene and gonadotropins. However, patients with PCOS treated with gonadotropins often have a polyfollicular response and are exposed to the risks of ovarian hyperstimulation syndrome (OHSS) and multiple pregnancy. Although effective, it is an expensive, stressfull and time-consuming form of treatment requiring intensive monitoring. Hence, the new surgical therapy, laparoscopic ovarian “drilling” gained popularity since it avoids or reduces the use of gonadotropins for inducing ovulation. The procedure can be done on an outpatient basis with less trauma and fewer postoperative adhesions. It has been claimed in many uncontrolled observational studies that it is followed, at least temporarily, by a high rate of spontaneous postoperative ovulation and conception, or that subsequent medical ovulation induction becomes easier.

A PRACTICAL APPROACH TO OVULATION INDUCTION

The “antiestrogenic compounds” (primarily clomiphene citrate) are the most commonly used agents for ovulation induction, as the “first line” of treatment for women with PCOS-related anovulatory infertility. The ovulation rate with clomiphene is more than 80%. However, 15–20% women remain anovulatory despite treatment with incremental doses of clomiphene. Furthermore, in spite of a high ovulation rate, the pregnancy rate is only between 40% and 50% and the abortion rate is as high as 30–40%.

In the patients resistant to clomiphene citrate, gonadotropin therapy has traditionally been the next step. “Gonadotropins” have the same disadvantages as clomiphene citrate, which include increased rates of multiple gestation and spontaneous abortions. The risk of OHSS, a well-known complication with use of human menopausal gonadotropin (hMG), also necessitates careful monitoring during its administration.

The prevalent complications of OHSS and multiple pregnancies can largely be avoided by administering follicle stimulating hormone (FSH) in a low dose and individualized regimen. Hyperinsulinemia can be corrected by weight loss or insulin-sensitizing agents, such as metformin, which alone or in combination with other agents are capable of restoring ovulation. Advice about weight loss is critical in modern management of PCOS and infertility.
According to current data, metformin has gained popularity as a first-line management in clomiphene citrate-resistant women with PCOS. If ovulation does not occur within several months after treatment with metformin, after the evaluation of all pros and cons related to each treatment, laparoscopic ovarian drilling or gonadotropins may be considered as an effective option according to patient choice. An alternative to medical approach is surgical treatment. The most popular treatment is laparoscopic ovarian drilling. Operative laparoscopy has renewed the interest in the surgical approach to ovulation induction in patients resistant to clomiphene therapy or hMG therapy. The results are promising with a high ovulation rate ranging between 70% and 90% and a pregnancy rate of 70%. Advocates of laparoscopy claim a lower risk of postoperative adhesions compared to laparotomy. Other arguments in favor of the laparoscopic approach include the minimal morbidity associated with the procedure and virtually no cyclic monitoring of ovulation induction. In addition there is no increased risk of multiple gestation and ovarian hyperstimulation. Some studies have noted a lowered rate of miscarriage after laparoscopic electrocauterization of ovarian surface (LEOS) than medical therapy. It has also shown to produce significant endocrine changes with better results in obese patients with higher preoperative luteinizing hormone (LH) values and LH-FSH ratio.

Several methods of laparoscopic treatment have been studied, including ovarian electrocauterization, laser drilling, and multiple biopsy. Each of these methods share a common goal of creating focal areas of damage to the ovarian cortex and/or stroma, with the most extensively studied method being LEOS. However, there is no standard technique among different reproductive surgeons. The aim of newer studies is to compare different laparoscopic techniques and study the hormonal profile, ovulation rate and pregnancy rate after surgery. Takeuchi et al. performed a prospective, randomized study of infertile women with PCOS and compared a group who underwent laparoscopic ovarian drilling using a harmonic scalpel laser to a group who underwent laparoscopic ovarian drilling using a neodymium-yttrium-aluminum-garnet (Nd:YAG) laser. Change in the hormonal profile after surgery, ovulation rate and pregnancy rate were compared between both groups. LH and testosterone serum levels and the LH-FSH ratio showed a statistically significant reduction after surgery, and the spontaneous ovulation rate was 94% in both groups. The cumulative pregnancy rates within 2 years of follow-up were 77% in those who underwent laparoscopic ovarian drilling using a harmonic scalpel laser and 60% in those who underwent laparoscopic ovarian drilling using a Nd:YAG laser. This study shows that the technique of laparoscopic ovarian drilling using a harmonic scalpel resulted in ovulation and conception without major complications. Malkawi et al. studied how many punctures per ovary are needed to improve the reproductive outcome? To evaluate the biochemical, clinical and reproductive results after laparoscopic ovarian drilling they carried out a different number of punctures in the ovaries. They concluded that five, instead of more than equal to 10, punctures per ovary are sufficient to ameliorate the hyperandrogenic status in these women, improving their clinical and reproductive outcome.

Currently, the choice of the “number of punctures” to be applied at laparoscopic ovarian drilling (LOD) is empirical. Historically, the amount of ovarian tissue removed during bilateral ovarian wedge resection varied between one-third to three-quarters depending on the size of the ovary. Some gynecologists apply the same principle to LOD by empirically making different numbers of punctures in each ovary depending on its size. Between three punctures and 25 punctures have been reported with power settings between 30 W and 400 W. As a general principle, increasing the amount of thermal energy delivered to the ovarian stroma may increase the efficacy of the procedure but at the expense of increasing the risk of ovarian atrophy. Gjonnaess reported that ovulation occurred more frequently if five or more holes were applied compared with three holes per ovary. However, others found that four diathermy holes per ovary were sufficient to achieve good results and that no improvement was achieved when applying more holes. There are a number of difficulties in comparing the experience of various authors due to variation in the techniques used in LOD, including:

- Using different instruments (needles, scissors, biopsy forceps, etc.) to deliver the energy to the ovary
- Applying different amount of energy to the ovary (measured in joules, equivalent to power in watts multiplied by the duration of electricity applied in sec per puncture).
- Distribution of the thermal energy, either localized to a few holes or more widely spread over many holes with varying depths of penetration.

**Calculation of Thermal Energy**

Gjonnaas in 1984, correlated the ovulation rates after LOD to different numbers of points cauterized. He reported that the best results [ovulation rate = 96.7% (n = 30)] were obtained when the number of points was more than five per ovary (> 10 points per patient). However, this referred to the use of biopsy or sterilization forceps applied against the ovarian surface and activating the electricity at 200–300 W for 3 ± 1 second. Hence, the amount of thermal energy delivered to each ovary, on an average, was 250 watts × 3 second × more than 5 = more than 3,750 J. Armbr in 1990s found that four diathermy holes per ovary were sufficient to achieve good results and that no improvement was achieved when applying more holes. This referred to the use of a specially designed needle to penetrate the ovary with activation of the electricity (40 W) for 4 second at each point. The amount of thermal energy delivered to each ovary was 40 watts × 4 seconds × 4 = 640 J, which is significantly lower than that used by...
Gjonnaess. Another study compared the amounts of thermal energy used where 2, 3, 4, 5, 6 and 7 punctures were applied. The calculation of thermal energy was watts applied × no. of seconds × no. of punctures. It is important that the comparison between different studies should take into consideration the total amount of thermal energy delivered to each ovary, not just the number of holes made in the ovary.

**Threshold Dose**

The application of two holes per ovary, equivalent to the delivery of 300 J, was found to produce significantly poorer results than the other groups, measured in terms of restoration of menstrual regularity, ovulation rate and conception rate. The threshold dose may therefore be higher than two punctures per ovary.

**Plateau Dose**

The plateau dose refers to the lowest dose at which all subjects who will respond are observed to respond. There does not appear to be significant differences in the outcomes (menstrual pattern, ovulation and conception) of groups where 2–6 punctures are applied. It seems that three punctures (450 J) per ovary produce results as good as higher numbers of punctures. A prospective dose-finding study is required to estimate more accurately the optimal amount of energy required for LOD.

**Excessive Thermal Energy**

Ovarian atrophy and failure is a rare complication of LOD. A case of severe ovarian atrophy following LOD has been reported in which eight punctures were created at 400 watts for 5 second per puncture, equivalent to 16,000 J. It is therefore possible that application of excessive amounts of thermal energy to the ovary during LOD will produce irreversible damage to the ovary, leading to ovarian failure.

Follicle-stimulating hormone is considered to be a reasonable marker of ovarian reserve and function. It seems possible that the application of seven or more punctures per ovary represents an excessive amount of thermal energy used for LOD and should therefore be discouraged.

**Depth of Penetration of Energy**

Where a significantly greater amount of thermal energy (> 3,750 J per ovary) was applied, it was done so using a pair of biopsy or sterilization forceps, which applied the thermal energy to the ovarian surface and the depth of penetration was therefore between 2 mm and 4 mm, i.e. superficial. In contrast, the depth of penetration using the specially designed ovarian diathermy needle (Rocket of London) is up to 8 mm. Similar instruments used by others, found that the amount of thermal energy used to produce a good result was approximately 640 J per ovary. It is therefore possible to conclude that with deeper penetration during LOD, the amount of thermal energy can be reduced without compromising the outcome. Furthermore, achieving good results with deep penetration using low energy supports the hypothesis that LOD works by destroying androgen-producing ovarian stroma.

“Preoperatively” the routine tests for any laparoscopic surgery are performed along with the special hormonal investigations such as day 3 FSH, LH, prolactin, total testosterone and dehydroepiandrosterone (DHEAS).

**Postoperative Monitoring**

Following ovarian diathermy, women are asked to keep a record of their menstrual cycle. If the patient started a menstrual period within 6 weeks of the surgery, a blood sample is taken on day 2 of that cycle for measurement of serum concentrations of LH, FSH, testosterone, androstenedione and sex hormone-binding globulin (SHBG). Another blood sample is taken on day 21 of the same cycle for measurement of serum concentration of progesterone. Ovulation is diagnosed when the progesterone level is more than 30 nmol/L. Two more midluteal phase blood samples are taken in the subsequent cycles to measure serum progesterone levels. If spontaneous menstruation does not occur during the 6 weeks following surgery, a random blood sample is taken to measure all the above hormones.

In order to comprehend the mechanism of action of LEOS, it is necessary to understand the pathophysiology of PCOD.

**PATHOPHYSIOLOGY OF POLYCYSTIC OVARY SYNDROME**

Elevated LH levels may stimulate androgen production in stromal and hyperplastic thecal cells in the ovarian follicle. Although abundant substrate for estrogen synthesis is available, the low levels of FSH in the follicle prevent induction of aromatase activity and result in a lack of ovarian estrogen production. As granulosa cell mitosis and follicular growth require an estrogenic follicular microenvironment, follicular maturation is arrested. High intraovarian androgen levels may also contribute to follicular atresia. Peripheral availability of ovarian testosterone that is converted by 5-alpha reductase in the skin to dihydrotestosterone, accounts for acne and hirsutism in these women. Increased androstenedione secretion leads to increased androgen secretion in the skin. Elevated LH levels may stimulate androgen production in stromal and hyperplastic thecal cells in the ovarian follicle. Although abundant substrate for estrogen synthesis is available, the low levels of FSH in the follicle prevent induction of aromatase activity and result in a lack of ovarian estrogen production. As granulosa cell mitosis and follicular growth require an estrogenic follicular microenvironment, follicular maturation is arrested. High intraovarian androgen levels may also contribute to follicular atresia. Peripheral availability of ovarian testosterone that is converted by 5-alpha reductase in the skin to dihydrotestosterone, accounts for acne and hirsutism in these women. Increased androstenedione secretion leads to increased androgen secretion in the skin.
MECHANISM OF ACTION OF LAPAROSCOPIC ELECTROCAUTERIZATION OF OVARIAN SURFACE IN OVARIAN OVULATION INDUCTION

The mechanisms responsible for the ovulation inducing properties of LEOS have as yet to be satisfactorily elucidated. Various hypotheses have been suggested, based on the hormonal changes observed after LEOS:

- Marked decrease in circulating levels of androgens, i.e. androstenedione and testosterone\(^\text{10,15,16,33}\)
- Decrease in levels of DHEAS\(^\text{14}\)
- Decrease in circulating levels of estradiol
- Reduction in the concentration of immunoreactive LH as well as in LH bioactivity\(^\text{10,15,16,18,20}\)
- Decrease in LH/FSH ratio
- Central opioid and dopaminergic control over gonadotropin secretion appears to remain unaffected by LEOS\(^\text{34}\)
- Temporary decrease in inhibin levels which reach baseline values in 1 week\(^\text{35}\)
- Significant reduction in serum concentration of homocysteine.\(^\text{36}\)

Possible Mechanisms

- “Destruction of ovarian stromal elements” and release of androgen rich follicular fluid from the puncture of subcapsular cysts causes a fall in local and circulating levels of androgens. Decrease in substrate for follicular aromatase and damage to the follicle walls itself, produces a fall in circulating estradiol levels, release of the pituitary from negative feedback of estradiol on FSH, producing positive feedback effects on LH secretion and normalization of LH-FSH ratio leading to follicular development followed by ovulation.\(^\text{37}\)
- The observations which support the above hypotheses are:
  - Pituitary LH secretion in response to infusions of gonadotropin-releasing hormone (GnRH) is reduced postoperatively, compared to the preoperative response.\(^\text{38,39}\)
  - Ovulation rates and continuation of ovulatory cycles are best in patients in whom LH levels are high preoperatively,\(^\text{40}\) proving that the decrease in LH levels is directly proportional to the success of LEOS.
  - Pregnancies occur more often when the follicular fluid is rich in androgen content at the time of surgery.\(^\text{40}\)
  - Transvaginal ultrasound guided follicular aspiration of sub-capsular cysts without causing significant stromal damage has yielded a 50-85% ovulation rate and 50% pregnancy rate. This may suggest that “removal of the androgen rich follicular fluid” eventually helps to restore LH-FSH ratio.\(^\text{41}\)
  - Hyperemia” associated with the postoperative healing process may play a role by increasing the delivery of gonadotropins to the ovary.\(^\text{42}\)

OUTCOME ANALYSIS OF LAPAROSCOPIC ELECTROCAUTERIZATION OF OVARIAN SURFACE

The results are promising with a high ovulation rate ranging between 70% and 90% and a pregnancy rate of around 70%.\(^\text{22,23}\) Majority of patients have spontaneous ovulation after surgery.

The crude pregnancy rates after ovarian drilling in one study varied between 52% and 80% with electrocoagulation and 0–56% with laser.\(^\text{44}\) Using life table analysis, Heylen et al.\(^\text{2}\) reported pregnancy rates of 68%, 73% and 73% respectively at 12, 18 and 24 months after laparoscopic treatment with argon laser. Li et al.\(^\text{18}\) reported a cumulative pregnancy rate of 54%, 62% and 68% respectively at 12, 18 and 24 months using argon laser. Felemban et al.\(^\text{45}\) reported in a recent study a pregnancy rate of 54%, 68% and 82% respectively at 12, 18 and 24 months using insulated needle cautery for ovarian drilling. In our personal series\(^\text{46}\) the ovulation rate achieved was 82% and a 58% pregnancy rate.

Table 1 shows the summary of conceptions following LEOS.

Three-dimensional (3D) sonographic characterization of polycystic ovaries has been performed recently, including the study of the effect of laparoscopic ovarian drilling on ovarian volume.\(^\text{47}\) Ovarian volume decreased, and an increase in intraovarian flow intensity after laparoscopic electrocautery has been observed. Besides, hormonal levels correlated well with changes of 3D sonographic features. Therefore, 3D ultrasonography (USG) may be a useful adjunct and noninvasive method for correlating clinical parameters with the blood flow alterations in PCOS patients.

In our experience of 296 prospectively studied cases of LOD till 2005, the ovulation rate was 82% and pregnancy rate of 58%.

The routine protocol for management of infertile PCOS patients is to begin with insulin sensitizing agents along with ovulation stimulating drugs for 6 months (33% pregnancy rate). In case the patients do not respond, they are subjected to LOD (58% pregnancy rate).

PREDICTIVE FACTORS OF LAPAROSCOPIC ELECTROCAUTERIZATION OF OVARIAN SURFACE

Although LOD has been widely used to induce ovulation in women with PCOS, predicting the clinical response to this treatment remains to be elucidated further. Amer et al.\(^\text{48}\)
### Table 1: Summary of conceptions following laparoscopic ovulation induction

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>N</th>
<th>Method</th>
<th>Ovulation (%)</th>
<th>Pregnancy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aakvaag and Gjonnaess</td>
<td>1985</td>
<td>58</td>
<td>LEOS</td>
<td>91</td>
<td>42</td>
</tr>
<tr>
<td>Greenblatt and Casper</td>
<td>1987</td>
<td>6</td>
<td>LEOS</td>
<td>83</td>
<td>67</td>
</tr>
<tr>
<td>van der Weiden and Alberda</td>
<td>1987</td>
<td>11</td>
<td>LEOS</td>
<td>82</td>
<td>45</td>
</tr>
<tr>
<td>Sumioki et al.</td>
<td>1988</td>
<td>7</td>
<td>Biopsy</td>
<td>86</td>
<td>57</td>
</tr>
<tr>
<td>Daniell and Miller</td>
<td>1989</td>
<td>85</td>
<td>CO₂/KTP</td>
<td>71</td>
<td>56</td>
</tr>
<tr>
<td>Yanagibori et al.</td>
<td>1989</td>
<td>6</td>
<td>Nd:YAG</td>
<td>–</td>
<td>50</td>
</tr>
<tr>
<td>Abdel Gadir et al.</td>
<td>1990</td>
<td>29</td>
<td>LEOS</td>
<td>87</td>
<td>48</td>
</tr>
<tr>
<td>Keckstein et al.</td>
<td>1990</td>
<td>27</td>
<td>Nd:YAG</td>
<td>70</td>
<td>37</td>
</tr>
<tr>
<td>Tasaka et al.</td>
<td>1990</td>
<td>11</td>
<td>LEOS</td>
<td>91</td>
<td>36</td>
</tr>
<tr>
<td>Utsunomiya et al.</td>
<td>1990</td>
<td>16</td>
<td>Biopsy</td>
<td>94</td>
<td>50</td>
</tr>
<tr>
<td>Kovacs et al.</td>
<td>1991</td>
<td>10</td>
<td>LEOS</td>
<td>90</td>
<td>40</td>
</tr>
<tr>
<td>Rossmanith et al.</td>
<td>1991</td>
<td>11</td>
<td>Nd:YAG</td>
<td>72</td>
<td>36</td>
</tr>
<tr>
<td>Gurgan et al.</td>
<td>1992</td>
<td>40</td>
<td>Nd:YAG</td>
<td>70</td>
<td>50</td>
</tr>
<tr>
<td>Ostrzenski</td>
<td>1992</td>
<td>12</td>
<td>CO₂</td>
<td>100</td>
<td>75</td>
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<tr>
<td>Armar and Lachelin</td>
<td>1993</td>
<td>50</td>
<td>LEOS</td>
<td>92</td>
<td>62</td>
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<tr>
<td>Campo et al.</td>
<td>1993</td>
<td>23</td>
<td>Biopsy</td>
<td>61</td>
<td>56</td>
</tr>
<tr>
<td>Verhelst et al.</td>
<td>1993</td>
<td>17</td>
<td>CO₂</td>
<td>82</td>
<td>65</td>
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<tr>
<td>Titinen et al.</td>
<td>1993</td>
<td>10</td>
<td>LEOS</td>
<td>70</td>
<td>20</td>
</tr>
<tr>
<td>Greenblatt and Casper</td>
<td>1993</td>
<td>8</td>
<td>LEOS</td>
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<td>88</td>
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<tr>
<td>Szilagyi et al.</td>
<td>1993</td>
<td>4</td>
<td>Nd:YAG</td>
<td>75</td>
<td>25</td>
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<tr>
<td>Balen and Jacobs</td>
<td>1994</td>
<td>10</td>
<td>LEOS</td>
<td>100</td>
<td>40</td>
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<tr>
<td>Gjonnaess</td>
<td>1994</td>
<td>219</td>
<td>LEOS</td>
<td>92</td>
<td>69</td>
</tr>
<tr>
<td>Naether et al.</td>
<td>1994</td>
<td>206</td>
<td>LEOS</td>
<td>77</td>
<td>70</td>
</tr>
<tr>
<td>Heylen et al.</td>
<td>1994</td>
<td>44</td>
<td>Vaporization</td>
<td>–</td>
<td>73</td>
</tr>
<tr>
<td>Shah DS</td>
<td>1997</td>
<td>125</td>
<td>LEOS</td>
<td>82</td>
<td>58</td>
</tr>
<tr>
<td>Li TC et al.</td>
<td>1998</td>
<td>31</td>
<td>Argon</td>
<td>–</td>
<td>68</td>
</tr>
<tr>
<td>Li TC et al.</td>
<td>1998</td>
<td>80</td>
<td>LEOS</td>
<td>–</td>
<td>68</td>
</tr>
<tr>
<td>Felemban</td>
<td>2000</td>
<td>112</td>
<td>LEOS</td>
<td>73</td>
<td>54–82</td>
</tr>
<tr>
<td>Takeuchi S et al.</td>
<td>2003</td>
<td>17</td>
<td>Harmonic scalpel</td>
<td>94</td>
<td>77</td>
</tr>
<tr>
<td>Al-Fadhli R</td>
<td>2004</td>
<td>–</td>
<td>LEOS</td>
<td>80</td>
<td>50–60</td>
</tr>
<tr>
<td>Cleemann L</td>
<td>2004</td>
<td>–</td>
<td>LEOS</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>Api M</td>
<td>2005</td>
<td>45</td>
<td>Drilling</td>
<td>93</td>
<td>64</td>
</tr>
<tr>
<td>Yildirim M</td>
<td>2004</td>
<td>134</td>
<td>Minilaparotomy and ovarian wedge resection</td>
<td>78–90</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: LEOS, laparoscopic electrocauterization of ovarian surface; KTP, potassium titanyl phosphate; Nd:YAG, neodymium-doped yttrium aluminum garnet.
carried out a study to identify factors that may help to predict the outcome of LOD. The results showed that women with body mass index (BMI) more than or equal to 35 kg/m², serum testosterone concentration more than or equal to 4.5 nmol/L, free androgen index (FAI) more than or equal to 15 and/or with duration of infertility more than 3 years seem to be poor responders to LOD. In LOD responders, serum LH levels more than 10 IU/L appeared to be associated with higher pregnancy rates. Marked obesity, marked hyperandrogenism and/or long duration of infertility in women with PCOS seem to predict resistance to LOD. High LH levels in LOD responders appear to predict higher probability of pregnancy.

**FACTORS INFLUENCING POSTOPERATIVE OVULATION INDUCTION AFTER TREATMENT WITH LAPAROSCOPIC ELECTROCAUTERIZATION OF OVARIAN SURFACE**

- Presence of any additional factors responsible for infertility.
- Patients with elevated LH levels (>10 mIU/mL) seem more likely to conceive postoperatively, while those with absence of postoperative fall of LH levels are unlikely to ovulate.²⁷
- Early resumption of anovulatory state postoperatively is associated with return to the pretreatment hormonal milieu and indicates the need for other therapeutic modalities.²⁹
- Overweight patients experience a lower rate of ovulation than patients with normal body weight.³⁰,⁴⁹
- Smoking adversely affects the pregnancy rates in these patients.⁵⁰
- Metformin improves insulin resistance, reduces androgen levels and significantly increases the ovulation and pregnancy rates in infertile women, following LOD.⁵¹

**ADVANTAGES OF LAPAROSCOPIC ELECTROCAUTERIZATION OF OVARIAN SURFACE**

- LEOS yields a better ovulation rate and pregnancy rate than other modalities of laparoscopic surgery for ovulation induction in patients with PCOS.
- It has been suggested that patients who had previously developed OHSS during gonadotropin therapy, either ovulate spontaneously or with clomiphene citrate (CC) after LEOS and even the incidence of OHSS reduces in subsequent gonadotropin cycles.

**COMPLICATIONS**

**Adhesion Formation**

Adhesion formation was a significant complication of OWR which was due to tissue handling and serosal trauma at laparotomy. Adhesions resulted in nonavailability of ovarian surface for ovulation and peritoneal ovum transport was hindered. LEOS has gained importance as it is expected to minimize adhesion formation postoperatively (Table 2).

The definite etiology of pelvic adhesion formation is not clearly well known, but the following risk factors have been incriminated in this process:

- Intra-abdominal infection
- Tissue hypoxia or ischemia
- Tissue drying
- Rough manipulations of tissues during surgery
- Presence of reactive foreign body
- Presence of intraperitoneal blood
- Dissection of prior adhesions.

**Adjuvants for Adhesion Reduction**

Adhesion formation and reformation are still an unavoidable event in reproductive pelvic surgery in spite of the variable skills in microsurgery, endoscopic or laser surgery. This fact

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Number of patients</th>
<th>Method</th>
<th>Number of patients with adhesion/Number of patients undergoing second-look laparoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naether et al.⁵¹</td>
<td>1993</td>
<td>199</td>
<td>LEOS</td>
<td>19.3%</td>
</tr>
<tr>
<td>Gurgen⁵⁹</td>
<td>1991</td>
<td>7</td>
<td>LEOS</td>
<td>85.3%</td>
</tr>
<tr>
<td>Shah DS⁴⁶</td>
<td>2003</td>
<td>207</td>
<td>LEOS</td>
<td>12%</td>
</tr>
<tr>
<td>Yildirim M⁶⁸</td>
<td>2004</td>
<td>44</td>
<td>Minilaparotomy and ovarian wedge resection</td>
<td>11.4%</td>
</tr>
</tbody>
</table>

Abbreviation: LEOS, laparoscopic electrocauterization of ovarian surface.
necessitates the search for an adjuvant(s) that can be used in the perioperative period. The field of these adjuvants becomes large enough to require a classification (Table 3).

**Fibrinolytic Agents**

Fibrinolytic agents act directly by reducing the fibrinous mass and indirectly by stimulating plasminogen activator activity.

**Anticoagulants**

Heparin is the most widely investigated anticoagulant used for prevention of adhesions. Its mechanism of action is probably through one of the following: first, heparin may interact in the clotting cascade by a combination with antithrombin III. Second, heparin directly stimulates the activity of plasminogen activators, thereby promoting breakdown of fibrin clots once they form. Lastly, heparin may act by binding to fibroblast growth factor (FGF) leading to considerable improvement in healing of cutaneous wounds. Heparin has been added to peritoneal irrigants with concentrations of around 5 U/mL. In a study, a significant reduction in adhesion formation was only observed with the combination of Interceed® (TC7) and heparin where Interceed® was utilized as a carrier to deliver heparin to traumatized surfaces.

**Anti-inflammatory Agents**

This group of agents was used to reduce the initial inflammatory response to tissue injury and hence, subsequent adhesion formation. This goal is probably achieved through the capability of these agents to reduce vascular permeability, inhibit synthesis and release of histamines and/or stabilize lysosomes. Anti-inflammatory agents that have been investigated included corticosteroids, nonsteroidal agents, progesterone and progestogens, antihistamines and calcium channel blockers.

Nonsteroidal anti-inflammatory drugs (NSAIDs) act through several postulated mechanisms. NSAIDs have an anti-prostaglandin effect, thereby blocking the adhesiogenic action of prostaglandins instilled intraperitoneally. They have also been shown to inhibit platelets’ aggregation, leukocyte migration and phagocytosis, and lysosome release. Tolmetin, an NSAID was presumed to enhance macrophage function, and hence, allow rapid phagocytosis of tissue debris or fibrin. Tolmetin and ibuprofen have also been shown to increase fibrinolysis through decreasing the secretion of plasminogen inhibitors resulting in enhanced plasmin production. Results support the view that there is a common mechanism through which NSAIDs act to prevent adhesions.

**Antibiotics**

The rationale behind the use of antibiotics is prophylaxis against infection, and hence the inflammatory response, that leads to adhesion development. Systemic broad-spectrum antibiotics, particularly cephalosporins were widely used in the past. Nowadays, tetracyclines are commonly used to protect from Chlamydia, a potentially infectious organism in the female genital tract. Unfortunately, there is no sufficient published data supporting this practise.

**Mechanical Separation**

Mechanical separation of peritoneal surfaces of the pelvic organs during the early days of the healing process postoperatively was a practical way to prevent postoperative adhesions. This separation may be accomplished by intra-abdominal instillates and barriers whether endogenous tissue or exogenous material.

**Crystalloid Solutions**

Crystalloid solutions were the most commonly used instillates put into the abdominal cavity after completion of the surgical procedure. In addition to its mechanical action in separation of the raw peritoneal surfaces, crystalloid solutions dilute fibrin and fibrinous exudate released from the traumatized surfaces.

Unfortunately, crystalloid solutions are absorbed from the peritoneal cavity at an estimated rate of 35 mL/hour. Thus a volume of 500 mL will be absorbed within about 14 hours and 5 L of crystalloid solution are needed to cover the first 6 days postoperatively. The process of peritoneal repair, fibrin deposition and adhesion formation extends quite beyond the time during which a reasonable volume of crystalloid persists. The other drawback is the possible increased risk of infection with instillation of such a large volume of fluid into the peritoneal cavity.

In an attempt to prolong the period of instillate persistence inside the peritoneal cavity, more viscous solutions have been tried in both experimental and clinical studies. A “32% dextran-70 solution” (Hyskon®) was among the most commonly used viscous solutions. Usually 200 mL of it is instilled into the posterior cul-de-sac at completion of the surgery. Hyskon® acts as a siliconizing agent, coating raw surfaces. As an osmotic agent, it results in hydroflotation of the pelvic viscera, and additionally it stimulates plasminogen activators. Complications reported from its use include, anaphylaxis, pleural effusion, vulvar edema, transient liver function abnormalities, wound separation, disseminated intravascular coagulation and abdominal bloating after its instillation.
Section: Endoscopy

Table 3: Classes of adhesion-reduction adjuvants and their proposed mechanism of action

I. Fibrinolytic agents (fibrinolysis, stimulation of plasminogen activators)
   - Fibrinolytic agents
     - Streptokinase
     - Urokinase
     - Hyaluronidase
     - Chymotrypsin
     - Trypsin
     - Pepsin
     - Plasminogen activators

II. Anticoagulants (prevention of clot and fibrin formation)
   - Heparin
   - Citrates
   - Oxalates

III. Anti-inflammatory agents (reduce vascular permeability, reduce histamine release and stabilize lysosomes)
   - Corticosteroids
   - Nonsteroidal anti-inflammatory agents
   - Antihistamines
   - Progesterone
   - Calcium channel blockers
   - Colchicine

IV. Antibiotics (prevent infection)
   - Tetracyclines
   - Cephalosporins

V. Mechanical separation (surface separation, hydroflotation)
   A. Intra-abdominal instillates:
      - Dextran
      - Mineral oil
      - Silicone
      - Vaseline
      - Crystalloid solutions
      - Carboxymethylcellulose
      - Hyaluronic acid
      - Chelated hyaluronic acid
      - Poloxamer
   B. Barriers:
      - Endogenous tissues:
        - Omental grafts
        - Peritoneal grafts
        - Bladder strips
        - Fetal membranes
      - Exogenous materials:
        - Fibrin glue
        - Polytetrafluoroethylene
        - Oxidized cellulose
        - Oxidized regenerated cellulose
        - Gelatin
        - Rubber sheets
        - Metal foils
        - Plastic hoods


*Carboxymethylcellulose*

Carboxymethylcellulose (CMC) is a high molecular weight polysaccharide that acts as an adjuvant for prevention of adhesion by coating the intraperitoneal surfaces and creating hydroflotation of intra-abdominal structures. A novel CMC sponge has been developed for prevention of surgical wound adhesions. Hyaluronic acid is a glycosaminoglycan that under aqueous conditions forms a viscous solution.

*Exogenous Barriers*

Exogenous barriers such as metal foils, plastic hoods, silk and rubber sheets were used in the past to reduce postoperative adhesions. However, these substances have been abandoned because of lack of success and the need for its removal by a second surgical procedure.

*Fibrin Glue*

Fibrin glue is a combination of highly concentrated fibrinogen, thrombin, calcium and factor VIII. It is postulated that fibrin glue acts by separating the raw surfaces through its rapid sealant effect.

*Surgicel®*

Surgicel® is an oxidized regenerated cellulose (ORC) that was initially designed as a hemostatic agent. It was investigated as an adjuvant for prevention of adhesions because it is easy to apply and becomes a gel within hours after application. Initial studies showed that Surgicel® is effective in preventing adhesions in rat cecal trauma model. However, other studies failed to realize any reduction in adhesion formation.

*Interceed® (TC7)*

Interceed® (TC7) is an “altered relative” to Surgicel® also composed of oxidized regenerated cellulose but differs in several characters including its degree of oxidation, weave, and smaller pore size. Interceed® becomes a gel about 8 hours after its intra-abdominal application. The material usually cannot be identified in the field within 3–4 days, and usually is degraded by the body without evidence of a foreign body reaction at the site of application. Interceed® is metabolized into glucose and glucoronic acid within a few days.

To evaluate the efficacy of Interceed® in prevention of postsurgical ovarian adhesions many studies were carried out. One such study was by Franklin and The Ovarian Adhesion Study Group. It was a multicenter randomized study including 55 patients with bilateral ovarian disease. One ovary was randomly wrapped with Interceed® at the completion of laparotomy and the other was left uncovered. At the time of second-look laparoscopy, they found that treatment of ovaries with Interceed® significantly reduced the occurrence and severity of postsurgical ovarian adhesions. As regards laparoscopic ovarian surgery, Interceed® was
found to be safe and effective also in reducing the incidence of postoperative adhesion formation in patients undergoing laparoscopic ovarian cystectomy. These results are consistent with most studies.

A modified version of Interceed® is neutralized Interceed® (nTC), that is blood insensitive, has also proved efficacious in reducing adhesion formation and reformation in animal studies. The results using the nTC Interceed® are comparable to those obtained with Interceed® in combination with heparin.

Following LEOS, translucent adhesions judged of limited consequence to the normal tubo-ovarian relationship were noted.

Animal research on pigs (Naether et al.—unpublished data) suggested that one major effect of LEOS is an increase in ovarian blood supply and adhesion formation which are classified as mild to minimal.

In women failing to conceive postoperatively, a follow-up laparoscopy was performed. A high incidence of mild adhesion formation was documented. However, their extent and severity was not influenced by the number of ovarian punctures; however, the left ovary appeared more prone to develop severe adhesions than the contralateral one.

Laparoscopic ovarian drilling with laser appears to produce more adhesion formation than electrocoagulation. Table 2 shows the rate of adhesion formation in various studies during second look laparoscopy.

Filmy adhesions confined to the ovarian surface do not seem to affect the success rate of the surgery. However, because of consequences of intra-abdominal adhesions such as abdominal pain and small bowel obstruction, adhesion prevention is necessary. Felleman et al. suggest that the best method for decreasing adhesion formation is with the use of an insulated needle electrode, which minimizes injury to the ovarian surface. As the insulated part of the needle is inside the ovarian stroma, thermal injury to the surface of the ovary is limited.

Thus, although a high rate of adhesion formation is undeniable, adhesiolysis may not improve subsequent pregnancy rates (or perhaps that the adhesions are not of sufficient severity to prevent conception).

Interceed®, a widely used therapeutic agent to prevent adhesions formation after conservative operative procedures on the reproductive organs, was not of benefit in preventing adhesion formation after electrocauterization.

One recent study suggests “microlaparoscopy” as a cost-effective alternative with the advantage of significantly less adhesion formation than with the conventional operative laparoscopy (24% versus 48%, p < 0.05). This may be due to reduced exposure and amount of CO₂, which has minimal effect on peritoneal microcirculation and cell protective systems, which are proposed mechanisms for adhesion formation and closely related to peritoneal injury.

Some questions still need more investigations to be answered: Why some patients are more susceptible for adhesion formation and others are not? Can those patients be identified preoperatively? Which stage of adhesion formation is more suitable to interfere with by an agent to reduce it? Further studies are needed, but the results thus far appear quite promising.

## OTHER COMPLICATIONS

### Ovarian Atrophy

In addition to adhesion formation, a case of unilateral ovarian atrophy has been reported following the procedure and even questions regarding the potential for including epithelial ovarian cancers have been raised.

### Abortion Rates

Rate of spontaneous abortions in women with PCOS is elevated as compared to women without PCOS and is approximately 30%. This could be due to elevated levels of LH in many of the women. The rates of abortion did not change in patients with PCOS having normal LH values. The excess LH may allow premature resumption of meiosis resulting in a prematurely aged oocyte. Such postmature oocytes are associated with lower rates of fertilization, cleavage and implantation (as has been observed in in vitro fertilization). Further, adverse effects of elevated LH levels on the oocyte might be mediated via changes in the antral steroidogenic environment, such as premature progesterone production. No differences have been noted in ovulation or pregnancy rates in patients treated with LEOS as compared to medical therapy. However, it is noted that the group treated with LEOS had fewer cycles with multiple dominant follicles, consistently lower luteal phase testosterone levels and lower rates of early pregnancy loss.

Abortion Rates

<table>
<thead>
<tr>
<th>Study/Group</th>
<th>Pregnancy Rates</th>
<th>Early Pregnancy Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMG group</td>
<td>55.4%</td>
<td>14.3%</td>
</tr>
<tr>
<td>LEOS group</td>
<td>21.4%</td>
<td>7.7%</td>
</tr>
</tbody>
</table>

Abortion rates in patients with PCOS undergoing laparoscopic electrocautery. HMG group, Feleman et al. reported an early pregnancy loss in 14.3% of 89 patients who conceived following laparoscopic electrocautery. While Abdel Gadir et al. reported an early pregnancy loss in three out of fourteen (21.4%) patients treated with LEOS and 55.4% in the hMG group. Feleman et al. had a miscarriage rate of 7.7% in his study of LEOS.

On the other hand, Gjonnaess has proposed LEOS as the first line of treatment for all patients of PCOS, undergoing laparoscopy for any reason even if pregnancy is not desired at that time. He has noted that majority of the patients continue to have ovulatory cycles for up to 10 years following electrocautery and a pregnancy rate of 89% in anovulatory cases of PCOS. In Gjonnaess series, those patients who underwent the procedure had no difficulty of conceiving after a period of 2 years of contraception after LEOS.

Cleemann et al. used LOD as a first line of treatment, as a second line of treatment after patients had proved resistant...
to clomiphene or as a third line of treatment after failed ovulation induction with gonadotropins. This strategy with diagnostic laparoscopy and LOD as the first line of treatment of infertility in women with PCOS shortened the time of pregnancy for many women, reduced the need for medical ovulation induction and enabled diagnosis of those women with anatomic infertility, who could achieve pregnancy only by in vitro fertilization treatment.

While the considerable experience of Gjonnaess should not be discounted, more controlled studies have to be performed to judge the efficacy of the procedure. These studies do provide compelling preliminary evidence that LEOS is comparable (or even superior) to available methods of ovulation induction for that small group of PCOS patients who are resistant to CC therapy. Little is known about the long-term effect of LEOS on the age of menopause and risk of ovarian cancer.

**Hyperprolactinemia**

Hyperprolactinemia after ovarian cauteryization may be considered as a possible cause of anovulation in women with polycystic ovaries and improved gonadotropin and androgen levels. The cause of hyperprolactinemia is unknown. Hormonal assay particularly prolactin level test in anovulatory patients after ovarian cauteryization is recommended.75

In view of the above facts, LEOS should be reserved for patients unresponsive to CC therapy, who cannot or do not wish to undergo gonadotropin therapy. Nevertheless, the high pregnancy rate, and economic aspect of the procedure offer an attractive management for patients with PCOS.87

**CONCLUSION**

Notwithstanding the shortcomings of the available data, there seem to be some real benefits of LEOS for carefully selected patients who fail to respond to CC therapy.

The LEOS has to be performed in patients when all other available options have been exhausted, taking into consideration the possibility of adhesion formation as well as the cost and risk associated with any operative procedure. Thus, it would be in the interest of the patient, to perform LEOS after a complete infertility evaluation and a determined attempt with CC therapy. LEOS can have a place in the therapeutic armamentarium of the clinician, only when it has been shown to do no harm to the patients’ fertility potential and long-term health and all noninvasive options have been explored.

**REFERENCES**

The operative laparoscopy has widened its field to the extent that all gynecological procedures that previously required laparotomy can now be performed laparoscopically. Laparoscopic procedures like management of ectopic pregnancy, endometriosis and benign ovarian cyst are well-established procedures, while some procedures like total laparoscopic hysterectomy, myomectomy, Burch’s colposuspension, tubal anastomosis and gynecological oncological procedures are in the process of standardization. These advances were achieved by the refinement of the technical skills and the technological improvements in endoscopic equipment. This article reviews some of the unconventional laparoscopic procedures and newer developments in the technology.

TUBAL ANASTOMOSIS

Tubal factor is responsible in 20% of the women with infertility. The most common predisposing factors are pelvic inflammatory disease, previous pelvic surgery, endometriosis, pelvic tuberculosis and appendicitis. The common presentations are tubo-ovarian adhesions, proximal tubal block and distal tubal block or hydrosalpinx. Adhesions are treated by adhesiolysis laparoscopically. Proximal tubal block is now treated by hysteroscopic cannulation. Hydrosalpinx can be managed by salpingoneostomy. Major degree of tubal damage is now better treated by in vitro fertilization (IVF) than surgery.

Approximately, 1% of the women who undergo this procedure subsequently request reversal of tubal sterilization. The conventional method for reversal of tubal sterilization is microsurgical tubal anastomosis by laparotomy. Recent improvements in laparoscopic microsurgical instruments allow tubal anastomosis to be performed by laparoscopy.

Principles

Microsurgical tubal anastomosis is the gold standard for reversal of sterilization. The traditional technique involves the use of an operating microscope after gaining access to the abdominal cavity via a laparotomy. Fine scissors or monopolar diathermy is used to dissect the serosa over the area of blockage, resecting the affected area and applying 3–4 concentric sutures in the tubal muscularis with the knots placed outside the tubal lumen. The serosa is then approximated over the site of reanastomosis with a further layer of fine sutures, generally 6/0 in size.

Even though this method offers a high success rate with intrauterine pregnancy rates of 60–80%; there are a number of drawbacks. They are requirements of a laparotomy, prolonged hospitalization and the increased possibility of adhesion formation leading to impaired fertility.

Minimal access techniques using laparoscopy have recently been developed which allow successful reanastomosis without the need for laparotomy or microscopes. Laparoscopy avoids tissue drying, foreign body contamination, and tissue abrasion from packs and bleeding from an incision. It also allows for meticulous hemostasis and reduced tissue manipulation. Hospitalization can be reduced considerably and the development of adhesions is uncommon when the open approach is avoided.

A number of different minimal access techniques have been proposed for tubal anastomosis, including sutures, tissue glues, clips, combined hysteroscopic and laparoscopic approaches and combined laparoscopy and minilaparotomy.

Reversal of tubal sterilization by laparoscopy first was attempted by Sedbon et al. with the use of biologic glue as a tissue adhesive material and an intraluminal guide wire.
In 1992, Koh and Janik presented the world’s first laparoscopic tubal anastomosis for reversal of sterilization using microsurgical techniques. Since then, advances in both instrumentation as well as in surgical technique have led to the acceptance of laparoscopic microtubal anastomosis as an acceptable alternative to the open technique with major advantages and comparable results.

**Patient Selection and Prognostic Factors**

Multiple factors affect the outcome of microtubal anastomosis. They include the type of prior sterilization, the site of anastomosis, the length of the reconstructed tube, presence of other pelvic disease, the interval between the sterilization and the tubal surgery, the age of the patient, the presence of other factors affecting fertility, and the type and quality of surgery.

Preoperative evaluation includes an ultrasound of the pelvis, a hysterosalpingogram and semen analysis of the male partner. Although, a preliminary laparoscopic evaluation prior to surgery may be useful in planning the surgical approach, we perform laparoscopic anastomosis as a single step procedure.

**Equipment and Instruments**

A magnification of 20–40x is essential for identifying healthy mucosa and muscularis, before anastomosis can be performed. Quality of the picture depends on both the camera and the monitor. This magnification can be achieved by using a three-chip charged couple device (CCD) camera with zoom facility and a 20-inch high-resolution video monitor.

Microinstruments are essential for effective laparoscopic suturing. Needle holders and graspers with sandblasted tips to reduce glare, atraumatic terminal serrations, jaw apposition without slippage of fine sutures and a sensitive handle design are essential. A range of instruments is available like 3 mm Koh ultra-microsurgical instruments from Karl Storz. 7-0 or 8-0 polypropylene/nylon sutures with easily penetrable needles are ideal for tubal anastomosis.

**Surgical Technique**

Four types of anastomosis are possible: isthmoisthmic, isthmooampullary, ampulloampullary and tubocornual. The lumen size is very small in isthmoisthmic anastomosis, but a thick muscularis allows a technically easier anastomosis and good pregnancy outcome. Luminal disparity is a technical problem in isthmoampullary anastomosis. In ampulloampullary anastomosis, the thin muscularis and prolapse of mucosal folds can be a problem. Tubocornual anastomosis is the most technically difficult tubal surgery.

The surgical procedure involves transection of the tubal stumps and removal of scar tissue, approximation of the mesosalpinx, anastomosis of the muscle and mucosa, and approximation of the serosal layer.

The operative technique is as follows:

- A 10-mm laparoscope is introduced through the umbilicus and three-chip camera is connected. Three secondary ports for 3-mm instruments are created.
- A uterine manipulator capable of injecting dye transcervically is placed.
- Distending the proximal segment by transcervical chromopertubation identifies the site of obstruction. Dilute vasopressin is infiltrated into the mesosalpinx for hemostasis and hydrodissection.
- It is very important to prepare the tube in two layers for a good anastomosis. Inclusion of any scarred portion in anastomosis can lead to poor healing.
- The site of tubal obstruction is identified and held with a fine grasper. A circular incision is made on the serosa of the proximal stump about half a centimeter from the probable site of transection with a fine monopolar needle. Sharp scissors are used to excise the obstructed portion of fallopian tube, leaving a smooth edge to the patent lumen.
- It is important that the dissection is halted at the level of the mesosalpinx to avoid injuring the blood vessels and compromising the vascularity of the tube.
- Chromopertubation is performed through the cervix to check the patency of the proximal stump.
- The distal segment is also prepared in two layers in a similar manner. The patency of the segment is also checked by retrograde chromopertubation.
- The mesosalpinx is approximated with a 6-0 polypropylene suture.
- The tube is then approximated with four equidistant 7-0/8-0 polypropylene sutures at 6 o’clock, 12 o’clock, 9 o’clock, 3 o’clock positions (Figs 1 to 5). The sutures may be taken through the lumen ignoring the mucosa. The 12 o’clock suture is tied last for proper placement of the other sutures. The sutures are tied carefully by the intracorporeal technique.
- After approximation of the inner layer, chromopertubation should demonstrate tubal patency.
- The serosa is then approximated with two or three interrupted 7-0 sutures.
- Postoperative care is the same as for any other laparoscopic surgery. The patient is usually discharged on the evening of surgery or the first postoperative day.

**Results**

The results obtained by laparoscopic microsurgical anastomosis look promising with good intrauterine pregnancy rates of 60–80% and a very low ectopic pregnancy rate of 1–6%. The major published series are shown in Table 1.

We have performed 124 cases of laparoscopic tubal anastomosis since 1996. The technique of anastomosis is similar to the one in open microsurgery. The tubectomy site was prepared in two layers and anastomosis was done with four 7-0 prolene sutures. 3 mm Koh instruments were...
used for the anastomosis. Seventy-five cases were following tubectomy by Pomeroy’s method and 45 cases were of those following sterilization using Fallope’s rings. In 104 cases, an anastomosis was done on only one side. Seventy patients (56%) became pregnant and the majority conceived within 9 months. Nine patients had ectopic pregnancies (7.2%).

**LAPAROSCOPIC HYSTERECTOMY IN FROZEN PELVIS**

Frozen pelvis refers to the surgical condition where reproductive organs and adjacent structures are distorted by extensive adhesive disease and fibrosis, which obscure the normal anatomic landmarks and surgical planes, making dissection extremely difficult and increasing the risk of damage to vital organs. Hysterectomy in frozen pelvis is a challenging surgical condition whether done by laparotomy...
or laparoscopy. The overall keys to success in such cases depend on the knowledge in the pelvic anatomy and operative experience involving varying degrees of pelvic distortion. Surgeon should have the flexibility to change the course of surgery when a particular pathway proves too risky. He should have a realistic expectation that the operation will be difficult and fraught with hazards and patience to take things as slowly as necessary. Laparoscopic hysterectomy is now performed for severe pelvic adhesions or severe endometriosis as the surgical techniques have improved and surgeons have gained more experience. We describe our experience in performing laparoscopic hysterectomy in frozen pelvis due to severe endometriosis or pelvic adhesions. It includes some cases where a previous laparotomy has failed.

### Causes for Frozen Pelvis

The common causes of extensive pelvic disease leading to frozen pelvis:

**Infection**

Adhesions and fibrosis secondary to infectious processes such as salpingitis, tubo-ovarian abscess, infected pelvic hematoma and ruptured appendix can create severe pelvic adhesions. Abdominal Kochs can cause extensive pelvic adhesions.

**Surgery**

The type of surgery a patient has undergone may provide important clues to potential problems. Laparotomy myomectomies and surgery for endometriosis can also cause gross adhesions. Residual ovaries and remnant ovaries after abdominal hysterectomy may require extensive dissection of the ureter and bowel.

**Benign and Malignant Growth**

Severe endometriosis can lead to a frozen pelvis. Malignant growths of the adnexa, such as ovarian carcinoma, can necessitate en bloc resection of portions of the gastrointestinal tract along with the tumor.

### Radiation Therapy

When a woman has undergone radiation, pelvic structures are commonly adherent to the uterus and each other, making hysterectomy a challenge. The intestinal and urinary tracts also must be handled with great care. Even a small degree of intraoperative trauma to these structures can lead to postoperative complications including fistula formation.

### Patient Evaluation

The potential for a frozen pelvis, as well as its causes, can usually be identified by taking a careful history and documenting previous surgeries or pelvic problems. When evaluating a patient, it is important to determine which of above etiological conditions exist. The physical examination also can be revealing. The type of laparotomy scars and drain sites will give a clue to the difficulty of the previous surgery. Be alert for any anatomic changes apparent at the pelvic examination, which should include a rectovaginal assessment. If a lesion is palpated, attempt to define its size and determine whether it is fixed or mobile. Also ascertain whether the cul-de-sac is free, the uterus can be lifted out of the pelvis and the disease process is predominantly uterine, adnexal, or involves adjacent organs.

Preoperative transvaginal sonography will be of immense value. Magnetic resonance imaging may be worthwhile in some cases. It is particularly important to learn preoperatively whether there is hydronephrosis and involvement of the ureters.

Other diagnostic steps, such as cystoscopy and sigmoidoscopy, can be performed at the time of diagnostic laparoscopy or postponed until the actual surgery.

### Preparation for Surgery

Give the patient as much information as possible about potential problems with pelvic structures such as the ureters, bowel and bladder. Also advise her that other surgeons may be called into assist or to help repair damage to surrounding structures.

In anticipation of possible enterolysis or intestinal tract surgery, all patients should undergo preoperative bowel preparation.
Plan for an intraoperative ureteral catheterization if gross pelvic side wall pathologies like severe endometriosis is diagnosed. The use of catheters helps the surgeon to identify the ureters intraoperatively and may therefore prevent their injury.

Postoperative wound infections and deep venous thrombosis, with the potential for life-threatening pulmonary embolization, are both significantly increased in patients who undergo pelvic surgery. The prophylactic use of antibiotics and low-molecular-weight heparin is recommended.16-18

Surgical Technique

Abdominal Entry

The most important step of the surgery is the abdominal entry. We create pneumoperitonum with a Veress needle at the Palmer’s point. The primary trocar entry is with a Ternamian endotip (Figs 6 and 7) at the umbilicus, Palmer’s point or 5 cm above the pelvic mass.

Omental and Bowel Adhesiolysis

After entering the abdomen, identify pelvic structures and their location in relation to one another. Omental adhesions to parietal peritoneum are very common. Omental adhesions to parietal peritoneum are released with scissors, unipolar hook electrode or harmonic scalpel. A combination of blunt and sharp dissection is necessary in dense adhesions to visualize the presence of intestine behind the omental adhesions.

Bowel adhesiolysis is difficult if there is no space between the peritoneum and bowel (Fig. 8). Dissection is done with hook electrode, scissors or harmonic scalpel in this situation. A combination of sharp and blunt dissection can make a space between the bowel and abdominal wall. Cutting close to peritoneum is safer (Fig. 9).
Identify Landmarks

After omental or intestinal adhesions have been separated, move the small and large intestines from the pelvis. Uterine manipulation with a suitable manipulator will allow the surgeon to identify the pelvic structures more clearly. We use a Clermont Ferrand uterine manipulator (Karl Storz) for hysterectomies. Then identify the following pelvic structures: uterine fundus, round ligaments, infundibulopelvic (IP) ligaments, posterior cul-de-sac, anterior cul-de-sac, prevesical peritoneum and pelvic brim. These structures may be difficult to recognize and to mobilize because of fibrosis and adhesions in frozen pelvis.

Entry into the Retroperitoneum

Once the pelvic structures have been identified, determine how you will be entering the retroperitoneum. This decision is important because the blood supply to the uterus and adnexa lies in the retroperitoneum, as do the ureters, which must be identified and kept under direct vision during coagulation and division of the IP ligaments, and dissection of the peritoneum around the uterus.

Retroperitoneal entry and elaboration of the retroperitoneal spaces are keys to the safe performance of a difficult hysterectomy or removal of retained adnexa in a patient with a frozen pelvis. The retroperitoneal approach makes it possible to reach around structures that are fixed in the pelvis, to identify the blood supply and other vital structures, and to proceed safely. Several entry sites are possible. In the frozen pelvis, the round ligament is the ideal location. Identify and divide this ligament as it enters the internal ring, and incise the peritoneum cephalad along the course of the IP ligaments.

Adnexal Mobilization and Division of Infundibulopelvic Ligament

In severe endometriosis, the adnexa are released from the pelvic side wall with blunt and sharp dissection. Dissection starts from a normal area of pelvis and adnexa is released from the pelvic side wall by sharp and blunt dissection. The ureter is identified on both sides before coagulating the IP ligament. This technique is possible in a good number of cases.

Ureter Identification

Never assume the position of the ureter without confirming it; a major deviation of its course can occur secondary to pathologic processes in the pelvis. The ureter can be identified by direct visualization, peristalsis and palpation with a probe. Near the level of the pelvic brim on the left side of the body, the ureter will be closer to the IP ligament than it is on the right side, due to the location of the sigmoid colon and its mesentery on the left side, which elevate the ureter in the ventral direction.

RARELY AN ILLUMINATED URETERIC CATHETER IS PLACED IF URETERS CANNOT BE CLEARLY IDENTIFIED. URETERIC CATHETERIZATION CAN BE DONE WITH AN OPERATING Hysteroscope WITH LITTLE TRAINING (Fig. 10). THE ILLUMINATED URETERIC CATHETER CAN BE VISUALIZED LAPAROSCOPICALLY BY REDUCING THE LAPAROSCOPIC LIGHT (Fig. 11). IT ALSO MAKE THE URETERS RIGID FOR PALPATION AND DISSECTION (Fig. 12).

Bladder Separation

A history of surgery in the area of the bladder, such as cesarean section or bladder advancement with uterine suspension, may leave the bladder adherent to or hard to separate from the cervix and vagina. Normally, the vesicouterine peritoneum is flexible, mobile, and easy to free from the cervix and vagina. A history of disease processes such as endometriosis, infection, or tumors makes this dissection difficult, with a real risk of inadvertent cystotomy.
One technique to make this dissection easier and safer is to enter the retroperitoneum laterally near the round ligament. In this location, the bladder may not have been involved in the prior dissection, and the tissue may be more areolar and less dense than it is in the midline. Bladder is then separated from the cervix by a hook electrode or harmonic scalpel, remaining close to cervix. Fornix bulger of uterine manipulator can help in deciding the limit of bladder dissection. Very rarely filling the bladder with 200 cc of saline can help in identifying the bladder limit (Figs 13 and 14).

**Coagulation and Division of Uterine Vessels**

Once the bladder separation is done, uterine vessels are identified at the isthmus and skeletonized. The vessels are coagulated with bipolar forceps and divided. Since the ureters are already identified, this step of laparoscopic hysterectomy is similar to any other hysterectomy.

**Cul-de-sac Obliteration**

In pelvis, the posterior cul-de-sac is bounded laterally by the uterosacral ligaments, posteriorly by the rectum and sacrum, and caudally by the vagina—but these relationships are usually lost in the frozen pelvis. Extensive inflammatory disease, tumors of the tubes and ovaries, extensive pelvic endometriosis, and prior infection due to a ruptured appendix can obscure the normal confines of the cul-de-sac. Freeing the peritoneal attachments both anteriorly and posteriorly, as well as at the sides of the pelvis, allow elevation of the uterus with the manipulator. Then the ureter, uterine vasculature and supporting ligaments can be identified. Dissection becomes simpler after this point.

However, when the rectum is densely adherent, as they often are in the frozen pelvis, dissection can become difficult with a real danger of rectal perforation. A basic principle in any hysterectomy is to remain close to the uterus, staying near the posterior surface of the uterus and cervix using both blunt and sharp dissection. This eventually makes it possible to find a reasonable plane to enter the rectovaginal space at the superior portion of the cul-de-sac between the uterosacral ligaments. The tissue below this level is not usually involved in the frozen pelvis and will give way readily once the uterosacral ligaments are divided. It is unnecessary to operate beyond this level to any great extent because the surgery already extends distal to the cervicovaginal junction.
In some circumstances, it may be necessary to open the vagina anteriorly to define the relationship between the posterior cervix and adherent bowel (Fig. 15). The hysterectomy is completed in a retrograde fashion. The adherent rectum is then separated from the uterus by sharp dissection in small steps (Fig. 16).

**Vaginal Closure and Hemostasis**

Vagina is now closed laparoscopically after removing the specimen vaginally. The vaginal angle sutures incorporates the uterosacral and cardinal ligaments for vault support (Fig. 17). Peritoneal cavity is lavaged with saline and complete hemostasis is ensured. A drain is kept in the pelvis overnight.

**Identifying Bowel Injury**

If rectal injury is suspected, insufflate the submersed rectosigmoid with air (Fig. 18). Bubbles signal a breach in the integrity of the bowel wall. If the bowel has been prepped and rectal enterotomy occurs during dissection, closure and drainage are the only necessary steps.
Cystoscopy

Cystoscopy is performed to look for any bladder injury and see the urine reflux from both ureteric orifices.

Results

We describe our experience in performing laparoscopic hysterectomy in frozen pelvis due to severe endometriosis or pelvic adhesions. There were 16 cases and all had history of previous surgery for endometriosis. Four patients had two laparotomies, eight had one laparotomy, one had three laparoscopic surgeries, four had two laparoscopic surgeries, five had one laparoscopic surgery. It includes four cases where a previous laparotomy had failed to complete hysterectomy. All had frozen pelvis and endometriosis or without adenomyosis. Laparoscopic adhesiolysis with total laparoscopic hysterectomy with bilateral/unilateral salpingo-oophorectomy was done for all. In one patient, the biopsy report was well differentiated adenocarcinoma of the tubal stump. Average duration of surgery was 2 hours 30 minutes. Blood loss was less than 500 mL. No blood transfusion was given for any patient. There was no bowel or bladder injury in this series. Postoperative hospital stay was 2–3 days. Three patients had postoperative fever which was treated with antibiotics.

Conclusion

Hysterectomy in frozen pelvis is a difficult surgical procedure whether done by open or laparoscopic route. A good preoperative evaluation and planning helps the surgeon to prepare for a difficult hysterectomy and organize intraoperative urological or gastrointestinal surgical consultation. Surgical technique has to be modified for a particular case and surgeon should be prepared to change the course of surgery. It is possible and safe to perform total laparoscopic hysterectomy in cases of frozen pelvis by experienced surgeons.

LAPAROSCOPIC PRESACRAL NEURECTOMY

Dysmenorrhea is a very common gynecological complaint and medical treatments are very successful. But there is a 20–25% failure rate and surgery has been an option for cases of dysmenorrhea that fail to respond to medical therapy. Presacral neurectomy is usual procedure performed for intractable dysmenorrhea. It is usually performed along with conservative management of endometriosis for pelvic pain. Laparoscopic presacral neurectomy has been developed to provide an outpatient surgical treatment of central pelvic pain.

Principle

Pain impulses from cervix, uterine corpus and proximal fallopian tubes are transmitted through afferent sympathetic neural fibers traversing cephalad from the central pelvis. These small, scattered, neural fibers exit in the true pelvis as inferior hypogastric plexus and coalesce into the intermediate hypogastric plexus at approximately the level of the upper sacral and lower lumbar vertebral regions. The intermediate hypogastric plexus is composed of two or three separate trunks lying on the L5 vertebral body. These neural fibers further coalesce into superior hypogastric plexus which continues up and over the bifurcation of the aorta.

In performing a presacral neurectomy, the superior and upper intermediate hypogastric plexus are the structures resected. A presacral neurectomy is neither presacral in location nor a neurectomy, because it is performed at the level of L4–L5 and there is no single nerve but a nerve plexus.

Technique

Any pelvic abnormalities are treated laparoscopically. Patient is then given deep Trendelenburg position and sigmoid colon is displaced to left side. The aortic bifurcation, the common iliac arteries and veins, the ureters, and the sacral promontory are identified. A transverse incision is made over the peritoneum 2–3 cm above the angle of the sacral promontory. The right margin of the dissection is marked by the right common iliac vessels, the left margin by the edge of sigmoid mesentery and left common iliac vein (Fig. 19). The left ureter is hidden by sigmoid mesentery.

A window is created by blunt dissection through the retroperitoneal areolar tissue at each margin of the peritoneal incision up to the periosteum. The intervening tissue of the superior hypogastric plexus is grasped, elevated and transected with a unipolar hook or harmonic ace (Fig. 20). All the remaining retroperitoneal neural and lymphatic tissues are removed laying the sacral promontory bare, except any presacral vessels. Closing the peritoneum is optional.

Intraoperative complications related to presacral neurectomy are rare. Injury to left common iliac vein is possible. Nezhat in his long-term follow-up of 67 patients had more than 50% pain relief in 83.1% of patients. Constipation and urinary symptoms were reported to have worsened in only...
a minority of patients. However diarrhea and dyspareunia improved in large proportion of patients.

**ROBOTIC SURGERY**

Although laparoscopic surgery provides several advantages to patient, it poses several obstacles to the surgeon. In abdominal surgery, human wrist provides six degrees of freedom for suturing but in laparoscopic surgery, the fulcrum point created by the trocar limits the surgeon to four degrees of freedom, reducing the dexterity. Tremor amplification can also occur from the use of long rigid instruments for prolonged periods of time in fixed position. Other obstacles are two dimensional vision and counterintuitive movements. Robotic technology offers opportunity to bridge this gap between laparotomy and laparoscopy by enabling minimally invasive surgery with three dimensional vision, ergonomically optimal positioning, tremor filtration and laparoscopic instruments with intra-abdominal articulation.

One of the first robots developed was by Leonardo da Vinci in 1495; a mechanically armored knight that was used to amuse royalty. Robots have been used in the industry for decades. These robotic devices are used to perform tasks that required precise repetitive motions. With the rapid development of robot language, speech recognition, and better mechanical dexterity; robotic technology is beginning to enter the medical field as well. Robots such as AESOP (Automatic Endoscopic System for Optimal Positioning), Zeus and the Da Vinci robots are now commercially available. These robots were primarily developed to perform surgery that requires extensive, precise microsurgical technique that would be difficult to perform during conventional laparoscopy.

The Da Vinci surgical system consists of three components. The surgeon's computer console is positioned remotely from the patient. The surgeon’s hand movements are converted to electric signals. These are then converted to computer commands to direct robotic instruments to perform the same movements in the operative field. The console has controls for three dimensional viewing, height of console, ability to choose a 0° or 30° laparoscope, motion scaling and tremor filtration. Video cart has two video camera control boxes and two light sources. Surgical cart supports either three or four robotic arms. Surgical instruments are attached to robotic arms through an adapter, which uses an 8 mm Da Vinci-specific port. The robotic instruments are capable of intra-abdominal articulations with seven degrees of freedom.

The first clinical trial in gynecology was to assess the use of a robot for performing a laparoscopic tubal anastomosis. They performed a prospective pilot study to evaluate the feasibility and safety of a robotic device. Ten patients with previous tubal ligation underwent laparoscopic tubal ligation reversal using a robotic suturing device. Tubal surgery was performed with the ZEUS robotic system. A two-layered closure was used for all tubes. Four stitches of 8-0 polyglactin sutures were used for each layer. The Zeus system has three remote controlled robotic arms, allowing a single surgeon to manipulate the laparoscopic camera and two laparoscopic surgical instruments, simultaneously. The robotic arm that holds the laparoscope is directed by voice commands. The procedure was completed successfully in all 10 patients. No patient required conversion to an open procedure. The mean time (+SD) required for completing the anastomosis of both tubes was 159 ± 33.8 minutes. Chromotubation at the end of the procedure showing patency in all tubes anastomosed. The pregnancy rate of 50% was achieved. Degueindre and colleagues in Belgium performed a laparoscopic tubal reanastomosis using Da Vinci system on eight patients.

Subsequently, robotically assisted and laparoscopic sacrocolpopexy, hysterectomy, myomectomy have been reported.

The main limitation of both robotic systems is the technical skill required for setting up the robotic system around the patient. It requires a very sophisticated support staff to be able to manage any technical problems that occur during a surgical procedure.

Another potential application of robotics in gynecology is telesurgery. A surgeon in another city can move the laparoscope and visualize a particular operative site. This gives surgeons the potential to obtain immediate intraoperative consultations from colleagues who are far away. However limitations in band width of internet lines results in a delay that does not permit the surgeon to control the robotic arms that perform the surgery.

**SUMMARY**

Any procedure thought to be impossible to perform by laparoscopy, or procedures that are based on conventional wisdom should not be done laparoscopically, are being performed or developed now. Technical advances in the endoscopic equipment and development of laparoscopic equipment have allowed for performance of sophisticated procedures with laparoscopic assistance. Appropriate laparoscopic
skills allow surgeons to perform these procedures in a fashion nearly identical to open procedures; however, with necessary modifications. The future promises many exciting technologies like robotic surgery and telemedicine.

REFERENCES

INTRODUCTION

Hysteroscopy is a very simple and well-established procedure which allows direct visualization of the endometrial cavity and tubal ostia. Moreover, it can also be used to treat the intrauterine lesions in the same sitting. Till recently hysteroscopy has been a hospital or outpatient surgery center procedure, usually necessitating general anesthesia or regional block. With newer advances in optics, hysteroscopes with smaller diameter are now available, thus reducing the need for major anesthesia, and making office-based hysteroscopy a reality. Office hysteroscopy is a safe, efficient and routinely practiced procedure worldwide.

Diagnostic Indications
- The hysteroscopy can be routinely combined with a concomitant laparoscopy, while investigating a case of infertility.
- It can also be used as a routine procedure prior to undergoing ART.
- It can be used in patients who have an abnormal hysterosalpingography (HSG) or sonohysterography.
- It can be used in infertile patients associated with Asherman’s syndrome (Koch’s, PID, etc.).
- It can be used in women presenting with secondary infertility because of recurrent abortions.
- Hysteroscopy can diagnose Müllerian anomalies such as septate, subseptate or bicornuate uterus. It can also be used to effectively treat some of these conditions.
- Hysteroscopic adhesiolysis for Asherman’s syndrome.

HYSTEROSCOPY IN AN OFFICE SETTING

In this technique hysteroscopes with outer sheath diameters varying from 1.2 mm to 5 mm are used in an office-based setting without or with minimal local anesthesia to perform diagnostic and limited operative hysteroscopic work.

The patient should be examined in the counseling room and informed about the hysteroscopy. It is necessary to perform this procedure in a room, which has got access to oxygen and emergency resuscitation trolley. This is in anticipation of an occasional vasovagal shock or anaphylaxis secondary to the usage of local anesthetic.

Recovery room: Following this procedure a recovery room with reclining chairs is necessary for the patient to recuperate for half an hour to 1 hour prior to getting discharged. It should be ideally performed in the early or mid-proliferative phase of the cycle. During this phase the bleeding has stopped and the endometrium has not grown enough to obscure the vision of the hysteroscope. One can do it any time provided the patient is not pregnant.

COMPONENTS OF HYSTEROSCOPY

Hysteroscope

There is a range of hysteroscopes starting from the 1.2 mm flexible hysteroscope with a 2.5 mm diagnostic sheath, to the standard 4 mm scope with a 5 mm diagnostic sheath. The 1.2 mm scope is a flexible scope, which can be easily passed...
into the uterine cavity without dilatation. However, it is very fragile, and generates a small image. Neither does it allow any degree of operative work to be performed. On the other hand a standard 4 mm Hopkins scope is rigid and gives a very good image. In case of doing operative procedures it need to be combined with an operative sheath with a diameter of 7.0–8.5 mm, necessitating anesthesia and cervical dilatation procedures. In order to overcome the above shortcomings, there have evolved two systems that can be effectively utilized for diagnostic and operative office hysteroscopy. With these systems it is possible to perform operative procedures such as a polypectomy, adhesiolysis, tubal cannulations and myomectomies (< 2 cm).

**Bettochi Hysteroscope (Karl Storz and Company)**

- The standard Bettochi hysteroscope with Hopkins based rods lens system is a miniature version of the famous Hamou 2 hysteroscope. The scope has an external diameter of 2.9 mm. It can be used as a panoramic hysteroscope (1x) as well as a microcontact hysteroscope (80x). For diagnostic purpose, it can be used with a single flow outer sheath of 3.6 mm or a continuous flow outer sheath of 4.4 mm. In case of operative office hysteroscopy it can be combined with a continuous flow operative sheath of 3.9 mm × 5.9 mm (average diameter 5 mm). This sheath has an operative channel to accommodate 5 French instruments to pass through.
- The modified Bettochi: This is a new version with a 1.9 mm diameter optic along with corresponding decreased diameters of diagnostic and operative sheath.

**Versascope® System (Gynecare Div—Johnson and Johnson)**

The Versascope® is a flexible telescope made up of a set of 50,000 fused optical fibers, providing a 0° field of vision with an outer panoramic angle view of 75°. The scope has an external diameter of 1.8 mm and length of 28 cm. The density and optical quality of the image system produces an image, which is similar to the conventional rod lens panoramic hysteroscope. The scope is used with a continuous flow diagnostic-cum-operative sheath, which has an outer diameter of 3.5 mm and a distal curvature of 10°. A proximal collar is rotatable. This allows manipulation of the scope for full peripheral viewing, without disturbing the instrument position. The operative channel has an expandable instrument channel which can easily accommodate instruments till 7 French in diameter. This operative channel also simultaneously functions as an independent outflow port for continuous flow during the procedures.

Unlike Storz, the Versascope® has got a disposable sheath. However, in practice the sheath can be reused, after resterilization in Cidex®, at least 10–20 times, making the instrument much more cost effective. Both the scopes come with fiberoptic cables.

**Light Source**

There are various light sources, which one can use for illumination:
- **Halogen:** This 150–250 W cold light sources is sufficient for vision. However, it tends to give of a reddish tinge to the image.
- **Xenon:** A 175 W xenon light source provides an outstanding illumination and enables a good depth of field. Although, the light is extremely hot at its source, most of the heat gets dissipated along the length of the fiberoptic cable. Despite of this, a significant amount of heat can be generated at the distal tip. This can cause thermal injury to the patient or burn paper drapes or clothing with prolonged contact. Hence, one should keep the intensity of the light as less as possible.

**Endoscopic Camera and Monitor**

In office hysteroscopy, the image size is quite small. Hence, it is preferable to use cameras with zoom system to select the appropriate size of the picture. A single chip endoscopic camera is sufficient for diagnostic and minor operative work. A three-chip camera will not be of additional help, unless it has additional filters to eliminate the pixelization and digitalization of the image.

**Distention Systems**

**Carbon Dioxide**

Carbon dioxide gas has been routinely used to distend the cavity, in an office setting. The gas insufflators use low gas flow rates, and are easy to maintain. It gives excellent visualization. The gas is rapidly absorbed and cleared by the lungs. With proper criteria for pressure and flow rates, there is a very low incidence of CO₂ intoxication or embolism. However, the gas has major disadvantages. The CO₂ often leaks around the hysteroscope, making diagnosis difficult. A mild contamination of the lens by blood or mucus can form troublesome bubbles, during the use of CO₂. This can greatly obscure the picture cavity. Besides this, CO₂ use necessitates the use of a dedicated gas hysteroflator. One cannot use laparoscopic insufflators, which have high flow rate. Inadvertent use of these laparoscopic insufflators can lead to CO₂ embolism and even death.

In case one wants to use CO₂ for distention, the pressure should be kept in the 100–120 mm Hg range with a flow rate of 30–60 mL/min, corresponding to a final working intrauterine pressure of 40–80 mm Hg.

**Ionic media:** In case one comes across intrauterine pathology and wants to perform intrauterine procedures, one can
not do it. Hence, with office hysteroscopy, it is best to use fluid distention systems rather than CO₂ gas distention for visualization of the uterine cavity.

**Fluid Distention Media**

These can be used for both diagnostic and operative purposes. These consist of the high viscosity—high molecular weight liquid media (e.g. lyskon) or the low viscosity—low molecular weight media such as saline or glycine.

*High viscosity media*: High molecular weight dextran has been used in the past. However, it is viscous and messy in consistency and if not cleaned from the instrument, can immobilize moving parts of the hysteroscope. If the amount exceeds 500 mL, there is a risk of pulmonary edema, disseminated intravascular coagulation (DIC) or anaphylaxis. This medium is rarely used in present day practice.

*Low viscosity media*: They can be of two types: (1) nonionic media and (2) ionic media.

*Nonionic media*: These are mediums such as glycine, mannitol, or sorbitol. Glycine is easily available and frequently used. One can use monopolar as well as bipolar current with these solutions. However, the biggest problem with these solutions is water intoxication and fluid overload, especially if the net fluid intravasation into the patient exceeds 800–1,000 mL. Therefore, it is critical to measure accurately the input-output of the distention media. As soon as the intravasation exceeds 1,000 mL, the procedure should be stopped. In an office setting, this is a rare possibility, as the operative hysteroscopy.

*Ionic media*: These mainly consist of saline or ringer. These are very safe media and can be easily used with operative procedures such as mechanical surgeries with scissors or forceps, versapoint bipolar coagulation or the standard bipolar coagulation. These media, coupled with continuous flow sheaths with inflow and outflow channels are preferred for both diagnostic as well as therapeutic (barring monopolar cautery probes and monopolar resection) visualization of the uterine cavity.

**Distention Machines**

There are various distention systems that can be used. These are:

- Gravity
- Pressure cuff
- Hysteromat
- Endomat
- Total input-output system.

Of these the endomat is the ideal system especially for office hysteroscopy purposes, as it correctly maintains intrauterine pressure to around 70 mm Hg, thus preventing peritoneal reflux and resultant discomfort. However, a simple pressure cuff can do the trick.

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**Energy Sources**

**Mechanical Energy**

These are in the form of 2 mm semi-rigid sharp as well as blunt scissors, biopsy forceps and the myoma screw. These instruments can be passed through the operating channel to obtain biopsy specimens, transecting base of small polyps, excising uterine septa and synechiae.

**Unipolar**

This has been the traditional energy used for operative hysteroscopy. However, one cannot use this energy in the office hysteroscopy as the fully conscious patient will not tolerate it and will complain of pain.

**Bipolar Versapoint**

This bipolar cautery, marketed by Gynecare division has many advantages:

- It can be used with saline thus eliminating the side effects of using glycine.
- The electrodes can easily pass through the operative channel of office hysteroscopy.
- Instant vaporization and desiccation can eliminate resection chips.
- Decrease in the amount of blood loss.
- The pain is minimal if you restrict the surgery to the endometrial level.

**Contraindications**

There are no real contraindications except pregnancy, acute PID and may be Ca cervix.

**Premedications**

Most of the time the procedure can be performed without giving any medication. Occasionally, one can give non-steroidal anti-inflammatory drugs either orally or rectally 1 hour before the procedure. Occasionally, a mild sedative may be administered intramuscularly.

**Patient Position**

Normally the patient is in dorsal lithotomy position. An adjustable electronic table is ideal for giving comfortable position. As has been mentioned very few need some degree of anesthesia. If at all, one can give a paracervical or intracervical block.

**Cervical Preparation**

One can do vaginal preparation with povidone iodine. Some units are not preparing the vagina with any antiseptic.
However, this is a risky move and can lead to a rare PID. One can expose the cervix with a bivalve speculum, which can be removed after hysteroscope enters the uterine cavity. This gives flexibility of moving the hysteroscope much more easily. Instead of using the speculum, one can insert the hysteroscope into the vagina, without using the speculum. Once the vagina distends with media, one can locate the cervix and gently pass the hysteroscope into the uterine cavity.

The hysteroscope is gently inserted through the external os, and the endocervical canal is inspected, distention of cavity is obtained using gas or media the distention allows visualization of the cavity, which appears as a dark spot. The hysteroscope is directed toward the dark spot (spot at 6 O’clock) until the cavity is entered. Systemic inspection of the cavity is performed keeping the pressure between 60 mm and 100 mm. Examination of fundus, anterior, posterior and lateral walls, both ostia and endocervical canal is done.

**Precautions:** There should be no air bubbles when using liquid as distention media pressures should be below 100 mm to prevent pain remove bubbles when using versapoint.

**Complications:** There are hardly any complications with diagnostic hysteroscopy. These are:

- **Inadequate visualization:** Mainly due to lack of flow of the distention media, as well as non-use of continuous flow sheath.
- **Perforation:** This is hardly the case with office hysteroscopy as one enters the uterine cavity under vision.
- **Infection is rare:** An adequate prophylactic antibiotic cover will prevent infection.
- **Bleeding:** This is rare with office hysteroscopy.

### HYSTEROSCOPY IN AN OPERATION THEATER SETTING

These procedures are carried in the operation theater. The size of the hysteroscope optics is 4 mm with a 30° oblique view. The diagnostic scope along with its sheath has a diameter of 5 mm, while the operative hysteroscope with a 2 mm operating channel is about 7 mm in diameter. The versapoint bipolar resectoscopes or the standard monopolar resectoscopes are 9–10 mm in diameter. Due to its larger sizes, besides giving general anesthesia one needs to dilate the cervix. Barring this and the configuration of the resectoscope, the remaining instrumentation is similar to that which has been described in the section of office hysteroscopy instrumentation. Hence, a detailed subscription of the resectoscopes would be carried out.

### Operative Resectoscopy

The size of the whole assembly is 26 French. It consists of:

- The external outflow sheath for efflux of the distention medium
- The internal inflow sheath for influx of the distention medium
- The standard 4 mm diameter Hopkins hysteroscope
- The working element with either monopolar or bipolar electrodes.
  - The monopolar electrodes are either in the shape of loops, ball, cylinders or knife. Normally, a good high frequency generator with a blended cutting—coagulating current of 80–120 W or a pure cutting current of 100–120 W is used.
  - The bipolar versapoint electrodes are in the form of loop or cylinder. The current is automatically controlled by the bipolar generator.
  - The distention media is in the form of 1.5% glycine for the monopolar resectoscopes. In case of bipolar resectoscopes, one can use normal saline. Please note that the normal saline should never be used with monopolar resectoscopes. The uterine distention should be maintained between 90 mm and 150 mm of mercury. It is important to use a safe distention system such as the endomat which controls the flow, pressure and calculates the fluid intravasation into the patient’s circulation, while performing septum resection or myoma resection. Although many operators use gravity or pressure cuff systems, these can be dangerous and can cause mortality. Many European nations have made it compulsory for doctors to use an endomat during resectoscopy. In any case, a strict maintenance of input minus output of distention fluid is desired. One should be cautious when the deficit crosses 750 mL and stop the procedure at 1,000 to 1,100 mL. These safeguards can prevent pulmonary edema, cerebral edema and the dreaded transurethral resection of the prostate (TURP) syndrome, which can occasionally lead to a mortality.

In the bipolar resectoscopes, saline is used as a distention medium. If proper precautions are not taken, this can also lead to pulmonary edema; however, unlike glycine complications, this can be rapidly reversed with intravenous furosemide.

### COMPLICATIONS

#### Complications due to Anesthesia

It is preferable to use either no anesthesia or regional block, spinal and epidural. In case one is using monopolar resectoscopes with glycine, fluid overload the most likely complication of operative hysteroscopy. Patient will first complain of double/blurred vision, start yawing, be dis-oriented, and will have sudden rise of BP before the onset of pulmonary edema.

#### Complications due to Patient Positioning

Pressure on peroneal nerve from lithotomy position may result in paresthesia and foot drop. Though this sounds trivial, it is quite disturbing to the patients. It recovers fully within
Uterine rupture during pregnancy: This problem is encountered in 1 out of 1060 pregnancies. This can be prevented by gentle cervical dilatation and introduction of the hysteroscope under direct vision. One should not proceed if vision is obscured or there is sudden loss of distention of the uterine cavity. One should use energy setting appropriate for procedure, making all strokes of resectoscope from fundus to cervix. Special care should be taken in the cornual region, where the uterine wall is thin. If perforation has occurred due to a large dilator or resectoscope then one needs to do laparoscopy or laparotomy to assess and treat the resultant damage.

During endometrial resection, perforation is most likely to occur in the region of the uterine cornua, an area which is very thin. One can use a rollerball instead of the loop in this area.

Bleeding: This is commonly seen during the resection of large submucous myomas, when one opens up large sinuses while performing the resection. Besides rapid blood loss, this can also result in massive intravasation of distention media into the circulation. It is important to promptly coagulate these bleeders with the rollerball cautery. Sometimes it is necessary to abandon the procedure and either pack the uterine cavity with a roller pack or create tamponade by passing a Foley's catheter into the cavity and distending the bulb. This can be removed after 6 hours.

Long-term Complications

- Incompetent os due to cervical damage at the time of dilatation
- Cervical stenosis leading to hematometra
- Postoperative intrauterine adhesions (IUA)
- Uterine rupture during pregnancy: Uterine rupture during pregnancy has been reported after operative hysteroscopic procedure like myoma resection, septum incision and adhesiolysis.

DISCUSSION

In the early days, hysteroscopy was performed for purely diagnostic reasons, especially if there were symptoms or findings on clinical or radiological examination (abnormal ultrasound, HSG or CAT scan/MRI) suggestive of an intrauterine pathology. However, there have been recent studies that have shown an abnormal hysteroscopic finding in patients with previous normal USG/HSG findings. This has prompted many clinicians to routinely perform hysteroscopy in association with a diagnostic laparoscopy. Although, this may not be universally acceptable, there is a definite consensus of routinely performing a hysteroscopy prior to an ART procedure. It is also indicated in patients with recurrent implantation failures following ART.

Operative hysteroscopic procedures related to infertility may be done in the following circumstances:

- Asherman’s syndrome
- Severely stenosed cervix
- Intrauterine adenomatous polyps
- Submucous myomas
- Fallopian tube recanalization
• **Genital malformation:** Septate or subseptate uterus
• Foreign body in the uterine cavity
• Hysteroscopic embryo transfer (ET).

**Asherman's Syndrome**

Asherman’s syndrome, first described around 1920, is characterized by the development of IUAs following infection or uterine curettage for postpartum hemorrhage or incomplete or missed abortion, with subsequent damage to the basalis endometrium. In India, these adhesions are commonly seen in patients with genital tuberculosis. These adhesions can cause infertility, recurrent pregnancy loss, hypomenorrhea, amenorrhea, ectopic pregnancy, preterm labor, abnormal placentation and fetal demise, if pregnancy is achieved.

It is demonstrated on HSG as single or multiple lacuna-shaped filling defects of variable size in uterine cavity. These filling defects are characterized by their irregularity, angulated form, very sharp contours, homogeneous opacity, and persistent appearance on several exposures taken at various intervals. Hysteroscopy is used to confirm the HSG findings and permits surgical correction as well. These adhesions are classified based on the hysteroscopic findings according to the IUA classification of the European Society for Gynecological Endoscopy (ESGE) as shown below.

**Grade Extent of Intrauterine Adhesions**

- **Thin or filmy adhesions**
  - Easily ruptured by hysteroscope sheath alone
  - Cornual areas normal
- **Singular dense adhesion**
  - Connecting separate areas of the uterine cavity
  - Visualization of both ostia normal
  - Cannot be ruptured by hysteroscope sheath
- **Occcluding adhesions only in the region of the internal os**
  - Upper uterine cavity normal
- **Multiple dense adhesions**
  - Connecting separate areas of the uterine cavity
  - Unilateral obliteration of ostial areas of the tubes
- **Extensive dense adhesion with (partial) occlusion of the uterine cavity**
  - Both tubal ostial areas (partially) occluded
- **Extensive endometrial scarring and fibrosis**
  - In combination with grade I or grade II adhesions
  - With amenorrhea or pronounced hypomenorrhea
- **Extensive endometrial scarring and fibrosis**
  - In combination with grade III or grade IV adhesions
  - With amenorrhea.

Treatment of IUAs by "blind intrauterine procedures such as D and C can deteriorate the possibilities for hysteroscopic treatment by creating a false passage or perforation and reducing the amount of residual endometrium, required for adequate regeneration after adhesiolysis. Thin or filmy adhesions can be lysed under direct vision by pushing in the hysteroscope sheath. More substantial adhesions will require division by sharp instrumentation. The hysteroscopic semirigid scissors are the instrument of choice as they do not employ a current, thereby reducing the risk of damage to the surrounding endometrium. Areas of healthy endometrium are often scant in Asherman’s syndrome, and it is essential to maintain their integrity so that re-growth of the endometrium is possible postoperatively. Adhesions are divided at their midpoint allowing the cut edges to retract.

Thick vascular and dense adhesions are incised using resectoscopes utilizing the thin electrosurgery (Collins) knife. Monopolar current using 90–100 W cutting or 30 W coagulating current is used. Alternatively bipolar versapoint cautery can also be used.

In situations where the adhesions completely obliterate the uterine cavity, selective dissection should begin at the internal os creating a neocavity, and then proceeding toward the fundus and tubal ostia. The uterine contour must be followed closely during the dissection. Concomitant laparoscopy should be used in order to avoid uterine perforation.

Postoperative balloon catheter or plastic IUDs can be used in cases of severe adhesions to avoid apposition of the uterine walls. Estrogen is usually prescribed postoperatively for 1–3 months to hyperstimulate the endometrial lining. An HSG is obtained at the completion of hormonal therapy to assess the uterine cavity and decide upon the course of care. The results of hysteroscopic treatment of IUAs depend upon the type and the extent of adhesions. The more extensive and severe the adhesions, the more difficult they are to treat and therefore, the more difficult it is to achieve a viable pregnancy. The worst prognosis is in those who have suffered from genital tuberculosis. Of those women who become pregnant, about 40–80% will have a normal pregnancy.

**Fallopian Tube Cannulation and Recanalization**

Tubal pathology is one of the common causes of infertility. Proximal tubal occlusion constitutes 25–30% cases of tubal pathology.

Proximal tubal occlusion can be classified as:

- Nodular-salpingitis isthmica nodosa or endometriosis
- Non-nodular:
  - True fibrotic
  - Pseudoocclusion: Polyps (15–19%), hypoplastica tubes, syndeche, mucosal alteration (10–15%).

In about 50% of the infertile patients with proximal tubal block there are tubal plugs due to amorphous material responsible for occlusion. Remaining 50% of the patients have true pathological block. Until the recent past laparotomy with microsurgical reconstruction was the only choice to overcome proximal tubal occlusion.
Though microsurgical reconstruction and tubocornual anastomosis is associated with good pregnancy rates (57%), it is a prolonged surgery, associated with significant postoperative morbidity and prolonged hospital stay. After the introduction of operative hysteroscopy, hysteroscopic cannulation for proximal tubal occlusion has attracted a great deal of interest.

Unfortunately, the conventional methods used to study tubal patency such as HSG or chromopertubation by laparoscopy and selective chromoperturbation, frequently do not allow differentiating between an insufficient filling of the tubules, tubal spasm or a true mechanical obstruction. The selective tubal cannulation technique, with hysteroscopic guidance is highly useful in the diagnosis of tubal patency or in the confirmation of partial or total proximal tubal disease. The procedure permits to precisely reach the diagnosis the tubal obstruction due to the presence of a true pathology or simply functional, or secondary to a tubal spasm; besides it also works as a therapeutic procedure since in the first case, it permits the lysis of lax adhesions and the removal of the amorphous material that obstructs the tube and permits the catheterization. Distal tubal disease with rigid tubes as a result of infection especially tuberculosis and presence of hydrosalpinx on ultrasound are the relative contraindications of this procedure.

As proximal tubal cannulation requires simultaneous laparoscopy to confirm the status of the distal fallopian tubes as well as negotiation of the block, general anesthesia is preferred. Diagnostic survey of the uterine cavity is carried out to note the anatomy and to rule out intrauterine pathologies like adhesions especially near the ostium, polyp, submucus fibroid, etc. Mesh like adhesions can be seen in some patients, which cannot be detected on HSG. Laparoscopic inspection of pelvis is then carried out especially to note the distal tubes to ascertain the cause and type of obstruction. Laparoscopy also allows evaluation of rest of the pelvis. If the distal tubes appear normal, only hysteroscopic cannulation should be performed. Diseased distal tubes are associated with poor outcome of the hysteroscopic cannulation. After dilating the cervix to number 8 mm Hegars, the operating channel with the 4 mm hysteroscope is introduced into the uterine cavity with continuous flow of saline to distend the uterine cavity. Simple cannula with the guidewire inside is then introduced through the operating channel. One-sided tubal ostium is then identified and the tip of the hysteroscope is brought in near proximity to the ostium. The tip of the cannula is then advanced near the ostium under constant hysteroscopic visualization. Guidewire is then advanced into the ostium for about 1-1.5 cm to negotiate the cornual block. Guidewire should not be pushed further as it may result in perforation due to sinusoidal shape of the intramural portion of the fallopian tube. The Terumo guidewire is relatively stiff and should not be used to cannulate the distal fallopian tube. After introduction of the guidewire into the intramural portion, the cannula is railoaded over the guidewire to fix the tip of the cannula into the proximal part of the intramural portion. Guidewire is then removed and dye is injected through the proximal portion of the cannula. Simultaneous visualization by laparoscopy can identify the exit of the dye through the fimbrial end of the tube. Cannula is then removed and the same procedure is repeated on the other side.

**Advantages**

- Works as a therapeutic procedure, which permits the lysis of lax adhesions, and removal of amorphous material and permits catheterization.
- Differentiation between the spasm of the tube, true pathological block and the functional block.
- Low rate of complications
- Low cost
- Valuable information about the proximal and distal tubes.

When compared to microsurgical anastomosis in patients with normal distal tubes, intrauterine pregnancy rates are similar and ectopic pregnancy rates are lower in the cannulation group. 1 year patency rates in nonpregnant patients are higher in the anastomosis group (80% vs. 33%). Recurrence of the tubal obstruction is seen in 50% of the patients in 6 months of time after the cannulation.

**Uterine Septum Resection**

Uterine septum cause reproductive failure in about 25% of patients with this condition. Septate uterus is apparently linked to a high rate of fetal loss generally occurring in the first half of pregnancy. It has been proposed that miscarriages may be due to vascularization problems at the implantation site, especially if located in the septum itself.

Uterine septum resection in a patient presenting with infertility is as yet controversial. Most of us, including the author, would resect such septae.

To differentiate between bicornuate and septate uterus, HSG and hysteroscopy apart from a clinical examination are useful imaging techniques. 3D/4D ultrasound and especially MRI is also now advocated for diagnosing and correctly classifying Müllerian abnormalities and malformations. Laparoscopy, however, continues to be the method of choice as it affords a definite differential diagnosis and distinguishes between bicornuate and septate uterus.

Several different procedures have been adopted and yield more or less the same results. The basic concept involves hysteroscopic transcervical observation of the uterine septum followed by resection.

Scissors are the most commonly used method for septum resection. Division is performed systematically from side to side until the uterotubal openings can be seen and bleeding is observed at the myometrical junction. Once septal division is complete, the intrauterine pressure of the distending fluid can be decreased; if arterial bleeding occurs, selective coagulation can be performed with a 7-F ball-tipped electrode. If bleeding
has occurred, the resectoscope can be used to coagulate selectively each bleeding arteriole.

The final goal is to produce a satisfactory uterine cavity. The most delicate part of the procedure is probably the decision when to stop the resection in order to prevent damage to the myometrium and immediate complications, such as perforation, or more delayed difficulties, e.g. the postoperative formation of synechiae. Simultaneous laparoscopic control is also extremely suitable for this purpose. Recently, it has been proposed to use ultrasound for precise preoperative measurement of the septum, which can easily be distinguished from the myometrium, and subsequent continual monitoring of the operation, so that an extremely precise decision can be made about when to stop resecting so that the myometrium is not affected. Preoperative treatment with danazol or LHRH antagonists decreases the bleeding at the time of resection. The author uses scissors to cut the septum and bipolar versapoint cautery to cauterize the bleeders.

Follow-up examination should be performed 1–2 months after the operation depending on the type of postoperative management used. A second-look hysteroscopy can be performed at this time. The full-term pregnancy rate obtained by various authors ranges from 70% to 80%, which is very similar to the results of traditional laparotomic metroplasty by various authors ranges from 70% to 80%, which is very similar to the results of traditional laparotomic metroplasty.

**Advantages of Hysteroscopy**

- The operation may be performed as an office procedure without hospitalization of the patient
- No scar tissue remains on the abdominal and uterine walls
- There is a lower rate of intra- and postoperative morbidity compared to traditional surgery
- There is no reduction in the volume of the uterine cavity.

**Submucous Myoma**

Protrusion of a myoma inside the uterine cavity with anatomical distortion of the cavity, with the symptoms like menorrhagia or associated infertility, is the most common indication for a hysteroscopic myomectomy.

Intrauterine myoma can be classified as per the ESGE:

- **Grade 0**: Pedunculated myome or myoma limited within the cavity or small base.
- **Grade 1**: Myoma with partial intramural development, with more than 50% of intracavitary component. Angle of protrusion between the myoma and the uterine wall is less than 90°.
- **Grade 2**: Predominantly intramural myoma with cavitary component less than 50%. Angle of protrusion between the myoma and the uterine wall is greater than 90°.

**Preoperative Diagnostic Assessment**

An accurate transvaginal ultrasound examination is most of the times sufficient to diagnose an intracavitary fibroid. However, the gold standard is of course a diagnostic hysteroscopy performed under gas distension viz. CO₂ rather than a liquid distension. Use of CO₂ as distension media also helps to distinguish between polyps and myomas. An ultrasound may give a clue to the intramural extent of the myoma. It is also important to assess the amount of myometrial tissue between the outer border of the myoma and the serosal surface of the uterus. A tissue of at least 1 cm thickness indicates a much easier and safer removal during surgery. However, newer studies have shown that a thickness as less as 0.6 cm is also good enough. Researchers have demonstrated increase in the thickness as the resection progresses.

The technique used is either the standard monopolar resectoscope-glycine method or the new bipolar versapoint vaporization-resectoscope-saline method.

In the latter method, saline can be used instead of glycine to decrease the complications of bowel burns and fluid overload.

**Resection of Submucous Fibroids**

The loop is placed behind the myoma to be resected and then withdrawn with application of the current. Sometimes a backward and forward movement can be used in conjunction and tandem to facilitate the fast removal of the myoma under vision. The extent of completion is identified by the presence of the adjacent endometrial surface.

Various methods are being suggested for the removal of intramural extension of the myoma, as this may present more technical difficulties during removal. However, depending upon the size, the commonly used method remains the same as the use of cutting angled loop. The slicing technique helps, but one may have to gauge the extent of resection intermittently so as to avoid over-resection. If one can see the myometrium, the procedure can be considered complete in that area. Coagulation of the base of myoma is usually recommended by a roller ball or cylinder to prevent hemorrhage, especially in case of larger myomas with large intramural component. Myometrial contraction, however, is sufficient to arrest the hemorrhage in most cases.

The administration of GnRH analogs preoperatively helps reducing the size and vascularity of the fibroid. In case of a large intramyometrial component, one can stop the procedure, give a postoperative GnRH agonist and perform a repeat resection few weeks or few months after the primary procedure.

A second-look hysteroscopy may be performed after 2–3 months of a primary procedure to evaluate the cavity in cases for infertility or before in vitro fertilization (IVF).

**Adenomatous Polyps**

These may vary from very small 1–2 mm polyps to large 2–3 cm polyps. The small polyps may be located in the region
of the ostia. They may be blocking the ostial opening, thus causing a pseudocornual block, during chromoperturbation of methylene blue at laparoscopy or during HSG. The small polyps may also cause foreign body reaction in the endometrium, which is bad enough to result in infertility, especially in those patients going for ART.

As these polyps are soft, they can be easily removed by using a combination of scissors and grasping forceps. Alternately, they can be desiccated—vaporized using versapoint bipolar cautery. Very rarely, one has to use the resectoscopes for removal of large polyps.

**Stenosed Cervical Canal**

This condition often presents itself in nulliparous patients with smaller than normal size uterus, in patients with PCOS, in postmenopausal women wanting children who have restarted their menstruation following hormonal replacement therapy and in women who have had a history of difficult previous ET or intrauterine insemination. In these patients it is wise to make use of smaller sized mini hysteroscopes. Sometimes one needs to do a vaginoscopy, visualize the cervix, increase the cervical diameter by using sharp scissors and then negotiate the hystroscope under vision into the uterine cavity. One can also make use of prostaglandin (PGE₂, misoprostol) tablets and insert them in the vagina, 1 day prior to the surgery. The prostaglandin tends to soften the cervix, thus making it easier to perform a hysteroscopy.

**IVF and Embryo Transfer**

Hysteroscopy, as a routine examination, should be performed before the first IVF-ET cycle in all patients. A statistically significant difference in pregnancy rate was found between women who performed hysteroscopy before IVF-ET cycle and in women who did not perform it. Hysteroscopic revision of the cervical canal results in easier ET and improves pregnancy rates in patients with cervical stenosis and histories of difficult ET. Many groups have performed ET under hysteroscopic control, with excellent results.

**CONCLUSION**

Assessing the endometrial cavity is an integral part of the infertility evaluation. It appears that hysteroscopy is the most sensitive method amongst the tools to evaluate the cavity, recognizing the benefits of hysteroscopy from both a diagnostic and therapeutic viewpoint, the clinician must decide in which setting to perform the procedure.

Thus to conclude, “the hystroscope which was literally looking for an indication a decade ago has become an indispensable tool today.” —Alan Decherney, 85.

**BIBLIOGRAPHY**

INTRODUCTION

Though the mode of removal of the uterus has been a matter of debate since many decades, yet there is little controversy that hysterectomy is still the most commonly performed major gynecological surgery in elderly women. 

It is known that vaginal hysterectomy carries the minimal morbidity, however depending on the skill of an individual surgeon, the choice of this route varies from 90% to as low as 30% with different surgeons.

In 1988, when Harry Reich performed the first laparoscopic hysterectomy, it opened up new horizons, however it also invited controversies.

There is a significant overenthusiasm to perform a total laparoscopic hysterectomy both by gynecologists and general surgeons. This approach has come like a storm full of potential due to its apparent advantages; however, it is only after the dust settles that few gynecologists or surgeons actually would stand up to claim the genuine merits of this procedure.

INDICATIONS

Common indications for hysterectomy are menorrhagia, fibroids, uterine prolapse, endometriosis, dysmenorrhea, gynecological cancer or adenomatous endometrial hyperplasia, chronic bad cervicitis. Other indications including pelvic infection, ovarian tumor account for 15–21% of hysterectomies.

APPROACH FOR Hysterectomy

Mode of removal of uterus depends upon surgical indications, surgeon’s preference and skill. Though perhaps India has few of the best vaginal surgeons in the world, it is a myth that every gynecologist in India is a very good vaginal surgeon. In many of the hospitals 75% of hysterectomies are done abdominally and 25% vaginally.

Vaginal hysterectomy is performed mainly for prolapsed uterus and other indications depending upon the uterine size, surgeon’s skill and preference, this situation is rapidly taking a turnaround to vaginal route. The decision to perform abdominal hysterectomy rather than vaginal hysterectomy is based on uterine size (very bulky > 10–12 weeks) or associated severe endometriosis, prior abdominal surgeries, previous cesarean sections, pelvic adhesions, poor laxity and other additional nongynecological pathologies. Laparoscopic hysterectomy is useful in such cases and patients for abdominal hysterectomy can be converted drastically to either total laparoscopic hysterectomy or laparoscopic-assisted vaginal hysterectomy. However, the suitability of any particular route is not decided by the indication, but by the skill of the surgeon and the patient’s safety.

Again presuming that every endoscopist is capable of doing laparoscopic hysterectomy is a gross mistake. The contribution to morbidity or occasional mortality by the neo laparoscopists or less experienced yet overambitious surgeons and gynecologists will be significant.

CLASSIFICATION SYSTEM

A classification system for the types of laparoscopic hysterectomy being performed has not been universally agreed.

- Classification by Harry Reich: He has suggested that if the uterine vessels are secured laparoscopically then the procedure is considered to be a laparoscopic
hysterectomy. If the uterine vessels are secured vaginally then the procedure is described as laparoscopic-assisted vaginal hysterectomy.

- Classification by Alan Johns.\textsuperscript{9} He has described laparoscopically-assisted vaginal hysterectomy stages.

**Stage**

0 Laparoscopy done—no laparoscopic procedure performed prior to vaginal hysterectomy

1 Procedure included laparoscopic adhesiolysis and/or excision of endometriosis

2 Either or both adnexae freed laparoscopically

3 Bladder dissected from uterus

4 Uterine artery transected laparoscopically

5 Anterior and/or posterior colpotomy or entire uterus freed as total laparoscopic hysterectomy.

1, 2 and 3 are Laparoscopic-assisted vaginal hysterectomy (LAVH).

Laparoscopic radical hysterectomy with lymphadenectomy is not covered in this chapter.

**Indications of Laparoscopic Hysterectomy at our Center**

At our center whenever an abdominal hysterectomy is necessary in a given patient then we do consider and give the option of laparoscopic hysterectomy to the patient. There is no dispute that traditional contraindications to the time honored vaginal hysterectomy form the indications for a laparoscopic removal of uterus, if a minimally invasive method is offered to the patient. Kovac\textsuperscript{10} (1988), Thompson and Smith\textsuperscript{11} (1986) felt that the employment of laparoscopic approach is totally dependent on surgeon’s skill and experience and we found that the advantage of laparoscopic route was good in the following cases:

- Previous pelvic surgery with uterine pathology (fibroids, dysfunctional uterine bleeding, adenomyosis) more than 14 weeks till 20 weeks size uterus
- Significant endometriosis/endometriomas
- Chronic pelvic pain
- Significantly large uterus—though expert vaginal surgeon may perform a vaginal hysterectomy for even up to 14–18 weeks size uterus or more, beyond that the choice is abdominal or laparoscopic approach
- Suspected or confirmed adnexal pathology, e.g. tubo-ovarian mass secondary to severe pelvic inflammatory disease, or any ovarian pathology (benign or malignant)
- Suspected bowel or appendicular disease
- Previous uterine suspension
- Previous one or more cesarean section (relative)
- Need of salpingo-oophorectomy, especially in women over 48 years of age
- Urinary incontinence or pelvic floor defect like enterocele along with any of the above pathologies. This is also changed more to vaginal route and transobturator sling suspensions.

Kovac et al.\textsuperscript{12} (2002) proposed guidelines for deciding the route of hysterectomy according to the given situation.

The precise indications for performing a laparoscopic hysterectomy is still a matter of debate. Nevertheless, the most convincing and persuasive reason for this procedure is to replace the more commonly done abdominal hysterectomy.

A massive rise in removal of uterus vaginally is seen in last 5 years and expertise has been increased to removing very big size uterus and we have removed uterus with even 54 fibroids vaginally. Indian gynecologists will be in the forefront for removing maximum uteri vaginally or laparoscopically. Abdominal route will remain for malignancies, uterus of more than 20–24 weeks in size and in patients of previous laparotomies with significant bowel adhesions.

**Preoperative Evaluation**

Usually a thorough preoperative evaluation is necessary little more than conventional hysterectomies. Besides routine investigations in all the cases, thyroid function tests are also done. We always intend to detect or rule out any medical ailment or disorder contrainindicating pneumoperitoneum, e.g. compromised pulmonary function tests, etc. We have come across an incidence of 14% of abnormal tests like deranged thyroid profile or blood sugar levels leading to accidental detection of hypothyroidism or diabetes mellitus. The surgeon should be well prepared for any modification or even laparotomy, in case it is difficult to treat the pathology by laparoscopy, as the patient’s safety and treatment is the prime concern. Conversion to a total vaginal hysterectomy with or without salpingo-oophorectomy on examination under anesthesia has increased to nearly 33% irrespective of size of uterus and/or previous cesarean sections 1/2/3 in last 5 years.

**Preoperative Preparation**

We, at our center, prefer to give a simple bowel preparation to every patient undergoing a laparoscopic hysterectomy, as the distended bowel loops may interfere with the surgical maneuvers, thus exposing them to the risk of accidental injury. Another advantage is that in a situation of accidental injury the empty bowel is always better to suture. A day prior to the surgery, bowel-preparing solution like polyethylene glycol solution with electrolytes is taken by the patient. The patients are kept on soft diet for 12 hours before surgery and then nil by mouth 6–8 hours before surgery. When we anticipate extensive intra-abdominal adhesions or pelvic pathology, we keep the patient on liquid diet for 24 hours prior to the surgery. A bowel preparation is also good for the patient in postoperative period. A broad-spectrum injectable antibiotic, viz. third generation cephalosporin or fluoroquinolones, is administered 1 hour before the surgery, which may be continued postoperatively in prescribed dosage for 2–3 days maximum. Adequate blood cross-matched with patient’s blood is kept reserved, even if it is required rarely. It is worth mentioning that a detailed valid informed consent
is mandatory in today’s medicolegal environment with an option to undergo abdominal hysterectomy, if necessary.

**Patient’s Position**

The patient is placed in a “low” modified lithotomy position on the Allen’s stirrups with adjustable and padded leg-rest, specially designed for gynecological surgeries. The hips are extended, and legs are at 135° to the horizontal so that the movement of the instruments is easier. We use the OR-direct padded adjustable leg rest stirrups, but if Allen’s stirrups are not available then standard lithotomy rods with padded rest for the knee joint is suitable, which is kept at 45° downward. The operation table should have a double pelvic cut for free movement of the uterine manipulator during the surgery. A shoulder rest is mandatory to prevent the patient from sliding down as surgery is performed in Trendelenburg’s position. The left hand is kept in the line with the body wrapped by cushion towel to facilitate comfortable operating position of the surgeon (Fig. 1).

This also prevents any neurological injury of the brachial plexus, which may occur due to accidental or sudden stretching of the hand if it is kept in abducted position. General anesthesia is administered with endotracheal intubation. A nasogastric tube may be very useful especially in cases of large myomatous uteri, when there is less space and higher risk of trocar injury to the stomach. Ventilation may also distend the stomach, which may expose the stomach to the risk of injury during trocar insertion. Trendelenburg’s position is very helpful in keeping the bowel (by gravity) away from the operative site, i.e. beyond the pelvic brim, enhancing the surgical exposure of pouch of Douglas. A 14/16 G Foley’s catheter is placed in the urinary bladder to keep the bladder empty throughout the procedure. A Hulka’s uterine manipulator or Rumi’s manipulator is inserted to manipulate and mobilize the uterus, or our new Trivedi’s detachable colpotomizer (See Fig. 51) reasonably affordable with different sizes with remote manipulation of uterus, thus facilitating better visualization and operability. The colpotomizer is always used at the end of near full separation of uterus. Patient is under general anesthesia with a multiparameter monitor with heart rate, $\text{PO}_2$, $\text{EtCO}_2$, ECG and temperature. An advanced model with in-built spirometry with the anesthesia machine is recently preferred.

**Abdominal Incisions and Port Placement**

A special mention of the port placement is necessary and will help the readers to understand the intricacies, not only of laparoscopic hysterectomy, but also for all advance laparoscopic surgery. The techniques employed by us has remarkably improved the ease of laparoscopic surgery for practicing gynecologists, in terms of decreased operating time, decreased fatigue and physiological suturing techniques simulating an open surgery. Hence, these can be rapidly mastered by budding endoscopists.

A 1 cm intraumbilical incision, two 5 mm incisions in both iliac fossa at the junction of the medial two-third and lateral one-third of the anterior superior spinoumbilical line, lateral to the deep inferior epigastric artery. The third ancillary (left upper) port is placed at the intersection of the vertical line from the left lower port and horizontal line from the umbilicus (Figs 2A to C). A 10 mm 0° laparoscope or in occasional difficult cases, a 30° laparoscope is introduced through the umbilical port. We use trocar sheaths with flower valve as secondary ports for various 5 mm instruments required at the different stages of the surgery. They facilitate effortless suturing and the thread does not get trapped in these trocar sheaths, as is the case with customary flap valve trocar sheaths. When morcellation of the uterus is to be carried out, the left lower 5 mm secondary port is removed and the incision is widened to 15 mm for a 15 mm morcellator. All port sites are injected with 0.25% Sensorcaine 3 mL prior to incision to reduce postoperative pain at port site.

**Operative Technique**

Laparoscopic hysterectomy was performed in 1,188 patients in modified lithotomy position without head down position, with $\text{CO}_2$ insufflation through Veress needle controlled by electronic $\text{CO}_2$ endoflator (Karl Storz-Tuttlingen, Germany) and Trivedi’s or thick Hulka’s uterine manipulator for manipulation. $\text{CO}_2$ was used for pneumoperitoneum at the rate of 3–9 L/minute with a pressure cut off at 15 mm Hg. A thorough inspection of the abdominal cavity, especially the pelvis is done to assess the extent of pathology and to decide whether any modification or adjuvant surgery is required. Liver, appendix and other organs are also inspected as a rule. Then, Trendelenburg’s position is given and ancillary ports are introduced under vision.

**Steps of Conventional Laparoscopic Hysterectomy**

The basic steps of laparoscopic hysterectomy are like a routine abdominal hysterectomy viz.:  
1. Division of the major pedicles viz. infundibulopelvic ligaments or utero-ovarian ligaments and round ligaments.

![Fig. 1: Patient’s position—modified lithotomy position](image-url)
5. Colpotomy
6. Removal of the uterus through the vagina or by morcellation.

**Round Ligaments and Utero-ovarian Ligaments**

Desiccation of the round ligaments is done by using bipolar forceps (Richard Wolf, Germany—dedicated bipolar generator or RoBi—Robust bipolar, Karl Storz, Germany) or new vessel sealing device. These instruments are very effective in achieving coagulation using 30–40 watts. The round ligament can be then safely divided by scissors with monopolar cautery. The utero-ovarian ligaments are then coagulated and divided by scissors, only after ensuring complete coagulation of the ovarian vessels (Figs 3 to 5). When an oophorectomy is to be performed, the infundibulopelvic ligaments are coagulated first. However, before proceeding it is prudent to determine the course of the ureter, which lies lateral to the infundibulopelvic ligaments. After inspecting the ureter, we used earlier specially designed Trivedi’s thread carrier to carry the suture (polyglactin 910 No. 1) through the anterior leaf of the broad ligament and the end is drawn posteriorly (Figs 6 to 11). This carries the thread from anterior to posterior, making an exit from the posterior aspect so that the ends of the thread can be pulled out from the lower port of the respective side. An extracorporeal knot is tied which is placed lateral to the infundibulopelvic ligament on either side (Fig. 12). The pedicle is then divided using the scissors. Hemostasis is checked and if the need be, coagulation is done using bipolar forceps. The utero-ovarian ligaments are thoroughly coagulated and divided subsequently. Reich preferred to dissect the ureter before the procedure. In our experience we dissected the ureters in 68 cases (5.7%) in cases of enterocele, early cervical malignancy or extensive endometriosis with distorted lateral pelvic anatomy. We, however, feel that it may be sometimes necessary in some cases of distorted pelvic anatomy, where it is difficult to discern the normal relations of ureter with the concerned pathology. Hence, apart from these exceptional situations, it is not mandatory to dissect the ureter as it may occasionally cause inadvertent injury to the ureter, if the surgeon is not well trained and is inexperienced.

**Bladder Mobilization**

The vesicouterine fold of peritoneum is then held in the midline using a Maryland forceps introduced through the right port and cut using a spatula with monopolar cautery, through the left lower port, with 100 watts (Figs 13 to 15). The incision is further extended by sharp scissors, till the round ligaments on both sides. The cutting current should be used carefully as it may cause thermal injury to the urinary bladder, which may in fact go unnoticed and manifest later.
Fig. 3: Right round ligament coagulation

Fig. 4: Right tubo-ovarian ligament coagulation

Fig. 5: Left tubo-ovarian ligament coagulation

Fig. 6: Trivedi's thread carrier for right tubo-ovarian pedicle

Fig. 7: Trivedi's thread carrier for right tubo-ovarian (1)

Fig. 8: Trivedi's thread carrier for right tubo-ovarian (2)
Fig. 9: Trivedi's thread carrier for right infundibulopelvic ligament (1)

Fig. 10: Trivedi's thread carrier for right infundibulopelvic ligament (2)

Fig. 11: Trivedi's thread carrier for right infundibulopelvic ligament (3)

Fig. 12: Trivedi's thread carrier for right infundibulopelvic ligament (4)

Fig. 13: Dissection of the uterovesical peritoneum (1)

Fig. 14: Dissection of the uterovesical peritoneum (2)
in the postoperative period, may be 5th or 7th day. The curve of the spatula, with convexity downward, can then be used to mechanically push the bladder down (Fig. 15). Adequate dissection should be achieved; otherwise there may be difficulties in suturing the vaginal vault after removal of the uterus. The minimal oozing from the vesical plexus can be coagulated using bipolar forceps. Due to adequate dissection of the bladder ureters automatically go laterally and hence are safe.

Some surgeons (Reich et al.⁷) recommend aquadissection in difficult cases like history of previous cesarean section or any other pelvic surgery, in which bladder may be adherent to the uterus. However, we advocate sharp dissection using a good quality scissors (Karl Storz or disposable scissors, Johnson & Johnson). The identification of the urinary bladder margins will surely circumvent any risk of inadvertent injury. In a case of previous cesarean section, expert vaginal surgeons can still dissect the anterior pouch vaginally after laparoscopic posterior colpotomy, vaginal approach of anterior pouch in such a situation is much safer for bladder as per the authors’ experience or else sharp dissection with scissors or monopolar hook or harmonic scalpel is useful.

**The Uterine Artery**

It is not axiomatic to say that skeletonizing the uterine artery laparoscopically is the real essence of the laparoscopic hysterectomy. Lateral transection of the uterine artery is a crucial step in a laparoscopic hysterectomy.¹³,¹⁴

It is mandatory to skeletonize the uterine artery to ligate it and avoid injury to the bladder or the ureter. This is done by blunt dissection in the folds of the broad ligament, up to the level of the isthmus. At this site the uterine artery can be seen pulsating and entering the uterine body. We normally prefer to suture the uterine artery. We always coagulate a segment of the skeletonized uterine artery (1–2 cm), if not ligated. If the previous pedicles are not sutured but divided after coagulation (Figs 19 and 20), then we introduce the curved needle with the suture at this stage by Harry Reich’s technique.⁷ The uterine artery is stabilized with a ureteric grasper and the needle is driven through the pedicle. The first knot is tied extracorporeally (Figs 16 to 18), and the subsequent knot is tied intracorporeally (Figs 21 to 23). The pedicle now can be safely divided with no risk of hemorrhage (Fig. 24). It is important to understand at this stage that suturing the uterine artery or desiccation not only ensures safe division of this pedicle but also makes the surgery safe, because any hemorrhage at this stage, not only puts the patient at high-risk of morbidity, but also defeats the purpose of buttonhole surgery.
Fig. 18: Left uterine artery ligation (3)

Fig. 19: Medial coagulation of the uterine artery

Fig. 20: Division of left uterine artery after suturing and medial coagulation

Fig. 21: Suturing of the right uterine artery

Fig. 22: Intracorporeal suturing of the right uterine artery

Fig. 23: Intracorporeal suturing—first knot
The intracorporeal ipsilateral knot has 3–4 throws to prevent any loosening or slippage of ligature (Figs 21 to 23). After the division of this pedicle, the surgeon should always vigilantly assess the integrity of the knot and not to mention, that of the ureter.

As this is the most difficult step in a laparoscopic hysterectomy and we have designed this simplified method of performing it with great precision.

It is very important to dissect 1 cm below the uterine pedicle after ligating the uterine artery before proceeding for colpotomy (Figs 24 and 25). This prevents any risk of avulsion of the ligated artery during subsequent steps, even if performed vaginally.

Colpotomy

Colpotomy is done anteriorly by inserting a wet sponge on holder vaginally and posteriorly on a CCL trocar (Colpo-Chirurgie Lausanne Karl Storz, Tuttlingen, Germany). We occasionally prefer to do a posterior colpotomy prior to the anterior colpotomy to avoid gas leak. This takes care of the cervicovaginal attachments like the cardinal ligaments and the uterosacral ligament and the vaginal branch of the uterine artery before advancing ahead. The CCL trocar is inserted vaginally in such a manner that it protrudes between the two uterosacral attachments to the uterus. A horizontal incision is made on this most prominent part of the pouch of Douglas using a spatula with monopolar cutting current upto 100 watts (Fig. 26), taking care that bowel are pushed away from the field by the assistant and the head-low position. This incision is then extended anteriorly from both the sides, by manipulating the uterus to aid proper visualization while completing the circumferential incision (Figs 27 to 29). Any hemostasis required is achieved effectively by the flat surface of the spatula with monopolar cautery itself. The uterus sometimes may have to be manipulated and stabilized
using a myoma screw, from the left upper port, in case of a large myomatous uterus. As the uterus is detached from the terminal attachments, there might be sudden leakage of CO₂ from the vagina causing loss of pneumoperitoneum. To prevent this, the uterus is gently drawn in the vagina and is kept in the place, which prevents gas leak and CO₂ insufflator is kept at higher flow rate to maintain the pneumoperitoneum (Figs 30 and 31).

An alternative to this step is another method of colpotomy using a specific colpotomizer designed by Charles Koh. Various vaginal tubes made of different materials like polyvinyl chloride, or silicon or steel/metal tube with insulated vaginal edge and a detachable pneumo-occluder at the other end, are available. These tubes are of various diameters ranging between 3 cm and 5 cm. The commonly used ones include the McCartney’s tube. The pelvic assistant inserts the colpotomizer in the vagina with the lid closed after securing the uterine artery. We are, however, not sold out to people using vague type of plastic or sanitary tubes and the dogmatism of a few endoscopists to essentially do a circumferential incision wherein, since the tip of this tube is sharp and not bossed or blunt like a cup, there is excessive bleeding and also few cases of ureteric injuries have been witnessed. Invariably it is done with monopolar current using a spatula. However, the ideal instrument at this stage is the harmonic scalpel with open blade on full setting. This not only does the colpotomy without any risks of electrosurgical burns but also keeps the entire pericervical rim of the fascia useful for the support of the vaginal vault. The uterus is then completely separated and pushed into the tube, which is maintained in place till the vaginal vault is sutured either laparoscopically or vaginally.
A useful instrument, though costly, is the Clermont-Ferrand uterine manipulator with a colpotomizer having a rubber ring for prevention of gas leak. This instrument has the added advantage of manipulating the uterus in both axes (like Valtchev manipulator). Further, the colpotomy is only three-eighths of the circle on the projecting colpotomizer, which can rotate through 180° (facilitating even a circumferential colpotomy, if needed).

The vault is then sutured by extracorporeal or intracorporeal method (Figs 31 to 34). Normally, 3–4 intermittent sutures are required, using a polyglactin 910 no. 1. The closed vaginal vault is tied with the uterosacral ligaments by taking a “figure of 8” suture ensuring proper suspension (Figs 35 to 37).

A simultaneous McCall culdoplasty may be required in patients with lax pelvic floor or with enterocele. This is usually performed before initiating the hysterectomy. The
ureters are dissected from the brim downward and pushed quite easily laterally. Then the McCall culdoplasty suture is taken from the left uterosacral ligament, passing through the rectovaginal septum made prominent by a CCL trocar (at a point lower than the imaginary site of posterior colpotomy) and then through the right uterosacral ligament with double bites. The free ends of the suture are then drawn through the left upper port and kept untied till the vaginal vault closure. These are tied extracorporeally after giving thorough saline wash ensuring complete hemostasis.

A thorough saline wash is given after achieving complete hemostasis by bipolar coagulation. An “underwater inspection” of all the pedicles is a method of proven benefit to avoid oversight of any bleeding vessel. We consider introducing an intraperitoneal drain (14 or 16 G Ryle’s tube) through one of the lower ports, which rests in the pelvis, in cases requiring extensive surgical dissection to remove exudate. This drain can be removed after 24–36 hours.

**Place of Supracervical Hysterectomy**

Many centers in India do not prefer performing a supracervical hysterectomy due to the fear of cervical stump carcinoma. However, we feel that this may still be a preferable method especially in a mentally retarded girl where a day care laparoscopic supracervical hysterectomy assures discharge within a day or in an occasional young patient, who voluntarily desires to retain the cervix and keep the pelvic floor intact or for satisfactory sexual function. In a case of previous two cesarean sections, wherein the urinary bladder is densely adherent, making the dissection difficult increasing the possibility of accidental injury to the urinary bladder, supracervical hysterectomy is an acceptable option.

In this method, the cervix is incised at the level of internal loss and uterus divided completely from the cervix by spatula with monopolar cautery (cutting current 100 watts) (Fig. 38). The cervical edges are then approximated with intermittent sutures using polyglactin 910 no. 1 along with the peritoneum as well (Fig. 39). The uterus is finally removed by morcellation (Fig. 40).

**USE OF SPECIAL INSTRUMENTS**

**Morcellator**

When uterus is very large, instead of removing vaginally one has the option of removing it by morcellation. The procedure of morcellation is similar to that of fibroids, which is dealt with a reusable Rotocut Morcellator (Karl Storz) or similar.
Harmonic Scalpel (Laparosonic Coagulating Shears, Ethicon) (Figs 41 to 47)

This is a very versatile and multifunctional instrument. It works on the principle of using mechanical energy to achieve coagulation or cutting of the tissue by “cavitational effect.” The tip has an active blade, which can vibrate at the frequency of 55,000/second. This generates cavitational effect, which can be effectively utilized to coagulate, cut or dissect any tissue. The advantage of this instrument is that it is safer than monopolar cautery. It can be used for coagulating vessels of less than 5 mm thickness and achieves complete hemostasis effectively.

GENERATION 4 HARMONIC ACE

It obviates the need of changing the instrument frequently as it performs many functions alone. It does not have
the disadvantage of “capacitation coupling” nor requires insulation, reduces surgical time safely. The instrument is excellent to dissect beyond the uterine vessels especially 1 cm below them, as it maintains the pelvic fascia and a circumferential incision can be easily made with one blade around the cervical ring of this fascia over a McCartney’s tube inserted vaginally. This keeps the pelvic floor intact and vault closure can be successfully done laparoscopically. The major disadvantage is that it is a disposable instrument and the cost of the primary unit is very high for Asian circumstances. Furthermore, the uterine artery may still need ligation or coagulation. Hence, it finds application in selective cases and significantly reduces the duration of the surgery.

Trivedi’s Knot Pusher and a Pair of Especially Designed Curved Needle Holder cum Toothed Grasper and Other Straight Needle Holder for the Dominant Hand

Trivedi’s knot pusher and a pair of especially designed curved needle holder cum toothed grasper and other straight needle holder for the dominant hand is very useful. A closed Trivedi’s simple knot pusher is useful for extracorporeal simple knot designed by the author. Another instrument is specially designed, which is a curved needle holder with tip of toothed grasper type, excellent for grasping structures to be sutured and curve helps to slide the intracorporeal knot. This saves a lot of time and also avoids the need of needle manipulation for vertical zone suturing.

Special Problems

Few steps may consistently pose difficulties, especially for a novice surgeon:

1. The single most important step of a laparoscopic hysterectomy is proper skeletonization of uterine artery. We always advise to dissect 1 cm below the uterine pedicle to avoid avulsion of the attached ligated uterine pedicle. This freeing of the pedicle from the specimen totally prevents hemorrhage from an accidentally avulsed uterine pedicle.

2. The second difficulty that may be encountered is the opening of the vaginal vault. With increasing expertise and acquired skill, large uterine corpus with fibroid can be extirpated laparoscopically employing the following methods according to the suitability of the surgeon:
   - A silicon tube in vagina or gauze packed in a surgical glove is introduced vaginally to prevent gas leak after anterior colpotomy can be done laparoscopically over this pack and extended circumferentially to detach the uterus completely.
   - Use of a Koh’s colpotomizer or McCartney’s tube of 3.5–4 cm diameter or a Hohl manipulator may also facilitate easy colpotomy and hence the division of the uterosacrals becomes easy.
3. Removal of large masses or leiomyoma of more than 18 weeks. Various methods are used and the preferred methods are:20-22
   - Debulking or myomectomy before hysterectomy.
   - Supraumbilical port providing room for vision and surgery.
   - Securing uterine vessels properly ensures a bloodless operative field and makes the subsequent steps easy for the surgeon.
   - Use of a 30° 10 mm laparoscope also aids good anterior and posterior dissection in cases of such large masses.
   - In some cases of less space a nasogastric tube is introduced to keep the stomach deflated.

4. Ureteric dissection (Figs 48 and 49). As mentioned earlier, H Reich5 preferred to dissect the ureters prior to the procedure in all the cases as a routine step. We feel that it may not be necessary in all cases except when lateral pelvic wall disease is present. Stenting the ureter, with an illuminating or nonilluminating, as some researchers feel, may offer certain protection to the ureter, but it has been proved beyond doubt that it does not decrease the incidence of ureteric injury. It definitely helps to recognize the site of injury in case there is an accidental ureteric injury.

**OUR EXPERIENCE**

After performing a significant number of vaginal and abdominal hysterectomies, we would like to share our experience of over 1,188 laparoscopic hysterectomies performed at National Institute of Laser and Endoscopic Surgery (NILS), Mumbai, Jaslok Hospital and Research Center, and other endoscopic surgery workshops done by Faculty in India and abroad.

This has helped us to evaluate the feasibility of performing laparoscopic hysterectomy in India and also critically evaluate the morbidity, operation time taken,23 patient’s recovery and complications. Further, to evaluate whether laparoscopic approach really helps to convert an abdominal hysterectomy into a vaginal route especially for difficult and suitable indications (Table 1).

In our series we had 197 patients (16.55%) who had previous cesarean section (1 cesarean in—108 and more than 1 cesarean in—79 cases).
- 283 patients (23.76%) had associated medical problems like diabetes, hypertension, hypothyroidism, mild ischemic heart disease, asthma
- 157 patients (13.17%) had previous laparotomy scars
- 49 patients (4.05%) had associated stress urinary incontinence
- 14 patients (1.12%) had associated enterocoele
- 150 patients (12.61%) had associated appendicitis
- 5 patients (0.41%) underwent pelvic lymphadenectomy24
- 1 patient had inguinal hernia.

Over a period of 14 years from June, 1993 to April, 2007 we have performed 1,188 total laparoscopic hysterectomies, in India and abroad. The age of the patients varied from

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Indication</th>
<th>Trivedi et al.</th>
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<tbody>
<tr>
<td>1.</td>
<td>Menorrhagia/bulky uterus with restricted mobility adenomyosis</td>
<td>426 (35.8%)</td>
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<tr>
<td>2.</td>
<td>Fibroids (single or multiple up to 22 weeks size)</td>
<td>439 (36.93%)</td>
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<tr>
<td>3.</td>
<td>Associated benign adnexal mass (ovarian cyst)</td>
<td>69 (5.74%)</td>
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<td>4.</td>
<td>Previous cesarean section</td>
<td>197 (16.55%)</td>
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<tr>
<td>5.</td>
<td>Endometriosis</td>
<td>73 (6.08%)</td>
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<td>6.</td>
<td>Associated chronic PID /adhesions</td>
<td>22 (1.8%)</td>
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<tr>
<td>7.</td>
<td>Endometrial or early cervical malignancy</td>
<td>7 (0.56%)</td>
</tr>
<tr>
<td>8.</td>
<td>Enterocoele</td>
<td>14 (1.12%)</td>
</tr>
</tbody>
</table>

(Abbreviation: PID, pelvic inflammatory disease)
38–64 years (mean age 44.5 to ± 2.32). 376 patients had additional procedures along with laparoscopic hysterectomy like laparoscopic appendicectomy, enterocele repair, Burch colposuspension, lymphadenectomy and laparoscopic repair inguinial hernia due to presence of associated abnormality (Table 2).

We had only 98 laparoscopically-assisted vaginal hysterectomies, in which the uterine and uterosacral pedicles were tackled from below, and vaginal vault closure done, and 21 laparoscopic supracervical hysterectomies were done. However, most of them were in the earlier period of our series. We nowadays preferably perform total laparoscopic hysterectomy wherever indicated or else a vaginal hysterectomy, if feasible. Uterosacrals were clamped, cut and ligated vaginally and used for vaginal vault suspension before vaginal closure. Uterus with or without adnexa was removed vaginally and was sent for histopathology.

In 62 cases, laparoscopic McCall culdoplasty suture was taken suspending the vaginal vault to uterosacral ligaments to correct posterior compartment.

Table 2: Associated abnormalities requiring other surgery

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Associated pathology</th>
<th>Trivedi et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Associated appendicitis</td>
<td>150 (12.61%)</td>
</tr>
<tr>
<td>2.</td>
<td>Associated enterocele</td>
<td>14 (1.12%)</td>
</tr>
<tr>
<td>3.</td>
<td>Inguinal hernia</td>
<td>1 (0.11%)</td>
</tr>
<tr>
<td>4.</td>
<td>Stress urinary incontinence</td>
<td>49 (4.05%)</td>
</tr>
</tbody>
</table>

In 53% of the cases, only bipolar coagulation was used for all pedicles and in 3% of the cases Harmonic Scalpel (Ethicon) or Linear Stapler-Endo GIA (US Surgicals) was used.25

Appendicectomy was done in 96 cases and pelvic lymphadenectomy in 5 cases. Stress urinary incontinence repair by Burch’s laparoscopic colposuspension in 31 cases after urodynamic study earlier, now suburethral polypropylene or Transobturator sling designed by the author is preferred. Enterocele repair laparoscopically was done in 14 cases. Average operating time was 82 minutes (51–186).

Results and Analysis

The results from our series of 1,188 laparoscopic hysterectomies are as depicted in Tables 3 to 5. We had 14 conversions to laparotomy, giving a conversion rate to laparotomy of 1.35%. Reasons for laparotomy in the 14 cases are described in Table 4.

- The average age of patients in our series of total laparoscopic hysterectomy was 44.52 ± 2.32 (range 38–64 years). Twelve patients undergoing supracervical hysterectomy in the age group of 17–24 years had mental retardation or severe physical or neurological problems and were not able to manage their menstrual bleeding, 11 previous cesarean sections, with only 1 patient aged 37 years who had 3 previous cesarean sections as a total laparoscopic hysterectomy was difficult. The average duration of surgery was 82 + 10.42 minutes (range 51–244 minutes). The minimum duration was 51 minutes and 1 case of severe endometriosis required around 4 hours. Duration of surgery was calculated from the time of commencement of insufflation to the closure of the ports. The average blood loss was 168 mL (range 55–880 mL). Fourteen patients in our series required perioperative blood transfusions due to intraoperative blood loss more than 600 mL. Twenty-one patients had complications, medical or surgical, overall complication rate being 2.36%. Twelve patients (1.35%) required laparotomy for various reasons.

- In 192/1,188 patients, bilateral salpingo-oophorectomy26 was performed. In the 5 cases, this was along with laparoscopic pelvic lymphadenectomy for early cervical carcinoma (cancer Stage 1A–1B).

- Reasons for conversion to abdominal hysterectomy are summarized in Table 4. We had to perform laparotomy in 4 cases of severe endometriosis (grade III–IV), in 2 cases of large multiple fibroids (uterus > 22 weeks size) and in 3 cases of severe intraperitoneal and bowel adhesions. Retrospectively, we felt that this was mainly due to poor case selection rather than an actual complication. We observed that these were in earlier phase and conversion rate reduced significantly in the later part due to proper case selection and increase in the experience and skill.

Table 3: Details of the surgery

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Parameters</th>
<th>Trivedi et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Average age</td>
<td>44.52 ± 2.32 (range 38–64 years)</td>
</tr>
<tr>
<td>2.</td>
<td>Average duration of surgery</td>
<td>82 ± 10.42 minutes (range 51–244 minutes)</td>
</tr>
<tr>
<td>3.</td>
<td>Mean blood loss</td>
<td>168 mL (range 55–880 mL)</td>
</tr>
<tr>
<td>4.</td>
<td>Average postoperative stay</td>
<td>38 hours (range 36–72 hours)</td>
</tr>
<tr>
<td>5.</td>
<td>Conversion to laparotomy</td>
<td>14 (1.33%)</td>
</tr>
<tr>
<td>6.</td>
<td>Complication rate</td>
<td>21 (2.36%)</td>
</tr>
</tbody>
</table>

Table 4: Indications for conversion to laparotomy

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Indications</th>
<th>Trivedi et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Endometriosis (Grade III–IV)</td>
<td>4</td>
</tr>
<tr>
<td>2.</td>
<td>Very large uterus (&gt; 22 weeks size)</td>
<td>2</td>
</tr>
<tr>
<td>3.</td>
<td>Severe intraperitoneal and bowel adhesions</td>
<td>3</td>
</tr>
<tr>
<td>4.</td>
<td>Iatrogenic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Urinary bladder injury</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>• Bowel injury</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>• Intraoperative hemorrhage</td>
<td>Nil</td>
</tr>
<tr>
<td></td>
<td>• Ureteral injury</td>
<td></td>
</tr>
</tbody>
</table>
Complications (Table 5)

We emphasize that in 5 cases of urinary bladder injury we had to perform laparotomy for bladder repair in one case, where hysterectomy was completed abdominally. The other four cases were tackled laparoscopically as the margins of the injury were clearly defined and small. A Foley’s catheter was kept in situ for 7 days postoperatively and removed thereafter. One of these patients had urinary tract infection and responded to antibiotics. We observed that 3 out of these 5 cases had a history of previous cesarean section. These injuries occurred during a laparoscopic-assisted vaginal hysterectomy or total laparoscopic hysterectomy while opening the anterior peritoneum vaginally. One case of right ureteric injury, when new vessel sealing device was used, needed stenting.

In our series we had 3 cases of hemorrhage from the uterine artery. Laparotomy was required in 2 cases to arrest the hemorrhage, where the hemorrhage was from the left uterine artery in both the cases. In one case the uterine artery pedicle was coagulated laparoscopically by using bipolar forceps with coagulating current of 30–40 watts, successfully. Subsequently, the postoperative course was uneventful in all the cases. The remaining 6 cases were due to associated endometriosis and adhesions, selected improperly for laparoscopic hysterectomy, which finally required open hysterectomy.

We had one small bowel injury in our series. It was caused during adhesiolysis due to thin bowel wall integrity. The rent was less than 1 cm, which was sutured laparoscopically by placing a single layer suture using polyglactin 910. A Foley’s catheter was kept in situ for 7 days postoperatively and removed thereafter. One of these patients had urinary tract infection and responded to antibiotics. We observed that 3 out of these 5 cases had a history of previous cesarean section. These injuries occurred during a laparoscopic-assisted vaginal hysterectomy or total laparoscopic hysterectomy while opening the anterior peritoneum vaginally. One case of right ureteric injury, when new vessel sealing device was used, needed stenting.

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We had one small bowel injury in our series. It was caused during adhesiolysis due to thin bowel wall integrity. The rent was less than 1 cm, which was sutured laparoscopically by placing a single layer suture using polyglactin 910. The patient was kept on parenteral fluids, nasogastric aspiration for 72 hours. Liquid diet was started on the 4th day postoperatively after ensuring adequate peristalsis and the patient resumed her regular diet and bowel habits 5th day onward. The recovery was complete thereafter without any residual sequelae.

We had an unexplained mortality in a patient of chronic anemia (Hb: 6 g/dL) who was given 4 units of blood transfusions preoperatively. The procedure was uneventful requiring 70 minutes. The patient had a normal recovery with normal vital parameters, soft abdomen, good peristalsis and normal sensorium. She had an unexplained cardiac arrest 15 hours after surgery and could not be revived. There was no obvious surgical cause contributing to the mortality. Relatives insisted on avoiding a postmortem.

Postoperative Course

In general, postoperative recovery was better than abdominal hysterectomy but not superior to vaginal hysterectomy. However, patients who had undergone a laparoscopic supracervical hysterectomy had a faster recovery than a vaginal hysterectomy. Postoperative analgesia was given in the form of injectable analgesics and rectal suppositories (Diclofenac). We also observed significantly less morbidity after the use of filter for CO2 insufflator. Additionally, the use of injection sensorcaine (0.25–0.5%) at the port sites reduces local postoperative pain significantly. Some patients insisted for discharge even within 14–16 hours of surgery.

Two patients had postoperative vaginal vault induration due to small hematoma, which resolved spontaneously. One patient had left lower port infection, which was treated with antibiotics and regular dressing. Another case had port site tuberculosis confirmed on histopathology and treated.

We did not come across any case of deep vein thrombosis or pelvic hematoma. The duration of hospital stay was 38 hours (range: 36–72 hours). On follow-up, patients did not require prolonged bed rest and could resume normal work within a range of 1–3 weeks. None of the patients required re-admission.

Laparoscopic Route for Management of Gynecological Malignancies

We have a strong and clear opinion and few reservations for laparoscopic radical hysterectomy for cervical or uterine malignancy. A laparoscopic surgeon cannot be excused for doing a laparoscopic radical hysterectomy or laparoscopic pelvic lymphadenectomy leaving residual disease, which would have to be removed by an oncosurgeon by open laparotomy.

This field is truly meant for gynecologists or surgeons who have consistently done a high number of open surgeries for malignancy. For the rest it is worthwhile not to misuse this golden technique on a trial and error or as a learning process since this does not benefit patient.
We today feel that laparoscopic approach for genitourinary malignancy is still in a very experimental stage. The extent of radical excision of pathology by laparoscopic approach is still debatable even in leading cancer institutes.

**COMPLICATIONS OF LAPAROSCOPY**

Instrumentation in laparoscopy is often complicated and may lead to additional hazards. Good surgical training including knowledge of instruments and techniques is very important before starting laparoscopic surgery. Overlooking these essential aspects is the reason for complications. Overall surgical risk is lower for laparoscopic procedures than laparotomy.

**Risk Factors**

- **Obesity**: Thick abdominal wall makes insufflation as well as trocar entry difficult. Increased amount of extraperitoneal fat also adds to the difficulty.
- **Age**: As the age increases, concomitant problems like cardiovascular disease will also be present, which increase anesthetic risk.
- **Previous abdominal surgery**: Adhesions involving bowel loops will be present in more than 20% of the patients who have had previous abdominal surgeries. Adherent bowel loops are at risk of injury by the Veress needle as well as trocars.

**Pneumoperitoneum Related Complications**

**Gas Embolism**

Gas embolism is one of the dangerous complications of laparoscopy. The incidence of gas embolism is much less when carbon dioxide is used for insufflation. Carbon dioxide is 200 times more soluble than air. Immediately after entering the circulation it will be converted to carbonic acid which dissociates to bicarbonate and hydrogen ions. However, carbonic acid formed in the peritoneal surface will cause shoulder pain postoperatively. Escape of large amounts of carbon dioxide can cause embolism. Various factors affect the incidence of gas embolism as well as other complications of pneumoperitoneum.

**Insufflation volume and rate**: The total volume of gas to be insufflated for introducing the needle is 2–2.5 liters. The rate of gas flow initially is set at 1 liter/minute and later may be increased to 2.5–3 liters/minute. The intra-abdominal pressure at the time of Veress needle insertion is kept at 20 mm Hg to help the insertion. After inserting the primary trocar and telescope, the pressure should be reduced to 12 mm Hg. Maintaining intra-abdominal pressure more than 12 mm Hg while performing surgical procedures can increase the risk of gas embolism as well as reduction of venous return and cardiovascular compromise. The capnograph will show increased end-tidal CO₂ level when there is hypercarbia due to prolonged absorption of CO₂ and restriction of diaphragmatic movement. Hence, it is mandatory that the anesthesiologist should monitor the end-tidal CO₂, heart rate, heart sounds as well as the color of the blood so that the early signs of CO₂ retention can be diagnosed. Sudden unexplained hypotension, cardiac arrhythmia, cyanosis and heart murmurs should raise the suspicion of gas embolism. There will be a sudden drop in CO₂ level when there is gas embolism or pulmonary embolism. If embolism is suspected or diagnosed, the surgeon should immediately evacuate the CO₂ from the peritoneal cavity and the patient should be kept in the left lateral position with the head end of the table below the level of the heart. A large bore central venous line can be inserted so that the gas can be aspirated from the heart.

**Cardiac Arrhythmias**

Hypercarbia and acidemia can cause cardiac arrhythmias. Maintaining a low intra-abdominal pressure less than 12 mm Hg greatly reduces the incidence of hypercarbia (CO₂ pressure > 65 mm Hg).

**Gastric Reflux and Aspiration**

The stomach must be decompressed, if distended. Always a cuffed endotracheal tube should be used. Obese patients and those with hiatus hernia are prone for aspiration. Use of preoperative metoclopramide along with H₂ blockers will reduce the risk of aspiration.

**Extraperitoneal Insufflation**

Extraperitoneal insufflation of gas usually occurs due to inadvertent placement of the insufflation needle in the preperitoneal space. Hence, checking proper placement of the insufflation needle as described earlier is important. Since, maintaining intra-abdominal pressure above 12 mm Hg during the surgical procedure will push gas into the extraperitoneal space around cannula sites, it is mandatory that the pressure be kept at 12 mm Hg or less. Mild subcutaneous emphysema does not need any aggressive management. If the edema extends to the neck, pneumomediastinum or pneumothorax might result. Pneumothorax can be treated by intercostal drainage.

**Complications of Electro surgery**

Electrical injuries can occur due to direct or indirect electrical trauma. Direct thermal injury occurs due to direct extension of thermal effect when the zone of vaporization or coagulation extends to the neighboring structures like ureter, bowel, or urinary bladder. Bipolar instruments reduce the incidence of thermal injury, but will not completely avoid it. To avoid unintended activation of electrodes, the surgeon should be in control of the activation of the electrode.
Electrosurgical instruments should not be retained inside the abdomen when not in use. While in use, the uninsulated part of the electrosurgical instrument should be completely under vision. Otherwise, part of the electrode tip touching the viscera may not be seen and hence will not be noticed.

Thermal injury to the bladder, bowel or ureter should be managed immediately. Laceration injuries should be managed by suturing. If a zone of coagulative necrosis is identified at the time of laparoscopy, wide excision and repair should be done as the area of thermal damage might extend wider than the area of necrosis.

Thermal injury to the bowel can be unnoticed at the time of surgery. Necrosis of the site of injury and consequent leakage can occur from 2 days to 10 days after the procedure. Hence, it is advisable to warn patients that they should report if they have pain, distention of abdomen or any other unusual symptom.

**Vascular Injuries**

**Injury to the Abdominal Wall Vessels**

Both superficial and deep inferior epigastric vessels can get injured while introducing secondary trocars. The superficial inferior epigastric vessel can be transilluminated and avoided. The deep inferior epigastric vessels lie between the rectus muscle and the peritoneum and cannot be transilluminated. It could be identified inside the abdomen lateral to the medial umbilical ligament which is formed by the obliterated umbilical artery. Accessory trocars should be introduced under vision, avoiding the superficial as well as the deep inferior epigastric vessels. In the case of accidental injury to the vessel, it can be coagulated with bipolar forceps introduced through another accessory port. If this method fails, a Foley catheter can be introduced through the cannula which injured the vessel and tamponade can be effected by inflating the bulb and pulling on the catheter after removing the cannula. The Foley catheter can be removed after effectively controlling hemorrhage which may take a few hours.

**Injury to Major Vessels**

Major vessel injury is a catastrophic event in laparoscopy. Injury to the aorta, inferior vena cava, common iliac vessels, external iliac vessels and superior mesenteric vessels has been reported. Several factors have been identified as contributing to the injuries. Inexperienced operator, dull trocar, inadequate pneumoperitoneum, failure to stabilize the abdominal wall, perpendicular or lateral direction of trocar, etc. have been suggested as causing these vessel injuries.

Resorting to proper technique is important in the prevention of these injuries. The Veress needle should be tested for its spring action as well as its patency before use. Patient should be in supine position while introducing the Veress needle as well as the primary trocar. Trendelenburg position will cause the aortic bifurcation to be rotated anteriorly and is more likely to be injured. Tilt should be given only after the insertion of the primary trocar and telescope. The needle should be held like a dart and thrust toward the center of the pelvis after raising the abdominal wall sufficiently outward. The needle should not be directed perpendicular to the abdominal wall. The valve of the needle should be kept in open position. Aspiration of the needle should be done to exclude unintended placement inside vessel or bowel. When preperitoneal insufflation occurs, multiple attempts may be resorted to with increased risk of injuries. It is advisable to proceed to open laparoscopy (Hassan’s technique) in such instances.

In the event of a suspicion of major vessel injury due to the presence of blood gushing through the Veress needle or cannula the abdomen should be immediately opened through a midline vertical incision. Bleeding should be controlled by digital pressure or with mops till the vascular surgeon comes for help.

**Urinary Tract Injuries**

**Bladder Injury**

The urinary bladder can be injured while introducing the accessory trocar if it is pulled up as in the case of previous cesarean section, myomectomy or endometriosis, and when the bladder is full. The bladder can be lacerated while performing laparoscopic hysterectomy especially if the anatomy is distorted due to adhesions from a previous surgery. Suspected injury should be confirmed by methylene blue instillation. All injuries diagnosed during the procedure should be managed by suturing.

Thermal injuries may go unnoticed during surgery, but should be suspected if the patient shows any of the following symptoms:

- Hematuria
- Decreased urine output
- Mass in the abdominal wall
- Peritonitis.

The bladder should be emptied before introducing the needle or trocar to prevent injury to a distended bladder. Before introducing the secondary trocar the upper limit of the bladder should be identified especially when the anatomy is distorted by previous surgery or tumors.

Trocars injuries which are very small, less than 1 cm in width can be managed by postoperative continuous bladder drainage for about 7 days. Lacerations of the bladder wall should be repaired either through the laparoscope or by laparotomy. Injuries near the trigone should be sutured after inserting ureteric stents to prevent injury to the intramural portion of the ureter. The usual injuries occur in the region of the dome which does not need such precaution. Thermal
injuries should be inspected through the cystoscope to make out the extent of thermal damage.

**Ureteric Injury**

Ureteric injuries can occur in patients with extensive endometriosis, pelvic inflammatory disease or broad ligament myomas. Even though ureteric injuries can occur anywhere in the course of the ureter, majority of them were seen in the vicinity of the uterosacral ligaments.

The common situations in which ureteric injuries occur are the following:

- While an adherent ovary is being dissected from the pelvic side wall
- When the uterosacral ligament is transected
- While coagulating or transecting the uterine arteries
- When trying to control bleeding in the pelvis
- While enucleating a broad ligament myoma
- Releasing endometriotic adhesion or coagulating endometriotic implants over the peritoneum in relation to the ureter.

To prevent ureteric injuries, the ureter should be identified before dissection. Aqua-dissection should be preferred over sharp dissection near the ureter. To prevent thermal injury due to lateral spread of heat, always use bipolar diathermy near the ureter and avoid monopolar diathermy. Even when using bipolar diathermy, try to include only small chunks of tissue. Trying to coagulate large amount of tissue with bipolar diathermy will cause more lateral spread of heat and if the ureter is nearby it can be damaged. Catheterization of the ureter with illuminated stents can be resorted to when ureteric damage is anticipated, as in open surgery.

Most ureteric injuries are diagnosed postoperatively when urine collects in the peritoneal cavity and distends the abdomen. Thermal injuries can cause ureteric stenosis which will lead to hydronephrosis and hydroureter several weeks after the surgery.

Injuries sustained during surgery can be diagnosed by injecting indigocarmine. These injuries should be repaired by suturing the lacerated ends over a stent passed retrograde through the bladder. Minimal damage might heal over a ureteric stent without suturing.

Postoperatively, injuries can be diagnosed by intravenous pyelography (IVP). Urologist should be consulted and injury should be repaired.

**Gastrointestinal Injuries**

Gastrointestinal injuries can occur during laparoscopic surgery. The stomach, colon or small bowel can be injured. Bowel injuries can occur due to the presence of bowel adhesions sustained during previous laparotomies. The stomach can be injured when it is unduly distended due to improper intubation. In the presence of inadvertent intubation into the stomach, it should be decompressed before proceeding to Veress insertion. The colon can get injured while placing the accessory trocars. If intestinal or gastric injuries are detected, immediate suturing is required with either laparotomy or laparoscopy depending upon the expertise available. When bowel adhesions are anticipated, preoperative mechanical preparation should be done.

**Neurological Injury**

Neurological injuries usually occur due to improper positioning of the patient. The common peroneal nerve can get compressed against the stirrup. Excessive flexion or external rotation of the hip can overstretch the femoral or the sciatic nerve. Proper positioning is important in preventing these types of injuries. The arm can be kept in the adducted position by the side of the body or by proper padding to prevent brachial plexus injuries. The legs should not be unduly abducted or laterally rotated. Most injuries recover spontaneously. Full recovery usually occurs in 3–5 months time. Recovery can be hastened by physiotherapy.

**Morcellators**

One of the major difficulties in laparoscopic surgeries is to remove large volumes of tissues such as fibroids, ovarian tissue, or even the uterus from the peritoneal cavity.

Suprapublic minilaparotomy or transvaginal extraction through colpotomy are methods of tissue removal during laparoscopic surgery. Electromechanical morcellator is a novel instrument for removing large masses thus avoiding need for colpotomy or minilaparotomy. A variable speed motor drives the rotation of the sharp outer sleeve. Cylindrical pieces of tissue can be extracted very easily with this device. It is possible, with the aid of this morcellator, to extract even large amounts of tissue from the abdomen, using the size 15 trocar, in a short period of time. Because of the good quality cutting of the rotating morcellator, the tissue structure is minimally damaged enabling a reliable histological examination.

**ROLE OF NEW VESSEL SEALING DEVICES IN LAPAROSCOPIC HYSTERECTOMY**

With laparoscopic hysterectomy knocking all potential doors of removal of uterus gave an impetus to companies to hybrid science and ease for the gynecologists and surgeons, the birth of vessel sealing devices (VSD) is a marriage of international technologies with skills. Major concern in laparoscopic hysterectomy is operating time, secured hemostasis, reducing complications and finally search for an ideal uterine manipulator with colpotomizer to avoid final dependence to go vaginally which itself takes a lot of time and at the most crucial time may lead to avulsion of uterine vessels during removal of uterus.

Uterine manipulators have fixed colpotomizer tube (McCartney vaginal tube), thus when used vaginally...
from the beginning, manipulation of the uterus is highly restricted. Whereas the remaining manipulators with a rotatable small segment colpotomizer lead to massive leak of pneumoperitoneum forcing surgeon to go vaginally in spite of highest gas flow rate. Many gynecologists thus abandon laparoscopic hysterectomy in utter frustration. To conquer this difficulty we designed new uterine manipulator with detachable colpotomizer. Using this new device both time is saved along with excellent safety. We used the new Trivedi’s uterine manipulator with detachable colpotomizer (Figs 50 to 52).

The new device has easy to use handle with two separate rotating knobs, one upper for grasping the cervix (anticlockwise), then a long shaft with two 8 mm rigid detachable tips of 8 cm and 12 cm in length which can be anteverted remotely with the lower knob by clockwise rotation for bulky and very large uterus.

- The new T’s uterine manipulator without colpotomizer cap only is inserted into uterus after dilating cervix, cervical grasper of the manipulator holding the posterior lip of cervix, enabling the uterus to be anteverted, retroverted or laterally flexed to facilitate the dissection, suturing and offers a best anatomy view (Figs 53 to 55).

The surgical steps are as follows:

1. Division of the round ligaments (Fig. 56).
2. Next the cornu or infundibulopelvic ligaments are desiccated and cut (Fig. 57) after inspecting the ureter, desiccation and automatic cutting of pedicles was achieved by using vessel sealing and cutting device. Anterior and posterior leafs of the peritoneum are dissected till the uterine vessels.
3. Bladder mobilization: The vesicouterine fold of peritoneum can be incised by vessel sealing device pushing the bladder downward.
4. Skeletonization of uterine artery: This is done perfectly using vessel seal and cutting device which definitely save time (Figs 58A and B). We would like to impress on the fact that till this stage, colpotomizer tube is not needed at all but is almost used universally.

We now prefer to introduce colpotomizer tube vaginally. Any additional bladder pillars are dissected so the rim of the
Fig. 54: Retroverted uterus

Fig. 55: Anteverted uterus

Fig. 56: Division of round ligament

Fig. 57: Right tubo-ovarian ligament

Fig. 58A: Left uterine desiccated

Fig. 58B: Uterine vessels separated
tube can be visualized anteriorly and all around (Figs 59A and B).

Conventional colpotomy leads to sudden loss of pneumoperitoneum from vagina. Further 30–40 minutes are taken to finish hysterectomy unlike our expectation.

These disadvantages are overcome by the new T’s uterine manipulator with colpotomizer. Major and most important advantage of this new device is that, it has got a firm, fixed grasp at the posterior cervical lip and allows easy manipulation of uterus either lateral flexion, anteversion or retroversion. Colpotomy is facilitated by pushing the colpotomizer tube up and it also prevents the gas leak33 (Figs 60A and B). The same spatula is used to incise the vagina following the projecting part of the tube which is rotated by the vaginal assistant. The detached uterus is removed vaginally due to grasp of manipulator on the posterior cervical lip. Bleeding from the vaginal cuff is reduced due to pressure effect of the colpotomizer tube.

The vault is then sutured by laparoscopic ipsilateral technique (Figs 61A and B). Most important part is you do not go vaginally and all persons are at same place, saving lot of time and a total laparoscopic hysterectomy can be done with efficiency and elegance. Only when the uterus is more than 16 weeks size, we elevate uterus with a 5 mm Myoma screw going sequentially down through a suitable port to expose the vagina.

The technical difficulties associated with conventional total laparoscopic hysterectomy have been largely solved by new manipulator—colpotomizer and vessel sealing device. It allows dissection of bladder, displaces ureters laterally out of the operative field and when in situ facilitates vaginal vault suturing under direct vision. The newer vessel sealing
device focuses on achieving hemostasis and cutting the tissue with the same instruments.

The newer vessel sealing device promises a lot with high quality of desiccation, hemostasis, no charring, definitely reducing the operative time but can have occasional bladder injury due to lateral spread of even bipolar current in the initial period and cost is a definite matter of concern.

The following new vessel sealing devices have been evaluated by the author:
- Plasma Kinetic Energy source—Gyrus
- LigaSure of Valleylab
- Martin Maxi with Robi grasper
- HARMONIC ACE Generation 4 from Ethicon
- BiClamp from ERBE
- Supercut from Wolf.

The biggest problem of laparoscopic hysterectomy is multiple instruments are changed and hence excess time for surgery. Technological advances have been made wherein a single instrument can be used to grasp, dissect, seal and cut; in addition there is no need for using sutures. Further, as the vessel to the nerves is sealed first, hence pain reduces and saves a lot of time avoiding instrument exchange. Further the same energy can be delivered by a clamp through vaginal or abdominal route. The salient features of each VSD is shown below.

**Plasma Kinetic: Gyrus**

Hereby a 5/10 mm instrument, the desired cornual or infundibulopelvic ligament is safely desiccated and seals up to 7 mm vessels, then cut with a flip movement bringing the cutting knife outside (Fig. 62). We can dissect the bladder and also the ureters before sealing and cutting the uterine vessels. This procedure is done very fast and we can reach for colpotomy within 20–30 minutes. We prefer to take the right port of 10 mm in line with the umbilicus, this allows the right side dissection and vessel sealing easily (Figs 63 and 64). For the left side, a 30° laparoscope is used with cable toward the left side and the 10 mm plasma kinetic instrument used from the umbilical port (Fig. 65) making this separation very swift. Since the 10-mm VSD and cutting hand piece (Fig. 66) is disposable, in Asian scenario it can be resterilized and used maximum for 3–4 cases only. The similar 5 mm instrument is not satisfactory and can be defunctional during the first case also, hence we prefer to use a 5 mm Maryland type of grasper (Figs 67A to D) to deliver the same energy with a wider opening. The ports used for the 5 mm plasma kinetic energy delivery is the same as conventional laparoscopic hysterectomy ports. This is very versatile and being a Maryland grasper the instrument is excellent and can be resterilized for
20 cases which is cost effective. Further the same main unit (Fig. 68) can be used for bipolar hysteroscopy or urological endoscopic surgery with normal saline or Ringer’s lactate and also vaginal hysterectomy with clamps delivering the energy not requiring sutures, so also for abdominal hysterectomy.

**LigaSure of Valleylab (Fig. 69)**

This yet another 10/5 mm instrument with a catch and can be used effectively with change in the sound like all other VSD machines. Once sealing is complete, Valleylab is a devoted company to electrocautery. The 10 mm instrument (Fig. 70) can be used for four cases maximum and is a little less versatile at colpotomy. It is a useful add-on instrument.

**Martin Maxi with Robi Grasper**

Again a product of a devoted company making good electrocautery machines, the computerized main unit (Fig. 71) can be set for requirements of outputs for gynecologists, surgeons and urologists, both for laparoscopic or hysteroscopic and urologic work. In hysterectomy the main unit is attached to the Robi grasper (Figs 72A to C) from Karl Storz 5 mm and is a good instrument for the said purpose.

**Harmonic ACE Generation 4 (Figs 41 to 47)**

Modifying the original harmonic machine, which has effect of VSD an active blade generating cavitational effect by moving 55,000/second. Availability of the 5 mm curved angle is useful in laparoscopic hysterectomy for vessels upto 5 mm size. A major advantage of the harmonic is that it cuts with hemostasis and after the uterine vessels you can core down medially to detach the separated uterine vessels, thus reducing chances of avulsion pull by the pelvic assistance. The final advantage over other techniques is that it cuts along with manipulations.
Fig. 67A: Right tubo-ovarian ligament sealed with 5 mm Maryland grasper Gyrus

Fig. 67B: Uterovesical peritoneum cut and dissected with 5 mm Gyrus

Fig. 67C: Right uterine artery sealed with 5 mm Gyrus

Fig. 67D: Left uterine artery sealed with 5 mm Gyrus

Fig. 68: Gyrus main unit

Fig. 69: Main unit of LigaSure
BiClamp from ERBE

This is similar to above, but limitation is that it depends more on the 5 mm laparoscopic hand piece of other company, again an instrument useful for laparoscopic or vaginal route.

Supercut of Wolf

This is a good design in 10/5 mm but as of now it is not available in India. The main unit is the same as the Wolf’s Bipolar Generator dedicated to laparoscopic surgeries.

Disadvantages of Vessel Sealing Device

- Cost
- Hand instruments are actually disposable after one case only. Further the new inventory cost of the main unit

Figs 72A to C: (A) Right tubo-ovarian ligament cauterized with Robi grasper (Martin Maxi); (B and C) Left uterine artery cauterized with Robi grasper
In the hands of less experienced or overconfident gynecologists or surgeons this can cause damage to the ureter or bladder, if not satisfactorily used.

**DISCUSSION**

Laparoscopic hysterectomy has been extensively evaluated all over the world as an alternative to abdominal hysterectomy.

The emphasis in our study was to evaluate feasibility in India to do laparoscopic hysterectomy for difficult indications and comparing the difference in operating time, morbidity, complications, patients’ recovery and surgeons’ comfort.

Comparing with meta-analysis of 3,189 laparoscopic hysterectomies by Garry et al. 6 and 317 laparoscopic hysterectomies by Bolger, Lopes and Monaghan 34 our results provide a remarkably similar pattern of low complications indicating that introduction of laparoscopic hysterectomy is not associated with very high complication rate. The decrease in number of complications in later part of series was due to better experience and skill over a period of time.

One criticism of laparoscopic hysterectomy is the assured increase in surgical time, but reduces with experience and skill of the surgeon.

These results are comparable with those by Trehan 35 on a total of 119 laparoscopically-assisted vaginal hysterectomies where mean operating time was 1 hour 31 minutes. In difficult indications like large fibroid, endometriosis, previous cesarean section, etc. laparoscopic hysterectomy was not actually difficult since principle of dissection, skeletonizing the uterine artery and safeguarding the ureter and bladder was same like in a simple case of laparoscopic hysterectomy.

Apart from the claimed advantages of laparoscopic hysterectomy we strongly believe that by persisting to do laparoscopic hysterectomy, we could become better surgeon and could also understand limitations of such approach. Further, we opened up new avenues for correcting associated conditions like stress urinary incontinence, enteroccele, appendicular pathology, lymphadenectomy, inguinal hernia, etc. It is interesting to note that 90% of complications of laparoscopic hysterectomy were also corrected by operative laparoscopy, thus not adding to conversion rates.

We believe that more and more difficult cases are now considered suitable for laparoscopic hysterectomy including those with previous abdominal surgeries, obesity and some patients even with high-risk medical disorders. With the advent of modern gadgetry for continuous monitoring of vital parameters like pulse, blood pressure, oxygen saturation, CO₂ saturation, temperature and electrocardiogram intraoperatively and decreasing operative time with experience, endoscopic surgery has definitely earned a place for management of such high-risk cases, significantly decreasing the morbidity.

The inhibition on the part of a gynecologist not to utilize laparoscopic hysterectomy in selected cases of definite abdominal hysterectomy according to us is a comparable dogmatism on the part of an endoscopic surgeon to do all hysterectomies laparoscopically.

Laparoscopic hysterectomy is glamorized more than its actual scientific value. In any center where there are significant numbers of abdominal hysterectomies done, then role of laparoscopic hysterectomy to convert to vaginal is worthwhile, provided safety to the patient is assured. But laparoscopic hysterectomy should not be taken only for glitter or glamor especially in cases were vaginal hysterectomy is possible.

### Changing Trends in Treatment of Menorrhagia and Impact of Advanced Technology

The graph in Figure 73 shows that the incidence of performance of vaginal hysterectomy is on the rise consistently, while abdominal hysterectomy is largely being replaced by other modalities like transcervical resection of the endometrium (TCRE), or laparoscopic hysterectomy.

![Fig. 73: Changing trends in management of menorrhagia 1992–2007 (our experience)](https://example.com/fig73)

( *Abbreviation: TCRE, transcervical resection of the endometrium* )
CONCLUSION

In our experience, we are convinced that laparoscopic hysterectomy has a definite place to convert an abdominal hysterectomy into a vaginal route. This was especially true for indications like large or multiple fibroids, previous cesarean sections or laparotomies, associated endometriosis, pelvic inflammatory diseases, adnexal masses, appendicular pathology, stress urinary incontinence, enterocèle, unmarried or nulliparous women.

We prefer laparoscopic hysterectomy to abdominal hysterectomy not only because we can remove the uterus with esthetically-pleasing incisions, but also because it has a better outcome in our hands. We would like to emphasize on a sustained learning curve in advanced laparoscopic surgery since in inexperienced hands laparoscopic hysterectomy can have more complications. Our persistence to do laparoscopic hysterectomy taught us more about the actual limitations and some disadvantages inherent with this approach, relevant more for hysterectomy but not for laparoscopic myomectomy or adnexal surgeries; where laparoscopic approach is far superior to abdominal approach.

The general demotivation on presumption of longer operating time and probable higher complication rate will unnecessarily deprive excellent conventional surgeons not to explore the advantages of laparoscopic approach.

Vaginal hysterectomy is truly minimal access surgery with less morbidity in expert hands. An Indian surgeon is blessed with the skill of vaginal surgery. However, there are many specific indications to do abdominal hysterectomy wherein a laparoscopic surgeon can achieve skill of performing total laparoscopic hysterectomy or LAVH with utmost care to minimize complication with marginal increases in surgical time.

No gynecologist should resort to laparoscopic hysterectomy for the glamor involved, to be called that he/she is also doing laparoscopic hysterectomy. Every gynecologist should compulsorily increase the vaginal hysterectomy skill, which is mandatory.

REFERENCES

Complications of endoscopic surgery can be divided into two groups:
1. Complications of the laparoscopic surgery
2. Hysteroscopic surgery.

CHAPTER 118
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(Chapter updated by Meenal Jain)

Complications of Endoscopic Surgery in Gynecology

Introduction
Over the last 20 years, laparoscopy has developed into a major tool in gynecologic surgery. Initially used as a diagnostic procedure in female infertility and for tubal sterilization, it now allows one to perform almost any surgery previously performed by laparotomy.

Despite the degree of caution used, complication often occurs in laparoscopy. Since the complications can occur in relatively easy procedures, it is imperative that all surgeons must learn to recognize the complications expeditiously and manage the events. The risks increase exponentially with the complexity of the procedures, the inexperience of the surgeon and with any deviation from the standard techniques. It is important to realize that as the operative laparoscopy becomes more complex, the ability to handle these complications endoscopically becomes a significant necessity.

Three national surveys conducted in the Netherlands, France and Finland included 25,764, 29,966 and 70,607 laparoscopic procedures, respectively. The total complication rates were 5.7, 4.6 and 3.6 per 1,000 procedures.

In this chapter, technical and general surgical aspects of laparoscopic complications, their management and recommendation for prevention will be described.

Prevention
Following are some key points on prevention and thus avoiding complications:
- Thorough preoperative evaluation and consultation
- Proper patient selection
- Familiarity with normal and abnormal anatomy (Figs 1A to E)
- Be familiar with instrumentation and energy sources
- Be sure to have a properly trained assistants and operation theater (OT) staff
- Always have adequate pneumoperitoneum before insertion of trocar
- Always have adequate incision
- Place patient below the waist level of the surgeon and ensure proper patient positioning.

Contraindications
In some patients, laparoscopy may not be appropriate. However, improvement in laparoscopic skills and experience, combined with the availability of the proper instruments, had reduced the number of conditions that are considered absolute contraindications for laparoscopy. These conditions include obesity, severe adhesions, previous abdominal operations, cancer, abdominal hernia, pregnancy, hypovolemic shock and bowel perforation with generalized peritonitis.

Complications of Laparoscopic Surgery
Complications can be divided into few major categories:
- Anesthesia related
- Veress needle and trocar related
Endoscopy

Anesthesia-related Complications

Possible intoxication from absorption of carbon dioxide ($CO_2$) gas, extreme Trendelenburg and increasing intra-abdominal pressures during laparoscopy may compromise patient. A vasovagal reaction and cardiac arrhythmias developing from $CO_2$ absorption are avoided by administering atropine preoperatively. Difficulties in ventilation result from a steep Trendelenburg position, high intra-abdominal pressures and obesity.

Reconditioning laparoscopic gas by filtering, heating and hydrating the gas may reduce or eliminate laparoscopically induced hypothermia, shortening recovery room, length of stay and reducing postoperative pain.
Arrhythmias, including junctional rhythm, bradycardia, bigeminy and asystole, have been associated with CO₂ insufflation of the abdomen. Bradycardia results from pressure on the peritoneum with an increased vagal response.

**Veress Needle and Trocar-related Injuries**

Injury by Veress needle or trocar by far is the most common of all complications in laparoscopy. The possibility of complication is increased during the insertion of the Veress needle and primary and secondary trocars in patients with multiple previous laparotomies, very obese, and very thin patients. Bowel preparation is recommended if there is a risk of bowel injury. Veress needle and trocar insertion is modified in the presence of a large pelvic mass, e.g. large fibroid uterus, hematometra, endometriomas, etc. Various studies suggested that about half the complications occur during the insertion of the Veress needle and laparoscopic trocars.

**Veress Needle**

Intra-abdominal placement of the Veress needle is required to establish a pneumoperitoneum. Since the Veress needle is inserted “blindly”, it can enter inappropriate spaces or puncture organs or can cause major vessel injury. Further instillation of CO₂ under pressure through the Veress needle can create serious complications, e.g. if the tip of Veress needle is placed in a blood vessel then patient can have gas embolism. Gas embolism initially presents as cardiorespiratory distress with cardiac bradycardia or arrhythmia. A large vessel injury caused by Veress needle requires immediate laparotomy.

Factors increasing the risk of perforation or laceration include bowel adhesions, lateral displacement of the needle during its insertion.

When an upper abdominal site is used to establish a pneumoperitoneum, the needle can puncture the pleural cavity, stomach, liver or spleen. The stomach becomes distended after prolonged manual ventilation with a mask, or when endotracheal intubation is difficult. The stomach can be punctured even with umbilical placement of the Veress needle. A nasogastric tube lessens the risk of gastric distention. An overdistended bladder also is at risk of injury. Routine placement of a Foley catheter before the procedure should eliminate the risk of bladder injury.

Veress needle injuries generally are not apparent until CO₂ insufflation or after the insertion of the laparoscope. Abnormally high insufflation pressures are encountered if the needle is misplaced.

When the initial flow rate or intra-abdominal pressure is high, elevating the abdominal wall can correct the placement of the needle, particularly if initially it was placed within the omentum. If the pressure does not fall immediately to normal levels, the needle is withdrawn and examined to confirm that the spring action of the device works properly and no tissue is occluding the tip. If a second placement attempt fails, consideration is given to insertion of the needle at another site, open laparoscopy, or direct trocar entry.

Puncture of a hollow viscus with the Veress needle generally does not require any active surgical management.

**Subcutaneous Emphysema**

Subcutaneous emphysema is reported to occur during laparoscopy at a rate between 0.4% and 2%. This phenomenon results from improper positioning of the insufflation needle. The introduction of CO₂ into the preperitoneal space will allow its dissection up along the anterior chest wall, neck and face. The diagnosis made by the palpation of the CO₂ bubbles under the skin. It is not a major complication, but the distension of the preperitoneal space could occupy the operation area and thus make the exposure of organs more difficult. Preventing this complication is easy, by respecting the technique of introducing the insufflation needle and respecting the limits of the insufflating pressure.

If this is recognized early, the CO₂ line is disconnected and the gas is allowed to escape. If this is not recognized early and enough gas is instilled, the preperitoneal gas collection will be discovered after trocar placement and insertion of the laparoscope. The spiderweb appearance of the tissue becomes apparent and gas is allowed to escape before the surgeon attempts to reinsert the needle. Preperitoneal insufflation can extend to the mediastinum and endanger cardiac function. If this occurs, the laparoscopy is stopped and the gas is allowed to escape.

**Soft Tissue Emphysema**

Subcutaneous emphysema most commonly results from preperitoneal placement of an insufflation needle or leakage of CO₂ around the cannula sites, the latter frequently because of excessive intraperitoneal pressure. Although the condition is usually mild and limited to the abdominal wall, it can become extensive, involving the extremities, the neck and the mediastinum. Another relatively common location for emphysema is the omentum or mesentery.

*Diagnosis:* Often the diagnosis of subcutaneous emphysema is not a surprise because the surgeon may have had difficulty positioning the insufflation needle, primary cannula, or both, within the peritoneal cavity. Subcutaneous emphysema may be readily identified by the palpation of crepitus in the abdominal wall; if it extends along contiguous fascial planes to the nick, it can be visualized directly. This finding can be a reflection of the development of mediastinal emphysema, which, if severe, may lead to pneumothorax and cardiovascular collapse.

*Risk reduction:* The risk of subcutaneous emphysema is reduced by proper positioning of an insufflation needle, if the needle is used. No one test absolutely predicts intraperitoneal placement. A variety of tests, such as aspiration, creation
SECTION between the anterior abdominal wall and the pelvic viscera, an adequate pneumoperitoneum provides a safe distance of the large diameters of trocars. Aorta and inferior vena cava) are potentially serious because insertion (small intestine, colon, large blood vessels, e.g. punctures or lacerations of pelvic structures during trocar insertion (small intestine, colon, large blood vessels, e.g. aorta and inferior vena cava) are potentially serious because of the large diameters of trocars.

An adequate pneumoperitoneum provides a safe distance between the anterior abdominal wall and the pelvic viscera, but trocar injuries can result from poor technique or adherent bowel. Excessive force while inserting the trocar can be caused by an inadequate umbilical incision, scar tissue, or a dull trocar. Uncontrolled sudden entry of the trocar, its lateral displacement during insertion and too steep an angle for placement increase the risk of injury. Even with meticulous technique, abdominal wall bleeding, hollow viscus perforation, blood vessel laceration, and liver and spleen injury can occur.

The trocar should be pyramidal-tipped and sharp to penetrate muscle and fascia. Establishing a large pneumoperitoneum and elevating the abdominal wall to increase the distance between the abdominal wall and the viscera decrease the chance of intestinal and vascular injury. The syringe test can indicate the presence of adhesions. Nezhat et al. showed that direct insertion of the umbilical trocar without prior pneumoperitoneum is safe.

Recognition
When the trocar is removed, signs of complications requiring immediate evaluation are bleeding from the trocar sleeve or a fecal odor. Insertion of the laparoscope allows assessment of the injury. If the laparoscope enters the bowel lumen, the instrument is left in place to prevent the escape of bowel contents and help to locate the injury.

Small bowel injuries caused by trocars can be repaired in one layer by using 3-0 silk or 2-0 vicryl without complication or laparotomy. Injuries less than 2 cm (small or large bowel) may be repaired transversely or longitudinally; however, injuries more than 2 cm should be repaired transversely. Repair of bowel perforation should be done with intra-abdominal laparoscopic suturing.

For small colonic wounds associated with minimal contamination, laparotomy with primary suture closure has been the accepted therapy. In addition, copious lavage of the peritoneal cavity, broadspectrum antibiotics and drainage minimizes the risk of infection. Under the proper circumstances, a small wound to the colon may be closed through the laparoscope. Copious irrigation and antibiotic coverage are essential.

Vascular Injuries
Major vascular injuries include lesions of the principal vessels, arteries and veins. Perforation of the aorta, vena cava, common right and left iliac arteries and veins superior mesenteric and inferior epigastric vessels has been reported (Figs 2A to C).

A vascular injury is suspected in the presence of one of these signs:
1. Return of blood from the open insufflation needle.
2. Sudden deterioration in blood pressure of a previously stable patient after needle or trocar insertion, especially if the positioning of the needle was difficult.
3. The presence of an unexplained volume of blood in the peritoneal cavity, and if this blood reappears after aspiration.
4. Hematoma in the retroperitoneal space.

Intraperitoneal CO₂ pressure on the bleeding vessels and decreased venous return caused by the steep Trendelenburg position may explain the failure to recognize the injury during the laparoscopy itself.

**Management**

If vascular injury with the insufflation needle is strongly suspected, the needle is left in place to help mark the site of injury while an expeditious midline incision is made for laparotomy. A trocar injury of the major vessels is more serious. Usually, in the case of a major vessel injury, the retroperitoneal hematoma occupies all of the fields of view, and once laparotomy is performed, the first priority is the compression of the aorta. This can be accomplished with the hand or with a vascular clamp and may reduce the bleeding until a vascular surgeon arrives. If bleeding is very minimal, endoscopic repair must be considered for small vessels, but laparotomy is necessary for major vessel injury.

The bleeding from minor vessels is controlled by bipolar coagulation or with laparoscopic suture (Figs 3A to D). It is rare that the bleeding necessitates a laparotomy (Figs 4A and B). Bleeding from the uterine artery can be controlled by bipolar coagulation (Figs 5A and B).

**Epigastric Vessel Perforation by Secondary Trocars**

Perforation of the inferior and/or superficial epigastric vessels is the most common complication encountered during laparoscopic surgery. The inferior epigastric artery extends from the external iliac artery and lies beneath the rectus muscle and above the peritoneum. If injured, these large vessels can produce a rapid and massive hemorrhage. Injured inferior epigastric artery creates retroperitoneal or intraperitoneal bleeding.

An essential rule to bear in mind is that the sleeve cannot be removed, as it is the only mark of the vessel’s location. In case of minimal bleeding and a small hematoma, no repair is required. Sometimes, the bleeding can be extremely swift, and repair using several techniques might be necessary. Both ends of the transected vessel must be secured for an adequate hemostasis. Bipolar coagulation of the vessel through the peritoneum is the best and fastest way to ensure optimal hemostasis. Hemostasis can also be achieved by simple compression. As soon as the swift bleeding is noticed around the sleeve, a number 12 Foley catheter is passed through the sleeve into the abdominal cavity. The Foley balloon is inflated with fluid. The sleeve is pulled out and the Foley balloon is pulled up against the abdominal wall. The pressure maintained on the Foley balloon occludes the bleeding vessel. As soon as hemostasis is obtained, a second trocar is
Fig. 3A: Removal of lymph nodes from obturator fossa in a case of radical hysterectomy

Fig. 3B: Bleeding occurred from vessels from obturator fossa

Fig. 3C: Bleeders coagulated with bipolar forceps

Fig. 3D: Bleeding controlled in obturator fossa

Fig. 4A: Prolene mesh is at the sacral promontory in the case of vault prolapse

Fig. 4B: Bleeding occurred from the presacral vessels while dissection was done at sacral promontory
inserted and the operation can continue. In some rare cases, hemostasis cannot be achieved, the skin incision must be enlarged around the trocar sleeve and the vessel promptly secured by ligature.

**Small and Large Bowel Injury**

Injury of the small bowel may occur during dissection of adhesions. Furthermore, electrosurgery or laser may create unrecognized thermal lesions which will become apparent after 48–72 hours with peritonitis. Nezhat reported that superficial intestinal burns less than 5 mm in diameter can be managed in anticipation of this complication. When a frank bowel perforation is present, laparotomy is indicated for transverse suture or for resection of the necrotic zone and reanastomosis.

Electrical injury to the right colon is managed by resecting the injured segment and doing a primary anastomosis. Diverting ileostomy facilitates healing and reduces morbidity and mortality. Injury to the descending colon, sigmoid, or rectum in unprepared bowel is not amenable to primary closure or resection with primary anastomosis. Diverting colostomy with resection of the injured portion is recommended.

Colonic or rectal lacerations in prepared bowel can be repaired laparoscopically. A single layer repair using 2-0 vicryl suture is done (Figs 6A to C).

**Urinary Bladder Injury**

The bladder could be injured during the dissection from the pubocervical fascia. Electrocoagulation or laser increases the possibility of occult damage of the bladder during laparoscopic hysterectomy. Previous cesarean section and endometriosis could increase the likelihood of this complication. The presence of gas and blood in the urinary bag allows early recognition of bladder perforation. In suspicious cases, a cystoscopy or filling the urinary bladder with methylene blue dye may highlight a lesion intraoperatively.

Since trocar injury often involves entry and exit punctures, locating both is important. Some bladder complications become apparent postoperatively, particularly those caused by electrocoagulation. If a vesical injury is suspected, a retrograde cystogram may reveal the defect.

Small holes in the bladder generally heal without sequelae. Trocar injuries to the bladder dome require closure followed by urinary drainage for 5–7 days. Drainage promotes healing, encourages spontaneous closure, and reduces further complications. Lacerations may require a laparotomy, although some laparoscopists repair the laceration laparoscopically. Bladder injury can be managed laparoscopically by using vicryl 2-0 with continuous suture in single layer followed by bladder drainage by Foley catheter for 5–7 days (Fig. 7).

**Ureteral Injury**

Ureteral injuries during laparoscopic hysterectomy or other complex surgery must be considered as one of the surgeon’s major concerns. The course of the ureter should be evaluated through the peritoneum before surgical maneuvers. In some cases, retroperitoneal dissection evaluating the portion close to the uterosacral ligaments is indicated. Lesions of
the ureter may occur during sharp dissection, electrosurgery or laser for uterine arteries or the isolation of uterosacral ligaments. Adhesions, endometriosis or myomas may alter the anatomical course of the ureter and cause inadvertent ureteral injuries. The diagnosis of a ureteral lesion is generally made 48–72 hours postoperatively with pelvic pain and peritonitis. An intravenous pyelogram is indicated for final diagnostic assessment. Reanastomosis of the ureter should be performed with the urologist. Some surgeons report surgical repair through laparoscopy (Figs 8A to F).

Whether the discovery of ureteral complications is immediate or delayed, a urologist should be consulted. If the intravesical pressure (IVP) indicates ureteral injury, initial therapy should involve attempts at retrograde or antegrade stenting. Therapeutic options by laparotomy include ureteroureterostomy and ureteroneocystostomy. Both require stenting and drainage with a ureteral catheter.

A patient who had a long-term ureteral obstruction caused by endometriosis needed an incidental partial resection of the ureter laparoscopically. A laparoscopist familiar with delicate laparoscopic suturing can repair ureteral injuries laparoscopically with good results.

**Uterine Injuries**

Complications involving the uterus include cervical lacerations or uterine perforation from sounding the uterus and the use of a uterine dilator or uterine manipulator. Cervical lacerations are treated with pressure from a sponge stick or are sutured. Bleeding from uterine perforations is controlled with bipolar electrocoagulation or observed.

**Bleeding**

Uncontrolled bleeding and hemorrhage are the cause of most emergency laparotomies. Bleeding occurs during sharp
Fig. 8A: Urinary bladder is mobilized from the anterior abdominal wall

Fig. 8B: Bladder is hitched with psoas tendon

Fig. 8C: Bladder is opened

Fig. 8D: Submucosal tunnel is made in bladder

Fig. 8E: Ureter is pulled through submucosal tunnel

Fig. 8F: Ureter is stitched with bladder
dissection of adhesions, transection of vessels during excision or dissection and rough handling of tissues. Lacerations of the oviduct, mesosalpinx and infundibulopelvic ligament can bleed profusely. Distorted anatomy is an important compounding factor in many cases of major retroperitoneal vascular injury.

When pressure gradients return to normal, bleeding into the intraperitoneal or retroperitoneal space may begin, eventually leading to hematomata and hypovolemic shock. All exposed vessels should be evaluated at the end of the procedure with the patient is lying in supine position and intra-abdominal pressure reduced. Blood clots in the pelvic side wall should be evacuated before complete hemostasis is confirmed.

Unipolar and bipolar electrocoagulators, vasopressin, clips, sutures and loop ligatures should be available to control bleeding. The choice of methods depends on the surgeon’s preference.

**Complication due to Carbon Dioxide Gas Insufflation**

Venous air embolism is a complication in laparoscopy that can happen at any time during the surgical procedure. In gynecological procedures, venous air embolism is usually sudden, and therefore, it is crucial to detect it immediately. Any delay in exsufflation and treatment can prove to be fatal.

Clinical signs such as decreased blood pressure, tachycardia, arrhythmia and increasing central venous pressure come too late to be useful as warning signals. An easy and noninvasive way of embolism detection is measurement of end-tidal CO₂. As soon as the end-tidal CO₂ drops, abdominal pressure must be immediately reduced. If this maneuver is not followed by an increase in end-tidal CO₂ or if there is any sign of cardiovascular problems, venous air embolism must be considered to have occurred and appropriate measures must be taken.

The patient should immediately be ventilated with 100% oxygen to prevent hypoxemia. The Trendelenburg position should be maintained and the pneumoperitoneum emptied. A large catheter must be inserted into the right atrium through the internal jugular vein to aspirate the gas.

**Incisional Hernias**

Herniation of the small bowel or the omentum through the trocar incision is a complication of laparoscopy well described in the literature. The risk increases with trocars greater than 10 mm in particular.

Mostly, hernias occur after 1 week of surgery. However, some cases of early herniation in the postoperative phase are known. Indeed, if reversal of the general anesthesia is too early at the end of the surgical procedure, herniation can be precipitated by the coughing movements of the patient. Symptoms of incisional hernia are (chronic) pain in the region where the trocar has been inserted and the classic symptoms of bowel obstruction (nausea, vomiting, pain).

If incisional herniation is suspected, a laparoscopy must be performed to reduce the hernia. Sometimes, bowel resection is necessary if the tissue is necrotic.

One source of confusion in the literature is the lack of distinction among the terms evisceration, wound dehiscence and true hernia, nomenclature that seems to be used interchangeably. Indeed, the distinction may be moot as dehiscence of a laparoscopic wound may be irrelevant unless bowel or other intraperitoneal tissue herniates into and through the defect. One of the more sinister complications, involving only a portion of the bowel wall is Richter’s hernia, which is some what more difficult to diagnose and may result in perforation, peritonitis and death.

**Diagnosis**

The most common defect appears immediately postoperatively when bowel or omentum passes through the unopposed or inadequately repaired incision. The patient may be asymptomatic or can present with pain, fever, periumbilical mass, obvious evisceration, and signs of mechanical bowel obstruction, or a combination of these factors often within hours and usually within the first postoperative week. Because the patients are usually discharged shortly after surgery, the symptoms usually manifest when the patient is at home; reporting of symptoms is often by telephone. Consequently, the surgeon should take care not to casually disregard the patient who telephones to report symptoms consistent with herniation.

Because Richter’s hernia contains only a portion of the circumference of the bowel wall in the defect, diagnosis is often delayed. These lesions probably occur most commonly in incisions made away from the midline. The initial presenting symptom is usually pain because incomplete obstruction allows some passage of intestinal content. Fever may be present if incarceration occurs, and peritonitis may result from subsequent perforation. The diagnosis is difficult and requires a high index of suspicion. Ultrasound or computed tomography (CT) scanning may be useful in confirming the diagnosis.

Many defects probably remain asymptomatic, but late presentation may occur if bowel or omentum has become trapped. The symptoms and findings are similar to symptoms for earlier presentations.

**Risk Reduction**

Whenever possible, the smallest diameter cannulas should be used; hernia has been reported in conjunction with the use of 5 mm trocars. The Z-track insertion method offsets skin and fascial incisions, which potentially reduces the incidence of hernia. The subcutaneous tissue is entered with a conically tipped trocar that is slid along the fascia for a short distance.
4. Infection.
3. Distension medium complications
2. Hemorrhagic complications
1. Traumatic complications

To avoid them, there are four groups of complications of hysteroscopic surgery:

**Complications of Hysteroscopic Surgery**

Although complications are infrequent, their description helps us to understand their causes and thus take steps to avoid them. There are four groups of complications of operative hysteroscopy:

1. Traumatic complications
2. Hemorrhagic complications
3. Distension medium complications
4. Infection.

**Traumatic Complications of Hysteroscopy**

Dilating the cervix to accommodate wide-caliber operating instruments may cause cervical laceration and/or uterine perforation, with or without hemorrhage.

Cervical lacerations are diagnosed only if cervical bleeding occurs. Uterine perforation is suspected if the depth of passage of the sound or the dilator is greater than the apparent size of the uterus. Very rapid flow of liquid or very low distension pressure with CO₂ at the time of insertion of the hysteroscope should raise this suspicion. Diagnosis is sometimes made by visualization of the bowel. Any hemorrhage before the beginning of the surgical procedure is highly suggestive of traumatic damage.

**Management**

If perforation is diagnosed before the surgical procedure, surgery must be delayed and the patient observed for 24 hours. If perforation is diagnosed intraoperatively or after the surgical procedure, a diagnostic laparoscopy is recommended to ensure that no damage has been caused to adherent or adjacent structures and that there is no unsuspected laceration of the large blood vessels.

Patients benefit from preoperative cervical softening or dilation. Clinically, 200 µg of vaginal misoprostol inserted intravaginally prior to surgery was associated with a reduced need for cervical dilation, minimized cervical complications and reduced operative hysteroscopic time in comparison to women given placebo. Other authors have also found oral misoprostol 100–400 µg, taken 8–12 hours before the procedure equally effective in softening and dilating the cervix.

**Hemorrhagic Complications of Hysteroscopy**

Intraoperatively, rapid bleeding can be controlled by coagulation, using electrical loop. Postoperative and uncontrolled intraoperative bleeding may sometimes require intrauterine tamponade. A Foley catheter is introduced into the uterine cavity and the balloon is inflated with 15 mL of liquid. After approximately 3 hours, one-half of the liquid is removed; if no bleeding recurs over the next hour, the catheter is removed and the patient is usually discharged. If active bleeding recurs, the balloon is re-inflated and left in place overnight.

**Types of Fluid and Distention Media**

**Fluid Management**

Poor visualization precludes any intrauterine investigation or procedure. The uterine cavity is a potential or virtual space and it is critical for good visualization to adequately distend the organ under study. Otherwise, visualization is analogous to that of the inside of a collapsed balloon. The distending pressure may also provide a measure of hemostasis.
At this time, three media for distending pressure are in common use: gas (CO₂); low-viscosity electrolytic fluids (saline and lactate, which cannot be used with electrical power) and low-viscosity non-electrolytic fluids (5% and 10% dextrose, glycine, sorbitol/mannitol), and high-viscosity fluids (dextran 70).

Carbon dioxide: Today, CO₂ is primarily used for diagnostic procedures and is used mostly in the office setting. Bubble formation and frothing from blood or mucus in operative procedures obscure visualization, thus CO₂ is not suitable for operative procedures. Moderate CO₂ absorption by the patient may cause metabolic acidosis and cardiac irregularities. Massive absorption can be fatal and is associated with a characteristic “metallic” or “mill wheel” murmur. Early recognition is mandatory and aspiration of the CO₂, particularly from the right heart with the patient in the left lateral position, may be lifesaving.

Preventive measures include pressures of less than 120 mm Hg, flow metering as low as 100 mL/min, and the ++.

Use of CO₂-cooled sapphire tips and laser fibers has been contraindicated by the Food Drug Administration (FDA) because of reports of fatal CO₂ emboli from the high flow rates and volumes generated. Nitrous oxide (N₂O) is unsuitable for hysteroscopy.

Fluids: Fluid under pressure is absorbed through the uterine vasculature. The amount absorbed depends on fluid pressure in the uterus as controlled by inflow and outflow pressures, the patient’s mean arterial pressure, the balance between these pressures, tightness of the cervical collar, and most important, the integrity of the vascular compartment. Vulgaropoulos and colleagues demonstrated that one critical factor is trauma (not only pressure) because reducing pressure does not prevent intravasation, if the vascular compartment has been breached through surgery, perforation, or cervical tears. Complex surgeries and longer surgeries allow more intravasation, thus operator experience is also a factor.

The fluid may be delivered by gravity (3” = 75 mm Hg), pressure cuff, hypodermic syringe, or pump. The pump should be one of constant pressure with variable flow. Collection of fluid outflow should be through a continuous pressure cuff, hypodermic syringe, or pump. The pump may be cooled sapphire tips and laser fibers has been contraindicated by the Food Drug Administration (FDA) because of reports of fatal CO₂ emboli from the high flow rates and volumes generated. Nitrous oxide (N₂O) is unsuitable for hysteroscopy.

Early detection and active management of over absorption is critical and quite complex because the mechanisms are different for low- and high-viscosity fluids.

Low-viscosity fluids: Transurethral resection of prostate syndrome (TURP) has long been recognized by urologists and occurs in 5–10% of their cases. The condition is not strictly analogous because the uterus represents a tough muscular resistance that requires more pressure for distention, but we have learned lessons from our colleagues. The original distending fluid was sterile water, which 50 years ago was shown by Creevy to cause an intravascular hemolytic reaction. Even at that time, saline was discounted as a distending medium because it is electrolytic and renders ineffective the diathermy current of the resectoscope.

Patients with TURP present with diastolic hypertension and bradycardia, followed by hypotension, headache, nausea, vomiting, visual disturbances and confusion. If untreated, patients progress to coma, convulsions and death.

The pathophysiology of overabsorption of glycine, sorbitol/mannitol and dextran 70 is well described in a superb review by Witz et al. Low-density fluid overload results in hypervolemia and hyponatremia followed by hypoosmolality and an excess of free water because the glycine is absorbed intracellularly, very quickly. Hyponatremia may cause unpredictable, irreversible brain damage and respiratory arrest very suddenly; prompt intervention is critical and expectant treatment is unacceptable.

Treatment of water intoxication involves removal of excess fluids and correction of hyponatremia, but the speed of correction of the hyponatremia remains problematic. Because of the unpredictable nature of choice, both water and electrolytes are mobilized. Sodium levels must be followed carefully. If hyponatremia is detected early, normal saline administered slowly may be helpful. A paradox exists, however too rapid correction may lead to an osmotic demyelinating syndrome called central pontine myelinolysis (CPM). The brain seems to tolerate best moderate correction during the first 24 hours. If this method is used, brain dehydration and demyelination may not occur. Late detection with the same treatment after 3 days may lead to myelinolysis and death.

Glycine may also cause ammonia toxicity and crystals in the urine. There may also be changes in visual acuity and blindness.

Hypothermia has been reported in extended cases with the use of large fluid volumes.

High-viscosity fluids: Thirty two percent dextran 70 in 10% glucose (hyskon) has long been used as a plasma expander; it is slowly metabolized and removed during a period of several days through the reticuloendothelial system. Dextran 70 has the marked advantage of being immiscible with blood and providing excellent visualization. It is, however, very sticky, instruments must be cleaned promptly and thoroughly for their preservation. Carmelization of dextran 70 may occur from the heat of electrocoagulation or lasers.

Dextran 70 has a variety of serious metabolic complications and its use is becoming less popular. On entering the vascular compartment, 300 mL (the usual limitation on absorbed dextran 70) increases the circulating volume by 3,000 mL. Dextran 70 increases oncotic pressure intravascularly and draws water and electrolytes into the circulatory space, which leads to pulmonary edema. Some experts attribute the pulmonary edema to noncardiogenic effects, namely a direct toxic effect on the pulmonary vasculature. There are also case
report of anaphylactic shock, disseminated intravascular coagulation, and adult respiratory distress syndrome. Renal failure and anuria may develop.

Management of dextran 70-induced pulmonary edema is difficult because the fluid overload is not easily handled. Diuresis alone does not confront the oncotic overload and dialysis is ineffective. Plasmapheresis may be necessary in intractable situations. Anaphylaxis is treated with antihistamines, hydrocortisone, pulmonary support and epinephrine. A "dry" (underhydrated) patient may have relative protection. Prevention is the key.

Meticulous tracking of fluid absorbed is essential. The amount of fluid absorbed varies according to the procedure, the pressures used and the experience and speed of the surgeon. With low-viscosity fluid, one should measure electrolytes, particularly sodium, before the procedure and keep pressure as low as possible to acquire good visualization. The patient’s fluid balance must be measured every 15 minutes and the procedure must be terminated if excessive absorption occurs (1,000 mL in healthy women, 750 mL in older women). Some studies report adding ethanol to the fluid. A breathalyzer can be used to measure absorption.

Although use of dextran 70 is decreasing, it is still a useful medium. As noted, limits of 300 mL on absorption or a 45 minutes limit on operating time have been suggested.

The search for an ideal distending medium continues. A fluid with the characteristics described by Creevy—clarity, nonconductivity, a fluid immiscible with blood, and low incidence of side effects—is still being sought.

Irrigation Complications

If a monopolar instrument is used, then 1.5% glycine should be used. Bipolar operative hysteroscopy can be performed using saline or Ringer’s lactate solution.

Classic hallmarks of fluid overload leading to cerebral edema include: mental agitation, apprehension, confusion, weakness, nausea, vomiting, visual disturbances, blindness and headache. If left untreated and unrecognized, bradycardia and hypertension develops rapidly followed by pulmonary edema, cardiovascular collapse and death. Additionally, glycine 1.5% is metabolized to glycolic acid and ammonia. Free ammonia also contributes to central nervous system disorders. Recognition and prompt treatment by a critical care specialist may prevent permanent neurologic sequelae, death and law suits.

Modern gynecologic suits have employed fluid irrigation systems that rapidly measure input and output on a continuous basis.

The monitoring of intake and output of liquids during and after the procedure is mandatory to assess the fluid balance. A discrepancy of 1,000 mL requires assessment of serum electrolytes to permit diagnosis. If a discrepancy of 1,500 mL is noted during surgery, the procedure must be stopped immediately.

If the serum sodium level is normal and the patient has no particular complaint, no further treatment is necessary. In the case of decreased sodium levels and hemodilution, the patient should observe fluid restrictions and intravenous diuretics (furosemide) should be administered.

In cases of severe hyponatremia causing neurological symptoms, perfusion of hypertonic saline solution is required.

Infection

Pelvic inflammatory disease (PID), necrotic residual tissue, multiple insertions of the endoscope, long procedures and extensive endomyometrial destruction place a patient at increased risk. In general, prophylactic antibiotics are not routinely used unless the patient has a history of artificial joints, documented mitral valve regurgitation, or prior history of PID.

Mechanical Problems

Perforation

The most common single complication is perforation, occurring in 2% of patients. Benign predisposing factors are acutely retroverted or anteverted uterus, uterine atrophy or hypoplasia and cervical stenosis. Pathologic disposing factors confound the usual uterine landmarks and include adhesions and distortions from fibroids, particularly of the cervix and lower uterine segment; structural abnormalities; carcinoma; and the T-shaped uterus of the diethylstilbestrol-exposed patient. Complications related to perforation are similar to those for dilation and curettage (D & C), namely, cervical perforation and fracture, uterine false passages and perforation at the time of dilatation or by the hysteroscope itself.

All perforations are serious, but they are more problematic if electrical or laser power is being applied at the time of the perforation or if the injury is made with sharp instruments. Most important, perforations greatly dispose introduction of distending media, gas or fluids, into the patient’s circulatory system, which results in metabolic problems.

Technique

Careful patient selection after complete history and physical examination is important; inappropriately selected patients may very quickly result in problems. Every surgeon must be familiar with all the equipment, should be able to troubleshoot, and assemble the instruments and video equipment, if necessary. The use of a constant-pressure pump with variable flow for the distending medium maximizes visualization.

Positioning of the patient is important. Poor position unnecessarily complicates placement of the speculum and alters the angle of approach. Pressure on the patient’s peroneal nerve may cause footdrop, thus, the fibular head area must not be compressed. Extreme hyperflexion may
damage the femoral nerve and aggravate leg, hip, or back problems.

Ascertaining the true position of the uterus is mandatory because most perforations occur at the time of dilatation of the cervix. Anterior perforation of the lower uterine segment may occur if the uterus is unrecognizably and vice versa. Dilatation must be gentle and no force should be used. If necessary, ultrasound guidance is recommended. It is important to brace the dilator (e.g. with the little finger on the patient’s thigh) in all situations, but especially if there is cervical stenosis. An alternative is to “brake” the dilator at the depth premeasured by the uterine sound. Use of sounds and long dilators should be done with caution because the fundus may be inadvertently pierced in a small uterus. Laminaria, introduced the day before surgery, may be used to produce gentle and considerable dilatation to facilitate introduction of particularly large instruments.

If there is difficulty in introducing the hysteroscope, the patient’s cervix should be gently dilated to a larger diameter. Perforation may occur with introduction of the hysteroscope; the more serious perforations occur with larger scopes. Important technical precautions are: (1) advancement of the scope without force under direct vision, especially advancement beyond the level of the cervix; (2) good visualization with appropriate irrigation; (3) adherence to the principle of easy advancement to the fundus; and (4) panoramic review of the uterus as the scope is withdrawn. Incidentally, a single-toothed tenaculum is more likely to share through the cervical lip; a double-toothed tenaculum, seemingly more traumatic, may be preferable to prevent cervical tears.

Management

When a perforation is recognized, the procedure must be stopped immediately and assessment made of the anatomic site and the severity of the perforation. Most perforations are fundal or midline, and these areas have minimal vascular supply. Perforations in the lower uterine segment or into the adnexal or cornual areas are more significant and carry more risk of local vascular damage and damage to adnexal structures, bowel, urinary tract, omentum, and major vessels. Unrecognized perforations should be suspected if one is unable to maintain proper distention of the uterus.

If the perforation is caused by a blunt instrument in the midline, observation of the patient may suffice. The patient must be observed for evidence of bleeding by following vital signs, serial blood counts, pad counts (although the bleeding may be internal), and for signs of an acute abdomen, fever, or both.

The patient must be advised of the perforation, particularly if pregnancy is anticipated because there are numerous reports of uterine rupture in advanced pregnancy, especially with multiple gestations. The perforation and its management should be thoroughly documented by the surgeon.

CONCLUSION

Most studies consistently demonstrate the safety, effectiveness and high patient satisfaction rates with operative hysteroscopy. Currently, hysteroscopy is underutilized due to lack of training, hysteroscopic competence and unfounded fear of operative complications. Certainly, the uterine cavity, characterized by its small size, easy access and notable landmarks can be conquered. Surgical disasters and complications are minimized by expert preoperative evaluation.

BIBLIOGRAPHY

Miscellaneous
INTRODUCTION

Menopause is a natural process that occurs in women's lives as a part of normal aging. However, it is considered as an unwelcome phenomenon among many women. Partly this belief is due to misconceptions about menopause and partly due to the realistic reflection of social position of older women in our society.

MENOPAUSE

The word "menopause" is derived from Greek word "men" meaning month and "pauses" meaning cessation. Menopause is defined by the World Health Organization (WHO) and the Stages of Reproductive Aging Workshop (STRAW) working group as the permanent cessation of menstrual periods that occurs naturally or is induced by surgery, chemotherapy or radiation. Natural menopause is recognized if there is complete cessation of menstrual periods after 12 consecutive months that are not associated with a physiologic (e.g. pregnancy, lactation) or pathologic cause. It is physiologically correlated with the decline in estrogen secretion resulting from the loss of follicular function (Fig. 1).

PERIMENOPAUSE (FIG. 2)

The years prior to menopause wherein the change from normal ovulatory cycles to cessation of menses occurs are known as the perimenopausal transitional years. A more general and less precise term used for this period is climacteric (in Greek, climacteric = ladder). This period is marked by irregularity of menstrual cycles. The length of this period varies from 5 years to 10 years but it is usually considered to last approximately 7 years, beginning with the decline in ovarian function in the forties, and continuing until menopause.

The three classical ways in which the period ceases are:
1. Sudden cessation.
2. Gradual diminution in the amount of blood loss with each regular period until menstruation stops.
3. Gradual increase in the spacing of the periods until they cease for at least an interval of 6 months.
During the reproductive period most women have cycles that last from 24 days to 35 days, but at least 20% of women experience irregular cycles. However, when they are in their forties, anovulation becomes more prevalent. Prior to anovulation, length of the menstrual cycle increases, and may begin 2–8 years before menopause. It has been observed that when the cycle length exceeds 42 days, menopause predictably follows within 1 or 2 years. This period of longer cycles uniformly precedes menopause no matter when menses cease, whether menopause is early or late. This change in the menstrual cycle prior to menopause is marked by elevated follicle-stimulating hormone (FSH) levels and decreased levels of inhibin, but normal level of luteinizing hormone (LH) and slightly elevated levels of estradiol.

**Facts (International Menopause Society)**

Thousands of women reach menopause everyday:
- As many as 75% of women going through menopause experience hot flashes, insomnia. In about 30% of women, these symptoms can be severe.
- Menopause also can affect physical and mental health in positive ways for instance, symptoms of migraine headache or endometriosis may disappear after menopause, fibroids may shrink.

**AGE OF MENOPAUSE**

Based on cross-sectional studies, the median age is estimated to be somewhere between 50 and 52. The Massachusetts Women’s Health Study found that the median age of menopause was 51.3 years while Trelle et al. in their longitudinal study observed that 95% women reached menopause by 44–56 years, with an average of 50.7 years. Some of the Indian studies have found that average age of menopause is about 49–50 years.

**Factors Affecting Age of Onset of Menopause (Table 1)**

Earlier onset of menopause is associated with malnourished women, thinner women, lower education, low socioeconomic status, vegetarians and a high altitude. Finally, if a woman herself was a small for date baby whose growth pattern was restricted (intrauterine growth restriction, low birth weight) in late gestation, she may have an earlier menopause. Smoking has also being found as a cause of earlier menopause in many women.

Late onset of menopause is associated with prior use of oral contraceptives, obesity and frequent consumption of alcohol. There does not appear to be any relation between age at menarche and age at menopause.

In most of the studies, race, parity and height have no influence on age at menopause. Late menopause is also common in women suffering from uterine fibroids and in those prone to endometrial carcinoma.

**PREMATURE OVARIAN FAILURE**

About 1% of women have experienced menopause before age of 40 years, which is known as premature ovarian failure. The genetic relation of early menopause and premature ovarian failure has a dominant pattern of inheritance through maternal or paternal relatives.

**Premature Ovarian Failure and Abdominal Hysterectomy**

Premature ovarian failure can occur in women who have previously undergone abdominal hysterectomy or endometrial ablation, presumably because ovarian vascular flow has been compromised, but the only prospective study could find no elevation of FSH within the first 2 years after surgery.

**HORMONAL CHANGES (FLOW CHART 1)**

**Gonadotropins: Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH)**

During perimenopausal years, postmenopausal levels of FSH (> 20 IU/L) can be seen despite continued bleeding, while LH levels still remain in the normal range and there is risk of unexplained pregnancy until elevated levels of both FSH (> 20 IU/L) and LH (> 30 IU/L) can be demonstrated. Eventually, there is a 10- to 20-fold increase in FSH and approximately a 3-fold increase in LH after menopause. The changes in levels of female hormones with menopause are shown in Table 2.

**Estrogen**

Even though the amount of estrogen secreted from the postmenopausal ovary is negligible, postmenopausal women continue to have measurable amount of both estrone and...
estradiol. The average postmenopausal production rate of estrogen is approximately 45 µg/24 hours. The circulating estradiol level after menopause is approximately 10–20 pg/mL, most of which is derived from peripheral conversion of androstenedione. Obese women have higher levels of circulatory estrogen and hence are at a higher risk for endometrial cancer, though these levels provide some skeletal protection.

**Progesterone**

After menopause, progesterone production ceases. Decreased progesterone levels affect organs that are responsive to gonadal hormones, such as endometrium and breast. The protective effect of progesterone on endometrium (due to regulation of estrogen receptors as well as by inhibition of trophic effect of estrogen) is lost in postmenopausal period, which explains high-risk of endometrial hyperplasia and cancer found during this time.

**Androgens**

During the reproductive years ovaries produce approximately 50% of circulating androstenedione and 25% of testosterone. However, after menopause, total androgen production decreases mainly because of decrease in androgen synthesis by the ovaries and the adrenals. The androgen/estrogen ratio changes in favor of androgens drastically because of more marked decline in estrogen, and an onset of mild hirsutism is common, reflecting this marked shift in the sex hormone ratio.

**Surgical Menopause**

Instead of following the normal decline in hormonal output, surgery cuts off the ovarian contribution to total hormone levels dramatically and totally.

**Effects of Radiation**

The ovarian function may be suppressed by external gamma radiation in woman below age of 40 years. However, the castration is not permanent. The menstruation may resume in 2 years and even conception is possible. Intracavitary introduction of radium can cause destruction of endometrium. However, menopausal symptoms are not so severe as found in surgical menopause or menopause following external radiation.

**ANATOMICAL CHANGES**

**Uterus**

The uterus atrophies and becomes smaller. Fibroids, if present, become less symptomatic, sometimes shrinking to the point that they can no longer be palpated on pelvic examination. Endometriosis and adenomyosis, if present previously, are alleviated with the onset of menopause, and many patients with pelvic pain finally achieve permanent pain relief.

**Endometrium**

The endometrium is represented only by the basal layer with its compact, deeply staining stroma, and by a few simple tubular glands. The lymphoid tissue also disappears. It is common for some of the endometrial glands to become

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**Table 2: Changes in circulating hormone level at menopause**

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Premenopausal</th>
<th>Postmenopausal</th>
</tr>
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<tbody>
<tr>
<td>Estradiol</td>
<td>40–400 pg/mL</td>
<td>10–20 pg/mL</td>
</tr>
<tr>
<td>Estrone</td>
<td>30–200 pg/mL</td>
<td>30–7 pg/mL</td>
</tr>
<tr>
<td>Testosterone</td>
<td>20–8 ng/dL</td>
<td>15–7 ng/dL</td>
</tr>
<tr>
<td>Androstenedione</td>
<td>60–300 ng/dL</td>
<td>30–15 ng/dL</td>
</tr>
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</table>
cystically dilated even before menstruation has ceased and such cystic glands often can be demonstrated in the endometrium after the menopause.

**Cervix**
The cervix becomes smaller and its vaginal portion is represented by a small prominence in the upper part of the vagina.

**Ovaries**
The ovaries diminish in size and are no longer palpable during gynecologic examination. A palpable ovary on pelvic examination warrants a full evaluation in all women who are menopausal or postmenopausal. If it is measuring over 8 cm³, it is considered abnormal. Fifteen years after menopause, ovaries should measure less than 2 cm³.⁷⁻¹¹

**Fallopian Tube**
The plain muscle of the fallopian tube undergoes atrophy, cilia disappear from the tubal epithelium, and the tubal plicae are no longer prominent.

**Vulva and Vagina**
The vulva atrophies, and the vagina becomes smaller and tends to be conical with the apex of the cone in the situation of the cervix. The fornices gradually disappear as the cervix regresses after the menopause. With loss of estrogen, the vaginal epithelium appears inflamed because of thinning of the epithelial layer and increased visibility of the small capillaries below the surface. Later, as the vaginal epithelium further atrophies, the surface becomes pale because of the reduced number of capillaries. Due to the loss of protective effects of estrogen, it is readily infected and results in senile vaginitis. As the vaginal pH changes due to absence of the *Döderlein’s bacilli*, there is a change in the vaginal bacterial flora resulting in pruritis and a foul smelling discharge. These changes often result in dyspareunia and, for many women, eventually lead to sexual abstinence if left untreated.⁸⁻¹⁻²³⁻²⁵

**Labia and Pubic Hair**
The skin of the labia minora and of the vestibule becomes pale and dry, and there is a reduction in the amount of fat contained by the labia majora. The pubic hairs are reduced in amount and become gray.

**Pelvic Cellular Tissue**
There is loss of pelvic tone which manifests as prolapse of reproductive or urinary tract organs. Vaginal pressure, lower back pressure, or bulging at the vaginal introitus is common in women with prolapse. On examination, a cystocele, rectocele and uterine prolapse are found and this explains the cause of genitourinary symptoms.

**Urinary Bladder**
As the bladder undergoes atrophy during the menopausal period, it can result in atrophic cystitis. These women report symptoms of urinary frequency, urgency and incontinence.

**Fat Deposition**
Fat is deposited around the breasts, hips and abdomen. Although the mammary glandular tissue atrophies, the deposition of fat frequently makes the breasts more pendulous, thus, making mammography more difficult.

**Other Systems**
The skin becomes wrinkled and quite commonly hair grows round the lips and chin.⁴⁶ In most cases, the blood pressure rises, and cardiac irregularity and tachycardia sometimes occur. Arthritic changes often develop in the joints, and in some women a well-marked osteoporosis may be seen, particularly in the spine and pelvic girdle, which renders these bones liable to fracture.

**BEHAVIORAL CHANGES**

**Mood Swings**
Mood swings is characteristic of perimenopausal women rather than the postmenopausal women. Similar to the symptoms of premenstrual syndrome (PMS), these mood changes are also caused by changing hormone levels. However, during perimenopause, hormone levels rise and fall unpredictably and at times can make dealing with the changes more difficult. Luckily this is a temporary attribute of this transitional phase.

From observational studies, there is limited evidence that ovarian changes associated with menopause might be a cause of depression, anxiety and/or irritability. History of prior depression, stress and general health are the major predictors of mood symptoms during midlife. Because of the multiple potential causes of mood changes and the relatively high proportion of women reporting one or more of these symptoms, it is difficult to establish whether menopause causes any increase in the prevalence of mood symptoms during the perimenopausal years. The evidence from estrogen treatment trials is mixed, with only weak evidence of improvement in depression or anxiety relative to placebo for a small subset of moderately or highly symptomatic women treated with estrogens.

**Depression**
It is particularly common problem for women and older patients and accounts for more than 20% of visits of those
who seek medical care.\textsuperscript{47} Though depression is increased in perimenopausal period, studies have failed to show a relationship between clinical depression and hormone status.\textsuperscript{38} This suggests that many psychiatric symptoms occurring during this period may be more related to psychosocial and other life events than to change in hormone status.\textsuperscript{49}

**Anxiety and Irritability**

Many women report increased level of anxiety and irritability during the perimenopausal period and have become a prominent part of what sometimes is termed as climacteric syndrome.\textsuperscript{50} These feelings can be exacerbated by sleep deprivation as a result of vasomotor symptoms. Although a popular notion is that these are due to estrogen deficiency, multiple studies have failed to show the association.\textsuperscript{51,52}

**Decreased Libido**

This is a major concern for some women. Though the sexual activity remains relatively stable in menopausal women, only one-half of them report being sexually active.\textsuperscript{53} Vaginal changes associated with menopause may also contribute to decreased sexual satisfaction. Estrogen supplementation or vaginal lubricants [in cases where estrogen replacement therapy (ERT) is contraindicated] are useful. In some women, libido is often increased when the menopause is in progress, and is probably induced by a raised androgen secretion from the adrenal cortex.

**Neurological and Emotional**

Paresthesia, which takes the form of sensations of pins and needles in the extremities, is again extremely common. Headache and noises in the ears are complained of, while physical disturbances, which take the form of irritability, depression and even melancholia, are frequent.

**EFFECTS OF POSTMENOPAUSAL ESTROGEN DEPRIVATION**

**Amenorrhea**

The most obvious symptom of cessation of cyclic ovarian function is prolonged amenorrhea. This indicates that amount of estrogen produced by the ovaries is no longer enough to promote endometrial proliferation. But hormone replacement therapy (HRT) results in vaginal bleeding in most women.\textsuperscript{16,54-56} This effect is common cause of discontinuation of HRT and also can delay the diagnosis of malignancy.

Although, by definition, menopause is said to have occurred only 1 year after the cessation of menstruation, any woman who bleeds after a gap of 6 months must be considered to be suffering from postmenopausal bleeding and treated as such. Continuous bleeding, menorrhagia or irregular bleeding is not normal and must be investigated despite the common belief that they are “signs of change”.\textsuperscript{16,54-58}

**Vasomotor Symptoms (Hot Flashes and Night Sweats)**

**Hot Flash**

This is viewed as hallmark of female climacteric. This consists of sudden onset of reddening of skin over head, neck and chest, accompanied by a feeling of intense body heat and concluded by sometimes profuse perspiration. Duration varies from few seconds to several minutes and may recur as many as 30 times per day, although 5–10 times per day is more common.\textsuperscript{59} Flashes are more frequent and severe at night (referred to as night sweats) or during time of stress. Although hot flashes can occur in premenopause, it is a major feature of postmenopause, lasting in most women for 1–2 years but in some for longer than 5 years.

The physiology of hot flashes is still not understood, but it apparently originates in the hypothalamus and is brought about by estrogen deprivation. It is accompanied by a discrete and reliable pattern of physiologic changes.\textsuperscript{60} It coincides with a LH (not FSH) surge and is preceded by subjective prodromal awareness that a flash is beginning. These changes are probably secondary to hypothalamic changes in neurotransmitters that increase neuronal and autonomic activity.\textsuperscript{61} They also occur with a higher frequency and greater severity in younger women who undergo a sudden onset of menopause due to surgical removal of their ovaries or medical conditions or treatments that decrease the ability of ovaries to produce hormones.

**Treatment of Hot Flashes**

**Estrogen replacement therapy:** This results in resolution of hot flashes in most women in 2–3 weeks.

**Progestins:** In women for whom ERT is contraindicated alternative therapies like medroxyprogesterone (10–30 mg/day orally)\textsuperscript{62} or megestrol acetate (20–40 mg/day orally)\textsuperscript{63} are effective. The progestins act through the central neurotransmitter and raise the hypothalamic thermoregulatory set point.

**Alpha-2 adrenergic agonist:** Clonidine, an alpha-2 adrenergic agonist, is a nonsteroidal drug used for hot flashes in a dose of 0.1–0.2 mg BD. It works through both central and peripheral mechanism. Centrally, clonidine stabilizes the thermoregulatory center by altering the neurotransmitter and peripherally it blocks the cutaneous vasodilation. The other drugs in this group that can be used are alpha-methylldopa in a dose of 250 mg TDS and lofexidine 0.1 mg BD.

**Antidepressants:** A few well-designed, short-term studies with small numbers of participants have assessed the use of
antidepressants for the treatment of hot flashes. Results have been mixed. Some agents, such as paroxetine and venlafaxine, may decrease hot flashes to a moderate degree and improve quality of life for symptomatic women undergoing normal menopause, as well as for breast cancer survivors. Known adverse effects for antidepressants include diminished libido, insomnia, headache and nausea. Long-term effects are unknown.

Isoflavones and other phytoestrogens: A substantial number of studies of phytoestrogens and isoflavones have been conducted, motivated by epidemiologic data showing differences in levels of menopausal symptoms in countries with different levels of these nutrients in their diets. Because most of these products are not manufactured in a standardized way, they may differ in composition from trial-to-trial. Several studies of soy extracts suggested that they might have some mitigating effect on hot flashes.

Behavioral Interventions for Hot Flashes and Other Menopausal Symptoms

Behavioral interventions may be an important area of investigation for the treatment of menopause-related symptoms because adverse effects are rare. However, the effectiveness of such interventions has not yet been demonstrated in large, well-controlled studies. In several small studies:

- Exercise resulted in improved quality of life but did not affect vasomotor symptoms, vaginal dryness or other menopause-related symptoms.
- Health education resulted in improved knowledge about menopause and menopause-related symptoms but did not change the symptoms themselves.
- Paced respiration (a type of slow, deep breathing that requires training) for hot flashes showed early promise in a very small group of patients.

Sleep Disturbances

Changes in sleep pattern occur in both sexes with age. However, perimenopausal women experience increased sleep difficulties and insomnia, and may be related to estrogen deficiency.

Genitourinary Changes and its Treatment

Recurrent urinary tract infections are effectively prevented by postmenopausal vaginal estrogen therapy. Dyspareunia, sometimes with postcoital bleeding, is the inevitable consequence of a severely atrophied vagina and scanty lubrication. Although it is argued that the genuine stress incontinence is not affected by treatment with estrogen, some investigators showed improvement or cure in more than 50% of cases.

However, Heart and Estrogen/Progestin Replacement Study (HERS) indicated worsening of incontinence with HRT and Nurses’ Health Study reported a small increase of incontinence in hormone users.

Psychophysiologic Effects

The Women’s Health Initiative (WHI) study concluded that estrogen-progestin therapy had no beneficial impact on health-related quality of life. Thus, the overall “quality of life” reported by women can be improved by better sleep and alleviation of hot flashes.

Cardiovascular Disease

Cardiovascular disease (CVD) including coronary artery disease is a leading cause of death in old women and in recent past the number of deaths due to CVD for women has exceeded to those in men. One in five women suffers form some form of CVD.

Most CVD results from atherosclerosis, which has been associated with multiple causes like age, high blood pressure, smoking, diabetes mellitus, abnormal lipid profile and obesity. The risk for CVD increases for men and women throughout their lifetime. In premenopausal years, this risk is three times lesser for women as compared with men. For this reason, women lag behind men in incidence of CVD by 10 years and have an advantage of 20 years for myocardial infarction and sudden death. The reason for this protection can be assigned to high levels of high-density lipoprotein (HDL), an effect of estrogen and lower levels of testosterone.

After menopause, hypoestrogenemia is major and a treatable cause of CVD. Recent studies had shown that estrogen deficiency significantly increases risk of CVD and this risk may be reduced by HRT. Estrogen helps to maintain higher levels of HDL cholesterol; the level of which is strongest predictor of CVD in women.

Average HDL cholesterol level in women is 5–6 mg/dL and a decrease by 10 mg/dL increase CVD risk by 40–50%. Low levels of HDL cholesterol are also a component of metabolic syndrome related to insulin resistance.

Along with hypoestrogenemia, other risk factors mentioned above are also equally important. Probably most significant risk factors are hypertension (HTN) and smoking. Hypertension increases the risk by tenfolds and cigarette smoking by at least three-folds. To decrease CVD in postmenopausal women, screening for these risk factors must be performed and lifestyle changes must be recommended. These changes (smoking cessation and body weight reduction) have shown decline in smoking- and CVD-related morbidity and mortality.

Osteoporosis

Osteoporosis is decrease in bone mass with a normal ratio of mineral to matrix, leading to an increase in fractures. It is...
a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue with consequent increase in bone fragility and susceptibility to fracture.

WHO has defined osteoporosis as bone mineral density (BMD) 2.5 SD or more below the young adult peak mean, while osteopenia is defined as bone mineral density between 1 SD and 2.5 SD below the young adult peak mean.

Osteoporosis is a major global public health problem and is an epidemic not only in the developed countries but also in India. Along with tremendous increase in elderly population, less physical activity, a dietary decrease in calcium intake and smoking are the causative factors for greater bone loss.

At the age of 40, total bone calcium amounts to 1,200 g. When the critical level of 750 g is reached, the woman becomes susceptible to fracture. Bone resorption follows estrogen deficiency after menopause. The rate of resorption becomes higher than the rate of formation. The trabecular bone loss is more than the cortical bone loss and hence results in fractured vertebral bodies, distal radius and femoral neck. Although the rate of bone loss significantly increases at the time of menopause, the maximum incidence of osteoporosis-related fractures occurs several decades later. So, by the time sign of osteoporosis becomes apparent, treatment is difficult.

Pathophysiology

The cause of osteoporosis is multifactorial. Age is most important factor. The peak bone mass is gained at around 30 years of age. In perimenopausal women, bone loss is 1% of total bone tissue per year and increases as high as 5% postmenopausally. Heredity plays a major role to determine the peak bone mass and subsequent rate of bone mass. A family history of osteoporosis is a strong risk factor. Next important risk factor is estrogen status. Hypoestrogenemia has a direct effect on function of osteoblasts and appears to exert adverse effects by altering calcium balance. For women who do not take ERT after menopause have an accelerated rate of bone loss of about 3-5% per year. Exercise, avoidance of smoking and dietary supplementation of calcium are the protective factors.

Diagnosis

The vertebral bones, the distal end of the radius and the head of the femur bone are the most affected, causing vertebral bone compression, diminution in height and fractures like Colles’ fracture and fracture neck of the femur.

Measurement of Bone Mineral Density (Table 3)

For each degree reduction in standard deviation in bone mass, there is 50–100% increase in risk for fracture. Bone mineral density (BMD) should be measured in women requiring decision regarding HRT, smokers, who are on long-term glucocorticoids and to assess bone mass in postmenopausal women who present with fracture.

Standard X-ray does not provide an early assessment of bone loss and requires 30–40% reduction in bone mass. Other methods, which are more useful for this purpose are:

- Single-photon absorptiometry
- Dual energy X-ray absorptiometry (DEXA)
- Progamed computed tomography (CT).

Treatment

Hormonal treatment for osteoporosis is discussed in detail in other chapter. Excluding this other treatment options are—lifestyle modification, calcium supplementation, vitamin D supplementation, bisphosphonates and newer drugs like recombinant human parathyroid hormone (PTH).

Lifestyle modification: With so much awareness being generated about a better quality of life, it becomes necessary to review one’s lifestyle and see where changes can be made. These changes start with developing a positive attitude to life and include change of diet to a more healthier one and adaptation to an active pattern of life rather than a sedentary one. These can have significant effects on BMD and include weight-bearing exercise, running aerobics, stair climbing and sports. Cessation of smoking and excessive alcohol consumption also helps to improve the condition by decreasing the rate of bone loss.

Calcium supplementation: Calcium absorption decreases with age due to decrease in biologically active vitamin D. So to prevent osteoporosis a positive calcium balance is must. Daily calcium supplementation of 1,000 mg reduces bone loss and decreases fracture rate.

Milk and dairy products form main bulk of calcium in diet. Locally grown cereals like ragi which is cheaper and a very rich source of calcium can also be incorporated in the diet. Calcium is available in various forms in market like calcium carbonate, calcium lactate, calcium gluconate, calcium phosphate and calcium citrate. Citrate form does not require acidic media for absorption and is best choice in postmenopausal women.

Vitamin D: With the increasing age, synthesis of active form of vitamin D (vitamin D3) by skin and kidney decreases;
also intestinal absorption of vitamin D decreases. In postmenopausal women with osteoporosis, treatment with calcitriol (vitamin D3) produced a three-fold reduction in vertebral fractures.108 But one should remember that effective response to vitamin D requires adequate calcium intake.

**Bisphosphonates:** This group of drugs is effective preventing bone loss by enhancing osteoclast apoptosis and inhibiting bone absorption. First-generation drugs (etidronate) also inhibit bone mineralization and were given intermittently. Second-generation drugs (alendronate and risedronate) do not have this problem and can be given continuously, in fact are most commonly used drugs for prevention and treatment of osteoporosis.

Bisphosphonates are given 30 minutes prior to any other food (on empty stomach) and patient should maintain an upright posture for next 30 minutes to prevent esophageal injuries. A newer bisphosphate, zoledronate, can be given intravenously.

**Selective estrogen receptor modulators (SERMs):** They are tissue-specific in action. Of many SERMs, raloxifene has shown to increase BMD. Raloxifene inhibits the estrogen receptors at the breast and endometrium. Risk of breast and endometrial cancer is therefore reduced. It does not relieve hot flashes but reduces low-density lipoprotein (LDL) and raises HDL levels.

**Calcitonin:** It inhibits bone resorption. Simultaneous therapy with calcium and vitamin D is advisable. Recommended dose is 50–100 IU daily subcutaneously.

**Fluoride:** It prevents osteoporosis and increases bone matrix. Recommended dose is 1 mg/kg for short-term only. Long-term therapy induces side effects like brittle bones.

**Recombinant human parathyroid hormone:** Teriparatide, a recombinant PTH has been shown to be effective in osteoporosis. It is paradoxically a bone-building agent, which acts by simulating osteoblasts, thus increasing their activity. Thus, teriparatide increases BMD, improves bone strength and reduces fracture risk. The preparation available is synthetic human 1-34 parathormone produced by mRNA genetica. It is used mostly as treatment in patients with established osteoporosis, those with particularly low BMD or several risk factors for fracture or cannot tolerate the oral bisphosphonates. It is given as 20 µg injection in daily dose and course of therapy is 18–24 months. Headache is a common side effect of the drug.

**Phytoestrogen**

**Menstrual Irregularities**

**Exposure to Unopposed Estrogen**

Menstrual irregularities occur in more than one-half of all women during perimenopausal transition.16 Although greatest concern provoked by this symptom is endometrial neoplasia, usual finding is non-neoplastic tissue displaying estrogen effects unopposed by progesterone.

In all women, whether premenopausal or postmenopausal, whether on or off hormone therapy, specific organic cause must be ruled out. In addition to careful history and physical examination, abnormal bleeding requires evaluation. Transvaginal sonographic measurement of endometrial thickness (ET) can be utilized in postmenopausal women to avoid unnecessary biopsies.54 In perimenopausal and postmenopausal women with abnormal bleeding, endometrial biopsy is considered unnecessary when ET is less than 5 mm because the risk of endometrial hyperplasia or cancer is remote.55–57 Biopsy is indicated when clinical history suggests long-term unopposed estrogen exposure even when ET is normal (5–12 mm) and in all cases with ET more than 12 mm even if clinical suspicion of disease is low. Complete description of management of abnormal bleeding is out of scope of this chapter.

### TREATMENT OF MENOPAUSAL WOMAN

The patient often fears a pregnancy and possibility of cancer at the menopause. The gynecologist should investigate her thoroughly: palpate the breasts, do a speculum examination, take a smear for cytology and do a bimanual pelvic examination. A histological evidence of the endometrial condition is recorded in women in whom “HRT” is contemplated.

Blood pressure should be determined, and blood sugar levels be checked for diabetes, lipoprotein profile evaluated, and whenever feasible, tests undertaken to detect disturbed thyroid function by estimating serum thyroid-stimulating hormone (TSH) value as a screening test.

It is a good practice to document baseline recordings of the following investigations: pelvic ultrasound scan noting uterine size and myometrial texture. The pathologies like presence of fibroids, alterations in ET and adnexal masses are to be looked for. A baseline mammography documentation is always desirable.

### PATIENT CONCERNS ABOUT MENOPAUSE

Numerous emotions are often associated with hormonal and bodily changes characteristic of this period. The physician should be sensitive to the potentially significant emotional distress faced by women entering menopause and be prepared to offer psychological support. For some women in whom childbearing and childrearing have been a major source of status and self-esteem, loss of fertility may cause great distress.45 For other women who have delayed childbearing, menopausal symptoms may represent tangible evidence of their inability to have children.

In our society, young age is looked upon with great pride whereas maturity often is not; thus menopause, which symbolizes loss of youth produces distress, may be subtle
yet disturbing. Hence, family support at this time especially from the husband and grown up children is very important. Women peer groups, Mahila Mandalas and counselors also play a major role in influencing lifestyle changes. Our society will certainly benefit if women get together and involve themselves in constructive activities which will allow them to be busy and at the same time to enjoy the work they do.

REFERENCES

Miscellaneous


INTRODUCTION

Genetics, one of the advanced sciences, deals with the origin of similarities and differences between parents and offspring. It is concerned with the nature of these similarities and differences, their source and how they develop. In short, genetics is the study of the inheritance of developmental potentialities (genes) and how they come into existence.

We inherit from our parents the potentialities for various characteristics that can be observed and the determiners of many other characteristics that we never exhibit. When we take heredity into account, we do not refer to those characters that are common to all members of a group or species, but to variations in body and mental traits that may be possessed by both parents and offspring. Thus, we are not ordinarily concerned with the fact that both father and son each have two eyes, but we are more concerned about the color and other characteristics of their eyes. This is because the eye color of the son may not be the same as that of the father. The characteristics of the son may be like those of neither the father nor the mother, and thus, we may discover that heredity involves differences as well as likeness between parents and offspring.

DEFINITION OF GENETICS

Genetics may be defined as the study of heredity and variations. Both heredity and variations always play significant role in the organic evolution as well as in speciation, i.e. formation of new species. Actually, the term “genetics” was used by Bateson (1906) and this was derived from Greek word “gen” meaning “to grow into”. Therefore, genetics may be defined as the science of “coming into being” or existence.

NEED OF STUDY OF GENETICS

Before going for the study of genetics, a normal and usual question strikes in mind that why study genetics? There are many reasons, each of them excellent, in answer to the question. The first reason being the understanding of genetics is essential for an understanding of all other fields of biology. The topics studied in genetics overlap directly with molecular biology, cell biology, physiology, evolution, behavior and ecology. Genetics is therefore said to unify biology and serves as its “core”.

Second reason about the need of study of genetics is that we are always curious about ourselves, i.e. in the past, in the present and in future. We always wanted to know about how we got here, what are we and what will be in future. In genetics, countless initial concepts have been investigated in a logical fashion till they were dearly and definitely understood. Thus, genetics has a rich history which exemplifies the nature of scientific discovery and analytical approach used to acquire information.¹

Still, there is another reason why the study of genetics is needed and that is because since it began, the field has been expanding day-by-day. Every year, new findings and investigations are made. That is why, this science though quite young, has become more advanced to many other sciences. It is always very enthusiastic and stimulation to be involved in old and new development and findings, whether studying or teaching.
SOME BASIC CONCEPTS OF GENETICS

In this introductory chapter, we would like to take up some basic concepts of genetics which you might have known.

**Genotype and Phenotype**

This concept is one of the very fundamental of genetics. Genotype is defined as the genetic constitution of an organism and phenotype is defined as the physical expression of an organism. For example, there must be two alleles for blue eyes to produce a blue-eyed person. Such a person has a genotype of two alleles for blue eyes and a phenotype of blue eyes. And if a person has one allele for brown eyes and one allele for blue eyes, his phenotype will be brown-eyed because the expression of brown eyes is dominant to the expression of blue eyes.

**Heredity and Environment**

Phenotype is the expression of genotype, but we must keep in mind that environment is absolutely critical about phenotypic expression. For example, evolution of genes that produce a normal respiratory system for the utilization of oxygen ($O_2$) for normal health and existence. But these genes would be useless if the environment does not contain $O_2$. Most phenotypes are neither the result of the genotypes nor the environment alone but are a consequence of the interaction of the genotypes with the environment.

Environmental variations may influence the individual cells of the body as well as with the whole organisms. Here, one thing must be clear that environment does imply only to the external environment of the organism. But it must also involve other genes also under consideration. The best example of influence of environment to phenotypes is met with identical twins which is explained in coming chapters.

**Genetic Material**

In eukaryotes and prokaryotes, deoxyribonucleic acid (DNA) serves as the molecules storing genetic information. In viruses, either DNA or RNA serves this function. DNA (Fig. 1), which is single-stranded in a few viruses and bacteria, is usually double stranded molecule arranged in a helical manner. It contains many hereditary units called genes which are parts of longer elements—the chromosomes. Any sudden change in number or structure of these chromosomes and genes gives rise to chromosomal and gene mutation, respectively forming sources of genetic variations.

**GENETICS IN RELATION TO SOCIETY**

Genetics is appreciated by us because it has had such an exciting history in which theory has evolved out of observation and led to experimental proof of fundamental operation mechanisms. A fraction of a century ago the scientists were unaware of genetic mechanisms. Now, however, we are able to construct molecular models of genes, atom by atom to considerable accuracy. Genetics has many significant practical applications to our society. Some of them are given below:

**Genetics and Breeding**

Genetics has provided ample tools to improve the food crops and domestic animals by selective breeding. This involves increase in yield of crops like corn and rice, improvement in flavor and size, the production of seedless varieties of fruits, and increase in meat production of cattle and swine. The problem of breeding disease resistant plants is likewise a never ending one. Applied research in genetics has developed superior breeds of animals.

**Genetics and Medicine**

Equivalent strides have been made in medicine as a result of advances in genetics. Knowledge of several disorders in human being has come to us, resulting due to mutations. Just to name some of the diseases, we have knowledge of sickle-cell anemia, erythroblastosis fetalis, hemophilia, color blindness, muscular dystrophy and different types of syndromes. The knowledge of genetic basis of such disorders has provided the need for the development of treatment and preventive measures. Increase in science of immunogenetics has made possible compatible blood transfusions as well as organ transplant.

**Genetic Counseling**

Some estimation of the likelihood of a particular desirable or undesirable trait appearing in the offspring of a given parent can be made clear by one who has sound genetic training and pedigree knowledge.

**Legal Applications**

Analysis of blood type (a genetically determined character) may be used to solve problem of disputes among parents. Questions of baby suffering in hospitals, illegitimate children and actual claims can be justified by the application of genetics.

**Betterment of Human Race**

One of the foremost applications of genetics goes in foremost of eugenics or the betterment of human race. Control of the inherited diseases can also be set right by applying genetics in term of eugenics.

**CHROMOSOMAL ABNORMALITIES**

Human cells normally contain 23 pairs of chromosomes; any change causes problems with growth, development and
function of body system. Presence of an extra chromosome is “trisomy” (Greek for “three”), e.g. Down’s syndrome—three copies of chromosome 21 in each cell. Monosomy—“mono” (Greek for “one”) is one copy of a particular chromosome, e.g. Turner’s syndrome—only one copy of the X-chromosome in every cell. Rarely, extra sets of chromosomes are present as in “triploid”—69 chromosomes, or in tetraploid—92 chromosomes, which are not compatible with life. In some cases, change in the number of chromosomes occurs only in certain cells leading to two or more cell populations in one individual—“mosaicism”, e.g. Turner mosaic. Many cancer cells also have changes in number of chromosomes in somatic cells during the formation or progression of the tumor.

Structural abnormalities in chromosomes are: deletion (portion of the chromosome missing/deleted), duplication (portion of chromosome is duplicated, resulting in extra genetic material), translocation (portion of one chromosome is transferred to another chromosome: reciprocal-segments from two different chromosomes exchange, Robertsonian—an entire chromosome attached to another at the centromere), inversion (portion of the chromosome has broken off, turned upside down and reattached), ring (portion of a chromosome has broken off and formed a circle or ring, with or without loss of genetic material).

In humans, mitochondrial DNA spans about 16,500 DNA building blocks (base pairs), representing a fraction of the total DNA in cells. Mitochondrial DNA contains 37 genes, all of which are essential for normal mitochondrial function—oxidative phosphorylation; transfer RNAs (tRNAs) and ribosomal RNAs (rRNAs), which help assemble protein building blocks (amino acids) into functioning proteins. The following conditions are related to changes in mitochondrial DNA—some forms of cancer, including breast, colon, stomach, liver, kidney tumors, leukemia, lymphoma, Leber hereditary optic neuropathy.

**Autosomal Chromosomal Disorders**

- Down’s syndrome (trisomy 21) occurs in 1:800 births, 93–95% of cases are sporadic and show a distinctive relationship with maternal age, 3–5% result from translocations and 2–3% are due to mosaicism.\(^2\) **DYRK1A** (dual-specificity tyrosine phosphorylation-regulated kinase 1A) overexpression may be the cause of mental retardation (MR).\(^3\) Organ systems may be affected (e.g. congenital heart defect), or there is increased risk for otitis media; increased risk of leukemia and seizures; early Alzheimer’s disease.\(^4\)

- Trisomy 18 is the second most common autosomal trisomy, occurs in 1:6,000 to 1:8,000 live births. Approximately, 95% of conceptuses with trisomy 18 die as embryos or fetuses; 5–10% of affected children survive beyond the first year of life. The high mortality rate is usually due to the presence of cardiac and renal malformations, feeding difficulties, sepsis and apnea caused by central nervous system (CNS) defects. Severe psychomotor and growth retardation are invariably present in those who survive beyond infancy.\(^5\)

- Patau syndrome/trisomy 13 occurs in 1:20,000 live births, characterized by cleft lip or palate, close-set eyes, decreased muscle tone, polydactyly, umbilical hernia, inguinal hernia, coloboma, low-set ears, MR, scalp defects, seizures, single palmar crease and skeletal (limb) abnormalities.\(^5\)

**Sex-Linked Chromosomal Disorders**

- Turner’s syndrome (XO) is often associated with miscarriage; only 1% of affected fetuses are born with a missing X-chromosome (XO), some are XO/XX mosaics. Phenotype is female with dysmorphic features—small stature, poorly developed secondary sex characteristics, sexual dysfunction in puberty/adulthood, webbed neck, broad chest, deformed bend in forearm, low set hairlines, low set ears and atypical facies; usually no neurological abnormalities.

- Fragile X syndrome is the second most common form of MR (second to Down’s syndrome); most common inherited form [responsible for as much as 10% of all MR cases]. Fragile X males (1:1,500 births), have head circumference and weight greater than peers; by adulthood only the head remains large; elongated face; enlarged testicles; intellectual quotient (IQ) ranges from normal to profoundly mentally retarded (70% moderate to severe MR; 20% seemingly normal). Dysfluency, apraxic speech, echolalia, palilalia and cluttering are characteristic; receptive language relatively preserved, there may be frequent behavioral abnormalities, mood disorder, repetitive purposeless involuntary movements, autism, etc.

Fragile X females (1:3,000 births), in contrast to other sex-linked disorders, one-third of female carriers express some of its characteristics. They often lack dysmorphic features seen in males, there may be attention deficits, distractibility, shyness, impaired organizational skills and difficulty with transitions, IQ 80–100; often below 85. Behavioral abnormalities less common than in boys.

- Rett’s syndrome: Seen in females only; abnormality is assumed lethal in males. Onset begins after about 6 months of normal development, then regress in all areas of psychomotor development over several years until no language, walking, cognitive capacity, profound MR. Two virtually unique physical characteristics are stereotypies (often incessant hand clapping and wringing) and acquired microcephaly (after 6 months of normal growth). About 50% have seizures; they share features with autism. Rett’s, Angelman’s and fragile X should all be differentials for autism.

- Klinefelter’s syndrome (XXY): Seen in males; tall stature, but “eunuchoid” after puberty (often diagnosed after puberty, sometimes in context of fertility workup—sterile, testicular dysgenesis). In general, IQ below average
• XYY syndrome afflicted patients are extremely tall; severe acne persists beyond adolescence, maturational delays, negative mood and temper tantrums. Historically, research on "supermales" conducted in prisons indicated deviant, violent, aggressive behavior. They may have delayed speech acquisition, psychiatric difficulties, average to below normal IQ and violent criminal behavior.

• Lesch-Nyhan syndrome is an X-linked disorder with self-injurious behavior, extrapyramidal involvement, neuropsychiatric presentation is variable.

Molecular and Mendelian Genetics

Single gene hereditary disorders can be subdivided into autosomal dominant, autosomal recessive, or X-linked conditions.

• An autosomal dominant disorder (Fig. 1) is one in which the abnormal phenotype is evident when a mutation is present in one autosomal gene of a pair. Approximately, 50% of the children born to an affected individual will be affected, providing the partner is unaffected, e.g. Marfan’s syndrome, achondroplasia, neurofibromatosis and retinitis pigmentosa. Severely affected offspring may be born to minimally affected adults.

• An autosomal recessive disorder (Fig. 2) is one which is fully expressed only when a mutation is present in both genes of a pair. The parents of an affected child are usually clinically normal. When both parents are carriers, there is a 25% chance with each pregnancy of having an affected child. Examples of autosomal recessive single gene disorders include: β thalassemia, albinism, cystic fibrosis, mucopolysaccharidosis, and phenylketonuria.

• An X-linked disorder (Figs 3A and B) is one in which the altered gene is located on the X-chromosome, so there is no male to male transmission, since males pass only Y-chromosomes to their sons. Unaffected males cannot transmit the disorder because they do not carry the abnormal X-linked gene. Affected males have clinically normal offspring—sons receive a Y-chromosome and are free of the trait, daughters receive an X-chromosome and are normal, but obligate carriers. Carrier females may be mildly symptomatic due to unequal inactivation of the X-chromosomes and have a 50% chance, with each pregnancy, of passing on the abnormal gene. Sons who inherit the gene will be affected and daughters will be carriers like their mothers. Although unlikely, a female can express an X-linked disorder if her father is affected and her mother is a carrier.

Polygenic/Multifactorial Disorders

Polygenic or multifactorial disorders (Fig. 4) are believed to be caused by the interaction between a variety of genes as well as environmental factors, e.g. cleft lip and palate, neural tube defects (NTDs) and pyloric stenosis. The recurrence risk to siblings or the offspring of an affected individual is approximately 3–5%. The recurrence risk increases, however, when more family members are affected or the parents are related.

Thus, chromosomal syndromes are usually characterized by multiple malformations, MR, intrauterine growth retardation (IUGR) and postnatal growth retardation and anomalies of many organ systems, especially the craniofacial, skeletal, cardiac and genitourinary systems. Chromosomal abnormalities are associated with 50–60% of first trimester abortions and 5% of stillbirths. 

**Prenatal Genetic Diagnosis**

Prenatal diagnostic techniques for diagnosing congenital and genetic disorders in utero have proved to be a major advance in medical genetics and have altered the outlook for families at risk of having an affected child with a serious and untreatable disorder (Fig. 5). Advances in genetic research are occurring simultaneously with the development of new techniques for prenatal genetic testing. Reproductive genetic counseling offers options to patients related to testing (prenatal or carrier) and child bearing. The focus of the counseling is often on decision making by the patient, including accepting the consequences of the choice(s), as it is the patient and the family who have to live with the decision. The strategy of population screening, offering genetic counseling, prenatal diagnosis (PND) and termination of affected pregnancy has been successfully applied worldwide. Appropriate laboratory
molecular techniques are useful for identification of defects in single genes. Preimplantation genetic diagnosis (PGD) is an advanced alternative giving the couple the chance to start a pregnancy ensuring that the baby is free from the genetic disease.

**Indications for PND**

- Maternal age greater than 35 years
- Previous abortus, stillbirth or livebirth with a trisomy or other chromosomal abnormality
- Potentially transmissible chromosomal rearrangement
- Relatives, other than offspring, with Down’s syndrome
- X-linked disorders
- Fragile X-syndrome
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1. Syndromes with elevated chromosomal breakage or other cytogenetic aberrations, e.g. Fanconi anemia, Bloom’s syndrome, ataxia telangiectasia (AT)
2. Therapeutic radiation exposure in males
3. Infertility treated with intracytoplasmic sperm injection (ICSI)
4. Microdeletion/microduplication syndromes, e.g. DiGeorge’s syndrome
5. Abnormal ultrasound scan
6. Biochemical/molecular disorders
7. Abnormal carrier screening.

Techniques for Prenatal Diagnosis

1. Based on fetal cell/tissue sampling
   - Amniocentesis
   - Chorionic villus sampling
   - Cordocentesis

2. Maternal serum screening studies

Maternal serum screening studies identify pregnancies that are at increased risk of adverse outcomes, such as NTDs and chromosome abnormalities. The varied spectra of maternal serum tests available for screening of Down’s syndrome are: triple, quadruple, combined test, integrated test [integration of nuchal translucency measurement and pregnancy-associated plasma protein A (PAPP-A) in the first trimester with maternal serum alpha-fetoprotein (MSAFP), β-hCG (human chorionic gonadotropin) and unconjugated estriol measurement in the second trimester].

Data from the serum urine and ultrasound screening study (SURUSS) study of screening performance with a constant early second trimester risk cut-off of 1:250 is shown in Table 1.

**GENETIC AMNIOCENTESIS**

Amniocentesis is a procedure in which a small amount of amniotic fluid is removed from the sac surrounding the fetus and is tested. The sample of amniotic fluid (less than one ounce) is removed through a fine needle inserted into the uterus through the abdomen, under ultrasound guidance. The fluid is then sent to a laboratory for analysis. Different tests can be performed on a sample of amniotic fluid, depending on the genetic risk.

**Table 1: Data from SURUSS study**

<table>
<thead>
<tr>
<th>Screening test</th>
<th>Detection rate (%)</th>
<th>False positive rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triple test</td>
<td>81</td>
<td>6.9</td>
</tr>
<tr>
<td>Quadruple test</td>
<td>84</td>
<td>5.7</td>
</tr>
<tr>
<td>Combined test</td>
<td>83</td>
<td>5.0</td>
</tr>
<tr>
<td>Integrated test</td>
<td>90</td>
<td>2.8</td>
</tr>
</tbody>
</table>

**Procedure**

A physician performs genetic amniocentesis by passing a thin needle through the mother’s abdominal wall and up to amniotic sac under ultrasonography (USG) guidance. A small amount of amniotic fluid, then is withdrawn (Fig. 6). This fluid contains cells that have been shed from the fetal skin surface, which may be used to detect certain genetic disorders. Amniocentesis and ultrasound studies are performed on an outpatient basis, usually between the 15th and 17th week of pregnancy.

Cells from the amniotic fluid sample are grown in a laboratory culture with cytogenetic results, usually available within 14 days.

Amniocentesis does not detect all birth defects, but it can be used to detect the following conditions, if the parents have a significant genetic risk:

- Sickle cell disease
- Cystic fibrosis
- Muscular dystrophy
- Tay-Sachs disease

Amniocentesis also can detect certain NTDs (development disorders of the brain and spinal column) such as spina bifida.

**CHORIONIC VILLUS SAMPLING**

Chorionic villus sampling (CVS) involves passing a needle into the placenta (at this stage, the placenta is called the "chorion") and drawing a few small fragments of tissue up into the syringe (Fig. 7). The placenta has the same genetic make-up as the fetus.
CORDOCENTESIS

Some Currently Available DNA-based Gene Tests

- Alpha-1-antitrypsin deficiency (AAT; emphysema and liver disease)
- Amyotrophic lateral sclerosis (ALS; Lou Gehrig’s Disease; progressive motor function loss leading to paralysis and death)
- Alzheimer’s disease [apolipoprotein E (ApoE); late-onset variety of senile dementia]
- AT; progressive brain disorder resulting in loss of muscle control and cancers
- Gaucher’s disease (GD; enlarged liver and spleen, bone degeneration)
- Inherited breast and ovarian cancer (BRCA 1 and 2; early-onset tumors of breasts and ovaries)
- Hereditary nonpolyposis colon cancer (CA; early-onset tumors of colon and sometimes other organs)
- Central core disease (CCD; mild-to-severe muscle weakness)
- Charcot-Marie-Tooth (CMT; loss of feeling in ends of limbs)
- Congenital adrenal hyperplasia (CAH; hormone deficiency; ambiguous genitalia and male pseudohermaphroditism)
- Cystic fibrosis (CF; disease of lung and pancreas resulting in thick mucus accumulations and chronic infections)
- Duchenne muscular dystrophy/Becker muscular dystrophy (DMD; severe to mild muscle wasting, deterioration, weakness)
- Dystonia (DYT; muscle rigidity, repetitive twisting movements)
- Emanuel syndrome (severe MR, abnormal development of the head, heart and kidney problems)
- Fanconi anemia, group C (FA; anemia, leukemia, skeletal deformities) factor V-Leiden (FVL; blood-clotting disorder)
- Fragile X-syndrome (FRAX; leading cause of inherited MR)
- Galactosemia (GALT; metabolic disorder affects ability to metabolize galactose)
- Hemophilia A and B (HEMA and HEMB; bleeding disorders)
- Hereditary hemochromatosis (HFE; excess iron storage disorder)
- Huntington’s disease (HD; usually midlife onset; progressive, lethal, degenerative neurological disease)
- Marfan’s syndrome (FBN1; connective tissue disorder; tissues of ligaments, blood vessel walls, cartilage, heart valves and other structures abnormally weak)
- Mucopolysaccharidosis (MPS; deficiency of enzymes needed to breakdown long chain sugars called glycosaminoglycans; corneal clouding, joint stiffness, heart disease, MR)
- Myotonic dystrophy (MD; progressive muscle weakness; most common form of adult muscular dystrophy)

Chorionic villus sampling allows PND of certain genetic disorders during the first trimester of pregnancy. Chorionic villus (placental) tissue originates from the same cells that form the fetus, and usually reflects fetal genetic constitution. In CVS, a physician passes a very small catheter through the woman’s cervix and beneath the placenta under ultrasound guidance. A small amount of villus tissue is then suctioned from the placenta.

Chorionic villus sampling is performed only at the Center for Advanced Medicine on an outpatient basis 10–12 weeks following the start of the last normal menstrual period. The chorionic villus sample is delivered to the laboratory, where it undergoes microscopic analysis of cultured villus cells. Cytogenetic results usually are available within 8 days.
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- Neurofibromatosis type 1 (NF 1; multiple benign nervous system tumors that can be disfiguring; cancers)
- Phenylketonuria (PKU; progressive MR due to missing enzyme; correctable by diet)
- Polycystic kidney disease (PKD1, PKD2; cysts in the kidneys and other organs)
- Adult polycystic kidney disease (APKD; kidney failure and liver disease)
- Prader Willi/Angelman syndromes (PW/A; decreased motor skills, cognitive impairment, early death)
- Sickle cell disease (SS; blood cell disorder; chronic pain and infections)
- Spinocerebellar ataxia, type 1 (SCA1; involuntary muscle movements, reflex disorders, explosive speech)
- Spinal muscular atrophy (SMA; severe, usually lethal progressive muscle-wasting disorder in children)
- Tay-Sachs disease (TS; fatal neurological disease of early childhood; seizures, paralysis)
- Thalassemias (THAL; anemia reduced red blood cell levels)
- Timothy syndrome (CACNA1C)

**TECHNIQUES OF GENETIC DIAGNOSIS**

**Karyotyping**

Karyotype is the observed characteristics (number, type, shape, etc.) of the chromosomes of an individual or species. Metaphase cells are required to prepare a standard karyotype and virtually any population of dividing cells could be used. Blood is easily the most frequently sampled tissue. Other tissue which can be used are cultured skin fibroblasts, amniotic fluid, chorionic villi. Structural and numerical chromosomal abnormalities can be studied by this technique.

**Polymerase Chain Reaction/DNA Amplification**

A particular DNA sequence is copied several times in order to facilitate its analysis; billions of copies of a small piece of DNA are produced in several hours.

**Indications for Polymerase Chain Reaction**

- Single gene defects in autosomal disease
- Single gene defects in male infertility
- Identification of sex in X-linked diseases

**Fluorescence in situ Hybridization**

This is a relatively new sensitive molecular cytogenetics technology utilizing fluorescently labelled DNA probes to detect chromosome abnormalities.

**Indications for Fluorescence in situ Hybridization (FISH)**

- Aneuploidy screening in women of advanced maternal age
- Aneuploidy screening for male infertility
- Identification of sex in X-linked diseases
- Recurrent miscarriages caused by parental translocations

**DNA Microarray Technology**

This is the result of automation and miniaturization in the detection of differential gene expression. It is based on the classic technique of southern DNA hybridization where a labeled DNA probe is hybridized to single stranded DNA that is bound to a solid support matrix. The truly revolutionary aspect of microarray analysis lies in the fact that, within a given cell population, the expression of tens of thousands of genes, and ultimately the entire genome can be assayed simultaneously. This capability, when coupled with powerful data analysis software, allows researchers to rapidly compare gene expression between two cell populations. In the cancer field, this enables researchers to compare gene expression between normal and malignant cells and to identify genes that are differentially regulated during cancer development. Microarray data can also be used to categorize tumors on the basis of their molecular profile, which may provide important biological, diagnostic and prognostic information. By using this technology one can make a parallel analysis of RNA abundance and DNA homology for thousands of genes in a single experiment. Future applications of this technology are for analyzing gene expression in ovarian cancer.

**Preimplantation Genetic Diagnosis**

Prenatal diagnosis and selective pregnancy termination for adult-onset disorders is emotionally difficult and, in some cases, socially not well accepted. PGD appears as an attractive alternative to PND, as it ensures the establishment of a pregnancy free of the mutation from the onset, circumventing the potentially difficult decision of termination of pregnancy. Several inherited diseases can now be diagnosed by genetic analysis of single cells biopsied from human eggs and preimplantation embryos following in vitro fertilization (IVF). The couples at risk can, therefore, have only unaffected embryos replaced in the uterus and avoid the possibility of terminating a pregnancy that might only be diagnosed as affected later is gestation. Single-cell genetic analysis has emerged as a powerful tool for studying genetic defects. The process starts with a basic IVF. When the embryo is at the 6–8 cell stage, 1–2 cells (blastomeres) are removed and tested using either PCR or FISH techniques, depending on which disease is being sought. The unaffected embryos are then transferred into the mother’s uterus.
Indications for Preimplantation Genetic Diagnosis

- Couples in whom at least one partner has a family history of inheritable genetic disease, carries such a disease, or is otherwise affected by such a disease
- Women 35 years or older (To test for aneuploidy due to maternal age)
- Women with recurrent pregnancy losses, which could be caused by an abnormal chromosomal set coming from either the male or female partner
- Couples with chromosome translocations, which can cause implantation failure, recurrent pregnancy loss, or mental or physical problems in offspring
- Couples with repeated IVF failure
- Men with infertility requiring ICSI

Methods of Preimplantation Genetic Diagnosis

- Polar body biopsy maintains embryo integrity as only by-products of meiosis are used for analysis. The polar bodies can be analyzed at the chromosome and at the monogenic level.
- Cleavage stage biopsy, also called blastomere biopsy, is the most commonly used biopsy technique. Embryos are grown in vitro until they reach their third division (eight-cell stage), which normally occurs on the third day after insemination. At this stage, the embryos are biopsied to obtain one or two individual blastomeres for analysis. There is no consensus on the number of blastomeres that can be removed safely during cleavage stage embryo biopsy. PGD at the cleavage stage has the advantage of testing disorders of both maternal and paternal origin and those originating after fertilization. There is substantial evidence for significant chromosomal mosaicism in cleavage-stage embryos. Therefore, the biopsied cells may not be representative of the whole embryo.\(^{13}\)
- The blastocyst stage is the latest stage at which an embryo can be biopsied. At this stage, 5–6 days after fertilization in the human, the embryos contain approximately 150 cells, consisting of inner mass cells and trophectoderm cells. Removal of trophectoderm cells during blastocyst biopsy is achieved by herniation through the zona pellucida (ZP) followed by laser or mechanical excision. The advantage is that more cells can be obtained; the disadvantages being that usually less than 50% of embryos reach that stage in culture, and that there is little time left for the diagnosis, as embryos should be transferred before day 5 or day 6. The applicability of blastocyst biopsy on a large scale needs validation.\(^{14}\)

Mutations in the adenomatous polyposis of the colon (APC), neurofibromatosis type II (NF2) and BRCA1 genes cause adult-onset cancer predisposition syndromes. Spits et al.\(^{15}\) successfully developed a total of five duplex—PCRs, three for APC, one for NF2 and one for inherited breast and ovarian cancer caused by BRCA1 mutations. Eleven clinical cycles of PGD were performed resulting in the birth of an unaffected girl. For one of the couples undergoing PGD for NF2, a spontaneous pregnancy ensued after five unsuccessful PGD cycles. The couple underwent chorionic villus sampling (CVS) and the application of the same protocol as used during PGD showed an unaffected fetus.

Prenatal Diagnosis by Fetal Cells in Maternal Blood

Cell-free fetal DNA in maternal serum was first discovered by Lo et al.\(^{16}\) in 1997, when Y-chromosome specific sequences were found in plasma of women carrying male fetuses. This has opened up a novel approach for noninvasive evaluation of fetal and fetus-initiated maternal diseases. But the current limitation of use of this type of chromosomal screening is that maternal serum fetal DNA measurements are currently based on quantifying the Y-specific sequences, and hence, can be applied only for pregnancies with a male fetus. As of now, the search is on for a sex-independent DNA marker that can be readily quantified by real time PCR.

Clinical applications of cell-free DNA from maternal serum:

- Fetal sex determination: This can be done for X-linked recessive disorders and CAH. The sensitivity of plasma PCR for sex determination reaches its maximum at 10 weeks’ gestational age, with very low false positive rates.
- Fetal rhesus-D status: Molecular analysis of cell free fetal DNA to identify fetuses that are Rh positive in sensitized Rh negative women has a sensitivity close to 100% with a specificity of 97% according to a recent series of 72 cases by Rjinders et al.\(^ {17}\)
- Single gene disorders: Conditions such as cystic fibrosis, achondroplasia, CAH have been assayed from maternal plasma, according to some recent individual case reports. Noninvasive PND of beta thalassemia was performed correctly in 20 of 23 pregnancies using mass spectrometric analysis of maternal plasma for the paternally inherited fetal genotype by Ding et al.\(^ {18}\)
- Fetal chromosomal abnormalities: Down’s syndrome pregnancies exhibit a 1.7 fold increase in free fetal DNA levels in maternal serum, in comparison with matched controls. Combining estimation of the same with the routine second trimester maternal serum tests increases the detection rate of trisomy 21 from 81% to 86% at a 5% false positive rate.
- Fetal-placental induced maternal disease: High levels of fetal cell free DNA have been demonstrated in conditions such as pre-eclampsia, hyperemesis gravidarum, placenta accrete and HELLP (hemolysis, elevated liver enzymes and low platelet count) syndrome. Pre-eclampsia appears to be associated with a two-stage elevation of fetal DNA. Elevation between 17 and 28 weeks is due to placental necrosis and infarction. Elevation subsequent to that may reflect impaired DNA clearance from the maternal...
circulation. This two-stage elevation has opened up the possibility of this variable being used not only for screening, but also to indicate impending clinical disease.

### GENETICS IN PREGNANCY LOSS

More than 50% of clinically recognized pregnancy losses result from a fetal cytogenetic abnormality. Genetically, abnormal concept occur earliest in gestation, with rates declining after the embryonic period (> 30 mm crown-rump length). The rate of abnormal (aneuploid) abortuses increases with maternal age. Rubio and et al.\(^1\) performed PGD on 71 couples with recurrent miscarriage and 28 couples undergoing PGD for sex-linked diseases (control group). He found that the percentage of abnormal embryos was significantly increased in recurrent miscarriage patients compared with controls and anomalies for chromosomes 16 and 22 were significantly higher (\(P < 0.01\)) in recurrent miscarriage cases.

Chromosomal aberrations are categorized as follows:

- **Aneuploidy:** One-half the cytogenetically abnormal abortuses in the first trimester involve autosomal trisomy.\(^2\) Trisomy 16, which accounts for 30% of all trisomies, is the most common. Viable trisomies have been observed for chromosomes 13, 16, and 21. Approximately, one-third of fetuses with Down’s syndrome (trisomy 21) survive to term. All chromosome trisomies except for trisomy 1 are reported in abortuses. Triploidy is found in 16% of abortions,\(^3\) with fertilization of a normal haploid ovum by two sperms (dispermy) as the primary pathogenic mechanism in humans. Most cases abort early in pregnancy and often only an empty sac is recovered. Triploid abortuses often show hydatidiform placental degeneration. These abnormalities are not compatible with life. Tetraploidy occurs in approximately 8% of chromosomally abnormal abortions, resulting from failure of an early cleavage division in an otherwise normal diploid zygote. Tetraploid embryos cease to develop very early (2–3 weeks) and recognizable embryonic differentiation has not been observed in recovered specimens. Autosomal monosomies are rarely, if ever, observed. In contrast, monosomy X (Turner’s syndrome) is frequently observed, and it is the most common chromosomal abnormality observed in pregnancy losses prior to 20 weeks gestation. Turner’s syndrome accounts for 20–25% of cytogenetically abnormal abortuses.\(^4\)

- **Parental chromosomal abnormalities:** Structural chromosomal abnormalities are thought to be most commonly inherited from the mother. Structural chromosomal problems found in men often to lead to low sperm concentrations, male infertility, and therefore, a reduced likelihood of pregnancy and miscarriage. The exception to this situation is the couple undergoing assisted reproductive technologies in which selected sperm can be injected into oocytes to force fertilization by using potentially genetically abnormal sperm.

Among structural rearrangements, translocations (most commonly reciprocal and Robertsonian) can be balanced or unbalanced. The incidence of translocations increases with the number of abortions. Slightly more than one-half of unbalanced rearrangements result from abnormal segregation of Robertsonian translocations. Approximately, one-half of all unbalanced translocations arise de novo during gametogenesis. In reciprocal translocations, children created from these gametes have normal and carrier karyotypes. Adjacent segregation results in unbalanced distribution of the chromosomes involved in the translocation, leading to partial trisomy for one chromosome and partial monosomy for the other chromosome. The severity of the phenotype depends on the chromosomes involved and on the positions of their breakpoints. The risk is increased if the female partner carries the translocation.

Other structural rearrangements, such as inversions or ring chromosomes, are relatively rare. These chromosomal abnormalities can be associated with congenital malformations and MR, as well as spontaneous abortions.

- **Genetic abnormalities:** Certain genetic mutations thought to be involved with implantation may predispose a patient to infertility or even miscarriage. An example of a single gene disorder associated with recurrent pregnancy loss is myotonic dystrophy, an autosomal dominant neuromuscular disorder with high penetrance. The cause of the abortion is unknown, but it may be related to abnormal gene interactions combined with disordered uterine function. Other presumed autosomal dominant disorders include lethal skeletal dysplasias (e.g. thanatophoric dysplasia and type II osteogenesis imperfecta).

### Risk of Recurrence

According to Regan et al.\(^5\) the most important predictive factor for spontaneous abortion is a previous abortion and the outcome of a woman’s first pregnancy has profound consequences for all subsequent pregnancies. The risk of further miscarriage increases after each successive pregnancy loss. The risk of miscarriage in nulliparous women and those who have had a successful pregnancy rises from approximately 5% to over 20% after one miscarriage. The risk increases thereafter with each successive miscarriage, reaching over 40% after three consecutive losses.

### Management

For couples who have had pregnancy loss due to a suspected genetic cause, the standard of care is to offer expert genetic counseling. Karyotyping of both parents should be performed as this may reveal couples with abnormal chromosomal rearrangements. PND in ongoing pregnancies is recommended, as occasionally a pregnancy with an
unbalanced karyotype will progress to term, resulting in the birth of an abnormal infant. Karyotyping of the products of conception from any future miscarriages is mandatory. Pre-implantation genetic diagnosis can be offered to patients with high-risk of chromosomal recurrent miscarriages. But patients should be forewarned that the live birth rate per cycle for those with reciprocal translocation undergoing PGD is just around 29% per oocyte retrieval, rising to 38% per embryo transfer.24

It is advisable to give a positive, rather than negative prognosis to these couples. Tender loving care and reassurance will lead to a successful pregnancy outcome.

### COMMON GYNECOLOGICAL DISORDERS

With advances in genetic research, several gynecological disorders have been found to result from mutant genes, and several others influenced by genetic factors. Some of the common gynecological conditions with genetic origin are discussed below.

#### Normal Variations in Physiology

Age of menarche differs less between monozygotic twins than between dizygous twins. The age of menarche also differs less between sisters than between unrelated women, pointing toward a strong genetic influence. Rybo and Hallberg25 demonstrated that the amount of blood lost each menstruation may be influenced by genetic factors.

The correlation between mother and daughter is better than between unrelated individuals for length of cycle, regularity of menstruation and presence of dysmenorrhea and premenstrual tension.26 Age at menopause is more similar among siblings or relatives than among the general population.27 Also, menstrual abnormalities may result from genetically determined hematological disorders such as von Willebrand’s disease.

#### Leiomyomas

Myomas exhibit cytogenetic diversity. Almost 40% of fibroids have consistent non-random chromosomal abnormalities such as translocation between chromosome 12 and 14.28 Spontaneous chromosome rearrangements may be responsible for the initiation and proliferation of leiomyoma growth. Investigating the genetic processes of fibroid growth and development may eventually lead to development of innovative treatment options for uterine fibroids including growth factor-directed therapy and gene therapy.

#### Endometriosis

Endometriosis is a steroid-dependent disease with a particular genetic background, but the locations of possible genomic aberrations are still poorly defined. Certain studies have determined the possible genetic etiologies for endometriosis. These are enumerated here:

- PROGINS 306 base pair insertion polymorphism in intron G of the progesterone receptor (PR) gene association29 was found in patients with more severe forms of endometriosis, such as an infiltrating disease or a disease characterized by severe pelvic adhesions.
- Three base pair insertion/deletion (I/D) polymorphism of the CYP19 gene may be weakly associated with the susceptibility of endometriosis.30
- A recent study by Jiang et al.31 demonstrated that recombinant human endostatin YH16 affects the maintenance and growth of endometriotic tissues by inhibiting angiogenesis and reducing the expression of vascular endothelial growth factor (VEGF) in ectopic lesion. If efficacy is confirmed in humans, this could be an important step toward the nonhormonal and nonsurgical alternatives of endometriosis, which not only avoids adverse effects of estrogen therapy, but also reduces the rate of re-operation. When symptoms of endometriosis have been relieved by hormones or surgery, anti-angiogenic agent may be applied to eradicate residual and/or microscopic endometriosis.

#### Polycystic Ovarian Syndrome

Polycystic ovary syndrome (PCOS) characterized by hyperandrogenism, oligo-ovulation, and polycystic ovarian morphology, is a leading cause of infertility and affects 7% of women.32

In an effort to identify the genetic basis of hyperandrogenemia in PCOS, a number of genes encoding major enzymes of the androgen biosynthetic pathway have been examined and associations reported. Some of them have been enumerated below:

- Loci proposed and investigated as possible PCOS genes are CYP11A, the insulin gene and a region near the insulin receptor gene.33
- An inappropriate elevation in plasminogen activator inhibitor-1 (PAI-1)34 contributes to the development of polycystic structures; these findings may thus reorient the efforts aimed at the development of therapeutic agents for the treatment of this increasingly common syndrome.
- Anti-Müllerian hormone concentrations are increased in peripubertal PCOS35 which leads to increased follicular mass that is established during early development and persists during puberty.
- Increased rates of hyperandrogenemia are seen in family members of PCOS probands, both with and without PCOS. Ovarian hyperandrogenism is a key diagnostic feature and is a heritable PCOS trait.36
- Increased functional activity of cytochrome P450 steroidogenic enzymes, 3β-hydroxysteroid dehydrogenase enzyme, and intracellular kinase proteins important for ovarian theca cell steroidogenesis constitute the molecular phenotype of PCOS theca cells.37,38
• Recent studies using DNA microarrays in cultured theca cells from PCOS women identified the genes encoding aldehyde dehydrogenase-6 and retinoil dehydrogenase-2 as candidate genes for PCOS. These factors play a role in all-trans-retinoic acid synthesis and the transcription factor GATA6 that, in turn, increase the expression of 17α-hydroxylase, a functional characteristic of PCOS theca cells.39

All these various studies imply that genetically determined hyperandrogenism during intrauterine life may program the human fetus for the development of PCOS in adulthood, This has opened up new prospects in the understanding and treatment of PCOS in humans. Further, research directed toward determining the genetic influence of the hormonal environment during prenatal life and programming the differentiation of fetal target tissues may pave the way for possible intervention at this critical period of prenatal life to facilitate a favorable outcome during adult life.

Premature Ovarian Insufficiency/
Premature Ovarian Failure

Premature ovarian failure (POF) is a condition in which the ovarian function stops in women less than 40 years of age after normal development.40

The etiology of POF encompasses genetic disorders, surgery or ovarian tissue damage due to radiation or chemotherapy. Genetic causes of POF have been described here:

X-chromosome Genes

Xp (short arm) genes: Deletions or disruptions of critical regions of the short arm of the X-chromosome (Xp11, Xp22.1-21.3) have been described in association with gonadal dysgenesis and primary or secondary amenorrhea. The importance of the genes located on the short arm of the X-chromosome for normal ovarian development and survival is evident from the fact that half of the patients with partial deletions of the short arm of the X-chromosome have amenorrhea.

Xq (long arm) genes (Xq26.2-q28) deletion: Inheritance of an interstitial deletion of the long arm of the X-chromosome is associated with premature menopause in the same family.41

• FMR1 gene: This gene is located on Xq27.3. Full mutation is associated with MR, while women with premutation demonstrate a 20–30 times increased incidence of premature menopause and are not affected by MR.42

• XIST locus (X inactivation site): Located on Xq13, this locus is required for the reactivation of the silenced X-chromosome during oocyte maturation. Two X-chromosomes with two intact XIST loci are necessary for normal meiosis to occur in oocytes. Thus, impairment of the XIST locus results in meiotic arrest and oocyte depletion due to apoptosis.

• DIA gene (diaphanous gene): This gene, located on Xq21, is homologous to the diaphanous gene in Drosophila. DIA protein is abundantly expressed in the ovaries and other tissues and is important for establishing cell polarity and morphogenesis. DIA mutations in drosophila lead to sterility in both sexes. The Xq21 region contains at least 7 other genes involved in ovarian development. This region is pseudoautosomal (present on both X- and Y-chromosomes).

• Balanced autosomal translocations have been found in otherwise healthy women with POF.

• 46,XX gonadal dysgenesis/agenesis: Approximately two-thirds of cases with gonadal dysgenesis in individuals, who are 46,XX, are genetic. The inheritance is autosomal recessive and the penetrance is variable. Therefore, a possibility exists that some of the sporadic cases of karyotypically normal POF/premature ovarian insufficiency (POI) could be due to a mutant somatic gene for XX gonadal dysgenesis.

• 46,XX gonadal dysgenesis sometimes is a part of a genetic syndrome, such as gonadal dysgenesis and neurosensory deafness (Perrault syndrome); gonadal dysgenesis and cerebellar ataxia; gonadal dysgenesis, arachnodactyly, and microcephaly; and gonadal dysgenesis, short stature, and metabolic acidosis.

• Autosomal recessive disorders associated with POF/POI include Cockayne syndrome, Nijmegen breakage syndrome, Werner syndrome, Bloom syndrome.

• ATM gene (ataxia-telangiectasia MR gene), mutations in this gene, located on chromosome 11q22-23, are associated with ovarian atrophy and amenorrhea despite normal female sexual differentiation.

• BRCA1—earlier menopause in carriers of the mutation is associated with hypergonadotropic activity and may predispose to ovarian cancer at younger age.43

In a patient of POF suspected to have a genetic etiology, karyotype should be performed as a part of the routine evaluation after the diagnosis of POF/POI is established. A history of previous pregnancies or age older than 35 years should not discourage the test. X-chromosome abnormalities have been described in women who have had normal puberty, have delivered children without abnormalities and subsequently have developed POF/POI. In addition, unexpected karyotype findings may have important implications for relatives and for future pregnancies. A normal karyotype may be reassuring to the patient while an abnormal one could provide an explanation of the patient’s problem. Also, referral to a genetic counselor and testing for the FMR1 premutation may be required if a family history of POF, MR or a tremor/ataxia syndrome is present.

Genetics of Amenorrhea

Among 77 patients with primary amenorrhea, 27.3% revealed chromosomal abnormalities compared to 3.8% in 103 patients
with secondary amenorrhea. The term “ovotesticular dysgenesis” is used for the first time in the literature to describe a specific histologic type of streak gonad which contains ovarian stroma and dysgenetic testicular tubules. Important genetic causes of primary amenorrhea are:

Hypergonadotropic Hypogonadism
- Turner’s syndrome: This is caused by a 45, XO karyotype. Clinical manifestations of Turner’s syndrome include a webbed neck, short stature, broad shield-like chest, anomalous auricles, and hypoestrogenemia resulting in sexual immaturity.
- Gonadal dysgenesis fits the same pattern of high follicle-stimulating hormone (FSH) and luteinizing hormone (LH) and low estradiol (E2) levels. Gonadal dysgenesis is caused by a mosaic karyotype with an abnormal X-chromosome or with a normal karyotype (46, XX) and streak ovaries.
- Sawyer syndrome is illustrated by a phenotypically immature female with a 46, XY karyotype without testis-determining factor on the Y-chromosome.
- 22q11.2 deletion may be considered in females with Müllerian agenesis, in association with a history of learning difficulties and speech delay.

Hypogonadotropic Hypogonadism
Kallmann syndrome manifests with anosmia pubertal delay and a normal response to exogenous gonadotropins from an embryonic lack of protein coded for by the gene KAL1 which prevents gonadotropin releasing hormone (GnRH)-producing cells from migrating from the olfactory area to the hypothalamus.

Hirsutism
Hirsutism is defined as the excessive growth of thick dark hair in locations where hair growth in women usually is minimal or absent. PCOS is the most common cause of androgen excess and hirsutism. Virilization is minimal and hirsutism often is prominent in patients with PCOS. In women with PCOS, polymorphisms in the genes for the two isoforms of 5-reductase (SRD5A1 and SRD5A2) were evaluated as risk factors for PCOS and SRD5A1 haplotype was associated with severity of hirsutism.

Genetic causes of hirsutism are:
- Congenital adrenal hyperplasia (CAH): Children with CAH, the classic form of adrenal hyperplasia, may exhibit hirsutism. These children may be born with ambiguous genitalia, symptoms of salt wasting, and failure to thrive, and they may develop masculine features.
- Late-onset CAH: This condition usually occurs as an incomplete version of CAH and affects approximately 1-5% of women who are hyperandrogenic. In patients with late-onset CAH, hirsutism (without salt wasting symptoms) may not develop until adulthood.

Hirsutism and oligomenorrhea suggest 21-hydroxylase deficiency (elevated 17 alpha-hydroxyprogesterone). Another uncommon disorder is 3 beta-, 11-hydroxysteroid dehydrogenase deficiency (elevated 3 beta-, 11-hydroxysteroid levels), which may result in early-onset or late-onset CAH.

Genetics of Female Cancers
The concept of cancer as a genetic disorder resulting from accumulative genetic cellular damage (sporadic mutations) has long been recognized. Identification of these hereditary cancer syndromes may prove beneficial for an individual patient, but there are inherent difficulties. A reported family history may be erroneous, or a person may be unaware of relatives affected with cancer. In addition, small family sizes and premature deaths may limit the information obtained from a family history. Breast or ovarian cancer on the paternal side of the family usually involves more distant relatives than on the maternal side and thus may be more difficult to obtain.

Some of the known genetic factors involved in gynecological malignancies are listed below:
- p53 mutations are involved in about 50% of cases of sporadic ovarian cancers (Marks JR et al.).
- Inherited germline mutations account for 5-10% cases of ovarian cancers and 3% endometrial cancers.
- Absence of MSH2 expression is associated with a high-risk profile in early stage cervical cancer, but does not predict lymph node status with sufficient accuracy.

Hereditary Breast-ovarian Cancer Syndrome
BRCA1 or BRCA2 mutation account for about 75% and 10% of familial ovarian cancers, respectively. Breast and ovarian cancer are components of several autosomal dominant cancer syndromes. Those most strongly associated with both cancers are BRCA1 (on chromosome 17q) or BRCA2 mutation syndromes. There are no pathognomonic features distinguishing breast and ovarian cancers occurring in BRCA1 or BRCA2 mutation carriers with those occurring in noncarriers. Breast cancers occurring in BRCA1 mutation carriers are more likely to be estrogen receptor (ER)-negative, PR-negative, and human epidermal growth factor receptor 2 (HER2/neu) receptor-negative and have a basal phenotype. BRCA1-associated ovarian cancers are unlikely to be of mucinous or borderline histopathology.

In cross-sectional studies of adult populations, 5–10% of women have a mother or sister with breast cancer, and about twice as many have either a first-degree relative or a second-degree relative with breast cancer. Although reproductive, demographic, and lifestyle factors affect risk of ovarian cancer, the single greatest ovarian cancer risk factor is a family history of the disease. A large meta-analysis of 15 published studies by Stratton et al. estimated an odds ratio (OR) of 3.1 for the
risk of ovarian cancer associated with at least one first-degree relative with ovarian cancer.

Breast cancer is also a feature of the following inherited cancer syndromes:
- Li-Fraumeni syndrome due to TP53 mutations
- Cowden’s syndrome due to phosphatase and tensin homolog (PTEN) mutations and with mutations in CHEK2
- Heterozygous carriers of the AT gene
- Peutz-Jeghers syndrome
- Ovarian cancer has also been associated with:
  - Hereditary nonpolyposis colorectal cancer (HNPCC) in 3–5% cases
  - Basal cell nevus (Gorlin) syndrome
  - Multiple endocrine neoplasia type 1 (MEN1)

The family characteristics that suggest hereditary breast and ovarian cancer predisposition include the following:
- Cancers typically occur at an earlier age than in sporadic cases. For BRCA1 mutations, the lifetime risk of breast and ovarian cancer is about 80% and 40% respectively, compared with an 11% risk of sporadic breast cancer and about a 1% risk of ovarian cancer in the United Kingdom (UK). By 50 years of age, the risk of breast cancer in BRCA1 mutation carriers is 51% and 28% in BRCA2 compared with a 2% risk in the general population.
- Two or more primary cancers in a single individual. These could be multiple primary cancers of the same type (e.g. bilateral breast cancer) or primary cancer of different types (e.g. breast and ovarian cancer in the same individual).
- Cases of male breast cancer.
- Possible increased risk of other selected cancers and benign features for males and females.

Hereditary Non-polyposis Colorectal Cancer Syndromes

These cancers stem from germline mutations of one of five mismatch repair genes (MSH2, MLH1, PMS1, PMS2 and MSH6). Lynch II, which is a variant of hereditary non-polyposis colorectal cancer syndromes (HNPCC) is associated with an increased risk of endometrial cancers59 (30–39% cumulative risk by 70 years of age) and ovarian cancers53 (9% cumulative lifetime risk).

Lynch’s data for HNPCC families give a mean age for developing ovarian cancer at 43 years, about 15 years less than that for non-hereditary cancer.

Carcinoma Endometrium

Mutations in exon 3 of the beta catenin gene associated with beta catenin nuclear expression has been demonstrated to be a relatively early event during the endometrial hyperplasia-carcinoma sequence. A study by Moreno-Bueno G et al. evaluated the immunoreactivity of E- and P-cadherin in premalignant and malignant endometrial lesions and correlated their membranous expression with clinico-pathological features. Immunohistochemical staining was performed in 21 atypical endometrial hyperplasias (AEHs), 95 endometrioid carcinomas (EECs), and 33 non-endometrioid carcinomas (NEECs). Reduced E-cadherin expression was observed in 57.8% of the cases, being more frequent in NEECs (87.1%, p = 0.001) and carcinomas of more advanced stage (85.7% of stage III–IV carcinomas, p = 0.01). Upregulation of P-cadherin was observed in 28.6% of cases. This alteration was associated with the histology of the lesion, since it was found in 9.5% of AEHs, 27.7% of EECs, and 46.2% of NEECs (p = 0.021).

Management Strategies for Inherited Gynecological Cancers

- **Hereditary breast-ovarian cancers due to BRCA1/BRCA2:**
  - **For breast cancer risk:**
    - Start X-ray mammography at 35 years
    - Value of prophylactic mastectomy uncertain
  - **For ovarian cancer risk:**
    - Combined oral contraceptive pill use reduces risk by 60%
    - Screening for early ovarian cancer with CA-125 levels and transvaginal sonography
    - Prophylactic oophorectomy
    - Role of HRT after surgery is controversial as there is a relative risk of breast cancer of 1.3% with greater than 5 years of use.
- **Hereditary non-polyposis colorectal cancer:**
  - **For endometrial cancer risk:**
    - Annual screening from 25 to 35 years of age using transvaginal ultrasound and endometrial biopsy
    - Hysterectomy after completion of family
  - **For ovarian cancer risk:**
    - Prophylactic bilateral oophorectomy with prophylactic hysterectomy.

Cancer Stem Cell Therapy

Not all cancer cells have the same capacity to proliferate. In a variety of cancers it appears that most cancer cells have a limited ability to proliferate, while in the same tumors rare cells retain the capacity to proliferate indefinitely and to form new tumors. These tumorigenic cancer cells are called “cancer stem cells” because, like normal stem cells, they can self-renew and give rise to phenotypically diverse nontumorigenic progeny. Cancer stem cells are often phenotypically and functionally similar to normal stem cells from the same tissue.

These similarities have raised the question of whether it will be possible to develop therapies that eliminate cancer stem cells without eliminating normal stem cells. By understanding the mechanisms that regulate normal stem cell self-renewal, it is possible to identify rare mechanistic differences relative to cancer stem cell proliferation. Once
identified, these differences between the maintenance of normal stem cells and cancer stem cells can thus be targeted to eliminate cancer stem cells without damaging normal stem cells. Identification of drugs which can do so will reduce the toxicity of chemotherapy and facilitate regeneration of normal tissue after cancer treatment.

**GENETICS OF MALE INFERTILITY**

With advances in diagnostic modalities, it is now known that a significant proportion of infertile male with azoospermia and severe oligospermia have a genetic etiology for reproductive failure. Management of male factor infertility took a giant leap forward with the introduction of ICSI. But ICSI bypasses all the physiological mechanisms related to fertilization as well as all protective barriers against sperm with genetic defects and allow even altered spermatozoon to fertilize an oocyte.

Since infertile patients with nonobstructive azoospermia are able to achieve pregnancy with surgically retrieved testicular sperm, ICSI carries risk of transmitting both genetically determined diseases and genetically determined infertility. It is imperative for the gynecologist involved in the treatment of these couples to initiate genetic evaluation and counseling prior to any therapeutic procedures.

Some genetic causes of male factor infertility are described as:

- **Congenital bilateral absence of the vas deferens:** This is an important cause of obstructive azoospermia in otherwise healthy men. It is also present in 95% of men with an autosomal recessive systematic disease—cystic fibrosis. However, clinically affected cystic fibrosis (CF) patients present a spectrum of genital phenotypes ranging from normal fertility to severely impaired spermatogenesis and congenital bilateral absence of the vas deferens (CBAVD). Genetic studies revealed that 50–83% of patients with CBAVD have at least one known cystic fibrosis conductance regulator (CFTR) gene mutation and that approximately 10% have two known CFTR mutations. Most men with CBAVD have only one detectable gene mutation or variant. The most commonly found mutations are 508 (70%), 5T, R117H, R75Q, G542X, N1303, W1282X, G551A and R347H. In those men with mutations identified in both CFTR alleles at least one mutation is mild. More than 95% of CF men have abnormalities in the structures derived from Wolffian duct.

If a man with CBAVD is contemplating microsurgical epididymal sperm aspiration with subsequent ICSI, the complete spousal CF mutation analysis is mandatory to define the risk of passing along CF or CBAVD. If spouse is negative for the common mutation, her CF carrier risk is about 0.4%. A risk for this couple to have a child with CF genotype is no more than 0.2%. If the wife is a carrier, then the chances for child to have CF genotype is 50%.

- **Karyotype evaluation:** Chromosome studies in male infertility revealed abnormalities in 11.5% of 69 patients with azoospermia and 9.1% of 165 patients with oligospermia. The most common karyotype abnormality in men with severe male factor infertility is Klinefelter’s syndrome, affecting 7–13% of azoospermic men. Prevalence of Klinefelter’s syndrome is estimated at about 1 in 600 live-born males. The classic triad includes small firm testes, gynecomastia and azoospermia. 90% of all patients have 46XXY karyotype and 10% are mosaic with karyotype 46XY/47XXY. Sperm retrieval is possible in these patients despite severe histological changes (hyalinization of the seminiferous tubules and hyperplasia of the Leydig cells) with subsequent fertilization and pregnancy.

It has been suggested that almost one in twenty oligospermic men have an abnormal karyotype (mainly Robertsonian and reciprocal translocations). Karyotyping should therefore be regarded as a mandatory part of the pretreatment screening process for all men referred for ICSI.

- **Y-chromosome Microdeletions:** Constitute an important cause of male infertility. The spermatogenesis locus azoospermia factor (AZF) in Yq11 has been delineated into three microdeletion intervals designated as AZFa, AZFb and AZFc. AZFc is the most frequently deleted region. The Y-chromosome microdeletions cannot be predicted on the basis of clinical findings or the results of semen analysis, testing involves extraction of DNA from white blood cells and amplification of specific region of Y-chromosome in PCR containing 5–8 primer pairs. Each primer pair amplifies a specific region of Y-chromosome (a sequence-tagged site). Y-chromosome abnormalities will be passed on to any male child who is produced after the assisted reproduction. Since men with these genetic disorders are usually perfectly healthy, apart from infertility, it is uncertain if any other medical conditions will be present in the offspring.

**Management**

Testing is indicated in men with azoospermia and severe oligospermia, and in patients considering assisted reproduction. Genetic counseling is important prior to treatment. The detection for Y-chromosome microdeletions may provide the diagnosis for infertility and allow physician to direct patients to assisted reproduction or adoption. Komori et al. conducted chromosomal analysis of three male infants fathered by severe oligozoospermic males with Y-chromosomal microdeletions through ICSI. Two of the infants had the same Y-chromosomal microdeletions as their fathers. The third infant also had a Y-chromosomal microdeletion, which was longer than that found in his father. The results confirm that Y-chromosomal microdeletions are transmitted from a father to a son via ICSI and also
suggest that the microdeletions may be expanded during such transmission. Since sons of men with Y-chromosome microdeletions conceived with assisted reproduction will be infertile, child’s male factor infertility needs to be discussed.

Sperm Nuclear DNA Damage

“Paternal effect” can cause repeated assisted reproduction failures. In particular, with increasing experience of ICSI, it became evident that spermatozoa from some patients repeatedly fail to form viable embryos, although they can fertilize the oocyte and trigger early pre-implantation development. Pathologically increased sperm DNA fragmentation is one of the main paternal-derived causes of repeated assisted reproduction failures in the ICSI era.

An important subset of infertile men (about 5–15%), but not of fertile men, possess a complete protamine deficiency. Studies on transgenic animal models with targeted protamine deficiency suggest a link between protamine deficiency, sperm DNA damage and poor fertilizing capacity during IVF. This association between sperm DNA damage and protamine deficiency suggests that the damage may be due to a defect in spermiogenesis (the period during which sperm protamines are deposited). Sperm DNA damage has been associated with high levels of reactive O₂ species, high levels of which have been detected in the semen of 25% of infertile men which results in sperm dysfunction. Advancing age and gonadotoxins (e.g. cancer therapies) have been associated with reduced levels of germ cell apoptosis in the testis and an increased percentage of ejaculated spermatozoa with DNA damage, which suggests that in these men both spermatogenesis and apoptosis have been disrupted.

Direct assessment of DNA damage can be obtained by means of single-cell gel electrophoresis assay or “comet” assay (electrophoresis causes DNA fragments to migrate away from the central DNA core, revealing a “comet”), terminal deoxynucleotidyl transferase-mediated dUTP-nick end-labeling or “TUNEL” assay (the ends of fragmented DNA are tagged) and liquid chromatography to measure DNA oxidation levels. DNA damage can also be assessed indirectly by means of sperm chromatin integrity assays and by evaluation of nuclear protein levels.

Based on the current evidence, the clinical indications for tests of sperm DNA damage as follows:

- Counseling people who are planning their first pregnancy: If the male partner has high levels of sperm DNA damage, the couples should be counseled to consider advanced forms of assisted reproduction (IVF or ICSI) to achieve a pregnancy.
- Counseling people planning to undergo IVF or ICSI.
- Monitoring the potential risk to offspring. Further study using longer follow-up periods is necessary to ascertain the real risk of birth defects and the potential future development of genetically linked diseases.

DISORDERS OF SEXUAL DIFFERENTIATION

According to Allens’ method of classification, there are five major categories of intersex patients:

Ovary Only: Female Pseudohermaphrodite

This is a 46XX patient with two normal ovaries and a uterus, with virilized external genitalia due to the endogenous overproduction of androgens by the fetal adrenal glands: CAH, adrenogenital syndrome (AGS). These patients account for approximately two-thirds of intersex states in clinical practice.

Maternal androgens intake and endocrine abnormality in the mother are other rare causes.

Testis Only: Male Pseudohermaphrodite

This is a 46XY patient with inadequate virilization of the external genitalia of a varying degree due to deficient biosynthesis of testosterone (TST), inadequate conversion of TST to dihydrotesterone (DHT) due to lack of 5α-reductase or inadequate androgen (TST/DHT) utilization (lack of androgen receptors). This category also includes patients with anti-Müllerian hormone (AMH) deficiency who exhibit adequate male external genitalia with retained Müllerian structures, i.e. tubes and uterus (hernia uteri inguinalis).

Androgen Insensitivity (Testicular Feminization)

- Currently, the basic pathophysiology of the lack of androgen effect on the genitalia is understood more fully. Some patients are receptor negative; their cytosol receptors cannot bind DHT. Another variant is receptor positive in which receptors apparently permit DHT binding, but DHT does not lead to normal differentiation toward the male phenotype. Assays of genital skin fibroblasts elucidate the difference between receptor-negative and receptor-positive types.
- Inheritance appears to be X-linked. Complete androgen insensitivity presents in infancy only if the child has a shallow blind-ending vagina, reflecting the lack of internal Müllerian development expected in an XY patient whose testes manufacture Müllerian-inhibiting substance (MIS) at reference range levels.
- Inguinal hernias are common in testicular feminization, and an occasional case is detected during inguinal herniorrhaphy when a gonad is present in the hernia and a fallopian tube cannot be seen. Failure to identify an internal Müllerian structure in a phenotypic female with an inguinal hernia should always raise the possibility of testicular feminization. If not detected in this fashion, diagnosis usually is not made until puberty, when the
patient presents with amenorrhea. Although, these characteristics are not noted early in life, these girls exhibit a body hair deficiency as they age and their breasts, although well formed, characteristically are deficient in stroma.

- Despite a 46XY karyotype and gonads with the typical appearance of testes (perhaps altered similarly to those with cryptorchidism), a feminine gender assignment is unquestionable because of the completely feminine phenotype and because end-organ failure prevents endocrinologically produced masculinization. Confirmation of the diagnosis is crucial because the syndrome is associated with a significant incidence of gonadal malignancies. Malignant tumors are termed germinomas or, more properly, seminomas because the tumors arise in a testis. The youngest reported age of occurrence was 14 years. Overall frequency of gonadal malignancies is approximately 6%, with incidence rising to more than 30% by age 50 years. Sertoli cell and Leydig cell tumors have been reported. Tubular cell adenomas, also fairly frequent, have a potential for malignancy because neoplastic transformation has been reported.

Testis Plus Ovary: True Hermaphrodite

In this disorder the patients possess both ovarian and testicular tissue in various combinations. Their karyotype also varies, i.e. 46XX, 46XY or mosaic 46XX/46XY. True hermaphrodites make up approximately 10% of intersex cases.

Testis Plus Streak Gonad: Mixed Gonadal Dysgenesis

This is the second most common category of intersexuality. The most common karyotype of these cases is 45XO/46XY mosaicism. The existing dysgenetic testis is infertile and Müllerian structures may be present on both sides. There is a high-risk of neoplastic degeneration (gonadoblastoma) of the existing testis after puberty.

Raifer and Walsh⁷⁰ prefer an elective feminine gender assignment for patients with mixed gonadal dysgenesis (MGD) because a uterus and vagina always are present and one-half of patients are markedly short and have a high incidence of inadequate external virilization.

Streak Plus Streak: Pure Gonadal Dysgenesis

This group of phenotypic females with bilateral gonadal streaks comprises three separate sub-groups based on their karyotypes: 45XO (Turner’s syndrome), 46XX and 46XY. The latter sub-group is particularly prone to malignant degeneration of the streak gonads. Therapy in these children (from an intersex standpoint) primarily is limited to appropriate estrogen and progesterone support.

REFERENCES


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INTRODUCTION

The breast is a dynamic organ throughout a woman’s life. As a primary healthcare provider for women, a gynecologist should thoroughly understand the preventive aspects and management of all common female breast problems.

Until the advent of modern specialization in the field of breast oncology, all aspects of breast pathology were parts of a gynecologist’s “kingdom”. No longer! The great tragedy of this modern trend is the plight of the female patient. All her life she has confided her reproductive health problems to her obstetric and gynecologist practitioner. She definitely considers the breast an area that she would be comfortable talking about to her gynecologist rather than to a breast oncologist.

Being the most common cancer in women, the ladies across all socioeconomic strata foster the quest for breast cancer prevention and early diagnosis. The medicolegal system holds the gynecologist as a primary healthcare provider, responsible for the breast assessment and detection of breast cancer. It is high time the gynecological realm regained its “lost kingdom”.

MASTALGIA

Mastalgia is the most common breast complaint in women and is often a concern for the patient because of the fear of cancer. In a study conducted in the US, 69% of women reported regular premenstrual discomfort and 36% consulted healthcare providers about the symptoms. Mastalgia was moderate to severe in 11% (Table 1). In patients with breast-related primary complaints, pain is most commonly reported in every age group over 34 years. Breast pain is either cyclic or noncyclic. Cyclic mastalgia is more common, 50–80% of women experience pain and swelling in breasts before menstruation. Cyclic breast pain peaks premenstrually, lasts for a mean period of 5 days and resolves with the onset of menses. The pain is usually moderate to severe in intensity and may be unilateral or bilateral. It is common in women receiving cyclical estrogen. In most women, there is a spontaneous cessation of pain or in some, cessation of pain is associated with hormonal changes, e.g. pregnancy or menopause (Table 1 and Flow chart 1).

Noncyclic Breast Pain

Noncyclic breast pain has three subtypes:

Idiopathic

This breast pain may be intermittent, continuous or irregular, bilateral or unilateral. It is sharp, burning or stabbing in nature and subsides spontaneously.

Secondary

Breast pain along with benign breast lesions (e.g. macrocysts, ductectasia and fibroadenoma). It is caused by tension on other breast structures.

Table 1: Mastalgia classification

<table>
<thead>
<tr>
<th>Feature</th>
<th>Cyclic</th>
<th>Noncyclic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of presentation</td>
<td>30s</td>
<td>40s</td>
</tr>
<tr>
<td>Site</td>
<td>Bilateral</td>
<td>Unilateral</td>
</tr>
<tr>
<td>Localization</td>
<td>Diffuse</td>
<td>Well localized</td>
</tr>
<tr>
<td>Type of pain</td>
<td>Dull, aching</td>
<td>Sharp, stabbing</td>
</tr>
<tr>
<td>Association with menopause</td>
<td>Rare</td>
<td>12%</td>
</tr>
<tr>
<td>Efficacy of hormonal treatment</td>
<td>80%</td>
<td>40%</td>
</tr>
</tbody>
</table>
Referred Pain

This pain arises from musculoskeletal structures of chest, e.g. costochondritis, pectoral muscle spasm.

Two major theories about causes of mastalgia are:

1. **Role of diet:** According to some sources, intake of methylxanthines causes breast pain. However, several randomized clinical trials of dietary caffeine reduction have shown minimal changes in pain.

2. **Role of hormones:** It seems logical that breast pain in phase with the menstrual cycle has a hormonal origin. The pain usually is relieved by a disruption of the hormonal milieu including drugs, menopause and surgery. Yet, few consistent abnormalities have been identified. Circulating hormone levels are normal in cyclic mastalgia patients. With normal levels of circulating hormones, attention has been turned towards theory of altered receptors sensitivity. The histopathological findings of patients with mastalgia do not appear significantly different from that of controls.

Treatment consists of symptomatic measures:

1. Support brassieres
2. Local application of heat or cold
3. Analgesics.

Dietary recommendations include elimination of methylxanthines and taking of vitamins E, A and B-complex which may have a placebo effect. Decreasing fat intake may improve breast swelling, tenderness and nodularity.

**Drug Therapy**

*Danazol:* 200 mg/day produced an improvement in 70% of cases of cyclical and 30% of cases of noncyclical mastalgia.

*Bromocriptine:* Less effective than danazol but may decrease mastalgia. Most effective for cyclical mastalgia. Dose should be 1.25 mg nightly for one week and then 2.5 mg nightly for 2 months.

*Evening primrose oil:* It is used as an initial attempt to control cyclic breast pain because of its low incidence of side-effects. It may be most useful in younger women who need long-term treatment as well as those who wish to avoid hormonal manipulation.
Tamoxifen: In dose of 20 mg/day improves 70% cases but is not Food and Drug Administration (FDA) approved for this indication.

Gonadotropin-releasing hormone (GnRH) analog (goserelin) 3.6 mg monthly depot injection is effective but influences the menstrual cycle and causes osteoporosis on prolonged use. Moreover, it is expensive.

Testosterone undecanoate (Restandol) 40 mg BD is effective. Androgenic side-effects after 3 months of treatment are often the limiting factor in its use.

The response to treatment can be assessed by Cardiff Breast Score (Table 2).

### NIPPLE DISCHARGE

The secretion of fluid from the nipple of a newborn baby or any mature woman is not unusual, nor is it a sign of underlying breast disease. Nipple discharge is more commonly associated with benign rather than malignant lesions. A bilateral nipple discharge usually has a systemic cause, rather than a local one. However, a unilateral nipple discharge may be due to individual breast responsiveness to systemic causes.

There are seven types of nipple discharge (Table 3):
1. Milky
2. Multicolored and sticky
3. Purulent
4. Clear or watery
5. Yellow or serous
6. Pink or serosanguinous
7. Bloody or sanguinous.

The first three types are usually managed by medical treatment. Although the cause of last four types is usually of a benign nature, they can be due to cancer or precancerous conditions and, therefore, require surgery to obtain tissue for histologic examination.

Discharge can also be classified as:
1. **Physiologic discharge**: It is serous, unilateral or bilateral and comes from multiple ducts. This discharge occurs from two neurogenic reflexes from the breast, one to the anterior pituitary that inhibits dopamine and stimulates prolactin and one to the posterior pituitary that stimulates oxytocin.
2. **Pathologic discharge**: It occurs in benign lesions such as intraductal papilloma and duct ectasia as well as carcinoma nipple discharge that is nonlactational, spontaneous, unilateral, serous or bloody and single duct in origin is more likely to have pathologic significance. The incidence of malignancy in patients with nipple discharge increases with age and with the presence of breast mass. A bilateral, spontaneous, multiple duct, milky type of discharge, that is usually seen in patients of childbearing age is referred to as galactorrhea. It is due to increased production of prolactin. The condition is most commonly observed after pregnancy and can last 1 to 2 years longer. The patient should be tested by obtaining a serum prolactin. A thin-layer chromatography test for lactose can be performed to verify that the discharge is actually milk. The treatment of a pathologic nipple discharge is surgical excision of the involved duct. Preoperatively mammography ductogram (in which contrast medium is cannulated into the duct, will identify the affected duct.

### BREAST LUMPS

Dominant lumps are clinically benign breast lesions that are persistent. Their diagnosis is important to distinguish them from carcinomas. The most common benign lumps are macrocysts, galactoceles and fibroadenoma. They can be diagnosed by fine needle aspiration but definitive diagnosis requires histologic proof of the nature of tumor (Table 4 and Flow chart 2).

#### Macrocysts

They are the most common lumps, manifested between 35 and 50 years. Usually these cysts disappear after menopause. Clinically these cysts can be silent or painful and may cause palpable lumps or be seen on ultrasonography. Aspiration is both diagnostic and therapeutic. A few patients will develop multiple cysts that can cause anxiety and discomfort. These cysts can be usually managed by periodic aspirations and menopause brings relief.

#### Galactocele

This cyst is formed by overdistention of a lactiferous duct. It is simply a milk-filled cyst. It presents as a firm nontender mass in the breast. Diagnostic aspiration is often curative.
Table 4: Diagnosis of breast lumps

<table>
<thead>
<tr>
<th>Method</th>
<th>Positive aspects</th>
<th>Negative aspects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical examination</td>
<td>Easy to perform</td>
<td>Low sensitivity in women aged &lt; 50</td>
</tr>
<tr>
<td>Mammography</td>
<td>Useful for screening women aged &gt; 50</td>
<td>Requires dedicated equipment and experienced personnel</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Low sensitivity in women aged &lt; 50. Unpleasant (discomfort)</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>Same sensitivity in all ages</td>
<td>Operator-dependent less sensitive and less specific than mammography</td>
</tr>
<tr>
<td></td>
<td>Useful in assessing impalpable lesions</td>
<td></td>
</tr>
<tr>
<td>Fine-needle aspiration</td>
<td>Cheap</td>
<td>Operator-dependent Needs an experienced cytopathologist</td>
</tr>
<tr>
<td>cytology</td>
<td>High sensitivity</td>
<td>Painful</td>
</tr>
<tr>
<td></td>
<td>Provides definitive diagnosis in most instances. Low</td>
<td></td>
</tr>
<tr>
<td></td>
<td>incidence of false positives</td>
<td></td>
</tr>
</tbody>
</table>

**Fibroadenoma**

These are the most common benign solid tumors of the female breast. They are most common in women younger than 25 years. They are hormone responsive tumors and may increase in size toward the end of each menstrual cycle. Clinically they present as a painless, well-circumscribed freely movable tumors also known as breast-mouse. These tumors do not regress spontaneously so simple gross excision is the treatment of choice.

**BREAST CANCER**

Past investments in basic science and breast cancer research have brought us to a point where numerous opportunities exist to advance our ability to prevent and treat breast cancer. The incidence of breast cancer is increasing day by day, perhaps due to dietary and lifestyle changes seen in urban populations of developing countries.

**Risk Factors (Table 5)**

The most remarkable risk factors are increased age, family history in a first-degree relative and geographical location.

**Flow chart 2: Investigation and treatment of breast lump**

Abbreviations: FNAC, fine-needle aspiration cytology; MRI, magnetic resonance imaging

of birthplace. First pregnancy and delivery at an earlier age appear to decrease breast cancer risk. Nulliparity, early age at menarche, older age at menopause increase the risk of breast cancer. Oophorectomy at an early age is considered protective, reducing the risk of cancer by 70%. The fact that the total duration of ovarian activity is related to the risk of breast cancer implicates natural ovarian hormones in the initiation or further progress of the disease. The risk increases in women taking oral contraceptives for 5 years or more. Mutations in gene \( BRCA 1 \) (located on chromosome 17 having tumor suppressor capabilities) produce susceptibility to both breast and ovarian cancer.

Carcinoma present clinically as ill-defined, firm mass without pain or cyclic variation. It is associated with inflammation or dimpling of skin and palpable axillary lymph nodes.

### Staging

It is staged initially on a clinical base, which includes physical examination, radiological evaluation and laboratory workout.

It includes physical examination, a complete blood count, mammography liver function tests and chest radiograph.

The staging system used is the malignant tumors (TNM) classification. This system more accurately assesses prognosis which is related to the extent of axillary disease.

### Management

Treatment consists of total mastectomy or breast conserving therapy.

Breast conserving treatment is recommended as the preferred treatment for stage I and II invasive breast cancer. This includes lumpectomy, axillary node dissection and postoperative radiation therapy. Modified radical mastectomy involves removing the breast totally, dissecting the axilla and preserving both pectoral muscles. The patients with large tumors and other associated unfavorable prognostic factors should be given adjuvant chemotherapy.

The most common regimens are:
1. Cyclophosphamide, methotrexate and 5-fluorouracil (CMF).
2. 5-fluorouracil, adriamycin and cyclophosphamide (FAC).

### PREGNANCY AND BREAST LUMPS

Two percent of breast carcinomas are diagnosed during pregnancy but pregnancy does not change the outcome of cancer. It has, however, been shown to delay diagnosis. Any breast lesion should be evaluated as it would in the nonpregnant patient to prevent diagnostic delay and early management. Screening mammography can be postponed to limit fetal exposure. If cancer is suspected, however, shielding will protect the fetus and diagnostic mammography can be performed.

If breast cancer is diagnosed, treatment options depend on what trimester the patient is in. In general, management remains the same as for the nonpregnant women during the first and second trimesters, mastectomy and axillary dissection may be done. Radiation is contraindicated because of fetal risks. If diagnosed in third trimester, the patient may elect to be observed until delivery when prompt treatment is initiated. Most tumors recur within 2 years of treatment. So patients are advised to avoid pregnancy during this time.

### AMERICAN CANCER SOCIETY GUIDELINES FOR PREVENTIVE BREAST CARE (FIG. 1)

- Breast self-examination
  - Monthly for women greater than 20 years of age
- Clinical breast examination
  - Every 3 years for women 20–40 years of age
  - Every year for women over 40 years of age

![The diagnostic triad](Fig. 1: The diagnostic triad)
Role of Obstetrician and Gynecologist

The obstetrician or gynecologist should know about the breast diseases, both benign and malignant. When a breast disorder is diagnosed requiring patient’s referral, the following must be done:

- Explain the patient about the disease.
- Explain that she needs further care.
- Provide her the names of qualified oncologist from whom she can receive care. Women with breast cancer require multidisciplinary team effort. The gynecologist must be an informant in their care.

Hormone Replacement Therapy and the Breast

The traditional belief that hormone replacement therapy (HRT) is an absolute contraindication in breast cancer survivors is now challenged and has led to a reassessment of its role in breast cancer etiology. Postmenopausal HRT acts on women who otherwise would be subject to little, if any, endogenous hormonal stimulation. As the late natural menopause increases the risk of breast cancer, there is concern about the use of HRT in women. But the reason for its use is the decreased sensitivity of mammary tissue to hormones with age. The body weight affects the relationship between HRT and breast cancer risk. The risk of having breast cancer increases with increasing duration of its use. The effect disappears about 5 years after stopping HRT use. Family history of breast cancer is of significance in concern about the safety of HRT. Combined HRT with progesterone carries more risk than unopposed (estrogen only) HRT. Whether HRT should be given after breast cancer is controversial. Some studies say that HRT is contraindicated for a woman who has had breast cancer as estrogen may stimulate proliferation of residual cancer cells. Others suggested that some women may be troubled by symptoms of estrogen withdrawal. So the decision whether to start HRT or not should be individualized.

Tissue-specific HRT Agents (Table 6)

Hormone replacement with estrogens has many beneficial effects in the body, but has some disadvantages, since it affects all estrogen-sensitive tissues, e.g. estrogens stimulate receptors in a breast tissue which can induce breast tenderness. Moreover, long-term use is potentially associated with a slight, albeit, small, increased risk of breast cancer. That is why various tissue-specific agents are developed (Table 7) so that long-term HRT can be safely given.

Phytoestrogens: These are naturally occurring plant sterols which have an action similar to estrogen. Diets rich in soy foods (phytoestrogens) increase LH levels and also reduce estrogen levels through various mechanisms. They modify the hormone production and hormone metabolism, thus limiting the cancer growth. Phytoestrogens relieve postmenopausal symptoms without stimulating breast tissue. These are known to inhibit the growth of breast cancer cell lines.

Raloxifene: This new agent is selective estrogen receptor modulators (SERMs). It reduces breast pain significantly as compared to HRT. It has antiestrogenic action in breast tissue and reduces the incidence of invasive breast cancer by 76% and estrogen receptor positive tumors by 90%. However, raloxifene is not approved for this indication in the United States.

Tibolone: Tibolone has important effects on the breast that are different from those of estrogens. Unlike conventional HRT, women using Tibolone rarely complain of breast tenderness. There is no evidence of carcinogenicity for preclinical studies of Tibolone. Tibolone and its metabolites are very potent inhibitors of the stimulation of breast tumors.

Benefits of Lactation

From embryo to puberty, the breasts of the human male and female are the same, both histologically and functionally. The increase of estrogen and progesterone beginning at puberty is responsible for ductal growth and lobuloalveolar development. Changes during pregnancy, both hormonal and structural, prepare the breast for lactation (Table 8). A modern contraceptive effect accompanies lactation. This effect is temporary and is less reliable. The effectiveness of lactation as a contraceptive depends on the level of nutrition of the mother, the intensity of suckling and the extent to which supplemental food is added to the infant diet. Women who wish to breastfeed but avoid pregnancy should use a mechanical method of contraception beginning 4–5 weeks postpartum.

When breastfeeding is used exclusively and menstrual bleeding has not occurred, ovulation does not occur before the end of the 10th postpartum week.
Enhancement/Suppression of Lactation

To improve adequate milk yield, following steps have to be taken:
1. To guide the mother about nursing the baby, mentioning the advantages of breastfeeding.
2. Nipple care and preparation including advising the patient how to express out the colostrum and to take care of the crust formed on the nipples.
3. Advise the mother to feed the baby every 4–6 hours.
4. To prevent engorgement and trapping of milk, manual expression prior to nursing.

Suppression of Lactation

This is required when the baby is born dead or dies in infancy or in conditions where nursing is contraindicated like women with cytomegalovirus, chronic hepatitis B and human immunodeficiency virus (HIV) infection. The hormones suppress lactation only if started soon after delivery. These suppress lactation through inhibition of pituitary hormone.

Treatment

- Drugs which can be given are:
  - Ethynyl estradiol 0.05 mg twice daily for 5 days.
  - Combination of testosterone and estrogen (Mixogen) 2 ampoules intramuscularly.
  - Pyridoxine 100 mg 2 tabs three times a day for 2 days and then 1 tab three times a day for 3 days.
- Tight compression bandage of breast for 3 to 4 days.
- Analgesics to relieve pain
- Application of cold packs
- Bromocriptine, a dopamine agonist stimulates the production of prolactin inhibitory factor, which in turn causes a fall in plasma prolactin and the suppression of lactation.

Breast Problems during Lactation

Breast Engorgement

This develops after 2 to 3 days of starting lactation. The breasts become distended, firm and nodular. This condition is also known as caked breasts. It produces considerable pain and may be accompanied by a transient elevation of temperature.

Table 8: Mechanism of amenorrhea and anovulation in lactating mothers

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repeated suckling stimulus of breastfeeding increased prolactin concentration</td>
<td>FSH concentration in normal range LH values below normal</td>
</tr>
<tr>
<td>FSH concentration in normal range</td>
<td>Ovaries show less follicular growth No LH surge</td>
</tr>
<tr>
<td>Ovaries show less follicular growth</td>
<td>Hypoestrogenic state amenorrhea Anovulation</td>
</tr>
<tr>
<td>Hypoestrogenic state amenorrhea</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: FSH, follicle-stimulating hormone; LH, luteinizing hormone.

Puerperal fever from breast engorgement is common. It ranges from 37.8°C to 39°C. The incidence and severity of fever associated with it was lower if treatment was given for lactation suppression. Treatment consists of supporting the breasts with a binder, applying an ice bag and any analgesic. Manual expression of milk may be required.

Mastitis

It is occasionally observed during the puerperium and lactation. Suppurative mastitis usually develops before the end of the first week postpartum. It is invariably unilateral and engorgement of breast precedes the inflammation, the first sign of which is chills followed by fever and tachycardia. Most commonly offending organism is *Staphylococcus aureus*, others are group B *Streptococcus* and *Streptococci viridans*. Source of organisms is usually infant’s nose and throat. Staphylococcal infections are caused by organisms sensitive to penicillin or cephalosporins. Erythromycin is recommended to penicillin-sensitive women.

Abscess

Abscess development is either from failure of deferences within 48–72 hours or development of a palpable mass. Surgical drainage under general anesthesia is required. The incision should be made corresponding to skin lines for a good cosmetic result.

Galactocele

It is produced by clogging of a duct by milk secretion, milk may accumulate in one or more lobes of the breast. Excess accumulation may form a fluctuant mass that may give rise to pressure symptoms. Mostly they resolve spontaneously or require aspiration.

Nipple Abnormalities

Retracted nipples: The lactiferous ducts open directly into a depression at the center of the areola. When the depression is superficial, milk can be expressed with use of a breast pump.

Cracked nipples: The fissures on the nipple almost invariably render nursing painful. Such lesions provide a convenient portal of entry for pyogenic bacteria. So for healing protect them from further injury with a nipple shield and topical medication.

Abnormalities of Secretion

There are individual variations in the amount of milk secreted, which are dependent upon the development of the glandular portions of the breasts. Very rarely, there is complete lack of mammary secretion (agalactia). Occasionally the milk secretion is excessive (polygalactia).
SUMMARY

As a primary healthcare provider, a gynecologist plays a vital role in the prevention and management aspects of breast problems. The most common breast problems faced by a woman are mastalgia, nipple discharge and breast lumps. Patients with breast problems should be thoroughly investigated for underlying breast pathologies. As breast carcinomas constitute the second most common cancers in women, women above age of 35 years should undergo screening for breast cancer regularly as per guidelines. Tissue-specific HRT agents like SERMs can be given safely to women without increased risk of breast cancer. Naturally occurring phytoestrogens play a major role in prevention of breast cancer globally in the near future by dietary means.

REFERENCES

INTRODUCTION

Litigation in obstetric practice has become an important issue. It has become mandatory for doctors in hospitals and private practices to acquire sufficient knowledge related to modern management, document carefully in writing their procedural and management plans and to become familiar with the legal aspects of medical practice. Adequate communication and a written patient’s consent form are of paramount importance.\(^1\)

The 2006 American College of Obstetricians and Gynecologists (ACOG) Professional Liability Survey revealed that 89% fellows had been sued during their careers. There was an average of 2.6 claims per obstetrician. Sixty-two percent of obstetrics and gynecology claims were from obstetrics.\(^2\)

A trend is noticed in the United States that doctors in obstetrics and gynecology now prefer to leave their field rather than risk a lawsuit. Some retire early, some move out of state while others switch careers. One-third of United States hospital residency positions in obstetrics were found to be empty in 2005.\(^3\)

The increasing trend of litigations has been forcing doctors all over the world to indulge in defensive practice. The cascade of unnecessary tests, procedures and interventions just to be at “safe” side has increased the cost of medical care manifold.\(^4\)

Once thought as a phenomenon of the west, litigation in medical practice is rapidly increasing in India.

REASONS FOR OBSTETRIC LITIGATION

A perfect baby is the expectation of all parents, and a perfect outcome is the mission of obstetrics. The public expectation of perfection in obstetric medicine reflects a belief that a bad outcome in obstetrics is always the result of negligence. It is suggested that this should not be tolerated and every maternal-fetal injury merits financial compensation and punishment.\(^5\)

Displeasure against the healthcare providers due to lack of communication, poor attitude or more so because of a poor outcome are causative factors for litigation. Sometimes financial benefits are sought and often rather unfortunately other members of the medical fraternity instigate the patient and her relatives.

Course of the Complainant

Medical negligence arises from an act or omission by a medical practitioner, which no reasonably competent and careful practitioner would have committed. What is expected of a medical practitioner is “reasonably skillful behavior” adopting the “ordinary skills” and practices of the profession with “ordinary care”.\(^6\)

There is, however, room for ambiguity and judicial interpretation, as what is “reasonable” and “ordinary”.

To establish a doctor as negligent, it has to be proved that
1. The doctor did not conform to the standard of medical care expected from him
2. The doctor was derelict and committed a breach of duty
3. The patient suffered actual damage
4. The doctor’s conduct was the direct or proximate cause of that damage.

It is the responsibility of the patient or her family to establish these four points.
Avenues of Redress

Local Professional Medical Body, usually the State Medical Council

If it finds the medical practitioner guilty, he can be punished by removing his name from the medical register either permanently or for a specified period.

Consumer Court under Relevant Sections of the Consumer Protection Act

In 1995, the Supreme Court decision in Indian Medical Association versus VP Shantha brought the medical profession within the ambit of a “service” as defined in the Consumer Protection Act (CPA), 1986. Patients who had sustained injuries in the course of treatment could now approach the Consumer Dispute Redressal Forum, which is easier and less expensive than going to court. The aggrieved person can represent himself and need not hire a lawyer.

Civil Law or the Law of Torts

In cases where the services offered by the doctor or hospital do not fall in the ambit of “service” as defined in the CPA, patients can take recourse to the law relating to negligence under the law of torts and successfully claim compensation. The onus is on the patient to prove that the doctor was negligent and that the injury was a consequence of the doctor’s negligence.

Criminal Law

In certain cases, negligence is so blatant that it invites criminal proceedings. Death owing to medical negligence is a matter for the criminal court under the Indian Penal Code (IPC). Section 304A of the IPC deals with death caused by rash and negligent acts. According to a recent Supreme Court decision, the standard of negligence required to be proved against a doctor in cases of criminal negligence (especially that under Section 304A of the IPC) should be so high that it can be described as “gross negligence” or “recklessness”, not merely lack of necessary care. Criminal liability will not be attracted if the patient dies due to error in judgment or accident. Even if a patient survives, but suffers from “the effects of alleged grievous injuries sustained during treatment”, the medical practitioner can be arrested under either Section 337 or 338 of the IPC. When a First Information Report (FIR) is filed against a doctor for the death of a patient under his treatment, the doctor can be arrested.

Drug Use in Pregnancy and Lactation

Prescribing drugs to pregnant women require the balancing of benefits and risks. Only a small proportion of drugs are known to be harmful to the fetus, but for the vast majority of drugs, little evidence of fetal safety exists. It has to be noted that the absence of evidence of harm is not the same as evidence of absence of harm.

The risk to the fetus should not be exaggerated. For a drug to cause birth defects, a number of criteria must be fulfilled.
- The drug exposure must take place at a critical stage of pregnancy
- The dose must be high enough to cause a threshold of exposure for an appropriate duration of time.

For most of the known human teratogens greater than 90% of pregnancies exposed during the first trimester still result in a normal offspring.

The dearth of randomized controlled trials confirming the efficacy, quality and safety of drugs used in pregnant women means that off-license prescribing in this vulnerable patient population is commonplace. A doctor could be exposed to a claim of negligence solely for using an off-license drug if harm was caused and if a licensed alternative was available. However, it is more likely that a failure to provide adequate information on which a patient can give informed consent will result in litigation.

The Food and Drug Administration (FDA) classification of drug use in pregnancy is helpful for guidance.

Congenital Abnormalities

Improvements in sonography have led to tremendous advances in prenatal care, but these advances have given rise to expectations that cannot always be fulfilled. In consequence, women who have had children with malformations not detected antenatally have sought legal recourse. Incidentally, 80% of suits in sonography are obstetric-related. These suits come under the category of tort law, where

Table 1: Causes for litigation in obstetrics

- Drugs in pregnancy and lactation
- Congenital abnormalities
- Sex selection tests
- Fetal surveillance tests
- CS by request and vaginal birth after cesarean (VBAC)
- Difficult and instrumental vaginal delivery
- Cerebral palsy and late sequelae
- Postnatal perineal trauma
- Perinatal and maternal mortality
damages are sought to compensate those whose interests have been harmed.

Early pregnancy interventions such as chorionic villus sampling and amniocentesis are done for fetal assessment. Counseling should involve the predictive values of the tests and procedure related complications. A written consent should be obtained.

By establishing a system of training, certification and quality control, physicians can be involved in patient care without the fear of litigation.

**Sex Selection**

In view of the falling sex ratio, the Indian Government promulgated the prenatal diagnostic techniques (PNDT) Act in 1994. The act was amended in 2002, considering the persistent widely prevalent practice of use of various regimens of sex preselection by people as well as unscrupulous medical practitioners. It is a fact that realization of the value of daughters by their own families is the need of the hour. Only the strict enforcement of PNDT act will not do.

**Fetal Surveillance Tests**

A small blip in the electronic fetal heart rate (FHR) tracing could be absolutely harmless, but may be of great significance in the courtroom should there be an adverse fetal outcome.

Fetal monitoring cases can be divided as follows:

- Medical management failures (misinterpretation of fetal monitor tracing, failure to respond promptly to fetal monitoring indicating distress, etc.)
- Technical failures (loss of monitor tracings, interruption in the tracing at a critical time, unreadable tracings, etc.)

A review of litigation cases reveal that the majority of claims relating to the intrapartum period arise because of misinterpretation of the cardiotocograph (CTG) or because inappropiate action was taken in the presence of FHR abnormalities. Compulsory education and training in the interpretation of CTGs are key factors in minimizing the threat of litigation. Newer methods, such as pulse oximetry or fetal electrocardiogram waveform analysis, if available, can serve as adjuncts to CTG and help to avoid birth asphyxia and hence litigation.

Meta-analysis of the randomized controlled trials comparing EFM with auscultation have found an increased incidence of cesarean delivery and decreased neonatal seizures but no effect on the incidence of cerebral palsy or perinatal death.

In a Swedish analysis of medicolegal cases related to intrapartum events, it was seen that in the majority, there had been a normal pregnancy and a spontaneous start of labor (78%). At the beginning of labor, 87% showed a normal FHR pattern. In 70%, however, there was adverse fetal outcome with brain damage or death. The most common reason for disciplinary action was improper interpretation of fetal monitor tracings and corresponding failure to recognize fetal distress (76%). Injudicious use of oxytocin was also common (68.5%), and was the primary reason for disciplinary action in 33% of the cases.

**Cesarean Section by Request and VBAC**

The increase in the rates of cesarean section (CS) is a global phenomenon. The number of women are requesting for CS, a rate of CS which is not medically indicated is also increasing. A survey of London female obstetricians found that 31% would prefer delivery by CS and fear of perineal damage was stated to be the main reason for this preference.

A study by the Indian Council of Medical Research (ICMR) in 33 tertiary care institutions noted that the average CS rate increased from 21.8% in 1993–1994 to 25.4% in 1998–1999. Contrary to the common belief, high CS rates have not contributed to an improved pregnancy outcome as revealed in the 2005 WHO global study. A higher rate of cesarean delivery in this study was associated with a greater risk of maternal and newborn illness and death. Strategies to curb the rates of CS call for a reduction in primary CS and to encourage vaginal delivery for those with previous CS. Very careful monitoring and facilities for emergency surgery are essential.

One must remember that a mother can also sue the doctor for an unnecessary CS, especially when something goes wrong.

**Difficult and Instrumental Vaginal Delivery**

An uneventful vaginal delivery is the most desired outcome in obstetrics but is unfortunately quite unpredictable. Difficulties in delivery like shoulder dystocia and the need of ventouse or forceps may arise at any stage.

Shoulder dystocia is a horrifying experience for any obstetrician and may end up in litigation. Despite the identification of various clinical risk factors, our ability to predict and prevent shoulder dystocia remains limited. Effective and timely clinical management is essential to offer the best chance of a satisfactory outcome.

American College of Obstetricians and Gynecologists in 1997 stated that there is no evidence to suggest that any one maneuver is superior to another in releasing an impacted shoulder and reducing the chance of injury.

Upon the resolution of the clinical event, it is important to document the entire event and to discuss the situation with the parents. These actions will reduce the risk of medical litigation and improve patient satisfaction.

In legal medical discussions, it is necessary to determine whether there were certain antecedent risk factors e.g. diabetes, previous large baby. If diagnosis was suspected and precautions taken, whether shoulder dystocia or its associated injuries e.g. Erb’s palsy could have been prevented.
Injuries to the brachial plexus in neonates present a malpractice dilemma not only for physicians who provide obstetric care, but also for those who administer immediate postnatal treatment for newborns. Although trauma remains the probable etiology for many brachial plexus injuries, other, nontraumatic etiologies need to be considered.25

Cerebral Palsy and Late Neurological Sequelae

The cost of cerebral palsy claims was once higher than all other categories of litigation. The old concept of cerebral palsy origin suggested that most of the damage occurred in labor and was related to substandard care. Recent epidemiological studies have, however, showed that the role of asphyxia during the birth process causing cerebral palsy is smaller than once believed and only 10–15% cases can be linked to birth events. Intrauterine exposure to infection, autoimmune and coagulation disorders and problems specific to multiple pregnancies are risk factors for cerebral palsy. In the court, the main question would be whether the particular case is due to substandard care or not. A concerted effort has been made by a group of professionals under the chairmanship of McLennan to define the prerequisites for providing a causal relationship between acute intrapartum events and cerebral palsy. The international consensus statement will help public, healthcare workers and when necessary the court of law to understand more readily the probability of whether in a particular case there is a convincing evidence to suggest that the pathology causing cerebral palsy occurred during labor and whether it was reasonably preventable. However, the consensus statement has not met with universal approval because of some flaws.26

There is no evidence that cesarean section can prevent cerebral palsy in term infants.27

Postnatal Perineal Trauma

Anal sphincter injury during childbirth—obstetric anal sphincter injuries (OASIs)—is associated with significant maternal morbidity including perineal pain, dyspareunia and anal incontinence.

A review of 2,078 records of vaginal deliveries within a 2-year period found 4.4% cases of documented anal sphincter injury. Forceps delivery was associated with a 10-fold increased risk of perineal injury. Increasing fetal weight and performance of a midline episiotomy were other risk factors. Patients should be counseled about the risk of anal sphincter injury when operative vaginal delivery is contemplated.28

A classification of OASI, development of national guidelines, formalized training, multidisciplinary management and further definitive research is strongly recommended.29

Maternal Mortality

Maternal mortality is still high in India. Most of the deaths are preventable. They may lead to litigation and are responsible for a high incidence of manhandling of doctors in our country. REMEDIES TO MINIMIZE MEDICOLEGAL PROBLEMS

- Medical Council of India (MCI) approved qualification and training from recognized centers are the primary safeguards against any litigation.
- Communication with the patient and her relatives about diagnostics and treatment procedures is the key to doctor-patient relationship.
- Informed consent: This is more than simply getting a patient to sign a written form. It is a process of communication between a patient and physician that results in the patient’s authorization or agreement to undergo a specific medical intervention. This is usually done in a language best understood by the patient in a comfortable and noncoercive manner. In some instances in obstetrics, obtaining consent could be difficult, e.g. woman in advanced labor or under analgesics depressing the CNS.
- Sympathy and polite: It is desirable to have a sympathetic attitude and try to answer queries patiently without getting irritated. We should not be averse for a second opinion if suggested.
- Interpersonal behavior: The human face of medical care decides the patient’s or her attendant’s reaction towards a medical mishap. The whole system of medical establishment should be made courteous and polite. Special training should be imparted to the staff from HRD experts for dealing with patients/relatives under grievous mental stress due to some injury/loss.
- Academic and technical upgradation: To keep pace with the fast changing scenario of medical care, one should regularly attend CMEs and workshops. Regular fellowship training will make doctors aware of various cases of medicolegal problems and their outcomes. It will also prohibit doctors from speaking foul about their own colleagues.
- Medical ethics laws: A thorough knowledge of medical ethics (Code of Medical Ethics, 2002) is essential for all medical professionals.
- Proper documentation: Documentation of records is essentially a mirror of our action in a Court of Law. All medical records should be legible, correct, complete and chronologically placed. They should correlate with ongoing events when recorded by different doctors. Forged records are often easily made out and run the risk of a criminal offence.
- Professional indemnity insurance cover: It is important for the protection of doctors against litigation or malpractice claims.
COURSE AFTER LITIGATION

There may be a letter from the complainant or the court stating that a doctor has been sued. The insurance company needs to be involved and lawyers are helpful in drafting the reply. We should always put up all possible points for defense in the first instance of making a reply to the complainant. Subsequent points during the hearing of the case are liable to be rejected.

The reply should consist of the following points:

- Mention your qualifications, training, experience, expertise, etc. and supporting the same with relevant documents.
- Mention hospital or clinic’s available infrastructure, special facilities, back-up support and prove it with documents.
- The complainant may have suppressed material facts, e.g. previous illness, treatment, etc. which need to be highlighted.
- Inconsistencies may exist in notices sent to the doctor directly or through consumer groups and the complaint made in the court.
- Written evidence of consent of the patient-relative/attendant in assumption of inherent and special risks involved during treatment is an important document.
- Circumstances of the case, e.g. emergency situation, lack of facilities (rural area).
- Burden of proof of: (i) duty of care; (ii) breach of that duty; (iii) causation; (iv) damage, etc. is on the complainant.
- Reasonable knowledge, skill and care were exercised. (Reply/quote standard textbooks with attested photocopies)
- Consolation/treatment by patient from other doctor/other systems of medicine simultaneously.
- Many other reasons/more than one reason/for occurrence of damage.

CONCLUSION

In obstetric practice, many medicolegal problems arise due to the presence of the two potential litigants: (1) the mother and (2) the unborn child. Emergencies and uncertainties in management are common, further increasing the litigation risk.

It is difficult for doctors to shun responsibility any longer. It is easy today for people to push negligent doctors to Consumer Protection Forums. Besides punishing guilty doctors, it is also important to protect doctors who act in good faith, from harassment. The courts must strike a perfect balance.

Every obstetrician should be aware of the ever-increasing legal environment in his or her field. Providing quality up-to-date care, maintaining good communication and adopting an honest and sincere attitude in dealing with our patients can go a long way in curbing the increasing trend of litigations.

REFERENCES

INTRODUCTION
Consumer Protection Act (CPA) of 1988 laid down the making of the word “Service”. In 1991, while deciding the case of VP Shanta versus IMA, Supreme court decided that the services, provided by the gynecologists fall within the meaning of the word “Services” as defined by CPA.

The word “deficiency” has been defined by Section 2(1)(g) of the CPA 1986 as thus: “Deficiency” means any fault, imperfection, shortcoming or inadequacy in the quality, nature and manner of performance which is required to be maintained by or under any law for the time being in force or has been undertaken to be performed by a person in pursuance of a contract or otherwise in relation to any service. Thus, deficient service provided by a gynecologist is actionable.

MEDICAL NEGLIGENCE
Negligence and rashness on the part of a gynecologist, whilst treating a patient, is considered by law as “deficiency in services”. Negligence is the opposite of diligence. An act is said to be performed negligently when it is performed without due diligence. That is to say that the standard of care exhibited whilst performing the act was below par. When an act is undertaken without the requisite care and caution, the act is labeled as a rash act. Negligence and rashness usually go hand-in-hand and, in general, denote carelessness.

Law
Negligence is defined as “the omission to do something which a reasonable man, guided upon those considerations which regulate the conduct of human affairs would do, or doing something which is prudent and reasonable man would not do”.

“Negligence is a tort which involves a person’s breach of duty that is imposed upon him to take care, resulting in damage to the complainant”. The essential components of the modern tort of negligence propounded by Percy and Charlesworth are as follows:

• The existence of a duty to take care, which is owed by the defendant to the complainant
• The failure to attain that standard of care, prescribed by the law, thereby committing a breach of such duty, and
• Damage, which is both causally connected with such breach and recognized by the law, has been suffered by the complainant.

If the plaintiff proves that the gynecologist was negligent, but fails to establish that any loss or injury was caused thereby, then he will not be entitled to claim any compensation. The general test for causation requires the plaintiff to establish that the injury would not have occurred, but for the negligence of the defendant.

Negligence under the Consumer Law
The consumer law was enacted to provide a cheap and speedy remedy to the aggrieved consumers. Hence, the consumer forums are empowered to adjudicate the dispute regarding deficiency in service rendered by medical practitioners for consideration.

Naturally, the complaint for deficiency in service rendered by gynecologist is not liable to be dismissed, merely because the complaint involves complicated questions of law and facts requiring detailed investigations. However, it is
observed by the Supreme Court that in complaints involving complicated issues requiring recording of evidence of experts, the complainant can be asked to approach the civil court for necessary relief. As a matter of policy and principle where subject-matter of a complaint is sub-judice before ordinary court, a concurrent adjudication in respect of the same should not be conducted under CPA by a Redressal Agency.

**Duty of Care and Standard of Care**

A gynecologist cannot be sued for negligence unless he has violated some “duty to take care”. The violation of this duty must inflict some damage to the person to whom this duty is owed.

A gynecologist has to evince reasonable degree of skill and knowledge and must exercise a reasonable degree of care while practicing his profession. He cannot be expected to apply the ideal or the highest degree of skill and care while handling a case. The duty of a gynecologist is based on the fact that he is handling a human being and is likely to cause physical damage unless proper care and skill is applied. A gynecologist who diagnoses and treats a person for a disease or performs an operation on a patient to remove or rectify a defect is presumably giving an undertaking that he possesses the required skill and knowledge for that purpose. He is duty bound in two respects viz., he owes a primary duty of care in deciding whether he should undertake the case and after having undertaken the case, the next duty is cast on him, the duty of care in the administration of the treatment wherein he should use diligence, care, knowledge and caution. His failure to perform either of the above two duties, if proved, will offer reasonable and valid ground to fasten negligence on him. He need not be expected to possess the highest or a very high standard nor should he have a very low standard. The law requires fair and reasonable standard of care and competence. Every gynecologist who enters into the medical profession thus has a duty to act with a reasonable degree of care and skill.

A gynecologist who professes to have some special skill is judged, not by the standards of an ordinary man but by the standards of his peers. The test is the standard of the ordinary skilled gynecologist exercising and professing to have that special skill. A man need not possess the highest expert skill at the risk of being found negligent. “It is well-established law that it is sufficient if he exercises ordinary skill of an ordinary gynecologist exercising that particular art”.

The prudent man is the man who has acquired the skill to do the act which he undertakes. If a man has not acquired the skill to do a particular act he undertakes, then he is imprudent, however careful he may be, and however great may his skill be in other things. The degree of care which a gynecologist is required to use in a particular situation varies with the obviousness of the risk. If the danger of injuring a person by the pursuance of a certain line of treatment is great, great care is necessary. If the danger is slight, only a slight amount of care is required. Thus, gynecologists must not act in such a way as to cause injury to his patients. The care that will be required of him will be the care that an ordinary prudent gynecologist is bound to exercise. But, gynecologists who profess to have special skills, or who have voluntarily undertaken a higher degree of duty, are bound to exercise more care than an ordinary prudent gynecologist.

The court will not expect a gynecologist working in extreme conditions to achieve the same results as his colleague operating within the confines of a hospital and will not judge the gynecologists conduct too harsh simply because, with hindsight, a different course would have been adopted had the situation not been an emergency. In case of emergency, the operating gynecologist has wider discretion about the treatment. Where the operation is a race against time, the court will make greater allowance for mistakes on the part of the gynecologist or his assistants taking into consideration the “risk benefit test”.

**ACCEPTED PRACTICES AND PROCEDURES**

A gynecologist is not guilty of negligence if he has acted in accordance with a practice accepted as proper by a responsible body of medical men skilled in that particular art. Accepted practice means practice accepted as proper by the gynecologist’s peers. If the gynecologist has complied with this practice then that is strong evidence that he is not negligent, if he does not, then it is likely he will be negligent. Not resorting to routine ultrasonography prior to termination of pregnancy was thus not considered as negligence.

**Deviation from Accepted Practices**

A gynecologist may be held liable in negligence when he departs from accepted practices. Departure from approved practices is in itself not negligence. If a gynecologist departs from the approved practice, and he is able to justify his actions he will not be negligent, but if he cannot justify his departure from the accepted practice, the patient should have little difficulty in establishing negligence. The negligent performance of an approved practice will also constitute a departure.

**ACCIDENTS, MISADVENTURES AND MISHAPS**

Courts have held that it would be wrong, and indeed bad law, to say that simply because a misadventure or mishap occurred, the hospital and the gynecologists are thereby liable. It would be disastrous to the community if it were so.

A gynecologist is not an insurer; he does not warrant accidents, mishaps and mistakes. It would be disastrous to the community if it were so.
cure. Naturally, he will not be liable if, a treatment which in ordinary circumstances would be sound, has unforeseen results. The standard of care which the law requires is not insurance against accident slips. It is not every slip or mistake that imports negligence. Law recognizes the dangers, which are inherent in surgical operations. Mistakes will occur on occasions despite the exercise of reasonable skill and care. Accidental opening of the urinary bladder was thus not considered as negligence.

**ERROR OF JUDGMENT**

An error of judgment does not of itself amount to negligence. Law allows errors of judgment which do not by themselves amount to negligence. The House of Lords in England held that some errors of judgment may be negligent and some may not. The error of judgment committed by a gynecologist, may or may not be indicative of negligence, but the proper test to be applied is whether he abided by the standards laid down by his peers (Bolam’s test).

The courts have held “No human being is infallible, and in the present state of science, even the most eminent specialist may be at fault in detecting the true nature of the diseased condition”. A practitioner can only be liable in this respect if his diagnosis is so palpably wrong as to prove negligence, that is to say, if his mistake is of such a nature as to imply absence of reasonable skill and care on his part, regard being given to the ordinary level of skill in the practitioner. With regard to junior gynecologists, inexperience is no defense. He must meet the standard of care expected of his rank and status.

**INHERENT RISKS OF TREATMENT**

Every gynecological procedure has its own risk factors. Just because one of these factors becomes manifest does not mean that the gynecologist is negligent and his services defective. He can be held negligent only when the standard of care exhibited by him falls below the standards expected of a reasonable prudent gynecologist practicing under the circumstances he is placed in.

**VICARIOUS LIABILITY**

Liability which is incurred for, or instead of, another can be defined as vicarious liability. Every person is responsible for his own acts or omissions but there are circumstances where for the acts committed by a person, the liability comes to lie, not on that person, but on someone else. A master is liable for the acts or omissions of his servant and the principal is accountable for the acts of his agent. The hospital authorities are responsible for the whole of their staff, not only for the nurses and the gynecologists but also for the anesthetists and the surgeons. It does not matter whether they are permanent or temporary, resident or visiting, whole-time or part-time. The hospital authority is responsible for all of them. The reason is because even if they are not servants, they are the agents of the hospital to give the treatment. The only exception is the case of consultants and anesthetics selected and employed by the patient himself.

**DEFICIENCIES IN STATUTORY REQUIREMENTS**

To practice medicine without proper registration with the State Medical Council, or the Medical Council of India, would violate the provisions of law. So also employing staff that is unqualified will violate the provisions of the Indian Medical Council (Professional conduct, Etiquette and Ethics) Regulations, 2002 as formulated by the Medical Council of India. Institutions where medical termination of pregnancy is undertaken must also be registered with the appropriate Authority under the Medical Termination of Pregnancy Act 1971. Ratios of judge-made laws or precedents are also applicable and binding on the gynecologists and violation of the same also constitutes offence that is actionable. Cross-pathy practice, that is, an allopathic practitioner prescribing Ayurvedic drugs is bad in law. Cross-specialty practice, that is, a surgeon undertaking a hysterectomy is also considered improper. Undertaking a tube ligation without the consent of the spouse is similarly actionable.

The one act which is very important for the gynecologists to follow is the PC-PNDT Act. The supreme court has taken a very positive steps in implementation of this act. As the child sex ratio in our country is deteriorating to unacceptable level, it is especially important for the gynecologists to realize that under this act even deficiency in filling forms is also taken as contravention of the act leading to severe punishments.

In conclusion, deficiencies in medical practice may arise in various ways and may lead to medicolegal liabilities.
INTRODUCTION
Audit is defined as a “systematic, critical analysis” of the quality of medical care, including the procedures used for diagnosis and treatment, the use of resources and the resulting outcome for the patient. It involves working on three main questions:
1. What do we think we are doing?
2. What are we really doing?
3. How can we improve what we are doing?
In a broader context, audit has become an essential component of establishing excellence in the clinical practice of obstetrics and gynecology.

HISTORICAL ASPECTS
Audit, in reality, is an old concept. There have been records of audit of doctor’s work in Babylon as early as 3000 BC. In countries like the United Kingdom, medical audit has been in practice even in 1342. However, Florence Nightingale drew up “Forms of Enquiry” in 1828 to assess standards of care in workhouses, which later revolutionized nursing care. One of the first ever clinical audits was undertaken by her during the Crimean War of 1853–1855. On arrival at the Barracks Hospital in Scutari in 1854, Florence was appalled by the unsanitary conditions and high mortality rates among injured or ill soldiers. Florence upgraded standards of hygiene and her team maintained meticulous statistical records. Following this change, the mortality rates fell from 40% to 2%, and were instrumental in overcoming the resistance of the British doctors and officers to Florence’s procedures. Her methodical approach, as well as the emphasis on uniformity and comparability of the results of healthcare, is recognized as one of the earliest programs of outcomes management. Another famous figure who advocated clinical audit was Ernest Codman (1869–1940) from Massachusetts, USA. Codman’s work anticipated contemporary approaches to quality monitoring and assurance, establishing accountability, and allocating and managing resources efficiently.
Whilst Codman’s “clinical” approach is in contrast with Nightingale’s more “epidemiological” audits, these two methods serve to highlight the different methodologies that can be used in the process of improvement to patient outcome.
In developed nations like the United Kingdom, the National Health Service (NHS) regulations have made audit an integral part of a doctor’s contractual obligation since 1993.

KEY COMPONENT OF CLINICAL AUDIT
The key component of clinical audit is that performance is reviewed (or audited) to ensure that what “should” be done is “being” done, and, if not, it provides a framework to enable improvements to be made.

A Gradual Integration into Contemporary Healthcare
Despite the successes of Nightingale in the Crimea and Codman in Massachusetts, clinical audit was slow to catch on. This situation remained for the next 130 years, with only a minority of healthcare staff embracing the process as a means of evaluating the quality of care delivered to patients. The concepts of audit have undergone a gradual change to evolve a more multidisciplinary approach used in modern healthcare. It also reflects the change in focus from a professionally-centered view of health provision to the view...
of the patient-centered approach. These changes can be seen from comparison of the following definitions:

In 1989, the White Paper, "Working for patients," saw the first move in the UK to standardize clinical audit as part of professional healthcare. The paper defined medical audit (as it was called then) as:

"The systematic critical analysis of the quality of medical care including the procedures used for diagnosis and treatment, the use of resources and the resulting outcome and quality of life for the patient."

Medical audit later evolved into clinical audit and a revised definition was announced by the NHS executive:

"Clinical audit is the systematic analysis of the quality of healthcare, including the procedures used for diagnosis, treatment and care, the use of resources and the resulting outcome and quality of life for the patient."

The National Institute for Health and Clinical Excellence (NICE) published the paper "Principles for Best Practice in Clinical Audit", which defines clinical audit as:

"A quality improvement process that seeks to improve patient care and outcomes through systematic review of care against explicit criteria and the implementation of change. Aspects of the structure, processes, and outcomes of care are selected and systematically evaluated against explicit criteria. Where indicated, changes are implemented at an individual, team, or service level and further monitoring is used to confirm improvement in healthcare delivery."

Purpose of Audit

Patients need to be reassured that professionals continue to examine and refine their own practices so that care is constantly and consistently improving. The basic purpose of audit is to ensure that clinicians can rightly take professional pride in their own work.

Audit Versus Research

Often there is confusion between audit and research. There are clear distinctions between the two. Research aims to increase knowledge and attempts to test a hypothesis, while audit reviews medical care to identify possible improvements. Research may involve allocating patients to different treatment groups while audit does not. Medical research may involve administration of a placebo or a completely new treatment. On the other hand, audit never involves a placebo or a new treatment.

**TYPES OF OBSTETRIC AUDIT**

Audits in obstetric practice could be:

- Numerical
- Case review
- Traditional
- Event-based
- Protocol- or criteria-based and
- Cost-benefit analysis type.

**Numerical Audit**

Numerical audit is purely administrative and deals with figures. It is useful for demonstrating trends, e.g. rates of induction of labor or cesarean section. Here the management is unchanged. Relatively fewer lessons are learnt; for example, decreasing cesarean section rate does not necessarily mean better patient outcome. However, it could be a measure to assess the potential experience of doctors in training.

**Case Review Audit or Peer Review**

An assessment of the quality of care is provided by a clinical team with a view to improving clinical care. Individual cases are discussed by peers to determine, with the benefit of hindsight, whether the best care was given. This is similar to the method described below, but might include "interesting" or "unusual" cases rather than problematic ones. Unfortunately, recommendations made from these reviews are often not pursued as there is no systematic method to follow.

**Event-based Audit or Adverse Occurrence Screening and Critical Incident Monitoring**

This is often used to peer review cases which have caused concern or from which there was an unexpected outcome. The multidisciplinary team discusses individual anonymous cases to reflect upon the way the team functioned and to learn for the future. In the primary care setting, this is described as a "significant event audit".

Audit for perinatal and maternal mortality (confidential inquiry into maternal deaths) is an event-based audit. It can also include low birth weight, low Apgar scores, inductions, breech deliveries and cesarean sections.

**Standards-based Audit/Criteria-based Audit**

A cycle which involves defining standards, collecting data to measure current practice against those standards, and implementing any changes deemed necessary.

A topic (e.g. management of hypertensive disease in pregnancy) is selected and standards are set for its management. If standards are achieved, it implies improvement or, if not, then they may need to be altered.

**Patient Surveys and Focus Groups**

These are methods used to obtain users’ views about the quality of care they have received. Surveys carried out for
their own sake are often meaningless, but when they are undertaken to collect data, they can be extremely productive.

Cost-benefit Analysis

This includes visits to the hospital, investigations, drugs and complications of a particular procedure. This type of audit is of importance to what the clinical budget holds.

THE PLACE OF CLINICAL AUDIT IN MODERN HEALTHCARE

Clinical audit is an essential and integral part of clinical governance. Clinical audit is an integral component of clinical governance. It forms part of the framework for improving the standard of clinical practice. The main components of clinical governance include (Fig. 1):

- Clinical effectiveness (setting gold standards)
- Research and development
- Openness (in a no-blame culture)
- Risk management (identification, analysis, prevention)
- Education and training (continuing professional development)
- Clinical audit.

KEYSTONES OF AUDIT: THE “WHY, HOW AND WHAT”

Assessing audit studies primarily involves answering three questions: (1) Why was it done?; (2) How was it done?; and (3) What did it find? Setting of standards prior to study is an important but difficult stage of audit. In selected situations there is often a “gold standard”. An example is breastfeeding, which has been undoubtedly proven the best for the mother and baby. Magnesium sulfate is an example of the “gold standard” in the treatment of eclampsia. It has stood as the time-tested drug of choice with the best possible maternal and fetal outcome. Another example of a “gold standard” would be the role of corticosteroids for acceleration of lung maturity in premature babies.

Whether objective or based on clinical judgment, criteria should be well defined. Targets should be set at a realistic level for defined patient groups and also take into account the existing local conditions. For example, amongst various screening methods, a simple speculum examination and Pap smear cytology are the most cost-effective to help in down staging cervical cancers in a developing country like India. The Pap test should be directed at women in poor socioeconomic circumstances, who are at the greatest risk of developing the disease.

It is equally important to identify who would be monitoring the audit and the manner in which it would be done. It is often impossible to exclude all biases. However, there should be an assessment of whether they could influence the study findings.

The “what” concerns interpretation of the immediate findings and their implications for healthcare. It addresses a planned program of change with active feedback of all staff involved. It involves recognizing deficiencies of care and proposal of specific solutions. To cite an example, it is safer, more practical and in the long-term more cost-effective to give all women iron supplements from 16 weeks of pregnancy.
The World Health Organization (WHO) recommends that a supplement of 30–60 mg per day be given to those pregnant women who have normal iron stores and 120–124 mg to those women with none.\textsuperscript{15,16} The pulse polio program is also a good example of identifying the deficiency and recommending a universally applicable and specific solution.\textsuperscript{17} For certain situations, deficiencies have been identified, yet there may be no uniformly specific solutions. For example, issues concerning perinatal transmission of human immunodeficiency virus (HIV) still remain controversial.\textsuperscript{18}

**STRUCTURE OF CLINICAL AUDIT**

“Structure” implies the organizational set-up including nurses, doctors, clinical setup, etc. An obstetric audit is multidisciplinary.\textsuperscript{7} It includes various other disciplines. Nursing staff, radiologists, physiotherapists, neonatologists, anesthetists, pathologists and pathology technicians, geneticists and general practitioners. There should be a representation from as many of the multidisciplinary teams to make the audit more relevant and sustainable.

**CLINICAL AUDIT: THE PROCESS**

The clinical audit process seeks to identify areas for service improvement, develop and carry out action plans to rectify or improve service provision and then to reaudit to ensure that these changes have an effect.

Clinical audit can be described as a cycle or a spiral (Fig. 2), that follows a “systematic” process of: establishing best practice; measuring against criteria; taking action to improve care; and monitoring to sustain improvement. As the process continues, each cycle aspires to a higher level of quality.\textsuperscript{19}

**Stage 1: Identify the Problem or Issue**

This stage involves the selection of a topic or issue to be audited, and is likely to involve measuring adherence to healthcare processes that have been shown to produce best outcomes for patients. Selection of an audit topic is influenced by factors including:
- Where national standards and guidelines exist; where there is conclusive evidence about effective clinical practice.
- Areas where problems have been encountered in practice.
- What patients and public have recommended that be looked at.
- Where there is a clear potential for improving service delivery.
- Areas of high volume, high risk or high cost, in which improvements can be made.

**Stage 2: Define Criteria and Benchmarking Standards**

Decisions regarding the overall purpose of the audit, either as what should happen as a result of the audit, or what question you want the audit will answer, should be written as a series of statements or tasks that the audit will focus on. Collectively, these form the audit “criteria”. These criteria are explicit statements that define what is being measured and represent elements of care that can be measured objectively. The “standards” define the aspect of care to be measured, and should always be based on the best available evidence.

- A criterion is a measurable outcome of care, aspect of practice or capacity. For example, "parents or carers are involved in negotiating or planning their child’s care”.
- A standard is the threshold of the expected compliance for each criterion (these are usually expressed as a percentage). For the above example, an appropriate standard would be: “there is an evidence of parent or carer in care planning in 90% of cases”.

**Stage 3: Data Collection (in a Uniform Protocol)**

To ensure that the data collected are precise, and that only essential information is collected, certain details of what is to be audited must be established from the outset. These include:
- The user group to be included, with any exceptions noted
- The healthcare professionals involved in the users’ care
- The period over which the criteria apply

Sample sizes for data collection are often a compromise between the statistical validity of the results and pragmatic issues around data collection. Data to be collected may be available in a computerized information system, or in other cases, it may be appropriate to collect data manually depending on the outcome being measured. In either case, considerations need to be given to what data will be collected, where the data will be found, and who will do the data collection.
Ethical issues must also be considered; the data collected must relate only to the objectives of the audit, and staff and patient confidentiality must be respected—identifiable information must not be used. Any potentially sensitive topics should be discussed with the local Research Ethics Committee.

**Stage 4: Compare Performance with Criteria and Standards**

This is the analysis stage, whereby the results of the data collection are compared with criteria and standards. The end stage of analysis is concluding how well the standards were met and, if applicable, identifying reasons why the standards were not met in all cases. These reasons might be agreed to be acceptable, i.e. could be added to the exception criteria for the standard in future, or will suggest a focus for improvement measures.

In theory, any case where the standard (criteria or exceptions) was not met in 100% of cases suggests a potential for improvement in care. In practice, where standard results were close to 100%, it might be agreed that any further improvement will be difficult to obtain and that other standards, with results further away from 100%, are the priority targets for action. This decision will depend on the topic area—in some “life or death” type cases, it will be important to achieve 100%, in other areas, a much lower result might still be considered acceptable.

**Stage 5: Implementing Change Through Stakeholders**

Once the results of the audit have been published and discussed, an agreement must be reached about the recommendations for change. Using an action plan to record these recommendations is good practice; this should include who has agreed to do what and by when. Each point needs to be well defined, with an individual named as responsible for it, and an agreed timescale for its completion.

Action plan development may involve refinement of the audit tool particularly if measures used are found to be inappropriate or incorrectly assessed. In other instances, new process or outcome measures may be needed or involve linkages to other departments or individuals. Too often audit results in criticism of other organizations, departments or individuals without their knowledge or involvement. Joint audit is far more profitable in this situation and should be encouraged by the Clinical Audit lead and manager.

**Reaudit: Sustaining Improvements**

After an agreed period, the audit should be repeated. The same strategies for identifying the sample, methods and data analysis should be used to ensure comparability with the original audit. The reaudit should demonstrate that the changes have been implemented and that improvements have been made. Further changes may then be required, leading to additional reaudits.

This stage is critical to the successful outcome of an audit process as it verifies whether the changes implemented have had an effect and to see if further improvements are required to achieve the standards of healthcare delivery identified in stage 2.

Results of good audit should be disseminated both locally via the strategic health authorities and nationally where possible.

**PROBLEMS ASSOCIATED WITH AUDIT**

Problems during the audit process could be categorized as:
- Incomplete data collection
- Misplacement of records
- Poor follow-up of information
- Financial constraints
- Problems of staffing
- Time and resource constraints.

The effects of litigation are double-edged. On the one hand, obstetricians and gynecologists would be tempted to produce strict protocols of care, as a form of patient management. Though this could encourage the use of audit, it could discourage innovation.

There is also a growing concern that the process of audit itself would provide ammunition for the lawyers. Junior staff with long working hours and secretarial staff often lack interest and discredit the value of audit. Overdependence on hardware and software to provide all answers could contribute towards the failure of audit.

**THE PROS AND CONS**

The outcomes of audit have revealed both useful information regarding the care of the patient, the degree of efficiency of the medical and nursing staff, areas of deficit and cost-effective measures. Audit helps in education of junior doctors and this is a very useful benefit.

Audit encourages the use of strict protocols for care but it discourages innovation. Audit may cause a restraint on research and evolution of medicine. Following a “sheep mentality” would retard improvisation of pre-existing methods.

**Success of Audit**

An audit that is successful will produce small changes in clinical practice as the study progresses, but it may be difficult to ensure that a lasting change is achieved. This is most likely to happen when audit is owned by all those who participate and boost professional pride in providing a good service to patients. It is unlikely to achieve change when it is used as a stick to beat for managerial change. It is, therefore, vital that all clinicians take active part in audit, however, small the project be.
RUMBA and KISS

Successful audit teams should start on the “relevant, understandable, measurable, behaviorally orientated and achievable” (RUMBA). The “keep it small and simple” (KISS) principle ensures a good chance of completing the audit.7

Audit of Evidence-based Practice in Obstetrics

The challenge, which faces us all, is putting evidence into practice. It is often assumed by lay public that the medical profession automatically practices “effective medicine using the best available evidence”. This is often not the case. Besides knowledge, many other factors affect the decision of when and how to intervene. These include patient demands, high expectations, “tradition”, financial rewards and concern about litigation. In terms of good clinical practice, clinical trials provide the best evidence on which to base effective therapeutic decisions.

CONCLUSION

Audit is of great value in obstetrics and gynecology. It is now an essential aspect of continuing medical education. It is a powerful tool for improving the quality of care, enhancing education and protecting the standard of clinicians. As doctors we are committed to good quality of patient care. With progress in medicine, everyone concerned must accept the need for change. Motivation, time, effort and finance are the key factors for success. It is also important to audit the effect of “audit” on patient care.

REFERENCES

**ABSTRACT**

In civilized society, citizen is governed by number of laws of the land. Numbers of laws are directly proportional to the state of civilization. India is not an exception. Acts which are applicable mainly to the obstetrician and gynecologist, such as Preconception and Prenatal Diagnostic Techniques (PCPNDT) Act, Consumer Protection Act (CPA), criminal laws and Biomedical Waste (BMW), are discussed. Labor laws are just mentioned. The application of certain Acts may vary from state to state as few Acts are central and few are state Acts. Certain rules under the Act may be different in some states.

**Keywords**


**INTRODUCTION**

Even nature is governed by laws of its own. The human behavior has always tried to run free of any burden of accountability and answerability. The intellectual has always revolted against the law.

Ignorance of law is sometimes an excuse, but it is better to be forewarned and forearmed.

All Indian laws are very well applicable to gynecologists and obstetricians practicing in India, as primarily they are citizens of India. There are many Indian laws which are directly or indirectly influencing the professional practice of medicos in general and gynecologist in particular. It is not possible to span across all those laws or Acts in this small chapter. There are some Acts, which are adequately covered in other chapters of this book, hold mere mention in this present chapter.

Intention of legal rules is to create “code of conduct” for medical practitioners and make them responsible as professional persons. Doctors are human beings with special skill and knowledge. In the era of intelligence, professionals want to convert their ability into money. Law has to safeguard the social welfare and human interest.

For sake of discussion, we have combined Acts/laws in three groups. First group of Acts are those which deal directly to the day-to-day practice of obstetrics and gynecology, e.g. Medical Termination of Pregnancy (MTP) Act, PCPNDT Act, sterilization law/guidelines, CPA, organ transplantation Act, etc. Second group of Acts are related to consent, evidence, certain provisions of criminal procedure code, Indian Medical Council Act, etc. And lastly, the group of Acts which may, at times, be relevant to obstetric and gynecological (OB/GY) practice according to situation or need, e.g. Indian penal code (IPC) in pregnancy due to rape.

**MEDICAL TERMINATION OF PREGNANCY ACT, 1971**

Medical Termination of Pregnancy (MTP) Act with amendments has received sufficient importance and mention in other chapters and needs to be known by each obstetrician and gynecologist thoroughly well. It is equally important to
follow the Act in its letter and spirit. It is a sad state of affairs that practically at least one member obstetrician from nearly every region of the country has faced litigation in some or the other courts under this Act.

**MTPS can only be conducted in places that have been approved under the Act.**

1. Application for approval of a place should be made in form A and must be addressed to the CDMO of the district.
2. The committee after recommendation of CDMO approves the place and grants a certificate of approval form B.
3. Certificate of approval form B is to be conspicuously displayed at the approved place.
4. Co-operate during monitoring or inspection with the authorities.
5. **Requirements for obtaining MTR:** 1. Indications, 2. Woman’s consent and 3. RMP(s) opinion.
6. **Record keeping:** Records have to be maintained for all MTP procedures conducted by the unit.

**Offences and Penalties**

The MTP Act recognizes offences committed by the RMPs or any other persons conducting MTPs without following the provisions of the law.

However, it must be noted that there is no liability on RMPs if it is shown that the MTP was conducted in good faith. The conduct of MTPs in places that are not registered, are penalized under this Act. A woman does not attract any penalties for a breach of the provisions of this Act. However, she may be prosecuted under the provisions of the IPC if she does not fulfill the conditions of this Act (Box 1).

**Prenatal Diagnostic Technique Act, 1994**

The prenatal diagnostic technique Act has been amended as the preconception and prenatal diagnostic techniques (prohibition of sex selection) Act in 2003.

The Act was enacted to provide for the regulation of the use of prenatal diagnostic techniques for detecting genetic or metabolic disorders or chromosomal abnormalities, the prevention of misuse of such techniques for the purpose of prenatal sex determination, leading to female feticide.

| **Box 1: Offences and penalties under IPC** |
|-----------------|-----------------|-----------------|
| **Nature of offence** | **Person liable** | **Penalty imposed** |
| Termination of pregnancy, by any person other than a RMP | Non-RMP, who terminates the pregnancy | Imprisonment for a term not less than 2 years which may extend to 7 years |
| Termination of pregnancy by any person in any other place other than an approved place | RMP or non-RMP whoever terminates the pregnancy—owner of such an unapproved place | Imprisonment for a term not less than 2 years which may extend to 7 years |
| Contravention of requirement of record-keeping | RMP | Fine which may extend to ₹1,000 |

In spite of the Act coming into force from 1st January 1996, there were problems in its implementation and interested persons have found out loopholes in the Act and continued sex determination and selective abortion. That has been obvious from the figures given in Table 1.

After the amendment in the original Act in 2003, there were still problems in its implementation. The implementing authorities (appropriate authority) were the medical officers of health in corporation areas and in other areas it is civil surgeon or district health officer. Government has realized after the “Hyderabad experience” that proper implementation of the Act is possible and therefore, the revenue authorities will be the appropriate authorities everywhere.

There has been unfounded criticism that there is harassment from the authorities while implementing the PCDNPT Act. Those who follow the provisions of the Act religiously will not face problems from the authorities. It is an open secret that some medicos are misusing the modern technique for ulterior motives and because of them, mainly obstetrician and gynecologists are blamed. The census figures speak for themselves regarding the disparity in sex ratio. It is very difficult to pinpoint or catch the individual while doing sex determination or selective sex abortion directly and hence authorities are concentrating on the “technicality of the law”. If decided it is not at all difficult to follow the rules and regulations and abide by them in the day-to-day practice of obstetrics, while doing ultrasound examination of a patient.

It is common practice that most of obstetrician do ultrasonography of their patients themselves and in a clinic owned by them. Just to give few examples of how easily rules can be followed made under PCDNPT Act:
- To keep the booklet of the Act readily available in the clinic and to give it to the patient on demand

| **Table 1: Age group 0–6 years per 1,000 males** |
|-----------------|-----------------|-----------------|
| **Year** | **Females (all India)** |
| 1991 | 945 |
| 2001 | 927 |
| **Maharashtra** | **Haryana** |
| 1991 | 934 | 865 |
| 2001 | 922 | 861 |
• To write a notice in particular format in English and regional language that sex determination is not done here and it is an offence
• Write full name of the person under the signature, while giving sonography report.

These are some simple and so called “technical things” but if someone is not observing the same, then, as per the PCPNDT Act, it is contravention of provisions of the Act and authorities are fully justified in taking action against that particular doctor. Authorities can seal the machine with or without giving notice. This cannot be called as “harassment of doctors”. It is in the interest of everyone that one should follow the rules made under PCPNDT Act in toto. All the offences under PCPNDT Act are cognizable, nonbailable and noncompoundable. If found guilty by the court, in the first offence, the appropriate authority can inform the state medical council and the council has got authority to suspend the registration for a period of five years and for subsequent offences the medical council can cancel the registration all together.

Following is the code of conduct to be observed by the concerned person working at a center:
1. Not to conduct or associate with detection and disclosure of sex.
2. Not to employ a person not possessing appropriate qualification in the clinic.
3. Not to conduct any procedure or technique to detect sex.
4. Not to conduct any test or procedure other than the place that is registered for.
5. Ensure that no provisions of the Act or these rules are violated in any manner.
6. Ensure to inform that if somebody is using the procedure, that such a thing will violate the law.
8. Display his/her name and designation prominently on the dress worn by him/her.
9. Write his/her name and designation in full under his/her signature.
10. On no account conduct or allow/cause to be conducted female feticide.
11. Not to commit any other Act of professional misconduct.

Above mentioned “code of conduct” is to be observed by each and everyone while doing ultrasonography examination, then it can be assured that they won’t have to face problems in the clinic.

**Offences and Penalties Under PCPNDT Act**

There is prohibition of advertisement relating to preconception and prenatal determination of sex. Here, it is important to note that no center will publish any advertisement in any form, including on internet, regarding facilities of prenatal determination of sex or sex selection before conception, available at such center.

Any person who contravenes provisions of the above shall be punishable with imprisonment for a term, which may extend to three years and with fine, which may extend to 10,000 rupees. Any person, employed or owner, contravenes the Act and the rules made thereunder shall be punishable with imprisonment for a term which may extend up to three years and fine which may extend up to ten thousand rupees and subsequent conviction with imprisonment which may extend to five years and a fine which may extend to fifty thousand rupees. The name of the RMP (As per PCPNDT Act) shall be reported to state medical council to take necessary Action including suspension of the registration, if the charges are framed by the court and till the case is disposed of and on conviction for removal of his name from the register of the council for period of five years for the first offence and permanently for subsequent offence.

Whoever contravenes any of the provisions of PCPNDT Act or any rules made there under for which no penalty has been elsewhere provided in this Act, shall be punishable with imprisonment for a term which may extend up to 3 months or with fine which may extend to one thousand rupees or with both and in case of continuing contravention, with the additional fine, which may extend to 500 rupees for everyday during which such contravention continues after conviction for the first such contravention.

Where any offence, punishable under this Act has been committed by a company (company includes partnership firm, private limited company and joint practice) every person who at the time of offence was committed was in charge of and who is responsible for the company and the conduct of business of the company shall be deemed to be guilty of the offence and shall be liable to be proceeded against and punished accordingly.

**THE TRANSPLANTATION OF HUMAN ORGANS ACT, 1994**

An Act to provide for the regulation of removal, storage and transplantation of human organs for therapeutic purpose and for the prevention of commercial dealings in human organs and for matters connected therewith or incidental thereto.

As far as our specialty is concerned, till date Dr Pravin Mhatre from Mumbai has done transplantation of ovaries. We have not heard of anybody transplanting uterus or Fallopian tubes; however in future, somebody thinks of doing transplantation of any of the reproductive organs, it will be governed by this Act. We have just mentioned this to remind researchers about the existence and extent of this Act.

The center or state will appoint appropriate authority under this Act. It is mandatory to register the nursing home/hospital engaged in removal, storage or transplantation of human organs.

Transplantation till date has been mainly of cornea and kidney, which is not in our professional purview and hence, this Act does not majorly affect our practice or us.
THE REGISTRATION OF BIRTHS AND DEATHS ACT

1. **Persons required to register births and deaths:** (1) It shall be the duty of the persons specified below to give or cause to be given, either orally or in writing, according to the best of their knowledge and belief, within such time as may be prescribed, information to the registrar of the several particulars required to be entered in the forms prescribed by the state government under subsection (1) of section 16,

A. In respect of births and deaths in a house, whether residential or nonresidential, not being any place referred to in clauses (b) to (e), the head of the house or, in case more than one household live in the house, the head of the household, the head being the person who is so recognized by the house or the household, and if he is not present in the house at any time during the period within which the birth or death has to be reported, the nearest relative of the head present in the house, and in the absence of any such person, the oldest adult male person present therein during the said period;

B. In respect of births and deaths in a hospital, health center, maternity or nursing home or other like institution, the medical officer in charge or any person authorized by him in his behalf;

C. In respect of births and deaths in a jail, the jailor in charge;

D. In respect of births and deaths in choultry, chattram, hostel, dharmasala, boarding house, lodging house, tavern, barrack, toddy shop or place of public resort the person-in-charge thereof;

E. In respect of any newborn child or dead body found deserted in a public place, the headman or other corresponding officer of the village in the case of a village and the officer-in-charge of the local police station elsewhere: Provided that any person who finds such child or dead body, or in whose charge such child or dead body may be placed, shall notify such fact to the headman or officer aforesaid;

F. In any other place, such person as may be prescribed.

2. **Notwithstanding anything contained in subsection (1),** the state government, having regard to the facilities available there in this behalf, may require that a certificate as to the cause of death shall be obtained by the registrar from such person and in such form as may be prescribed.

3. Where the state government has required under subsection (2) that a certificate as to the cause of deaths shall be obtained, in the event of the death of any person who, during his last illness, was attended by a medical practitioner, the medical practitioner shall, after the death of that person, forthwith, issue without charging any fee, to the person required under this Act to give information concerning the death, a certificate in the prescribed form stating to the best of his knowledge and belief the cause of death; and the certificate shall be received and delivered by such person to the registrar at the time of giving information concerning the death as required by this Act (Sec. 11).

**Informant to sign the register:** Every person who has orally given to the registrar any information required under this Act shall write in the register maintained in this behalf, his name, description and place of abode, and if he cannot write, shall put his thumb mark in the register against his name, description and place of abode, the particulars being in such a case entered by the registrar (Sec. 12).

**Extracts of registration entries to be given to informant:** The registrar shall, as soon as the registration of birth or death has been completed, give, free-of-charge, to the person who gives information under section 8 or section 9, an extract of the prescribed particulars under his hand from the register relating to such birth or death (Sec. 13).

### Delayed Registration of Births and Deaths

I. Any birth or death of which information is given to the registrar after the expiry of the period specifies therefore, but within 30 days of its occurrence, shall be registered on payment of such late fee as may be prescribed.

II. Any birth or death of which delayed information is given to the registrar after 30 days but within 1 year of its occurrence shall be registered only with the written permission of the prescribed authority and on payment of the prescribed fee and the production of an affidavit made before a notary public or any other officer authorized in this behalf by the state government.
III. Any birth or death, which has not been registered within 1 year of its occurrence, shall be registered only on an order made by a magistrate of the first class or a presidency magistrate after verifying the correctness of the birth or death and on payment of the prescribed fee.

IV. The provisions of this section shall be without prejudice to any action that may be taken against a person for failure on his part to register any birth or death within the time specified therefore and any such birth or death may be registered during the pendency of any such action (Sec. 14).

Registration of name of child: Where the birth of any child has been registered without a name, the parent or guardian of such child shall within the prescribed period give information regarding the name of the child to the registrar either orally or in writing and thereupon the registrar shall enter such name in the register and initial and date the entry (Sec. 15).

Correction or cancelation of entry in the register of births and deaths: If it is proved to the satisfaction of the registrar that any entry of a birth or death in any register kept by him under this Act is erroneous in form or substance, or has been fraudulently or improperly made, he may, subject to such rules as may be made by the state government with respect to the conditions on which and the circumstances in which such entries may be corrected or canceled, correct the error or cancel the entry by suitable entry in the margin, without any alteration of the original entry and shall sign the marginal entry and add there to the date of the correction or cancelation.

Penalties

1. Any person who:
   A. Fails without reasonable cause to give any information which is his duty to give under any of the provisions of sections 8 and 9; or
   B. Give or causes to be given, for the purpose of being inserted in any register of births and deaths, any information which he knows or believes to be false regarding any of the particulars required to be known and registered; or
   C. Refuses to write his name, description and place of abode or to put his thumb mark in the register as required by section 11, shall be punishable with fine which may extend to fifty rupees.
2. Any registrar or sub-registrar who neglects or refuses, without reasonable cause, to register any birth or death occurring in his jurisdiction or to submit any returns as required by subsection (1) 01 section 19 shall be punishable with fine which may extend to fifty rupees.
3. Any medical practitioner who neglects or refuses to issue a certificate under subsection (3) of section 10 and any person who neglects or refuses to deliver such certificate shall be punishable with fine, which may extend to 50 rupees.
4. Any person who, without reasonable cause, contravenes any provision of this Act for the contravention of which no penalty is provided for in this section shall be punishable with fine, which may extend to ten rupees.
5. Notwithstanding anything contained in the code of criminal procedure, 1898 (5 of 1898), an offence under this section shall be tried summarily by a magistrate.

INDIAN MEDICAL COUNCIL ACT 1956, ACT 102 OF 1956

The medical council of India formulates numerous regulations governing professional conduct of medical professional in the country. Therefore, due to constrain of space, we will not enumerate all the regulations but will highlight only few.

1. A physician should participate in professional meeting as part of continuing medical education program for at least 30 hours every five years, organized by reputed professional academic bodies or any other authorized organizations. The compliance of this requirement shall be informed regularly to medical council of India or the state medical councils as the case may be.
2. Every physician shall maintain the medical records pertaining to his/her indoor patients for a period of 3 years from the date of commencement of the treatment in a standard proforma laid down by the medical council of India.
3. If any request is made for medical records either by the patients/authorized attendant or legal authorities involved, the same may be duly acknowledged and documents shall be issued within the period of 72 hours.
4. Maintain a register of medical certificates giving full details of certificate and at least one identification mark and preserve a copy of the same.
5. Computerize medical records.
6. It is unethical to enter into contract of “no cure no payment” with patient.
7. The physician shall observe Acts, rules, regulation made by the central/state governments or local administrative bodies or any other relevant Act relating to the protection and promotion of public health.
8. The physician should neither exaggerate nor minimize the gravity of a patient’s condition.
9. A physician shall clearly display his fees and other charges on the board of his chamber and/or the hospital he is visiting.
10. A physician shall not give, solicit or receive, any gift, gratuity, commission or bonus in consideration of or return for the referring, recommendation or procuring of any patients for medical, surgical or other treatment.
11. Soliciting patients directly or indirectly by a physician, by a group of physician or by institutions or organizations is unethical.
12. On no account sex determination test shall be undertaken with intent to identify or terminate the life of a female
fetus developing in her mother’s womb, unless there are other absolute indications for termination of pregnancy as specified in the MTP Act 1971. Any Act of termination of pregnancy of normal female fetus amounting to female feticide shall be regarded as professional misconduct on the part of the physician leading to penal erasure besides rendering him liable to criminal proceedings as per provision of this Act.

13. Any registered practitioner who is shown to have signed or given under his name any authority and such certificate, notification, report or document of a similar character, which is untrue, misleading or improper, is liable to have his name deleted from the register.

14. A physician shall not claim to be a specialist unless he has special qualification in that branch.

15. No Act of in vitro fertilization or artificial insemination shall be undertaken without the informed consent of the female patient and her spouse as well as the donor. Such consent shall be obtained in writing only after the patient is provided at her own level of comprehension with sufficient information about the purpose, methods, risks, inconveniences, disappointments of the procedure and possible risk and hazards.

CONSUMER PROTECTION ACT 1986 WITH AMENDMENTS IN 2002

Consumer Protection Act was enacted in 1986 but consumer fora all over India were not unanimous in its applicability to medical professionals. It was the landmark judgment of honorable Supreme Court in the case of VP Shanta versus Indian Medical Association (IMA), delivered in 1995 that brought medico legal purview. The IMA lost the appeal against the judgment bringing the medical profession in the ambit of CPA. The media highlighted this case and it resulted in spurt of complaints from all over India in different fora against medical professionals. Our branch, obstetrics and gynecology is most vulnerable branch in medical profession. Most of our “consumers” are young in their 2nd and 3rd decades of life. Any morbidity or mortality causes lot of distress in the entire family which drives “consumers” to go to the court for redressal of their grievances and to “teach a lesson” to the service provider. Before 1986, there were civil courts; criminal courts, coroner court (in Mumbai and Kolkata) and medical councils were there for patient to go for redressal of their grievances. Those options, barring coroner courts are there today also. But consumer forums are supposed to give speedy justice and are practically inexpensive. There is no need of a lawyer to file and fight their case. Initial enthusiasm of media is fading away and therefore, we do not hear or read more about the consumer cases nowadays. In reality, many medicos today are facing the court cases for mishaps.

Consumer Protection Act is a social legislation. A rational approach and not a technical approach, it is the mandate of law. It is like a summary trial. The case most of the time is decided on the affidavits submitted by both parties. Cross examination of complainants, defendant, experts and other witnesses are rarely allowed and therefore documents play very important role in the defense of the doctor. The consumer court may not demand case paper of the patient or even complainer may not directly ask for the paper from the doctor concerned. The trend nowadays is that a complainant lodges complaint under CPA as well and lodges police complaint under IPC 304A (rash or negligent Act). When there is criminal complaint, at the time of incident itself (death or serious injury) police are expected to take case record in their possession.

If the postmortem (PM) is/has been done then PM surgeon would not proceed without the whole record (whether it is mandatory to give whole/detail record or just to give summary of the case is debatable). However, it is never advisable to argue either with police or PM surgeon at that situation and at that time. Therefore, it goes without saying that the record of each and every patient must be complete in all aspects from the time of admission. If one is habituated to proper practice and procedure, then it is not difficult at the time of mishap to complete the paper in time and to hand over the photocopy of the same to either police or PM surgeon. In your own nursing home also, one must sign all the clinical notes, operation notes and orders. Whenever one has to handover any document to any authority or to a patient’s relation, one must number the pages and take acknowledgment on the original documents with date and time.

Please do not leave everything to lawyer and do not become an audience. Take interest in your case, go through literature of that particular mishap and produce only what is relevant to your case. It is advisable to consult your colleagues, preferably medicolegal experts in such cases before completing the documents.

After the amendment in CPA, now it is possible at the stage of admission of the case, to take objection so that the consumore forum (at the district level) or consumer commission (at the state level) can dismiss the complaint. The objections can be raised on various grounds such as complainant is “consumer” or not, excessive demand of compensation/damages, pecuniary jurisdiction and one of the most important objections one can raise is the complaint is not supported by the medical evidence in the form of expert opinion. At this stage, the defendant should be also very careful, in submitting the medical references and expert opinion in his/her support. There were incidences that defendant’s medical references and expert opinion was smartly used by the advocate of complainant to support allegations of medical negligence and/or deficiency of service. We all know very well that medical literature is full of controversies and in the management of a particular problem, there are number of options. If there are guidelines framed by one professional body, the other professional body may have different guideline. It is not that one guideline or one way of management is wrong and second way of management is
correct. It all depends how one produces references and expert opinion to justify his/her way of management was acceptable and practiced at that particular time by a group of doctors.

There is some common misconception about the CPA. The most prominent among them is about charges. In most of the states in our country, there are no restrictions about how much one should charge about the particular service that one provides. That means for a common operation like MTP. One can charge ₹200 or ₹20,000. CPA will not come in the picture but as per MCI Act one is supposed to inform the patient before undertaking surgery, the charges for that particular surgery. It is a common observation that when there is a mishap, doctors do not charge that patient with misbelief that they have given “free service” and therefore they will not come under CPA. They should remember that even if you charge one patient out of one thousand then also CPA is applicable to you. Honorable Supreme Court has given a judgment on this in the landmark case of IMA versus VP Shanta in November 1995. If one foregoes his/her charges in the case where mishap had occurred then it might be actually taken as acceptance of guilt and indirect compensation as well as an effort to cover up the case.

It is advisable to consult lawyer and medicolegal expert at the time of mishap and not after receiving the legal notice from lawyer or complainant from the consumer forum.

Each and every medico ideally should take out professional indemnity insurance for him/her from the day one of practice, whether she/he is in private practice or in service. If she/he is having his/her own clinical establishment then at the time she/he should take out another policy called as “error and omission policy” for clinical establishment and should pay 7.5% extra premium to cover nonqualified staff of the nursing home (majority of the private nursing home, have unqualified staff). Nowadays, there are number of incidences of damaging the nursing homes, instruments and equipments after some mishap. To cover the loss, if it takes place, one should insure clinical establishment by taking out the policy for “riot and malicious damage policy”.

We hope the above discussion will help in minimizing apprehension and fear about CPA.

**Criminal Law**

As mentioned above, obstetrician and gynecologist is first an Indian citizen and then a medico. Criminal law is applicable equally to all. Few years back doctors were considered next to god but now the situation has changed. Everybody has become aware of his or her rights. Globalization is catching up fast. Media and especially electronic media play an important role in today’s life of a common man. Mechanism for redressal of grievances takes its own time and it is true even for so called “speedy justice” that was offered by CPA. It has not come in reality and therefore now there are two groups of people, one who do not believe in law and take law in their hands and second group of people who believe in law, resort to criminal law system along with CPA.

Indian penal code is applicable to all of us, but there are certain sections related to the medical profession. We will give brief idea of those sections.

**Section 202** Intentional omission to give information of offence by a person bound to inform.

**Section 269** Negligent Act likely to spread infection of disease dangerous to life.

**Section 304A** Whoever causes the death of any person by doing any rash or negligent Act not amounting to culpable homicide shall be punished. (Most of the deaths in our practice, caused by medical negligence and/or deficiency of service and complaint to police; they register the offence under this section)

**Section 312** Causing miscarriage, without woman’s consent, act done with intent to prevent child being born alive or to cause it to die after birth, causing death of quick unborn child by Act amounting to culpable homicide. (If one does termination of pregnancy without following the MTP Act and properly will attract this section of IPC)

**Section 319** Voluntarily causing hurt or grievous hurt which endangers life.

**Section 341** Wrongful confinement.

**Section 342** (Sometimes a patient or relatives refuse to pay doctor’s fees and if doctor does not give discharge to the patient, who has recovered then, it is a crime).

**Section 491** Breach of contract to attend on and supply wants of helpless person.

**Section 499** Defamation

If one does anything illegal in their course of practice, just to give example of manipulating notes on the case papers, keeping patients’ ornaments or anything valuable.

If she has not paid the full amount of the bill, giving false certificates, etc. will attract other sections of the IPC for medicos also.

**ENVIRONMENT PROTECTION ACT 1986, ACT 29 OF 1986**

Central government notified the rules for the management and handling of BMW in 1998. By now it is applicable all over India. These rules apply to all persons who generate, collect, receive, store, transport, treat, dispose or handle biomedical waste in any form.

In our nursing home we generate, collect, store and handle biomedical waste. It shall be the duty of every occupier of an institution generating biomedical waste which includes a hospital, nursing home, clinic, dispensary, veterinary, animal house, pathological laboratory, blood bank by whatever name called, to take all steps to ensure that such waste is handled without any adverse effect to human health and the environment.
Majority of the nursing home occupier do not give treatment and they do not dispose BMW. Segregation, packaging and storage of BMW is done in the nursing home/hospital. BMW should not be mixed with other wastes. It is segregated at the point of generation in accordance with schedule II. No untreated biomedical waste shall be kept stored beyond a period of 48 hours. Categories of biomedical waste are shown in Table 2.

Every authorized person shall maintain records related to generation, collection, reception, storage, transportation, treatment, disposal and/or any form of handling of biomedical waste in accordance with these rules and any guidelines issued. All records shall be subject to inspection and verification by the prescribed authority at any time.

Every occupier shall submit an annual report to the prescribed authority in form II by 31st January every year to include information about the categories and quantities of biomedical wastes handled during the preceding year.

What are the categories of BMW and the color codes for particular BMW is not discussed here for want of space. The government of every state and union territory has established a prescribed authority and it is responsible for everything under the Act.

### BIOMEDICAL WASTE ACT

#### Mandatory Things in the Hospital Premises
1. Needle destroyer
2. Syringe destroyer
3. Three colored bags or two combined color bags
4. Sodium hypochlorite solution
5. Segregation training of staff by the service provider.

#### Advices
1. Registration under biomedical waste Act is mandatory.
2. Send report to PCB every year before 31st January.
3. Renewal of PCB certificate every three years.
4. Display of PCB certificate—not mandatory.
5. Display of service certificate—not mandatory.
6. Preserve the bills and receipts of payment of every month of service provider.
7. Make a habit to give a certificate if you are handing over a missed fetus.

#### Fee Structure
- Bedless hospitals: ₹1,200/-
- Up to 50 beds hospitals: ₹2,000/-

#### Addresses of Authorities
1. Regional office: Pollution Control Board
2. Head office: Pollution Control Board

#### Duty of Occupier
It shall be the duty of every occupier of an institution generating biomedical waste, which includes a hospital, nursing home, clinic, dispensary, veterinary institutions, animal house, pathological laboratory, blood bank by whatever name called to take all steps to ensure that such waste is handled without any adverse effect to human health and the environment.

#### Authorization
A. Every occupier of an institution generating, collecting, receiving, storing, transporting, treating, disposing and/or handling biomedical waste in any other manner, except such occupier of clinic, dispensaries, pathological laboratories, blood banks providing treatment/service to less than 1,000 patients per month, shall make an application in form 1 to the prescribed authority for grant of authorization.
B. Every operator of a biomedical waste facility shall make an application in form 1 to the prescribed authority for grant of authorization.

C. Every application in form 1 for grant of authorization shall be accompanied by a fee as may be prescribed by the government of the state of union territory.

**Annual Report**

Every occupier/operator shall submit an annual report to the prescribed authority in form II by 31st January every year to include information about the categories and quantities of biomedical wastes handled during the preceding year. The prescribed authority shall send this information in a compiled form to the central pollution control board by 31st March every year.

**Maintenance of Records**

A. Every authorized person shall maintain records related to the generation, collection, reception, storage transportation, treatment, disposal and/or any form of handling of biomedical waste in accordance with these rules and any guidelines issued.

B. All records shall be subjected to inspection and verification by the prescribed authority at any time.

**Accident Reporting**

When any accidents occur at any institution or facility or any other site where biomedical waste is handled during transportation of such waste, the authorized person shall report the accident in form III to the prescribe authority forthwith.

**LABOR LAWS APPLICABLE TO MATERNITY AND NURSING HOME**

Town planning department defines hospital in different form as, nursing home, maternity home, polyclinic and clinic. Majority of obstetrician and gynecologist will have clinical establishment, which will not be categorized as “hospital”. In this chapter, we will briefly write of labor laws, which are applicable to maternity and nursing home, etc.

“Labor” is the state subject and, therefore, there will not be uniform laws all over India. There may be variations from state to state, however, basic structure will remain the same. We have mentioned here laws applicable in Maharashtra.

One may wonder how it will affect obstetrics and gynecological practice. Those who are having their own maternity and nursing home or hospitals may have to face labor problem some or other time so it becomes essential to know labor laws also. Here we will just mention salient features of these laws applicable in Maharashtra.

Nursinghome, maternity homes are considered, “industry”, till date and therefore, following Acts are applicable:

A. **Industrial Disputes Act 1947**
   It is applicable to nursing home, when numbers of employees are more than 10. Under the industrial disputes Act, nursing home is declared as “public utility service”.
   The advantage of this is that if employees want to go on strike, they have to give 14 days’ notice to the employer otherwise the strike is illegal.
   Employer cannot remove permanent employee from service without a valid reason and only after conducting domestic inquiry.

B. **Bombay Shops and Establishment Act 1948**
   The timing, weekly off and yearly leave to the nursing home staff are decided under this Act.

C. **Maternity Benefit Act 1961**
   Employer is supposed to give all maternity benefits to permanent employees of the nursing home. This includes leave for breastfeeding also.

D. **Payment of Wages Act 1936**
   As per this Act, payment should be made to employee before 7th of every month and only specific deductions are allowed.

E. **Minimum Wages Act 1948**
   As per this Act, minimum wages must be paid to their employees. If employer is not paying minimum wages as decided by the government for nursing home along with special allowance or taking signature without writing the amount it will attract criminal proceeding against the employer.

F. **Industrial Employment (Standing Orders) Act 1946**
   It is applicable if 50 or more employees are working in that establishment. These are regarding service rules of employees. Employer cannot change service condition or rules without permission of union and/or government.

G. **Payment of Gratuity Act 1972**
   This is applicable if employees are more than 10.

H. **Employees Provident Fund Act 1952**
   This Act is applicable to nursing home if there are 20 or more employees.

I. **Workmen’s Compensation Act 1923**
   If personal injury is caused to an employee by accident arising in the course of his/her employment, the employer shall be liable to pay the compensation in accordance with the provisions of this Act.

J. **Payment of Bonus Act 1965**
   This Act is applicable if there are more than 10 employees. Minimum bonus employer is supposed to give is 8.33% (whether there is profit or loss). The range of bonus is 8.33–20%.

K. **Maharashtra Recognition of Trade Unions and Unfair Labor Practices Act 1971 (Known As MRTU and PULP Act 1971)**
   This is applicable to all maternity and nursing homes. This is one of the popular Acts of union.
L. Indian Trade Union Act 1926
Under this Act, even employer can form union, association or federation or can join the existing one.

M. The Bombay Labor Welfare Act 1953
Under this Act, employer and employees are supposed to contribute certain amount to labor welfare fund.

THE BOMBAY NURSING HOMES REGISTRATION ACT, 1949 AND RULES THERE UNDER

This is an old Act applicable to all clinical establishments having indoor admission facilities. It is applicable by this name in old Bombay state—now Maharashtra and Gujarat.

In Maharashtra, unless the maternity and nursing home is registered under this Act, one does not get registration under MTP and PCPNDT Act.

It is necessary to renew the registration every year. Insurance companies and TPAs also require registration under this Act. Under this Act, one of the requirements is to have qualified nursing staff in the maternity and nursing home.

Acts in the Pipeline

1. In Maharashtra, clinical establishment Act. The main feature of this Act will be about fixing charges for various procedures.

2. Central government is planning to introduce new Act for nursing homes, by which refusal of an emergency patient (not only accident cases) without first aid and referring to other hospitals will attract fine as well as jail term for the owner of the nursing home.

We have discussed many but not all the laws related to our practice in obstetrics and gynecology. The intention is to make you aware of the laws and Acts. One must acquire its full knowledge; one should know that “ignorance of law is not an excuse”.

Income Tax Act

(cc.—books of account)

Books of account and other documents to be kept and maintained under section 44AA(3) by persons carrying on certain professions.

6F. 1. Every person carrying on legal, medical, engineering or architectural profession or the profession of accountancy or technical consultancy or interior decoration or authorized representative or film artist shall keep and maintain the books of account and other documents specified in subrule (2).

[Provided that nothing in this subrule shall apply in relation to any previous year in the case of any person if his total gross receipts in the profession do not exceed 1,50,000 rupees in any 1 of the 3 years immediately preceding the previous year, or, where the profession has been newly set up in the previous year, his total gross receipts in the profession for that year are not likely to exceed the said amount].

2. The books of account and other documents referred to in subrule (1) shall be the following, namely:
   I. A cash book;
   II. A journal, if the accounts are maintained according to the mercantile system of accounting;
   III. A ledger;
   IV. Carbon copies of bills, whether machine numbered or otherwise serially numbered, wherever such bills are issued by the person, and carbon copies or counterfoils of machine numbered or otherwise serially numbered receipts issued by him.

[Provided that nothing in this clause shall apply in relation to sums not exceeding twenty-five rupees].

V. Original bills wherever issued to the person and receipts in respect of expenditure incurred by the person or, where such bills and receipts are not issued and the expenditure incurred does not exceed fifty rupees, payment vouchers prepared and signed by the person. [Provided that the requirements as to the preparation and signing of payment vouchers shall not apply in a case where the cash book maintained by the person contains adequate particulars in respect of the expenditure incurred by him].

Explanation: In this rule,

A. Authorized representative means a person who represents any other person, on payment of any fee or remuneration before any tribunal or authority constituted or appointed by or under any law for the time being in force, but does not include an employee of the person so represented or a person carrying on legal profession or a person carrying on the profession of accountancy;

B. Cash book means a record of all cash receipts and payments, kept and maintained from day-to-day and giving the cash balance in hand at the end of each day or at the end of a specified period not exceeding a month.

3. A person carrying on medical profession shall, in addition to the books of account and other documents specified in subrule (2), keep and maintain the following, namely: (i) a daily case register in form no. 3c; (ii) an inventory [under broad heads] as on the first and the last day of the previous year, of the stock of drugs, medicines and other consumable accessories used for the purpose of his profession.

4. The books of account and other documents specified in subrule (2) and subrule (3) [other than those relating to a previous year which has come to an end] shall be kept and maintained by the person at the place where he is carrying on the profession or, where the profession is carried on in more places than one, at the principal place of his profession: Provided that where the person keeps and
maintains separate books of account in respect of each place where the profession is carried on, such books of account and other documents may be kept and maintained at the respective places at which the profession is carried on.

5. The books of account and other documents specified in subrule (2) and subrule (3) shall be kept and maintained for a period of six years from the end of the relevant assessment year.

[Provided that where the assessment in relation to any assessment year has been reopened under section 147 of the Act within the period specified in section 149 of the Act, all the books of account and other documents which were kept and maintained at the time of reopening of the assessment shall continue to be so kept and maintained till the assessment so reopened has been completed].

[(6) notwithstanding anything contained in subrules (1) to (3), it shall not be necessary for any person carrying on any of the professions specified in subrule (1) to keep and maintain the books of account and other documents specified in subrule (2) or subrule (3) in relation to any previous year commencing before the [first day of March, 1983].

Action Points

1. Register is to be maintained by every person carrying on medical profession under any system of medicine in respect of previous year commencing on or after March 1, 1983 (Table 3).

2. Entries in this register may be made chronologically every day. At the end of each day, it must be ensured that the total fees as entered in this register tallies with the corresponding details in the receipts issued, as well as with the entries in the cash book.

3. This register should be preserved for a period of 6 years from the end of the relevant assessment year. Where the assessing authority has reopened the assessment for any assessment year, this register should be preserved till the reassessment proceedings are completed, even if it entails retention beyond the period of 6 years mentioned above.

4. The register in this form is in addition to regular books of account (cash book, journal, ledger, bills, etc.) which are required to be maintained under rule 6F(2).

5. An inventory of stock of drugs, medicines and other consumable accessories is also required to be maintained in addition to this register.

6. Failure to maintain this register or to retain it for the prescribed period will entail penalty under section 271A of `25,000.

- Income tax return shall be filed in ‘SARAL’ form (form 2D)
- Application for allotment of permanent account number under section 139A of the income tax Act, 1961 form no. 49A
- Form of application for allotment of tax deduction and collection account number under section 203A of the income tax Act, 1961 form no. 49B.

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MEDICAL NEGLIGENCE

SPEECH ON MEDICAL NEGLIGENCE DELIVERED BY HON’BLE MR JUSTICE MARKANDEY CATJU, JUDGE, SUPREME COURT OF INDIA

Friends,

Cases, both civil and criminal as well as in Consumer Fora, are often filed against medical practitioners and hospitals, complaining of medical negligence against doctors or hospitals or nursing homes and, hence, doctors and nursing homes or hospitals naturally would like to know about their liability.

The general principles on this subject have been lucidly and elaborately explained in the recent three-Judge Bench decision of the Supreme Court in Jacob Mathew vs. State of Punjab and Others (2005) 6 SCC 1. However, difficulties arise in the application of those general principles to specific cases.

For instance, in para 41 of the aforesaid decision, it was observed:

“The practitioner must bring to his task a reasonable degree of skill and knowledge, and must exercise a reasonable degree of care. Neither the very highest nor a very low degree of care and competence is what the law requires.”

Now what is reasonable and what is unreasonable is a matter on which even experts may disagree. Also, they may disagree on what is a high level of care and what is a low level of care.

To give another example, in paragraph 12–16 of Jacob Mathew’s case (supra), it has been stated that simple negligence may result only in civil liability, but gross negligence or recklessness may result in criminal liability as well. For civil liability only, damages can be imposed by the Court but for criminal liability, the Doctor can also be sent to jail (apart from damages which may be imposed on him in a civil suit or by the Consumer Fora). However, what is simple negligence and what is gross negligence may be a matter of dispute even among experts.

The law, like medicine, is an inexact science. One cannot predict with certainty an outcome of many cases. It depends on the particular facts and circumstances of the case, and also the personal notions of the judge concerned who is hearing the case. However, the broad and general legal principles relating to medical negligence need to be understood.

Before dealing with these principles, two things have to be kept in mind:

1. Judges are not experts in medical science, rather they are laymen. This itself often makes it somewhat difficult for them to decide cases relating to medical negligence. Moreover, judges have usually to rely on testimonies of other doctors which may not necessarily in all cases be objective, since like in all professions and services, doctors too sometimes have a tendency to support their own colleagues who are charged with medical negligence. The testimony may also be difficult to understand, particularly in complicated matters, for a layman in medical matters, like a judge.

2. A balance has to be struck in such cases. While doctors who cause death or agony due to medical negligence should certainly be penalized, it must also be remembered that like all professionals doctors too can make errors of judgment but if they are punished in all cases for this, no doctor can practice his vocation with equanimity. Indiscriminate proceedings and decisions against doctors are counterproductive and serve society no good. They inhibit the free exercise of judgment by a professional in a particular situation.

Keeping the above two notions in mind, we may discuss the broad general principles relating to medical negligence.

GENERAL PRINCIPLES RELATING TO MEDICAL NEGLIGENCE

As already stated above, the broad general principles of medical negligence have been laid down in the Supreme Court Judgment in Jacob Mathew vs. State of Punjab and Others (supra). However, these principles can be indicated briefly here:

Bolam Rule

The basic principle relating to medical negligence is known as the Bolam Rule. This was laid down in the judgment of Justice McNair in Bolam vs. Friern Hospital Management Committee (1957) 1 WLR 582 as follows:

“Where you get a situation which involves the use of some special skill or competence, then the test as to whether there has been negligence or not is not the test of the man on the top of a Clapham omnibus, because he has not got this special skill. The test is the standard of the ordinary skilled man exercising and professing to have that special skill. A man need not possess the highest expert skill.”

It is a well-established law that it is sufficient if he exercises the ordinary skill of an ordinary competent man exercising that particular art.

Bolam’s test has been approved by the Supreme Court in Jacob Mathew’s case.

In Halsbury’s Laws of England, the degree of skill and care required by a medical practitioner is stated as follows:

“The practitioner must bring to his task a reasonable degree of skill and knowledge, and must exercise a reasonable
degree of care. Neither the very highest nor a very low degree of care and competence, judged in the light of the particular circumstances of each case, is what the law requires, and a person is not liable in negligence because someone else of greater skill and knowledge would have prescribed different treatment or operated in a different way; nor is he guilty of negligence if he has acted in accordance with a practice accepted as proper by a responsible body of medical men skilled in that particular art, even though a body of adverse opinion also existed among medical men”. Deviation from normal practice is not necessarily evidence of negligence. To establish liability on that basis it must be shown (1) that there is a usual and normal practice; (2) that the defendant has not adopted it; and (3) that the course in fact adopted is one no professional man of ordinary skill would have taken had he been acting with ordinary care. (emphasis supplied)

1. Eckersley vs. Binnie (1988) 18 Con LR 1 summarized the Bolam’s test in the following words: “From these general statements, it follows that a professional man should command the corpus of knowledge which forms part of the professional equipment of the ordinary member of his profession. He should not lag behind other ordinary assiduous and intelligent members of his profession in the knowledge of new advances, discoveries and developments in his field. He should have such an awareness as an ordinarily competent would have of the deficiencies in his knowledge and the limitations on his skill. He should be alert to the hazards and risks in any professional task he undertakes to the extent that other ordinarily competent members of the profession would be alert. He must bring to any professional task he undertakes no less expertise, skill and care than other ordinarily competent members of his profession would bring, but need bring no more. The standard is that of the reasonable average. The law does not require of a professional man that he be a paragon combining the qualities of polymath and prophet.”

2. A medical practitioner is not liable to be held negligent simply because things went wrong from mischance or misadventure or through an error of judgment in choosing one reasonable course of treatment in preference to another. He would be liable only where his conduct fell below that of the standards of a reasonably competent practitioner in his field. For instance, he would be liable if he leaves a surgical gauze or mop inside the patient after an operation vide Achutrao Haribhau Khodrea vs. State of Maharashtra AIR 1996 SC 2377, or operate on the wrong part of the body, and he would be also criminally liable if he operates on someone for removing an organ for illegitimate trade.

There is a tendency to confuse a reasonable person with an error-free person. An error of judgment may or may not be negligent. It depends on the nature of the error.

It is not enough to show that there is a body of competent professional opinion which considers that the decision of the accused professional was wrong, provided there also exists a body of professional opinion, equally competent, which supports the decision as reasonable in the circumstances. As Lord Clyde stated in Hunter vs. Hanley 1955 SIT 213:

“In the realm of diagnosis and treatment there is ample scope for genuine difference of opinion and one man clearly is not negligent merely because his conclusion differs from that of other professional men.... The true test for establishing negligence in diagnosis or treatment on the part of a doctor is whether he has been proved to be guilty of such failure as no doctor of ordinary skill would be guilty of if acting with ordinary care...” (emphasis supplied)

3. The standard of care has to be judged in the light of knowledge available at the time of the incident and not at the date of the trial. Also, where the charge of negligence is of failure to use some particular equipment, the charge would fail if the equipment was not generally available at that point of time.

4. The higher the acuteness in an emergency and the higher the complication, the more are the chances of error of judgment. At times, the professional is confronted with making a choice between the devil and the deep sea and has to choose the lesser evil. The doctor is often called upon to adopt a procedure which involves higher element of risk, but which he honestly believes as providing greater chances of success for the patient, rather than a procedure involving lesser risk but higher chances of failure. Which course is more appropriate to follow, would depend on the facts and circumstances of a given case but a doctor cannot be penalized if he adopts the former procedure, even if it results in a failure. The usual practice prevalent nowadays is to obtain the consent of the patient or of the person in-charge of the patient if the patient is not in a position to give consent before adopting a given procedure.

There may be a few cases where an exceptionally brilliant doctor performs an operation or prescribes a treatment which has never been tried before to save the life of a patient when no known method of treatment is available. If the patient dies or suffers some serious harm, should the doctor be held liable? In my opinion, he should not. Science advances by experimentation, but experiments sometimes end in failure, e.g. the operation on the Iranian twin sisters who were joined at the head since birth or the first heart transplant by Dr Barnard. However, in such cases, it is advisable for the doctor to explain the situation to the patient and take his written consent.

5. Simply because a patient has not favorably responded to a treatment given by a doctor or a surgery has failed, the doctor cannot be held straightway liable for medical
negligence by applying the doctrine of res ipsa loquitur. No sensible professional would intentionally commit an Act or omission which would result in harm or injury to the patient since the reputation of the professional would be at stake. A single failure may cost him dear in his lapse.

6. As observed by the Supreme Court in Jacob Mathew’s case: “A medical practitioner faced with an emergency ordinarily tries his best to redeem the patient out of his suffering. He does not gain anything by acting with negligence or by omitting to do an Act. Obviously, therefore, it will be for the complainant to clearly make out a case of negligence before a medical practitioner is charged with or proceeded against criminally. A surgeon with shaky hands under fear of legal action cannot perform a successful operation and a quivering physician cannot administer the end-dose of medicine to his patient.

If the hands be trembling with the dangling fear of facing a criminal prosecution in the event of failure for whatever reason—whether attributable to himself or not, neither can a surgeon successfully wield his life-saving scalpel to perform an essential surgery, nor can a physician successfully administer the life-saving dose of medicine. Discretion being the better part of valor, a medical professional would feel better advised to leave a terminal patient to his own fate in the case of emergency where the chance of success may be 10% (or so), rather than taking the risk of making a last ditch effort toward saving the subject and facing a criminal prosecution if his effort fails. Such timidity forced upon a doctor would be a disservice to society.”

When a patient dies or suffers some mishap, there is a tendency to blame the doctor for this. Things have gone wrong and, therefore, somebody must be punished for it. However, it is well-known that even the best professionals, what to say of the average professional, sometimes have failures. A lawyer cannot win every case in his professional career, and surely he cannot be penalized for losing a case provided he appeared in it and made his submissions.

7. To fasten liability in criminal proceedings, e.g. under Section 304A of IPC, the degree of negligence has to be higher than the negligence which is enough to fasten liability in civil proceedings. Thus, for civil liability, it may be enough for the complainant to prove that the doctor did not exercise reasonable care in accordance with the principles mentioned above, but for convicting a doctor in a criminal case, it must also be proved that this negligence was gross amounting to recklessness.

Thus, the difference between simple negligence and gross negligence has broadly been explained in paragraph 12–16 of Jacob Mathew’s case, although difficulties may arise in the application of the principle in particular cases. For instance, if a mop is left behind in the stomach of a patient while doing an operation, would it be simple negligence or gross negligence? Achutrao’s case (AIR 1996 SC 2377) dealt only with civil liability where a mop was negligently left behind by a doctor in the body of woman who had undergone a sterilization operation, resulting in death by peritonitis due to formation of pus. The question whether criminal liability also arose was not discussed in that decision. If a scissor or sharp-edged medical instrument is left in the patient’s body while doing the operation, would that make a difference from merely leaving a mop and result in criminal liability? These questions often arise.

8. The professional is one who professes to have some special skill. A professional impliedly assures the person dealing with him (i) that he has the skill which he professes to possess and (ii) that skill shall be exercised with reasonable care and caution.

Judged by this standard, the professional may be held liable for negligence on the ground that he was not possessed of the requisite skill which he professes to have. Thus, a doctor who has a qualification in Ayurvedic or Homeopathic medicine will be liable if he prescribes Allopathic treatment which causes some harm vide Poonam Verma vs. Ashwin Patel and Others (1996) 4 SCO 332. In Dr Shiv Kumar Gautam vs. Alima, Revision Petition No. 586 of 1999 decided on 10.10.2006, the National Consumer Commission held a homeopath liable for negligence for prescribing allopathic medicines and administering glucose drip and giving injections.

### PROTECTION TO DOCTORS IN CRIMINAL CASES

In para 52 of Jacob Mathew’s case, the Supreme Court, realizing that doctors have to be protected from frivolous complaints of medical negligence, has laid down certain rules in this connection:

a. A private complaint should not be entertained unless the complainant has produced prima facie evidence before the court in the form of a credible opinion given by another competent doctor to support the charge of rashness or negligence on the part of the accused doctor.

b. The investigating officer should, before proceeding against the doctor accused of rash or negligent Act or omission, obtain an independent and competent medical opinion, preferably from a doctor in government service, qualified in that branch of medical practice who can normally be expected to give an impartial opinion applying the Bolam’s test.

c. A doctor accused of negligence should not be arrested in a routine manner simply because a charge has been leveled against him. Unless his arrest is necessary for furthering the investigation or for collecting evidence or unless the investigating officer feels satisfied that the doctor proceeded against would not make himself available to face the prosecution unless arrested, the arrest should be withheld.
PRECAUTIONS WHICH THE DOCTORS OR HOSPITALS OR NURSING HOMES SHOULD TAKE

i. Current practices, infrastructure, paramedical and other staff, hygiene and sterility should be observed strictly. Thus, in Sarmati Ali Khan vs. Prof. R Gogi and Others, Original Petition No. 181 of 1997, decided on July 18, 2007 by the National Consumer Commission, the facts were that out of 52 cataract operations performed between 26th and 28th September, 1995 in an eye hospital, 14 persons lost their vision in the operated eye. An enquiry revealed that in the operation theater two autoclaves were not working properly. This equipment is absolutely necessary to carry out sterilization of instruments, cotton pads, linen, etc. and the damage occurred because of its absence in working condition. The doctors were held liable.

In the newspaper “Times of India”, Delhi Edition dated 02.10.2007, a news report was published of an award of ₹20 lacs compensation by the Delhi Consumer Forum against a Delhi hospital in favor of a woman whose legs had to be amputated because of gangrene which set in when a cesarean operation was conducted on her without sterilization and the doctor did not stitch the cuts properly. As a result, blood circulation to her lower limbs stopped, and her legs had to be amputated to save her life.

ii. No prescription should be given without actual examination. The tendency to give prescription over the telephone, except in an acute emergency, should be avoided.

iii. A doctor should not merely go by the version of the patient regarding his symptoms, but should also make his own analysis including tests and investigations where necessary.

iv. A doctor should not experiment unless necessary and even then he should get a written consent from the patient.

v. An expert should be consulted in case of any doubt. Thus, in Smt. Indrani Bhattacharjee, Original Petition No. 233 of 1996 decided by the National Consumer Commission on 09.08.2007, the patient was diagnosed as having “mild lateral wall eschemia”. The doctor prescribed medicine for gastroenteritis, but the patient expired. It was held that the doctor was negligent as he should have advised consulting a cardiologist in writing.

vi. Full record of the diagnosis, treatment, etc. should be maintained.

THE CONSUMER PROTECTION ACT, 1986

In Indian Medical Association vs. VP Shantha AIR 1996 SC 550, the Supreme Court has held that doctors are covered by the Consumer Protection Act if a fee was charged for services rendered by the doctor, since medical assistance for payment falls within the scope of “service” in Section 2(1)(o) of the Act.

After the aforesaid decision, many cases are being filed against the doctors or hospitals or nursing homes in the various Consumer Fora. Some of the decisions from the National Consumer Fora shall be referred to. It may be noted in this connection that when a patient goes to a nursing home or hospital, and the nursing home or hospital agrees to treat him, the liability in case of negligence will not only be of the particular doctor who treated the patient but also of the nursing home or hospital. Hence, penalties can be imposed against both vide Savita Garg vs. Director, National Heart Institute (2004) 8 SCC 56. Similarly, the government will be vicariously liable for the negligence of a doctor in a government hospital vide Achutrao Haribhau Khodwa vs. State of Maharashtra, AIR 1996 SC 2377 (para 12).

In the Indian Medical Association case (supra), the Supreme Court had observed that the medical service rendered free of charge to the patients by a doctor attached to a hospital or nursing homes or employed in government hospital or nursing homes where such services are rendered free of charge to everybody would not fall within the ambit of “service” as defined in Section 2(1)(o) of the Consumer Protection Act and such hospitals or nursing homes would not come within the ambit of the said Act. The payment of token amount for registration would not alter the position. However, where in a hospital or nursing home charges are required to be paid for the persons who are in a position to pay but free services are provided to those who are not in such a position to pay, the hospital or nursing home comes within the purview of the Consumer Protection Act, and even the free services given to the persons not able to pay would be a “service” under the Act.

Where as part of the service condition the employers bear the expenses of medical treatment of the employees and his family members, the service rendered to the employees and his family members would constitute “service” under the Act.

Thus, a railway hospital which treats railway employees free of charge but as a part of the conditions of service comes within the purview of the Consumer Protection Act vide Laxman Thamappa Kotgiri vs. GM Central Railway and Others (2007) 4 SCC 596. Similarly, medical services rendered by Employees’ State Insurance (ESI) doctors in ESI hospitals or dispensaries fall within the ambit of “service” under the Act vide Kishore Lai vs. Chairman, Employees’ State Insurance Corp. (2007) 4 SCC 579.

APPLICATION OF THE ABOVE-MENTIONED GENERAL PRINCIPLES TO PARTICULAR CASES

Decisions of the Courts and Consumer Fora

1. In Pt. Parmanand Katara vs. Union of India and Others AIR 1989 SC 2039, the petition was filed as a public interest
litigation. The petitioner referred to a report published in the newspaper “The Hindustan Times” in which it was mentioned that a scooterist was knocked down by a speeding car. Seeing the profusely bleeding scooterist, a person, who was on the road, picked up the injured and took him to the nearest hospital. The doctors refused to attend and told the man that he should take the patient to another hospital located 20 km away authorized to handle medicolegal cases. The injured was then taken to that hospital but by the time he could reach, the victim succumbed to his injuries.

The Supreme Court referred to the Code of Medical Ethics drawn up with the approval of the Central Government under Section 33 of the Indian Council Medical Act and observed: “Every doctor whether at a Government Hospital or otherwise has the professional obligation to extend his services for protecting life. The obligation being total, absolute and paramount, laws of procedure, whether in statutes or otherwise, which would interfere with the discharge of this obligation, cannot be sustained and must, therefore, give way.

The Supreme Court held that it is the duty of the doctor in an emergency to begin treatment of the patient and he should not await the arrival of the police or to complete the legal formalities. The life of a person is far more important than the legal formalities.

Although this decision has laid down that it is the duty of a doctor to attend to a patient who is brought to him in an emergency, it does not state what penalty will be imposed on a doctor who refuses to attend the said patient. Consequently, it will depend on the fact and circumstances of the case. However, this case is important because nowadays healthcare has often become a business as is mentioned in the play “The Doctor’s Dilemma” by the famous Irish playwright George Bernard Shaw. The medical profession is a noble profession and it cannot be brought down to the level of a simple business or commerce.

In Paschim Banga Khet Mazdoor Samity and Others vs. State of West Bengal and Others AIR 1996 SC 2426, the Supreme Court held that the denial of emergency aid to the petitioner due to the nonavailability of a bed in the Government Hospital amounts to the violation of the right to life under Article 21 of the Constitution. The Court went on to say that the Constitutional obligation imposed on the State by Article 21 cannot be abdicated on the ground of financial constraint.

2. In Md Suleman Ansari (DMS) vs. Shankar Bhandari (2005) 12 SCC 430, the respondent suffered a fracture of his hand. He was taken to the appellant who held himself out to be a qualified medical practitioner. The appellant bandaged the respondent’s hand and prescribed certain medicines. He was ultimately taken to another doctor but by this time the damage to his hand was permanent. In these circumstances, since it was found that the appellant was not a qualified doctor to give treatment to the respondent, the Supreme Court directed him to pay Rs 20,000 as compensation to the respondent.

In Surendra Chauhan vs. State of MP (2000) 4 SCC 10, the appellant was having a degree of Bachelor of Medicine in Electrohomeopathy from the Board of Electrohomeopathy Systems of Medicines, Jabalpur (MP). He did not possess any recognized medical qualification as defined in the Indian Medical Council Act, 1956. Yet, he performed an operation to terminate the three months’ pregnancy in a woman who died in the clinic due to shock because of the nonapplicability of anesthesia. The Supreme Court confirmed his sentence but reduced it to one and a half years’ rigorous imprisonment under Section 314/34 IPC and a fine of Rs 25,000 payable to the mother of the deceased.

3. In State of Haryana and Others vs. Raj Rani (2005) 7 SCC 22, it was held that if a child is born to a woman even after she had undergone a sterilization operation by a surgeon, the doctor was not liable because there cannot be a 100% certainty that no child will be born after a sterilization operation. The Court followed the earlier view of another three-Judge Bench in State of Punjab vs. Shiv Ram (2005) 7 SCC 1. These decisions will be deemed to have overruled the two-Judge Bench decision in State of Haryana and Others vs. Smt. Santra AIR 2000 SC 1888, in which it was held that if a child is born even after the sterilization operation, the surgeon will be liable for negligence.

4. In PN Rao vs. G Jayaprakasu AIR 1990 AP 207, the plaintiff was a brilliant young boy who had passed the pre-university course securing 100% marks in Mathematics and 93.5% in physical sciences. He was also getting a monthly scholarship. He was offered a seat in BE Degree course in four Engineering Colleges. He had a minor ailment—chronic nasal discharge—for which his mother took him to a doctor for consultation who diagnosed the disease as Nasal Allergy and suggested operation for removal of his tonsils. He was admitted in the Government General Hospital, Guntur and the operation was performed. He did not regain consciousness even after 3 days and thereafter for another 15 days he was not able to speak coherently. When he was discharged from the hospital, he could only utter a few words, and could not read or write and lost all his knowledge and learning. His father took him to Vellore where he was examined by a Professor of Neurosurgery and it was found that his brain had suffered due to cerebral anoxia, which was a result of improper induction of anesthetics and failure to take immediate steps to reduce anesthetics. The court after examining the witnesses including the Professor of Anesthesiology held that defendants were clearly negligent in discharging their duties and the State Government was also vicariously liable.

5. In Dr Laxman Balkrishna Joshi vs. Dr Trimbaks Bapu Godbole and Others AIR 1969 SC 128, a patient suffered
from fracture of the femur. The accused doctor while putting the leg in plaster used manual traction and used excessive force for this purpose, with the help of three men, although such traction is never done under morphia alone but done under proper general anesthesia. This had given a tremendous shock causing death of the boy. On these facts, the Supreme Court held that the doctor was liable to pay damages to the parents of the boy.

6. In *Dr Suresh Gupta vs. Government of NCT of Delhi and Others* AIR 2004 SC 4091, the appellant was a doctor accused “under Section 304A IPC” for causing death of his patient. An operation was performed by him for removing a nasal deformity. The Magistrate who charged the appellant stated in his judgment that the appellant while conducting the operation for removal of the nasal deformity gave incision at a wrong part due to which blood seeped into the respiratory passage and because of that the patient collapsed and died. The High Court upheld the order of the Magistrate observing that adequate care was not taken to prevent seepage of blood resulting in asphyxia. The Supreme Court held that from the medical opinions adduced by the prosecution, the cause of death is stated to be “not introducing a cuffed endotracheal tube of proper size as to prevent aspiration of blood from the wound in the respiratory passage”.

The Supreme Court held that this Act attributed to the doctor, even if accepted to be true, can be described as a negligent Act as there was a lack of care and precaution. However, for this Act of negligence, he was only liable in a civil case, and it cannot be described to be so reckless or grossly negligent as to make him liable in a criminal case. For conviction in a criminal case, the negligence and rashness should be of such a high degree which can be described as totally apathetic toward the patient.

7. In *Dr Sr Louie and Others vs. Smt Kannolli Pathumma and Others*, the National Consumer Commission found that Dr Louie showed herself as an MD although she was only MD Freiburg, a German Degree which is equivalent to MBBS degree in India. She was guilty of negligence in treating a woman and her baby who died. There was vacuum slip and the baby was delivered in such an asphyxiated condition.

8. In *Nihal Kaur vs. Director, PGIMSR* (1996) CPJ 112, a patient died a day after surgery and the relatives found a pair of scissors utilized by the surgeon while collecting the last remains. The doctor was held to be liable and a compensation of Rs1.20 lacs was awarded by the State Consumer Forum.

9. In *Spring Meadows Hospital and Others vs. Harjol Ahluwalia through KS Ahluwalia and Others* (1998) CPJ 1, a minor child was admitted by his parents to a nursing home as he was suffering fever. The patient was admitted and the doctor diagnosed typhoid and gave medicines for typhoid fever. A nurse asked the father of the patient to get an injection Lariago which was administered by the nurse to the patient who immediately collapsed. A doctor was examined who testified that the child suffered a cardiac arrest on account of the medicine having being injected, which led to brain damage. The National Consumer Commission held that the cause of cardiac arrest was intravenous injection of Lariago of such high dose. The doctor was negligent in performing his duty because instead of administering the injection himself, he permitted the nurse to give the injection. There was clear dereliction of duty on the part of the nurse who was not even a qualified nurse and was not registered with any nursing council of any State. Both the doctor and nurse and the hospital were found liable and Rs12.5 lacs was awarded as compensation to the parents. This judgment was upheld by the Supreme Court vide AIR 1998 SC 1801.

10. In *Consumer Protection Council and Others vs. Dr M Sundaram and Others* (1998) CPJ 3, the facts were that one Mrs Rajalaxmi was admitted to the nursing home which diagnosed the ailment as Hodgkin’s Lymphoma. She was administered Endoxan injection five doses in 5 days. She was referred to another doctor who was an ear-nose-throat (ENT) specialist, who after examination opined that no lymph glands were seen. A sample of her bone marrow was sent to an oncologist who opined that the picture does not fit with Hodgkin’s disease but the patient had megaloblastic anemia in the bone marrow. Subsequently, she was discharged from the nursing home and was advised to visit Christian Medical College (CMC), Vellore for treatment. The patient consulted another doctor who diagnosed the same as renal failure. The complainant alleged that the first doctor failed and neglected to refer the matter to a Cancer Specialist but wrongly diagnosed the ailment of the patient as Hodgkin’s Lymphoma and had unnecessarily administered injection of Endoxan and because of the toxicity of that drug, the kidney cells of the patient got destroyed resulting in renal failure for which she had to undergo kidney transplantation which led to her death. The National Commission held that there was no negligence on the part of the doctor who had consulted a pathologist and in the light of discussion with him and on inspection of some more slides of bone marrow specimens, which also revealed the same finding, namely, existence of deposits of Hodgkin’s Lymphoma, proceeded to administer the patient injections of Endoxan. It was held on the basis of medical opinion that any prudent consultant physician would not delay the commencement of chemotherapy where repeated examination of the bone marrow slides had yielded the report that the Hodgkin’s deposits were present. Endoxan is a drug of choice in the treatment of Hodgkin’s Lymphoma and there was no negligence on the part of the doctor.

11. In *Sethuraman Subramaniam Iyer vs. Triveni Nursing Home and Others* (1998) CPJ 110, the complainant’s
wife suffered from sinusitis and was advised surgery by the doctor. She suffered a massive heart attack while in the operation theater. The State Commission found that necessary precautions and effective measures were taken to save the deceased and dismissed the complaint. The State Commission relied on the affidavits of four doctors who opined that there was no negligence. The complaint had not given any expert evidence to support his allegation and in these circumstances it was held that no case was made out against the doctor.

12. In *AS Mittal vs. State of UP* (1989) 3 SCC 223, a free eye camp was organized for ophthalmic surgical treatment to patients. However, the eyes of several patients after operation were irreversibly damaged, owing to postoperative infection of the intraocular cavities of the eyes, caused by normal saline used at the time of surgery. The Supreme Court directed the State Government to pay ₹12,500 as compensation to each victim as there was a clear negligence.

### THE EXISTING MEDICAL ETHICS, CODES AND LAWS

(The Gazette of India, New Delhi, Saturday, April 6, 2002.) The Medical Council of India (MCI) has established a Code of Ethics called the Indian Medical Council (Professional Conduct, Etiquette and Ethics) Regulations, 2002 for all medical practitioners, which they are bound to follow.

### MEDICAL COUNCIL OF INDIA NOTIFICATION

(New Delhi, Dated 11th March, 2002). No. MC1-211 (2)(2001)–Regn. In exercise of the powers conferred under section 20A read with section 3(m) of the Indian Medical Council Act, 1956 (102 of 1956), the MCI, with the previous approval of the Central Government, hereby makes the following regulations relating to the Professional Conduct, Etiquette and Ethics for registered medical practitioners, namely:

- **Short title and commencement:** (1) These Regulations may be called the “Indian Medical Council (Professional Conduct, Etiquette and Ethics) Regulations, 2002”, and (2) They shall come into force on the date of their publication in the Official Gazette.

### CHAPTER 1

**Code of Medical Ethics**

**Declaration**

Each applicant, at the time of making an application for registration under the provisions of the Act, shall be provided a copy of the declaration. The applicant shall also certify that he or she had read and agreed to abide by the same.

**Duties and Responsibilities of the Physician in General**

**Character of a Physician**

(Doctors with qualification of MBBS or MBBS with post-graduate degree or diploma or with equivalent qualification in any medical discipline).

1. A physician shall uphold the dignity and honor of his profession.

2. The prime object of the medical profession is to render service to humanity; reward or financial gain is a subordinate consideration. Who so ever chooses his profession, assumes the obligation to conduct himself in accordance with its ideals. A physician should be an upright man, instructed in the art of healings. He shall keep himself pure in character and be diligent in caring for the sick; he should be modest, sober, patient, prompt in discharging his duty without anxiety; conducting himself with propriety in his profession and in all the actions of his life.

3. No person other than a doctor having qualification recognized by MCI and registered with MCI or State Medical Council(s) is allowed to practice Modern System of Medicine or Surgery. A person obtaining qualification in any other system of Medicine is not allowed to practice Modern System of Medicine in any form.

**Maintaining Good Medical Practice**

1. The principal objective of the medical profession is to render service to humanity with full respect for the dignity of profession and man. Physicians should merit the confidence of patients entrusted to their care, rendering to each a full measure of service and devotion. Physicians should try continuously to improve medical knowledge and skills and should make available to their patients and colleagues the benefits of their professional attainments. The physician should practice methods of healing founded on scientific basis and should not associate professionally with anyone who violates this principle. The honored ideals of the medical profession imply that the responsibilities of the physician extend not only to individuals but also to society.

2. **Membership in society:** For the advancement of his profession, a physician should affiliate with associations and societies of allopathic medical professions and involve actively in the functioning of such bodies.

3. A physician should participate in professional meeting as part of continuing Medical Education programs, for at least 30 hours every 5 years, organized by reputed professional academic bodies or any other authorized organizations.
The compliance of this requirement shall be informed regularly to MCI or the State Medical Councils, as the case may be.

**Maintenance of Medical Records**

1. Every physician shall maintain medical records pertaining to his or her indoor patients for a period of 3 years from the date of commencement of the treatment in a standard proforma laid down by the MCI.
2. If any request is made for medical records either by the patients or authorized attendant or legal authorities involved, the same may be duly acknowledged and documents shall be issued within the period of 72 hours.
3. A registered medical practitioner shall maintain a Register of Medical Certificates giving full details of certificates issued. When issuing a medical certificate, he or she shall always enter the identification marks of the patient and keep a copy of the certificate. He or she shall not omit to record the signature and/or thumb mark, address and at least one identification mark of the patient on the medical certificates or report. The medical certificate shall be prepared as required by the MCI Act.
4. Efforts shall be made to computerize medical records for quick retrieval.

**Display of Registration Number**

1. Every physician shall display the registration number accorded to him by the State Medical Council or MCI in his clinic and in all his prescriptions, certificates and money receipts given to his patients.
2. Physicians shall display as suffix to their names only recognized medical degrees or such certificates or diplomas and memberships or honors which confer professional knowledge or recognize any exemplary qualification or achievements.

**Use of Generic Names of Drugs**

Every physician should, as far as possible, prescribe drugs with generic names and he or she shall ensure that there is a rational prescription and use of drugs.

**Highest Quality Assurance in Patient Care**

Every physician should aid in safeguarding the profession against admission to it of those who are deficient in moral character or education. He shall not employ in connection with his professional practice any attendant who is neither registered nor enlisted under the Medical Acts in force and shall not permit such persons to attend, treat or perform operations upon patients wherever professional discretion or skill is required.

**Exposure of Unethical Conduct**

A physician should expose, without fear or favor, incompetent or corrupt, dishonest or unethical conduct on the part of members of the profession.

**Payment of Professional Services**

The physician engaged in the practice of medicine shall give priority to the interests of patients. The personal financial interests of a physician should not conflict with the medical interests of patients. A physician should announce his fees before rendering service and not after the operation or treatment is under way. Remuneration received for such services should be in the form and amount specifically announced to the patient at the time the service is rendered. It is unethical to enter into a contract of “no cure no payment”. The physician rendering service on behalf of the state shall refrain from anticipating or accepting any consideration.

**Evasion of Legal Restrictions**

The physician shall observe the laws of the country in regulating the practice of medicine and shall also not assist others to evade such laws. He should be cooperative in observance and enforcement of sanitary laws and regulations in the interest of public health. A physician should observe the provisions of the State Acts like Drugs and Cosmetics Act, 1940; Pharmacy Act, 1948; Narcotic Drugs and Psychotropic Substances Act, 1985; Medical Termination of Pregnancy Act, 1971; Transplantation of Human Organs Act, 1994; Mental Health Act, 1987; Environmental Protection Act, 1986; Prenatal Sex Determination Test Act, 1994; Drugs and Magic Remedies (Objectionable Advertisement) Act, 1954; Persons with Disabilities (Equal Opportunities and Full Participation) Act, 1995 and Biomedical Waste (Management and Handling) Rules, 1998 and such other Acts, Rules and Regulations made by the Central or State Governments or local administrative bodies or any other relevant Act relating to the protection and promotion of public health.

**CHAPTER 2**

**Duties of Physicians to their Patients**

**Obligations to the Sick**

1. Although a physician is not bound to treat each and every person asking his services, he should not only be ever ready to respond to the calls of the sick and the injured, but should be mindful of the high character of his mission and the responsibility he discharges in the course of his professional duties. In his treatment, he should never forget that the health and the lives of those entrusted to his care depend on his skill and attention. A physician should
endeavor to add to the comfort of the sick by making his visits at the hour indicated to the patients. A physician advising a patient to seek service of another physician is acceptable; however, in case of emergency, a physician must treat the patient. No physician shall arbitrarily refuse treatment to a patient. However, for good reason, when a patient is suffering from an ailment, which is not within the range of experience of the treating physician, the physician may refuse treatment and refer the patient to another physician.

2. Medical practitioner having any incapacity detrimental to the patient or which can affect his performance vis-à-vis the patient is not permitted to practice his profession.

Patience, Delicacy and Secrecy

Patience and delicacy should characterize the physician. Confidence concerning individual or domestic life entrusted by patients to a physician and defects in the disposition or character of patients observed during medical attendance should never be revealed unless their revelation is required by the laws of the State. Sometimes, however, a physician must determine whether his duty to society requires him to employ knowledge, obtained through confidence as a physician, to protect a healthy person against a communicable disease to which he is about to be exposed. In such instance, the physician should Act, as he would wish another to Act toward one of his own family in like circumstances of the patient, nor should he withdraw from the case “without giving adequate notice to the patient and his family”. Provisionally or fully registered medical practitioner shall not wilfully commit an Act of negligence that may deprive his patient or patients from the necessary medical care.

Engagement for an Obstetric Case

When a physician who has been engaged to attend an obstetric case is absent and another is sent for and delivery accomplished, the acting physician is entitled to his professional fees but should secure the patient’s consent to resign on the arrival of the physician engaged.

CHAPTER 3

Duties of a Physician in Consultation

Unnecessary Consultations Should be Avoided

1. However, in case of serious illness and in doubtful or difficult conditions, the physician should request consultation, but under any circumstances, such consultation should be justifiable and in the interest of the patient only and not for any other consideration.

2. Consulting pathologists or radiologists or asking for any other diagnostic laboratory investigation should be done judiciously and not in a routine manner.

Consultation for Patient’s Benefit

In every consultation, the benefit to the patient is of foremost importance. All physicians engaged in the case should be frank with the patient and his attendants.

Punctuality in Consultation

Umost punctuality should be observed by a physician in making themselves available for consultations.

Statement to a Patient after Consultation

1. All statements to the patient or his representatives should take place in the presence of the consulting physicians, except as otherwise agreed upon. The disclosure of the opinion to the patient or his relatives or friends shall rest with the medical attendant.

2. Differences of opinion should not be divulged unnecessarily but when there is irreconcilable difference of opinion, the circumstances should be frankly and impartially explained to the patient or his relatives or friends. It would be opened to them to seek further advice as they so desire.

Treatment after Consultation

No decision should restrain the attending physician from making such subsequent variations in the treatment if any, unexpected change occurs, but at the next consultation, reasons for the variations should be discussed or explained. The same privilege, with its obligations, belongs to the consultant when sent for in an emergency during the absence of attending physician. The attending physician may prescribe medicine at any time for the patient, whereas the consultant may prescribe only in case of emergency or as an expert when called for.

Patients Referred to Specialists

When a patient is referred to a specialist by the attending physician, a case summary of the patient should be given to the specialist, who should communicate his opinion in writing to the attending physician.

Fees and Other Charges

1. A physician shall clearly display his fees and other charges on the board of his chamber and/or the hospitals he is visiting. Prescription should also make clear if the physician himself dispensed any medicine.

2. A physician shall write his name and designation in full along with registration particulars in his prescription letter-head.

Note: In a Government hospital, where the patient-load is heavy, the name of the prescribing doctor must be written below his or her signature.
CHAPTER 4
Responsibilities of Physicians to Each Other

Dependence of Physicians on Each Other
A physician should consider it as a pleasure and privilege to render gratuitous service to all physicians and their immediate family dependents.

Conduct in Consultation
In consultations, no insincerity, rivalry or envy should be indulged in. All due respect should be observed toward the physician in-charge of the case and no statement or remark be made, which would impair the confidence reposed in him. For this purpose, no discussion should be carried on in the presence of the patient or his representatives.

Consultant not to Take Charge of the Case
When a physician has been called for consultation, the consultant should normally not take charge of the case, especially on the solicitation of the patient or friends. The consultant shall not criticize the referring physician. He or she shall discuss the diagnosis treatment plan with the referring physician.

Appointment of Substitute
Whenever a physician requests another physician to attend his patients during his temporary absence from his practice, professional courtesy requires the acceptance of such appointment only when he has the capacity to discharge the additional responsibility along with his or her other duties. The physician acting under such an appointment should give the utmost consideration to the interests and reputation of the absent physician and all such patients should be restored to the care of the latter upon his or her return.

Visiting Another Physician’s Case
When it becomes the duty of a physician occupying an official position to see and report upon an illness or injury, he should communicate to the physician in attendance so as to give him an option of being present. The medical officer or physician occupying an official position should avoid remarks upon the diagnosis or the treatment that has been adopted.

CHAPTER 5
Duties of a Physician to the Public and to the Paramedical Profession

Physicians as Citizens
Physicians, as good citizens and possessors of special training, should disseminate advice on public health issues. They should play their part in enforcing the laws of the community and in sustaining the institutions that advance the interest of humanity. They should particularly cooperate with the authorities in the administration of sanitary or public health laws and regulations.

Public and Community Health
Physicians, especially those engaged in public health work, should enlighten the public concerning quarantine regulations and measures for the prevention of epidemic and communicable diseases. At all times, the physician should notify the constituted public health authorities of every case of communicable disease under his care, in accordance with the laws, rules and regulations of the health authorities. When an epidemic occurs, a physician should not abandon his duty for fear of contracting the disease himself.

Pharmacists or Nurses
Physicians should recognize and promote the practice of different paramedical services, such as pharmacy and nursing as professions and should seek their cooperation wherever required.

CHAPTER 6
Unethical Acts
A physician shall not aid or abet or commit any of the following Acts, which shall be construed as unethical:

Advertising
1. Soliciting of patients directly or indirectly, by a physician, by a group of physicians or by institutions or organizations is unethical. A physician shall not make use of him or her (or his or her name) as subject of any form or manner of advertising or publicity through any mode either alone or in conjunction with others which is of such a character as to invite attention to him or to his professional position, skill, qualification, achievements, attainments, specialities, appointments, associations, affiliations or honors and/or of such character as would ordinarily result in his self-aggrandizement. A physician shall not give to any person, whether for compensation or otherwise, any approval, recommendation, endorsement, certificate, report or statement with respect of any drug, medicine, nostrum remedy, surgical, or therapeutic article, apparatus or appliance or any commercial product or article with respect to any property, quality or use thereof or any test, demonstration or trial thereof, for use in connection with his name, signature, or photograph in any form or manner of advertising through any mode nor shall he boast of cases, operations, cures or remedies or permit the publication of report thereof through any mode. A medical practitioner is however permitted to make a formal announcement in press regarding the following:
1. On starting practice
2. On change of type of practice
3. On changing address
4. On temporary absence from duty
5. On resumption of another practice
6. On succeeding to another practice
7. Public declaration of charges.

2. Printing of self-photograph, or any such material of publicity in the letter-head or on sign-board of the consulting room or any such clinical establishment shall be regarded as Acts of self-advertisement and unethical conduct on the part of the physician. However, printing of sketches, diagrams or a picture of human system shall not be treated as unethical.

Patent and Copyrights
A physician may patent surgical instruments, appliances and medicine or copyright applications, methods and procedures. However, it shall be unethical if the benefits of such patents or copyrights are not made available in situations where the interest of large population is involved.

Running an Open Shop (Dispensing of Drugs and Appliances by Physicians)
A physician should not run an open shop for sale of medicine, for dispensing prescriptions prescribed by doctors other than himself or for sale of medical or surgical appliances. It is not unethical for a physician to prescribe or supply drugs, remedies or appliances as long as there is no exploitation of the patient. Drugs prescribed by a physician or brought from the market for a patient should explicitly state the proprietary formulae as well as generic name of the drug.

Rebates and Commission
1. A physician shall not give, solicit or receive nor shall he offer to give, solicit or receive any gift, gratuity, commission or bonus in consideration of or return for the referring, recommending or procuring of any patient for medical, surgical or other treatment. A physician shall not directly or indirectly participate in or be a party to an Act of division, transference, assignment, subordination, rebating, splitting or refunding of any fee for medical, surgical or other treatment.
2. Provisions of para 6.4.1 shall apply with equal force to the referring, recommending or procuring by a physician or any person, specimen or material for diagnostic purposes or other study or work. Nothing in this section, however, shall prohibit payment of salaries by a qualified physician to other duly qualified person rendering medical care under his supervision.

Secret Remedies
“The prescribing or dispensing by a physician of secret remedial agents of which he does not know the composition, or the manufacture or promotion of their use is unethical and, as such, prohibited. All the drugs prescribed by a physician should always carry a proprietary formula and clear name.

Human Rights
The physician shall not aid or abet torture nor shall he be a party to either infliction of mental or physical trauma or concealment of torture inflicted by some other person or agency in clear violation of human rights.

Euthanasia
Practicing euthanasia shall constitute unethical conduct. However, on specific occasions, the question of withdrawing supporting devices to sustain cardiopulmonary function even after brain death, shall be decided only by a team of doctors and not merely by the treating physician alone. A team of doctors shall declare withdrawal of support system. Such team shall consist of the doctor in charge of the patient, Chief Medical Officer or Medical Officer in charge of the hospital and doctor nominated by the incharge of the hospital from the hospital staff in accordance with the provisions of the Transplantation of Human Organs Act, 1994.

CHAPTER 7
Misconduct
The following Acts of commission or omission on the part of a physician shall constitute professional misconduct rendering him or her liable for disciplinary action.

Violation of the Regulations
1. If he or she commits any violation of these Regulations.
2. If he or she does not maintain the medical records of his or her indoor patients for a period of 3 years as per Regulation 1.3 and refuses to provide the same within 72 hours when the patient or his or her authorized representative makes a request for it as per Regulation 1.3.2.
3. If he or she does not display the registration number accorded to him or her by the State Medical Council or the MCI in his clinic, prescriptions and certificates, etc. issued by him or violates the provisions of Regulation 1.4.2.

Adultery or Improper Conduct
Abuse of professional position by committing adultery or improper conduct with the patient or by maintaining an
improper association with a patient will render a physician liable for disciplinary action as provided under the Indian Medical Council Act, 1956 or the concerned State Medical Council Act.

Conviction by a Court of Law
Conviction by a Court of Law for offences involving moral turpitude or criminal Acts.

Sex Determination Tests
On no account shall sex determination test be undertaken with the intent to terminate the life of a female fetus developing in her mother’s womb, unless there are other absolute indications for termination of pregnancy as specified in the Medical Termination of Pregnancy Act, 1971. Any Act of termination of pregnancy of normal female fetus amounting to female feticide shall be regarded as professional misconduct on the part of the physician leading to penal erasure besides rendering him liable to criminal proceedings as per the provisions of this Act.

Signing Professional Certificates, Reports and other Documents
Registered medical practitioners are in certain cases bound by law to give, or may from time to time be called upon or requested to give certificates, notification, reports and other documents of similar character signed by them in their professional capacity for subsequent use in the courts or for administrative purposes, etc. Any registered practitioner who is shown to have signed or given under his name and authority any such certificate, notification, report or document of a similar character which is untrue, misleading or improper, is liable to have his name deleted from the Register.

A registered medical practitioner shall not contravene the provisions of the Drugs and Cosmetics Act and regulations made thereunder. Accordingly: (a) Prescribing steroids or psychotropic drugs when there is no absolute medical indication; (b) selling Schedule “H” and “L” drugs and poisons to the public except to his patient in contravention of the above provisions, shall constitute gross professional misconduct on the part of the physician.

Performing or enabling an unqualified person to perform an abortion or any illegal operation for which there is no medical, surgical or psychological indication.

A registered medical practitioner shall not issue certificates of efficiency in modern medicine to an unqualified or nonmedical person.

(Note: The foregoing does not restrict the proper training and instruction of bonafide students, midwives, dispensers, surgical attendants, or skilled mechanical and technical assistants and therapy assistants under the personal supervision of physicians.)

A physician should not contribute to the lay press articles and give interviews regarding diseases and treatments which may have the effect of advertising himself or soliciting practices; but is open to write to the lay press under his own name on matters of public health, hygienic living or to deliver public lectures, hold discussions on the radio or television (TV) or internet chat for the same purpose and send announcement of the same to the press.

An institution run by a physician for a particular purpose such as a maternity home, nursing home, private hospital, rehabilitation center or any type of training institution, etc. may be advertised in the lay press, but such advertisements should not contain anything more than the name of the institution, type of patients admitted, type of training and other facilities offered and the fees.

It is improper for a physician to use an unusually large signboard and write on it anything other than his name, qualifications obtained from a University or a statutory body, titles and name of his speciality, registration number including the name of the State Medical Council under which registered. The same should be the contents of his prescription papers. It is improper to affix a signboard on a chemist’s shop or in places where he does not reside or work.

The registered medical practitioner shall not disclose the secrets of a patient that have been learnt in the exercise of his or her profession except:

i. In a court of law under the orders of the Presiding Judge

ii. In circumstances where there is a serious and identified risk to a specific person and/or community

iii. Notifiable diseases.

In case of communicable or notifiable diseases, concerned public health authorities should be informed immediately.

The registered medical practitioner shall not refuse on religious grounds alone to give assistance in or conduct of sterility, birth control, circumcision and medical termination of pregnancy when there is medical indication, unless the medical practitioner feels himself or herself incompetent to do so.

Before performing an operation, the physician should obtain in writing the consent from the husband or wife, parent or guardian in the case of minor, or the patient himself, as the case may be. In an operation which may result in sterility, birth control, circumcision and medical termination of pregnancy when there is medical indication, unless the medical practitioner feels himself or herself incompetent to do so.

A registered medical practitioner shall not publish photographs or case reports of his or her patients without their permission, in any medical or other journal in a manner by which their identity could be made out. If the identity is not to be disclosed, the consent is not needed.

In the case of running of a nursing home by a physician and employing assistants to help him or her, the ultimate responsibility rests on the physician.
A physician shall not use touts or agents for procuring patients.

A physician shall not claim to be a specialist unless he has a special qualification in that branch.

No Act of in vitro fertilization or artificial insemination shall be undertaken without the informed consent of the female patient and her spouse as well as the donor. Such consent shall be obtained in writing only after the patient is provided, at her own level of comprehension, with sufficient information about the purpose, methods, risks, inconveniences, disappointments of the procedure and possible risks and hazards.

Research: Clinical drug trials or other research involving patients or volunteers as per the guidelines of Indian Council of Medical Research (ICMR) can be undertaken, provided ethical considerations are borne in mind. Violation of existing ICMR guidelines in this regard shall constitute misconduct. Consent taken from the patient for trial of drug or therapy which is not as per the guidelines shall also be construed as misconduct.

If a physician posted in a rural area is found absent on more than two occasions during inspection by the Head of the District Health Authority or the Chairman, Zila Parishad, the same shall be construed as a misconduct if it is recommended to the MCI or State Medical Council by the State Government for action under these Regulations.

If a physician is posted in a medical college or institution both as teaching faculty or otherwise, shall remain in hospital or college during the assigned duty hours. If he is found absent on more than two occasions during this period, the same shall be construed as a misconduct if it is certified by the Principal or Medical Superintendent and forwarded through the State Government to MCI or State Medical Council for action under these Regulations.

CHAPTER 8

Punishment and Disciplinary Action

1. It must be clearly understood that the instances of offences and of professional misconduct which are given above do not constitute and are not intended to constitute a complete list of the infamous Acts which calls for disciplinary action, and that by issuing this notice the MCI and/or State Medical Councils are in no way precluded from considering and dealing with any other form of professional misconduct on the part of a registered practitioner. Circumstances may and do arise from time to time in relation to which there may occur questions of professional misconduct which do not come within any of these categories. Every care should be taken that the code is not violated in letter or spirit. In such instances as in all others, the MCI and/or State Medical Councils have to consider and decide upon the facts brought before the MCI and/or State Medical Councils.

2. It is made clear that any complaint with regard to professional misconduct can be brought before the appropriate Medical Council for disciplinary action. Upon receipt of any complaint of professional misconduct, the appropriate Medical Council would hold an enquiry and give opportunity to the registered medical practitioner to be heard in person or by a pleader. If the medical practitioner is found to be guilty of committing professional misconduct, the appropriate Medical Council may award such punishment as deemed necessary or may direct the removal altogether or for a specified period, from the register of the name of the delinquent registered practitioner. Deletion from the Register shall be widely publicized in local press as well as in the publications of different Medical Associations or Societies or Bodies.

3. In case the punishment of removal from the register is for a limited period, the appropriate Council may also direct that the name so removed shall be restored in the register after the expiry of the period for which the name was ordered to be removed.

4. Decision on complaint against delinquent physician shall be taken within a time limit of 6 months.

5. Dicing the pendency of the complaint, the appropriate Council may restrain the physician from performing the procedure or practice which is under scrutiny. Professional incompetence shall be judged by peer group as per the guidelines prescribed by MCI.

CONCLUSION

In conclusion, it can be said that from the aforementioned principles and decisions relating to medical negligence, it is evident that doctors and nursing homes or hospitals need not be unduly worried about the performance of their functions. The law is a watchdog, and not a bloodhound, and as long as the doctors do their duty with reasonable care, they will not be held liable even if their treatment was unsuccessful.

However, every doctor should, for his own interest, carefully read the Code of Medical Ethics which is part of the Indian Medical Council (Professional Conduct, Etiquette and Ethics) Regulations, 2002 issued by the MCI under Section 20A read with Section 3(m) of the Indian Medical Council Act, 1956.
It is a bare fact that doctors and nursing homes are placed in commercial category by all government departments, but all government departments and society on humanitarian ground expect charity from doctors.

After successful competition of medical entrance and postgraduate entrance examination, a doctor becomes obstetrician and gynecologist. The problems a doctor has to face on opening a nursing or a maternity home are shown in Figure 1. These doctors, when start their practice, they have to face many registrations and laws as follows:

**LEGAL FORMS AND REGISTRATIONS FOR MEDICAL PRACTICE IN INDIA**

**MEDICAL COUNCIL OF INDIA REGISTRATION (TABLE 4)**

Every doctor should be registered under Medical Council of India (MCI) Act 1956. They should register themselves with Medical Council of India, Delhi as well as with State MCI. Doctors should register their PG Degree/Diploma (PG Registration) (Table 1).

---

**Fig. 1: Problems of nursing and maternity home**
APPLICATION FOR REGISTRATION OF INDIAN NATIONALS U/S 13(3)
OF THE INDIAN MEDICAL COUNCIL ACT, 1956

1. Name of the applicant (block capital letters): .................................................................
2. Father’s name (block letters): ...........................................................................................
3. Date and place of birth: ........................................................................................................
4. Preliminary education (full particulars of matriculation or equivalent examination passed with name of the
   examination body and with year of obtaining): .................................................................
5. Date of passing inter science or equivalent examination with name of the university: ..............
6. Name of the medical school/college attended with the date of joining and leaving (block capital letters): ...
7. Name of the medical degree/diploma obtained and university/licensing body with the year of obtaining the
   qualification: .........................................................................................................................
8. a. Whether she/he has undergone practical training before or after obtaining the medical qualification required by
    the rules of the concerned foreign country, give details: ....................................................... 
    b. If not, then has she/he undergone the prescribed training in and approved hospital in India, give details: ........
9. Was any recognized medical college/school in India attended before departure from India, outside countries
    (give names of period of study undergone and examination passed): ...................................
10. If the language of study in the country be other than English, please indicate if it was studied in India before
    departure or was studied in that country. Please indicate the time taken for that study and whether any examination
    was passed: ............................................................................................................................
11. Do the medical examination(s) passed ipso facto entitle one to register in the country in which they were taken or a
    separate examination for registration has to be passed: ......................................................
12. If she/he is registered in any foreign country? If so, give the name of the body with which registered and the number
    and date of registration: ....................................................................................................
13. Is he a citizen of India
   a. by birth or
   b. by domicile
   If (b) state the date of becoming Indian citizen
14. Present address (capital letter) with pin code and phone: ......................................................

Remarks of the State Medical Council
How the information contained above has been verified as authentic.

Date: ......................................................................................................................
Note: The application form should be properly and neatly filled in.
A. Attested xerox copies (two each) of the following certificates/testimonials must be attached.
   Degree/diploma (if the same in language other than English then an authentic translation)

Table 4: Procedure for getting Indian Medical Register (IMR) Certificate
The following are requirements for obtaining IMR Certificate:
1. A hand written/typed application addressed to the Secretary, Medical Council of India, New Delhi, requesting for getting IMR Certificate.
2. An attested xerox copy of registration with Medical Council of India or with any State Medical Council.
3. A demand draft of ₹100/- in favor of Secretary, Medical Council of India, payable at New Delhi at any Bank.
APPLICATION FORM
FOR REGISTRATION OF ADDITIONAL QUALIFICATION/S
U/S 26(1) OF THE INDIAN MEDICAL COUNCIL ACT, 1956

1. Name of the doctor: ...................................................................................................................................................................

2. Address as given in the Indian medical register: ................................................................................................................................................

3. Present address in block capitals with pin code and phone number: ..........................................................................................................................

4. Permanent addresses in block capitals with pin code and phone no: ............................................................................................................

5. a. Primary qualification (i.e. “MBBS” or equivalent) with year of obtaining: ........................................................................................................
    b. Name and address of college/institute attended for the same along with duration of course: .........................................................
    c. Date of completion of internship: ..................................................................................................................................................
    d. University awarding the qualification: ..................................................................................................................................................

6. a. Name of the state medical council with which registered: ....................................................................................................................
    b. Registration number (as it appears on the registration certificate): ....................................................................................................
    c. Date of registration: ........................................................................................................................................................................

7. Additional qualification for which certificate is requested with documentary proof (Please do not fill the remarks column)

<table>
<thead>
<tr>
<th>Qualification</th>
<th>College attended</th>
<th>University</th>
<th>Date of qualification</th>
<th>Remarks, R/NR, etc.</th>
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DECLARATION
8. I solemnly affirm and declare that the above entries made by me are correct.

Date: ..................................................................................................................

Signature of the candidate
Important Instructions

The following instructions should be read carefully before filling up the forms:

1. Incomplete documents will be rejected
2. The forms should be complete in all the respect and should be filled up in capital letters in candidate’s own legible handwriting
3. All the documents should be signed and dated by the applicant only
4. The addresses, wherever required, should be complete in all respect
5. The date, wherever required, should be mentioned in complete, i.e. year, month and the day
6. The fee is nonrefundable and is accepted by demand draft only in favor of Secretary, Medical Council of India and payable at New Delhi
7. Public dealing will be between 3:00 PM to 5:00 PM only
8. No enquiry will be entertained over telephone during office hours
9. Candidates are requested not to approach the office before 30 days of submission of the application form along with other documents/receipt of the verification from the concerned issuing authorities, if any
10. The certificate will be issued only to those who possess a registrable basic medical qualification and subsequently have obtained recognized postgraduate medical qualification(s) as per the provisions of the IMC Act, 1956
11. The candidates are requested to ensure that the documents are enclosed as per the order in the checklist. All the certificates should be submitted in original along with two clear attested photocopies of each of these certificates. All papers/documents should be numbered according to the checklist.

Checklist

Checklist for enclosures:

1. Bank draft @ ₹100/- (Rupees one hundred only) for each qualification in favor of secretary, Medical Council of India, New Delhi, payable at New Delhi.
2. The degrees/diplomas or provisional certificate of postgraduate qualification issued by the principal/dean of the college concerned, as shown in col. “7” of the application form.
3. The degrees/diplomas or provisional certificate of postgraduate qualification issued by the registrar of the university concerned, as shown in col. “7” of the application form.
4. The candidate is required to send the original as well as a copy, duly attested by magistrate/gazetted officer, of the originals will be returned along with the certificate of registration of additional qualification and the attested copies will be retained in this office.
5. Copy of permanent registration certificate
6. Attested copy of the pass certificate from the college
7. Those who are already registered with state medical council there is no need for re-registration with MCI
8. Two recent passport size photographs front view and two adhesive signature slips.

NURSING HOME REGISTRATION

Doctors who wish to start their nursing home; it should be registered by local bodies as Municipal Corporation/Nagar Nigam, etc.

In UP State due to Honorable High Court order every doctor should be registered under Chief Medical Officer and this registration should be renewed every year by 30th April apart from other registrations. Honorable Supreme Court has stayed for time being for annual renewal.

BIOMEDICAL WASTE RULES

As per this Act doctors are generating biomedical waste and we are occupier. This biomedical waste should be segregated at source, so that infectious waste should not infect noninfectious waste. Segregated waste in different color container should be stored at place from where operator will transport to incinerator plant. Liquid waste should be treated by chemical. Whole process can be understood from the Figure 2.
Fig. 2: Biomedical waste (management and handling)

Abbreviations: CBWTF, common biomedical waste treatment facility; MOEF, Ministry of Environment and Forests
FORM I
(See Rule 8)
Application for Authorization
(To be submitted in duplicate)

To,
The Prescribed Authority
(Name of the State Government/UT Administration)
Address

1. Particulars of the Applicant
   i. Name of the Applicant: ..................................................................................................................................................
      (In block letters and in full)
   ii. Name of the Institution: .............................................................................................................................................
      Address: ...........................................................................................................................................................................
      Tele No, Fax No, Telex No: ................................................................................................................................................

2. Activity for which authorization is sought: ............................................................................................................................
   i. Generation
   ii. Collection
   iii. Reception
   iv. Storage
   v. Transportation
   vi. Treatment
   vii. Disposal
   viii. Any other form of handling

3. Please state whether applying for fresh authorization or for renewal: ..................................................................................
   (In case of renewal, previous authorization—number and date)

4. i. Address of the institution handling biomedical wastes: ..............................................................................................
    ii. Address of the place of the treatment facility: ...............................................................................................................
    iii. Address of the place of disposal of the waste: ..............................................................................................................

5. i. Mode of transportation (in any) of biomedical waste: ....................................................................................................
    ii. Mode(s) of treatment: ....................................................................................................................................................


7. i. Category (see Schedule 1) of waste to be handled: ............................................................................................................
    ii. Quantity of waste (category-wise) to be handled per month: ........................................................................................

8. Declaration
I do hereby declare that the statements made and information given above are true to the best of my knowledge and belief and that I have not concealed any information.

I do also hereby undertake to provide any further information sought by the prescribed authority in relation to these rules and to fulfill any conditions stipulated by the prescribed authority.

Date: Signature of the Applicant

Place: Designation of the Applicant
FORM II
(See Rule 10)
Annual Report
(To be submitted to the prescribed authority by 31 January every year)

1. Particulars of the applicant:
   i. Name of the authorized person (occupier/operator):
   ii. Name of the institution:
   iii. Address:
       Tel No:
       Telex No:
       Fax No:

2. Categories of waste generated and quantity on a monthly average basis:

3. Brief details of the treatment facility:
   In case of off-site facility:
   i. Name of the operator:
   ii. Name and address of the facility:
       Tel No, Telex No, Fax No:

4. Category-wise quantity of waste treated:

5. Mode of treatment with details:

6. Any other information:

7. Certified that the above report is for the period from

Date
Place
Signature
Designation

FORM III
(See Rule 12)
Accident Reporting

1. Date and time of accident:

2. Sequence of events leading to accident:

3. The waste involved in accident:

4. Assessment of the effects of the accidents on human health and the environment:

5. Emergency measures taken:

6. Steps taken to alleviate the effects of accidents:

7. Steps taken to prevent the recurrence of such an accident:

Date
Place
Signature
Designation
Other Acts Important for the Doctors

Generator pollution: Nursing homes and doctors chambers are the soft target for installation of Canopy on generator.

Sales tax registration: If annual sale or distribution of medicines in doctor chamber or nursing homes is above ₹3 lac than they need registration by Sales Tax Department.

Minimum wages Act: In private sector even household employee’s minimum wages are ₹100 per day, but in government department this Act does not apply as in jail where the prisoner are getting only ₹12 per day.

Provident fund Act: If part time, full time or contractual employees are exceeding more than 20 including part time accountant than one has to obey the Provident Fund Act.

Employees’ state insurance Act: All the nursing homes even those run by only Obstetrician and Gynecologist have to follow ESI Act.

Consumer protection Act: As per this Act, patients are our consumer and they can sue the doctors under this Act for their inefficiency of services, so now doctors are advising many investigations to their patients just to safeguard themselves.

Commercial electricity and water: Doctors and nursing homes are billed on commercial rate of water and electricity.

IPC 304A: On complaint of patient, doctors are charged under IPC 304A. In the recent historic judgment by Honorable Supreme Court by Justice Lahoti.

DOCTORS ARE NOT TO BE CHARGED JUST BECAUSE THE PATIENT DIED

Jacob Mathew vs. State of Punjab and Anr. Date of Judgment: 05/08/2005
Bench: CJI RC Lahoti, GP Mathur, PK Balasubramanyan.

A Brief History of Proceeding Until Supreme Court

The informant’s father, late Jiwan Lal Sharma was admitted as a patient in a private ward of CMC and Hospital, Ludhiana. On 22.2.1995 at about 11 pm, Jiwan Lal felt difficulty in breathing.

The complainant’s elder brother, Vijay Sharma who was present in the room contacted the duty nurse, who in her turn called some doctor to attend to the patient. No doctor turned up for about 20–25 minutes.

Then, Dr Jacob Mathew, the appellant before us and Dr Allen Joseph came to the room of the patient. An oxygen cylinder was brought and connected to the mouth of the patient but the breathing problem increased further. The patient tried to get up but the medical staff asked him to remain in the bed.

The oxygen cylinder was found to be empty. There was no other gas cylinder available in the room. Vijay Sharma went to the adjoining room and brought a gas cylinder therefrom.

However, there was no arrangement to make the gas cylinder functional and in between, 5–7 minutes were wasted. By this time, another doctor came who declared that the patient was dead.

On the above said report, an offence under Section 304A/34 IPC was registered and investigated. Challan was filed against the two doctors.

The Judicial Magistrate First Class, Ludhiana framed charges under Section 304A, IPC against the two accused persons, both doctors. Both of them filed a revision in the Court of Sessions Judge submitting that there was no ground for framing charges against them. The revision was dismissed. The appellant filed a petition in the High Court under Section 482 of the Code of Criminal Procedure praying for quashing of the FIR and all the subsequent proceedings.

The learned single Judge who heard the petition formed an opinion that the plea raised by the appellant was available to be urged in defense at the trial and, therefore, a case for quashing the charge was not made out. Vide order dated 18.12.2002, the High Court dismissed the petition. An application for recalling the above said order was moved which too was dismissed on 24.1.2003. Feeling aggrieved by these two orders, the appellant has filed these appeals by special leave.

Observation of Honorable Supreme Court

1. The investigating officer and the private complainant cannot always be supposed to have knowledge of medical science so as to determine whether the Act of the accused medical professional amounts to rash or negligent Act within the domain of criminal law under Section 304A of IPC.
2. The criminal process once initiated subjects the medical professional to serious embarrassment and sometimes harassment. He has to seek bail to escape arrest, which may or may not be granted to him.
3. At the end he may be exonerated by acquittal or discharge but the loss which he has suffered in his reputation cannot be compensated by any standards.
4. The need for care and caution in the interest of society; for, the service which the medical profession renders to human beings is probably the noblest of all, and hence there is a need for protecting doctors from frivolous or unjust prosecutions.
5. Many times complainant prefers recourse to criminal process as a tool for pressurizing the medical professional for extracting uncalled for or unjust compensation. Such malicious proceedings have to be guarded against.

Guidelines for the Future

These should govern the prosecution of doctors for offences of which criminal rashness or criminal negligence is an ingredient.
1. A private complaint may not be entertained unless the complainant has produced prima facie evidence before the Court in the form of a credible opinion given by another competent doctor to support the charge of rashness or negligence on the part of the accused doctor.

2. The investigating officer should, before proceeding against the doctor accused of rash or negligent Act or omission, obtain an independent and competent medical opinion preferably from a doctor in government service qualified in that branch of medical practice who can normally be expected to give an impartial and unbiased opinion applying Bolam’s test to the facts collected in the investigation.

3. A doctor accused of rashness or negligence, may not be arrested in a routine manner (simply because a charge has been leveled against him). Unless his arrest is necessary for furthering the investigation or for collecting evidence or unless the investigation officer feels satisfied that the doctor proceeded against would not make himself available to face the prosecution unless arrested, the arrest may be withheld.

Direction Passed by the Supreme Court

Statutory Rules or Executive Instructions incorporating certain guidelines need to be framed and issued by the Government of India and/or the State Governments in consultation with the Medical Council of India. So long as it is not done, we propose to lay down certain guidelines for the future which should govern the prosecution of doctors for offences of which criminal rashness or criminal negligence is an ingredient.

Judgment on the Facts of the Case

Reverting back to the facts of the case before us, we are satisfied that all the averments made in the complaint, even if held to be proved, do not make out a case of criminal rashness or negligence on the part of the accused appellant. It is not the case of the complainant that the accused-appellant was not a doctor qualified to treat the patient whom he agreed to treat. It is a case of nonavailability of oxygen cylinder either because of the hospital having failed to keep available a gas cylinder or because of the gas cylinder being found empty. Then, probably the hospital may be liable in civil law (or may not be we express no opinion thereon) but the accused appellant cannot be proceeded against under Section 304A IPC on the parameters of Bolam’s test.

MEDICAL TERMINATION OF PREGNANCY ACT 1971

It is Medical Termination of Pregnancy Act, 1971. Every doctor who is doing MTP, they should know this Act. As per this Act, doctor as well as place (where MTP is done), both have to be registered separately. Doctors who are not having PG degree/diploma have to go for MTP training from government authorized center, then they can get registered. Doctor has to keep a record of all MTP done with their indication as per the Act. There should be opinion of two such registered doctors for doing MTP of 12–20 weeks. You cannot terminate pregnancy of above 20 weeks as per this Act. In any circumstance you cannot terminate sex determined pregnancy of any size. This is a punishable offence.
FORM-A

(See sub-rule(2) of rule 5)
Form of application for the approval of a place under clause (b) of section-4

<table>
<thead>
<tr>
<th>Category of approved place: A or B</th>
<th>Hospital Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong> Pregnancy can be terminated up to 12 weeks.</td>
<td></td>
</tr>
<tr>
<td><strong>B</strong> Pregnancy can be terminated up to 20 weeks.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Name of the Hospital, Nursing Home, Diagnostic Center, Clinic. or Place (in capital letters)</td>
</tr>
<tr>
<td>2.</td>
<td>Address in full, Phone No and Email ID</td>
</tr>
<tr>
<td>3.</td>
<td>Government Non-Government/Private/Nursing Home/Other Institutions and number of Beds</td>
</tr>
<tr>
<td>4.</td>
<td>Doctors Details: KMC Reg. Nos. or MTP Training certificate (enclose)</td>
</tr>
<tr>
<td>5.</td>
<td>State, if the following facilities are available at the place (Yes or No)</td>
</tr>
</tbody>
</table>

**Category A**

i. Gynecological examination/labor table

ii. Resuscitation equipment

iii. Sterilization equipment

iv. Facilities for treatment of shock, including emergency drugs

v. Facilities for transportation, if required.

**Category B**

i. An operational table and instruments for performing abdominal or gynecological surgery.

ii. Drugs and parental fluid in sufficient supply for emergency cases.

iii. Anesthetic equipment, resuscitation equipment and sterilization equipment.

Place:

Date: 

Signature of the owner of Hospital, Nursing Home Diagnostic Center, Clinic. Or Place.
PREGNANCY TERMINATION ACT

Form “A”
(See subrule (1) of rule 5)

Application for Registration and Grant of Certificate

I, ____________________________ a registered medical practitioner within the meaning of section 2 (d) of the Medical Termination of Pregnancy Act, 1971 (34 of 1971), hereby apply for the registration of my name and issue of certificate to the effect that I possess the prescribed experience or training referred to in the said section. My other particulars are as follows:

1. Address: ____________________________

2. Designation: ____________________________

3. Name of the State Medical Register in which registered and the registration no. ____________________________

4. Qualification:

<table>
<thead>
<tr>
<th>Qualification</th>
<th>Year</th>
<th>University</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Medical degree or equivalent qualification</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. Postgraduate medical degree or diploma</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5. Experience in practice of gynecology and obstetrics:

6. Training in termination of pregnancy: Duration ____________________________

   Place of training: ____________________________

   Certified that the particulars given above are correct to the best of my knowledge.

Place: ____________________________

Date: ____________________________

Signature ____________________________

N. B. For ready reference the relevant rule is reproduced below:

“5. (1) For the purpose of establishing that he possesses such degree or diploma and experience or training or both in Gynecology and Obstetrics as is referred to in rule 4. Every registered medical practitioner who intends to terminate any pregnancy in accordance with the provisions of the Act shall make an application Form “A” to the State Family Welfare Officer for the registration of his name and for the issue of a certificate to him to the effect that he possesses the said degree or diploma and the said experience or training or both”.

FORM B
(See subrule (6) of rule 5)
Certificate of approval

The place described below is hereby approved for the purpose of the Medical Termination of Pregnancy Act, 1971 (34 of 1971).

As read within up to ......................... weeks

Name of the Place: ........................................................................................................................................................................
..................................................................................................................................................................................................
..................................................................................................................................................................................................
..................................................................................................................................................................................................
..................................................................................................................................................................................................

Address and other descriptions: ...................................................................................................................................................
..................................................................................................................................................................................................
..................................................................................................................................................................................................
..................................................................................................................................................................................................
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..................................................................................................................................................................................................
..................................................................................................................................................................................................

Name of the owner: ........................................................................................................................................................................
..................................................................................................................................................................................................
..................................................................................................................................................................................................
..................................................................................................................................................................................................
..................................................................................................................................................................................................
..................................................................................................................................................................................................

Place: ......................
Date: ......................

To the Government of the .................................................................
FORM C
(See Rule 8)

I __________________________ daughter/wife of __________________________
aged about ________________ years of __________________________
______________________________
(here state the permanent address)
at present residing at __________________________
do hereby give my consent to the termination of my pregnancy at __________________________
______________________________
(State the name of place where the pregnancy is to be terminated)

Place: _________________
Date: _________________ Signature

(To be filled in by guardian where the woman is a mentally ill person or minor)

I __________________________ son/daughter/wife of __________________________ aged
about ________________ years of __________________________ at present residing at (Permanent address)
______________________________ do hereby give my consent to
the termination of the pregnancy of my ward __________________________ who is a minor/lunatic at
______________________________
(place of termination of my pregnancy)

Place: _________________
Date: _________________ Signature
DOCTOR’S OPINION FOR MEDICAL TERMINATION OF PREGNANCY

FORM I

[See Regulation 3]

I

(Name and qualifications of the Registered Medical practitioner in block letters)

(Full address of the Registered Medical practitioner)

I

(Name and qualifications of the Registered Medical practitioner in block letters)

(Full address of the Registered Medical practitioner) hereby certify that *I/We am/are of opinion, formed in good faith, that it is necessary to terminate the pregnancy of

(Full name of pregnant women in block letters) resident of

(Full address of pregnant women in block letters) for the reasons given below**.

*I/We hereby give intimation that *I/We terminated the pregnancy of the woman referred to above who bears the serial no. ___________________ in the Admission Register of the hospital/approved place.

Signature of the Registered Medical Practitioner

Place: _________________
Date: _________________

*Strike out whichever is not applicable,
** of the reasons specified items (i) to (v) write the one which is appropriate.

i. in order to save the life of the pregnant women,
   ii. in order to prevent grave injury to the physical and mental health of the pregnant women,
   iii. in view of the substantial risk that if the child was born it would suffer from such physical or mental abnormalities as to be seriously handicapped,
   iv. as the pregnancy is alleged by pregnant women to have been caused by rape,
   v. as the pregnancy has occurred as result of failure of any contraceptive device or methods used by married woman or her husband for the purpose of limiting the number of children

Note: Account may be taken of the pregnant women’s actual or reasonably foreseeable environment in determining whether the continuance of her pregnancy would involve a grave injury to her physical or mental health.

Place: _________________
Date: _________________

Signature of the Registered Medical Practitioner
MONTHLY REPORT TO BE SENT TO DISTRICT MEDICAL AUTHORITY

FORM II
[See Regulation 4(3)]

1. Name of the State: .....................................................................................................................................................................

2. Name of the Hospital/approved place: ...................................................................................................................................

3. Duration of pregnancy (give total No. only): ...........................................................................................................................
   (a) Up to 12 weeks
   (b) Between 12 weeks and 20 weeks

4. Religion of woman: ...................................................................................................................................................................
   (a) Hindu
   (b) Muslim
   (c) Christian
   (d) Others
   (e) Total

5. Termination with acceptance of contraception: ....................................................................................................................
   (a) Sterilization
   (b) IUD

6. Reasons for termination:
   (give total number under each subhead)
   (a) Danger to life of the pregnant woman
   (b) Grave injury to the physical health of the pregnant woman
   (c) Grave injury to the mental health of the pregnant woman
   (d) Pregnancy caused by rape
   (e) Substantial risk that if the child was born, it would suffer from such physical or mental abnormalities as to be seriously handicapped
   (f) Failure of any contraceptive device or method

Signature of the Officer in charge with Date
**FORM III**
(See Regulation 5)

**Admission Register**

(To be destroyed on the expiry of 5 years from the date of the last entry in the Register)

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Date of admission</th>
<th>Name of the patient</th>
<th>Wife/Daughter of</th>
<th>Age</th>
<th>Religion</th>
<th>Address</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
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</tbody>
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<tr>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of pregnancy</td>
<td>Reasons on which pregnancy is terminated</td>
<td>Date of termination of pregnancy</td>
<td>Date of discharge of patient</td>
<td>Result and remarks</td>
<td>Name of Registered Medical Practitioner(s) by whom the opinion is formed</td>
<td>Name of Registered Medical Practitioner by whom pregnancy is terminated</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>

**Tubal ligation:** For doing tubal ligation you are supposed to apply for it to district medical authority and permission should be obtained. To secure yourself you have to fill 5 page consent form for postoperative legal complication. Consent Forms are as follows:
ANNEXURE-1
Checklist to be Filled in before Sterilization Operation of a
Male/Female by the Doctor Concerned

1. Whether the age of the client is within laid down norms (Male clients should be below the age of 60 years, for Female should be below the age of 45 years and above 22 years) Yes/No
2. Whether information relating to marital status, No. of living children and age of the youngest child obtained. Yes/No
3. Whether the client has been counseled regarding sterilization so as to help the clients make informed and voluntary decision. Yes/No
4. Consent form—whether the client has understood the consent for and the following relative contraindications.
   (a) Psychiatric disorder
      (i) Acute febrile illness
      (ii) Jaundice or other chronic liver disease
      (iii) Anemia (hemoglobin less than 8 g%)
      (iv) Chronic systemic disease, including tuberculosis, bronchial asthma, blood dyscrasias, heart disease, uncontrolled diabetes, hypertension and thyrotoxicosis
      (v) Malignancy
      (vi) Skin conditions, including infection involving operative site
      (vii) Pelvic infection, adhesions or mass
      (viii) Severe nutritional deficiency, such as generalized edema, anemia and vitamin deficiency
   (b) Physical illness
      (i) Acute febrile illness
      (ii) Jaundice or other chronic liver disease
      (iii) Anemia (hemoglobin less than 8 g%)
      (iv) Chronic systemic disease, including tuberculosis, bronchial asthma, blood dyscrasias, heart disease, uncontrolled diabetes, hypertension and thyrotoxicosis
      (v) Malignancy
      (vi) Skin conditions, including infection involving operative site
      (vii) Pelvic infection, adhesions or mass
      (viii) Severe nutritional deficiency, such as generalized edema, anemia and vitamin deficiency
5. Whether the client has been examined for excluding medical contraindication, i.e. psychiatric disorder and physical illness. The surgeon/doctor should examine for the following relative contraindications. Yes/No
   (c) Allergy to local anesthesia (alternative anesthesia or procedure must be provided)
   (d) Gross obesity
   (e) The following conditions in postpartum clients:
      (i) Puerperal fever
      (ii) Prolonged rupture of membranes (24 hours)
      (iii) Pre-eclampsia or eclampsia
      (iv) Antepartum or postpartum hemorrhage resulting in hemoglobin less than 8 g%
      (v) Trauma to the genital tract
      (vi) History of postpartum psychosis
6. Whether assessment and screening of the client has been done as follows:
   6.1 Whether the client has been physically examined—pulse, blood pressure, respiratory rate, temperature, body weight, general condition and nutritional status, auscultation of heart, lungs, examination of abdomen, pelvic examination and other examination as indicated by the client’s medical history or general physical examination. Yes/No
   6.2 Laboratory Examination: Blood test for hemoglobin, urine analysis for sugar, and albumin and other laboratory examination. Yes/No
   6.3 Final Medical Assessment of the Operating Surgeons: Whether surgeon has verified fitness of the client including abdominal/pelvic examination before conduction of the surgery. Yes/No
7. Whether instructions relating to prevention of infection has been followed?
   7.1 Whether cleaning and fumigation of the OT has been done. Yes/No
   7.2 Proper arrangement for decontamination of articles after surgery is available for items that come in contact with blood or other body fluids by placing in solution of disinfectant for 10 minutes
      (surgical instruments, gloves, needles and syringes, cotton gauze, etc.) Yes/No
   7.3 Sterilization procedure of equipments/instruments required for surgery has been carried out as laid down in the guidelines. Yes/No

Signature
Name of the Surgeon
Date
ANNEXURE-2

A. APPLICATION FOR STERILIZATION OPERATION AND CONSENT FORM

1. Name: Shri/Smt ________________________________

2. Husband’s Name and Address ________________________________

3. Father’s Name and Address ________________________________

4. Operation Center ________________________________

Dear Sir/Madam

Kindly make arrangements for my sterilization operation. My age is ________ years and my husband/wife’s age is ________ years.

I am married and my husband/wife is alive. We have ________ male and ________ female living children.

The age of my youngest living child is ________ years. I have decided to undergo sterilization operation independently and on my own without any outside pressure, inducement or force. I am aware that other methods of contraception are available to me. I know that for all practical purpose this operation is permanent and that after the operation will be unable to have any more children. I also know that there are still some chances of failure of the operation for which the hospital/institution and operating doctor will not be held responsible by me or my relative or any other person whomsoever. My husband/wife has not been sterilized previously. I am aware that I am undergoing operation, which carries an element of risk. I have been explained the eligibility criteria for the operation and I affirm that I am eligible to undergo operation according to criteria. I agree to undergo the operation under any type of anesthesia which the doctor thinks suitable for me. After sterilization operation if I get pregnant, then I shall report within 4 weeks to the doctor/hospital and will get abortion done free of cost. Under such circumstances, the State Government will pay a compensation of ₹5,000/- to me which will be acceptable to me. I know that if I am unable to get the pregnancy aborted within 4 weeks of pregnancy, then I will not be entitled to claim any compensation from any court of law in this regard. I agree to come for follow-up to the center/doctor as instructed, failing which I shall be responsible for the consequences, if any.

I have read the above-mentioned facts/information* in my own language.

Religion: ________________________________________________
Age: __________________________________________________
Business/Occupation: __________________________________

Signature of the acceptor/applicant

Signature of the witness
Full Name: ______________________________________________
Full Address: ____________________________________________

*(Only for those beneficiaries who cannot read and write)

Shri/Smt ________________ have been explained other methods of contraception available and the failures associated with other methods have been explained fully.

**Signature of Counselors
Full Name: ______________________________________________
Full Address: ____________________________________________

I know very well Shri/Smt ________________ and the information given by me/her is correct. His/her name has been registered with health center/city center at Sal. No. ________________

Signature of Promoter
Full Name: ______________________________________________
Full Address: ____________________________________________
B. CERTIFICATE OF MEDICAL OFFICER

I certify that I have satisfied myself that Shri/Smt ________________, is within the eligible age-group and is mentally and medically fit for a sterilization operation. There is no evidence that he/she has undergone a sterilization operation previously. I have explained all clauses to the client and that this form has the authority of a legal document.

*Signature of Operating Doctor
(Name and Address)

Signature of Medical Officer
(Name and Address)

C. DENIAL OF STERILIZATION

I certify that Shri/Smt ________________, is not suitable client for resterilization/sterilization for the following reasons.

1. ____________________________________________________________
2. ____________________________________________________________

He/she has been provided the following alternative methods of contraception.

Signature of counselor** or
Doctor making decision
(Name and Address)

**Counselor can be any health personnel including doctor.

D. FOR OFFICIAL USE ONLY

To be filled by examining doctor
Note: If the surgeon is himself health examiner, the certificate may be given by him.

Age of the client according to appearance ________________________

Urine analysis for sugar __________________________________________

Blood pressure _________________________________________________

Whether client has gone sterilization earlier or not _______________________

As per examination by the doctor, the client is mentally and medically fit for sterilization operation

I have confirmed from the client regarding his/her marital status and number of living children. I have explained pros and cons of the sterilization operation to the client and he himself is mentally ready for the operation.

Signature of the client __________________

Signature of the surgeon (Name in capital letter) __________________

Present place of posting __________________

E. CERTIFICATE OF THE SURGEON

I have performed sterilization operation. During the operation there were no visible signs of earlier sterilization and as per appearance he/she was within the age limit for sterilization. If it is female sterilization, the type of operation performed.

Abdominal/Vaginal/Laparoscopic/Minilap

General/Local anesthesia used.

Signature of the surgeon (Name in capital letters) __________________

Present place posting __________________
ECONOMIC, SOCIAL AND DEMOGRAPHIC DETAILS OF THE CLIENT UNDER GOING STERILIZATION OPERATION

Monthly report of the District Family Welfare Bureau should be accompanied by the following proforma:

1. Name of Client:

2. Name of head of the family: Shri:

3. Name of Father/Husband:

4. Mohalla: ___________________________ House No.: ___________________________


9. Whether Married (Yes/No)

10. Age of Applicant (complete years ___________________________)

11. Age of Husband/Wife (complete years ___________________________)

12. No. of alive children
   (a) Sons ___________________________ (b) Daughters ___________________________
      Age__________________________ Months__________________________
      Husband_______________________ Wife__________________________

13. Age at Marriage ___________________________

14. Educational qualification
   Husband: Illiterate/Literate/Primary/Junior High School/High School/Graduate and above.
   Wife: Illiterate/Literate/Primary/Junior High School/High School/Graduate and above.

15. Difference from the last termination of pregnancy (Delivery or abortion) ___________________________ years ___________________________ and ___________________________

Payment Particulars

Amount given to applicant Rupees _____________ Paise _____________
For ___________________________ Sterilization

Date: _____________

Signature of applicant
Name ___________________________

FOLLOW-UP

Person concerned with the service of the applicant name ___________________________ Post ___________________________

Place of Appointment ___________________________


If tubectomy methods adopted.
Abdominal/Vaginal/Laparoscopic/Laparotomy

Type of Anesthesia: General/Local/Spinal

Full name of the person going to give follow-up ___________________________ Present Address: ___________________________
OTHER INFORMATION

(1) Whether any contraceptive method has been adopted earlier Yes/No
   If yes (1) Name of the Method ____________________________
   (2) Period of the Method ____________________________
(2) Whether promoter of applicant is regional worker of family welfare program Yes/No
   If yes, whether applicant is inhabitant of the jurisdiction of that worker: Yes/No
(3) Reason for the application of sterilization: Limited family/diseases/financial or other
I certify that above mentioned particulars are correct.

Place: ____________________________
Full Name ____________________________
Present Address ____________________________

THE APPLICATION FOR THE APPROVAL OF PRIVATE MEDICAL PRACTITIONER/CLINIC/ NURSING HOME/MATERNITY HOMES FOR CARRYING OUT TUBECTOMIES

1. Name of Applicant Doctor:
2. Qualification:
3. Registration No:
4. Experience in the performance of Tubectomy Operation
5. Address in full
6. Whether has Clinic/Nursing Home/Maternity Hospital
7. State, if the following facilities are available with him/her:
   (i) Beds for Gynecological Cases No.
   (ii) Operation Table
   (iii) Shadowless Lamp
   (iv) Oxygen Cylinder
   (v) Apparatus for Resuscitation
   (vi) Suction Apparatus
   (vii) Instrument sets for carrying out tubectomies
       [Give Name of Instruments & Quantity]
   (viii) Autoclave with drums:
   (ix) Sterilizer for Instruments:
   (x) Necessary equipment and Instruments for instilling anesthesia:
   (xi) Separate Operation Room:
   (xii) Availability of Drugs for Pre- & Postoperative Medication as well as for Emergencies:

Place: ____________________________
Date: ____________________________

Signature of Applicant

Mafia/Goondas: Doctors are soft target for Mafias and Goondas

PCPNDT Act: It is Pre Conception and Prenatal Diagnostic Techniques [Prohibition of Sex Selection] Act 1994. This is at present a very dangerous Act. Morally, Legally and Ethically NO ONE SHOULD DO ANY SEX DETERMINATION OF FETUS AND IT’S TERMINATION. As per this Act gynecologist or sonologist has to be registered in following category:
1. Genetic Counseling Center
2. Genetic Laboratory
3. Genetic Clinic or Ultrasound Clinic or Imaging Center
4. Any combination of above or all.
CHAPTER 5
The Obstetrician and Gynecologist and the Indian Laws

PROVISIONS PRENATAL DIAGNOSTIC TECHNIQUES ACT

The qualifications of the employees, the requirement of equipment, etc. for a Genetic Counseling Center, Genetic Laboratory, Genetic Clinic, Ultrasound Clinic and Imaging Center shall be as under:

1. Any person being or employing
   (i) a gynecologist or a pediatrician having 6 months experience or 4 weeks training in genetic counseling or
   (ii) a medical geneticists, having adequate space and educational charts/models/equipments for carrying out genetic counseling may set up a genetic counseling center and get it registered as a genetic counseling center.

2. Any person having adequate space and being or employing
   (i) a Medical Geneticist and
   (ii) a laboratory technician, having a BSc degree in Biological Sciences or a degree or diploma in medical laboratory course with at least one year experience in conducting appropriate prenatal diagnostic techniques, tests or procedures may set up a genetic laboratory.

3. Any person having adequate space and being or employing
   (a) Gynecologists having experience of performing at least 20 procedures in chorionic villi aspirations per vagina or per abdomen, chorionic villi biopsy, amniocentesis, cordocentesis fetoscopy, fetal skin or organ biopsy or fetal blood sampling, etc. under supervision of an experienced gynecologists in these fields,
   (b) a Sonologist, Imaging Specialist, Radiologist or Registered Medical Practitioner having Postgraduate degree or diploma or 6 months training or one year experience in sonography or image scanning, or.
   (c) A medical geneticist may set up a genetic clinic/ultrasound clinic/imaging center.

4. The Genetic Clinic/ultrasound clinic/imaging center should have or acquire such of the following equipments, as may be necessary for carrying out the tests or procedures
   (a) Equipment and accessories necessary for carrying out clinical examination by an obstetrician or gynecologist
   (b) An ultrasonography machine including mobile ultrasound machine, imaging machine or any other equipment capable of conducting fetal ultrasonography
   (c) Appropriate catheters and equipment for carrying out chorionic villi aspirations per vagina or per abdomen
   (d) Appropriate sterile needles for amniocentesis or cordocentesis
   (e) A suitable fetoscope with appropriate accessories for fetoscopy, fetal skin or organ biopsy or fetal blood sampling shall be optional.
   (f) Equipment for dry and wet sterilization.
   (g) Equipment for carrying out emergency procedures such as evacuation of uterus or resuscitation in case of need.
   (h) Genetic Works Station.

5. Application Fee - (1) Every application for registration under Rule 4 shall be accompanied by an application fee of:
   (a) ₹3,000.00 for Genetic Counseling Center, Genetic Laboratory, Genetic Clinic, Ultrasound Clinic or Imaging Center.
   (b) ₹4,000.00 for an institute, hospital, nursing home, or any place providing jointly the service of a Genetic Counseling Center, Genetic Laboratory and Genetic Clinic, Ultrasound Clinic or Imaging Center or any combination thereof. Provided that if an application for registration of any Genetic Clinic/Laboratory/Center etc. has been rejected by the Appropriate Authority, no fee shall be required to be paid on re-submission of the application by the applicant for the same body within 90 days of rejection. Provided further that any subsequent application shall be accompanied with the prescribed fee. Application fee once paid will not be refunded.

Form A Application form for any clinic with acknowledgment slip
Form B Certificate of Registration
Form C Rejection of Application/Renewal of application
Form D Form maintained by Genetic Counseling Center
Form E Form maintained by Genetic Laboratory
Form F Form maintained by Sonologist
Form G Consent Form for any Prenatal Diagnostic Procedure
Form H Form maintained by Appropriate Authority

All these forms are as follows:
FORM A

[See Rules 4(1) and 8(1)]
(To be submitted in Duplicate)

With supporting documents as enclosures, also in duplicate form of application for registration or renewal of registration of a genetic counseling center/genetic laboratory/genetic clinic

1. **Name of the applicant** (specify Shri/Smt/ Km/Dr)
2. **Address of the applicant**
3. **Type of facility to be registered** (specify Genetic Counseling Center/Genetic Laboratory/Genetic Clinic/any combination of these)
4. **Full name and address/addresses** of Genetic Counseling Center/Genetic Laboratory/Genetic Clinic with Telephone/Telegraphic Telex/Fax E-mail numbers.
5. Type of ownership and Organization
   (Specify individual ownership/partnership/company/co-operative/any other). In case of type of organization other than individual ownership, furnish copy of articles of association and names and addresses of other persons responsible for management, as enclosure.
6. Type of Institution (Govt. Hospital/Municipal Hospital/Public Hospital/Private Hospital/Private Nursing Home/Private Clinic/Private Laboratory/any other to be stated.)
7. **Specific prenatal diagnostic procedures/tests for which approval is sought** (for example amniocentesis, Chorionic villi aspiration/chromosomal/biochemical/molecular studies, etc.)
   Leave blank if registration sought for Genetic Counseling Center only.
8. **Equipment available with the make and model of each equipment.**
   List to be attached on a separate sheet.
9. (a) **Facilities available in the Counseling Center.**
   (i) Ultrasound
   (ii) Amniocentesis
   (iii) Chorionic villi aspiration
   (iv) Fetoscopy
   (v) Fetal biopsy
   (vi) Cordocentesis
   (b) **Whether facilities are available in the Laboratory/Clinic for the following tests:**
   (i) Chromosomal studies
   (ii) Biochemical studies
   (iii) Molecular studies
10. **Names, qualifications, experience and registration number of employees may be furnished as an enclosure (Refer Schedules I, II or III).**
11. State whether the Genetic Counseling Center/Genetic Laboratory/Genetic Clinic qualifies for registration in terms of minimum requirements laid down in Schedule I, II and III and if not, reasons therefore.
12. **For renewal applications only:**
   (a) Registration No.
   (b) Date of issue and date of expiry of existing certificate of registration.
13. **List of Enclosures:**
   Please attach a list of enclosures giving the supporting documents enclosed to this application.

Date: ................................
Place: ................................

( ____________________________ )
Name and signature of applicant
DECLARATION

I, Sh./Smt./Kum./Dr. ________________________ son/daughter/wife of ________________________ aged ______ years resident of ________________________ hereby declare that I have read and understood the Prenatal Diagnostic Techniques (Regulation and Prevention of Misuse) Act, 1994 (57 of 1994) and the Prenatal Diagnostic Techniques (Regulation and Prevention of Misuse) Rules, 1995.

I also undertake to explain the said Act and Rules to all employees of the Genetic Counseling Center/Genetic Laboratory/Genetic Clinic in respect of which registration is sought and to ensure that Act and Rules are fully complied with.

Date: __________________________
Place: _________________________
Name and signature of applicant

ACKNOWLEDGMENT

[See Rules 4(2) and 8(1)]

The application in Form A in duplicate for grant*/renewal* of registration of Genetic Counseling Center*/Genetic Laboratory*/Genetic Clinic* by ________________________ (Name and address of applicant) has been received by the Appropriate Authority ________________________ on (date).

*The list of enclosures attached to the application in Form A has been verified with the enclosures submitted and found to be correct.

OR

On verification it is found that the following documents mentioned in the list of enclosures are not actually enclosed.
This acknowledgment does not confer any rights on the applicant for grant or renewal of registration.

( ________________________ )
Signature and Designation of
Appropriate Authority, or
authorized person in the Office
of the Appropriate Authority

Date: ________________________

Seal

Original

Duplicate for display
FORM B
[See Rules 6(2), 6(5) and 8(2)]

CERTIFICATE OF REGISTRATION
(To be issued in duplicate)

1. In exercise of the powers conferred under Section 19 (1) of the Prenatal Diagnostic Techniques (Regulation and Prevention of Misuse) Act, 1994 (57 of 1994), the Appropriate Authority ................................................ hereby grants registration to the Genetic Counseling Center*/Genetic Laboratory*/Genetic Clinic* named below for purposes of carrying out Genetic Counseling/Prenatal Diagnostic Procedures*/Prenatal Diagnostic Tests as defined in the aforesaid Act for a period of five years ending on ................................................

2. This registration is granted subject to the aforesaid Act and Rules thereunder and any contravention thereof shall result in suspension or cancellation of this Certificate of Registration before the expiry of the said period of five years.

A. Name and address of the Genetic Counseling Center*/Genetic Laboratory*/Genetic Clinic* ..........................................................................................................................................................................................................

B. Name of Applicant for registration ...............................................................................................................................................

C. Prenatal diagnostic procedures approved for (Genetic Clinic) ..................................................................................................
   (i)  Ultrasound
   (ii)  Amniocentesis
   (iii)  Chorionic villi biopsy
   (iv)  Fetoscopy
   (v)   Fetal skin or organ biopsy
   (vi)  Cordocentesis
   (vii)  Any other (specify)

D. Prenatal diagnostic tests* approved (for Genetic Laboratory) ....................................................................................................
   (i)  Chromosomal studies
   (ii)  Biochemical studies
   (iii)  Molecular studies

3. Registration No. allotted ....................................................................................................................................................................

4. For renewed Certificate of Registration only ....................................................................................................................................

   Period of validity of earlier Certificate From ................................................... To ................................................... Or Registration.

Signature, name and designation of the Appropriate Authority

Date: ................................

Display one copy of this certificate at a conspicuous place at the place of business
FORM C

[See Rules 6(3), 6(5) and 8(3)]

Rejection of application for registration or renewal of registration

In exercise of the powers conferred under Section 19(2) of the Prenatal Diagnostic Techniques (Regulation and Prevention of Misuse) Act, 1994, the Appropriate Authority ................. Hereby rejects the application for grant*/renewal* of registration of the Genetic Counseling Center*/Genetic Laboratory*/Genetic Clinic* named below for the reasons stated.

Name and address of the Genetic Counseling Center*/Genetic ..........................................................................................................

Laboratory*/Genetic Clinic* ....................................................................................................................................................................

Name of Applicant who has applied for registration ............................................................................................................................

Reasons for rejection of application for registration ............................................................................................................................

Signature, name and designation of
The Appropriate Authority

Date: ............................

Seal

*Strike out whichever is not applicable or necessary.
FORM D

[See Rule 9(2)]

Name, address and registration no. of genetic counseling center record
To be maintained by the genetic counseling center

1. Patient’s name: ................................................................................................................................................................................
2. Age: ....................................................................................................................................................................................................
3. Husband’s/Father’s name: ..............................................................................................................................................................
4. Full address with Tel. No., if any: .....................................................................................................................................................
5. Referred by (Full name and address of Doctor(s) with registration No.(s) (Referred note to be preserved carefully with case papers): ............................................................................................................................................................................................
6. Last menstrual period/weeks of pregnancy: ...................................................................................................................................
7. History of genetic/medical disease in the family (specify) basis of diagnosis: ............................................................................
   (a) Clinical
   (b) Bio-chemical
   (c) Cytogenetic
   (d) Other (e.g. radiological)
8. Indication for prenatal diagnosis: ...................................................................................................................................................
   A. Previous child/children with: .................................................................................................................................
      (i) Chromosomal disorders
      (ii) Metabolic disorders
      (iii) Congenital anomaly
      (iv) Mental retardation
      (v) Hemoglobinopathy
      (vi) Sex linked disorders
      (vii) Any other (specify)
   B. Advanced maternal age (35 years)
   C. Mother/father/sibling has genetic disease (specify)
   D. Others (specify)
9. Procedure advised: ...........................................................................................................................................................................
   (i) Ultrasound
   (ii) Amniocentesis
   (iii) Chorionic villi biopsy
   (iv) Fetoscopy
   (v) Fetal skin or organ biopsy
   (vi) Cordocentesis
   (vii) Any other (specify)
10. Laboratory tests to be carried out: ...................................................................................................................................................
    (i) Chromosomal studies
    (ii) Biochemical studies
    (iii) Molecular studies
11. Result of prenatal diagnosis: ............................................................................................................................................................
    If abnormal give details. Normal/Abnormal
12. Was MTP advised? ..........................................................................................................................................................................
13. Name and address of Genetic Clinic* to which patient referred.
14. Dates of commencement and completion of genetic counseling.

Name, Signature and Registration No. of the
Medical Geneticist/Gynecologist/Pediatrician

Date: .................................
FORM E

[See Rule 9(3)]

Name, address and registration no. of genetic laboratory record
To be maintained by the genetic laboratory

1. Patient’s name: ................................................................................................................................................................................
2. Age: ................................................................................................................................................................................................
3. Husband’s/Father’s name: ..............................................................................................................................................................
4. Full address with Tel. No., if any: ....................................................................................................................................................
5. Referred by/sample sent by (full name and address of Genetic Clinic) (Referral note to be preserved carefully with case papers): ................................................................................................................................................................
6. Type of sample: Maternal blood/Chorionic villus sample/amniotic fluid/Fetal blood or other fetal tissue (specify): ............
7. Specify indication for prenatal diagnosis: ........................................................................................................................................
   A. Previous child/children with: .................................................................
      (i) Chromosomal disorders
      (ii) Metabolic disorders
      (iii) Malformation(s)
      (iv) Mental retardation
      (v) Hereditary hemolytic anemia
      (vi) Sex linked disorder
      (vii) Any other (specify)
   B. Advanced maternal age (35 years)
   C. Mother/father/sibling has genetic disease (specify)
   D. Other (specify)
8. Laboratory tests carried out (give details): ......................................................................................................................................
   (viii) Chromosomal studies
   (ix) Biochemical studies
   (x) Molecular studies
9. Result of prenatal diagnosis: ............................................................................................................................................................
   If abnormal give details. Normal/Abnormal
10. Date(s) on which tests carried out.
   The results of the Prenatal diagnostic tests were conveyed to ................................................. on .............................................

Name, Signature and Registration No. of the
Medical Geneticist

Date: .........................
FORM F

[See Rule 9(4)]

Name, Address and Registration No. of Genetic Clinic
Record to be Maintained by the Genetic Clinic

1. Name and address of the Genetic Clinic/Ultrasound Clinic/Imaging Center: .................................................................
2. Registration No.: ..............................
3. Patient’s name and her age: ......................................................................................................................................................
4. Number of children with sex of each child: ...........................................................................................................................
5. Husband’s/Father’s name: .......................................................................................................................................................
6. Full address with Tel. No., if any: ...........................................................................................................................................
7. Referred by (full name and address of Doctor(s)/Genetic Counseling Center (Referral note to be preserved carefully with case papers): ........................................................................................................................................
8. Last menstrual period/weeks of pregnancy: ..........................................................................................................................
9. History of genetic/medical disease in the family (specify) Basis of diagnosis:
   (a) Clinical
   (b) Bio-chemical
   (c) Cytogenetic
   (d) Other (e.g. radiological-specify)

10. Indication for prenatal diagnosis
   A. Previous child/children with:
      (i) Chromosomal disorders
      (ii) Metabolic disorders
      (iii) Congenital anomaly
      (iv) Mental retardation
      (v) Hemoglobinopathy
      (vi) Sex linked disorders
      (vii) Single gene syndrome
      (viii) Any other (specify)
   B. Advanced maternal age (35 years)
   C. Mother/father/sibling has genetic disease (specify)
   D. Other (specify)

11. Procedures carried out (with name and registration No. of Gynecologist/Radiologist/Registered Medical Practitioner) who performed it
   (i) Ultrasound
   (ii) Amniocentesis
   (iii) Chorionic Villi aspiration
   (iv) Fetal biopsy
   (v) Cordocentesis
   (vi) Any other (specify)

12. Any complication of procedure—please specify

13. Laboratory tests recommended
   (i) Chromosomal studies
   (ii) Biochemical studies
   (iii) Molecular studies

14. Result of prenatal diagnostic procedure and specify Normal/Abnormal abnormality detected, if any.

15. Was MTP advised/conducted: ..............................................................................................................................................

16. Date(s) on which procedures carried out: ...........................................................................................................................

17. Date on which MTP carried out: ...............................................................................................................................................

18. Date on which consent obtained: .............................................................................................................................................

19. The result of prenatal diagnostic procedure were conveyed to ......................................................... on .............................................. .

Date: .....................................
Place: .................................

Name, Signature and Registration number of the
Gynecologist/Radiologist/Registered Medical Practitioner
DECLARATION OF PREGNANT WOMAN

I, Ms. __________________________ (name of the pregnant woman) declare that by undergoing ultrasonography/image scanning etc. I do not want to know the sex of my fetus.

Signature/Thump impression of pregnant woman

DECLARATION OF DOCTOR CONDUCTING ULTRASONOGRAPHY

I, __________________________ (name of the person conducting ultrasonography/image scanning) declare that while conducting ultrasonography/image scanning on Ms. __________________________ (name of the pregnant woman), I have neither detected nor disclosed the sex of her fetus to anybody in any manner.

Name and signature of the person conducting ultrasonography

FORM G

[See Rule 10]

FORM OF CONSENT

I, __________________________ wife/daughter of __________________________ Age __________________________ years residing at __________________________ here by state that I have been explained fully the probable side effects and after effects of the prenatal diagnostic procedures. I wish to undergo the prenatal diagnostic procedures in my interest to find out the possibility of any abnormality (i.e. deformity or disorder) in the child I am carrying.

I undertake not to terminate the pregnancy if the prenatal procedure and any prenatal tests conducted show the absence of deformity or disorders. I understand that the sex of the fetus will not be disclosed to me.

I understand that breach of this undertaking will make me liable to penalty as prescribed in the Prenatal Diagnostic Techniques (Regulation and Prevention of Misuse) Act, 1994 (57 of 1994).

Date: __________________________ Signature

Place:

I have explained the contents of the above consent to the patient and her companion (Name __________________________
Address __________________________ Relationship __________________________) in a language she/they understand.

Name, Signature and/Registration number of Gynecologist

Date: __________________________

Name, Address and Registration number of Genetic Clinic
### FORM H

[See Rule 9(5)]

**Permanent Record of Application for Registration, Grant of Registration, Rejection of Application for Registration and Renewals of Registration**

1. Sl. No.: ...........................................................
2. File number of Appropriate Authority: ...........................................................
3. Date of receipt of application for grant of registration: ...........................................................
4. Name, Address, Phone/Fax etc. of Applicant: ................................................................................................................................
5. Name and address(es) of Genetic Counseling Center*/Genetic Laboratory*/Genetic Clinic*: .................................................
6. Date on which case considered by Advisory Committee and recommendation of Advisory Committee, in summary: ..........
7. Outcome of application (state granted/rejected and date of issue of orders): ............................................................................
8. Registration number allotted and date of expiry of registration: ..................................................................................................
9. Renewals (date of renewal and renewed up to): ............................................................................................................................
10. File number in which renewals dealt: ............................................................................................................................................
11. Additional information, if any: .........................................................................................................................................................

---

**Guidance for Appropriate Authority**

(a) Form H is a permanent record to be maintained as a register, in the custody of the Appropriate Authority.

(b) *Means strike out whichever is not applicable.

(c) Against item 7, record date of issue of order in Form B or Form C.

(d) On renewal, the Registration Number of the Genetic Counseling Center/Genetic Laboratory/Genetic Clinic will not change. A fresh Registration Number will be allotted in the event of change of ownership or management.

(e) No Registration Number shall be allotted twice.

(f) Each Genetic Counseling Center/Genetic Laboratory/Genetic Clinic may be allotted a folio consisting of two facing pages of the Register for recording Form H.

(g) The space provided for “additional information” may be used for recording suspension, cancellations, rejection of application for renewal, change of ownership/management, outcome of any legal proceedings, etc.

(h) Every folio (i.e. 2 pages) of the Register shall be authenticated by signature of the Appropriate Authority with date, and every subsequent entry shall also be similarly authenticated.

The following are requirements for obtaining IMR Certificate

1. A hand written/typed application addressed to the Secretary, Medical Council of India, New Delhi, requesting for getting IMR Certificate.

2. An attested Xerox copy of registration with Medical Council of India or with any State Medical Council.

3. A demand draft of ₹100/- in favor of Secretary, Medical Council of India payable at New Delhi at any Bank.
INTRODUCTION

For several decades, physicians have realized that the human body has immune mechanisms that protect against disease. Sometimes, the disease process overcomes the protective mechanism and manifests as illness. Though immune response to infections was the first and best understood, there is involvement of immune system in the causation of almost all diseases, including neoplasia. Hence, attempts have been made to utilize the immune mechanisms to treat several conditions. The application of principles of immune system has been limited in the field of obstetrics and gynecology and is gaining more and more importance. This chapter attempts to review the current status of immunotherapy in this field.

DEFINITION

Immunotherapy is defined as the administration of agents that can modulate, induce, modify and alter the inflammatory and immune responses. The use of patients’ own biological system or natural biological reagents to generate the immune response in an attempt to treat disease forms the basis of this.

Basis of Immunotherapy

Sir Macfarlane Burnet suggested the term “immunosurveillance” to indicate the host immune response to foreign antigens which will result in their destruction. Overwhelming infections, neoplasia and certain disorders of immune system may result in failure of this protective effect causing disease.

Causes of Failure of Immunosurveillance

- Mechanisms causing decreased immunogenicity of the disease causing factors ending in immune ignorance. Tumor cells by themselves may be poor antigen-presenting cells and the absence of co-stimulatory molecules like B7 can lead to T-cell anergy or apoptosis.
- Mechanisms causing immunosuppression may result from the pathological stimulus itself like neoplasia where interleukin (IL)-10 and transforming growth factor-beta (TGF-β) are secreted which decrease T-cell responses. There may also be production of enzymes like indoleamine 2, 3 dioxygenase which increases the catabolism of tryptophan and this inhibits T-cell proliferation. In some conditions, there may be deficiency of IL-2, IL-15, so cytotoxic T-cells die out after a few cell divisions. Immunotherapy aims to overcome immune escape mechanisms. This is achieved by using certain agents like tumor-associated antigens (TAAs) which actively or passively act on the immune system. The results of immunotherapy in neoplasia have been encouraging when tumor burden is less than 10⁸ malignant cells.

TUMOR-ASSOCIATED ANTIGENS

Each tumor is identified by the host immune system because of unique tumor antigens presented on it and they are called tumor-associated antigens (TAAs). TAAs can be grouped as self or nonself antigens.
- *Self antigens* form a group of antigens that have been generated from native molecules and maintain their
original amino acid sequences. This group includes repressed or silent antigens like carcinoembryonic antigen, α-feto protein and overtly expressed antigens like HER 2/NEU.

- Nonself antigens include products of genetic mutation and oncogenic and other pathogenic viruses or other microorganisms. Genetic mutation like point mutation or translocation may lead to the development of altered novel peptides like oncogene RAS and tumor suppression gene p53. Oncogenic viruses may be DNA or RNA viruses that integrate their genome into human cells resulting in the expression of foreign proteins that form potential TAAs. For example, Human papilloma viruses, Epstein Barr virus, Hepatitis B and Hepatitis C viruses.

Some Specific Tumor-associated Antigens

**HER 2/NEU**

This is a transmembrane protein of human epidermal growth factor receptor (HER) family. It is amplified in 20–30% ovarian cancers and is also considered to have importance in breast cancer. It has cysteine-rich extracellular domain that is highly immunogenic. In studies with mice, protective immunity against HER 2/NEU expressing tumor challenge is achieved by vaccination with full length HER 2/NEU antigen or subunit and has been found to generate CD8+ specific T-cell response.

**Folate-binding Protein**

Folate-binding protein functions as a transmembrane transporter of folate. It is expressed more than 80 times normal in certain ovarian malignancies.

**MUC-1**

MUC-1 is a high molecular weight glycoprotein that is rich in serine and threonine residues that are O-glycosylated. This is expressed on membranes of many glandular epithelial cancer cells including ovary, breast and gastrointestinal malignancies. There is increased expression of MUC-1 associated with change in profile of glycosyltransferases. This leads to aberrant glycosylation which makes cancer-associated mucin structurally different from normal mucin and, hence, easily recognized by immune system.

**Carcinoembryonic Antigen**

Carcinoembryonic antigen is a 180 kd glycoprotein that is normally expressed on the cell surface of fetal colonic mucosa. It is overexpressed in more than 50% of ovarian mucinous carcinomas and about 15% in other ovarian malignancies.

**p53**

p53 is a tumor suppressor gene mutated in 30–50% of ovarian cancers. Mutated form of p53 causes increased half-life and, hence, increased intracellular expression of the abnormal gene. Hence, p53 acts as TA by its mutated form (nonself) and by overexpression (self), p53 also causes cisplatin resistance. Cisplatin causes DNA breaks which are detected by p53, which in turn directs the cell to undergo apoptosis. Hence, the absence of normal p53 favors resistance.

Cytotoxic T-lymphocytes derived by vaccinating mice with mutant p53 can kill tumor cells expressing mutant forms. Vaccinating mice with mild type (original) p53 can protect mice from challenge with tumor cells expressing mutant p53.

**Sialyl-Tn**

This is a disaccharide antigen that is expressed in the core region of aberrant glycosylated mucins. This is very common in mucinous tumors and is extremely immunogenic.

**TYPES OF IMMUNOTHERAPY**

- **Active immunotherapy:**
  - Specific, e.g. vaccines
  - Nonspecific like chemical and biological agents

- **Passive immunotherapy:**
  - Specific like antisera and monoclonal antibodies (MoAb)
  - Nonspecific agents like lymphokine-activated killer and tumor-infiltrating lymphocytes.

**Active Immunotherapy**

Immunizing the host with materials designed to elicit an immune reaction capable of preventing disease is called active immunotherapy.

**Specific or Vaccines**

Vaccines are used because they present the antigens in a better fashion than the original antigen. These vaccines can be administered directly or pulsed with dendrite cells or along with Bacillus Calmette-Guérin (BCG), granulocyte-macrophage colony-stimulating factor (GM-CSF), recombinant ILs or other adjuvants.

**Defined antigen-directed vaccines:** These vaccines are prepared using definite TAAs which may be single or multiple, e.g. HER 2/neu, MUC-1 and Sialyl-Tn. Disis et al. identified immunodominant epitopes from HER 2/neu protein and then used 15–18 amino acid peptides intradermally with GM-CSF to ovarian cancer patients with minimal disease. Patients were able to generate specific immune response to lyse tumor cells.

**Nondefined antigen-directed vaccines:** These vaccines contain a collection of potential antigens derived from the tumor. These include:

- **Whole cell vaccine:**
  - Here the entire tumor cell is inactivated and presented
• **Whole cell lysate**: The tumor cells are subjected to lytic methods and extracted antigens are used for vaccinating. Zhao et al. showed that cytoxic T-cell generated against dendritic cells pulsed with ovarian cancer cell lysate showed significant killing activity against autologous tumor cells.

**Nonspecific**

- **Biological immunostimulants**:
  - *Bacillus Calmette-Guérin*: This live attenuated strain of *M. bovis* (BCG) causes activation of both humoral and cellular immunity and also activation of macrophages. Activation of macrophages is manifested by increased phagocytosis, microbicidal activity and increased metabolism. Most studies were in treatment of melanoma and leukemia. Dramatic work with BCG was by Rappet et al. with transplantable hepatoma in guinea pig. They showed that injection of BCG into group intradermal nodule was capable of eliminating the nodule and tumor cells in draining lymph nodes. BCG can be given intramuscularly, intradermally or by scarification. Results have not been very encouraging in gynecological malignancies. Disadvantage is BCG infection.
  - **Methanol extraction residue**: This is methanol extraction residue of BCG with same effect as that of BCG but without BCG infection.
  - **Corynebacterium parvum**: Like BCG, *C. parvum* has also been found to induce macrophage activation and can be given subcutaneously, intramuscularly, intravenously or intraperitoneally. Intraperitoneal administration of *C. parvum* has been noted by Mantovani et al. to be useful for palliative treatment of ascites in women with advanced ovarian carcinoma. In animal studies *C. parvum* has been found to induce regression of local and pulmonary metastasis.

- **Chemical immunostimulants**: These include levamisole, cimetidine and lysosome containing macrophage-stimulating substances. Levamisole is believed to cause maturation of thymus-derived immature lymphocytic precursors. It has been termed ‘immunomodulator’ by some in that it seems to reconstitute immunological competence in patients who are immunologically suppressed. Administration of levamisole before or after bacterial adjuvants, like BCG has been found to augment the activity of the latter.

- **Cytokines**: Cytokines are soluble proteins that have hormone-like action and exhibit their effect on immune system through regulation of other cells. Some important cytokines in use are IL-2, IFN-α, IL-3, IFN-γ, IL-12.

- **Interleukin-2**: IL-2 causes:
  - Activation and proliferation of T lymphocytes
  - Promotion of B-cell activation and maturation
  - Activation of monocytes and natural killer (NK) cells
  - Induces interferons and other cytokines.

Interleukin-2 has been used in paclitaxel and cisplatin-resistant tumors by intraperitoneal route and has been found to increase survival. Side-effects are flu-like syndrome, hypotension, gastrointestinal side-effects, drowsiness, depression, pancytopenia, altered renal function and hypothyroidism. Long-term data have been presented from a trial of intraperitoneal IL-2 in patients with refractory ovarian cancers. Among 34 patients, seven who had laparotomy confirmed complete response and two had partial response.

**Inter-12**: IL-12 can induce IFN-γ and together with IL-2 becomes potent activator of cytotoxic T lymphocytes and NK cells. It also enhances IFN-γ-mediated upregulation of adhesion molecules on tumor-associated blood vessels (ICAM-1, VCAM-1) providing access to circulating lymphocytes. Phase I–II clinical trials with intraperitoneal and systemic IL-12 are in progress.

- **IFN-α**: This has also been tried through intraperitoneal route with minimal residual disease in ovarian malignancies either alone or with carboplatin (< 5 mm). Response rate had been 30–50%; there was no improved response to combination therapy. In ovarian cancers within 24 hours of initiating therapy with IFNα, there were increased NK effectors, macrophages and tumor-specific lymphocytes.

**Other cytokines**: Granulocyte-macrophage colony-stimulating factor and IL-3 are known to cause faster bone marrow rescue after chemotherapy.

**Anti-idiotype Antibodies**

Idiotype is the variable region of an antibody that reacts with an antigen. These antibodies are used to stimulate immune response in malignancies and are produced as follows:

**Step 1**

Tumor-associated antigen is introduced into murine model which develops antibody against it (Fig. 1).
**Step 2**
Another murine model immunized with Ab₁ to get another antibody response Ab₂ (Fig. 2).

**Step 3**
When Ab₂ is introduced into tumor-bearing host, he develops Ab₃, a third antibody which closely resembles Ab₁ but reacts much more effectively with TAA than Ab₁ (Fig. 3).

**Passive Immunotherapy/Adoptive Immunotherapy**
This involves the transfer of preformed substances or cells that have antitumor activity into the host.

**Specific**
- Heterologous antisera from immunized humans
- Monoclonal antibodies
  Monoclonal antibodies were developed by Kohler and Milstein by hybridoma technique. The potential for MoAb and their conjugates is enormous given the specificity of antigen-antibody reactions. MoAb exert their antitumor action by:
  - Blocking the targeted receptor and preventing its function in transmitting proliferative signals to the nucleus
  - Activating antibody-dependent cellular cytotoxicity, internalizing the receptor and, hence, delivering toxic substances to the cell.

**Nonspecific**
*Lymphokine-activated killer cell:* These are peripheral lymphocytes cultured in the presence of IL-2 which then gain the ability to kill tumor cells without major histocompatibility complex restriction. It has been used in combination with IL-2.

*Tumor infiltrating leukocytes:* These are lymphocytes found infiltrating the tumor site. When these are cultured in vitro in the presence of IL-2, lymphocytes with better tumor-destroying properties are obtained.

**Monoclonal Antibodies as Therapeutic Agents**
*Anti-HER 2/NEU MOAB (trastuzumab):* This has been approved by Food and Drug Administration for metastatic breast cancer with taxol. In ovarian cancers, Ceullo et al. found that HER 2/NEU downregulates the expression of HER 2/NEU receptors in tumor cell lines. But phase II clinical trials show limited value with response rate less than 10%.

*Anti-CA 125 antibodies: (B 43.14):* Ca125 is overexpressed and also secreted into blood stream in more than 97% advanced ovarian cancers. MoAb B 43.14 is murine MoAb against Ca125. It binds with circulating Ca125 antigen and is recognized as foreign. This leads to development of human antimonoclonal antibody (HAMA) and anti-idiotype antibody response. This can also be used for Ca125 assays.

**Bispecific Monoclonal Antibodies**
These antibodies work by binding to antigen at one end and receptor for immune effector cell at the other end. This generates immune-mediated lytic activity (Fig. 4).

**Examples include:**
- MDX 210 which has receptor for HER 2/NEU and for FC g receptor 1 of monocyte and macrophages.
- OCTR which has receptors for folate receptor and CD3 T lymphocytes.
  Phase II trial with 28 patients showed that 27% patients had complete or partial intraperitoneal response.

*Radioimmunoconjugates:* Monoclonal antibodies are also used along with radionuclide β emitter conjugates. For example, yttrium 90 monoclonal antibody-human milk fat globule 1 which binds specifically to polymorphic epithelial mucin, an antigen expressed in more than 90% ovarian cancers, conjugated to yttrium 90 isotope has been used in a phase I and II trial in ovarian cancer. These conjugates need not be internalized for their action.

*Immunotoxins:* MoAbs can be linked to chemotoxins to allow more specific targeting of these toxins to malignant cells. Examples of some chemotoxins tried are:

**Fig. 4:** Mechanism of action of bispecific monoclonal antibodies
• Ricin A
• Pseudomonal exotoxin
• Salmonella endotoxin,
• Methotrexate, Adriamycin.

These immunotoxins require internalization into the cell for their action, hence they are highly specific. But some tumor cells may shed their antigens into the general circulation and MoAbs may be trapped with free antigens and not reach tumor per se. Furthermore there may be sharing of antigens between normal and malignant cells.

Pai and colleges conducted a trial using OVB3-PE which is a MoAb that recognizes ovarian cancer and is linked to Pseudomonal exotoxin. Phase I trial showed no effect when used intraperitoneally.

**Disadvantages of monoclonal antibodies:** These include allergic reaction, delayed serum sickness, development of HAMA. HAMAs bind to MoAb and can affect their activity and distribution. This can be overcome by “humanization” of the biological agents by substituting Fc murine portion for the human equivalent, e.g. Herceptin developed against HER 2/NEU.

### OTHER AREAS OF APPLICATION OF IMMUNOTHERAPY IN OBSTETRICS AND GYNECOLOGY

**Cancer Cervix**

Oncogenic viral products of human papillomaviruses (HPV) act as TAAs.

**Vaccines in Cervical Cancer**

*Prophylactic vaccines:* Principal goal in prophylactic vaccines is to prevent infection by etiological cause. Accordingly they are based on inducing humoral immune response to generate neutralizing antibodies. It has been found that HPV vision composed of late proteins L1 and L2 is highly immunogenic and generates humoral response. L1 and L2 when cultured in vitro assembled to form “virus-like particles”. They resemble the native vision and have the same immunogenicity. Vaccination through mucosal route generates IgA response. Vaccines for cancer cervix seem to have evoked great enthusiasm. There are likely to be ethical issues involved in having vaccines for sexually transmitted infections like HPV.

*Therapeutic vaccines:* Early protein products of HPV E6 and E7 are used in clinical trials in dysplasia and advanced CaCx to elicit cell-mediated immunity. They have been fused to HSP-65 (heat shock protein) to enhance antigen processing.

**Immunotherapy in Cervical Atypias and Cervical Dysplasias**

Topical IFN-α has been used in persistent atypia and dysplasia at dose 1 × 10⁶ IU for 14–21 days with favorable outcome.

### Gestational Trophoblastic Disease

One study with paternal leukocyte immunization done by Cinander et al. showed complete disappearance of choriocarcinoma and pulmonary metastasis.

### Endometriosis

Studies in immunotherapy are underway as endometriosis is believed to be due to abnormal NK cell function. NK cells normally do not allow ectopic endometrium to proliferate. Hence the hypothesis that NK cell dysfunction could lead to endometriosis.

**Immunotherapy in Recurrent Pregnancy Loss**

Immune regulation which maintains pregnancy is reported to involve both cellular and humoral immunity.

- Suppressor cells found in maternal decidua suppress the maternal immune response to fetus.
- Human leukocyte antigen-G antigens expressed on trophoblast cells inhibit NK cells.
- Antipaternal cytotoxic antibodies have been found with high frequency in sera of normal pregnant women.
- T-cell receptor anti-idiotype antibodies capable of inhibiting autologous T-cell responses are seen.

As immunotherapy for recurrent spontaneous abortion, women are immunized with their partner’s lymphocyte in an attempt to enhance the production of immune-suppressing antibodies. High success rates of maintaining pregnancy have been achieved.

**Immunotherapy in Antiphospholipid Antibody Syndrome**

Immunotherapy in the form of immunoglobulin therapy has usually been reserved for women with overt disease or heparin-induced thrombocytopenia or both. Immunoglobulin is administered intravenously in doses of 0.4 mg/kg daily for 5 days for a total of 2 g/kg. This is repeated monthly or given as a single dose of 1 g/kg each month.

**Immunotherapy in Septic Shock**

Antiendotoxin antibody serum has been studied extensively for gram-negative sepsis and septic shock. Studies are underway with monoclonal antibody to Lipid A, E5 murine monoclonal IgM, antiendotoxin antibody for adult respiratory distress syndrome and recombinant fusion protein of p55-TNF-α to competitively block TNF-α.

Immunotherapy seems to have an exciting future in the management of several conditions in obstetrics and gynecology. As better understanding occurs about the role of immune system in the pathogenesis of diseases, more application for the use of immunotherapy are likely to be discovered.
INTRODUCTION

Managing a woman in labor always has its challenges! This chapter aims at clarifying an area where there are widely divergent opinions and protocols among the peers of the profession! Although a matter of daily affair, there is scant attention and almost no consensus about hydration during labor. Upon an informal inquiry among the resident doctors manning the labor wards a startling fact emerged! About 25% wanted “nil by mouth” policy and another 50% wanted “fluids only” during labor. When asked about the choices of intravenous (IV) fluid for hydration, a variety of cocktails were described by the junior colleagues, mixing crazy quantities and order, for dextrose (D) 5, D10, dextrose saline and Ringer’s lactate! Normal saline was almost relegated to an obscure unwanted position! I have tried to analyze the available information and do sincerely hope that the following few pages will bring a measure of sanity in the “fluid fracas” during labor.

WHY FLUID MANAGEMENT?

Pregnancy is “accelerated starvation syndrome”. The effect is accentuated in labor by the muscular exertion and forced starvation. The average plasma ketone level in nonpregnant state is 0.13 mmol/L compared to 0.43 mmol/L during pregnancy. Early morning ketonuria was found in 7% of normal pregnant women using Ketostix (indicates presence of acetoacetic acid in urine at concentrations > 1.0 mmol/L). Forty percent women in labor show positive reaction to Ketostix. This is a milder state of starvation, but a large glucose loading to cover it may lead to iatrogenic hyperinsulinemia and resultant postnatal hypoglycemia in the fetus! Although a small infusion of 5% glucose does not produce significant hyperglycemia in either the mother or the fetus, a cumulatively high dose of glucose infusion (especially in a long protracted labor) causes a significant rise in lactate concentration and a significant fall in fetal pH. Since the ability to excrete water is impaired during labor, an assessment based on urine output may be fallacious. The laboring patient has an insensible loss of free water through the skin and lungs (more with panting in final stages of labor). The sweating represents significant hypotonic loss [sweat sodium (Na) 0.3%]. These issues become more relevant in long labors and especially where the intake is restricted.

ORAL INTAKE DURING LABOR

The restriction of oral intake policies started after the influential study published by Dr Curtis Lester Mendelson (1946) to demonstrate the high death rate associated with aspiration of stomach contents during general anesthesia. He showed that two factors that increased the risk of maternal problems were a gastric pH of less than 2.5 and a volume of an aspirate of 25 mL. It was postulated that oral intake leads to higher gastric volume due to delayed gastric emptying and solids in food might block the airway when aspirated. This was particularly true when narcotics were used for pain relief as they significantly reduced the gut motility. As a result, the anesthesiologists evolved a policy of restricting oral intake during labor. Many studies have shown recently that contrary to the established thinking, restricting oral intake leads to lower pH and there is paradoxical increase in gastric fluid volume during fasting (gastric volume > 0.4 mg/kg and pH < 2.5). Thus, in order to justify these policies, obstetric anesthesiologists must provide evidence that they are beneficial. In another prospective study when women were given 150 mL water 2 hours before surgery, the gastric content volume was lesser at the time of surgery compared to the similar control group of fasting women! National Birth Center Study (1989) has demonstrated in a large study of 11,814 women that “although 95% drank or ate
while in labor, there was no aspiration-related morbidity and 22% had solid food before emergency cesarean section (CS), but none aspirated! Authors also observed that antacids given within 4 hours of delivery reduced the “at risk” (gastric pH < 2.5 and volume of gastric aspirate > 25 mL) to 3% compared to 24% among those who did not take antacids.\(^5\)

There is a move back to a less interventional approach to childbirth fueled recently by critical reevaluation of the active (mis)management of labor. There is evidence to suggest that starvation policies are distressing to the laboring woman. The metabolic consequences of fasting might even be detrimental to the progress and outcome of labor. A woman in labor should be equated with an athlete running the marathon! Both the athlete and the laboring woman need quick energy from food to maintain their increased cardiac output. Both take more time than usual to digest solid foods but can use oral fluids to keep blood glucose levels up. Women in early labor should be encouraged to eat meals similar to the meals of athletic competitors: “high in carbohydrates for quick energy, and fluids for hydration, and low in fats for digestive ease”. Such foods, as well as electrolyte-replenishing fruit juices and fluids (such as electrolyte, etc.) can be used during active labor (recommended 125 mL/hr) as long as narcotic analgesia (which slows digestion dramatically) is avoided. An interesting study has demonstrated that increased hydration (250 mL/hr vs 125 mL/hr) for nulliparous women in labor, is associated with a lower frequency of prolonged labor and possibly less need for oxytocin.\(^7\) Thus inadequate hydration in labor may be a factor contributing to dysfunctional labor. The stomach is never completely empty regardless of the time of the patient’s last meal. Fasting does not eliminate stomach contents; it increases the concentration of hydrochloric acid. Prolonged fasting may cause gastric volume and acidity to increase, thereby augmenting rather than solving the problem.

In a survey by Simkin, 27% parturient women were reported dissatisfied with the policy of withholding food, 52% found fluid restriction moderately or most stressful and 24% compared to 24% among those who did not take antacids.\(^5\)

Physiological Alterations during Pregnancy: Electrolytes—Na and K

- 1,000 mEq of sodium (Na) and 300 mEq of potassium (K) are retained
- Glomerular filtration and tubular reabsorption—both increase
- Plasma levels remain at the lower level of normal range.

Hyponatremia

- Hyponatremia is not uncommon during labor. Oral fluids, when permitted, should be recorded and IV administration of hypotonic fluids should be avoided. When abundant drinking is unrecognized or IV fluid administration liberal, life-threatening hyponatremia may develop. The possibility that hyponatremia may influence uterine contractility merits further investigation.

Hazards of Hyponatremia

- Hyponatremia correlated significantly with prolonged second stage of labor, instrumental delivery and emergency CS for failure to progress
- Maternal hyponatremia can also be reflected in the fetus and some studies have reported increased incidence of respiratory distress and hyperbilirubinemia in hyponatremic infants.

The osmolality of a solution is defined as total number of dissolved particles per kilogram of solvent. Water without any dissolved solutes, i.e. with zero osmolality (0 mOsm/kg) is considered “free water”. Water (and not the solutes or electrolytes) moves quickly from low to high osmolality space (intracellular to extracellular or vice versa) according to the gradient of osmolality. Therefore, the osmolality of any infused fluid becomes very vital in its effects on internal homeostasis. Net persistent osmotic effect depends upon metabolism of component. Sodium does not undergo metabolic transformation and will remain in the plasma for a long time. As compared to this, glucose (5% D) will be metabolized quickly and the final net osmotic effect will be “zero” that of free water. This will either dilute the plasma or lead to passage of water into cells [osmotic swelling of red blood cells (RBCs) and subsequent hemolytic jaundice, cerebral edema, etc.]. During normal pregnancy, as a result of fall in Na and associated anions, the plasma osmolality is about 10 mOsm/kg below nonpregnant state. The differences between saline and free water are shown in Table 1. Fluid compartment of the body as percentage of total body water is shown in Flow chart 1.

1. **Nonpregnant woman**: 285 mOsm/kg
2. **Pregnant woman**: 275 mOsm/kg

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**PARENTERAL INFUSIONS IN LABOR**

One may need to infuse fluids by an IV line if the patient is disinclined to oral intake, has repeated vomiting or in case of dehydration of prolonged labor. There has emerged a measure of consensus in this regard and a little background of fluid mechanics may be illuminating.
With this background of understanding, one can make a judicious choice among the following commonly available IV fluids:

- **Normal saline**: It produces sustained volume expansion with no effect on cell size and function. It causes minimal brain edema, and has almost no effect on osmolarity. It does not cause infection. As it raises pulmonary capillary wedge pressure by sustained expansion of plasma volume, excess of input may cause pulmonary edema.

- **Dextrose 5% and 10%**: Dextrose 5% provides a transient volume expansion, and if given in large volume, will cause cell edema. This is specially a matter of concern in hypoxic fetus where cerebral edema may aggravate the condition. Given in small quantity, it is a good choice to provide energy in fasting state, but can cause infection if contaminated. Dextrose 10% has little clinical application in obstetrics. Glucose infusions are electrolyte free and an infusion of greater than 3,500 mL can cause maternal postpartum cerebral edema, fits and coma.

- **Dextrose saline**: It combines the effects of both the dextrose as well as saline, but difficult to interpret and predict clinical events. A better option is to give dextrose and saline separately as the condition demands.

- **Ringer’s lactate**: This is an excellent choice for volume expansion as well as an IV drug vehicle. In asphyxia, its use is inappropriate.

- **Albumin 5%**: Although sparingly used, it produces sustained volume expansion, and does not cause any interference in electrolyte balances. When vascular damage is expected (inflammation or capillary damage, etc.) it is best avoided as it will leak into interstitial space and cause a sustained edema there!

- **Mannitol**: Another excellent choice for volume expansion and being hyperosmolar can help in reducing cellular edema. It has a sustained and relatively longlasting effect, but may interfere in coagulation mechanism.

### RECOMMENDATIONS
To avoid ketosis as a result of prolonged labor, small amounts of glucose may be given slowly. However a large amount of glucose is avoided with an upper limit of total glucose kept at 6–15 g/hr (a 500 mL of 5% D solution has 25 g of glucose). Morton et al. compared 1 L of sodium chloride (NaCl), Ringer’s lactate, dextrose 5% in water (D5%W), dextrose 10% in water (D10%W) in women with ketonuria and observed that both dextrose and Ringer raise lactate, and concluded that NaCl is best and total dextrose per hour should be less than 25 g. IV fluids are seldom necessary in first 12 hours of labor and total input is kept less than 3,000 g. For expansion of plasma volume, the choice is crystalloid solution like normal saline. Lactated Ringer is also a good choice in volume replacements of hemorrhages, but in protracted labors, the lactate may be harmful for the compromised fetus.

### SPECIAL SITUATIONS

#### Preterm Labor
It is now realized that initial therapy for a preterm labor is hydration and saline loading has emerged as frontline of treatment in some centers. In addition to routine oral intake, an infusion of 1,500–2,000 mL/24 hours is given. Tocolytic agent ritodrine can cause pulmonary edema when
infused with saline and one needs to be cautious. Five percent albumin is another good option for a sustained volume expansion.

**Pre-eclampsia and IUGR**

There is usually a reduced blood volume during both these conditions [pre-eclampsia and intrauterine growth restriction (IUGR)], which often are coexistent. In extreme cases of hypovolemia, the hemodynamic stability is impaired and treatment with vasodilators lead to marked hypotension (Bezold-Jarisch reflex). As compared to this, a quick volume expansion raises cardiac output and lowers vascular resistance without affecting mean arterial pressure (MAP) and hence, improves hemodynamic stability and increases uterine blood flow.

Crystalloids remain the mainstay of therapy and colloids are generally avoided.

If given too energetically, there is a risk of postpartum pulmonary edema due to sudden volume expansion resulting from sustained uterine contraction and elimination of uteroplacental circulation. If dextrose is given a chance of cerebral edema is likely. These risks are more pronounced in obese and chronically hypertensive patient with very labile hemodynamic system.

**Epidural/Spinal Analgesia**

The choice of anesthesia for CS has decisively moved to regional anesthesia. Before employing either epidural or spinal analgesia, a preload with 500–1,000 mL normal saline is greatly beneficial to limit the fall in BP in response to sympathetic block. Regional anesthesia leads to peripheral enlargement of vascular compartment, and needs to be rapidly filled to avoid dangerous hypotension. Preloading is better than treating hypotension with fluids as there is lesser chance of developing pulmonary edema. A policy of free oral intake is likely to cause friction between the two arch fighters; “at the water’s edge: where obstetrics and anesthesia meet” Kenneth Williams.

**Induction and Augmentation**

Antidiuretic property of oxytocin leads to retention of water and hyponatremia, especially if the delivery solution is glucose. Studies have shown a reduced cord blood Na⁺ and higher neonatal jaundice when glucose is used. Normal saline is the preferred solution for oxytocin infusion and a policy of using concentrated infusion with an eye on limiting total fluid inputs will be beneficial.

**Fetal Distress**

In a mistaken belief of providing energy during fetal asphyxia, many institutions have a policy of infusing the concentrated glucose (10% dextrose). Studies have shown that hypoxia is more harmful to fetal brain after maternal feeding or glucose infusion compared to starving, due to anaerobic oxidation of glucose resulting in lactate accumulation and cerebral edema.¹² Acute maternal hyperglycemia (> 150 mg%) before delivery has a high risk of perinatal asphyxia. Glucose and lactated Ringer are best avoided and small quantities of saline infusion to expand the blood volume can help by increasing the uteroplacental perfusion. Oxygen and lateral position to restore the cardiac output are other beneficial measures.

**Hypovolemia**

To correct hypovolemia of exsanguinations or hemorrhage, saline or Ringer’s lactate is the best choice. Saline resuscitation can cause hyperchloremic acidosis. Blood and/or plasma are reserved only to replace clotting factors, or when there is a marked drop in hemoglobin concentration. Albumin is a good option but has a very short shelf life. Haemaccel® having a long shelf life is an excellent volume expander but interferes with clotting mechanism.

**Diabetes**

Glucose is utilized at 2.5 mg/kg/min during the active phases of labor. As consumption increases during labor, insulin needs diminish. Insulin and oxytocin should be in different IV bottles.¹⁴ Neutralizing drips should have preferably 10% dextrose.

**Ketoacidosis**

If ketoacidosis is detected, an infusion of normal saline 1–2 L in 30–60 minutes is given and then maintained at 200–250 mL/hr. Glucose is started only after blood sugar falls below 200 mg%. Insulin is started at a rate of 12 U/hr and reduced when blood sugar is less than 200 mg%. Bicarbonates are given when pH falls below 7.1 and K is given if serum K⁺ is less than 3 mEq/L.

**Anemia**

It is interesting to note that even in moderately severe anemic patients who do not have cardiopulmonary and renal decompensation will not require any special modification of management for fluids and electrolytes in labor.¹⁵,¹⁶

**CONCLUSIONS**

- Pregnancy and various pathological processes alter the fluid and electrolyte balance significantly.¹⁵
- Fluid management in labor deserves special thought.¹⁶
- Oral intake of liquids are generally allowed during uncomplicated labor.
Antacids within 4 hours of delivery reduce aspiration morbidity
Saline is the solution of choice for infusion except when betamimetic therapy is to be given
All IVs are given slowly except in hemorrhage
Total inputs should not cross 3 L/24 hours
Dextrose is best avoided, especially in fetal asphyxia, and should be reserved for energy inputs!
Ringer’s lactate is the fluid of choice in pre-eclampsia and hemorrhagic shock
Higher incidence of neonatal hyperbilirubinemia is seen in mothers receiving dextrose infusion during labor.17

REFERENCES

4. Roberts, et al. Restricting oral intake leads to lower pH and there is paradoxical increase in gastric fluid volume during fasting.
INTRODUCTION

Sex ratio is an important social indicator to measure the extent of prevailing equity between males and females in the society. We are all concerned about the declining child sex ratio, which has declined from 946 in 1991 census to 917 in 2001 census. The declining sex ratio is particularly worrisome, as it points to the increased incidence of sex determination and then elimination of girls. What is more appalling is the fact that the child sex ratio is lowest not in the socioeconomically poor, less developed and tribal districts, but in the most socioeconomically advanced districts of the states, including Mumbai.

SOME BASIC FACTS

- Child sex ratio has shown a decline from 927 (2001) to 914 (2011).
- The child sex ratio (0–6 years) that stood at 976 girls to 1,000 boys in 1961 has declined to 927 girls to 1,000 boys in 2001. The most dramatic decline was seen in the decade 1991–2001, from 945 down to 927.
- In certain parts of the country, there are less than 8 girls for every 10 boys.
- Prosperity is no guarantee and sex selection is happening across India, especially in some of the most prosperous parts of the country such as Punjab, Haryana and Delhi.
- Sex selection adversely impacts the delicate equilibrium of nature and destroys our moral and social fabric.

Sex Selection and Abortion

In India, abortion is legal under certain conditions. However, abortion for the reason of sex selection is not. Accurate portrayal of this fact, and not implying that abortion per se is illegal, is important. Otherwise it could limit a woman’s rightful access to safe and legal abortion services.

Myths and Misconceptions

- Contrary to what many believe, lesser number of girls in a society will not enhance their status. Instead, in places where sex selection is rampant, there can be an increase in violence against women, rape, abduction, trafficking and onset of practices such as polyandry.
- The notion that only couples with two or more daughters are going in for sex selection, and therefore, does not affect the overall child sex ratio, is misleading. In fact, data indicates that even for the first born, there is a preference for a male child. This trend is even more noticeable where the first born is a girl.
- Sex selection is not a solution to dowry—the system of dowry will continue as long as people look upon daughters as a liability. What is important is to address the root cause for the subordinate status of women in the society.
- The thought that it is more humane to eliminate a female fetus than subjugate her to a life of discrimination does not hold water. By the same logic, it would be justifiable to eliminate poor people than let them suffer a life of poverty and deprivation. The girl child is not the problem, the practice of sex selection is.
- Another misleading notion is that banning sex selection amounts to denying a mother her unalienable right to choose the sex of her child. Choice in the absence of autonomy is no choice. Fears of violence and rejection or desertion and also the desire to establish one’s value in the family, often pressurize women into opting for sex selection.
- The argument that sex selection is an effective tool for controlling population is misplaced. We want population
stabilization for improving quality of life. This is the ultimate goal. If along the way we resort to things that damage our quality of life, is that desirable?

States like Punjab, Haryana and Rajasthan, because of declining sex ratio of girls, are experiencing increase in violence against women, increase in sex-related crimes and increase in sexual exploitation of women. Our whole social system is at stake due to the declining sex ratio. Maharashtra which is one of the progressive states in the country, faces the threat of a serious mismatch in the young male-female ratio, a decade from now. What is more worrying is that the declining ratio is no more a phenomenon confined to prosperous urban areas, but is spreading to the rural parts. Apart from the male-oriented approach of the society (as seen in yearning for male child as a property heir, etc.) the growing misuse of medical technology for sex determination and illegal abortions was a key factor behind the declining ratio.

Due to the rising incidence of prenatal sex detection and sex selective abortion, Parliament came out with Prenatal Diagnostic Techniques (PNDT) Act in 1994, which was further amended in 2003 and now called as Preconception Prenatal Diagnostic Techniques (Prohibition of Sex Selection) (PCPNDT) Act, specifically to curb misuse of medical technology for sex determination, has yet to prove effective in curbing this decline.

This was mainly because of limitation in establishing cases of preconception and prenatal sex determination and the state indifference in effectively monitoring the activity of the panels established under the PCPNDT Act to deal with the reported incidents.

The final step is the misuse of technology for both sex selection and abortion done by doctors. As a respected member of the society, doctors can play a major role to reverse declining child sex ratio. What doctors can do:

- Can take initiatives in Information Education Communication (IEC) or advocacy activities.
- As counselors doctors get an opportunity to interact with newly married couples, when approached for family planning advice or other issues and concerns and during these interactions, they would be in a better position to counsel clients on reproductive rights, on status of women and girls in the society, on sex selection and its adverse social implications.
- During antenatal period, when clients for the first time come for pregnancy confirmation and thereafter for regular antenatal checkups, the doctors can always advice clients to refrain from determination of sex, and can advise on legitimate use of ultrasonography (USG) techniques.
- When the clients come for USG, the doctors can strongly say “no” to communicate the sex of fetus to the client, even if the clients are demanding, and use this as an opportunity to counsel them.
- When the clients come for Medical Termination of Pregnancy (MTP), on detail history taking, doctors can always suspect and make out if a client has come for MTP just to abort a female fetus. They can strongly say “no” to this and also convince clients not to differentiate between a male and female child.
- Abide by the PCPNDT Act.
- Stop sympathizing with the perpetrators. Doing this will only justify the crime.
- Be vigilant toward misuse of technology and create a moral pressure on doctors, who are indulging in sex selection.
- Break the silence around this issue and impress upon people that times have changed.
- Counsel clients who come for sex selection and link up with local non-governmental organizations (NGOs) to provide community support to vulnerable couples.
- Value and celebrate girl child’s life in your family and community. Advocate to promote positive image of girl child.
- Make use of opportunities available to doctors to counsel clients and for advocacy.

**AN APPEAL**

I wish for a healthy society of my state, and, therefore, I need to start working on this issue from today, sex selection is an issue close to my heart, I take a Pledge to work for this cause. At least for my wife’s, my daughter’s, my sister’s social security-safety and their future, I need to work from today. Our journey has just begun...We have miles to go before we reach our destination of a society without discrimination...Yes! it is very true, a dream “A society without discrimination”.


**INTRODUCTION**

Obstetric practice is often fret with massive hemorrhage which often requires blood transfusion (BT). Hence, it is important for the obstetrician to have knowledge of BTs.

**INDICATIONS FOR BLOOD TRANSFUSION**

- Increased oxygen carrying capacity
- Increased intravascular volume.
  Increasing oxygen carrying capacity is the main reason for BT. But in obstetric practice when the patient is hemorrhaging, blood is often given to increase both.

**Compatibility Testing**

Compatibility testing is done in three steps:

1. ABO-Rh typing
2. Crossmatch
3. Antibody screening.

**ABO-Rh Typing**

Determination of the patient’s correct blood type is exceedingly important and is done by testing red blood cells for A and B antigens and the serum for A and B antibodies. Rh typing is also carried out.

**Crossmatching**

Crossmatch is essentially a trial transfusion in which donor cells are mixed with recipient serum to detect potential for serious transfusion reactions. It takes about 45–60 minutes for crossmatching and is carried out in three phases:

1. First phase is carried out at room temperature and is a check against errors in ABO typing and those naturally occurring antibodies in the M, N, P and Lewis systems.
2. Second phase involves incubation of the first phase reactions at 37°C in albumin which aids in detection of incomplete antibodies. This step primarily detects antibodies in Rh system.
3. Third phase involves addition of antiglobulin sera to incubated test tubes. This antiglobulin phase detects most incomplete antibodies in the blood group systems including Rh, Kell, Kidd and Duffy blood group systems.
   While all the three phases are important, the first two stages are of prime importance in preventing serious hemolytic transfusion reactions.

**Antibody Screening**

This is also carried out in three phases and is similar to the length of crossmatch. The screen for unexpected antibodies is also carried out on donor serum. This screen is performed primarily to prevent reactions between transfused donor units.

**STORAGE OF BLOOD**

Blood is stored in citrate-phosphate-dextrose-adrenaline anticoagulant preservative at 1–6°C. Citrate acts as an anticoagulant, phosphate acts as a buffer and dextrose is energy source for red blood cells. Blood can be stored for
35 days in this system. Shelf life can be extended to 42 days when AS-1 (adsol) or AS-3 (nutrice) is used.

**COMPPLICATIONS**

- **Changes in oxygen transport:** Shift of oxygen dissociation curve to left as respiratory function of red blood cells is impaired during preservation making it difficult for them to release oxygen to the tissues immediately after transfusion.
- **Coagulation:** A bleeding tendency is often present in massively transfused patients. The coagulopathy is caused by a combination of factors of which the most important are the volume of blood given and the duration of hypotension or hypoperfusion. Coagulopathy could be because of disseminated intravascular coagulation (DIC) or dilution of coagulation factors.
  - Dilutional thrombocytopenia
  - Low factors V and VIII
  - DIC
  - Hemolytic transfusion reactions. Dilutional thrombocytopenia: At a storage temperature of 4°C, platelets in stored blood are damaged sufficiently to be readilly trapped and absorbed by the reticuloendothelial system soon after infusion. After 24–48 hours of storage, platelet activity is only about 5–10% of normal activity respectively. Thus, infusion of stored blood for more than 24 hours causes dilution of available platelet pool.
  - **Citrate intoxication and hyperkalemia:** Citrate intoxication occurs due to citrate binding to calcium, thus signs of hypocalcemia occur, i.e. hypotension, narrow pulse pressure and elevated intraventricular end-diastolic pressure and central venous pressure. It occurs if BT is given at a very fast rate that is one unit in 5 minutes in an average sized adult. Serum potassium levels may be as high as 19–30 mEq/L in blood stored for 21 days. These complications are rare to occur.
- **Temperature:** Administration of unwarmed blood that has been stored at 4°C can decrease the recipient’s temperature. If the temperature decreases to less than 30°C then ventricular irritability and even cardiac arrest can occur.
- **Acid base abnormalities:** pH of most storage media is very acidic [citrate-phosphate-dextrose (CPD)—5.5]. When this is added to blood, the pH of blood decreases to 7.0–7.1 as a result of accumulation of lactic and pyruvic acids by red blood cell metabolism and glycolysis the pH of bank blood continues to decrease to about 6.9 after 21 days of storage.
- **Infusion of microaggregates:** Amounts of clots and debris in bank blood increase with duration of storage. Respiratory insufficiency in patients with hemorrhage or acute respiratory distress syndrome (ARDS) may be a result of accumulation of particulate material in the lungs resulting in vascular obstruction.

**TRANSFUSION REACTIONS**

**Hemolytic Transfusion Reactions**

The incidence of hemolytic transfusion reactions varies from 1:4,000 to 1:6,000. Fatal hemolytic transfusion reactions occur in about 1:100,000.

Signs and symptoms include fever, chills, chest and flank pain, flushing, nausea, dyspnea, hemoglobinuria and bleeding diathesis is how a patient with hemolytic transfusion reaction would present.

**Treatment**

1. Stop the BT.
2. Maintain urine output at 75–100 mL/hour by generously administering intravenous (IV) fluids and possibly mannitol 2.5–50 g given over 5–15 minutes period. If this is ineffective in maintaining urine output, then administer furosemide 20–40 mg IV.
3. Alkalinize the urine since bicarbonate is preferentially excreted in the urine. Only 40–70 mEq/70 kg of sodium bicarbonate is required to raise the urine pH to 8.
5. Determine platelet count, partial thromboplastin time and serum fibrinogen level.
6. Return unused blood to the blood bank for re-crossmatch.
7. Send patient’s blood sample to blood bank for antibody screen and direct antiglobulin test.
8. Prevent hypotension to ensure adequate renal flow.

**Delayed Hemolytic Transfusion Reactions**

In many cases of hemolytic transfusion reaction, the transfused donor cells may survive well initially, but after a variable delay of 2–21 days will be hemolyzed. This type of reaction occurs usually in patients sensitized to red cell antigens by previous BTs or pregnancy. These patients manifest as decreased hematocrit, sometimes jaundice or hemoglobinuria. They can also sometimes cause impairment in renal function but rarely cause demise.

Unlike immediate transfusion reactions, antibodies most commonly involved in delayed hemolytic reactions is Rh and Kidd systems rather than the ABO systems.

**Nonhemolytic Transfusion Reactions**

These reactions are febrile or allergic in nature. The symptoms consist of chills, fever, headache, myalgia, nausea and nonproductive cough occurring shortly after BT. Allergic transfusion reactions are mild and caused by foreign protein in transfused blood. The most common symptom is urticaria associated with itching. Three percent of all transfusions cause allergic reactions. Antihistaminics are used to relieve symptoms.
Transfusion-associated Acute Lung Injury

It is ARDS within 2–6 hours after transfusion in which:
- Choking noncardiogenic pulmonary edema occurs manifested as hypoxia with bilateral infiltrate on chest X-ray
- Seen one in every 2,000–5,000 BTs
- Pathogenesis is antibody-mediated against human leukocyte antigen or granulocyte specific antibody. Treatment is supportive with the mechanical ventilation and IV fluid for hypotension
- Diuretic worsens the situation.

Transfusion Transmitted Infections (TTIs)

These are infections transmitted by blood from donor to recipient. The incidence has decreased dramatically due to advanced technology and strict laws. The common TTIS are human immunodeficiency virus (HIV), hepatitis B, hepatitis C, West Nile virus, malaria, etc.

Infecctivity of Blood

- Hepatitis: 90% of all cases are probably hepatitis C. About 70% are anicteric, but of which, about 75% of anicteric cases may result in subclinical disease. About 40% preceding cases may have chronic hepatitis. A 0.5% patients die due to fulminant hepatitis. Thirty percent of those with chronic disease results in chronic persistent hepatitis.
- Acquired immunodeficiency syndrome: Transmission of HIV is a real threat as blood banks only do enzyme-linked immunosorbent assay testing of blood which detects only antibodies. There is a long window-period before antibodies develop and this is where the blood is most infectious.
- Human T-cell leukemia virus (HTLV) type 1: It can be transmitted by BTs and has been associated with adult T-cell leukemia and progressive myelopathy.
- Cytomegalovirus (CMV): Asymptomatic chronic infection with CMV can occur. It can cause infectious mononucleosis like picture.
- Other infections like malaria, syphilis, Yersinia enterocolitica, etc. can be transmitted.

Fresh Blood

It refers to the blood that is administered within 24 hours of its donation. But blood unit kept at 4°C for 4 hours is no longer “fresh” and storage results in loss of different constituents because of need for different storage temperatures for different constituents.

Besides, there is an increased risk of disease transmission of intracellular pathogens (CMV, HTLV) which survive in leukocyte in fresh blood.

Increased chances of syphilis transmission are there because Treponema cannot survive for more than 96 hours in stored blood.

Malaria transmission is also more as malarial parasite cannot survive for more than 72 hours in stored blood.

Fresh blood is therefore rarely indicated and is a poor source of platelets and factor VIII.

BLOOD COMPONENT THERAPY

Packed Red Blood Cells

It is a general thumb rule now that losses less than 2,500 mL/70 kg should be given packed cells, while blood loss greater than 2,500 mL/70 kg should be given whole blood. Whole blood should be only used in cases of severe hemorrhage where intravascular volume is to be replaced. Otherwise, packed cells are to be used so as to retain plasma and components for component therapy (Table 1).

Platelet Concentrates

Platelet concentrates are prepared by differential centrifugation. If platelets are stored at room temperature, they can be used till 5 days after collection with constant and gentle agitation.

Indications for use:
- Immune thrombocytopenia, after massive BTs, prophylactically after cardiopulmonary bypass
- Thrombocytopenia of less than 20,000 cells/mm² or clinical signs of bleeding require BT
- Platelet transfusion should be ABO compatible. One platelet transfusion usually increases platelet count by 5,000–10,000/µL.
- It is preferred that donor platelet are compatible with recipient RBC
- However, ABO incompatible platelets can be transfused as platelet have shorter life span

Table 1: Whole blood (WB) versus packed red blood cells (PRBC)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>WB</th>
<th>PRBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume</td>
<td>350–450 mL</td>
<td>200–240 mL</td>
</tr>
<tr>
<td>Increment in Hb</td>
<td>1–1.5 g/dL</td>
<td>1–1.5 g/dL</td>
</tr>
<tr>
<td>Red cell mass/mL</td>
<td>Same as PRBC</td>
<td>Same as WB</td>
</tr>
<tr>
<td>Viable platelets</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Labile factors</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Plasma citrate</td>
<td>++++</td>
<td>+</td>
</tr>
<tr>
<td>Allergic reactions</td>
<td>++++</td>
<td>+</td>
</tr>
<tr>
<td>FNHTR</td>
<td>++++</td>
<td>+</td>
</tr>
<tr>
<td>Risk of TTI</td>
<td>++++</td>
<td>+</td>
</tr>
<tr>
<td>Waste of components</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

Abbreviations: Hb, hemoglobin; FNHTR, febrile nonhemolytic transfusion reaction; TTI, transfusion transmitted infections
Rh incompatibility should always be considered in obstetric population
- Administer anti-D immunoglobulin, if Rh-positive platelet are administered to Rh-negative individual
- Most often associated with risk of bacterial contamination.

**Fresh Frozen Plasma**

Fresh frozen plasma (FFP) is stored at –18°C to –30°C. It must be thawed before administration which takes 20–30 minutes. Once thawed, should be used in 6 hours. Dosis 10–15 mL/kg, usually 3–4 units are required.

It is prepared at the time that blood is obtained from a donor. It contains all the plasma proteins particularly factor V and VIII which gradually decline during the storage of blood. It carries all the risks of BT.

Indications for FFP transfusion:
1. Replacement of isolated factor deficiencies
2. Reversal of warfarin effect
3. In antithrombin III deficiency
4. Immunodeficiencies
5. Thrombotic thrombocytopenic purpura
6. Massive BT
7. Requirements for indications 1 and 6 would be a prothrombin and partial thromboplastin time at least 1.5 times normal or prothrombin time greater than 21 second.

**Cryoprecipitate**

It is extracted from slowly thawing FFP. Cryoprecipitate contains significant levels of factor VIII, fibrinogen, von Willebrand factor and fibronectin. It is frequently administered as ABO compatible; however, this probably is not very important since the concentration of antibodies is very low. Paradoxical bleeding has been described after cryoprecipitate transfusion which means bleeding persists even after adequate levels of factor VIII. This is because it also contains fibrinogen so that if the hemophiliac is transfused with enough cryoprecipitate, serum fibrinogen levels may also rise increasing the risk of bleeding. Dose required is 10 packs or one pack per 10 kg. Aim is to restore fibrinogen level to greater than 100 mg/dL.

**Prothrombin Complex**

Factor IX can be recovered from plasma or plasma fractions by absorption with ion exchanges or inorganic chemicals.

Main indication for this product is treatment of factor IX deficiency or hemophilia B.

**Single Donor Plasma**

Single donor plasma is very effective as volume expander. It is removed from stored blood without any effort being made to preserve coagulation factors. All precautions of FFP administration should be followed.

**Table 2: Blood storage**

<table>
<thead>
<tr>
<th>Blood products</th>
<th>Storage</th>
<th>Shelf life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red cells</td>
<td>2–6°C</td>
<td>35 days</td>
</tr>
<tr>
<td>Frozen red cells</td>
<td>2–6°C</td>
<td>24 days</td>
</tr>
<tr>
<td>Washed red cells</td>
<td>2–6°C</td>
<td>6 days</td>
</tr>
<tr>
<td>Platelet concentrate</td>
<td>Room temperature</td>
<td>5 days</td>
</tr>
<tr>
<td>Fresh frozen plasma</td>
<td>–20 to –40°C</td>
<td>12 months</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
<td>–20 to –40°C</td>
<td>12 months</td>
</tr>
<tr>
<td>Granulocyte concentrate</td>
<td>Room temperature</td>
<td>24 hours</td>
</tr>
</tbody>
</table>

**INFORMED CONSENT**

Informed consent should be taken before BT as compensations have been awarded for complications of BT where consent for transfusion has not been taken.

**National AIDS Control Organization Guidelines for Transfusion of Blood and Components**

- Informed written consent
- Identification of recipient, donor, attach compatibility report
- Set transfusion-medical, 0, 5, 15, 30 and 60 months
- Optimum temperature, use blood warming device for massive BT
- Sterile, disposable transfusion set with filter
- Give no medication except 9% sodium chloride injection
- PRBC should take no longer than 4 hours
- Use FFP immediately after thawing, never after 6 hours.

**NEWER REPLACEMENT OF BLOOD—RED BLOOD CELL SUBSTITUTE**

- Perfluorochemical—only approved substitute
- Flussol—removed from market
- Oxygant—second generation perfluorochemical that was suspended from phase III studies
- Liposome encapsulated hemoglobin—not proven efficacy
- Hemoglobin based oxygen carrier—dangerous.
BIBLIOGRAPHY

How to Answer Questions in Theory and Viva in Postgraduate Examination?

DEFINITION
There is significant change in the pattern of examinations in medical subjects in general and postgraduate examinations in particular. The author was an examinee and also an examiner in various universities in India for more than 50 years. I am a witness to these changing trends. Postgraduate examination till the 1980s was a more subjective evaluation and examiner’s word was final. All papers related to marking were destroyed and only the final result sheet was submitted to the university. There was hardly any scope for verification. The students used to accept the verdict of the examiner’s. The spectrum of postgraduate examination has changed over the last 2 decades. It is trying to be more objective and transparent. The records are not destroyed. The students have become more vocal and often challenge the examiner’s verdict or ask for reassessment. You have to use not only your academic knowledge but it is developing into “an art” to give answers in theory and viva examinations. It is true that knowledge is the primary requirement for passing an examination. However, the way you present your knowledge in theory and viva makes the difference. There are students whose knowledge is very good but they are not able to exhibit their knowledge well. In contrast, some students who have some basic knowledge but have better way of presentation may do better in the examination. There are several myths and misconceptions about-facing postgraduate examination (Table 1). I would like to discuss approach to theory and viva separately.

Table 1: Myths and misconceptions about postgraduate examination

- Write long answers to give impression that you know a lot
- Write in poor handwriting so that examiner cannot read
- Fill more supplementaries writing irrelevant things
- Writing God’s name or some religious words in the answer book
- Write request notes to examiner saying you are poor or have failed 2–3 times

MYTHS AND MISCONCEPTIONS ABOUT POSTGRADUATE EXAMINATION
There are several myths and misconceptions among students facing postgraduate examination. Some students feel that writing long answers in illegible handwriting so that examiner may not be able to read the answers, marks may be given according to the number of pages in answer books. This is not true. Examiners get annoyed if your handwritings are not readable. Writing unnecessary items to increase the number of supplementaries is not appreciated.

Some students have the habit of writing God’s names in the answer book. Though it may not annoy the examiner, it does not help. Examiners do not give more marks to those who write such names. Some students write a personal note to the examiner saying that “This is their third or fourth attempt and so they may be liberal”. Please never do this. It does not please the examiner. Such myths and misconceptions should not be entertained.
HOW TO WRITE ANSWERS IN THEORY?

The students and the teachers, till a few years ago, used to pay less attention to theory papers while evaluating the candidate. Since the examiners in theory and viva were the same, adjustment in evaluation was possible. If the student has done very well in viva but not so well in theory, examiners used to take a liberal view. Now the situation has changed. There are separate examiners for theory and viva in most universities. Therefore, adjustment in marking is not possible. It is necessary to pass in theory and viva separately. Moreover, it is mandatory to pass in theory examination before being allowed to face the viva. The National Academy of Medical Sciences permits only those candidates to appear for viva who have passed in theory examination. Therefore, do not underestimate the theory examination. Give equal importance to viva and theory examination. There are about 4–5 questions in theory paper and mostly, all questions carry equal marks. Therefore, one should plan to write answers in such a way that all questions could be answered in the time schedule. There is no sense in giving more time to one question at the cost of other questions because you cannot get marks more than the maximum allotted to the question. On the contrary, if you write incomplete answers to other questions for want of time, you lose in marking.

First read the whole question paper and select the question that is to your liking. Do not start scribbling immediately. You do not have to answer the questions in the same sequence as in the question paper. Select the questions that you know most and start answering that question. Leave half an hour for going through the entire answer sheet to find out if you have missed any important point. This would also give you an opportunity to correct some mistake. Plan the answer in format before answering. It is good to write the plan of answer giving salient points. This would allow you to mention all relevant points. Moreover, in case you could not write complete answer, the examiner would know from the preface what points you wanted to cover.

The preface should cover introduction, titles of points you wish to cover and conclusion. Your handwritings should be readable. If your handwriting is not readable, examiner will not give credit. On the contrary, he may give fewer marks. Do not write long answers. Cover only relevant points. Be brief and to the point. Do not write what is not asked because you do not get any credit for writing unnecessary points. The examiner gets disturbed if the answer covers irrelevant points. If the question is “Give detailed management of PPH”, you do not have to write about etiology or clinical features. You may touch on those points that are relevant to management. It may look nice if you can draw a diagram or picture of relevant items.

If advantages and disadvantages of a particular mode of treatment are asked, you may make two columns and enumerate advantages and disadvantages in relevant columns. If you know that differences of opinion exist on a particular point, be guarded in answering. It is good to mention both the debatable points. This will give an impression to the examiner that you know that controversy exists.

There are questions of “write short notes”. In such questions, you do not have to write an essay. Be brief and write only relevant points. If etiology is asked, write about etiology only. If management is asked, stick to management only. Short notes as the name suggest, should be short and brief. Some universities have a paper on “essay”. You have to write full answer on only the topic of the essay. You should give summary of the entire essay in the beginning. It should be in 10–15 lines. This will enable the examiner to know what you are going to write in the paper. Do not write anything about which you are not sure. Writing incorrect answer has a negative impact on the examiner.

Table 2: Do’s and don’ts in theory paper

<table>
<thead>
<tr>
<th>Do’s</th>
<th>don’ts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Write to the point. Be brief. Do not write about items not asked.</td>
<td>Do not write any religious slogans or personal note to the examiner.</td>
</tr>
<tr>
<td>Write in good handwriting so that examiner can read without difficulty.</td>
<td>First read all the questions and then select which one you want to answer first.</td>
</tr>
<tr>
<td>Keep margin in the answer book.</td>
<td>Allot time limit for each question.</td>
</tr>
<tr>
<td>Draw diagram or picture when appropriate.</td>
<td>Give outline of the answer in 8–10 sentences giving points you wish to cover.</td>
</tr>
<tr>
<td>Write to the point. Be brief. Do not write about items not asked.</td>
<td>Write only relevant points.</td>
</tr>
<tr>
<td>Quote correct references when indicated.</td>
<td>Do not write any religious slogans or personal note to the examiner.</td>
</tr>
</tbody>
</table>

HOW TO FACE THE VIVA?

You are facing the examiner directly in the viva. Therefore your looks, your dress, your ability to communicate is as important as the correct answer. Examiners are after all human beings and they have their own likes and dislikes and also their idiosyncrasies. Some examiners want to test how you face “provocation”. Examiner may want to find out how you face “stress”. Therefore remain “cool”. Do not loose your presence of mind. Do not provoke the examiner. If your answer is different from the expectation of the examiner, you must be able to quote reference to prove your point. Do not be dogmatic. Remember, most examiners are supportive and may guide you or may give a hint so that you may pass.

Have a good sleep the previous night. Be well-dressed and well-groomed. You must look fresh and presentable. Greet the examiners saying “good morning” or ‘good afternoon’
depending on the time of the day. Some students face the viva under tension—hair not properly combed, dress not suitable for examination. Some students want sympathy from the examiners and if they have failed previously, they write on the apron ‘second attempt’ or ‘third attempt’. This should not be done. Rely on your own abilities rather than the mercy of the examiner.

Some students prefer to visit on the previous day the room where viva is going to be conducted. The purpose of the visit is to know the instruments, specimens and the patients who are likely to be kept in the viva test. The registrar or the tutor briefs the students about the specimens, instruments and the patients. They are also briefed about the whims of the examiners. I am not sure if it is helpful. Examiners are smart. They may bring new patients from the OPD. You may thus be misguided. Therefore, rely on your own findings and your knowledge.

The houseman/registrar had told one student facing the viva that it is a case of vertex presentation. The student found on examination that it was a breech presentation. However, the student thought that registrar is more reliable and presented the case as “vertex”. Examiners were not pleased. Therefore, have faith in your clinical examination and have courage of conviction. You must be brief while presenting the case. You should not miss any relevant point. Try to anticipate the questions that could be asked when you are waiting for your turn.

Some examiners (usually at the fag end of the day) have a habit of asking “select any instrument” or “select any specimen”. Therefore you must not fumble and plan in advance what specimen/instrument you would select if asked to do so. When a specimen is shown to you, do not tell the diagnosis immediately. This will give an impression to the examiner that you have been shown the specimen beforehand by the registrar or the tutor. Describe the specimen and then say what it is. You must first give anatomical diagnosis and then give its pathology, for example, if the specimen of solid ovarian tumor is shown to you, say it is a specimen of ovary (if its anatomical landmarks exist). Then say it is a solid ovarian tumor. Then the examiner may ask “what type of solid ovarian tumor?” You can then give possible differential diagnosis. Please remember that microscopic diagnosis is not always possible by mere looking at the specimen. If you make mistake after selecting a specimen/instrument, it will have adverse effect on the examiner. Do not be vague while answering questions. There is a story of an Indian student facing viva test in UK. The examiner asked “Tell me yes or no whether this patient has mitral valve disease?” Indian student after a minute’s pause replied, “Perhaps”. If you have made a mistake, promptly correct it. If you do not know the correct answer, you may ask for change of topic. Give answer to the questions in a simple correct English. Think well before opening your mouth. You must have courage of conviction. Do not make a blank face to the examiner.

When the viva is over, say “Thank you” to the examiner and leave with grace and smile (Table 3).
WHY DO WE PUBLISH A PAPER?

The aim of research in medicine is to improve patient care. This is only possible if the findings of your research are publicized either by a verbal presentation at a conference or by publishing in a scientific journal. The reach of a journal is far wider than that of a conference. Add to this the fact that a printed word lasts much longer than a spoken word. Hence, it becomes obligatory for a researcher to publish the findings of his research in a reputed journal. Also it is your moral obligation to fund providers and to those participating in your study. Needless to say that the publication of your study enhances your reputation and professional standing and advances your career by facilitating promotions. It is normally expected from everybody holding an academic position that he does research which gets published. Not doing so usually goes against him and affects his future. He must publish or perish.

SCIENCE OF WRITING OF A PAPER

It is important to understand that writing of a scientific paper is mainly a science.

Artistic, literary, decorative and flowery language has little scope in a scientific journal though in medical books and monographs it could be judiciously used. Journalistic language may be occasionally used by you to attract the reader and not to baffle him by bombastic confounding words. It must be recognized that publishing a medical journal is very expensive and the editors have no space for any superfluous, repetitive and decorative word or sentences. Basically a medical journal need to be more reader oriented than author oriented. The readers subscribe to the journal and hence are consumers. Being clinicians and scientists they are hard up for time.

The author must convey to the readers his research in unambiguous, clear and compact language without beating around the bush. This requires expertise acquired by experience. Junior authors should write, revise, rewrite and re-revise their manuscript. They should get their colleagues and juniors read the manuscript to find out whether their presentation is clearly and correctly understood by them. They should also take help of the seniors to improve their manuscript.

Before beginning to write, the author must carefully study the instructions to the contributors printed in the relevant journal and follow them very meticulously. Unfortunately, many authors fail to do so. Although they are not blinded they remain blind to the instructions. They either do not read them or do not follow them. Every journal has its specific requirements and style. The authors must diligently comply with these. Such variations apart most medical journals follow a more or less standard format for research papers. This format consist of:

1. Title
2. Capsule
3. Authorship
4. Abstract, usually structured
5. Keywords
6. Body or text of the paper known by the acronym of IMRAD and consisting of—
   I—Introduction: Why was the study done?
   M—Methods: How was the study done?
   R—Results: What was found in the study?
   A—And
   D—Discussion: What do the findings imply?
7. Conclusion
8. Acknowledgments
9. Reference list and
10. Conflicts of interests or vested interests.
Title

The title of an article must comprehensively inform the reader what the article is about.

It must be short but adequate. It must be specific but relevant. It must be easy to grasp.

Do not use any abbreviations. Do not dramatize. You can make it catchy but make sure that it is accurate.

Authorship

Who should deserve and get the authorship of a paper is an issue difficult to decide. The International Committee of Medical Journal Editors (ICMJE) often called the Vancouver group laid down the following criteria of substantial contribution to the research study to merit authorship:

• Conception and design of the study.
• Analysis and interpretation of data.
• Drafting the article or revising it critically for important intellectual content.
• Final approval of the paper sent for publication.

The Lancet and British Medical Journal (BMJ) abandoned the concept of authorship and replaced it by the concept of contributorship. No one is credited as author of a paper but contributors are cited at the end of the paper listing their contribution to the study and to the writing of the paper, e.g. carrying out or conducting or executing the trial, doing data management and analysis interpreting the data, writing and revising the paper, shouldering the responsibility for integrity of the study and guaranteeing the same.

The crucial issue in authorship is gift authorship or ghost authorship which implies crediting the authorship to somebody who had made no contribution at all to the study. ICMJE lists the following as not deserving authorship:

• Obtaining funds for the study
• Collection of data
• General supervision of the data.

It must be added that granting permission for the study, allowing the use of instruments or equipment, encouraging the study, giving technical help, and merely being the Head of the Department, do not justify authorship. Irrespective of any guidelines, the ground reality is that gift authorship cannot be easily abolished. Exploitation of a junior research worker by the person he is working under and is dependent on for crucial benefits is still prevalent.

This apart, if including undeservingly an important name in the authorship credit facilitates acceptance of a paper by the journal, the junior researcher would happily do it. It is ideal to define everybody’s role and responsibility in a research project and the credit to be given to each of them—authorship, contributorship, acknowledgment—before the study begins. This is very often difficult to implement in Indian scenario.

Capsule

Not all journals publish a capsule which is to be printed under the title of the article in the table of contents. Publishing a capsule is very reader friendly since he gets essential information about the papers published in the journal at a glance. Capsule is not the same thing as the conclusion. The capsule is meant to convey to the reader the essence of your research study in a nutshell, usually in just a sentence or two.

Institutional Affiliation

You must mention the academic position of each author at the institution or institutions at which the study was carried out.

Address for Correspondence

You must give the name, complete postal address, telephone numbers, mobile phone number and e-mail ID of the author with whom the editor and the readers can correspond.

Abstract

This is the summary of your paper. It is printed at the beginning of the paper. It is usual to use a structured abstract for research paper. Although most journals publish structured abstract, the structure of the abstract various from journal to journal and the author must follow the policy of the relevant journal as described in the instructions to authors. The minimal segments of a structured abstract consist of Aim or Objective, Methods, Results and Conclusion. The other divisions of the structured abstract, some of which are used by different journals are—Background, Introduction, Design of the study, Settings (location of the study), Intervention, Participants or subjects, Main outcome measures, and Statistical analysis. Usually 150–250 words are permitted in the abstract.

Abstract is a very important part of your paper. Almost everyone who opens the journal he has subscribed to is bound to read the contents to know the title, authors and the capsule if any. Those who find these interesting would next go through the abstract. The abstract should tempt and stimulate the reader to read the entire paper. Hence the abstract has the great importance. It is advised that the abstract be written after writing the rest of the paper.

Keywords

These are words or phrases that help to locate the paper in various database of indexing agencies, e.g. Medical Literature Analysis and Retrieval System Online (MEDLINE), MedIND, EmBase, Springer Link, etc. They are usually printed after the abstract and before the text. About 5–6 words or short phrases are permitted. Avoid nonspecific words, long phrases, and abbreviations. It is better to use Medical Subject Headings (MeSH).
Introduction

This section basically justifies the need for undertaking the study. It summarizes in brief our current knowledge of the subject being dealt with and points out the gaps in our existing knowledge. These contentions can be supported by just two or three pertinent references. A common mistake is that many authors give a detailed history and review of the subject. This is no place to show off your scholarship. All the gaps in our knowledge need not be emphasized or discussed. Only the gaps the present study was intended to fill up need to be described. One must make sure that the readers clearly understand the purpose and importance of the study. This section of the paper must be short though strictly relevant.

Methods

Methods describe how you obtained your results. This is the most important section of your study and publication. If proper methodology is not employed, your study has hardly any value. My experience as an editor is convincing that this is a neglected area of many research studies and faulty research methodology is the most common reason for rejection of a paper sent for publication. Remember that good research results in good science which leads to better patient care. No good journal will publish poor science.

This section should describe the type of study undertaken and the hypothesis being tested. The study design should be given in detail. It should give the criteria for enrolling participants and describe the inclusion and exclusion criteria. It should justify the number of subjects studied by describing how the sample size was calculated to give adequate power to your study. Randomization procedure followed and blinding methods employed must be adequately described. Number of controls employed should be at least equal to the number of study subjects unless the condition studied is rare. The intervention carried out must be meticulously and accurately described. The relevant baseline characteristics must be properly enumerated along with the criteria employed for assessing the changes effected by the intervention. How the safety of the participants was ensured and what side effects were encountered must be properly described. Compliance by the participants and reasons for dropouts need to be adequately given. End points, both primary and secondary, must be clearly defined and strictly adhered to. You should also explain how you eliminated various biases and took care of the confounding factors. Every study involving human volunteers must be approved by the Ethics Committee. Such approval of your study must be recorded. Statistical tools used for evaluation of the data must be properly enumerated. In short the methods section should be able to convince the readers that the study was properly done and that they can trust the conclusions arrived at. Lastly, it is important that this section gives all necessary information to a reader who desires to replicate the study exactly the way you did your study.

Results

This is the easiest section to write. In this you describe your findings without interpreting them or indulging in any discussion. Besides the text you can resort to tables, charts, graphs and figures. But make sure that data given in the text is not repeated in tables, graphs or figures and vice versa. Pertinent statistical analysis of the data can be justifiably given, but do not discuss the rationale of the tools statistical employed which can be done in the discussion section. Remember that your results confirm or reject your hypothesis but they not prove anything. You tell the results like a story in a chronological order. Describe the findings in order of their importance. Use logical headings for describing relevant findings. Each paragraph should deal with only one item. Follow the order described under methods section. There is a standardized method of presenting tables. The tables are serially numbered in the order in which they appear in the text.

Each table should have a clear explanatory title. Only three horizontal lines are used apart from partial horizontal lines for groups of subheadings when required. Vertical lines should never be used. There should be clear and appropriate column headings. Pertinent units like gm, ml, µg, etc. should be employed. All explanations including those pertaining to the abbreviations should only be given as foot notes. Each table must give complete self-contained information and should be able to stand alone not requiring the reader to refer to the text for its interpretation. All figures should follow the instructions to contributors. They should have serial numbers in the order in which they appear in the text. They should have self explaining legends. Photographs, histomicrophotographs, sonographic pictures, radiological images, etc. must comply with the requirements of the relevant journal. Histomicrophotographs must mention the staining used and the magnification employed. Graphs should have traditional x- and y-axis with proper scales carefully selected so as not to distort the data. Bar charts, pie diagrams and histograms can also be used to convey the results or data effectively. Avoid three dimensional histograms and figures as they add nothing to scientific information. No references should ever be used in the results section.

Discussion

This is the most important part of your paper. It is also the most difficult part to write. The senior most authors should shoulder the responsibility of writing it. Merely knowing your findings is not of much use to the reader. The interpretation, implication and clinical application of your findings are most important. Do not repeat your findings but merely reiterate or summarize your main findings. Discuss the extent to which the aim or objective of your study as mentioned in the introduction is achieved or fulfilled. Discuss the strengths and limitations of your study. Compare your findings with those published by earlier workers. If your findings are
in disagreement with current beliefs and practices give a plausible realistic explanation for the same. Discuss the importance of your study to clinicians, research workers, administrators and policy makers. Remember that any conclusion that you draw from your study must be based on the findings in your study. Lastly you should also mention the questions that remain unanswered and discuss the future research aimed to resolve these questions.

**Conclusion**

This is the final paragraph of the discussion. Your conclusion must be clear to the readers. They must be based on and, supported entirely by the findings of your study. Do not make political, philosophical and generalized conclusion like, if the Government would change its policy or build roads or spend more on health care, the maternal mortality would be reduced unless your study scientifically derives such a conclusion. Implication of your study as related to the present understanding of the subject should be included in the conclusion along with suggestions for the future studies.

**Acknowledgment**

In this section, the author acknowledges the help received from all those whose contribution to the study was not adequate to justify authorship. Help from head of the department or institution, technicians, assistants working under you, your colleagues, artists, statisticians, and others must be acknowledged.

**References and their Citations in the Text**

Published literature provides the justification and the basis on which your study is based. At the end of your paper you give a list of references indicating that in the published literature you have made use of them in conducting your study and in making comparative evaluation of your findings. These references need to be cited at appropriate places in the text of your paper. You must carefully study the style of citing and listing references that is followed by the journal to which you are sending your article for publication. This is given in necessary details in the instructions to contributors published by all journals in the issues of their journal. You must follow them very meticulously. Most of the journals use Vancouver style for the reference list. In this, the references are listed in the order in which they are cited in the text. Usually this is done in the text by a superscript number after the name of the author or at the end of the sentence if the author’s name is not mentioned. This superscript number is the number of that reference in the reference list. If there is a single author his surname is mentioned (e.g. Malhotra) if there are two authors their surname are mentioned (e.g. Malhotra and Gupta) and if there are more than two authors the surnames of the first author is followed by et al. (e.g. Malhotra et al.). No initials are mentioned in the text. In the reference list the references are cited in the order in which they appear in the text and are given serial numbers that appear as superscript in the text. Some journals use the number in brackets instead of giving it as superscript. In the reference list the author’s surname is followed by the initials using no punctuation marks. Where there are more than one author their names are separated by commas with a full stop after the last authors name. Most journals print the name of only three or six authors followed by et al. if the number of authors exceeds this number. This is followed by a space and the title of the article followed by a full stop. After a space, follows the name of the journal abbreviated as per the guidelines on Index Medicus. This is followed by a space without any punctuation and thereafter, the year of publication, a semicolon, the volume number, a colon, the number of the first page of the article, a small dash and the number of the last page of the article followed by a full stop. Some journals selectively use italics, bold font and number of the issue of the journal. One must strictly follow the instructions of the relevant journal. Very few journals follow the Harvard style wherein the references are listed in alphabetic order of the surname of the first author. References are cited in the text by giving in brackets the surname of the author and the year of publication.

Unpublished work is not referred to in the reference list but personal communication about the relevant unpublished work of another worker is cited in the text by giving in brackets his name and the date of such communication. References to monographs, books, chapter in multiauthor books, etc. can be cited and listed in reference list by strictly following the instructions of the journal.

The references must be recent, relevant and important ones. The number of references is restricted by most journals. Every reference must be absolutely accurate so that the reader wishing to read that reference is not driven to a time consuming frustrating, and futile hunt of that reference. It is expected that the author has gone through the references quoted by him. Second hand reference or cross references listed in other articles should never be used. This and neglecting the instructions of the relevant journal are the main reasons for inaccuracy for which no reader can pardon you.

**Conflicts of Interests or Vested Interests**

Conflicts of interest are ties with activities that could inappropriately influence judgment, whether or not the judgment is actually affected. There could be many parties interested in the publication of the paper and the favorable findings contained therein. They include providers of research funds, sponsors especially Pharmacy companies supplying funds, drugs, equipment and special personal favors or benefits—direct or indirect—to the investigators, etc. They may sponsor your participation in a conference
and/or your holidays and shower gifts on you. All such vested interests are invisible to the readers but have the potential to introduce bias into your research and hence, must be declared and revealed.

**Abbreviations**

Universally accepted abbreviations like cm, mm, HIV can be freely used. Other abbreviations when first mentioned should be given in brackets preceded by their full form. Once so described they must be subsequently used throughout, the paper ignoring their full form. Abbreviations should not be used in the title nor in the abstract. Do not invent your own abbreviations which are confusing and irritating to the readers. Some journals give a list of abbreviations that are permitted by them.

**The Finished Product and Final Checks**

When the paper is finished, it is very useful to put it aside for a few days and then re-read it—a surprising number of errors may be found! Additional comments can also be added at that stage when you return to the paper refreshed.

Always check for consistency, particularly with respect to data and headings, which should be consistent across the text, tables and figures. Also eliminate any “clutter”, e.g., repetitions and jargon. Check carefully for any aspects that may appear ambiguous and amend them accordingly.

Prior to sending the manuscript, double check that it is in accordance with the journal’s instructions. Always send an electronic version (CD/DVD) along with hard copies. The title page should contain all information as per the requirements of that journal. Also, ensure that, if you have used previously published material, you have written permission to reproduce it. If there is any way that individual patients can be identified, then either ensure that you have that individual’s written permission or the content of the paper should be modified to protect the patient’s identity.

**Revisions**

If the paper is returned to you requesting revisions, make sure these are done as quickly as possible. Think very carefully about all aspects that have been raised and discuss the appropriate way to proceed with you coauthors. When the revised manuscript is returned, always include a covering letter detailing your responses to each of the points raised by the referees. It makes it much easier for the editor to assess whether the issues raised have been addressed appropriately.

**Checking the Proofs**

When proofs are sent to the authors, they frequently have to be returned very quickly in order to fit in with the publisher’s schedule. However, even with these time constraints, always check the proofs carefully as this is your responsibility. Areas where errors can frequently occur are data tables and references, so check these carefully. Always keep a copy of the proofs for your own records.

**Rejection**

If the paper is rejected, it may be that the study had a fundamental flaw (i.e. the sample size was too small or the methodology inappropriate) or it may just be that the paper is inappropriate for that journal. The editor’s letter will usually give some indication of what applies and whether it is worth submitting elsewhere. Above all, do not be despondent at this stage, act on the referees’ reports and consider trying again.

“Making the simple complicated is commonplace; making the complicated simple, awesomely simple, that’s creativity.”

**English Language**

English is not our mother tongue. Like any other language English has its nuances and strict grammatical requirements. Position of a mere comma can radically change the meaning of a sentence as can be seen below.

- Woman, without her man, is nothing.
- Woman, without her, man is nothing.

Your paper must convey the readers precisely and unambiguously what you mean to convey. It is advisable that, unless you have necessary expertise in writing correct English, you should submit your manuscript to a professional English writer for scrutiny. Most of the journals employ a professional copy editor.

**BIBLIOGRAPHY**

INTRODUCTION

Medical ethics is inextricably entwined with everyday clinical practice, particularly in obstetrics and gynecology where issues surrounding the rights of mother and fetus, infertility, sexual health, and fertility control have a high public profile.

AUTONOMY AND THE PATIENT-DOCTOR RELATIONSHIP

This has traditionally been seen as a covenant relationship defined within a mutual, unspoken agreement between the parties that recognizes the duties and obligations each to the other. Mutual trust is at the heart of this relationship and there is no doubt that trust has been eroded by a variety of high profile medical cases over recent years. As a result, it is now being suggested that the previous implicit compact between doctors, patients and society has broken down. It is important to restore this relationship of trust between doctors and patients.

What are the obligations of the doctor in this relationship? Competence, compassion, caring and good communication are, of course, central; recognition of their autonomy means that patients must be treated with respect, be properly informed, give their consent voluntarily and without coercion and have their confidentiality fully respected. Does the patient have any reciprocal obligations? Draper and Sorell have recently considered patient’s responsibilities in medical ethics. They argue, “medical ethics is one-sided” because “it dwells on the ethical obligations of doctors to the exclusion of those of patients”. They continue, traditionally, medical ethics has asserted that, as autonomous agents, competent patients must be allowed to decide for themselves the course of their medical treatment. It is for the doctor to communicate effectively all the relevant information, assess the patient’s competence, persuade without coercing, and abide by whatever, decision the patient makes. Little or nothing is said about what kinds of decisions a patient ought to make. Indeed mainstream medical ethics implies that a competent patient’s decision is good simply by virtue of having been made by the patient. They suggest that taking responsibility for what is chosen is intrinsic to the exercise of autonomy. In practice this may be manifested in two very different ways. In the first, the very act of taking responsibility for an autonomous decision about one’s health may make it more effective. For example, a freely reached decision to stop smoking is more likely to succeed than any external attempt to ban it. On the other hand, if one freely chooses and consents to an option with a specific risk of an adverse or unwanted outcome that has been fully explained, one can have no complaint if that adverse outcome occurs despite the procedure being performed competently. For example, a woman with multiple fibroids who requests myomectomy and who is informed of a small risk that hysterectomy may be required and consents to the procedure on that basis has no cause for complaint if it does actually occur, even if the myomectomy was performed competently. Another very important issue falls within this second category, namely what is the responsibility of the individual for the effects of lifestyle on their health? This debate cannot be pursued further here but certainly needs more serious consideration than it is currently given.
The patient-doctor relationship works best when each can fully trust the other. However, it can be argued that the imbalance of power usually heavily weighted in favor of the doctor means that they have the greater responsibility to be trustworthy.

**CHOICE OF TREATMENT**

Choice implies offering options from which patients can indicate their preference including treatment. Properly informed choice and valid consent are very important in medical ethics. The best practice that expresses a proper patient-doctor relationship in which each fully respects the true autonomy of the other, typically involves:

- A full and comprehensible explanation by the doctor of the problem(s) requiring intervention.
- An authoritative statement of the benefits and risks of the various options, including doing nothing. Accessible written information should be available wherever possible.
- The doctor’s opinion on the course of action they would advise, including a second opinion if requested.
- The patient understanding the information provided.
- Time for the patient to consider the options. The appropriate length of time will vary depending on, for example, the urgency of the situation and the patient’s state of mind, need for reflection and, perhaps discussion with family members.
- A freely arrived at decision about the patient’s preferred choice, including no intervention.
- The gaining of valid consent to any procedure-based intervention. This consent should be obtained by a practitioner who fully understands the procedure and who preferably, but not necessarily, can perform it. Whether this should be verbal or written depends on the nature of the procedure.
- An unspoken covenant and trust between the doctor and patient that the latter’s wishes expressed in the consent process will be honored.
- Obligation on the part of the doctor to fill in the appropriate forms as laid down by the various acts such as Medical Termination of Pregnancy (MTP) Act, Preconception and Prenatal Diagnostic Techniques (PCPNDT) Act, etc. in a correct manner thus preserving all the information in an ethically correct manner so that it does not raise any issue of forgery in the future.

Unfortunately the very complexity of some areas in obstetrics and gynecology makes it difficult to make sure that patients have given their consent on the basis of properly informed choice. For example, some of the new developments in fertility treatment may require a basic knowledge of human biology beyond some patients. This, however, increases rather than lessens the doctor’s responsibility to impart the information in a way the patient is best able to understand.

Much greater attention is now paid to:

- The wording of consent forms (are they unnecessarily technical?)
- The areas specifically covered in the consent forms provided in the formats under various acts and laws.
- Whether or not choices have been discussed adequately with patients before signing.

Proper understanding in ethical terms choice or consent is typically a process rather than a single act. Legally, it is important to assess whether or not a person has the capacity and necessary information to make choices. Ethically it is important to be sure that the choices people make when signing a consent form really does reflect their settled will. It is also important that even when people voluntarily consent to have an elective operation (or to take part in a research project), they subsequently have the right to withdraw if they so wish. Unfortunately, emergency operations may not always allow for this.

The doctor has a duty to inform patients of all appropriate forms of treatment (including those which may not be available and why). They can then choose from those available and should be able, where appropriate, to seek transfer to where that treatment is available. The patient does not, however, have a right to any specific intervention if that would be detrimental to the rights of others. A competent patient has the legal right to refuse medical treatment or intervention and doctors should not then intervene medically, however, justified that intervention might be in medical terms. Among the areas in which this has at present been tested in obstetrics and gynecology are performing a cesarean section against the wishes of the woman involved, sterilizing a woman without her consent during an operation for other purposes and removing healthy ovaries at hysterectomy without specific consent.

**REQUESTS FOR TREATMENT**

A potential clash occurs between the individual autonomy of patient and doctor in those situations where patient requests, or even demands, a particular form of treatment and the doctor considers it to be unjustified. This can, for example, be because, in their informed opinion:

- The risk of the procedure outweighs the potential benefits
- It is medically inappropriate for that patient
- It would consume a scarce resource needed by other patients whose needs have a higher priority.

Among the possible examples are some requests for elective cesarean section or some novel forms of fertility treatment. It can also apply when the patient is requesting an intervention to which the doctor has a moral objection, for example, termination of pregnancy on the basis of sex selection.
Of the above criteria, the first two are more easily ethically justified than the third. In the first two, the doctor is acting on their informed view of the patient’s best interests. The third is much more difficult to justify and enters the problematic area of rationing and priorities.

Exercise by doctors of their clinical judgment is frequently attacked as “paternalism”. While, in some instances, this could be so but it is also the doctor fulfilling their duty to the patient by exercising their autonomy and, as such, is entirely justified. Indeed, there will be some occasions in which acquiescence to a requested intervention against one’s clinical judgment will be abrogation of one’s duty as a doctor.

Another vital issue in today’s day and age is treating a human immunodeficiency virus (HIV) positive female. It would be unethical to refuse treatment to such a patient merely because she is HIV positive. The ideal protocol to be adopted in such cases is treat her with the doctor’s capacity and thereafter referring her for counseling to prevention of parent-to-child transmission (PPTCT) center, which will guide her accordingly. She could follow-up with the doctor on daily basis for routine checkup and visit the center at less frequent intervals and in cases of emergency.

The Key to Good Doctoring is not Regulation, But the Ability to Put Ourselves in Our Patients’ Shoes

The crucial distinction is between thought and action. We aim, as far as possible, to be pure in word and deed, but we can allow ourselves to be as ugly as we like in thought. The more aware we are of our reactions to a patient however, bizarre, irrelevant, or unprofessional these may seem the less likely we are to use the power imbalance between us to act in untoward ways. When bad things happen between doctors and patients it is usually due to a confluence of the unconscious needs of both. If the lonely doctor had been aware of and been able to articulate the extent of his sexual fantasies he would have been far less likely to end up in bed with his sexually abused and depressed patient. We often find that a few minutes irreverent moaning about patients with colleagues before a ward round leads to better and more compassionate consultations.

The feelings a doctor has, or actions he or she carries out in relation to patients, are often a manifestation of the patient’s inner world, via a mental mechanism known as “projective identification”. If a doctor is bored with a patient, this may be because the patient is feeling dull or uninteresting or is angry about something but cannot express the anger. Excessive worry about a patient may be the result of being infected by the patient’s anxiety but out of proportion to the objective situation.

Although these are undoubtedly useful, most doctors consciously subscribe to them anyway, and the question of why bad or harmful practice continues remains unanswered. I believe this is because, like all human beings, we are less coherent than we like to think, and are motivated by forces of which we are unaware as much as by the conscious wish to heal and do a good job. Ultimately, the key to good doctoring is not regulation, but the ability to put ourselves in our patients’ shoes to imagine what it might be like to be on the receiving end of our treatment. There are many ways to acquire this capacity for reflexive practice: Role play, listening to users’ perspectives, being a patient (through illness or through therapy or counseling). “Balint” groups, widely used in general practice, attempt to explore doctors’ feelings about their patients through facilitated case discussion. I believe that all doctors should attend Balint-type groups in their training.

The search for the good doctor is an illusion our unconscious minds will make sure of that. The psychoanalyst Donald Winnicott reassured mothers that to be “good enough” was preferable to striving to be ideal. Mothers who are good enough provide children with the opportunity to learn to cope effectively with disappointment and failure in the context of love. Similarly, if we can without complacency bring our good and bad parts together to become a good enough doctor, we should be content. More importantly, so will our patients be, despite sometimes feeling let down by us.

**BIBLIOGRAPHY**

4. Gillick v West Norfolk and Wisbech Area Health Authority (1985) 3 All ER 402 (HL).
INTRODUCTION
India is a unique country. It has the best brains in the world and at the same time tops in cultural taboos. Health scenario is no exception to this paradox. How else can we explain the literacy rate of over 60% against health illiteracy to the tune of 90%, demonstrated by the lack of awareness of basic health parameters like height-weight-hemoglobin%? The same paradoxical situation prevails in the domain of health care providers. Clients by and large do not differentiate between qualified and unqualified health care providers. A lady doctor for all practical purposes is an obstetrician. Added to this is the confusion created in the minds of the clients by different “pathies” in India.

Federation of Obstetrics and Gynecological Societies of India (FOGSI) is the world’s largest professional body of obstetricians and gynecologists. However, it has not yet applied its mind toward making itself synonymous with “woman’s care”. India is a hugely diversified country and yet marketers have been able to make a particular product, for example, Colgate synonymous with dental care. The aim of this chapter is to look at the making of FOGSI as a brand for woman’s health. Any woman facing a health problem should think of approaching a FOGSI member to begin with. A better end point could be college students approaching FOGSI member before she is faced with a health problem.

MEMBER BENEFITS
Federation of Obstetrics and Gynecological Societies of India is strong and active in academics, trainings and social work.

Along with these strengths, what member’s need is a unique identity. This identity will ensure that client’s will consult a FOGSI member whenever, any woman across the country has a health problem. The community will look at FOGSI societies to provide health promotion services. The Government will consult FOGSI on all health-related matters. The membership will increase and it will have a multiplier effect.

BRANDING BASICS
Successful branding is about promoting your strengths. FOGSI’s strength is member qualification. FOGSI and individual societies must ensure that this strength is highlighted and the clients understand, how being treated by a qualified member will benefit them. Let us also build on the preventive medicine platform through adolescent health, height-weight-Hb–blood group initiatives. In fact, FOGSI is already doing this in a big way.

The American Marketing Association (AMA) defines a brand as a name, term, sign, symbol or design, or a combination of them intended to identify the goods and services of one seller or group of sellers and to differentiate them from those of other sellers.

Therefore, it makes sense to understand that branding is not about getting your target market to choose you over the competition, but it is about getting your prospects to see you as the only one that provides a solution to their problem.

The objectives that a good brand will achieve include:
- Delivery of the message clearly
- Confirmation of your credibility
- Connecting to your target prospects emotionally
• Motivation of the buyer
• Concrete user loyalty

A brand resides within the hearts and minds of customers, clients and prospects. It is the sum total of their experiences and perceptions. Brands give potential clients a firm idea of what to expect beforehand, making the consultation decision easier. And existing customers trust strong brands because they know what to expect.

**What Customers Want?**

• Safety
• Reliability
• Reasonable charges
• Transparency
• Punctuality

We do this by integrating our brand strength—member qualification—at every point of public contact. Members will need to be consistent in service and every other point of contact clients have with you, for example, phone calls, letters, faxes, etc.

**Brand Building**

Federation of Obstetrics and Gynecological Societies of India has to decide on the basic framework of brand building. Then FOGSI’s role will be to guide the member societies to galvanize all its 22,000 plus members into action. FOGSI should organize one mega event every year to reinforce the brand. This type of activity is being undertaken by individual societies, FOGSI and society committees already. Safe motherhood cycle rallies since 1998 and the Suprabha Ganga Yatra have been major efforts towards this end. These have to be uniform with a common message:

- For safe delivery—Consult a FOGSI member!
- Once FOGSI has defined its brand values and client’s needs, we can start to build our brand by consistently communicating our brand values.
- Remember that every possible contact, we have with a customer or potential customer needs to reinforce our brand values.

**Key Areas to Consider**

• Any slogan we use
• Our logo
• FOGSI website—which can probably be the best opportunity to reach out to people.

If all these are consistently in line with our brand values, our brand will be strengthened. But if all of them are not in line, our brand could be seriously damaged. A brand makes promises to customers and if they are not fulfilled, our customers will be far less likely to buy again.

**Time Frame**

Federation of Obstetrics and Gynecological Societies of India (FOGSI) has to give brand building exercise a minimum of 2–4 years for the initial impact. This will have to be a permanent activity later on. This would include time taken for generating the brand, utilizing it to the fullest and getting a feedback on what impact it has made on the general public.

**Managing and Reviewing Brand**

It is a good idea to get a committee to take responsibility for our brand. Keep members/societies involved by setting up a suggestion scheme, or regularly taking the time to discuss brand and how our client load is behaving. Continually reinforce the message that what we do is important. And make sure they know that breaking the promises to customers that your brand makes—even just once—can damage the brand and client load.

A successful brand can have a long life, provided it is kept up-to-date and in line with customers’ needs and expectations.

**Budgeting for a Brand**

Creating and managing a brand can cost you as little or as much as you want it to. The cost of your time to set it up and to manage it is the only area of expenditure that is guaranteed. But it is a good idea to set a budget, otherwise, it is easy to spend money unnecessarily. A budget will focus the mind and force you to prioritize your spending on your branding effort.

The key areas you could budget for are:

• Design needs, such as a logo, signage, business stationery or product packaging
• Your advertising.

**Well Begun is Half Done**

Pune Obstetrics and Gynecological Society (POGS) has made a beginning and the experience will provide the necessary inputs.

The key features are:

• Each member contributes ₹1,000/- for brand building activity.
• Printing member directory in local language—areawise, for free distribution amongst the general population. The directory will highlight why woman should consult a POGS member in first 8–10 pages.
FOGSI as a Brand for Woman’s Health

• Printing and distribution of cards with a clear message:
  - For safe delivery—consult a POGS member!
  - These cards will be distributed at temples and other religious places where people gather in large numbers.
• Insurance companies—reimbursement of bills for obstetrics and gynecology problems to be given only if treatment is provided by POGS member.
• All schools and colleges will be provided with a board for display which says—“For any query about height-weight-Hb, consult a POGS member”.

• In lessons on woman’s health in textbooks—a line to be added “Consult a POGS member for any query relate to woman’s health”.

To conclude, in today’s competitive world, the generation next believes in brands. Anything that is branded attracts people and they believe that it is the best thing available. It is time that FOGSI changes itself into a brand and one day FOGSI would be considered standard in woman’s health care. Thus, FOGSI as a brand for woman’s health has an exciting future.
 Doctors’ Liability Under Consumer Protection Act and Preventive Steps to Avoid Litigation

The classical concept of doctor-patient relationship born in the earlier years of family physicians has undergone a drastic change in this materialistic world where doctors are treated as service providers and patients as consumers under the Consumer Protection Act. It is unfortunate to put the medical professional service providers under the same consumer laws and courts who deal with faulty pressure cookers and substandard air conditioners.

A doctor is definitely not making pressure cookers and air conditioners of his patients, as the human body’s complexities and response to drugs and stress are still not fully understood.

The medical professional is answerable to the patient and the law if he/she is negligent in performing his/her duty.

This chapter deals with the Doctor’s liability under Consumer Protection Act and Preventive Steps to avoid litigation and its outcome with important Do’s and Don’ts for the doctors.

CONSUMER PROTECTION ACT, 1986

General

This Act is enacted to provide better protection of the interests of the consumers and for the establishment of consumer councils for settlement of consumer’s disputes.

Application

It is applicable to all goods and services unless otherwise expressly provided by the central government by notification.

Consumer

Any person who buys any good or avails/hires any service against consideration, which has been paid/promised/under system of deferred payment is a consumer.

Deficiency

Any fault, imperfection, shortcoming, inadequacy in the quality, nature and performance of a service which is required to be maintained under law or has been undertaken by the opposite party to be performed under a contract.

Medical Service

Services rendered by doctors and hospitals which comes in the purview of personal service has been held by courts to be within the jurisdiction of the Act. In India, there are several kinds of medical Pathies in vogue, i.e. Allopathy, Homeopathy, Ayurvedic, Unani, Acupuncture, Electropathy,
Acupressure, Naturopathy, Hydrotherapy, etc. and they all provide services to the consumer and come under the Act.

**Reliefs**
The court may direct the complainant the following:
- To remove the defect
- To replace the goods with new goods
- To return to the complainant the price paid by him
- To pay compensation to the consumers for any loss/injury suffered by him due to negligence of the opposite party
- To remove the defects on deficiencies in the service in question
- To discontinue unfair trade practice/restrictive trade practice/not to repeat it
- Not to offer/withdraw hazardous goods for sale
- To provide for adequate cost to the parties.

**Rights of Consumer as Patients**
- The right to be protected against marketing of goods and services, which are hazardous to life and property
- The right to be informed about the quality, quantity, potency, purity, standards and price of goods and services to protect against unfair trade practices
- The right to be heard and receive due consideration at appropriate forums
- The right to seek redressal against unfair trade practices
- The right to consumer education.

**Consumer Agencies**
- For speedy, inexpensive and simple quasi-judicial machinery of redressal agencies to adjudicate consumer complaints have been set-up at the district, state and national levels.
- These bodies decide disputes keeping in mind
- The basic principles of natural justice and have power to grant certain reliefs as provided in the Act.

**Power of Consumer Agencies**
They are vested with same powers as in a Civil Court under the Code of Civil Procedure 1908. The details of the agencies are given in Table 1.

**Who can File a Complaint?**
- Consumer (patient/purchaser)
- Registered consumer organization
- Central/State government
- One or more consumers together
- In case of death of consumer his legal heir or representative.

**Basis of the Complaint**
- Deficiency in service (treatment)
- Misrepresentation about the type, quality and standard of service
- False claim that the service/treatment is recognized by some institution or government.

**Time Limit**
It specifically provides that the District Forum, State Commission or the National Commission shall not admit a complaint unless it is filed within 2 years, from the date on which the cause of action has arisen.

The delay maybe condoned if the complainant satisfies the Forum/Commission that he had sufficient cause for not filing that complaint within such period.

**Procedure**
Complaint can be filed on plain paper through ordinary post or in person by the patient. It must contain details of deficiency in service with proof in four copies. It bears no court fees.

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**Table 1: Details of the consumer forum agencies**

<table>
<thead>
<tr>
<th>S. No</th>
<th>Details</th>
<th>District Forum</th>
<th>State Commission</th>
<th>National Commission</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Total members</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>2.</td>
<td>Chairman</td>
<td>District Judge</td>
<td>High Court Judge</td>
<td>Supreme Court Judge</td>
</tr>
<tr>
<td>3.</td>
<td>Members</td>
<td>Social worker one female</td>
<td>Social worker one female</td>
<td>Social worker one female</td>
</tr>
<tr>
<td>4.</td>
<td>Jurisdiction</td>
<td>In district where dispute arose</td>
<td>In state where dispute arose</td>
<td>Whole of India except Jammu and Kashmir</td>
</tr>
<tr>
<td>5.</td>
<td>Amount</td>
<td>Up to 2 million</td>
<td>Up to 20 million</td>
<td>More than 10 million</td>
</tr>
<tr>
<td>6.</td>
<td>Time limit</td>
<td>Within 2 years</td>
<td>Within 2 years</td>
<td>Within 2 years</td>
</tr>
<tr>
<td>7.</td>
<td>Appeal where time limit</td>
<td>State Commission within 30 days</td>
<td>National Commission within 30 days</td>
<td>Supreme court within 30 days</td>
</tr>
</tbody>
</table>
Where to File a Complaint?

Complaints in which claim for compensation is up to 2 million is filed before District Forum within whose jurisdiction the opposite party actually and voluntarily resides/carries on business has a branch office.

Complaints in which claim of compensation is more than 2 million but less than 10 million is filed before State Commission.

Complaints in which claim of compensation is more than 10 million is filed before the National Commission.

Punishment for Noncompliance of Order of Forum or Commission

Noncompliance of any order of Forum or Commission warrants imprisonment for a term not less than 1 month, may be extended to 3 years or with fine, which shall be not less than Rs. 2,000 but may be extended to Rs. 10,000 or both.

Frivolous/Vexatious Complaints

Section 26 of CPA clearly states that any complaints found to be frivolous or vexatious shall be dismissed. Forum/Commission will apply its mind to contemplate the bona fides of allegation, to test the truth and veracity of evidence.

For such complaints an order is also passed that the complainant shall pay to the opposite party such cost not exceeding Rs. 10,000 as may be specified in the order.

Appeal

District Forum any person aggrieved by an order passed by the District Forum can file an appeal to the State Commission within a period of 30 days from the date of the order Appeal can only be filed after the appellant has deposited 50% of the amount he is required to pay in terms of the order of District Forum or Rs. 25,000 whichever is less.

State Commission

Appeal is filed to the National Commission within 30 days from the date of the order.

Appellant has to deposit 50% of the amount he is required to pay in terms of order of State Commission or Rs. 35,000, whichever is less.

National Commission

Appeal can be filed to the Supreme Court within 30 days from date of order appellant has to deposit 50% of the amount he is required to pay in terms of order of National Commission or Rs 50,000 whichever is less.

Preventive Steps to Avoid Litigation and Its Outcome

Preventive Steps

Level I: Primary prevention/protect against complaint being filed.
Level II: Secondary prevention/protect against the defendant from being held negligent.
Level III: Tertiary prevention/protect against direct financial consequence in case compensation is awarded.
Level IV: Quartic protection/protect against professional and psychological stresses.

Level I/Primary Prevention

- Behavior:
  - Commercial behavior is to be discouraged
  - Behavior of the entire team matters
  - Should be courteous and sympathetic
- Counseling:
  - All queries of the patient and attendants should be patiently heard and answered in simple language
  - Details regarding the disease, risks, complication and treatment modality must be given
  - No false guarantees should be given
  - Communication between the patient and doctor must be two way
  - Compassionate care should be provided
- Second opinion/Referral:
  - In case a doctor needs a second opinion or the attendants demand the same then the doctor should accept such demands
  - Referral to a higher center with better facilities to save the life of a patient should always be sought for after explaining the attendants the need
- Facilities/Training:
  - All the facilities available in the institute should be displayed
  - Prescription heads/sign boards should depict the true qualifications, designation training experience and facilities
  - The doctor and the staff should regularly update their knowledge, skills and facilities according to the claims made by the clinic/hospital.

Level II/Secondary Prevention

- Medical ethics:
  - Knowledge of medical ethics and laws in practice are very useful in improving practicing methods of doctors
- Grievance redressal cell
  - In very big institutions a cell can be established to tackle a potential problem of dissatisfaction on the spot.
Level II/Secondary Prevention

The keywords are:
- Exercising reasonable skill and care in diagnosis and treatment
- Proper documentation
- Legally valid consent.

Reasonable skill and care: It has three aspects with it:

Medical: Every doctor/medical establishment must exercise reasonable skill and care as expected of an average person with equivalent qualifications and experience in similar circumstances.

Social: Reasonable skill and care must be exhibited to the patient/attendants/relatives through expressions, actions and discussions on the part of the doctor.

Legal: Documentation about doctor exercising reasonable skill and care in consultation, diagnosis and treatment of the patient.

Proper documentation and record keeping: Date, time, history, positive physical findings investigations, treatment and instructions given should be mentioned.

History of drug allergies, referrals and second opinions should also be mentioned. A note of erring patients should be made, e.g. unreliable history, refusing admission, not following instructions, etc. The prognosis should be explained to the patient/attendant in simple comprehensible language and preferably in writing especially in complicated and serious cases.

Preservation of record: Record of patients should be preserved for 3 years because:
- Under CPA limitation of filing a complaint is 2 years
- Under law of tort limitation is 3 years. Legally valid consent should be taken in all the cases as and when required.

Level III/Tertiary Prevention

Professional indemnity insurance: In India, all insurance companies are nationalized and hence terms and conditions are almost identical. The following points should be kept in mind while taking a policy:
- Take a policy of a company where you know somebody as it will be easy dealing when actual need arises.
- The insurance company takes liability for “Policy Period” so pay the premium on time.
- Inform the company:
  - Change of your address of clinic/hospital
  - Attachments with other hospitals
  - Specialty in which doctor is practicing
  - Receive a notice/complaint.
- The company is not responsible for:
  - Unqualified employee
  - Claims arising from specific facilities like X-ray, USG, etc. unless mentioned in the form
- If doctor practices a specialty other than mentioned on the form
- A specific contract of 100% cure/similar is made by doctor.
- No liability will arise on part of the company in respect of:
  - Any criminal act/unlawful act
  - Service rendered under influence of intoxicants or narcotics
  - Claims arising from any condition directly/indirectly caused by HIV
  - Third party public liability
  - Use of drugs for weight reduction, cosmetic surgery, dental surgery, liability caused by use of radioactive substance
  - Other doctors using the nursing home under contract without knowledge of the company.
- The policy is void if there is a mis-statement in or if a material fact is suppressed or omitted from the proposal.

Level IV/Defending Litigation by Forming Medical Defense Societies and Strong Peer Support

The professional, social and psychological aspects of litigations and its absence can only be fought by providing a strong peer support and by formation of medical defense organizations at the district, state and national levels to:
- Assist in such situations
- Help the doctor collect literature on the subject of litigation from standard textbooks and judgments
- Get senior and experienced doctors to give their opinion about the merits of the case
- Take up cover of defense on behalf of the doctors against medical negligence. However, no attempt should be made in diagnosis and treatment to defend cases of gross negligence or glaring deviations from the accepted norms of Code of Ethics for medical professionals.

NINE Rs OF PREVENTIVE STEPS

1. Rapport: Maintain a healthy rapport and communication with the patient, attendants, fellow doctors and subordinate staff.
2. Rationale: The doctor must have in his mind the provisional diagnosis and the planned treatment and this diagnostic and therapeutic rationale must be mentioned in the medical record.
3. Record: It should be carefully prepared, complete, accurate, legible, germane, relevant, timely and generously informative.
4. Remarks: Derogatory remarks to the patient, attendants and other doctors should always be avoided. The patient’s ailment should always be kept confidential.
5. RS: A doctor should not prescribe/administer any medication without an appropriate medical indication. He should be aware of the possible side effects and
contraindications of the drugs he is using. Drug allergy histories should be documented in the records.

6. *Res ipsa Loquitur*: Situations when a layman could presume malpractice without the testimony of an expert witness, e.g. instruments left in the abdomen of a patient who undergoes laparotomy.

7. *Respect*: Doctor should always give due respect and show concern to a patient as an individual, as a human being and as a person. “A humanistic approach solves more problems, melts more hostilities and eliminates more law suits.”

8. *Results*: The patient and family should be made aware of the possible outcome of the diagnostic and therapeutic efforts.

9. *Risks*: These should always be discussed with the patient/attendants before obtaining consent to proceed.

   Physician should tell about the relevant risks involved according to the patient in question, the serious ones that may have a slight chance of occurring and the minor ones which might occur with significant frequency.

**RISK MANAGEMENT**

New mantra to avoid litigation risk management involves the development of strategies to optimize the patient well-being and to prevent or limit health risk to the patient as well as the legal risk to the caregiver.

It involves the following:

- **Identification of risk**: Risk can be identified by the history and examination of the patient and patient’s marked as “high risk” patients.
- **Risk assessment**: Assessment of individual risks must be done as:
  - Frequency of risk.
  - Cost of risk and its effect on progress of the case.
  - Under what circumstances is the likelihood of risk to increase.
- **Risk management strategies**:
  - **Avoidance**: A doctor can stop taking care of high risk cases.
  - **Prevention**: Clinical practice guidelines in the form of flow charts or ready reckoners should be provided to the staff to deal with situations and these may prevent events from occurring which could lead to adverse outcomes and thereby litigations.
  - **Transfer**: A “high risk” case may be transferred to a better-equipped center.
  - **Reduction**: A reduction in risks can be done if the doctor is aware of them, outlines a thorough investigation and takes preparatory measures to deal with them.
  - **Segregation**: In difficult and complicated cases, consultation or second opinion should be obtained and step by step treatment of complications must be undertaken.

**DO’S FOR DOCTORS**

- Mention your qualifications/training/experience/designation on the prescription. Qualification means recognized degrees/diplomas as regulated by the Indian Medical Degrees Act, 1916 as amended from time-to-time. Mention of scholarships/membership/awards, which are no qualifications, should be avoided.
- Always mention date and timing of the consultation.
- Mention age and sex of the patient. In a pediatric prescription weight of the patient must also be mentioned.
- Always put your hand on the part that the patient says is painful. Apply your stethoscope on him, even if it is for cosmetic reasons.
- Listen attentively. Look carefully. Ask questions intelligently.
- If, after completing the examination, the patient/attendant feels that something has been left out or wants something to be re-examined, oblige him.
- Always face the patient. Maintain eye contact that is comfortable to the patient. Do not stare. Some patient tolerates very little eye contact. Learn to observe out of the corner of your eyes.
- In case you have been distracted/inattentive during the history taking, ask the patient/attendant to start all over again. He will never mind it. As far as possible consultations should not be interrupted for nonurgent calls.
- Ask the patient to come back for review the next day, in case you have examined him hurriedly or if you are not sure about the diagnosis/treatment.
- Mention “diagnosis under review” or “under evaluation” until the diagnosis is finally settled.
• In complicated cases record precisely the history of illness and substantial physical finding about the patient on your prescription.
• If the patient/attending are erring on any count (history not reliable, refusing investigations, refusing admission) make a note of it or seek written refusal preferably in local language with proper witness.
• Mention the condition of patient in specific/objective terms. Avoid vague/nonspecific terminology.
• Record history of drug allergy.
• Write names of drugs clearly. Use correct dosage (by revising knowledge periodically) and mention clearly method and interval of administration. Here one must use local or sign language. Do not forget writing precautions like AST/PO/IM/IV/locally with milk/HS/OD/BD/TDS/pc/ac/locally with milk/hs, etc. in local language.
• If a drug is a poison (e.g. certain local applications), warn in writing.
• Mention additional precautions, e.g. food, rest, avoidance of certain drugs, allergens, alcohol, smoking, etc. if indicated.
• Give instructions to the patient in comprehensible terms, making sure that the patient understands both the instruction and the importance of strictly adhering to them, e.g. while prescribing a potent anti-inflammatory drug, warn that if he experiences any stomach trouble he should stop taking the drug and consult a doctor immediately.
• Mention likely side effects, and action to be taken, if they occur.
• Remember to advise in writing pathological tests/radiological tests at specified intervals for certain drugs, which require such monitoring, if such drugs are prescribed. Some examples are: Sodium valproate, carbamazepine, methotrexate and other immunosuppressives.
• Always advise the patient not to stop taking a drug suddenly which is required to be tapered before it is stopped.
• Remember major drugs interactions.
• Specifically mention review, SOS/or follow-up schedule.
• Mention if patient/attendant(s) is/are under effect of alcohol/drugs.
• In case a particular drug/equipment is not available, make a note.
• Prescription with caution during pregnancy/lactation.
• Adjust doses in case of a child/elderly patient and in renal or hepatic disorders.
• In case of chronic ailments, mention treatment to be taken immediately in case of an emergency. For example, a patient on anti-epileptic treatment should be advised to take an injection of diazepam when convulsions occur.
• In case of any deviation from care mention reasons. Mention whether prognosis explained. If necessary take a signature of patient/attendant, after explaining the prognosis in written local language.
• Mention where the patient should contact in case of your nonavailability/emergency.
• If you are not sure what disease the patient has after a thorough work-up, get a consultation. Develop a list of physician you trust and respect in each of the specialties. Nurture your relationship with them, and consult them in difficult cases.
• Whenever referring a patient, provide him with a referring note. In case of emergency/serious illness, ring up the concerned doctor in the patient’s presence. Show your concern.
• Always keep with you and refer to the latest edition of the standard textbook of your branch of medicine. Always subscribe to at least one standard journal and participate in at least two updates/conferences every year.
• Update your knowledge and skill from time-to-time. If a doctor does not keep pace with recent advances, the quality of care suffers and does not measure up to the standards of reasonable care and skill and attitude, over a period of time. Not only do they make any attempt to update themselves but also they slip downwards. Doctors may become incompetent due to other causes: age, mental illness, addiction to alcohol or drug abuse.
• Update not only your own knowledge and skill, but also that of your staff. Update the facilities and equipment according to prevailing current standards in your area.
• Preferably employ qualified assistants. If not available, impart proper training and skill at your or some appropriate center and obtain the same.
• Medication to relieve pain especially in postoperative and cancer cases must be carried out carefully.
• Always obtain a legally valid consent before undertaking a surgical/diagnostic procedure. Learn the difference between “informed persuasion” and “informed consent.” The first is legally wrong. Though at times it may be medically correct.
• It is important to screen every patient for hepatitis B/HIV infection before every surgery, blood transfusion so that false claims are not made at a later date.
• In case of medical termination of pregnancy (MTP)/sterilization, always follow the guideline issued by the Government of India.
• Before administering an injection/vaccination always check:
  - Name of the injection (a wrong injection may be given through mistake or oversight).
  - Reconfirm the route of administration.
  - If it is to be diluted, check the dilution factor (1:2, 1:4, etc.)
  - Rate of the administration (fast, slow, in drip, etc.)
  - Site of injection, e.g. anterolateral thigh (if age < 2 years), gluteal region, deltoid, etc.
  - That a disposable syringe and needle are used. If that is not possible use syringe and needle after proper sterilization.
  - In case the patient is agitated/not cooperating, restrain him properly with 1 or 2 assistants or wait until he calms
- Don’t insist on the patient to tell the history of illness or be examined in presence of others. He has a right to privacy and confidentiality.

- Routinely advice X-rays in injury to bones and joints and related diseases of bones/joints.

- Always rule out pregnancy before subjecting the uterus to X-rays.

- Always read reports carefully and interpret the results of tests/X-rays properly and make a note of it. In case of any doubts, recheck with the lab/diagnostic center.

- A patient who is undergoing labor should be attended to without any lapse.

- In a complex medical situation, a doctor would be expected to conduct more frequent and more extensive examinations, and would be expected in making his assessment to seek all ancillary assistance, e.g. by means of tests, etc.

- In all instances of “swab cases” and “instrument cases”, the surgeon incharge is generally held directly or vicariously liable for negligence. The surgeon incharge must therefore personally ensure that such mishaps do not occur.

- The period for the responsibility of the surgeon extends to and includes the postoperative care. He must, therefore, ensure proper postoperative care to the patient.

- In the case of death of the patient occurring while undergoing a surgery/diagnostic procedure, the higher hospital authorities/police authorities must be informed without loss of time. In such cases autopsy/postmortem is mandatory.

- In case the hospital/clinic claims to provide 24-hour emergency service, available of necessary equipment in working order and competent staff within reasonable time is mandatory.

- Always seek proper legal and medical advice before sending reply to the notice sent by the patient or his representative or to the complaint referred to you from a consumer court.

- Do not permit considerations of religion, nationality, race, party politics or social standing to intervene between you and your patient.

- It may not be reasonable for a doctor to assume what the patient is saying is truthful where what the patient/attendant says is clearly contradicted by the symptoms.

- Don’t smoke while examining a patient.

- Don’t examine a patient, when you are sick, exhausted, or under influence of alcohol or any intoxicating substance.

- Don’t be overconfident. Don’t look overconfident.

- Don’t prescribe a drug or indulge in a procedure if you cannot justify its indication.

- Don’t prescribe/administer a drug which is banned, e.g. analgin, oxyphenbutazone, etc.

- Don’t over-prescribe too much of the drug—too large a dose for too long.

- Don’t under prescribe—not prescribing the needed drug dose is too small, length of treatment is too short.

- Don’t prescribe multiple drugs. Such prescription, may be due to inability to form a correct diagnosis. Possibilities of drug interactions increase with polypharmacy.

- Don’t write instructions on a separate slip. Don’t allow substitutions.

- Don’t indulge in self-serving notes. A self-serving note is one in which the factual content or the general tone suggests that the writer’s principal aim was to protect himself from a subsequent complaint rather than to make a genuine record.

- Don’t adopt experimental method in treatment. If there is some rationale do it only after informed consent.

- Don’t do anything beyond your level of competence. Competence of doctors, nursing staff is defined by their qualification, training, experience and competence of a hospital/nursing home is defined by competent staff by the availability of various equipment in working order and back-up support, e.g. handling of cases of accident/emergency, severe reaction to drugs, anesthesia, etc. and availability of resuscitative equipment, etc.

- Don’t give a drug parenterally if it can be given orally. There may be some exceptions.

- When you are not sure what to do, consult your senior/specialist/colleague.

- Don’t refuse if the patient/attendants want to leave against medical advice. It is their right. Document this properly.

- Never avoid a call for help from a nurse on duty at night. In all probability a genuine emergency may be there.

- Never order an investigation unless the result is likely to help you direct the treatment or make a difference in what you tell a patient.

- Don’t allow modern diagnostic tests to substitute your clinical judgment. At best, they can only supplement it. Always analyze the cost-benefit rationale before rushing to get these tests done. In case a particular test has a high false-positive or false-negative results, explain this to the patient before getting it done.
• Never label any condition as “functional” until you have accurately ascertained that it is not due to any other cause.
• Don’t talk to an angry patient about any other subject until you understand the reason of his anger. Then take necessary time and steps to calm him down.
• Never scold attendants of a seriously or terminally ill patient.
• Don’t challenge anybody.
• Don’t refuse the patient’s right to know about diagnosis and treatment of his illness.
• Don’t withhold information; however, harsh and difficult, in seriously or terminally ill patient. It must be conveyed with compassion and gradually, if time permits. The doctors and especially their assistant must train themselves in the art of sensitive communication. It would be wise to take into confidence the family members, close relatives and friends; this would often make the acceptance easier and quicker.
• Don’t tell patient/attendant bad news until you are as certain as possible of the accuracy of the finding.
• Don’t leave at the moment of death. There is a tendency, especially on the part of senior doctors, to go away at this time when their presence and experience are most needed.
• Don’t hesitate to extend your condolences and sympathies to the bereaved persons.
• Don’t forget to provide genetic counseling to couples and parents with known family history/children having genetic abnormalities, e.g. thalassemia, hemophilia, etc.
• Don’t issue death certificates unless you have yourself verify it.
• Don’t divulge secrets you come to know during discharge of your professional duties unless there are exceptions as carved out in the Code of Medical Ethics. There are some exceptions to this general principal:
  - If the patient gives consent.
  - When it is undesirable on medical grounds to seek patient’s consent.
  - The doctor’s overriding duty to society.
  - The information is required due to legal process.
  - For the purpose of medical research, after obtaining permission from competent authority.
• Don’t deny medical care to a patient with HIV infection/AIDS. Observe all necessary precautions.
• Don’t inform that the person is infected with HIV unless confirmatory test results are received.
• Don’t issue a false medical certificate.
• Don’t give untrue, misleading or improper reports, documents, etc.
• Don’t refuse the patient’s right to examine and receive an explanation about your bill regarding the source of payment; whether or not it is reimbursed by the government or by his employer/insurance company.
• Don’t refuse the patient’s right to know about the hospital rules and regulations.
• Don’t purchase costly sophisticated equipment only for the sake of prestige. It may induce you to indulge in malpractice.
• Don’t dump hospital garbage including used disposables in the open. It is crime. It should be properly incinerated/destroyed to prevent spread of disease or reuse by unscrupulous persons.
• Don’t refuse first-aid/medical care to accident and emergency cases even if it is a medicolegal case. It is a primary duty of every doctor/hospital to provide treatment up to this/it’s true level of competence in such cases before referring them to a higher center, if required.
• Never talk loosely with your colleagues, despite intense professional rivalry. Never criticize your colleagues. The patients/attendants may incite you to say/do something. They may seek your comments on the other doctor’s treatment. There is always a polite way to set aside their comments and queries. Remember if you had seen the case from the start you would have done the same. If your colleague has made an error of judgment regarding diagnosis or treatment, you never know under what circumstances this happened.

CONCLUSION

Though, the inclusion of the medical profession in purview of CPA is gift from the West, the law makers of India fail to understand that the medical and health care system in India is different from the West as even today health and medical system is the responsibility of the state and not of the individual and is further more not insurance based.

In view of the Supreme Court affixing its seal of approval on the applicability of the Consumer Protection Act to the service provided by the medical profession it has become all the more imperative for the medical professionals to exercise a greater degree of caution while undertaking diagnosis and treatment of patients. It is, therefore, felt necessary to make the doctors aware of certain precautions, which ought to be taken. Furthermore, the doctors must be well informed of the law regarding this and also the latest amendments made in the legal procedures plus how to proceed in case a complaint is lodged against them.

It is also desirable for the patients and their attendants to observe certain norms, so that they benefit most out of the medical help sought and healthy relationship with the doctor/hospital is maintained.
SIM’S SPECULUM (FIG. 1)

**Material:** Stainless steel  
**Sterilization:** Autoclaving and boiling

**Uses**
- **Gynecologic**
  - Routine gynecological examination to visualize vagina and cervix  
  - To collect discharge from posterior fornix  
  - Hysterosalpingography (HSG)  
  - Gynecological operations.
- **Obstetric**
  - Routine per speculum examination  
  - Manual vacuum aspiration (MVA), first trimester medical termination of pregnancy (MTP)  
  - Cervical cerclage  
  - Diagnose and repair cervical tear.

SIM’S ANTERIOR VAGINAL WALL RETRACTOR (FIG. 2)

**Material:** Stainless steel  
**Sterilization:** Autoclaving and boiling

**Use**
Along with Sim’s speculum, to visualize cervix by retracting anterior vaginal wall.

DOYEN’S RETRACTOR (FIG. 3)

**Material:** Stainless steel  
**Sterilization:** Autoclaving
Uses

- Gynecologic
  - Abdominal hysterectomy
  - Wertheim’s hysterectomy
  - Tuboplasty
  - Sling operation
  - Purandare’s cervicopexy
  - Exploratory laparotomy for ovarian tumors
  - Myomectomy.
- Obstetric
  - Cesarean section
  - Cesarean hysterectomy
  - Exploratory laparotomy for ruptured tubal ectopic pregnancy.

CUSCO’S BIVALVED SELF-RETAINING VAGINAL SPECULUM (FIG. 4)

Material: Stainless steel
Sterilization: Autoclaving and boiling

Uses

- Routine per speculum examination in gynecology
- Colposcopy
- Endometrial biopsy
- Cervical punch biopsy
- Pap smear
- Insertion and removal of intrauterine contraceptive device (IUCD)
- Intrauterine insemination (IUI).

AUVARD’S WEIGHTED SELF-RETAINING POSTERIOR VAGINAL SPECULUM (FIG. 5)

Material: Stainless steel
Sterilization: Autoclaving

Uses

- Vaginal hysterectomy
- Anterior colporrhaphy
- Kelly’s repair
- Fothergill’s/modified Fothergill’s repair
- Vesicovaginal fistula repair
- Schauta’s hysterectomy.

SONAWALA’S SELF-RETAINING VAGINAL SPECULUM (FIG. 6)

Material: Stainless steel
Sterilization: Autoclaving

Uses

- Vaginal hysterectomy
- Vaginal tubal sterilization
- Vesicovaginal fistula repair
- Fothergill’s repair/modified Fothergill’s repair
- Schauta’s radical hysterectomy.

LANDON BLADDER RETRACTOR (FIG. 7)

Material: Stainless steel
Sterilization: Autoclaving and boiling

Uses

- To retract the bladder away from cervix and uterus during vaginal hysterectomy. It is introduced into anterior pouch after the uterovesical fold of peritoneum has been opened
- To retract lateral and anterior vaginal walls during any vaginal operation.
**TONGUE DEPRESSOR (FIG. 8)**

*Material:* Stainless steel  
*Sterilization:* Autoclaving and boiling

**Use**
To examine oral cavity.

**RIGHT ANGLE RETRACTOR (FIG. 9)**

*Material:* Stainless steel  
*Sterilization:* Autoclaving and boiling

**Uses**
- To retract abdominal wall during tubal ligation
- To retract bladder and posterior vaginal wall during hysterectomy
- To retract bladder during abdominal hysterectomy

**FLUSHING CURETTE (FIG. 10)**

*Material:* Stainless steel  
*Sterilization:* Autoclaving and boiling

**Use**
Dilatation and evacuation operation.

**TOWEL CLIP (FIG. 11)**

*Material:* Stainless steel  
*Sterilization:* Autoclaving and boiling

**Uses**
- For draping
- Can be used for hemostasis.
ALLIS TISSUE-HOLDING FORCEPS (FIG. 12)

Material: Stainless steel  
Sterilization: Autoclaving and boiling

Uses

- **General**: To hold the rectus sheath while opening and closing abdominal wall
- **Gynecologic**: To hold the edges of vagina  
  - In anterior colporrhaphy, enterocoele repair, colpo- perineorrhaphy
  - In vaginal hysterectomy, abdominal hysterectomy
  - Fothergill’s repair
  - Repair of vesicovaginal/rectovaginal fistula
  - To hold the cervix
  - Abdominal hysterectomy
  - To hold the lips of pediatric cervix
  - To hold the uterus
  - Vaginal and abdominal hysterectomy, myomectomy, utriculoplasty
  - Marchetti test for detection of stress urinary incontinence.
- **Obstetric**  
  - In lower segment cesarean section (LSCS) to hold angles of uterine incision  
  - For correction of acute inversion of uterus.

NEEDLE HOLDER (FIG. 13)

Material: Stainless steel  
Sterilization: Autoclaving

Use

To hold needle during suturing.

ARTERY FORCEPS (FIG. 14)

Material: Stainless steel  
Sterilization: Autoclaving

Uses

- For hemostasis
- Holding structures like peritonium, rectus sheath, vessels, muscles, etc. during any operative procedure
- For suture removal
- Can be used for clamping placenta after delivery of baby.

SPONGE-HOLDING FORCEPS (FIG. 15)

Material: Stainless steel  
Sterilization: Autoclaving and boiling
**Miscellaneous**

**Uses**
- **General**
  - Painting and preparing parts preoperatively
  - Swab out cavities like vagina and pelvic cavity
- **Gynecologic**
  - For applying pressure over deep bleeding points during pelvic surgery
  - To check hemostasis of stumps during vaginal hysterectomy
  - For packing away omentum and intestines out of pelvis in gynecological operations
- **Obstetric**
  - To hold lips of pregnant cervix during tightening of os
  - For diagnosis and repair of cervical tear
  - Swab out blood in uterine cavity.

**KIDNEY TRAY (FIG. 16)**

*Material: Stainless steel*

*Sterilization: Autoclaving and boiling*

**Uses**
- To collect and hold urine
- To hold swabs for painting before any operation
- To collect placentas after delivery of baby
- To collect blood in ruptured ectopic pregnancy
- To collect vomitus

**KOCHER’S CLAMP (FIG. 17)**

*Material: Stainless steel*

*Sterilization: Autoclaving and boiling*

The blades may be curved or flat or straight. One blade has a longitudinal ridge which fits in a longitudinal groove on the other blade. It has transverse serrations on its blade.

**Uses**

**Hysterectomy**

To clamp the uterosacral ligaments, uterine blood vessels and the cornual structures or the infundibulopelvic ligaments in vaginal hysterectomy.
- Oophorectomy for ovarian cysts or tumors
- Removal of pedunculated leiomyomatous polyps
- Salpingectomy for tubal ectopic gestation
- Cesarean hysterectomy
- Clamping the umbilical cord of the newborn
- Artificial low rupture of membranes
- To hold the uterus during abdominal hysterectomy.

**TENACULUM (FIG. 18)**

*Material: Stainless steel*

*Sterilization: Autoclaving and boiling*

**Uses**
- To hold the lips of nulliparous cervix
- To hold cervical stump in subtotal hysterectomy.

**Special Use**
- Hysterosalpingography
- Chromopertubation test
- Rubin’s test.

**BABCOCK FORCEPS (CURVED AND STRAIGHT) (FIG. 19)**

*Material: Stainless steel*

*Sterilization: Autoclaving and boiling*
Instruments in Obstetrics and Gynecology

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Uses
To hold tubular structures like:
- Fallopian tubes in tubal sterilization, ruptured tubal ectopic pregnancy
- Round ligaments
- Ureters in Wertheim’s hysterectomy
- Vas in vasectomy
- Appendix and cecum in appendicectomy.

GREEN ARMYTAGE FORCEPS (FIG. 20)

Material: Stainless steel
Sterilization: Autoclaving and boiling

Uses
- To achieve hemostasis by compressing the bleeding uterine vessels during LSCS
- To lift uterine edges during suturing of uterus
- To trace and repair cervical tears after vaginal delivery.

BLADDER SOUND (FIG. 21)

Material: Stainless steel
Sterilization: Autoclaving and boiling

Uses
- To define the limits of bladder during operation
- To confirm a suspected bladder injury during vaginal hysterectomy
- To determine length and direction of vesicovaginal fistulae
- To sound a calculus or foreign body in the bladder
- To differentiate bladder or urethral diverticulum from anterior vaginal wall cyst.

LEECH WILKINSON CANNULA (FIG. 22)

Material: Stainless steel
Sterilization: Autoclaving and boiling.

Uses
- Hysterosalpingography
- Chromopertubation test in laparoscopy
- Hydrotubation.

PLAIN FORCEP (FIG. 23)

Material: Stainless steel
Sterilization: Autoclaving and boiling

Uses
- To hold thin delicate structures such as peritoneum
- Muscles, vessels, thin fascia, intestinal wall, bladder wall, etc.
During suture removal  
Packing abdominal cavity during abdominal operations.

**TOOTH FORCEP (FIG. 24)**

*Material:* Stainless steel  
*Sterilization:* Autoclaving and boiling

**Uses**

- To hold tough structures like:
  - Tendon
  - Fascia
  - Skin
  - Rectus sheath
  - Uterine wall, etc.
- Can be used for hemostasis.

**HEGAR DILATOR (FIG. 25)**

*Material:* Stainless steel  
*Sterilization:* Autoclaving and boiling

It is a solid rod–curved near the tip and tapering towards the tip. The curve is shallow and the dilating portion is within terminal 1.5 cm of the dilator.

**Uses**

For the rapid dilatation in:
- Prior to endometrial curettage
- Prior to suction aspiration for first trimester MTP
- Prior to suction evacuation of mole
- Removal of endometrial polyp, placental polyp, leiomyomatous polyp
- Hysteroscopy
- Amputation of cervix, Fothergill’s operation, following cervical conization
- Cervical stenosis
- Application of intrauterine radiotherapy
- Primary dysmenorrhea
- Diagnosis of incompetent os.

**FENTON DILATOR (FIG. 26)**

It is similar to Hegar dilator except for two important differences—it is more tapering and hollow inside.

**Use**

Same as that of Hegar dilator.

**CUZZI PLACENTAL CURETTE (FIG. 27)**

*Material:* Stainless steel  
*Sterilization:* Autoclaving and boiling
It is a long instrument with a handle at one hand and curette at the other. The curette is spoon-shaped. The outer surface of curette has transverse serrations and the rim of spoon is somewhat sharp.

**Uses**
- Check curettage for incomplete abortion and retention of the placenta in second trimester
- Retained segments or bits of placenta after delivery of a viable fetus.

**UTERINE CURETTE (FIG. 28)**

**Uses**
- **Gynecological uses**
  - **Diagnostic**
    1. Primary or secondary infertility for ovulation detection
    2. Tuberculous endometritis
    3. Abnormal uterine bleeding
    4. Endometrial hyperplasia/endometrial carcinoma
    5. Carcinoma cervix
    6. Secondary amenorrhea
    7. Postmenopausal bleeding
  - **Therapeutic**
    1. Dysfunctional uterine bleeding (DUB)
- Asherman’s syndrome
- To remove embedded intrauterine device (IUD)
- **Obstetrical uses:**
  - MTP, check curettage
  - Blunt curettage in abortions
  - Secondary persistent pulmonary hypertension (PPH), subinvolution.

**AYRE’S WOODEN SPATULA (FIG. 29)**

*Material: Wood*
*Sterilization: Dry heat*

**IUCD REMOVING HOOK (FIG. 30)**

*Material: Stainless steel*
*Sterilization: Autoclaving and boiling*

**Uses**
- Removal of an embedded IUD from the uterine cavity
- Removal of tubal prosthesis from the uterine cavity.
VACUUM EXTRACTOR (FIG. 31)
A vacuum extractor has a suction cup, a traction handle, a source of creating vacuum and a vacuum gauge to note the negative pressure created. The cup may be made up of metal or softer material like silastic.

**Uses**
- Deep transverse arrest with adequate pelvis
- Delay in descent of high head in case of second baby of twins
- As an alternative of forceps operation
- Delay in late first stage due to uterine inertia or primary cervical dystocia
- As an adjunct to symphysiotomy.

VULSELLUM (FIG. 32)
*Material:* Stainless steel  
*Sterilization:* Autoclaving and boiling

**Uses**
- Anterior lip held in:
  - Endometrial biopsy
  - IUCD insertion
  - Intrauterine insemination
  - Vaginal hysterectomy
  - Cauterization of cervix and cervical biopsy
- Posterior lip held in:
  - Colpopincture for suspected ruptured ectopic pregnancy
  - Culdoscopy
  - Posterior colpotomy.

HULKA UTERINE MANIPULATOR (FIG. 33)
*Material:* Stainless steel  
*Sterilization:* Autoclaving and boiling

**Uses**
- It is used to elevate and manipulate position of uterus for following:
  - Laparoscopic sterilization
  - Sterilization by mini laparotomy
  - Visualization of pelvic structures by laparoscopy.

VITOON UTERINE MANIPULATOR (FIG. 34)
*Material:* Stainless steel  
*Sterilization:* Autoclaving and boiling
Uses

Same as that of Hulka uterine manipulator.

**DREW-SMYTHE CATHETER (FIG. 35)**

*Material: Stainless steel*  
*Sterilization: Autoclaving and boiling*

It is S-shaped and has a side opening to drain liquor amnii. It has a spring loaded stylet with a blunt tip.

**FLUSHING CANNULA (FIG. 36)**

*Material: Stainless steel*  
*Sterilization: Autoclaving and boiling*

**Uses**

- High amniotomy  
- To drain a hydrocephalic head through a spina bifida, in case of a breech delivered up to the head.

**LONG-CURVED OBSTETRIC FORCEPS (FIGS 37 AND 38)**

*Material: Stainless steel*  
*Sterilization: Autoclaving and boiling*  
*Measurement: Length is 37 cm; distance between the tips is 2.5 cm and widest diameter between the blades is 9 cm.*

**Uses**

- Delay in the second stage  
- **Fetal indications**  
  - Appearance of fetal distress in the second stage when the prospect of vaginal delivery is safe  
  - Cord prolapse  
  - After coming head of breech  
  - Low-birthweight baby  
  - Postmaturity  
- **Maternal indications**  
  - Maternal distress  
  - Pre-eclampsia  
  - Postcesarean pregnancy  
  - Heart disease.
WRIGLEY’S FORCEPS (FIG. 39)

**Material:** Stainless steel  
**Sterilization:** Autoclaving and boiling  
**Measurement:** Length 27.5 cm, light construction, English lock.

**Use**  
Used for low forceps delivery.

KIELLAND’S FORCEPS (FIG. 40)

**Material:** Stainless steel  
**Sterilization:** Autoclaving and boiling  
**Measurement:** Length 40 cm, straight obstetric forceps without any axis traction device. It has got a sliding lock which facilitates correction of synclitism of the head.

**Use**  
Same as other obstetric forceps.

MIXTER FORCEPS (FIG. 41)

**Material:** Stainless steel  
**Sterilization:** Autoclaving and boiling

**Uses**  
- To ligate internal iliac artery  
- Can be used for ligating any vessel.

SUCTION CANNULA (FIG. 42)

**Material:** Stainless steel, plastic  
**Sterilization:** Autoclaving or boiling for stainless steel; gamma irradiation for plastic.

**Uses**  
- First trimester MTP  
- Inevitable abortion in first trimester  
- Flexible plastic cannula for menstrual regulation  
- Suction evacuation of vesicular mole  
- Large suction cannula for second trimester pregnancy termination.

DOYEN’S MYOMA SCREW (FIG. 43)

**Material:** Stainless steel  
**Sterilization:** Autoclaving and boiling

**Use**  
To hold steady and apply traction on a fibroid during abdominal vaginal myomectomy.
SIMPSON PERFORATOR (FIG. 44)

Material: Stainless steel
Sterilization: Autoclaving and boiling

Its blade has triangular tips with outer cutting edges. There are two shoulders on the blades. There is a locking system between the ends of the handles which locks the blades in closed position.

Use
- Craniotomy
  - Opening fetal thorax or abdomen for evisceration.

OLDHAM PERFORATOR (FIG. 45)

Material: Stainless steel
Sterilization: Autoclaving and boiling

The blades are as in Simpson’s perforator, but have only one shoulder. There is neither any spring nor any lock.

Use
- Craniotomy
  - Opening fetal thorax or abdomen for evisceration.

BRAUN’S CRANIOCLAST (FIG. 46)

Material: Stainless steel
Sterilization: Autoclaving and boiling

Uses
- To crush the vault of skull after craniotomy
- To crush the base of skull after craniotomy
- To break-up the vault of skull and remove it piecemeal
- To extract the fetal head after craniotomy and crushing.

AUVAHRD-ZWEIFEL COMBINED CRANIOCLAST AND CEPHALOTRIBE (FIG. 47)

Material: Stainless steel
Sterilization: Autoclaving and boiling

Uses
- To crush the vault and base of fetal skull after craniotomy
- To extract fetal head after craniotomy and crushing
- Blades 1 and 2 can be used as cranioclast.

WILLETT SCALP TRACTION FORCEPS (FIG. 48)

Material: Stainless steel
Sterilization: Autoclaving and boiling
14 SECTION

Miscellaneous

TO AID DELIVERY OF FETAL HEAD AFTER CRANIOTOMY

Martin Pelvimeter (Fig. 50)

Material: Stainless steel

Uses

The instrument was used in past for external pelvimetry. Various diameters such as external conjugate, intercristal, intertuberous, interspinous diameters were measured in the past.

Rubber Ring Pessary (Fig. 51)

Material: Rubber or polyethylene

Sterilization: Plastic pessaries available presterilized; rubber ring pessaries can be sterilized by chemical methods.

Uses

- To control bleeding due to degree 1 or 2 placenta previa
- To give traction on fetal head after craniotomy, to hasten delivery
- To give scalp traction to deliver fetal head during cesarean section
- Scalp traction to prevent recurrence of cord prolapse after replacement of the prolapsed cord above the level of fetal head.

Material: Stainless steel

Sterilization: Autoclaving and boiling

BLUNT HOOK AND CROCHET (FIG. 49)

Uses

- Uses for the hook
  - To apply groin traction in case of a breech presentation
  - To pull down a fetal leg in case of a transverse lie
- Uses of the crochet
  - To extract decapitated head

Fig. 47: Auvard-Zweifel combined cranioclaster and cephalotribe

Fig. 48: Willett scalp traction forceps

Fig. 49: Blunt hook and crochet

Fig. 50: Martin pelvimeter

Fig. 51: Rubber ring pessary
Use
In uterocervical descent.

Indications
- Pregnancy up to 12 to 14 weeks
- During lactation
- When further child bearing is intended in near future
- When surgery is contraindicated in a patient
- If patient refuses operation
- As a therapeutic test to confirm whether the symptoms are due to prolapse
- To promote healing of the decubitus ulcer prior to surgery.

Action
Supports the uterus by resting on the two levator ani muscles acting as shelves.

PINARD’S STETHOSCOPE (FIG. 52)
Fetoscope
- Invented by Adolphe Pinard.
- Instrument to hear fetal heart sound.

Parts
- Simple hollow tube with one broad end and another narrow end.
- Narrow end has a wide rim which is used as an earpiece.
- Broad end is placed over the patient’s abdomen.

Technique
- The instrument is kept at right angle on patient’s abdomen.
- The instrument should not be touched with hand while listening to FHS.
- It is rarely used now since use of stethoscope and digital fetal Doppler.

STETHOSCOPE AND DIGITAL FETAL DOPPLER (FIGS 53 AND 54)
These instruments are to hear FHS with high acoustic sensitivity.
- Stethoscope has ear tips with ear tubes set to accommodate the anatomy of the ear.
- Digital fetal Doppler has display to give read out of fetal heart rate (FHR) in beats per minute (bpm).

Auscultation
The fetal heart is auscultated for one minute (normal 110–160 bpm) NICE guidelines. During labor fetal heart rate should be auscultated during and immediately after uterine contraction to detect late deceleration.
- Low-risk pregnancy
  - Auscultation in—1st stage labor: 30 minutes interval
  - 2nd stage labor: 15 minutes interval.
- High-risk pregnancy
  - Auscultation in—1st stage labor: 15 minutes interval
  - 2nd stage labor: 5 minutes interval.

OVUM FORCEPS (FIG. 55)
Designed by Haywood Smiths.

Parts
Blades
- Blades are spoon-shaped, fenestrated and have blunt ends
- Longitudinal fenestrations can hold good amount of tissue.
It is absent.
2. Anything held in blades is firmly caught but not nipped and so no crushing.
Ovum forceps is differentiated from sponge holding forceps by following points:
• It has no lock
• It has no serrations
   Catch lock is absent so less chances of injury to intra-abdominal structures.

**Technique**
- Consent
- Patient preparation. Empty bladder
- Anesthesia (LA/GA)

**Method**
- Retract posterior and anterior vaginal wall and catch cervix by vulsellum.
- Os is dilated with Hegar’s dilators.
- Ovum forceps is introduced with closed blades.
- Once in uterine cavity blades are opened and products of conception are grasped and removed by rotatory movements.

**Uses**
- Evacuation of products of conception in abortion and vesicular mole.
- Evacuation of products of conception in secondary PPH.

**Advantage**
- No catch ratchet so no crushing action.

**Disadvantages**
- Perforation
- Infection
- Injury to intra-abdominal structure.

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**KARMAN DOUBLE WHISTLE CANNULA, KARMAN MENSTRUAL REGULATION SYRINGE AND MANUAL VACUUM ASPIRATION SYRINGE**

**Karman Cannula (Fig. 56)**
A long tubular structure made of plastic or metal.
- **Types:** Rigid or flexible
- **Sizes:** 4–12 mm
- **Parts**
  - **Distal end:** Double whistle at the terminal end.
  - **Proximal end:** Fixes into syringe.
  - Superior overhanging edge acts as a curette.

   The number of cannula corresponds to diameter of cannula in millimeters. A plastic cannula is preferred because it is less traumatic, transparent and disposable.

**Karman Menstrual Regulation Syringe (MR Syringe) (Fig. 57)**
Used for aspiration of uterine contents within 42 days of missed period.

**Manual Vacuum Aspiration Syringe (MVA Syringe) (Fig. 58)**
For aspiration of uterine contents till 12 weeks. Superior version of MR is MVA.

   WHO recommends MVA a procedure of choice before 10 weeks and safely up to 12 weeks

**Syringe**
60 mL syringe capable of creating vacuum of 650 mm (65 cm) of Hg. It has a barrel and a piston. There is a pressure
Instruments in Obstetrics and Gynecology

Late
- PID and chronic pelvic pain
- Infertility caused by tubal infection and blockage
- Incompetent os following trauma to the cervix as this may lead to preterm births and habitual midtrimester abortions
- Adherent placenta in the subsequent pregnancy
- Asherman’s syndrome
- Ectopic pregnancy following PID
- Rh isoimmunization if anti-D has not been administered after the MTP to nonimmunized Rh-negative mother
- Psychiatric disorders if MTP was done without proper counseling and feeling of regret, especially if infertility follow-up procedure

Low failure rate < 1%
Mortality < 2/100,000 procedure.

Instrument Tray for MTP (Fig. 61)

controlled valve system. When the lock is pressed and piston pulled out a negative pressure is created in syringe (Figs 59 and 60).

Uses of Cannula
- Medical termination of pregnancy (MTP)
- S and E in incomplete abortion, missed abortion
- S and E in molar pregnancy
- Cannula is used in draining CSF after craniotomy in hydrocephalus/dead baby
- Endometrial aspiration for endometrial pathology.

Complications
Immediate
- Incomplete evacuation
- Continuation of pregnancy
- Uterine perforation
- Excessive bleeding
- Anesthetic complications, i.e. laryngospasm, vasovagal attack
- Infection.

Instrument Tray for D and C (Fig. 62)
LAMINARIA TENT (FIG. 63)

Made up of hygroscopic material derived from the stems of seaweed called *Laminaria japonica*. It swells up by absorbing fluid (hygroscopic) and is a slow dilator of cervix.

**Parts**
- Stem is 5.5–6 cm
- Small, medium, large sizes are available according to the diameter
- A string is looped through one end and tied to gauze for easy removal (Fig. 63).
  Two or three tents can be introduced side by side if required into the cervical canal.
  Tents swell up 3–5 times of their size after absorbing secretions of cervical canal in 12–24 hours and dilate cervix.
  Sterilized by dipping in absolute alcohol.

**Technique**
- Anterior and posterior vaginal walls are retracted
- Cervix is grasped by vulsellum
- Sterilized gauze is tied to loop of tent and tent is introduced in the cervical canal
- Tent is passed to lie just beyond the internal os
- 0.5 cm should be inside the uterus and 0.5 cm should be in the vagina
- The vagina is packed with sterile gauze.

**Uses**
- First and second trimester pregnancy termination
- Expulsion of POC in missed abortion, incomplete abortion
- Induction of labor.

**Advantage**
Gradual os dilatation, so minimal chances of injury and incompetent os.

Disadvantages
- False passage during insertion
- May go up in the uterine cavity
- Dumb bell formation as it swells up unequally when placed too high
- If tip is below os then os remains undilated.

BARD PARKER’S KNIFE (FIG. 64)

- Popularly known as surgeon’s knife.
- It has a straight handle with a notch. Different sizes of blades can be attached with different sizes of handles. Larger sizes of blades are used for larger tissues and incisions. Smaller sizes of blades are used for finer incisions (Fig. 65).
- The no. 10 scalpel blade is the most commonly used size.

**Technique**
When using no. 10 and 20 blades, scalpel is held at 20–30° angle to skin and drawn firmly along the skin using arm with minimal wrist and finger movement. Full length of scalpel belly is used avoiding burying of tip and incision cuts dermis. Scalpel with blade is held with shaft of scalpel in palm of hand with index finger on top of blade, i.e. knife holding position.

Avoid multiple tracks and irregular skin edges by giving firm traction on lateral aspect of incision. Surgeon makes the cut towards himself or herself.

Creating tension at the skin surface is necessary to reduce the amount of force required for penetration. Omission of this step can result in uncontrolled penetration of underlying structure.

Fig. 63: Laminaria tent

Fig. 64: Handle with blade

Fig. 65: Surgical blades
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Instruments in Obstetrics and Gynecology

**Pencil Grip (Figs 66A and B)**
Scalpel is held like a pencil and movement is directed by thumb and index finger.

**Power Grip (Fig. 66C)**
Scalpel is held between thumb and index finger and both exert downward pressure. End of blade is forced up against the thenar muscles of hand as the incision is given.

**Uses**
1. For opening the abdomen by incising skin and subcutaneous tissue
2. For cutting pedicles
3. For sharp dissection
4. For finer incision that is incision of tough walled abscess.

**UMBILICAL CORD CLAMP (FIG. 67)**
1. Disposable clamp made of plastic
2. Inner surface has transverse serrations for tight grip on cord
3. Open end can be locked after clamping the cord by giving pressure
4. Clamp sheds off when cord dries and falls off
5. By delaying cord clamping about 80 mL blood goes to fetus
6. Early cord clamping is done in:
   - Rh isoimmunization (to prevent antibody transfer from mother to baby)
   - Asphyxia
   - Preterm (to prevent hypervolemia)
   - Diabetic mother
   - Low birth weight.

**BONNEY’S MYOMECTOMY CLAMP (FIG. 68)**
- Designed by Victor Bonney
- It is used to reduce intraoperative blood loss in operations.

**Parts**

**Blades**
- These are at an angle of 120° to the shaft
- It has overlapping transverse bar dividing it into two compartments
- There is a rubber tubing in anterior half of the compartment which prevents trauma to the structures.

**Shaft**

**Handle**
- Handle has two pairs of finger grips (Fig. 68)
- Distal finger grip is used for applying and removing the instrument
- Proximal finger grip can open up the instrument wider in bulky uterus.

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**Figs 66A to C: Knife holding positions (A and B) Pencil grip; (C) Power grip**

**Fig. 67: Umbilical cord clamp**

**Fig. 68: Bonney’s myomectomy clamp**
Technique
- The clamp is applied with curve downwards from pubic end of abdominal wound.
- Two round ligaments are included in grip of blades to prevent the instrument from slipping and keeping it antverted.
- Uterine arteries are clamped at level of internal os. The ring forceps can be applied to the ovarian vessels.
- Clamp is released every 20 minutes to prevent tissue anoxia and accumulation of histamine.

Uses
To control bleeding during operation of:
- Myomectomy
- Hysterotomy
- Metroplasty.

Use has become less because myoma can be removed by latest methods:
1. Laparoscopic myomectomy
2. Motorized morcellation
3. Minilap incision.

**MERSILENE TAPE (FIG. 69)**
It is a nonabsorbable sterilized needle polyester fiber tape 30 cm x 5 mm on a ½ circle heavy round bodied double needle. It is used in cervical incompetence for giving McDonald stitch which is a cerclage operation (Fig. 69).

Technique
- **Anesthesia:** Regional anesthesia or GA.
- Vaginal preparation is done.
- Vaginal walls are retracted and cervix is visualized. Cervical lip is pulled down by sponge holding forceps.
- Purse string suture is given taking four successive deep bites as high as possible in the body of cervix and very near the level of internal os.
- At completion of encirclement, the suture is tightened around the cervical canal thus reducing diameter of the canal to 5–10 mm.
- Knot is tied
- Postoperative advice

- Rest and tocolytics
- Avoid journey and intercourse
- Report if bleeding or pain.

**Advantages**
- Simple
- Less blood loss
- Good success rate 85–95%

**Complications**
- Premature rupture of membranes (PROM)
- Chorioamnionitis
- Preterm labor (PTL)
- Vaginal bleeding due to cervical laceration/cutting through of suture
- Uterine contractions and irritability
- Rarely bladder injury
- Cervical dystocia
- Uterine rupture.

**Contraindications**
- Ruptured membranes
- Infection
- Uterine bleeding
- Uterine contractions
- Cervical dilatation > 4 cm
- Fetal anomaly.

*Instrument Tray for McDonald Suture (Fig. 70)*

**Fig. 69:** Mersilene tape

**Fig. 70:** Instruments for McDonald suture. 1. Sponge holder for cleaning; 2. Sims speculum; 3. Sponge holders; 4. Needle holder; 5. Mayo scissors; 6. Dissecting forceps; 7. Mersilene tape
**SHIRODKAR CERVICAL ENCERCLAGE NEEDLES (FIG. 71)**

- They are used for modified Shirodkar cerclage operation for incompetent cervix.
- A cervical encircling suture (nonabsorbable) is passed around cervix at the level of internal os.
- Uterine polarity is disturbed and thus prevents “Taking up” of lower segment.

**Parts**

- These are two right and left needles which are half circled and each has an eye at tip.
- Needles are mirror image of each other. They are 5 cm long (Fig. 71).

**Time**

- Cervical cerclage is given at 14 weeks or 2 weeks before the age of gestation at which the patient aborts.

**Technique**

- Consent
- Anesthesia: GA
- Lithotomy position
- Cervix is exposed by retracting the vaginal walls and held by Allis or sponge holding forceps. A 2 cm transverse incision is made anteriorly on vaginal wall below the base of bladder
- Bladder is pushed up. A transverse incision is then made posteriorly at cervicovaginal junction
- Nonabsorbable 5 mm mersilene tape is passed by Shirodkar needle
- Ends of suture are cut 3 cm long and knot is tied posteriorly
- Vaginal mucosa is repaired
- Stitch should be removed at 37th week gestation or early if any complication.

**Postoperative Advice**

- Rest and tocolytics
- To avoid journey and intercourse
- Report if there is pain or bleeding.

**Advantages**

- Stitch can be placed high at internal os
- Suture is buried under vaginal mucosa and thus reducing risk of infection.

**Disadvantages**

- Greater technical difficulty and dissection
- Difficulty in removing suture at term.

**INTRAUTERINE INSEMINATION CANNULA (FIG. 72)**

It is a thin flexible catheter which is placed in uterine cavity for intrauterine insemination (IUI).

**Indications**

Artificial Insemination Husband (AIH)

- Mild to moderate male subfertility: Oligospermia, asthenospermia, teratospermia, oligoasthenoteratozoospermia, pyospermia, semen volume and liquefaction defects.
- Impotency.
- Premature ejaculation, retrograde ejaculation.
- Anatomical defects, i.e. hypospadias, vaginal and cervical defects.
- Unexplained infertility.
- Cervical factor, i.e. hostile cervical mucus, antisperm antibodies in cervical mucus.
- Immunological factors: Presence of antisperm antibodies.
- Endometriosis: Mild or moderate.
- Chronic anovulation.
- HIV positive woman or man.

Artificial Insemination Donor (AID)

- Azoospermia
- Immunological factor if not correctable
- Genetic disease in the husband
  - Screening is done for HIV, STD, hepatitis B. To minimize HIV transmission frozen semen is stored for 6 months. By end of this period if donor remains HIV negative then insemination is thawed and used.
Techniques

Insemination can be:
• Intrauterine (most common)
• Intrafallopian
• Intracervical
• Vaginal
• Intraperitoneal.

IUI (intrauterine insemination): It is placement of 0.3 mL of washed processed and concentrated sperms (devoid of seminal plasma) into intrauterine cavity by transcervical catheterization (Fig. 72).

Purpose: To bypass endocervical canal and place increased number of motile sperms close to fallopian tube to reach ovulated eggs thereby increases chances of meeting.

Prerequisite: For the best pregnancy rates IUI sperm count is > 5 m/mL (forward progressive motile sperms). Proper selection and investigations of couple is necessary.

ELECTROSURGICAL LOOP (FIG. 73)

• Loop electrosurgical excision procedure (LEEP).
  Requires electrosurgical unit, wire loop electrode, insulated speculum and smoke evacuation system.
• Large loop excision of transformation zone (LLETZ).

Parts

Thin wire semicircular electrode made of stainless steel or tungsten.

Technique

• Consent is taken.
• Anesthesia and patient position:
  – Dorsal lithotomy position
  – Office anesthesia/GA.

Method

• Electrosurgical grounding pad is placed under buttock and insulated speculum inserted into vagina.
• Smoke evacuation tubing is attached.
• Application of Lugol iodine outlines lesion margins.
• Electric current is passed in tissue via 0.2 mm stainless steel or tungsten wire electrode.

Single pass excision (ideal)
• Correct loop diameter should incorporate entire lesion diameter to a depth of 5–8 mm.
• Cutting mode typically 30–50 W is required. Loop is positioned 3–5 mm outside the lateral perimeter of lesion.
• The loop is advanced into cervix lateral to lesion until required depth is reached.
• The loop is taken across to opposite side and cone of tissue is removed.

Multiple pass excision (if required).
Control of bleeding sites is done.

Advantages

• Specimen for HPE is available with local excision
• Preferred over cryosurgery, as low cost and minimal discomfort.

Disadvantages

• Short term: Abdominal pain, bleeding, cramping, spasm
• Long term: Persistence of disease, cervical stenosis, incompetent os, preterm labor, dystocia, bladder injury.

CERVICAL PUNCH BIOPSY FORCEPS (FIG. 74)

It is a strong instrument.

Parts

Blade

• There are two blades
• Smaller blade has sharp cutting edge and fits into larger blade (Fig. 74)
• Specimen is held in it like a basket.

Handle

• Handle is angulated to avoid obstruction of field of vision.

Lock and Finger Grips

Fig. 73: Electrosurgical loop

Fig. 74: Cervical punch biopsy forceps
Technique

- Anesthesia given is paracervical block with or without sedation.
- Vagina is prepared.
- Area of biopsy is marked out by VIA, Schiller’s iodine stain or colposcopy.
- Punched area should include adequate bite of normal and abnormal tissue. Four quadrant biopsy is taken.
- Biopsy tissue should contain sufficient subepithelial connective tissue so that possibility of microinvasion can be ruled out, i.e. 3–5 mm stroma in addition to surface epithelium.
- Hemostasis of raw area is done by packing or taking stitch. Tissue is sent for HPE in formalin.

Indications

- Bad cervix, recurrent cervicitis and nonhealing erosions
- Postcoital bleeding P/V
- Abnormal Pap smear
- Abnormal finding on Schiller’s test, i.e. iodine negative areas on colposcopy.

Disadvantage

Hemorrhage.

CRYOMACHINE (FIG. 75)

Used for cryosurgery (Syn:cryocautery/cryotherapy) which is an ablative method used to eliminate cervical intraepithelial lesion.

Compressed gas creates extremely cold temperature that necroses cervical epithelium. As compressed gas expands it drains heat away from cervical epithelium and causes destruction of cell by crystallization of intracellular fluid.

Parts

**Cryoprobe:** Tip is made of silver or copper and is in contact with surface of cervix.

**Refrigerating gas cylinder:**

i. *Nitric oxide:* Most common gas which is used.
   - Probe temperature can reach (–65°C)
ii. *CO₂:* Temperature (–60°C)
iii. *Freon:* Temperature (–60°C)

Cryogun is attached with connecting tube to a cylinder of refrigerating gas, i.e. nitrous oxide cylinder with pressure gauge.
- Pressure of at least 20 pounds is required.

Patient Evaluation

- CIN is confirmed by colposcopy/cervical biopsy and there should be no evidence of invasive cancer.
- Woman should not be pregnant or recently delivered.
- The entire lesion is located in ectocervix with no extension in endocervix and vagina.
- The lesion is visible in its entire extent and does not extend more than 2–3 mm into the endocervical canal.
- The lesion should be adequately covered by the largest cryoprobe and lesion should extend less than 2 mm beyond the cryoprobe.

Technique

- **Informed consent:** Preferred postmenstrually and generally no analgesia is required. Dorsal lithotomy position.
- **Cryoprobe placement:** Appropriate probe is placed firmly on cervix to cover transformation zone and lesion.
- **Ice ball formation:** Gas tank valve is opened and pressure of 20 pounds is created. The trigger is squeezed and gas forms a layer called ‘ice ball’ on cervix (Fig. 76).
- The portion of ice ball in which temperature falls below –20°C is called “lethal zone”.
- This zone extends from center of cryoprobe to a point 2 mm inside outer ice ball edge. Cells reduced to –20°C for one minute or more undergo cryonecrosis.
- When cryotherapy is performed the ice ball is allowed to enlarge until it reaches a mark 7 mm distal to probe margin.

![Fig. 75: Cryomachine](image1)

![Fig. 76: Cryocautery](image2)
SUTURE MATERIALS

A suture is any strand of material used to approximate tissues or ligate vessels (Fig. 77).

Selection of suture material is essential to maximize wound healing and tissue support (Table 1).

United States Pharmacopeia (USP) defines; Absorbable suture as a “sterile strand prepared from collagen derived from healthy mammals or a synthetic polymer which is capable of being absorbed by living mammalian tissue (Table 2).

Nonabsorbable sutures are strands of material that are resistant to the action of living mammalian tissue (Table 3).

Types

<table>
<thead>
<tr>
<th>Absorbable</th>
<th>Nonabsorbable</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Plain catgut (Biologic)</td>
<td>1. Silk (Biologic)</td>
</tr>
<tr>
<td>2. Chromic catgut (Biologic)</td>
<td>2. Cotton (Biologic)</td>
</tr>
<tr>
<td>3. Polyglactin 910 (Vicryl)</td>
<td>3. Nylon</td>
</tr>
<tr>
<td>4. Polydioxanone (PDS)</td>
<td>4. Steel</td>
</tr>
<tr>
<td>5. Polyglyconate</td>
<td>5. Polypropylene (Prolene)</td>
</tr>
<tr>
<td>6. Polyglycolic acid (Dexon-S)</td>
<td>6. Polyethylene terephthalate</td>
</tr>
<tr>
<td>7. Poliglecaprone 25 (Dacron mersilene)</td>
<td></td>
</tr>
</tbody>
</table>

Advantages

- Best tolerated
- Cheap
- Least painful.

Postoperative advice—Abstinence for 4 weeks. Cryocautery can be repeated after 3 months.

Complications

- Watery discharge (most common) and patient may require sanitary pads
- Bleeding
- Lower abdominal pain and cramping
- Cervical stenosis: Rare
- Infection.

Reading the suture label

![Suture Label Diagram]

**Fig. 77: Sutures**
Table 1: Selection of suture material depends on following factors

1. **Absorbable**
   - Destroyed enzymatically or hydrolyzed, so no foreign body is left.
   - Used in rapidly healing tissue like peritoneum, vagina.
   - Ideal for urinary tract and biliary tract as no stone formation.

   **Nonabsorbable**
   - Persists and is encapsulated, so used in long term approximation of tissues.
   - Used in slow healing tissues like pelvic floor construction, hernia repair.
   - Ideal for tissues made up of mainly collagen, i.e. fascia, tendon, aponeurosis.
   - Used in hypoproteinemic patients.

2. **Monofilament (e.g. Catgut, PDS, Prolene)**
   - Made of single strand.
   - Lower friction coefficient, pull easy less tissue injury.
   - Do not allow bacteria to adhere. It can be used in infection.
   - Knot security is less.

   **Multifilament (e.g. Vicryl, Silk, Cotton Dexon)**
   - Several filaments twisted or braided.
   - Easier to tie and handle.
   - Bacteria adhere to surface. Avoid in infection.
   - Knot security is more.

3. **Tensile strength**: Nonabsorbable have greater tensile strength. Ideally the tensile strength of material chosen should approximate the strength of tissue to be sutured.
   - Biological sutures have lowest tensile strength.

4. **Tissue reaction**: Sutures placed within tissue will incite inflammation. Tissue reaction of biological sutures is greater and minimal in polyglycolic acid.

5. **Capillarity and fluid absorption**: Increased capillarity and fluid absorption ability greatly increases the number of bacteria absorbed. Multifilament sutures have greater capillarity than monofilament.

6. **Caliber**: Diameter of suture reflects its size and is measured in tenths of millimeter.
   - Midpoint diameter size is 0. Suture diameter increases above this and decreases below this. Suture designation is from no. 5 to 10-0, e.g. 1 catgut is thicker than 0 catgut and 2–0 is greater in diameter than 3–0. Choice of suture caliber should be such as to limit tissue damage during placement and minimize tissue reaction.
   - Where cosmetic results are important use smallest inert monofilament suture.

7. **Ease of handling**: Good in silk, Mersilene, Dexon, Vicryl and poor in Prolene.

8. **Knot security**: Knot is the weakest link in tied suture and knot failure can lead to complication.
   - Knot security is good with silk, Mersilene, Dexon.

---

Table 2: Absorbable sutures

<table>
<thead>
<tr>
<th>Suture</th>
<th>Source</th>
<th>Color</th>
<th>Tensile strength</th>
<th>Tissue reaction</th>
<th>Absorption rate</th>
<th>Uses</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plain catgut (biologic)</td>
<td>Collagen from bovine intestinal mucosa of cow, sheep</td>
<td>Straw</td>
<td>70% loss in 7–10 days more rapid loss of tensile strength if infection is present</td>
<td>High</td>
<td>Enzymatic and proteolytic process 7–10 days</td>
<td>For rapidly healing tissues, subcutaneous tissue (general suture for small vessels)</td>
<td>Not for slow healing tissues</td>
</tr>
<tr>
<td>twisted monofilament</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chromic catgut (biologic)</td>
<td>Catgut is treated with 20% chromic acid to make it more inert and lessen tissue reaction as it binds with antigenic sites of collagen</td>
<td>Dark brown</td>
<td>Lost in 21–28 days</td>
<td>Moderate</td>
<td>Totally absorbed in 70 days by proteases released by WBC</td>
<td>Suture for tissue mucosa peritoneum. 3 knots (poor knot security)</td>
<td>Replaced by Vicryl and PDS in some countries</td>
</tr>
<tr>
<td>twisted monofilament</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Contd...
### Table 3: Nonabsorbable sutures

<table>
<thead>
<tr>
<th>Suture</th>
<th>Source</th>
<th>Color</th>
<th>Tensile strength</th>
<th>Tissue reaction</th>
<th>Absorption rate</th>
<th>Uses</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cotton (naturally occurring) twisted multifilament</td>
<td>Cotton fibers aligned and twisted</td>
<td>White</td>
<td>50% lost by 6 months 70% lost by 2 years</td>
<td>Moderate</td>
<td>Remains encapsulated in body tissues</td>
<td>Rarely used in modern surgical practice</td>
<td></td>
</tr>
<tr>
<td>Silk (naturally occurring) braided twisted multifilament</td>
<td>Protein thread secreted by silk worm for its cocoon</td>
<td>Black</td>
<td>It is used dry as tensile strength decreases in moisture</td>
<td>Moderate to high</td>
<td>Most or all by 1 year to 2 years</td>
<td>Used for suturing and ligation in noninfected tissue. Secure knot. Nidus in presence of infection</td>
<td></td>
</tr>
<tr>
<td>Surgical steel (naturally occurring) monofilament multifilament</td>
<td>Iron nickel chromium alloy</td>
<td>Silver metallic</td>
<td>Indefinite</td>
<td>Minimal</td>
<td>Remains encapsulated in body tissues</td>
<td>Little use in gynecological surgery</td>
<td></td>
</tr>
</tbody>
</table>
In Instruments in Obstetrics and Gynecology

<table>
<thead>
<tr>
<th>Suture</th>
<th>Source</th>
<th>Color</th>
<th>Tensile strength</th>
<th>Tissue reaction</th>
<th>Absorption rate</th>
<th>Uses</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolenepolypropylene (synthetic) monofilament</td>
<td>Polymer of propylene</td>
<td>Blue dyed, undyed</td>
<td>Indefinite</td>
<td>Low</td>
<td>Absorption rate</td>
<td>Used for skin closure, vascular surgery, pull out suture, tuboplasty, cosmetic surgery, hernia repair. 5–6 knots</td>
<td>None</td>
</tr>
<tr>
<td>Nylon monofilament multifilament braided</td>
<td>Polyamide Polymer</td>
<td>Dyed, undyed</td>
<td>Loss 15–20% per year</td>
<td>Low</td>
<td>Degradation 15–20% per year</td>
<td>Used in skin closure as retention suture pull out suture, cosmetic surgery, hernia repair, ophthalmic neurosurgery 6–7 knots</td>
<td>None</td>
</tr>
<tr>
<td>Polyethylene terephthalate (mersilene) braided multifilament monofilament</td>
<td>Polyester (Polyethylene terephthalate)</td>
<td>Green dyed, undyed</td>
<td>Indefinite</td>
<td>Low</td>
<td>Remains encapsulated in body tissues</td>
<td>Used in heart surgery, plastic surgery and general surgery 5 knots</td>
<td>None</td>
</tr>
</tbody>
</table>

**Points to remember**

- All the natural sutures, catgut, linen, cotton, silk are now replaced by polymeric synthetic materials in some countries because:
  - Inflammatory reaction is reduced
  - Strength is predictable
  - Absorption is more predictable and complete.
- Absorbable synthetic sutures impregnated with antiseptic prevent postoperative infections, e.g. Vicryl plus (Triclosan).
- **Rate of healing:** Tissues that heal slowly, i.e. skin, fascia, tendon are closed with nonabsorbable sutures. Rapid healing tissues are closed with absorbable suture material.
- **Urinary and biliary tracts:** Nonabsorbable sutures are not used in urinary tract and biliary tract as stone formation can occur.
- **Tissue contamination:**
  - Since genital tract is a potentially contaminated area absorbable sutures should be used.
  - For episiotomy repair polyglactin 910 rapide is preferred.
  - Multifilament sutures are avoided in infections.
  - Absorbable or monofilament sutures are used. Absorbable sutures cause minimal tissue reaction as they are absorbed. Monofilament sutures have no interstices in thread and so there is less risk of bacterial adherence.
- **Suture size:** The amount of suture material used should be minimum. The finest size of suture material should be used with respect to natural strength of the tissue.
- **Nutritional status:** In hypoproteinemice and undernourished patients nonabsorbable sutures should be used.
- **Cosmetic results:** Use the smallest, inert monofilament suture material such as polypropylene or polyamide (Nylon) for cosmetic results. Whenever possible give subcuticular stitches instead of skin sutures with poliglecaprone 25 monofilament, coated polyglactin 910, polyamide or polypropylene for cosmetic results.
- **Microsurgical procedure:** Polyamide monofilament 10–0 or coated polyglactin 910 no. 9–0 is used.
- Secure knots will prevent slippage.
- Retention sutures can be used if required.
- Polysters, i.e. Terylene and Dacron are sutures of choice in cardiovascular surgery.
AYRE’S SPATULA, CYTOBRUSH AND BROOM

Ayre’s spatula and cytobrush are used for collection of cells for cytology screening.

**Spatula**

It is made of plastic or wood. It has blades on both ends. One blade is bifid with one tongue smaller than other and predominantly samples ectocervix. The other end is broad, rectangular to take smears from vaginal wall for hormonal cytology (Fig. 78).

Plastic spatula is preferred to wood because cells are more easily released from plastic surface (Fig. 79A).

**Cytobrush**

Endocervical brush samples endocervical canal and is used in combination with spatula. It has plastic bristles (Fig. 79B).

**Plastic Broom**

It is for liquid-based cytology (Fig. 80). It samples both endo and ectocervical epithelia simultaneously. Broom has longer central bristles and is inserted in endocervical canal. Shorter bristles splay out over ectocervix (Fig. 79C). Cervex brush gives more reliable sampling reducing unsatisfactory smear.

- Pap test can detect 60–70% of cervical cancers, 70% of endometrial cancers.
- Sensitivity of Pap smear for HSIL is 70–80%, specificity is 95–98%.
- False-positive test can be in presence of infection.
- False-negative test (10–15%) can be due to screening error, sampling error, interpretation error, which can be reduced to 1% by repeated tests.
- Pap smear should be obtained prior to P/V examination because fingers may remove desquamated cervical cells and lubricant may prevent detection of organism which gives false-negative results.
- During pregnancy external os becomes patulous and squamocolumnar junction (SCJ) is well-exposed. Pap smear yields most accurate results.
- Pap smear in postmenopausal woman is sometimes inaccurate or negative due to indrawing of SCJ, dry vagina. This can be improved by giving estrogen cream locally for 10 days daily.

**Uses**

1. Cervical cytology
2. Posterior vaginal wall cytology
3. Cytohormonal evaluation.

**Cervical Cytology**

Cytology is a Greek word meaning study of cells. Pap test was first described by Papanicolaou and Traut in 1943. It is a screening test for cervical cancers. It is also called surface biopsy or exfoliative cytology.

Fig. 78: Conventional cytology

Fig. 80: Liquid-based cytology

Figs 79A to C: Cervical cytology
Technique

- Patient preparation:
  - Dorsal position.
  - Clean with plain water. No antiseptic is to be used. Smear is taken before P/V examination because fingers may remove desquamated cells and give false-negative report. Lubricants distort cell morphology.
  - Patient should abstain from vaginal intercourse, douching, use of tampons, medicinal or contraceptive creams for minimum 24-48 hours before test.
  - Treatment of vaginitis or cervicitis prior to test is optional.
  - Vaginal walls are retracted by Cusco’s speculum and cervix is visualized without use of lubricant jelly.
  - The squamocolumnar junction is scraped with Ayre’s spatula rotating it to 360°. Longer tongue of spatula rotating goes into endocervical canal.
    - Squamocolumnar junction is a vital zone to female since this is the focal point where cancer arises.
  - Endocervical brush is inserted into endocervical canal only until the outermost bristles remain visible just within external os. Brush is rotated only one quarter to one half turn.
  - The slides are labeled and numbered for reference and fixed by dipping in 95% ethylalcohol solution in bottle. The slide is stained by Pap method or Shorr’s stain.

Location

Sampling of transformation zone is essential. Smear should contain cells from SCJ, TZ and endocervix.

COLPOSCOPE (FIG. 81)

A binocular microscope to study the epithelium of lower anogenital tract under illumination and magnification. It was introduced by Hans Hinselmann in 1927.

Indications

Diagnostic Indications

Colposcopy is not needed routinely in all patients. Only those with positive Pap smear for suspicious cells or malignant cells needs colposcopy with clinically normal looking cervix.
- Abnormal Pap smear of the cervix, CIN-1 with positive HPV infection
- Abnormal areas on the vagina
- Abnormal areas on the vulva
- Locate the abnormal areas so that selective biopsy can be taken under magnification.

Therapeutic Indications

- Under colposcopic guidance precise conservative treatment with laser and cone can be done. Adequate depth of destruction is 4–5 mm in CIN lesions.
- Colposcopic directed biopsy can be performed in CIN lesions.
- Lifelong follow-up of conservative treatment is required.

Technique of Colposcopy

- Informed consent.
- Position: Lithotomy.
- No P/V examination. Cervix is exposed with bivalve speculum and inspect cervix and vagina.
- Colposcope is focused on external os at a distance of 20 cm.
- Magnification taken is 6 x–15 x.
- Pap smear is taken if required.
- Purpose of colposcopy is to identify SCJ (Fig. 82), detect suspicious area, take direct biopsy.
- Saline technique physiological saline is applied with cotton swab 2” x 2” before application of acetic acid and Lugol iodine. This helps in removing the cervical mucus and studying the subepithelial vascular pattern.
- Green filter to study vascular pattern. Blood vessels appear black (Fig. 83).
- Application of acetic acid 3–5% acetic acid is applied with cotton balls held by sponge holder.
Principle: Acetic acid precipitates protein (clumps nuclear chromatin) and abnormal epithelium appears white called acetowhite (AW) change (Fig. 84).

- Application of Schiller’s iodine (Lugol iodine test) (Fig. 85)
  Normal epithelium is mahogany or black due to glycogen content.
  Dysplastic epithelium is mustard or saffron yellow because it is glycogen free.
  Iodine uptake is only in glycogen containing squamous epithelium as iodine is glycophilic.
- Endocervical curettage and biopsy is taken if it is required.
- Findings are documented satisfactory or unsatisfactory (if SCJ is seen or not).
- Normal findings:
  - Normal columnar epithelium is red grape-like.
  - Normal squamous epithelium is homogeneous gray.
- Insignificant findings:
  - Acetowhite epithelium is shiny or semitransparent.
  - Borders are not sharp.
  - Vessels: Fine punctation, fine mosaic, ICD (intercapillary distance) is short.
- Abnormal findings significant:
  - Dense acetowhite area with sharp border. Appears faster and lasts longer (Fig. 86).
  - Vessels are dilated, irregular or coiled (coarse punctation and mosaic) atypical vessels.
  - Intercapillary distance is more.

Advantages
- Colposcopy can locate abnormal areas so that selected biopsy can be taken
- Unnecessary biopsy can be avoided if findings are normal
- Colposcopy can reduce size of biopsy and conization
- Therapeutically colposcopic ablative techniques can be done in preinvasive cancer of cervix and vagina.
CHAPTER 136

Specimens in Obstetrics and Gynecology

Fig. 1: Chorioadenoma destruens (cut specimen of uterus)

Fig. 2: Chorioadenoma destruens (uncut specimen of uterus)

Fig. 3: Chorion epithelioma (cut specimen of uterus)

Fig. 4: Chorion epithelioma (uncut specimen of the uterus)
Fig. 5: Chorion epithelioma

Fig. 6: Congenital anomaly (Case I)

Fig. 7: Congenital anomaly (Case II)

Fig. 8: Congenital anomaly (Case III)
Fig. 9: Congenital anomaly (Case IV)

Fig. 10: Congenital anomaly (Case V)

Fig. 11: Congenital anomaly (Case VI)

Fig. 12: Hydrops fetalis
Fig. 13: Conjoined twins thoracophagus

Fig. 14: Specimen of anencephaly

Fig. 15: Spina bifida

Fig. 16: Specimen showing fetus with hydrocephalus
Fig. 17A and B: Specimen of cleft lip and cleft palate

Fig. 18: Specimen showing omphalocele

Fig. 19: Copper T in uterine musculature

Fig. 20: Couvelaire uterus
Fig. 21: Double uterus (cut specimen)

Fig. 22: Double uterus (uncut specimen)

Fig. 23: Extra uterine horn discovered at cesarean section

Fig. 24: Hydrosalpinx with uterus

Fig. 25: Hysterectomy of couvelaire uterus

Fig. 26: Fundal rupture
Fig. 27: Hysterectomy for classical scar rupture

Fig. 28: Hysterectomy for rupture lower segment

Fig. 29: Hysterectomy for placenta accreta

Fig. 30: Obstetric hysterectomy for postpartum hemorrhage
Fig. 31: Obstetric hysterectomy for placenta accreta

Fig. 32: Procidentia

Fig. 33: Prolapse with carcinoma cervix (patient 1)

Fig. 34: Prolapse with carcinoma cervix (patient 2)

Fig. 35: Prolapse with carcinoma cervix (patient 3)

Fig. 36: Prolapse with carcinoma cervix after Schauta operation
Fig. 37: Sarcomatous degeneration of fibroid

Fig. 38: Septate uterus at cesarean section

Fig. 39: Supravaginal elongation of cervix in case of prolapse uterus

Fig. 40: Tripled abortion specimen

Fig. 41: Twins, one normal child, other twin is papyraceous

Fig. 42: Twins, one of which is papyraceous (indicated by an arrow) and other is macerated
Fig. 43: Vesicles of vesicular mole

Fig. 44: Wertheim's operated specimen

Fig. 45: Bicornuate uterus with single cervix

Fig. 46: Uterine fibroids with marked distortion of uterus

Fig. 47: Large intramural fibroid
Fig. 48: Submucous fibroid

Fig. 49: Specimen showing submucous fibroid

Fig. 50: Complete vesicular mole

Fig. 51: Partial vesicular mole

Fig. 52: Specimen showing chocolate cyst of left ovary

Fig. 53: Cut section of ovary with dark colored clotted blood suggestive of chocolate cyst of ovary
Fig. 54: Specimen showing adenomyosis

Fig. 55: Specimen showing ovary with multiple follicular cysts

Fig. 56: Carcinoma of vulva

Fig. 57: Squamous cell carcinoma

Fig. 58: Specimen showing endometrial carcinoma

Fig. 59: Endometrial adenocarcinoma
OBSTETRICS RADIOLOGY

Radiological examination has played an important role in obstetric practice and has made major contributions toward accuracy in diagnosis. The importance of radiological procedures in the demonstration of fetal posture, multiple pregnancy, fetal death and abnormalities has been unquestioned for many years. The contribution of radiology to the knowledge of fetal pelvic proportions and to the vital detection of disproportions has received a wide and just acceptance in the last 20 years. Radiology in obstetrics be regarded as a complement to thorough clinical examination, as it lends further to clinical judgment, by bringing into diagnosis an accuracy which is not attainable by clinical methods of examination alone.

Role of Plain Abdominal Radiographs

In plain radiography in pregnancy, both maternal and fetal movements independently may obscure the clarity of a radiograph, and therefore, it is of diagnostic value. Before exposing a film, the mother should be instructed to take several steady and deep breaths (in order to ensure that no fetal anoxemia, which tends to cause fetal movement, will occur). The breath is then held at the expiratory phase. Exposure time should be as short as feasible and the use of Potter-Bucky diaphragm or of a fine stationary grid is essential.

Plain radiography is no longer used to confirm or exclude pregnancy, ultrasound being the investigation of choice (Fig. 1). The fetus can usually be visualized radiographically ideally at 15th–16th weeks but as early as possible by 10th–11th week by a bone-free projection of pelvis in which the tube is angled 15° toward the feet, thus, showing the pelvic cavity clear of bony walls. Absence of fetal parts till 20 weeks is a sure indication of the absence of normal pregnancy. For estimation of fetal maturity, radiological methods are now of historic significance only. Calcaneal center appears at 28 weeks, tala at 26 weeks, distal femoral at 34 weeks and proximal tibial center appears at 37 weeks of gestation.

In one study, Bhargava et al. (1977) reported that tibia and humerus can be utilized to calculate weight of fetus or maturity of fetus antenatally with accuracy of 88%, 86–87%,
and 70%, respectively. Among these bones, femur has significance at 0.01 level.

The reliability of distal femoral epiphysis in prediction of fetal maturity is 96% (Bhargava SK, 1977). An accurate description of fetal position involving two planes cannot be obtained from a single film. But fetal lie (Fig. 2), breech (Fig. 3) or vertex presentation, position and attitude of flexion can normally be made out.

**FETAL ABNORMALITIES**

The following fetal abnormalities may be demonstrated radiologically.

**Fetal Death**

Radiology may demonstrate the following conditions in fetal death.

*Spalding's Sign*

This sign is evident between 4 days and 15 days after death of the fetus and consists of disalignment and overriding of the cranial bones (Fig. 4). The sign is not reliable in early pregnancy because fetal skull must be well ossified for correct interpretation. It is of no significance after engagement of head and particularly during labor owing to normal molding. It is the most reliable sign in the period between 26 weeks and 36 weeks of pregnancy in vertex presentation and in breech presentation till term.

*Gas Translucencies*

Gas translucencies seen in fetal blood vessels of chest, abdomen, and heart constitute certain evidence of fetal death. This sign is transient as gas may come out of solution within 12 hours but tends to redissolve after a few days.

*Hyperflexion of Spine*

It is evident only few days after fetal death and may not be well developed until as much as 4 weeks after death of the fetus. Extreme flexion associated with collapse of skull and thorax indicates a macerated fetus.

*Deuel's Halo Sign*

This is due to elevation of the pericranial fat by underlying soft tissue edema. The fine translucent fat line which should be close to the cranium is lifted and so resembles a halo above the cranium. This is not a very reliable sign. It appears within 2 days of fetal death but can only be seen in last month or two of pregnancy.

Other signs include failure to grow and constancy of fetal position. This requires two examinations separated by an interval.
Extrauterine Pregnancy
Radiological signs are:
- An unusual lie especially transverse
- An abnormal fetal position, i.e. unusually high or low in the abdomen
- An unusual fetal attitude—a limb stretched down in the maternal pelvis and a swimming attitude is characteristic
- Consistency of fetal position and attitude not associated with fetal death
- In the lateral view, the fetal parts may either overlap the spine or lie unusually close, beneath the anterior abdominal wall
- Unusual clarity of the fetus
- Absence of the surrounding shadow of the uterus
- On the lateral view, maternal gas shadows may overlie the fetus or lie anterior to it. Calcification of the fetal (lithopedion) may be seen and is an end result of extrauterine gestation.

Multiple Pregnancy
This is easily seen on radiographs. Conjoined/siamese twins may be suggested by: (i) consistency of position between the fetuses in repeated examination and (ii) deflexion of both fetal spines particularly when the fetuses face each other. They can be of various types:
- Craniopagus—fusion of head usually in parietal region
- Thoracopagus—fusion at thorax
- Xiphiopagus—fusion at sternum
- Omphalopagus—fusion at umbilicus
- Pyopagus—fusion at buttocks.

Abnormal Quantity of Liquor Amnii
Polyhydramnios
The radiological evidence is the disproportion between the size of the uterus and the fetus. Fetus may adopt an unusual attitude and position and lack normal clarity and definition.

Oligohydramnios
The uterus appears closely applied around the fetus, which may appear flexed.

Congenital Abnormalities of Fetus
Soft Tissues
Hydrops fetalis is characterized by the classic “Buddha attitude”. There is loss of the normal kyphotic curvature, arms are held at right angles to the body and thighs are widely abducted, due to gross subcutaneous edema. There may be loss of the normal halo of subcutaneous fat around the fetus because of the presence of edema. Elevation of pericranial fat produces a halo. The lower rib cage may be flared due to hepatosplenomegaly and skeleton may look frail.

Craniun
Hydrocephalus: There is a disproportion between the large size of cranium and the normal facial bones. Cranial vault is poorly calcified. The diagnosis should be made on posteroanterior (PA) film only as undue magnification can occur in anteroposterior (AP) view.
Anencephaly: The cranial vault fails to develop and the bones of the skull base and face are maldeveloped. Cervical spine often shows shortening with separation of pedicles. This condition usually occurs in females (Fig. 5).
Craniolacunia: Cranial vault ossifies irregularly with scalloped defects on its inner aspect. It is associated with spina bifida, meningocele, encephalocele hydrocephalus, and microcephalus.
Cyclops: In this abnormality, there is just one orbit centrally placed.

Spine
Spina bifida: The pedicles are widely separated, and there is often a local kyphos.
Fetal cervical hyperextension in breech presentation: This, so-called “star gazing” fetus, is associated with Down syndrome and also develops in association with umbilical cord being bound around the neck of the fetus.
Coronal vertebra: Failure of fusion of primary ossification centers leads to the presence of a translucent longitudinal band in the vertebra in lateral view. This congenital anomaly is seen in thoracic or lumbar vertebrae and is almost always seen in males.

![Fig. 5: Anencephalic fetus](image-url)
**Limbs**

*Symmelia*: It is the fusion of limbs in whole or in part.

*Amelia*: It is absence of a limb (Figs 6A to D).

*Hemimelia*: It is absence of distal segment of a limb.

*Phocomelia*: It is absence of proximal segment of a limb.

**Systemic Skeletal Abnormalities**

Osteogenesis imperfecta, osteopetrosis and achondroplasia may occasionally be recognized. Congenital syphilis and severe hypophosphatasia with characteristic changes at the metaphysis can occasionally be recognized.

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**PELVIMETRY**

The prognosis for successful vaginal delivery in any given pregnancy cannot be established on X-ray pelvimetry alone because pelvic capacity is one of the several factors that determine the outcome. Mengert has enumerated at least five factors: (i) size and shape of bony pelvis, (ii) size of fetal head, (iii) force of uterine contraction, (iv) moldability of fetal head, and (v) presentation and position of fetus.

X-ray pelvimetry can only give estimation of the first factor. X-ray pelvimetry has some potential advantages over manual estimation. Firstly, it can provide mensuration to a degree of precision unobtainable clinically. Secondly, it provides exact mensuration of two diameters not otherwise obtainable, i.e. transverse diameter of inlet and interischial spinous diameter (transverse diameter of midpelvis).

**Clinical Indications of Pelvimetry**

- Persistent breech presentation particularly in primigravida
- Following a forceps or a nonelective cesarean section, pelvimetry is performed as a postnatal examination prior to any ensuing pregnancy
- During prolonged labor to assess its progress
- Failure to engage in primigravida after 36th week
- Women in whom pelvic deformity is suspected—either congenital or acquired

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Figs 6A to D: Postnatal radiograph showing congenital anomaly involving limbs and spine
• The last three indications noted above are almost nonexistent.

**Planes and Diameters of Pelvis**

Pelvis is described as having four imaginary planes (Figs 7A and B): (i) plane of pelvic inlet, (ii) plane of pelvic outlet, (iii) plane of midpelvis, and (iv) plane of greatest pelvic dimension. Four diameters of pelvic inlet are described AP, transverse and two obliques. The transverse diameter is constructed at right angles to the obstetric conjugate. It intersects obstetric conjugate at a point 4 cm in front of the promontory. The segment of the obstetrical conjugate from the intersection of these two lines to the promontory is designated the posterior sagittal diameter of inlet. The conjugate diameter of pelvic inlet is 11 cm and transverse 12.5 cm. The interspinous diameter of midpelvis is 10 cm. The AP diameter through the level of ischial spine normally measures 11.5 cm. The posterior sagittal diameter at the inlet is much shorter than the anterior sagittal. The anterior pelvis is narrow and triangular. Pelvic sidewalls are convergent, ischial spines are prominent, subpubic arch is narrowed, sacrosciatic notches are narrow and highly arched.

**Types of Pelvis**

Caldwell and Moloy have classified pelvis into four main groups.

- **Gynecoid**
  The inlet is slightly oval or round. The posterior sagittal diameter is slightly shorter than the anterior sagittal. The transverse diameter is slightly greater or same as the AP diameter of the inlet.
  The sidewalls of pelvis are straight, spines are not prominent, pubic arch is wide and sacrosciatic notch is well rounded and never narrow. Gynecoid pelvis is seen in 50% of women.

- **Android**
  The posterior sagittal diameter at the inlet is much shorter than the anterior sagittal. The anterior pelvis is narrow and triangular. Pelvic sidewalls are convergent, ischial spines are prominent, subpubic arch is narrowed, sacrosciatic notches are narrow and highly arched.

- **Anthropoid**
  The AP diameter of inlet is greater than the transverse, sacrosciatic notches are large and sidewalls are convergent. The sacrum usually has six segments and is straight, ischial spines are prominent, subpubic arch is frequently narrowed.

- **Platypelloid Pelvis**
  It has a flattened gynecoid shape with a short AP and wide transverse diameter. The sacrum is well curved and rotated backward. The sacrum is short and pelvis shallow, creating wide sacrosciatic notches.

- **Abnormal Pelvis**
  **Congenital Causes**
  Achondroplasia associated with severely contracted conjugate with a prominent lumbosacral promontory and...
a steep inclination of the pelvic inlet. These features hinder engagement of the fetal head.

If the sacrum is incorporated in the fifth lumbar vertebra, sacral promontory will be higher (high assimilation pelvis). There is apparent lengthening of the sacrum and the pelvic brim has a steeper angle of inclination. In a patient who has only four sacral vertebrae, the pelvic brim lies horizontally. The sacrum is short and its promontory is lower than usual (low assimilation pelvis). In otto pelvis (protrusio acetabuli) the deep acetabula protrude medially to encroach on and distort the cavity of the true pelvis. Classical rarities include malformation of one or both sacral alae resulting in gross pelvic narrowing of the Naegeli or Robert type. In ectopia vesicae, the pelvis is split and held together by fibrous tissue which replaces the pubis.

**Acquired Influence**

Kyphosis of the thoracic spine usually promotes a compensatory lumbar lordosis. This results in contraction of the AP diameter of pelvic outlet and an increase in angle of inclination of pelvic brim. Kyphosis of lumbar spine promotes an almost horizontal pelvic inlet. In spondylolisthesis the subluxated vertebrae may impinge on the inlet. Certain conditions may arise during childhood and may secondarily affect the development of pelvis. These include unrecognized hip dislocation, tuberculosis (TB), suppurative arthritis (Perthes’ disease). Paralysis of hip muscles due to poliomyelitis produces unilateral pelvic atrophy, spinal paralysis resulting in lumbar kyphoscoliosis. The pelvic inlet may become quite asymmetric with relative smallness of the cavity on one side.

Direct pelvic trauma may cause fractures that alter the shape of the pelvis during childhood. The sacral promontory was pushed forward which narrowed the AP diameter of the pelvic brim so that the inlet appeared kidney-shaped. The angle of inclination of pelvic brim is reduced. The sacrum tends more backward and the pelvic cavity is usually sizable. Pelvic deformity caused by osteomalacia differs from that of rickets. The sacral promontory is pushed forward as well as pelvic walls are pushed inward. The forepelvis becomes backed and the pelvic outlet is narrowed in its transverse diameters.

**Radiographic Technique**

The objectives are:
- To produce films which will show the main anatomical features
- To allow measurements of pelvic dimensions to be taken
  The measurements taken directly on the films are subject to a geometric enlargement, which must be reduced by an appropriate correction factor. This is taken as:
  
  \[
  \frac{\text{Distance of plane of pelvis from focal spot}}{\text{Focus film distance}}
  \]

The focus film distance is arbitrarily fixed at 100 cm. To calculate numerator, a direct measurement is taken from an appropriate anatomical landmark to the film cassette or table top. The patient-film distance is then subtracted from the film-focus distance to give the patient-focus distance. Two views are required.

1. An erect lateral view of pelvis
2. The supine AP view of pelvis.

For the erect lateral view, X-ray beam is centered 5–8 cm above the greater trochanter and coned to cover a 30 cm × 40 cm film vertically placed. For the supine view, the vertical beam is centered 5–8 cm above the pubis and coned to cover 30 cm × 40 cm film.

**Observations**

**Erect lateral film:** True conjugate from the sacral promontory to the upper and posterior part of body of pubis is measured; pubosacral distance can be measured. Qualitative estimation as to the prominence of lumbosacral and sacrococcygeal junction is noted. With backward inclination of the sacrum, the sacrosciatic notches are wide and rounded, the angle at the notch being over 90° when sacral inclination is toward the pubis, the notches become narrower and the subtended angle is acute. Sacral inclination toward pubis causes outlet narrowing and funnel pelvis.

**Supine AP view:** This is used for a general appreciation of the pelvis and to show any gross deformities. The pelvic walls in a good obstetric pelvis converge slightly toward the outlet. The fetal presentation is well shown on this view and the degree of head flexion may be better appreciated.

The mean radiation dose absorbed by the fetus is approximately 1.1 rad and may be up to 4 rads when extra exposures are taken.

The four main drawbacks of pelvimetry are as follows:

1. A patient in labor may have to be transported to the radiology department.
2. Projection is taken at an improper angle endangering suboptimal interpretation or additional exposures.
3. Midpelvis cannot be quantitatively assessed since there is no way to place a radiopaque ruler in the plane of midpelvis to accurately measure it.
4. There is a potential risk of in utero X-ray exposure.

**RADIATION HAZARD**

The hazards to the fetus due to radiation are fetal death, malformation, childhood carcinoma, leukemia and mental retardation. The natural incidence of severe defects is 3% of livebirths and the incidence of major defects due to diagnostic irradiation (up to 5 rads) is under 1 in 1,000. This effect is virtually negligible. The natural rate of leukemia and carcinoma is between 0.5 and 1 per 1,000 livebirths. A dose of 5 rads might increase the incidence tenfold.
The International Commission on Radiological Protection (ICRP) (1977) recommended that radiological examination of abdomen and pelvis of women in reproductive age group should be limited to a 10 days interval following menstruation, when pregnancy is improbable. More recently, it has been suggested that irradiation of a mature ovum prior to fertilization may not be without hazard. Irradiation at later stage of pregnancy may also result in inducing malignancies or malformations. National Radiological Protection Board (NRPB) and the Royal College of Radiologists (RCR) have suggested some advices to be followed vis-a-vis radiation hazards in abdominal radiography.

- There is need of no special limitation on exposures during the menstrual cycle
- It is better to treat a pregnant woman when her period is known to be overdue or missed
- In any case where uterus lies near the useful beam the patient should be asked whether she is pregnant
- Special care should be taken to ascertain whether a radiographic examination is really required in a pregnant woman. Number of views should be minimized
- Radiography of areas remote from the fetus can be done safely at any time during pregnancy with good collimation and shields.

Diagnostic irradiation is not regarded as an indication for termination of pregnancy either by American College of Radiology (ACR) or British Institute of Radiology (BIR).

**PLAIN RADIOGRAPHS OF THE ABDOMEN**

**Normal Appearance**

An abdominal radiograph in gynecological practice is taken in supine position. An erect radiograph may be taken when there is suspicion of intestinal obstruction, pneumoperitoneum or ascites. Bladder must be emptied beforehand as it may mimic a gynecological mass lesion. An AP radiograph of the pelvic cavity normally shows the empty bladder and uterus as a soft tissue ovoid density separated by a fat plane.

**Abnormal Appearances**

Plain X-rays may show the presence of:

*Mass:* A pelvic mass may cause a homogeneous soft tissue density shadow within the pelvis or it may extend upward into the abdomen and displace gas filled bowel. Uterine masses lie in the midline and ovarian masses, unless large, tend to remain on their side.

*Calcification:* Uterine fibroids (Figs 8A and B) may undergo coarse patchy calcification especially after menopause. Ovarian lesions which undergo calcification include cystadenoma, cystadenocarcinoma, cystic teratoma, gonadoblastoma and ovarian fibroma. The identification of teeth or tooth remnants, possibly with areas of diminished radiographic density due to fat is strongly suggestive of a dermoid (Figs 9A and B). Cystadenocarcinoma may contain fine granular calcifications, which may also be seen in their omental and peritoneal metastases. Ovarian fibromas are uncommon tumors but may undergo dense calcification. Calcification is sometimes visible in corpora albicantia. TB causes calcification within fallopian tubes, in ovaries and pelvic abdominal lymph nodes.

*Ascites:* It is commonly associated with ovarian causes. It causes bulging of flanks, medial displacement of ascending and descending colon from the fat stripes lying immediately outside the peritoneum and loss of outlines of intra-abdominal structures such as kidneys, psoas muscle and liver. A large cystic ovarian tumor which may be clinically difficult to
distinguish from ascites displaces bowel loops cranially rather than medially and because of its anterior intraperitoneal locations does not obscure renal and psoas muscle outlines.

Pneumoperitoneum: It is a frequent sequela to abdominal surgery usually disappearing within 10 days. Peritoneal gas also results from laparoscopy, tubal insufflation, vaginal douching, from a patulous genital tract in the postpartum state or a multigravida woman when in a knee elbow position.

Plain radiographs are also used in localization of intrauterine contraceptive device (IUCD) (Fig. 10) and vaginal tampons.

ROLE OF PLAIN RADIOGRAPHS IN SPECIFIC GYNECOLOGICAL CONDITIONS

Inflammatory Disease of Female Genital Tract

Acute Salpingitis

On plain radiography, the normal pelvic fat lines are obliterated by inflammatory exudates; moderately dilated loops of small bowel with fluid level are sometimes seen in lower part of abdomen and represent localized ileus. A generalized paralytic ileus and free peritoneal fluid may result from widespread peritonitis in severe cases. A tubo-ovarian abscess is seen as a soft tissue mass radiographically. Occasionally, small radiolucent gas bubbles are visible within the abscess. Uterine gas gangrene is usually due to clostridial infection. Bubbles of gas may be seen either within the cavity or wall of the uterus. Cervical stenosis specially when due to a carcinoma cervix or following radiotherapy predisposes to pyometra. A large rounded pelvic mass which contains gas and fluid level is sometimes seen on plain radiographs.

Emphysematous Vaginitis

Emphysematous vaginitis is a benign, self-limiting condition in which gas filled cysts are present in the lamina propria of the vaginal wall and cervix, often due to Trichomonas infection. Small gas bubbles are seen behind and above symphysis pubis on plain radiographs. Vaginal tampons have a radiolucent rectangular appearance. They may be approximately 1 cm × 4 cm in the lower part of pelvis just above the symphysis pubis.
**Uterine Tumors**

Multiple and large fibroids may show a soft tissue pelvic mass often with a lobulated outline. Calcification within fibroids either follows necrosis in pregnancy or is secondary to postmenopausal degeneration. Small and scattered calcifications are initially seen increasing in size and number and eventually coalescing to form coarse aggregation. Less commonly, a peripheral rim of calcification may be present.

**Ovarian Masses**

Benign ovarian cysts are seen as well-defined, rounded soft tissue masses within the pelvic cavity sometimes rising into the abdomen, but distinct from the urinary bladder and uterus.

**Epithelial Tumors of Ovaries**

Soft tissue pelvic masses often extending into the abdomen are present. Psammoma body calcification is often visible in serous cystadenomas and in 12% of serous cystadenocarcinomas. Aggregation of psammoma bodies gives rise to a granular, hazy calcification. Metastatic deposits from these tumors in the peritoneum, liver, lymph nodes may also show the same pattern of calcification. Serosal metastases are often distributed along the colon and could be mistaken for previously ingested barium. Bizarre, dense and well-defined calcification is sometimes visible within serous cystadenocarcinomas. Mucinous cystic ovarian tumors rarely calcify but curvilinear calcification may develop in pseudomyxoma peritonei. Ascites is commonly associated with ovarian tumors.

**Meigs' Syndrome**

There are four criteria of Meigs’ syndrome:
1. A benign and solid ovarian tumor with the gross appearance of a fibroma, thecoma, granulosa cell tumor and Brenner tumor are included in this category.
2. Ascites—small to enormous in amount.
3. Pleural effusion especially on the right side.

**Chest Radiographs**

This may show the presence of active pulmonary TB, which is important in infertility patients. Infertility in such cases may be due to the toxic effect of pulmonary infection or due to concomitant tuberculous, endometritis, or salpingitis. In case of ovarian or uterine carcinoma, chest radiographs may show pulmonary metastasis or pleural effusion. Trophoblastic tumors (chorionepithelioma) may produce three main types of chest metastases, i.e. (i) discrete masses which may be single or multiple; (ii) multiple ill-defined metastases producing a snowstorm or mililiary appearance and (iii) arterial emboli producing the changes usually associated with pulmonary infarction or less commonly the changes of “primary” pulmonary hypertension.

**Skull Radiographs**

In gynecologic practice, plain radiographs of skull are usually obtained to demonstrate osseous metastases or to demonstrate the pituitary fossa as a part of investigation of infertility. Infertility may be secondary to pituitary or suprasellar tumor which may expand the bony pituitary fossa and erode dorsum sellae. Pituitary microadenoma, which may secrete prolactin and cause galactorrhea often do not cause enlargement of pituitary fossa. Minor alteration of the contour of the fossa, such as double floor may be associated with prolactin-secreting microadenomas.

**ROLE OF INTRAVENOUS UROGRAPHY IN GYNECOLOGY**

Intravenous urography (IVU) is performed in gynecology for demonstrating distortion, deviation or obstruction of urinary tract, to study the pelvis and to show presence of hydronephrosis. The study should be carried out without compression so as to demonstrate the effect of any pelvic obstruction. Full length films should be taken from the beginning of the examination for the proper assessment of the pelvic lesion. A pelvic mass by virtue of its location may cause a fundal impression on the bladder or may deviate/obstruct the ureters. Ureteric obstruction may also be observed in cases of procidentia. Late stages of uterine cancer may invade the bladder or the ureter. Carcinoma cervix causing hydronephrosis or leading to nonfunctioning kidney is grouped in stage III according to the American Joint Committee on Cancer (AJCC) classification. Tumor invading mucosa of bladder is grouped in stage IV.

The complications of hysterectomy that can be demonstrated by IVU include:
- Partial or complete occlusion of a ureter by a suture leading to a hydronephrosis kidney or failure to excrete on the same side
- Division of the ureter may lead to extravasation of contrast into the pelvic fascia or a vaginal fistula. The ureterovaginal fistula may heal spontaneously over a length of time
- Pelvic accumulation of blood or lymph (i.e. hematoma or lymphocyst) may be made out. If these accumulations are large, they may distort the shape of the bladder or deviate the course of ureter
- Vesicovaginal fistula may be observed on the IVU films utilizing supine, prone, oblique and lateral projections.
Role of Cystography

Cystography may demonstrate usefulness in investigating cases of stress incontinence and vesicoureteric reflex in patients with urinary symptoms.

The vesicovaginal fistula may be studied using a modified technique. The technique of micturating cystogram is used with an indwelling catheter connected to a bottle of contrast via an irrigation set. The patient is screened in a lateral position with the help of a fluoroscope as contrast is seen with the patient lying on her side. The contrast can be siphoned and optimum radiographs can be taken with the patient rotated suitably and the bladder filled optimally.

Barium Enemas

Barium enemas may be required for assessing bowel involvement by spreading pelvic carcinomas, endometriosis or to demonstrate irradiation colitis. Rectovaginal fistulae may be demonstrated using water soluble contrast media better than with barium.

Lymphangiography

Bipedal lymphangiography is the only direct radiological method of visualized lymphatic system of pelvic and para-aortic area. It is useful in detecting metastatic spread from carcinoma of genital tract. This procedure was used in staging of invasive cervical carcinoma and in localization of involved lymph nodes before radiation therapy. It also provides useful information about the relative completeness of operative lymphadenectomy during radical surgery. The use of lymphography is, however, now obsolete. Lymphangiography is done with an oily contrast. The contrast passes through the lymphatics of leg to the external iliac, common iliac, and para-aortic nodes. It then passes through cisterna chyli and thoracic duct to drain into venous system usually through left brachiocephalic vein. Lymph nodes in the inguinal, external and common iliac chains and the paracaval and para-aortic nodes are opacified. Internal iliac, hypogastric obturator, paracervical and presacral nodes are not opacified.

Abnormal Findings

Filling Defect

Defects due to the metastases usually have sharply defined margins. They may be peripheral or central, metastases can sometimes cause enlargement, displacement or motting of lymph nodes. Extensive lymph node involvement causes their obliteration with stasis in lymph vessels and formation of collateral lymphatic vessels. With carcinoma cervix, the initial spread is parametrial nodes and to obturator, internal and external iliac nodes and then to the common iliac and para-aortic lymph nodes. The internal iliac and obturator lymph nodes, however, are not shown in bipedal lymphangiography.

Lymphangiography has been considered to be unreliable in determining treatment in stage I and stage II disease, but was of value in combination with operative findings when the aim was to remove nodes which had been classified as positive or equivocal for metastasis. Increase in size of nodal defect over a 6-week period is the most reliable sign of metastasis and differentiates it from reactive hyperplasia, infection, and fibrous or fatty defects.

Ovarian carcinomas metastasize in about 46% of patients to para-aortic and iliac lymph nodes. While tumors, which have spread to adjacent pelvic viscera and peritoneum, metastasize to iliac lymph node, serious cystadenocarcinoma spread more frequently to lymph nodes than mucinous tumors do.

ANGIOGRAPHY

Arteriography

It is used in gynecology to demonstrate the blood supply to a pelvic mass, as an aid in planning the surgical approach to the lesion. It may be used to assess the spread to vascular malignancies to the pelvic wall and to demonstrate vascular metastases to the liver. Pelvic arteriography is a relatively infrequently used procedure in the reproductive age female as it entails considerable radiation exposure. The uterine artery in parous women is markedly tortuous; whereas in nullipara, it follows a relatively straight course along the lateral margin of the uterus. The large branches of uterine artery are generally visible, as are the terminal branches to the adnexa. The blood supply of a leiomyoma is derived from intramural branches of the uterine artery and tumor is generally vascular. In the ovarian tumors, blood vessels tend to be sparse and blood supply is derived from a single adnexal vessel. Adnexal tumors usually do not have the capsular blood vessels characteristic of a leiomyoma.

Venography

Pelvic venography will demonstrate iliac vein thrombosis which may follow gynecological surgery or radiotherapy. Direct spread from uterine carcinoma and ovarian malignancies may compress iliac veins and cause secondary venous thrombosis.

Uterine Phlebography

Contrast medium is directly injected into fundal myometrium via a special metal cannula. Intravasation of contrast medium
into the venous plexus of the uterine wall is followed by visualization of uterovaginal and ovarian venous plexus. Intrauterine phlebography is used to demonstrate pelvic varicoceles.

**VAGINOGRAPHY**

A Foley catheter is inserted into vagina and its balloon is distended by 20–30 mL air to provide a snug fit just above the introitus. A water soluble contrast medium is then injected through the catheter into the vagina.

**Indications**

- To demonstrate fistulae between the vagina and ureter, bladder, skin, or rectum
- Congenital or acquired abnormalities of the vagina such as diverticula
- To localize, by reflux, an ectopic ureter opening into the vagina.

Vaginography is, however, now almost out of use.

**PNEUMOGYNECOGRAPHY**

This involves the visualization of the pelvic cavity and its organs through the introduction of an artificial pneumoperitoneum. The pneumoperitoneum is generally produced by instillation of carbon dioxide through the transabdominal, transuterine or posterior vaginal approach. The soft tissue density of the uterus, ovaries and broad ligament is readily visualized against the dark contrast of carbon dioxide bubble. Simultaneous hysterosalpingogram with contrast material can be performed under fluoroscopic control to provide further delineation of pelvic organs. It is indicated in the evaluation of pelvic masses in the obese patient, in children for diagnosis of congenital anomalies of the pelvic organ and in the assessment of the adnexa in infertility patients or in patients with endocrinopathies. The technique is contraindicated in cases of significant cardiopulmonary disorders, acute pelvic inflammatory disease (PID) and in the presence of large tumors in the pelvic cavity. This technique has been largely replaced since the availability of sonography.

**HYSTEROSALPINGOGRAPHY**

Hysterosalpingography (HSG) is the radiographic demonstration of uterus and fallopian tubes by injection of contrast material through the cervical os. It demonstrates the uterine cavity by filling it and the lumen course and patency of fallopian tubes. HSG is done under fluoroscopic monitoring.

**Indications**

- Suspected congenital uterine anomalies
- Repeated abortions
- Infertility evaluation
- In cases of abnormal uterine bleeding
- Incompetence of cervical os
- Locating a lost intrauterine device
- Pre- and postsurgical tubal evaluation
- Evaluation of intrauterine adhesions (Asherman syndrome)
- Following ectopic pregnancy
- Prior to artificial insemination and in vitro fertilization
- After tubal sterilization procedures
- Following myomectomy.

**Contraindications**

- Acute pelvic infection
- Pregnancy
- Active per vaginal (PV) bleeding
- Prior to 7 days of last menstrual period (LMP) and after 10 (at times 12) days of LMP. In the former condition, the venous sinuses may be open resulting in contrast intravasation and in the latter situation, the patient may have conceived
- Sensitivity to contrast media
- Severe renal/cardiac disease
- Recent dilatation and curettage.

**Historical Perspective**

Hysterosalpingography is derived from the Greek words hystér (uterus), salpinx (trumpet) and graphein (to write). The first HSG was carried out by Rindfleisch who injected a watery bismuth paste through the cervical canal, to examine a 21-year-old patient suspected of having a tubal pregnancy. Rubin injected 10–15% solutions of the silver salt callargol into postmortem human and live rabbit’s uteri. In 1924, Henser injected lipiodol into the uterine cavity of a pregnant woman with TB for inducing an abortion. Newell in 1926 used iodopin (a 40% iodine solution in vegetable oil) for HSG in 38 women. Stein and Arens combined HSG and pneumoperitoneum; the iodized oil outlined the uterine cavity and the lamina, and the pneumoperitoneum showed periadnexal adhesions, irregular uterine contours, and tubes and ovaries.

**Radiation dose:** The average radiation dose to ovaries is approximately 75–550 mrad.
The cervix is caught by the tenaculum, atropine may be given.

Intravenous diazepam may be required in an exceptionally nervous patient. Morphine and its congeners are not used as they inhibit the smooth muscle contraction of the fallopian tubes. The patient is positioned in the dorsal lithotomy position and a preliminary PV examination is carried out to determine the position of the uterus and the cervix. Vagina and the perineum are cleansed and prepared. The speculum is introduced into the vagina and the anterior lip of the cervix is caught by the tenaculum. The physician can lessen the pain inflicted by the procedure by injecting approximately 30 mg of lidocaine with a 22-gauge spinal needle just beneath the cervical epithelium, at the 12 o’clock position. The tenaculum should be closed gently to further lessen the pain.

Cannulas used for HSG should prevent cervical leakage, enable maximal delineation of the uterine cavity be easy to use, allow manipulation during the procedure and cause minimal discomfort to the patient. Balloon catheters (8F Foley) are valuable for studying genital tract duplications because of the proximity of the structures and narrowness of the working channel.

Disadvantages
- Filling defect due to the inflated balloon
- Occasional extrusion of the balloon
- Difficulty of insertion through the internal os in some patients.

The Malmström vacuum apparatus creates a vacuum and suction between the cannula. The radiographic quality is excellent when the apparatus is applied correctly but the frequent loss of apparatus parts, loss of the vacuum and need to have several sets available are disadvantages.

Cannulas
- Jarcho cannula
- Leech-Wilkinson cannula
- Everard Williams cannula
- Green-Armytage cannula

The Jarcho cannula has a rubber acorn placed about 2 mm from the end and is fixed securely in position by a set screw. It is easy to use and is reliable.

The Leech-Wilkinson cannula has a screw threaded olive at its distal end which enables watertight fit to be made easily into the cervix, and this prevents the reflux of the contrast medium into the vagina. It can produce cervical laceration. The Everard Williams pattern has a smooth olive near the distal end and the tip of the cannula is bent to allow easy introduction into the cervical canal. It is a satisfactory cannula, but a good seal at the cervix must be maintained to prevent reflux of the contrast medium. The Green-Armytage cannula has a rubber acorn which is variable in position along the length of the straight metal cannula. It provides a fairly watertight junction with the cervix.

Contrast medium is a water-soluble contrast agent, such as urografin 60% and conray 280. The contrast is injected by slow constant injection under fluoroscopic guidance. Routinely two to three films are taken with the help of image intensifier. PA views are generally acquired, oblique and lateral views being required only rarely. Oily contrast media have been abandoned due to the risk of acute tubal blockage, reactivation of infection and oil embolism hazards. The films should show:
- Early uterine filling
- Early genital filling including tubes
- Late film showing spill
- A radiograph taken 20 minutes later will show the pattern of peritoneal spill. A prone radiograph may be required for questionable loculation on supine X-ray.

Complications

Pain and discomfort: This is the most common complication. Hypogastric pain is due to contrast distending uterus and peritoneal spill of contrast which causes peritoneal irritation. It only requires reassurance and generally no treatment is needed.

Venous intravasation (Figs 11A and B): This is a harmless condition which does not require any treatment. It may obscure the picture. This is due to blocked/diseased tubes, excessive injection pressure and recent uterine surgery or if performed early.

Pelvic infection: This may occur in presence of pre-existing chronic infection. It is treated with antibiotics which may be given prophylactically after the procedure in patients of PID. It is the most serious complication.

Bleeding: This is due to the improper application of tenaculum. It is usually of minor amount and no treatment is required. The other rare complications are uterine perforation and tubal receptive shock, allergic reactions and mortality.

NORMAL RADIOLOGICAL ANATOMY

The normal uterine cavity (Figs 11A and B) is usually seen as triangular in shape and it measures approximately 1.5 inches (uterine sides) while the cervical canal is approximately 1 inch. Many different shapes and appearances are possible. The uterine cornua show a linear lucency and constriction which may be indicative of a sphincter at the cornuotubal junction. The different parts of the fallopian tube are seen. The isthmic part of the fallopian tubes may be difficult to identify but their broader ampullary and infundibular parts are usually well delineated. Fallopian tubes are about 10 cm in length with a variable degree of tortuosity. The spill of the contrast from the tubal ends is seen as amorphous scattered collection of contrast with curvilinear opacities outlining peritoneal recesses and bowel loops. The pouch of Douglas...
may be identified and the elliptical outline of the ovaries may be seen.

Failure of contrast medium to pass through the tubes to the peritoneum may be due to cornual tubal spasm. Inhalation of amyl nitrate may help in such conditions (though its role is dubious). Gentle injection pressure and patience are the most important factors that help to relieve the spasm. Intravenous Buscopan may also prove helpful in such situations.

**HYSTEROSALPINGOGRAPHY APPEARANCES**

**Normal Variants**

Spiculated uterine outline is due to glandular filling in an atrophic endometrium. It is common in menopausal women.

*Longitudinal uterine folds*: These are probably due to Müllerian duct remnants. They are seen as linear lucencies parallel to the lateral border of the uterine cavity.

*Double outline of uterine cavity*: It is due to contrast penetrating endometrial glands in the secretory phase of the cycle.

*Polypoid filling defects*: They may be noticed along the uterine margins.

*Contrast-filled small cavities*: They are found just above the fundus of uterus or near the isthmus.

**Congenital Uterine Anomalies**

*Hypoplasia and agenesis*: In women with vaginal, cervical, fundal or combined agenesis, HSG is not possible. In case of tubal absence, the HSG shows the uterine cavity and the intramural tubal segment.

A hypoplastic uterine cavity is usually 5 cm or less in length, two-thirds cervix and one-third corpus. The volume of contrast medium needed to fill the uterine cavity and each of the fallopian tubes is usually 1 mL or less. The triangular shape of the cavity is preserved.

*Unicornuate uterus*: It results from failure of development of one Müllerian duct. It may be associated with ipsilateral renal agenesis or pelvic kidney. The problems associated are repeated abortion, premature labor, and malpresentation.

With a unicornuate uterus and a communicating horn, the HSG shows a uterine cavity and possibly a narrowed opacified area seeming to originate from one of the borders of the hemiuterus (Fig. 12). Noncommunicating and rudimentary horns without a cavity do not opacify. On HSG,
14 SECTION

Miscellaneous

the unicornuate uterus appears more or less oval, with the fallopian tube originating from the upper pole. The uterus points to the right or the left and is rarely in midposition.

It should be differentiated from an incompletely filled uterine cavity, intense spasm of one horn or synechiae blocking access to the opposite horn.

Didelphic uterus: Embryological cause is the total failure of Müllerian duct fusion. HSG is often technically difficult because two sets of instruments are needed and the vaginal partition narrows the available space. In this situation, the Foley catheter technique is very useful for performing HSG. The separate horns appear flexed toward each other or in opposite directions, they may communicate in the isthmic region. Two cervices appear with two separate fusiform uterine cavities and single fallopian tube arising from each of them (Fig. 13).

There is an increased frequency of twinning and of spontaneous abortion. The differential diagnosis is from bicornuate and unicornuate uterus.

Bicornuate uterus: This results from incomplete/partial fusion of the fundal segments leaving paired uterine horns and one cervix. The division may be complete to the cervix or partial (Fig. 14).

Clinical Implications

- Failed therapeutic abortion due to maneuver directed at the nonpregnant horn
- The nonpregnant horn may cause obstruction to vaginal delivery
- Vaginal bleeding following expulsion of decidua membrane in the nonpregnant horn can mimic placenta previa/threatened abortion.

Septate uterus: The septate uterus is either completely or partially divided by a longitudinal septum. A uterine septum should be suspected if the fundal angle caused by the separation of the horn is less than 90°. This separation remains constant even as the cervix is manipulated with a tenaculum during fluoroscopic control. Hysteroscopy and laparoscopy are essential for the proper diagnosis of septate uterus.

It is the most common cause of habitual abortion and it may also lead to premature labor.

Arcuate uterus: This is a minor uterine malformation caused by failure of Müllerian ducts to fuse completely. The diagnosis is presumed if a line drawn from one corner to the other, and another perpendicular to it and extending to the depth of the concavity, measures between 1 cm and 1.5 cm. Its angle is more than 100°, the horns appear symmetric and the contour is that of a saddle-shaped fundus. Asymmetric horns or an irregular depression suggests a fundal myoma, whereas the small septate uterus has a more or less V-shaped trough and the fundal depression exceeds 1.5 cm (Fig. 15).

Diethylstilbestrol-related Abnormalities

This synthetic estrogen was used in 1949 through 1971 in some patients with threatened abortion or poor obstetric history. The characteristics of diethylstilbestrol (DES) exposure seen on HSG are—a small hypoplastic endometrial cavity, concavities beneath the cornua giving the appearance of uterotubal constrictions, T-shaped uterine configuration and cervical widening.

Cervical abnormalities, including hypoplasia, hoods, collars and pseudopolyps are seen in many of the exposed women almost 90% of whom have upper genital tract abnormalities. Many of these women complained of infertility.

Gartner’s Duct Cyst

A persistent mesonephric duct can be opacified during HSG. It can extend from the cervical region to the corner. Gartner’s
duct cysts are anterolateral vaginal tumors that generally do not contain blood.

With a kite-shaped uterine cavity there is outpouching of contrast material in the fundal area.

**Uterine Tumors**

*Endometrial polyps*: These may be single/multiple, large or small, pedunculated or sessile. A single polyp does not distort the triangular shape of the cavity, but multiple polyps producing large defects cause some loss of the uterine outline. Polyps cause radiographic intrauterine defects with sharply defined borders in various shapes (Fig. 16). The defect along the outline of the uterine shadow corresponds to the pedicle of the polyp. An inner radiolucent area is seen because of partial coating of the polyp, with contrast medium. In case excessive material is used, the defect becomes obscured until some fluid is evacuated. Hence, there is need for fluoroscopic control and fractional instillation of contrast medium, with appropriate spot films.

*Leiomyomas*: Submucous and intramural myomas (Fig. 17) can be seen on HSG. The serosal/pedunculated types are seen radiologically when they are calcified. As a submucosal myoma can distort and enlarge the cavity, HSG demonstrates it as contrast material passes around it creating a crescent configuration. Myomas located in the lower segment/isthmus produce a ballooning of this region. The differential diagnosis includes an intrauterine pregnancy, uterine spasm or hypercontractility.

*Adenomyosis*: On HSG, diverticula are seen to branch out from the uterine cavity outlined by the contrast medium into the myometrium, when the abnormally located endometrial glands communicate with the endometrial lining. At times a honeycomb appearance may be seen due to contrast filling of these glands. Large, localized adenomyomas may produce radiographic shadow indistinguishable from a submucous myoma by distorting and enlarging the cavity. In endometrial hyperplasia, the appearance is nonspecific, the cavity appearing uniformly enlarged with wavy or scalloped borders.

**Intrauterine Adhesions**

The predisposing factors for these adhesions are pregnancy-related curettage; following tuberculous endometritis, metroplasty, submucous myomectomy, and diagnostic curettage.
The radiological diagnosis can be suspected from an HSG that reveals filling defects with irregular ragged contours. The normal uterine shadow may be useful in excluding the diagnosis of intrauterine adhesions.

Intrauterine adhesions appear on HSG as sharply outlined central or marginal filling defects that are relatively constant on segmental radiographs. One should not introduce excessive contrast as it may alter their shape and obscure even severe lesions. Intravascular and lymphatic intravasation may occur with extensive lesions.

**Obstruction of Tubes**

The causes are luminal fibrosis salpingitis isthmica nodosa (SIN), previous tubal sterilization, salpingitis, TB and polyps. HSG shows tubal dilatation, especially of the ampullary portion with loculation and absent or limited peritoneal spill.

Distal tubal obstructions have been classified into four groups based on the HSG findings.

1. **Degree I**: Congenital narrowing of the fimbrial folds (phimosis) with tubal patency.
2. **Degree II**: Complete distal occlusion with normal ampullary diameter.
3. **Degree III**: Complete distal occlusion with ampullary diameter 15–25 mm.
4. **Degree IV**: Occlusion with ampullary diameter more than hydrosalpinx simplex.

In cases of hydrosalpinx (Fig. 18), contrast medium will still be present in the obstructed tubes an hour after the examination. To differentiate hydrosalpinx from loculated spill, laparoscopic correlation may prove useful.

**Tubal Polyps**

In the presence of polyps, the intramural lumina appears dilated with small, persistent, oval defects that usually appear lateral to the cornua. Intratubal filling defects caused by air bubbles can be differentiated from polyps by adding contrast material, tilting the patient, manipulating the cervical tenaculum, or by repeating the study.

Congenital tubal abnormalities, such as accessory ostia, multiple lumina, diverticula, total duplication/absence are also seen on occasions.

**Pelvic Inflammatory Disease**

The common causes of PID are chlamydiae, gonorrhea and TB. On HSG, the appearances are:
- It may be normal in cases of minimal involvement
- Peritubal adhesions seen as crowding of ampulla known as the “clumping sign”
- Loculated peritoneal spill.

**Cervical Incompetence**

Cervical incompetence may be congenital or secondary to cervical trauma. On HSG, the appearance is of widened internal cervical os giving rise to “funnel-shaped” appearance of uterus and cervix. A canal more than 1 cm wide is considered abnormal.

For the evaluation of cervical incompetence, one of the methods used is obturating the external cervical os with a cannula and acorn large enough to prevent leakage of contrast medium, and performing HSG.

**Salpingitis Isthmica Nodosa**

This is the descriptive term for nodular thickenings in the isthmic or intramural segment of one or both fallopian tubes. The factors responsible for the pathogenesis of this condition include:
- Chronic salpingitis
- Developmental defect
- Endosalpingeal metaplasia
- Tubal endometriosis.

Salpingitis isthmica nodosa cannot be detected by physical examination. Most of the abnormalities are detected on HSG. Radiologically, it appears as a honeycombed or punctated accumulation of contrast material in the isthmic, isthmo-cornual or isthmo-ampullary segment. Numerous diverticula are present. On delayed radiographs, persistence of contrast material in many small channels may be discerned as white stippled areas. In some HSGs, the remainder of the tube appears normal; in others additional types of obstruction may be seen.

**Pelvic Tuberculosis**

Female genital TB (Fig. 19) is usually secondary to a lesion elsewhere in the body. The primary may be in the lung, gastrointestinal tract (GIT), urinary tract or elsewhere. Very rarely it is acquired from the ascent of the infection from the
introitus, which occurs in the rare circumstance of a girl child sitting on infected spit (direct contact)/after coitus with a man who has tuberculous epididymitis. The fallopian tubes are involved the earliest in the female genital tract.

Fallopian Tubes

Radiologically, latent TB frequently causes characteristic radiographic changes initially in the ampulla, then in the isthmus. TB is the presumptive diagnosis when calcified pelvic or mesenteric glands are associated with bilaterally occluded, rigid tubes. At times the tubes show proximal obstruction, they may also be partially obliterated by filling defects, ending in small terminal occlusions or pouches. Diverticula sometimes extend from the sac-like tubal ends. The borders of the tubal lumen are often sawtoothed with multiple filling defects.

The occluded ampulla appears tufted, with less dilatation than in other types of distal tubal obstruction. Stricutured tubes are characteristic of the oldest lesions. The gaps in the contrast material are caused by isolated groups of hypertrophic villi surrounded by areas of destroyed rugae. The ragged contours result from deep mucosal ulcerations.

The findings in tuberculous salpingitis may thus be:
- Salpingitis isthmica nodosa (Fig. 20)
- Beaded or pipestem tubes
- Irregular patulous tubal lumen
- Isthmic obstruction
- Occluded contracted ampulla
- Hydrosalpinx
- Characteristic calcification of fallopian tubes.

In cases of TB, tubal calcification can take the form of linear streaks which lie in the course of the fallopian tubes or appear as faint or dense tiny nodules.

The causes of tubal blockage can be summarized as:

Tubal Spasm

This may occur at the cornuotubal junction or along the tubal length. When under fluoroscopic observation, no or little contrast is seen to flow into the tubes—gentle injection pressure is maintained for a few minutes. This makes the tubal spasm relax so as to flow of contrast into the fallopian tubes.

Poor operative technique: If the cannula is not held in firm apposition to the cervix then back leak of the contrast can result. To ensure that no back leakage occurs, a proper seal should be maintained around the cervix and during screening a watch should be kept on the vaginal vault for any leakage.

Obstruction Following Infection of Tubes and Operation

Salpingitis can lead to obstruction of the lumen of the fallopian tubes by inflammatory adhesions. Postsalpingostomy, a similar appearance may be observed due to the loss of the patency of the tubes. It may be seen following tubal amputation as well. In case of hydrosalpinx on HSG, the contrast medium enters and outlines a club-shaped dilatation of the lateral part of the affected tube, the proximal part of which may be of normal caliber.

Fimbrial Adhesions

Adhesions may form around the lateral ends of the tubes and involve the fimbria in cases of pelvic peritonitis or salpingitis. The HSG in these cases demonstrated the entire length of the tubes with failure of free peritoneal spread. The contrast material is retained in small spots at and around its lateral end.
**Tubal pregnancy, tumors:** Obstruction may be seen in association with tubal pregnancy or tumors arising in the wall of tube/the parametrium.

**Sterilization procedures:** These include fallopian tube ligation, laparoscopic diathermy of the tubes and clip sterilization. At times HSG may be required for the confirmation of the occlusion.

**Uterus**

The uterus may be hypoplastic, enlarged, shrunken and deformed, or it may be normal. Endometrial TB is characterized by a shriveled, deformed uterine cavity associated with intrauterine adhesions and lymphatic intravasation. The endocervical canal seems dilated and the uterine cavity appears dwarfed due to endometrial destruction.

Advanced endometrial TB (Fig. 21) can cause scarring of the internal os, distortion of the endometrial cavity and intravasation of contrast. The cervical canal may be very long and dilated, with a small uterine cavity showing filling defects. T-shaped uterus along with tubal changes is virtually diagnostic of TB in India. This T-shape is due to scarring. When the scarring due to TB is more unilateral it leads to obliteration of that side of the uterine cavity, the pseudouicornuate uterus.

**Intravasation:** Lymphatic/venous intravasation may be caused by endometrial and myometrial TB.

**The ovaries:** Ovarian calcification is a rare finding.

**Fistulae**

Tubulointestinal fistulae are often caused by TB.

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**Tubal and Uterine Fistulae**

**Uterocutaneous fistulae:** These menstrual fistulas connect the skin and the uterine cavity resulting in a periodic bloody discharge from the skin. On the anterior abdominal wall, it occurs after rupture of a cornual pregnancy, previous cesarean section and ventral uterine fixation.

**Uterovesical fistulae:** These can result as a complication of cesarean delivery, gynecologic surgery, pelvic irradiation, severe pelvic infection and advanced genital malignancy. The term menouria denotes vesical cyclic menstruation that occurs if the tract is above the uterine isthmus. When the history and clinical findings suggest the possibility of a uterovesical fistula (Fig. 22), contrast medium is instilled into the urinary bladder or uterus. The agents or urine can be seen coming from the cervical os. The best diagnostic cystogram is obtained by filling the bladder to its capacity at the time of menouria. Asking the patient to assume the knee chest position or applying suprapubic pressure may result in the flow of urine into the uterine cavity and out of the cervical os. In cases of fistulas, HSG may delineate the fistulous communication, oblique and lateral views being useful.

**Uterointestinal fistula:** This fistula can result from uterine rupture and subsequent entrapment of an intestinal loop in the uterine defect. The contracting uterus compresses the bowel, causing necrosis resulting in a fistula. It can also result from complications of a pelvic abscess and a ruptured diverticulum.

The diagnosis can be confirmed by a lower gastrointestinal barium study outlining the colonic fistula. HSG is indicated because multiple fistulae may be present. The appearance of the contrast medium in the bowel loops following HSG is characteristic.
Tubocutaneous, tubovesical and tubointestinal fistulae also occur rarely.

**Therapeutic Effects of Hysterosalpingography**

- Expulsion of inspissated mucus or blood from the tubal lumen
- Dilatation of tubes in cases of fimbrial phimosis
- The ability of straighten kinks at the uterotubal junction or to stretch peritubal adhesions
- Creation of a favorable effect on the tubal epithelium because of the iodine content
- Stimulation of tubal contractility from a bolus of fluid
- Effects on the immune milieu in the posterior cul-de-sac.

In a study where all forms of infertility were include overall, the occurrence of pregnancy in the group where water soluble contrast was used was 13%. The group in which oil soluble contrast medium was used, 20% patients conceived subsequently. Another study reported a pregnancy rate of 35% within 6 months after the instillation of oil soluble contrast medium in women who had normal tubes and unexplained infertility. A randomized, prospective study compared pregnancy rates after the use of the two types of contrast media and revealed a statistically insignificant difference during the first 6 months after the procedure. An entranced pregnancy rate has not been proved, hence it should not dictate the choice of contrast medium. In a study by Bhargava et al. (1978), HSG was found to be therapeutically effective in 21% cases.
SECTION 15

Recent Advances
APPLICATIONS OF LASER IN GYNECOLOGY

The term LASER means Light Amplification by Stimulated Emission of Radiation. Any surgical procedure which requires cutting, coagulating or removing tissues can be effectively achieved by laser. Laser surgery vaporizes tissues layer by layer without touching them, with minimal thermal damage and good clinical results.

Lasers Used in Surgeries
Various types of lasers which are used for surgery are:
- Carbon dioxide (CO$_2$): 1,064 nm
- Erbium: 2,940 nm
- Diode: 810 nm
- Alexandrite: 755 nm
- Ruby long pulse: 694 nm
- Neodymium-doped yttrium aluminum garnet (Nd:YAG): 1,064 nm

LASER SURGERY FOR CERVIX

Vaporization Conization
Cervical conization is defined as removal of a volume of tissue from the central longitudinal axis of the cervix which includes the external os and some length of endocervical canal.

Requirements
Requirements for vaporization conization are:
- Lesion should be completely visualized
- Transformation zone should be completely seen
- Adenocarcinoma of endocervical canal should be ruled out
- CN should be confirmed.

Procedure
Vaporization conization using CO$_2$ laser through the colposcope can be performed in office, clinic or operating room. General anesthesia is usually not required. The margins of the transformation zone is outlined by vaporization caters using short bursts of laser energy. The craters are then connected and the cervix is divided into four quadrants and then the tissues are vaporized quadrant by quadrant to a depth of 7 mm.

Excision Laser Conization of the Cervix
This procedure produces a conization biopsy specimen which is adequate for pathologic examination and also if possible to excise the disease.

Indications for laser excisional conization are:
- Lesion extends into the canal and cannot be entirely seen
- The entire transformation zone cannot be visualized
- Abnormal cytology in absence of positive colposcopy
- Positive endocervical curettage
- Invasive cancer which cannot be ruled out by biopsy.

This procedure can be performed on an outpatient basis or under general anesthesia. After applying 4% acetic acid, borders of the lesion are noted and a cone shape excision is achieved. Advantages are that there is less bleeding than with scalpel, less tissue damage than with electric cautery, more percise than cryoautery and more procedures can be performed by using combination of vaporization and excision.

LASER SURGERY OF THE VULVA

Unlike cervical vaporization, depth of vaporization on vulva cannot be measured. Vulvar laser surgery is done with the aid of the colposcope.
**Condyloma Acuminata**

Human papillomavirus involves the epidermis and superficial portions of skin appendages. Each condyloma is identified and laser beam directed on the target. Laser vaporizes the condylomata rapidly with the beam.

**Vulvar Intraepithelial Neoplasia**

Local or general anesthesia can be used for vulvar laser surgery. In multiple lesions or large areas of involvement, general anesthesia is practical. Vulva is recolposcoped, 4% acetic acid is applied and affected area marked, and epidermis and superficial dermis are ablated with usual spot size of 2–3 mm and power setting of 15–50 W.

**LASER SURGERY OF THE VAGINA**

Vaginal intraepithelial neoplasia (VAIN) and associated human papillomavirus (HPV) infections are difficult to treat because vagina has a large surface area which is difficult to visualize colposcopically, there are many rugae and folds in vagina, fornices may be hidden by cervix and angle of vaginal axis makes treatment by beam difficult. Most patients with VAIN require general anesthesia for the procedure. A spot size of 2 mm and power settings of 15–30 W are used, and large areas are subdivided for more accurate ablation. Often the tops of rugae are removed and troughs and valleys in between contain dysplastic epithelium which has to be overcome by proper use of speculum.

**INTRA-ABDOMINAL LASER SURGERY**

This is a good alternative to knife and electrosurgical instruments for surgeries. It has several advantages like precision, limited adjacent tissue damage, rap’s healing, minimal scarring and ability to treat areas of difficult access.

**Gynecologic Laser Laparoscopy**

- **Carbon dioxide adhesiolysis:** Laser beam is delivered within the hollow ancillary probe to the pelvic adhesion. The distal end probe acts as a backstop and limits the vaporization to the tissue within the window of the probe. Advanced endometriotic adhesions can be treated with laser, omental adhesions to anterior abdominal wall are also handled rapidly and efficiently with laser. Flimsy adhesions can be vaporized and divided with low power density. Thick adhesions between tube and ovary may be lasered with intermediate power density.
- **Laser surgery of the fallopian tube:** Patients with pain associated with tubal disease or patients who do not choose assisted reproductive technique (ART) can select laser tubal surgery. The tube is opened using Bruhat’s procedure in which using laser three or four radial incisions are made in a closed tube with a small spot size laser beam followed by flowering of the tube using 3–5 mm spot size.
- **Laser myomectomy:** Pedunculated leiomyoma can be easily removed by laser but deeply embedded intramural myomas are difficult to remove. During laparoscopic myomectomy, laser is used to coagulate vessels on the surface of the leiomyoma and then the base is approached to coagulate and cut the vessels. CO$_2$, potassium titanyl phosphate (KTP), argon and YAG lasers have been used during myomectomy.
- **Laser surgery for endometriosis:** CO$_2$ or fiberoptic laser can effectively vaporize, coagulate or excuse small implants of mild-to-moderate endometriosis. Even the dense adhesions associated with advanced endometriosis can also be treated.
- **Salpingo-oophorectomy and laparoscopically assisted vaginal hysterectomy:** Laser energy in these operations is used mainly for dividing large pedicles which have been sutured or bipolar coagulated, dividing the peritoneum over bladder, mobilizing the bladder off the cervix and ablating endometrial implants.

**Hysteroscopic Laser Surgery**

**Nd:YAG Laser**

Yttrium aluminum garnet (YAG) represents an ideal laser for endometrial ablation because of its ability to penetrate tissues. It is used to effectively coagulate the endometrium and inner layers of myometrium. Advantage of hysteroscopic laser surgery is that normal saline distending medium avoids the dangers associated with vascular absorption of nonionic solutions used in electrosurgery.

Other hysteroscopic surgeries using laser include metroplasty, division of uterine septa, destruction of intrauterine synechiae and excision of submucous leiomyoma. In ovarian endometriosis, damage to the deeper stroma of the ovarian cortex can be minimized using a passed laser delivery.

**Uterosacral Ligament Surgery**

Carbon dioxide laser division of uterosacral ligament provided good success rates in cases of severe dysmenorrhea. The division of the uterosacral ligament is planned close to its insertion into the uterus.

**Tubal Pregnancy**

Ampullary ectopic pregnancies which are usually intramural are perfect for a laser incision. Laser is used for linear salpingostomy.

**Isthmic tubal pregnancy** usually requires partial salpingectomy in which excision of the segment is performed by coagulating on either side of the ectopic pregnancy and then excision with laser or laparoscopic scissors.
INTRODUCTION

Da Vinci® Surgical System

The da Vinci® Surgical system is a robotic surgical system made by the American company, Intuitive Surgical. Approved by the Food and Drug Administration (FDA) in 2000, it has been designed to facilitate complex surgery using a minimally invasive approach, and is controlled by a surgeon from a console.

The system is commonly being used for performing various gynecologic surgical procedures. According to the manufacturer, the da Vinci® system is called “da Vinci” in part “because Leonardo da Vinci invented the first robot”, according to Italian academician Mario Taddei. Da Vinci also used anatomical accuracy and three-dimensional (3D) details in his works.

Da Vinci® robots operate in hospitals worldwide, with an estimated 200,000 surgeries conducted in 2012, most commonly for hysterectomies and prostate removals. By January 2013, more than 2,000 units had been sold worldwide. The “Si” version of the system costs on an average slightly under US $2 million, in addition to several hundred thousand dollars of annual maintenance fees.

FDA Approval

Food and Drug Administration cleared the da Vinci® Surgical system in 2000 for adult and pediatric use in urologic surgical procedures, general laparoscopic surgical procedures, gynecologic laparoscopic surgical procedures, general noncardiovascular thoracoscopic surgical procedures and thoracoscopically assisted cardiotomy procedures. The FDA also cleared the da Vinci® system to be employed with adjunctive mediastinotomy to perform coronary anastomosis during cardiac revascularization.

FEATURES OF ROBOTIC SURGERY (FIG. 1)

High-definition 3D Vision

The da Vinci® Si system offers surgeons autonomous camera control for a stable, immersive, highly magnified 3D high-definition (HD) view of the surgical field.

Precise and Collision-free Movements

Surgeon’s hand movements are scaled, filtered and seamlessly translated to the instrument tips for precise instrument control. A large, open working space provides unrestricted range of motion without instrument crowding.

Ergonomic Comfort

The surgeon’s console features multiple ergonomic adjustments for increased comfort and reduced fatigue during surgical procedures.

Intuitive Motion

Advanced system software correlates the surgeon’s hand movements to the instrument tips, restoring intuitive control to what would otherwise be cross-handed surgery.

OVERVIEW

The da Vinci® system consists of a surgeon’s console that is typically in the same room as the patient, and a patient side cart with four interactive robotic arms controlled from the console. Three of the arms are for tools that hold objects, and can also act as scalpels scissors, bovies, or unipolar or bipolar electrocautery instruments. The fourth arm carries an endoscopic camera with two lenses that gives the surgeon full stereoscopic vision from the console. The surgeon sits at
the console and looks through two eye holes at the 3D images of the procedure, while maneuvering the arms with two foot pedals and two hand controllers. This system scales, filters and translates the surgeon’s hand movements into more precise micromovements of the instruments, which operates through small incisions in the body (Fig. 2).

To perform a surgical procedure, the surgeon must first use the system’s weight to judge how hard it should work. Then he/she uses the console’s master controls to maneuver the patient side cart’s three or four robotic arms (depending on the model). The instruments’ jointed wrist design exceeds the natural range of motion of the human hand; motion scaling and tremor reduction further interpret and refine the surgeon’s hand movements. The da Vinci® system always requires a human operator, and incorporates multiple redundant safety features designed to minimize opportunities for human error when compared with traditional approaches.

The da Vinci® system has been designed to improve upon conventional laparoscopy, in which the surgeon operates while standing, using hand-held, long-shafted instruments, which have no wrist. With conventional laparoscopy, the surgeon must look up and away from the instruments, to a nearby two-dimensional (2D) video monitor to see an image of the target anatomy. The surgeon must also rely on his/her patient-side assistant to position the camera correctly. In contrast, the da Vinci® system’s ergonomic design allows the surgeon to operate from a seated position at the console, with eyes and hands positioned in line with the instruments. To move the instruments or to reposition the camera, the surgeon simply moves his/her hands.

By providing surgeons with superior visualization, enhanced dexterity, greater precision and ergonomic comfort, the da Vinci® Surgical system makes it possible for more surgeons to perform minimally invasive procedures involving
complex dissection or reconstruction. For the patient, a da Vinci® procedure can offer all the potential benefits of a minimally invasive procedure, including less pain, less blood loss and less need for blood transfusions. Moreover, the da Vinci® system can enable a shorter hospital stay, a quicker recovery and faster return to normal daily activities.

**Set-up of the Operating Room**

Figure 3 illustrates set-up in an operating room utilizing the da Vinci® robotic equipment. The robotic surgeon operates from the remote master console and uses a combination of hand controls and foot pedals. The patient-side cart is positioned in between the patient’s legs, and the robotic arms are attached to stainless steel robotic trocars through a process termed as docking. One of the foot pedal (being managed by the surgeon) controls the movements of camera; another one may control the focus; another pedal helps in providing a range of motions to the robotic equipment, whereas yet
another one controls both monopolar and bipolar energy sources. The hand controls of the surgeon sitting on the side console help in the movements of the camera as well as the various robotic instruments. There are about three operative robotic arms. Despite all of these advancements, a bedside assistant is still required.

**ADVANTAGES OF ROBOTIC SURGERY**

**Advantages of Robotic Surgery for the Surgeon**

The da Vinci® Surgical system has the potential to change surgical procedure in three basic ways:

1. **Make existing minimally invasive surgery (MIS) operations easier**: Surgical procedures routinely performed today using MIS techniques will be performed more quickly and easily.

2. **Making difficult MIS operations routine**: Surgical procedures that today are performed only rarely using MIS techniques are expected to be performed routinely and with confidence using the da Vinci® Surgical system. Some procedures have been adapted for port-based techniques but are extremely difficult and are currently performed by a limited number of highly skilled surgeons.

3. **Making new surgical procedures possible**: A number of surgeries that could not be performed in a minimal invasive manner can be performed today using the robotic system.

**Advantages of Robotic Surgery for the Patient**

Possible benefits of robotic surgery in comparison to open surgery include the following:

- **Minimal scarring**: Robotic surgery is a type of minimally invasive procedure, in which several small incisions (0.25–0.75 inch) are made along the abdomen and the surgical equipment are inserted through these incisions. In traditional abdominal surgery a 7–8 inches long vertical or horizontal incision is usually given over the anterior abdominal wall (Fig. 4). Nowadays, an umbilical incision for minimally invasive surgery is commonly preferred. Transumbilical entry with da Vinci® single-site enables a virtually scarless surgery, providing patients one of the most cosmetically appealing results of any available surgical approach (Fig. 5).

- **Minimal pain**: The da Vinci® System’s remote center technology is designed to limit cannula movement at the patient’s abdominal wall, minimizing potential port-site trauma and postoperative pain.

- **Reduced blood loss**
- **Low conversion rate to open surgery**
- **Low rate of complications**
- **Short duration of hospital stay**

**RISKS OF ROBOTIC SURGERY**

Though the overall rate of complications with robotic surgery in quite low, some possible risks of robotic surgery in comparison to open surgery include the following:

- Bladder injury
- Abscess formation
- Urinary tract injury
- Bowel obstruction
- **Risks related to MIS**: These may include complications such as multiple incisions, conversion to another surgical technique and incisional hernia, pulmonary embolism, etc.
INNOVATIONS USED IN ROBOTIC SURGERY

EndoWrist® One Vessel Sealer

The EndoWrist® one vessel sealer is a fully wristed instrument, enabling an optimized approach for sealing and cutting of vessels up to 7 mm in diameter and tissue bundles. Available exclusively for the da Vinci® Si system, the EndoWrist® one vessel sealer is a single use 8 mm instrument, providing a pristine sealing surface and cutting blade for effective performance in each procedure. The EndoWrist® Stapler 45 System, however, is still awaiting FDA approval.

Features of EndoWrist® One Vessel Sealer (Fig. 6)

Uncompromised access and control: Fully wristed articulation allows surgeons to approach anatomy at optimal angles for effective sealing performance with hallmark da Vinci® precision, dexterity and control.

Optimal flexibility and efficiency: Independent seal/cut functions along with transection boundary indicator, facilitates efficient seal with confident transection, plus affords surgeons flexibility to assess the seal prior to cut.

Exceptional seal quality: The 16 mm length sealing surface and consistent computer-controlled closing pressures ensure excellent tissue sealing.

Remarkable versatility: Dual-hinged, thermally isolated jaws with 40° opening angle and unique tip profile offer efficient dissection.

Proven sealing technology: The vessel sealer and stapler vision cart upgrade includes the ERBE VIO 300D specially configured for the da Vinci® system. Its optimized algorithm offers reliable sealing and minimal thermal spread.

Fig. 6: Features of the EndoWrist® one vessel sealer
Unparalleled ease of use: Real-time system self-checks and onscreen feedback keeps the surgeon informed.

**EndoWrist® One Suction/Irrigator for Da Vinci® Myomectomy**

**Potential Benefits (Table 1)**

The EndoWrist® One Suction/Irrigator (Fig. 7) offers surgeons precise control of a fully articulated suction/irrigation instrument during the various steps of myomectomy (Figs 8A and B). Use of this instrument also provides console surgeons with the following benefits:

- Greater surgeon autonomy
- Management of fluids for optimal visualization of the surgical field during enucleation
- Access to difficult-to-reach anatomy, such as myomas in posterior locations
- Ability to maintain a clear surgical field, enabling surgeon to quickly identify bleeding vessels for managing hemostasis.

**Fluorescence Imaging**

Firefly fluorescence imaging for da Vinci® system allows for the identification of real-time anatomy using near-infrared guidance.

<table>
<thead>
<tr>
<th>Procedure step</th>
<th>Uses of suction/irrigator</th>
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<tr>
<td>Enucleation</td>
<td>• Help visualize tissue layers</td>
</tr>
<tr>
<td>Closure of deep layers</td>
<td>• Keep surgical site clear of blood to maintain good visualization</td>
</tr>
<tr>
<td></td>
<td>• Achieve adequate hemostasis before moving to serosal layer closure</td>
</tr>
<tr>
<td>Closure of serosal layer</td>
<td>• Optimize visualization by controlling bleeding</td>
</tr>
<tr>
<td>Site clean up</td>
<td>• Clean anatomy with suction and irrigation after morcellation</td>
</tr>
</tbody>
</table>

**Features**

- Provides real-time near-infrared guidance through visualization of injectable fluorescence dye (Figs 9A and B)
- Interface allows efficient toggling between normal illumination and fluorescence imaging modes
- Incorporates illuminator utilized light emitting diode technology.

**Potential Benefits**

- Enables enhanced visualization capabilities for:
  - Vessel identification
  - Soft tissue perfusion
- Allows real-time identification of anatomy in fluorescence imaging mode from the Si surgeon console, in 3-dimensional, high-definition quality
- Minimizes downtime, operating expense associated with lamp replacement.

**Figs 8A and B:** Using EndoWrist® one suction/irrigator at the time of da Vinci® myomectomy

**Fig. 7:** EndoWrist® one suction/irrigator for da Vinci® myomectomy
INDICATIONS FOR USE OF ROBOTIC SURGERY IN GYNECOLOGY

- Endometriosis resection
- Myomectomy
- Excessive menstrual bleeding
- Pelvic prolapse
- Treatment of cancer
- Hysterectomy.

ENDOMETRIOSIS

Endometriotic Resection Using the Robotic System

There are four ways in which the da Vinci® technology facilitates precise endometriosis resection.

Adhesiolysis

Three-dimensional HD vision provides improved visualization of tissue planes, making it easy to restore normal anatomy while avoiding injury to ureters, vasculature and other structures. In addition, Hot Shear (Monopolar Curved Scissors) offers two modes for meticulous freeing of adhesions throughout the pelvic cavity (Fig. 10).

Excision of Ovarian Endometrioma

Excellent visualization using the robotic system allows easy identification of the ovary/endometrioma wall, helping to avoid damage to the ovary and to preserve functionality. The PK dissecting forceps and long-tip forceps can be used together to provide traction/retraction for effective removal of the endometrioma (Fig. 11).

Ureterolysis

EndoWrist® instruments facilitate careful ureterolysis, even when the ureters are hidden by scar tissue and nodular disease. Wristed instrumentation also enables precise resection of lesions that have deeply infiltrated structures such as bowel and ureters. Complete autonomy can be achieved utilizing the third instrument arm to assist in tissue manipulation or retraction (Fig. 12).

Resection of Rectovaginal Nodules

Unparalleled visualization of the posterior cul-de-sac, combined with fully articulating instrumentation, enables the surgeon to identify and resect lesions and nodules throughout the pelvic cavity. The EndoWrist® instrumentation also facilitates easy and efficient access to intraperitoneal and retroperitoneal anatomy for excision of all nodules (Fig. 13).

Surgeon Benefits

Da Vinci® surgical system enables a reproducible surgical approach for complex, diffuse or deep infiltrating endometriosis with superior visualization for complete resection of endometriotic lesion. The visualization, depth perception, dexterity and control provided by the da Vinci® system offers potential for:
Recent Advances

• Ability to precisely resect stage IV disease, including deeply infiltrating endometriosis
• Extension of a minimally invasive approach to advanced or extremely extensive cases
• Control of the camera and all three operative arms provide ultimate accuracy in maintaining surgical autonomy, accuracy and efficiency.

### MYOMECTOMY

**Surgeon Benefits**

Robotic surgery enables gynecologists to perform uterine preserving myomectomies in a minimally invasive manner, with surgical precision and confidence in the ability to do a multilayer closure. The precision, dexterity and control provided by the da Vinci® system offer potential for:

- Minimally invasive access to the myoma, potentially minimizing complications associated with a large abdominal incision
- Precise dissection of myomas using EndoWrist® instrumentation
- Precise suturing of the uterine defect for a durable, multilayer closure
- Extending a minimally invasive approach to more complex types of myomas—larger, more numerous and less accessible
- 3D vision, improved ergonomics, wide range of movements, absence of the fulcrum effect and improved instrument dexterity to eliminate most of the limitations of traditional laparoscopy.

**Potential Patient Benefits**

Possible benefits of robotic myomectomy in comparison to traditional laparoscopic surgery include the following:

- Minimally invasive removal of heavier, more numerous and more difficult to access fibroids
- Fever complications during surgery.

**Potential Patient Risks**

Possible risks of robotic myomectomy include the following:

- Weakening of the uterus during labor
- Preterm birth
- Tears or perforations in the uterine wall

In addition to the above risks, there are risks related to MIS, such as pulmonary embolism, etc.

**Myomectomy Using the Robotic System**

The steps of robotic myomectomy have been illustrated in Figures 14A to F. There are four ways in which da Vinci® technology facilitates a precise myomectomy.

- 3D high-definition visualization of endometriotic lesions
- Ability to completely resect lesions, regardless of their location in the pelvic cavity
Figs 14A to F: Robotic myomectomy. (A) Using the robotic harmonic shears, a hysterotomy is made over the myoma; (B and C) Shelling out of myoma; (D) Myoma has been completely removed from the myoma bed; (E) A multilayer closure is performed employing sutures and suturing techniques that are identical to those of an open myomectomy; (F) Suturing of the uterine surface is complete.
**Hysterotomy**

The permanent cautery hook allows the surgeon to make a horizontal or vertical incision over the uterine surface, based upon the location of the pathology, while avoiding excessive divots or tunneling within the myometrium surrounding the myoma. The PK dissecting forceps help retract the incised myometrium and provide improved coagulation with minimal thermal spread to facilitate deliberate perpendicular cuts down to the myoma capsule.

**Multilayered Suture Closure of Defect: Deep Layers**

The SutureCut needle driver securely holds CT-2 needles as they pass through the myometrial layers while providing integrated cutting following knot tying for improved operative efficiency. The EndoWrist® large needle driver allows for interrupted figure-eight or running sutures to be thrown and tied intracorporeally for a deep multilayer closure. The unsurpassed visualization of the camera allows for accurate placement of imbricated stitches in additional layers and superior ability to reconstruct the uterine defect.

**Enucleation**

Consistent, careful counter traction can be attained by utilizing the EndoWrist® tenaculum forceps while avoiding entrance into the endometrial cavity or premature avulsion of the myoma. The PK dissecting forceps facilitate development of the correct dissection plane surrounding the myoma while also providing more site-specific counter traction, facilitating a more precise dissection and enucleation of the fibroid. The Hot Shears is used to peel the myoma free of all attachments. Coagulation with the PK dissecting forceps should be prudently used to pre-emptively deal with vascular attachments.

**Multilayered Suture Closure of Defect: Superficial Layer**

All EndoWrist® needle drivers are fully wristed, enabling quick and efficient knot tying. The Long Tip Forceps is used to perform a running baseball stitch with an SH needle, in order to close any dead space and avoid serosal pull-through. The SutureCut needle driver is used to manipulate the tissue for needle bite placement and to cut the suture upon completion of stitching for added surgical autonomy and operative efficiency.

**CRITICISM AND CONTROVERSIES**

The term "robotic surgery" which is commonly used to refer to this technology can give the impression that the da Vinci® system is used for performing the surgeries in an autonomous manner. In contrast, the current da Vinci® surgical system does not function on its own because it has not been designed as an autonomous system. It lacks a decision-making software and relies on a human operator for all its input. Moreover, all operative steps are performed through remote human-computer interaction. The current system has been deliberately constructed in a manner so as to effortlessly duplicate the movement of the surgeon’s hands with the help of the tips of microinstruments. The instrument cannot make decisions without receiving the surgeon’s direct input.

Critics of robotic surgery emphasize that the technique of robotic surgery is difficult for users to learn and that this technique is not likely to be more effective than traditional laparoscopic surgery. The available evidence presents with conflicting views related to the efficacy and various side effects related to the use of robotic equipment while performing various surgeries. Presently there is inadequate data related to the safety of this system and the likelihood of causing injuries to the patients due to electrical currents released from the various surgical tips used by the system. As of 2013, the FDA is inquiring problems related to the use of the da Vinci® robot, including fatalities that have occurred during surgeries using this device. A number of lawsuits related to the injuries and problems caused by this system are also in progress.

Also, the da Vinci® system uses the software manufactured by the proprietor, which cannot be modified by surgeon. This therefore, severely limits the surgeon’s ability to change the operation system. Furthermore, the cost involved in the installation and establishment of this system is quite high and may be beyond the reach of many institutions. There have also been much criticism and debate related to the procedure for obtaining the FDA approval of this system and provision of adequate training before using this system.

**BIBLIOGRAPHY**

INTRODUCTION

Inadvertent perioperative hypothermia is a common but preventable complication of perioperative procedures, which is associated with poor outcomes for patients. Regular measurement and recording of patient temperature is a key to the prompt identification and treatment of inadvertent perioperative hypothermia where preventative measures have failed. Any patient whose core temperature drops below 36.0°C at any stage of the perioperative pathway (from the hour before induction of anesthesia until 24 hours after entry into the recovery area) should be warmed using a forced air warming device.

Definition used here:
• Temperature means core temperature when used in relation to patients.
• Hypothermia is defined as a core temperature of below 36.0°C.
• Comfortably warm refers to the temperature range (adult patients) between 36.5°C and 37.5°C.
• Intraoperative phase is defined as total anesthesia time.
• Postoperative phase is defined as the 24 hours after entry into the recovery area in the theater suite (and includes transfer to and time spent in the ward).

KEY PRIORITIES FOR IMPLEMENTATION

Perioperative Care

Patients (and their families and carers) should be informed that:

• Staying warm before surgery will lower the risk of postoperative complications.
• The hospital environment may be colder than their own home.
• They should bring additional clothing, such as a dressing gown, a vest, warm clothing and slippers, to help them keep comfortably warm.
• They should tell staff if they feel cold at any time during their hospital stay.

When using any device to measure patient temperature, healthcare professionals should:
• Be aware of, and carry out, any adjustments that need to be made in order to obtain an estimate of core temperature from that recorded at the site of measurement.
• Be aware of any such adjustments that are made automatically by the device used.

Preoperative Phase

Each patient should be assessed for their risk of inadvertent perioperative hypothermia (Flow chart 1) and potential adverse consequences before transfer to the theater suite. Patients should be managed as higher risk if any two of the following apply:
• A subjective assessment (ASA) grade II to V (the higher the grade, the greater the risk)
• Preoperative temperature below 36.0°C (and preoperative warming is not possible because of clinical urgency)
• Undergoing combined general and regional anesthesia
• Undergoing major or intermediate surgery
• At risk of cardiovascular complications.
If the patient’s temperature is below 36.0°C:
- Forced air warming should be started preoperatively on the ward or in the emergency department (unless there is a need to expedite surgery because of clinical urgency; for example, bleeding or critical limb ischemia).
- Forced air warming should be maintained throughout the intraoperative phase.

**Intraoperative Phase**
- The patient’s temperature should be measured and documented before induction of anesthesia and then every 30 minutes until the end of surgery.
- Induction of anesthesia should not begin unless the patient’s temperature is 36.0°C or above (unless there is a need to expedite surgery because of clinical urgency; for example, bleeding or critical limb ischemia).
- Intravenous fluids (500 mL or more) and blood products should be warmed to 37°C using a fluid warming device.
- Patients who are at higher risk of inadvertent perioperative hypothermia and who are having anesthesia for less than 30 minutes should be warmed intraoperatively from induction of anesthesia using a forced air warming device.
- All patients who are having anesthesia for longer than 30 minutes should be warmed intraoperatively from induction of anesthesia using a forced air warming device.

**Postoperative Phase**
- The patient’s temperature should be measured and documented on admission to the recovery room and then at 15-minute intervals.
  - Ward transfer should not be arranged unless the patient’s temperature is 36.0°C or above.
  - If the patient’s temperature is below 36.0°C, they should be actively warmed using forced air warming until they are discharged from the recovery room or until they are comfortably warm.

In the ward:
- Measure and document patient temperature on arrival and in routine 4-hourly observations.
- Give patient at least one sheet and two blankets.
- Apply forced air warming if patient temperature falls below 36.0°C.
  - Record temperature every 30 minutes during warming.

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**Compiled from National Institute for Health and Clinical Excellence (NICE), 2008**

This guidance is written in the following context:
- NICE clinical guidelines are recommendations about the treatment and care of people with specific diseases and conditions in the National Health Service (NHS) in England and Wales.
- This guidance represents the view of the Institute, which was arrived at after careful consideration of the evidence available.
- Healthcare professionals are expected to take it fully into account when exercising their clinical judgment. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer, and informed by the summary of product characteristics of any drugs they are considering.

**Disclaimer:** Neon Laboratories Ltd. is only instrumental in bringing this abridged information as a service to the medical fraternity. A full text of the article is available on Internet at the URL: http://www.nice.org.uk/CG065 or send request to PMT, Neon Laboratories Ltd., 28 M. Caves Road, Andheri (E), Mumbai - 400093, INDIA or Email ID pmt@neonroup.com
Flow chart 1: Management of perioperative hypothermia

**Preoperative care:**
- Assess risk of perioperative hypothermia and its consequences.
- Keep patient comfortably warm (36.5–37.5°C):
  - Provide one sheet and two blankets.
  - Take special care, if the patient is given premedication (for example, tramadol, midazolam or opioids).
  - At all times, use temperature recording and warming devices correctly.
- Measure and document patient temperature in hour before transfer to theater.

**Transfer to theater:**
- Encourage patient to walk where appropriate.
- Keep patient comfortably warm.

**In the theater:**
- Measure and document patient temperature before inducing anesthesia.
- Consider incident reporting, if patient temperature is below 36.0°C on arrival.

**Induction of anesthesia:**
Continue forced air warming, if already started.
- Start forced air warming at induction of anesthesia for:
  - Patients at higher risk of perioperative hypothermia
  - All patients having anesthesia for longer than 30 minutes.

**Intraoperative care:**
- Measure and document patient temperature every 30 minutes.
- Adjust setting on forced air warming device to maintain patient temperature of at least 36.5°C
- Maintain ambient temperature at 21.0°C or above while patient is exposed:
  - This may be reduced once forced air warming is established
  - Consider using equipment to cool surgical team.
- Cover patient adequately and expose only during surgical preparation.
- Warm intravenous fluids (500 mL or more) and blood products to 37°C.

**In recovery:**
- Measure and document patient temperature on admission and then every 15 minutes.

**Below 36.0°C**
- Start (or continue) forced air warming
- Continue until transfer or until patient is comfortably warm.

**Below 36.0°C**
- Ward transfer can be arranged

**36.0°C or above**
- (or where need to expedite surgery)
### Doses of Some Drugs Commonly used in Office Practice

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Frequency</th>
<th>Preferred route</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Antibiotics:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>30 mg/kg/day</td>
<td>8 hourly</td>
<td>PO</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>50 mg/kg/day</td>
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<td>PO</td>
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<tr>
<td>Cefaclor</td>
<td>20 mg/kg/day</td>
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<td>PO</td>
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<tr>
<td>Cefadroxil</td>
<td>30 mg/kg/day</td>
<td>12 hourly</td>
<td>PO</td>
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<td>Ceftriaxone</td>
<td>50–75 mg/kg/day</td>
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<td>IM</td>
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<tr>
<td>Cefuroxime</td>
<td>50 mg/kg/day</td>
<td>8 hourly</td>
<td>PO</td>
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<td>Cephalexin</td>
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<td>6 hourly</td>
<td>PO</td>
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<td>Ciprofloxacin</td>
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<td>12 hourly</td>
<td>PO</td>
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<td>PO</td>
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<td>Cotrimoxazole (Trimethoprim)</td>
<td>8 mg/kg/day</td>
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<td>PO</td>
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<td>Erythromycin</td>
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<td>Furazolidone</td>
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<td>PO</td>
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<td>Nalidixic acid</td>
<td>50 mg/kg/day</td>
<td>6–8 hourly</td>
<td>PO</td>
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<td>Penicillin (Benzathine)</td>
<td>1.2 mg/kg/day</td>
<td>3 weekly</td>
<td>IM (ATD)</td>
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<td><strong>B. Antiamoebic drugs:</strong></td>
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<tr>
<td>Metronidazole</td>
<td>30 mg/kg/day</td>
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<td>Tinidazole</td>
<td>20 mg/kg/day</td>
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<td>PO</td>
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<td><strong>C. Anticonvulsants:</strong></td>
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<tr>
<td>Carbamazepine</td>
<td>10–20 mg/kg/day</td>
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<td>Diazepam</td>
<td>0.3 mg/kg/day</td>
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<td>Phenobarbitone</td>
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<td>Phenytoin</td>
<td>5 mg/kg/day</td>
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<td>Valparin</td>
<td>15–30 mg/kg/day</td>
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<td>Domperidone</td>
<td>0.3 mg/kg/day</td>
<td>SOS/6 hourly</td>
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<td>Metoclopramide</td>
<td>0.3 mg/kg/day</td>
<td>SOS/6 hourly</td>
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<td><strong>E. Antifilarial:</strong></td>
<td></td>
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<tr>
<td>Diethylcarbamazine</td>
<td>5 mg/kg/day</td>
<td>8 hourly</td>
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<td>(for 21 days)</td>
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<td><strong>F. Antifungal:</strong></td>
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<td>Griseofulvin</td>
<td>10 mg/kg/day</td>
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<td>Ketoconazole</td>
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<td><strong>G. Anthelminthics:</strong></td>
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<td>Albendazole</td>
<td>400 mg/dose</td>
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<td>Mebendazole</td>
<td>200 mg/day (for 3 days)</td>
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<td>Pyrantel</td>
<td>10 mg/kg/day</td>
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<td><strong>H. Antihistaminics:</strong></td>
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<tr>
<td>Astemizole</td>
<td>50 mg/kg/day</td>
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<td>Chlorpheniramine</td>
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<td>PO</td>
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<td>Promethazine</td>
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<td>Terfenadine</td>
<td>0.2–0.5 mg/kg/day</td>
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<td><strong>I. Anti-inflammatory:</strong></td>
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<td>Aspirin (Treatment of rheumatic fever)</td>
<td>75–100 mg/kg/day</td>
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<td><strong>J. Antimalarial drugs:</strong></td>
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<td>Chloroquine</td>
<td>25 mg/kg (total dose)</td>
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<td>Mefloquine</td>
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<td>(In children &gt; 15 kg)</td>
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<td>Primaquine (Base)</td>
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<td>Quinine sulfate</td>
<td>25 mg/kg/day (for 10 days)</td>
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<td><strong>K. Antipyretics/analgesics:</strong></td>
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<td>Ibuprofen</td>
<td>10 mg/kg/day</td>
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<td>PO</td>
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<tr>
<td>Paracetamol</td>
<td>10–15 mg/kg/day</td>
<td>SOS/4 hourly</td>
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<td>Dicyclomine</td>
<td>1 mg/kg/day</td>
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<td>Ethambutol</td>
<td>15–20 mg/kg/day</td>
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<td>Isoniazid</td>
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<td>Pyrazinamide</td>
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<td>Streptomycin</td>
<td>20 mg/kg/day</td>
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<td>Adrenaline (1:1,000)</td>
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<td>Theophylline</td>
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<td>SC</td>
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<td></td>
<td>15 mg/kg/day</td>
<td>8 hourly</td>
<td>PO</td>
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<td>Digoxin</td>
<td>0.01 mg/kg/day</td>
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<td>Pseudoephedrine</td>
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<td>Furosemide</td>
<td>1–3 mg/kg/day</td>
<td>6–8 hourly</td>
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<td>Spironolactone</td>
<td>3 mg/kg/day</td>
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<td>SOS</td>
<td>PO, PR</td>
</tr>
<tr>
<td>Magnesium</td>
<td>250 mg/kg/dose</td>
<td>SOS</td>
<td>PO</td>
</tr>
<tr>
<td>Sulfate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>S. Metabolic:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium gluconate</td>
<td>200–400 mg/kg/day</td>
<td>SOS</td>
<td>PO</td>
</tr>
<tr>
<td>Potassium chloride</td>
<td>200 mg/kg/day</td>
<td>SOS</td>
<td>PO</td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>20 mg/kg/day</td>
<td>SOS</td>
<td>PO</td>
</tr>
<tr>
<td><strong>T. Sedative:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chloral hydrate</td>
<td>25 mg/kg/dose</td>
<td>SOS</td>
<td>PO</td>
</tr>
</tbody>
</table>
### Drug Therapy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Frequency</th>
<th>Preferred route</th>
</tr>
</thead>
<tbody>
<tr>
<td>U. Steroids:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Betamethasone</td>
<td>0.2 mg/kg/day</td>
<td>12 hourly</td>
<td>PO</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>5–10 mg/kg/dose</td>
<td>SOS</td>
<td>IM, IV</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>2 mg/kg/day</td>
<td>6 hourly</td>
<td>PO</td>
</tr>
<tr>
<td>V. Vitamins and minerals:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin A</td>
<td>2,00,000 units</td>
<td>Single dose</td>
<td>PO</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>6,00,000 units</td>
<td>Single dose</td>
<td>IM, PO</td>
</tr>
<tr>
<td></td>
<td>60,000 units/day</td>
<td>Once daily</td>
<td>PO</td>
</tr>
<tr>
<td></td>
<td>(for 10 days)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Folate</td>
<td>5 mg/day</td>
<td>Once daily</td>
<td>PO</td>
</tr>
<tr>
<td>Iron (Elemental)</td>
<td>3–4 mg/kg/day</td>
<td>12 hourly</td>
<td>PO</td>
</tr>
</tbody>
</table>

### Reference Intervals: Biochemistry

Drugs (and other substances) may interface with any chemical method as these effects may be method-dependent, it is difficult for the clinician to be aware of all possibilities. If in doubt, discuss with the lab.

<table>
<thead>
<tr>
<th>Substance</th>
<th>Specimen</th>
<th>Reference</th>
<th>Interval</th>
<th>Your hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acid phosphatase (total)</td>
<td>S</td>
<td>1–5</td>
<td>IU/L</td>
<td></td>
</tr>
<tr>
<td>Acid phosphatase (prostatic)</td>
<td>S</td>
<td>0–1</td>
<td>IU/L</td>
<td></td>
</tr>
<tr>
<td>(ACTH)</td>
<td>P</td>
<td>&lt; 80</td>
<td>ng/L</td>
<td></td>
</tr>
<tr>
<td>Alanine aminotransferase (ALT)</td>
<td>P</td>
<td>5–35</td>
<td>IU/L</td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td>P</td>
<td>35–50</td>
<td>g/L</td>
<td></td>
</tr>
<tr>
<td>Aldosterone</td>
<td>P</td>
<td>100–500</td>
<td>pmol/L</td>
<td></td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>P</td>
<td>30–300</td>
<td>IU/L (adults)</td>
<td></td>
</tr>
<tr>
<td>–Fetoprotein</td>
<td>S</td>
<td>&lt; 10</td>
<td>kU/L</td>
<td></td>
</tr>
<tr>
<td>–Amylase</td>
<td>P</td>
<td>0–180 Smogyi UdL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiotensin II</td>
<td>P</td>
<td>5–35</td>
<td>pmol/L</td>
<td></td>
</tr>
<tr>
<td>Antidiuretic hormone (ADH)</td>
<td>P</td>
<td>0.9–4.6</td>
<td>pmol/L</td>
<td></td>
</tr>
<tr>
<td>Aspartate transaminase (AST)</td>
<td>P</td>
<td>5–35</td>
<td>IU/L</td>
<td></td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>P</td>
<td>24–30</td>
<td>mmol/L</td>
<td></td>
</tr>
<tr>
<td>Bilirubin</td>
<td>P</td>
<td>3–17</td>
<td>μmol/(0.25–1.5 mg/100 mL)</td>
<td></td>
</tr>
<tr>
<td>Calcitonin</td>
<td>P</td>
<td>&lt; 0.1</td>
<td>μg/L</td>
<td></td>
</tr>
<tr>
<td>Calcium (ionized)</td>
<td>P</td>
<td>1.0–1.25</td>
<td>mmol/L</td>
<td></td>
</tr>
<tr>
<td>Calcium (total)</td>
<td>P</td>
<td>2.12–2.65</td>
<td>mmol/L</td>
<td></td>
</tr>
<tr>
<td>Chloride</td>
<td>P</td>
<td>95–105</td>
<td>mmol/L</td>
<td></td>
</tr>
<tr>
<td>Cholesterol</td>
<td>P</td>
<td>3.9–7.8</td>
<td>mmol/L</td>
<td></td>
</tr>
<tr>
<td>VLDL</td>
<td>P</td>
<td>0.128–0.645</td>
<td>mmol/L</td>
<td></td>
</tr>
<tr>
<td>LDL</td>
<td>P</td>
<td>1.55–4.4</td>
<td>mmol/L</td>
<td></td>
</tr>
<tr>
<td>HDL</td>
<td>P</td>
<td>0.9–1.93</td>
<td>mmol/L</td>
<td></td>
</tr>
<tr>
<td>Cortisol</td>
<td>P</td>
<td>a.m. 450–700</td>
<td>nmol/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Midnight 80–280</td>
<td>nmol/L</td>
<td></td>
</tr>
<tr>
<td>Creatine kinase (CK)</td>
<td>P</td>
<td>625–195</td>
<td>IU/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>125–170</td>
<td>IU/L</td>
<td></td>
</tr>
<tr>
<td>Creatinine (related to lean body mass)</td>
<td>P</td>
<td>70–150</td>
<td>μmol/L</td>
<td></td>
</tr>
<tr>
<td>Ferritin</td>
<td>P</td>
<td>12–200</td>
<td>μg/L</td>
<td></td>
</tr>
<tr>
<td>Folate</td>
<td>S</td>
<td>2.1</td>
<td>μg/L</td>
<td></td>
</tr>
<tr>
<td>Follicle-stimulating hormone (FSH)</td>
<td>P/S</td>
<td>2–8</td>
<td>U/L (luteal)</td>
<td>18</td>
</tr>
<tr>
<td>Substance</td>
<td>Specimen</td>
<td>Reference</td>
<td>Interval</td>
<td>Your hospital</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>----------</td>
<td>-----------</td>
<td>-------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Gamma-glutamyl transpeptidase (-GT, GTT)</td>
<td>P</td>
<td>611–50</td>
<td>IU/L</td>
<td></td>
</tr>
<tr>
<td>Glucose (fasting)</td>
<td>P</td>
<td>17–33</td>
<td>IU/L</td>
<td></td>
</tr>
<tr>
<td>Glycated (glycosylate) hemoglobin</td>
<td>B</td>
<td>3.5–5.5</td>
<td>mmol/L</td>
<td></td>
</tr>
<tr>
<td>Growth hormone</td>
<td>P</td>
<td>&lt; 20</td>
<td>mU/L</td>
<td></td>
</tr>
<tr>
<td>Iron</td>
<td>S</td>
<td>614–31</td>
<td>mmol/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>111–30</td>
<td>mmol/L</td>
<td></td>
</tr>
<tr>
<td>Lactate dehydrogenase (LDH)</td>
<td>P</td>
<td>70–250</td>
<td>IU/L</td>
<td></td>
</tr>
<tr>
<td>Lead</td>
<td>B</td>
<td>&lt; 1.8</td>
<td>mmol/L</td>
<td></td>
</tr>
<tr>
<td>Luteinizing hormone (LH) (Pre-menopausal)</td>
<td>P</td>
<td>3–16</td>
<td>U/L (luteal)</td>
<td></td>
</tr>
<tr>
<td>Magnesium</td>
<td>P</td>
<td>0.75–1.05</td>
<td>mmol/L</td>
<td></td>
</tr>
<tr>
<td>Osmolality</td>
<td>P</td>
<td>278–305</td>
<td>mmol/L/kg</td>
<td></td>
</tr>
<tr>
<td>Parathyroid hormone (PTH)</td>
<td>P</td>
<td>&lt; 0.8–8.5</td>
<td>pmol/L</td>
<td></td>
</tr>
<tr>
<td>Phosphate (inorganic)</td>
<td>P</td>
<td>0.8–1.45</td>
<td>mmol/L</td>
<td></td>
</tr>
<tr>
<td>Potassium</td>
<td>P</td>
<td>3.5–5.0</td>
<td>mmol/L</td>
<td></td>
</tr>
<tr>
<td>Prolactin</td>
<td>P</td>
<td>6 &lt; 450</td>
<td>U/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 &lt; 600</td>
<td>U/L</td>
<td></td>
</tr>
<tr>
<td>Prostate specific antigen</td>
<td>P</td>
<td>0–4</td>
<td>nanograms/mL</td>
<td></td>
</tr>
<tr>
<td>Protein (total)</td>
<td>P</td>
<td>60–80</td>
<td>g/L</td>
<td></td>
</tr>
<tr>
<td>Red cell folate</td>
<td>B</td>
<td>0.36–1.44</td>
<td>µmol/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(160–640 µg/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renin (erect/recumbent)</td>
<td>P</td>
<td>2.8–4.5/1.1–2.7</td>
<td>pmol/mL/h</td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td>P</td>
<td>135–145</td>
<td>mmol/L</td>
<td></td>
</tr>
<tr>
<td>Thyroid-binding globulin (TBG)</td>
<td>P</td>
<td>7–17</td>
<td>mg/L</td>
<td></td>
</tr>
<tr>
<td>Thyroid-stimulating hormones (TSH)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NR widens with age</td>
<td>P</td>
<td>0.5–5.7</td>
<td>mU/L</td>
<td></td>
</tr>
<tr>
<td>Thyroxine (T4)</td>
<td>P</td>
<td>70–140</td>
<td>nmol/L</td>
<td></td>
</tr>
<tr>
<td>Thyroxine (free)</td>
<td>P</td>
<td>9–22</td>
<td>pmol/L</td>
<td></td>
</tr>
<tr>
<td>Total iron binding capacity</td>
<td>S</td>
<td>54–75</td>
<td>µmol/L</td>
<td></td>
</tr>
<tr>
<td>Triglyceride</td>
<td>P</td>
<td>0.55–1.90</td>
<td>mmol/L</td>
<td></td>
</tr>
<tr>
<td>Tri-iodothyronine (T3)</td>
<td>P</td>
<td>2.5–6.7</td>
<td>nmol/L</td>
<td></td>
</tr>
<tr>
<td>Urea</td>
<td>P</td>
<td>1.2–6.7</td>
<td>mmol/L</td>
<td></td>
</tr>
<tr>
<td>Urate</td>
<td>P</td>
<td>6.210–480</td>
<td>µmol/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1,150–390</td>
<td>µmol/L</td>
<td></td>
</tr>
<tr>
<td>Vitamin B$_{12}$</td>
<td>S</td>
<td>0.13–0.68</td>
<td>nmol/L/(&lt;150 ng/L)</td>
<td></td>
</tr>
</tbody>
</table>

**Keys:** P = plasma (heparin bottle); S = serum (clotted; no anticoagulant); B = whole blood (edetic acid-EDTA-bottle); IU = international unit; 6 = male; 1 = female

Desired upper limit of cholesterol would be 6 mmol/L.

### Arterial Blood Gases: Reference Intervals

- **pH**: 7.35–7.45
- **PaCO$_2$**: 4.7–60 kPa
- **PaO$_2$**: > 10.6 kPa
- **Base excess**: ± 2 mmol/L

**NB:** 7.6 mm Hg = 1 kPa (atmospheric pressure = 100 kPa)
Reference Intervals for Urine

<table>
<thead>
<tr>
<th>Substance</th>
<th>Reference</th>
<th>Interval</th>
<th>Your hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol (free)</td>
<td>&lt; 280</td>
<td>nmol/24h</td>
<td></td>
</tr>
<tr>
<td>Hydroxyindoleacetic acid</td>
<td>16–73</td>
<td>μmol/24h</td>
<td></td>
</tr>
<tr>
<td>Hydroxymethylmandelic acid (HMMA, VMA)</td>
<td>16–48</td>
<td>μmol/24h</td>
<td></td>
</tr>
<tr>
<td>Metanephrines</td>
<td>0.03–069</td>
<td>micromol mmol creatinine</td>
<td></td>
</tr>
<tr>
<td>(Or &lt; 5.5 micromol/day)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osmolality</td>
<td>350–1,000</td>
<td>mosmol/kg</td>
<td></td>
</tr>
<tr>
<td>17-Oxogenic steroids</td>
<td>628–30</td>
<td>μmol/24h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>121–66</td>
<td>μmol/24h</td>
<td></td>
</tr>
<tr>
<td>17-Oxosteroids (neutral)</td>
<td>617–76</td>
<td>μmol/24h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>114–59</td>
<td>μmol/24h</td>
<td></td>
</tr>
<tr>
<td>Phosphate (inorganic)</td>
<td>15–50</td>
<td>mmol/24h</td>
<td></td>
</tr>
<tr>
<td>Potassium</td>
<td>14–120</td>
<td>mmol/24h</td>
<td></td>
</tr>
<tr>
<td>Protein</td>
<td>&lt; 150</td>
<td>mg/24h</td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td>100–250</td>
<td>mmol/24h</td>
<td></td>
</tr>
</tbody>
</table>

Hematology: Reference Intervals

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Reference</th>
<th>Interval</th>
<th>Your hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td>White cell count (WCC)</td>
<td></td>
<td>4.0–11.0 × 10⁹/L</td>
<td></td>
</tr>
<tr>
<td>Red cell count</td>
<td></td>
<td>4.5–6.5 × 10¹²/L</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin</td>
<td></td>
<td>3.9–5.6 × 10¹²/L</td>
<td></td>
</tr>
<tr>
<td>Packed red cell volume (PCV)</td>
<td></td>
<td>13.5–18.0 g/dL</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.4–0.54 g/dL</td>
<td></td>
</tr>
<tr>
<td>Mean cell volume (MCV)</td>
<td></td>
<td>76–96 L</td>
<td></td>
</tr>
<tr>
<td>Mean cell hemoglobin (MCH)</td>
<td></td>
<td>27–32 pg</td>
<td></td>
</tr>
<tr>
<td>Mean cell hemoglobin concentration (MCHC)</td>
<td></td>
<td>30–36 g/dL</td>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td></td>
<td>2.0–7.5 × 10⁹/L; 40–75% wcc</td>
<td></td>
</tr>
<tr>
<td>Lymphocytes</td>
<td></td>
<td>1.3–3.5 × 10⁹/L; 20–45% wcc</td>
<td></td>
</tr>
<tr>
<td>Eosinophils</td>
<td></td>
<td>0.04–0.44 × 10⁹/L; 1–6% wcc</td>
<td></td>
</tr>
<tr>
<td>Basophils</td>
<td></td>
<td>0.0–0.10 × 10⁹/L; 0–1% wcc</td>
<td></td>
</tr>
<tr>
<td>Monocytes</td>
<td></td>
<td>0.2–0.8 × 10⁹/L; 2–10% wcc</td>
<td></td>
</tr>
<tr>
<td>Platelet count</td>
<td></td>
<td>150.0–400.0 × 10³/L</td>
<td></td>
</tr>
<tr>
<td>Reticulocyte count</td>
<td></td>
<td>0.8–2.0%*25–100 × 10³/L</td>
<td></td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate</td>
<td></td>
<td>Depends on age</td>
<td></td>
</tr>
<tr>
<td>Prothrombin time (factors II, VII, X)</td>
<td></td>
<td>10–14 seconds</td>
<td></td>
</tr>
<tr>
<td>Activated partial thromboplastin</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Only use percentages as reference interval, if red cell count is normal; otherwise use the absolute value. Express as ratio versus control.

Cerebrospinal Fluid: Reference Intervals

<table>
<thead>
<tr>
<th>Substance</th>
<th>Reference</th>
<th>Interval</th>
<th>Your hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>3.3–4.4</td>
<td>mmol/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Or ≥ 2/3</td>
<td></td>
<td>Of plasma glucose</td>
</tr>
<tr>
<td>Chloride</td>
<td>122–128</td>
<td>mmol/L</td>
<td></td>
</tr>
<tr>
<td>Lactate</td>
<td>&lt; 2.8</td>
<td>mmol/L</td>
<td></td>
</tr>
</tbody>
</table>
## Blood Chemistry: Normal Values

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alcohol (whole blood)</strong></td>
<td>Subclinical intoxication 0–1 g/L; Gross intoxication 2 g/L.</td>
</tr>
<tr>
<td><strong>Bilirubin</strong></td>
<td>Less than 15 µmol/L</td>
</tr>
<tr>
<td><strong>Calcium (serum)</strong></td>
<td>Male 2.26–2.58 mmol/L; Female 2.23–2.63 mmol/L</td>
</tr>
<tr>
<td><strong>Cholesterol (serum)</strong> (varies with age and sex)</td>
<td>3.8–6.2 mmol/in young adults</td>
</tr>
<tr>
<td><strong>Cortisol (plasma)</strong></td>
<td>200–720 nmol/L (9 am)</td>
</tr>
<tr>
<td><strong>Creatinine (serum)</strong></td>
<td>88–133 µmol/L (proportional to body size)</td>
</tr>
<tr>
<td><strong>Electrolytes (plasma)</strong></td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td>136–148 mmol/L</td>
</tr>
<tr>
<td>Potassium</td>
<td>3.8–5.0 mmol/L</td>
</tr>
<tr>
<td>Chloride</td>
<td>95–105 mmol/L</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>24–32 mmol/L</td>
</tr>
<tr>
<td><strong>Enzymes (serum)</strong></td>
<td></td>
</tr>
<tr>
<td>Amylase</td>
<td>70–300 U/L at 37°C</td>
</tr>
<tr>
<td>Aspartate transaminase</td>
<td>Less than 40 U/L</td>
</tr>
<tr>
<td>Hydroxybutyrate dehydrogenase</td>
<td>50–130 U/L at 25°C</td>
</tr>
<tr>
<td>5′ nucleotidase</td>
<td>2–17 U/L at 37°C</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>30–150 U/L at 37°C</td>
</tr>
<tr>
<td>Total acid phosphatase</td>
<td>Less than 5 U/L at 37°C</td>
</tr>
<tr>
<td>Prostatic acid phosphatase</td>
<td>Less than 2 U/L at 37°C</td>
</tr>
<tr>
<td>γ-Glutamyl transpeptidase</td>
<td>Depends on method used in laboratory</td>
</tr>
<tr>
<td>Creatinine kinase</td>
<td>Depends on method used in laboratory</td>
</tr>
<tr>
<td><strong>Glucose (whole blood)</strong></td>
<td>Fasting 3.3–5.6 mmol/L</td>
</tr>
<tr>
<td><strong>Iron</strong></td>
<td>14–35 mmol/L</td>
</tr>
<tr>
<td><strong>Iron binding capacity (TIBC in serum)</strong></td>
<td>54–76 mmol/L</td>
</tr>
<tr>
<td><strong>Lead (whole blood)</strong></td>
<td>0.5–1.7 mmol/L</td>
</tr>
<tr>
<td><strong>Magnesium (serum)</strong></td>
<td>0.7 nmol/L</td>
</tr>
<tr>
<td><strong>Osmolality (plasma)</strong></td>
<td>275–295 mosmol/kg of water</td>
</tr>
<tr>
<td><strong>Phosphorus (inorganic serum)</strong></td>
<td>0.65–1.4 mmol/L</td>
</tr>
<tr>
<td><strong>Protein</strong></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>60–80 g/L</td>
</tr>
<tr>
<td>Albumin</td>
<td>32–48 g/L</td>
</tr>
<tr>
<td>Globulin</td>
<td>18–38 g/L</td>
</tr>
<tr>
<td><strong>Thyroid stimulating hormone (TSH)</strong></td>
<td>Less than 7.0 mIU/L</td>
</tr>
<tr>
<td><strong>Thyroxine</strong></td>
<td></td>
</tr>
<tr>
<td>Total (T4)</td>
<td>50–165 nmol/L</td>
</tr>
<tr>
<td>Free (fT4)</td>
<td>9–26 pmol/L</td>
</tr>
<tr>
<td><strong>Tri-iodothyronine</strong></td>
<td></td>
</tr>
<tr>
<td>Total (T3)</td>
<td>1.1–2.8 nmol/L</td>
</tr>
<tr>
<td>Free (fT3)</td>
<td>3–9 pmol/L</td>
</tr>
<tr>
<td><strong>Triglyceride (fasting)</strong></td>
<td>Male 0.5–2.4 nmol/L; Female 0.4–2.1 nmol/L</td>
</tr>
</tbody>
</table>
### Urine Chemistry: Normal Values

<table>
<thead>
<tr>
<th>Substance</th>
<th>Normal Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>2.5–7.5 nmol/24h</td>
</tr>
<tr>
<td>Oxalate 0.22–0.44 mmol/24h</td>
<td></td>
</tr>
<tr>
<td>Potassium</td>
<td>50–100 mmol/24h</td>
</tr>
<tr>
<td>Sodium</td>
<td>120–250 mmol/24h</td>
</tr>
<tr>
<td><strong>17 Oxosteroids</strong></td>
<td></td>
</tr>
<tr>
<td>Men 19–50 years of age</td>
<td>28–76 µmol/24h</td>
</tr>
<tr>
<td>Women 19–50 years of age</td>
<td>21–52 µmol/24h</td>
</tr>
<tr>
<td>Men greater than 50 years</td>
<td>17–63 µmol/24h</td>
</tr>
<tr>
<td>Women greater than 50 years</td>
<td>10–31 µmol/24h</td>
</tr>
<tr>
<td><strong>17 Oxogenic steroids</strong></td>
<td></td>
</tr>
<tr>
<td>Men 19–50 years of age</td>
<td>28–70 µmol/24h</td>
</tr>
<tr>
<td>Women 19–50 years of age</td>
<td>21–63 µmol/24h</td>
</tr>
<tr>
<td>Men greater than 50 years</td>
<td>17–52 µmol/24h</td>
</tr>
<tr>
<td>Women greater than 50 years</td>
<td>10–31 µmol/24h</td>
</tr>
<tr>
<td>Uric acid</td>
<td>3–6 mmol/24h</td>
</tr>
<tr>
<td><strong>Vanillylmandelic acid (VMA)</strong></td>
<td>Less than 45 µmol/24h</td>
</tr>
</tbody>
</table>

**Glomerular filtration rate:**
- Male aged 20 years: 117–170 mL/min/1.73 m²
- Aged 50 years: 96–138 mL/min/1.73 m²
- Aged 70 years: 70–110 mL/min/1.73 m²
- Female aged 20 years: 104–158 mL/min/1.73 m²
- Aged 50 years: 90–130 mL/min/1.73 m²
- Aged 70 years: 74–114 mL/min/1.73 m²

**Osmolality urine (random):** 40–1,400 mmol/kg

### Hematology: Normal Values

**Blood counts—adults at sea level**

<table>
<thead>
<tr>
<th>Subcategory</th>
<th>Normal values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red blood cell (RBC) count</td>
<td>Male 5.5 ± 1</td>
</tr>
<tr>
<td></td>
<td>Female 4.8 ± 1</td>
</tr>
<tr>
<td>Hemoglobin (Hb)</td>
<td>Male 15.5 ± 2.5</td>
</tr>
</tbody>
</table>
|                                         | Female 14 ± 2.5 | g/dL
| Hematocrit                              | Male 0.47 ± 0.07 |
|                                         | Female 0.42 ± 0.05 |
| Mean corpuscular volume (MCV)           | 85 ± 8        | fl
| Mean corpuscular hemoglobin (MCH)       | 29.5 ± 2.5    | pg
| Mean corpuscular hemoglobin concentration (MCHC) | 33 ± 2 |
| Reticulocytes (0.2–2.0%)                | 10–100        | × 10⁹/L
| Leukocytes                              | 7.5 ± 3.5     | × 10⁹/L
| - Differential leukocyte count           |               |
| - Neutrophils (40–75%)                  | 2.0–7.5       | × 10⁹/L
| - Lymphocytes (20–45%)                  | 1.5–4.0       | × 10⁹/L
| - Monocytes (2–10%)                     | 0.2–0.8       | × 10⁹/L
| - Eosinophils (1–6%)                    | 0.04–0.4      | × 10⁹/L
| - Basophils (<1%)                       | < 0.1         | × 10⁹/L
| Platelets                               | 150–400       | × 10⁹/L
### Blood constituents and properties

<table>
<thead>
<tr>
<th></th>
<th>Range/mean</th>
<th>Units</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum iron</td>
<td>± 2SD</td>
<td>µmol/L</td>
<td></td>
</tr>
<tr>
<td>Total iron binding capacity (TIBC)</td>
<td>45–70 µmol/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum ferritin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>24–413 µmol/L</td>
<td></td>
<td>Radio-immunoassay</td>
</tr>
<tr>
<td>Female</td>
<td>15–314 µmol/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum vitamin B&lt;sub&gt;12&lt;/sub&gt;</td>
<td>150–1,000 ng/L</td>
<td></td>
<td>Microbiological</td>
</tr>
<tr>
<td>Schilling test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum folate</td>
<td>2.5–12 µg/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RBC folate</td>
<td>160–640 µg/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgG</td>
<td>6–15 g/L</td>
<td></td>
<td>Adults</td>
</tr>
<tr>
<td>IgM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.43–3.23 g/L</td>
<td></td>
<td>Adults</td>
</tr>
<tr>
<td>Female</td>
<td>0.66–3.52 g/L</td>
<td></td>
<td>Adults</td>
</tr>
<tr>
<td>IgA</td>
<td>1.0–4.5 g/L</td>
<td></td>
<td>Adults</td>
</tr>
<tr>
<td>ESR</td>
<td>Male</td>
<td></td>
<td>Up to 5 mm in first hour Westergren</td>
</tr>
<tr>
<td>Female</td>
<td>Female</td>
<td></td>
<td>Up to 9 mm in first hour</td>
</tr>
<tr>
<td>Plasma viscosity (relative)</td>
<td>1.5–1.72 cp</td>
<td></td>
<td>Harkness at 25° C</td>
</tr>
<tr>
<td>Red cell volume</td>
<td>Male</td>
<td></td>
<td>30 ± 5 mL/kg</td>
</tr>
<tr>
<td>Female</td>
<td>Female</td>
<td></td>
<td>25 ± 5 mL/kg</td>
</tr>
<tr>
<td>Plasma volume</td>
<td></td>
<td></td>
<td>40–50 mL/kg</td>
</tr>
<tr>
<td>51-chromium red cell half-life (t1/2)</td>
<td>25–33 Days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iron clearance (t1/2)</td>
<td>60–140 minutes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iron utilization</td>
<td>20–80% in 14 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA&lt;sub&gt;2&lt;/sub&gt;</td>
<td>1.5–3.2%</td>
<td></td>
<td>Adults</td>
</tr>
<tr>
<td>HbF</td>
<td>0.5–0.8%</td>
<td></td>
<td>Adults</td>
</tr>
<tr>
<td>*P50HBA</td>
<td>3.5 (26.5) kPa (mm Hg)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Oxygen tension corresponding to half-saturation of HbA

### Coagulation test

<table>
<thead>
<tr>
<th>Test</th>
<th>What is tested</th>
<th>Normal range</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding time</td>
<td>Platelet number, and function, behavior, of severed blood vessels</td>
<td>1–7 min</td>
<td>Ivy’ method</td>
</tr>
<tr>
<td>Whole blood Clotting time</td>
<td>Intrinsic system</td>
<td>&lt;10 min</td>
<td>At 37° C. Depends on technique</td>
</tr>
<tr>
<td>Kaolin cephalin time (partial) thromboplastin (time)</td>
<td>Intrinsic system</td>
<td>35–45 sec</td>
<td>Depends on reagents and technique</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>Extrinsic</td>
<td>10–14 sec</td>
<td>Depends on reagents and technique</td>
</tr>
<tr>
<td>Thrombin time</td>
<td>Fibrinogen to fibrin stage</td>
<td>10–12 sec</td>
<td>Sensitive to heparin and FDP; Depends on strength of thrombin</td>
</tr>
<tr>
<td>Fibrinogen assay</td>
<td>Plasma level</td>
<td>2–4 g/L</td>
<td></td>
</tr>
<tr>
<td>Test</td>
<td>What is tested</td>
<td>Normal range</td>
<td>Comments</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>-------------------------------</td>
<td>--------------------</td>
<td>------------------------------------</td>
</tr>
<tr>
<td>Fibrinogen titer</td>
<td>Plasma level</td>
<td>Titer of &lt; 81 is normal</td>
<td></td>
</tr>
<tr>
<td>Fibrin degradation products (FDPs)</td>
<td>Fibrinolytic activity</td>
<td>Absent or trace</td>
<td>&lt; 10 mg/L Crude but quick test</td>
</tr>
<tr>
<td>Assays of coagulation factors VIII and IX</td>
<td>Coagulant activity of</td>
<td>50–200%</td>
<td>Several methods serum and urine</td>
</tr>
<tr>
<td>Euglobulin clot lysis time</td>
<td>Fibrinolysis</td>
<td>2–6 hours</td>
<td>tested</td>
</tr>
</tbody>
</table>

**Immunohematology**

<table>
<thead>
<tr>
<th>Test</th>
<th>Range/mean</th>
<th>Units</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>± 2SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iso-agglutinin titers</td>
<td>Anti-A</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt; 32 – &lt; 2048</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anti-B</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt; 8 – &lt; 512</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterophile antibody</td>
<td>&lt; 80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cold agglutinin titer at 4°C</td>
<td>&lt; 64</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Third component (C3)</td>
<td>0.94–2.14</td>
<td>g/L</td>
<td>Nephelometer</td>
</tr>
<tr>
<td>• Fourth component (C4)</td>
<td>0.16–0.5</td>
<td>g/L</td>
<td>Nephelometer</td>
</tr>
<tr>
<td>• CI esterase inhibitor</td>
<td>0.12–0.3</td>
<td>g/L</td>
<td>Nephelometer</td>
</tr>
</tbody>
</table>

**Laboratory Reference Values**

**Electrolytes/renal**

<table>
<thead>
<tr>
<th>Test</th>
<th>Range/mean</th>
<th>Units</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>135–145 mmol/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potassium</td>
<td>3.5–5.0 mmol/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chloride</td>
<td>95–107 mmol/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>23–32 mmol/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urea</td>
<td>3–8.0 mmol/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>≥ 0.04–0.11; ≥ 0.04–0.13 mmol/L</td>
<td>g/L</td>
<td></td>
</tr>
<tr>
<td>eGRF</td>
<td>&gt; 60 mL/min/1.72 m²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR</td>
<td>&lt; 60 mL/min/1.72 m²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium</td>
<td>2.10–2.60 mmol/L (total)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phosphate</td>
<td>0.90–1.35 mmol/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magnesium</td>
<td>0.65–1.00 mmol/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uric acid</td>
<td>≥ 0.12–0.40; ≥ 0.15–0.45 mmol/L</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Liver function/pancreas**

<table>
<thead>
<tr>
<th>Test</th>
<th>Range/mean</th>
<th>Units</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin</td>
<td>&lt; 20 μmol/L (total)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST</td>
<td>&lt; 3 μmol/L (direct)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GGT</td>
<td>&lt; 45; ≥ 65 U/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alkaline phosphatase (ALP)</td>
<td>&lt; 120 U/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total protein</td>
<td>60–80 g/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td>38–50 g/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amylase</td>
<td>30–110 U/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipase</td>
<td>&lt; 80 U/L</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Therapeutic drugs**

<table>
<thead>
<tr>
<th>Test</th>
<th>Range/mean</th>
<th>Units</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digoxin</td>
<td>Ther. 1.3–2.6 nmol/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Ther. 40–80 nmol/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium valproate</td>
<td>Ther. 300–700 nmol/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Ther. 10–50 nmol/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appendixes</td>
<td>1345</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------</td>
<td>------</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Gentamicin**
- < 2.0 µg/mL (pre)
- < 12.0 µg/mL (post)

**Lithium**
- Ther. 0.5–1.0 mmol/L

**Cardiac/lipids**
- Troponin I or T
  - < 0.1 µg/L
- CK total
  - < 200; < 800 U/L
- CK-MB
  - < 25 U/L
- Cholesterol
  - < 5.5 mmol/L
- Triglycerides
  - < 2.0 mmol/L
- HDL cholesterol
  - > 1.00 mmol/L
- LDL cholesterol
  - < 3.5 mmol/L

**Thyroid tests**
- Free T<sub>4</sub>
  - 10.0–20.0 pmol/L
- Ultra-sensitive eTSH
  - 0.3–5.0 mU/L
- Free T<sub>3</sub>
  - 3.3–8.2 pmol/L

**Other endocrine tests**
- Serum cortisol
  - 8 am 130–700 nmol/L
  - 80–350 nmol/L
  - 1–9 IU/L (adult)
  - 10–30 IU/L (ovulation)
  - 4–200 IU/L (postmenopause)
- < 200 pmol/L
- Estradiol menopausal
  - < 3.5; 10–35 nmol/L
- Testosterone

**Tumor markers**
- PSA
  - 0.1.0 µg/L
- CEA
  - < 7.5 µg/L
- AFT
  - < 10 µg/mL
- CA-125
  - < 35 U/mL

**Iron studies**
- Ferritin
  - 20–250 µg/L
- Iron
  - 14–30 µmol/L
- Iron-binding capacity
  - 45–80 µmol/L
- Transferrin
  - 2–3.5 g/L
- Transferrin saturation
  - ≥20–55%; 20–60%

**Blood gases/arterial**
- pH
  - 7.38–7.43
- PaO<sub>2</sub>
  - 85–105 mm Hg
- PaCO<sub>2</sub>
  - 36–44 mm Hg
- Bicarbonate
  - 20–28 mmol/L
- Base excess
  - –3 + 3 mmol/L

**Glucose**
- Glucose fasting
  - 3.5–6.0 mmol/L
- Glucose random
  - 3.5–7.9 mmol/L
- HbA<sub>1c</sub>
  - 4.7–6.1%

**Hematology**
- Hb
  - ≥ 115–165; ≥ 130–180 g/L
- PCV
  - ≥ 37–47; ≥ 40–54%
- MCV
  - 81–98 fl
- Reticulocytes
  - 0.5–2.0%
- White cells
  - 4.0–11.0 × 10<sup>9</sup>/L
- Platelets
  - 150–400 × 10<sup>9</sup>/L
- ESR
  - < 20 mm
### Normal Values: Diagnostic Guidelines

The following is a type of checklist that one can use as a template in everyday practice and for teaching.

#### Hypertension
- **BP**
  - Men: >140–90 mm Hg
  - Women: >150–90 mm Hg

#### Alcohol excessive drinking
- **♂**
  - >2 SDs/d; ♂
  - >4 SDs/d

#### Anemia
- **Hemoglobin**
  - Men: <115 g/L; Women: <130 g/L

#### Body mass index
- **Wt (kg)/Ht (m²)**
  - Normal: 20–25
  - Overweight: >25
  - Obesity: >30

#### Jaundice
- **S bilirubin**
  - >19 μmol/L

#### Fever
- **Temperature**
  - Oral: >37.2°C
  - Rectal: >37.7°C
  - Morning: There is considerable diurnal variation in temperature so that it is higher in the evening 0.5–1°C

#### Diabetes mellitus
- **Blood sugar-random**
  - >11.1 mmol/L
- **Blood sugar-fasting**
  - >7.0 mmol/L

#### Hypokalemia
- **S potassium**
  - <3.5 mmol/L

#### Hyperkalemia
- **S potassium**
  - >5.0 mmol/L

#### Vital signs (average)

<table>
<thead>
<tr>
<th>Age in years</th>
<th>&lt; 6 months</th>
<th>6 months–3 year</th>
<th>3–12 years</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pulse (beats/min)</strong></td>
<td>120–140</td>
<td>110</td>
<td>80–100</td>
<td>60–100</td>
</tr>
<tr>
<td><strong>Respiration rate (Breaths/min)</strong></td>
<td>45</td>
<td>30</td>
<td>20</td>
<td>14</td>
</tr>
<tr>
<td><strong>BP (mm Hg)</strong></td>
<td>90/60</td>
<td>90/60</td>
<td>100/70</td>
<td>&lt;130/85</td>
</tr>
</tbody>
</table>

#### Children’s weight rule of thumb

| Wt = (age + 4) × 2 kg |

#### PEAK FLOW NORMAL VALUES (LITERS PER MINUTE)

<table>
<thead>
<tr>
<th>Men</th>
<th>Height</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>5 feet 3 inches</td>
</tr>
<tr>
<td>15</td>
<td>520</td>
</tr>
<tr>
<td>20</td>
<td>570</td>
</tr>
<tr>
<td>25</td>
<td>600</td>
</tr>
<tr>
<td>30</td>
<td>610</td>
</tr>
<tr>
<td>Age in years</td>
<td>Height</td>
</tr>
<tr>
<td>--------------</td>
<td>--------</td>
</tr>
<tr>
<td></td>
<td>5 feet 3 inches</td>
</tr>
<tr>
<td>35</td>
<td>615</td>
</tr>
<tr>
<td>40</td>
<td>605</td>
</tr>
<tr>
<td>45</td>
<td>590</td>
</tr>
<tr>
<td>50</td>
<td>575</td>
</tr>
<tr>
<td>55</td>
<td>565</td>
</tr>
<tr>
<td>60</td>
<td>555</td>
</tr>
<tr>
<td>65</td>
<td>545</td>
</tr>
<tr>
<td>70</td>
<td>535</td>
</tr>
</tbody>
</table>

Women

<table>
<thead>
<tr>
<th>Age in years</th>
<th>Height</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4 feet 9 inches</td>
</tr>
<tr>
<td>15</td>
<td>440</td>
</tr>
<tr>
<td>20</td>
<td>445</td>
</tr>
<tr>
<td>25</td>
<td>450</td>
</tr>
<tr>
<td>30</td>
<td>450</td>
</tr>
<tr>
<td>35</td>
<td>450</td>
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<tr>
<td>40</td>
<td>450</td>
</tr>
<tr>
<td>45</td>
<td>445</td>
</tr>
<tr>
<td>50</td>
<td>435</td>
</tr>
<tr>
<td>55</td>
<td>425</td>
</tr>
<tr>
<td>60</td>
<td>415</td>
</tr>
<tr>
<td>65</td>
<td>400</td>
</tr>
<tr>
<td>70</td>
<td>385</td>
</tr>
</tbody>
</table>

Children

<table>
<thead>
<tr>
<th>Height</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 feet 0 inch</td>
</tr>
<tr>
<td>(91 cm)</td>
</tr>
<tr>
<td>60</td>
</tr>
</tbody>
</table>

| 4 feet 4 inches | 4 feet 6 inches | 4 feet 8 inches | 4 feet 10 inches | 5 feet 0 inch | 5 feet 2 inches |
| (132 cm) | (137 cm) | (142 cm) | (147 cm) | (152 cm) | (157 cm) |
| 270     | 300     | 325     | 350     | 375     | 410     |
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