Gynecology

The Text Book for Undergraduates

Edited By

Hassan A Nasrat FRCS, FRCOG
Professor of Obstetrics and Gynecology
Director of the Fetal Medicine Unit
Chairman of the Bioethics Committee
Former Chairman of the Department of Obstetrics and Gynecolyg
Faculty of Medicine
King Abd Al-Aziz University
Jeddah – Saudi Arabia

Introduction

Why do we need another Text Book in for.

Hassan Nasrat
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Section 5
Gynecologic Oncology

Chapter 1

Approach to the Gynecological patient History and physical examination

Taking a professional and comprehensive history is a skill that should be taught but it can only be acquired by practice. In large proportion of cases history alone may provide the diagnosis. In gynecology some aspects of history taking are the same in other general medicine disciplines. Others are very specific to the obstetric and gynecological patients.

It is probably true that health care providers in all specialties are expected to have a sensitive and understanding attitude when dealing with their patients. However those qualities are particularly important when dealing with a gynecologic patient who not uncommonly may be shy, or nervous to discuss sensitive information, feelings or fears. This is particularly true in conservative societies. Hence special effort should be made to put the patient at ease.

By the end of this chapter you should be able to:

- **Realize** the importance of proper approach and "non-verbal clues" when dealing with gynecological patient.
- **To define** patient's "Chief complains" vs. a patient who comes for screening or "check up" gynecological visit.
- **Realize** the important elements of gynecological screening : i.e. significance of details of menstrual history, pelvic symptoms, bladder function, sexual history ..etc
- **Realize** the importance of sensitive sympathetic approach in undertaking gynecological examination.
- **Define** the specific standard elements of Gynecological examination.
- **Demonstrate** and describe the objectives of each of those elements: Inspection, speculum and bimanual examination.

➢ Initial approach and "non-verbal clues":

The first contact with the patient, which involves taking a comprehensive history, performing a complete general and gynecologic examination is critical since it is the time to build the initial bond of trust. In addition it is in many cases an excellent opportunity for teaching the patient about measures for maintenance of her health.

It is important to pay attention to the patient general appearance and non-verbal clues (e.g. happiness, shyness, apathy, fear, anger and sadness…etc). This will help the gynecologist to adopt an appropriate and understanding approach for conducting the interview.

E.g. to begin the interview by saying "Mrs. X you seems to be rather worried or sad why is that, could you tell me or how can I help you".

In general, a gynecologic history and examination may be undertaken to evaluate a specific problem; alternatively it may be in the course of a routine screening visit "check up visit" e.g. in menopausal health clinic .

➢ Personal Data:

Including age, marital status, occupation and level of education should be reviewed with the patient . This help to break some barriers that may be present with some patients.

➢ Chief Complaint:

The chief complaint is the primary reason for which the patient is seeking medical consultation.

It should be explored by direct open-ended questions (*e.g. is there any problem? Why did you come to the clinic?*)

If there is more than one complaint it should be stated in the order of its chronological development rather than significance. Establishing chronological organization of patient's complaint and symptoms is important as it may suggest a specific disorder.

During the interview the physician should face the patient with direct eye contact and acknowledge important points of the history either by nodding or by a word or two. Such an approach allows the physician to be involved in the problem and demonstrates a degree of caring to the patient.

➢ Analysis of chief complaint:

Each complaint or symptom should be analyzed in term of: Its duration/ onset /course/ severity.

If there is more than one complaints it is a good idea to repeat it to the patient by saying something like "Now Mrs. X, so you came to see me because" then you list the complaints this time beginning with the most important one.

There are several ways to address those issues *e.g. to ask the patient when the last time she felt well? Why did she decide to come now? any previous consultation? or medication, how does this complaint(s) interferes with her routine daily life?*

A. Menstrual pattern:

- Cycle interval.
- Duration of flow.
- Amount of flow.
- Premenstrual symptoms (Type, duration, severity, treatment)
- Dysmenorrhea (Onset, duration, severity, treatment)
- Intermenstrual bleeding.

Usually, menstrual fluid is medium or dark red, and flow lasts for 5 (± 2) days, with 21 to 35 days between menses; average blood loss is 30 mL (range, 13 to 80 mL), with the most bleeding on the 2nd day. Cramping is common on the day before and on the first day of menses. Uterine bleeding that is painless, scant, and dark, is abnormally brief or prolonged, or occurs at irregular intervals suggests absence of ovulation (anovulation).

B. If postmenopausal:

- Age of last menses.
- Recent vaginal bleeding.
- Vasomotor symptoms.
- Hormone replacement therapy or other relevant medications.

Obstetric History Description of each pregnancy (date, outcome, complications)

A. Para (P) means the number of births (life and stillbirths)

C. Gravida (G) means the total number of pregnancies.

D. Abortions (AB) mean the number of spontaneous or induced abortions.

Infertility: If there is a history suggestive of infertility enquire about:

- Ever difficulty becoming pregnant?
- Ever evaluated or treated for this problem?
  (Describe details of treatment or investigations)

Birth Control

- Current method (satisfaction, problems, any change desired?)
- Past methods (dates used, complications, reasons for change)

Sexual History: The depth of inquiries about sexual history depends on why the patient is seeking advice and the clinical circumstances. For some encounters, sexual history is irrelevant and can be omitted (*e.g. a complaint of menorrhagia, or recurrent miscarriage*).

For other encounters, an abbreviated sexual history is appropriate.

For some, a full and detailed sexual history is needed. In those cases, questions may include: problems (e.g. Dyspareunia, postcoital bleeding), concerns, questions, frequency of sexual activities, use of lubricants…etc.

Pap Smear History

Last Pap test, and its results? (If abnormal, ask about treatment, and follow-up)

Infection

- Vaginal discharge (if present ask about onset, pattern, color, odor, associated symptoms)
- Prior vaginal infections (type, frequency, treatment)
- Prior history of pelvic inflammatory disease.

Bladder and Bowel functions:

- Bladder control and symptoms of urinary. incontinence (description, duration, severity)
- Bowel function, constipation or symptoms of sphincter weakness (description, duration, severity)

Bowel and Bladder Function

History of GIT, such as functional bowel problems or, diverticulitis.

- Rectal incontinence of gas or stool
- Bladder functions include incontinence or symptoms of infection of upper or lower urinary tract.

Breast Disease:

- Masses
- Discharge
- Pain
- Past problems
- Family history of breast cancer
- Last time had breast screening (mammography)

Previous Surgery:

- Gynecologic surgery
- Other non gynecologic surgery

General Medical History, Past and Present

- Medication
- Allergies

- Hospitalizations
- Illnesses

Social History

- Educational background/ husband occupation.

Family History

- Cancer
- Diabetes
- Osteoporosis
- Cardiovascular disease
- Other familial disorders

Health habits

- Tobacco, Drugs …etc
- Diet
- Exercise

Review of systems:

Finally a complete review of systems is necessary to uncover symptoms from other areas (e.g., serious headaches, epileptic seizures, dizziness, or fainting spells) , intake of medications related to reproduction and/or gynecologic problems that may not have been addressed. The review of system include:

- Asking about constitutional systems; eyes, ears, nose and throat; skin problems; and musculoskeletal problems.
- Cardiovascular/respiratory history, as well as a history of hypertension, heart disease, or chest problems, such as asthma and lack of exercise and smoking

At the end of the history it is a good habbit to ask the patient if she has any questions or other information that she would like to add, since some patients will not bring up important information until they feel comfortable with the physician.

General Physical Examination

The physical examination should be considered as an opportunity to gather information about the patient as well as to teach the patient information she should know about herself and her body

- All new patients should have a complete physical examination as well as gynecological examination. The findings should be accurately recorded.
- A chaperone nurse should be present during all parts of the patient examination.
- It is often recommended that for examination the patient should disrobe completely and be covered by a hospital gown. There is no evidence that this is necessary, in addition many women particularly from conservative Islamic societies are very uncomfortable with such request, hence it is very acceptable to only adequately expose the area or part of the body that need to be examined.
- The general examination should begin with general evaluation of the patient appearance, posture, body build, state of nutrition, and state of well-being. Her vital signs (temperature, pulse rate and character, respiratory rate, and blood pressure), weight and height should be reviewed.

Systemic examination: Systemic examination begins with:

- The head (eyes, teeth, throat) and neck (for thyroid or nodular swelling). Inspection should be made for abnormal hair growth in the upper lip or chin, which may indicate increased androgen activity.
- Then the chest is examined by inspection, auscultation for lung ventilation and any adventitious sounds, wheezing or rales should be noted. The heart should be auscultated for irregularities of rate and evidence of murmurs and other adventitious sounds.
- **Breast examination**: careful breast examination should be carried out in a systematic fashion as described in chapter 10. This can only be performed after taking patient permission for breast examination.

Gynecological examination

Gynecological examination includes examination of abdomen, and pelvic organs.

Hair Distribution

The Typical female hair distribution is that of an inverted triangle over the mons pubis.

A male hair distribution takes a diamond pattern with hair growth between the area of the mons pubis and the umbilicus. If present it may indicate excessive androgen activity in a female patient

➢ Examination of the Abdomen:

The standard technique employed is composed of:

- **Inspection**: of the abdomen for symmetry, contour (e.g. flat, scaphoid, or protuberant), changes in skin color, mobility of the abdominal wall with breathing, hair distribution, presence of striae, surgical scars, and finally to ask the patient to cough while inspecting hernial orifices for abnormal bugling or defects.
- **Palpation**: should be performed in systematic way. It usually begins with superficial palpation to gain the patient confidence, cooperation and to feel for any location of discomfort or tenderness.

  This is followed by gentle deep palpation again in a systematic way starting away from the location of maximum pain or tenderness**.** The aims of palpation are:

  - To feel for organomegaly (abnormally enlarged organs), particularly involving the liver, spleen, kidneys, and uterus; and for any abnormal masses. It also includes palpation for both renal angles.
  - Elicit evidence of tenderness and or rigidity which would imply intraabdominal (peritoneal) irritation. *Rebound tenderness* usually confirms the presence of intraabdominal irritation.
  - Especial test for fluid wave suggest either ascites or hemo-peritoneum.

Abdominal Palpation

At the end you should be able to comments on:

- whether or not the liver, or spleen are palpable, any abnormal masses, and both renal angles.
- Softens or rigidity of the abdomen and any location of tenderness.
- Abnormal mass(s) should be described in details (size, site, mobility, borders, surface, consistency and tenderness).

- **Percussion and auscultation**: are then performed to confirm and/or define

the findings on palpation and the nature of suspected collection or masses (gases, ascites, and solid masses)

➢ **Examination of the legs:**

The legs are then examined for evidence of varicose veins, edema, or any other lesions.

➢ **Pelvic Examination**:

- Some patients especially if it is the first time and young females may feel rather nervous or shy with this step of examination. Therefore it is important to spend few minutes to explain the objective of the pelvic examination, what does it entails and how is it going to be performed.
- The patient should be asked to empty her bladder in order to decrease possible discomfort during the examination and to make the pelvic organs more easily palpable.
- Position of the patient: The pelvic examination is conducted with the patient lying supine on the examination table; the buttocks are positioned at the edge of the table, the legs in stirrups, and draped with a sheet.
- With Moslem women internal examination should be avoided if she is fasting or menstruating unless it is absolutely necessary.

Pelvic examination has three components: the external examination, the speculum examination, and the bimanual examination.

➢ **External Examination**:

- Inspect the hair pattern distribution, labia minora and majora, clitoris (for clitorimegaly), and any skin lesions (pigmentation, ulcers…etc), a note is made if the patient is circumcised.
- Inspect the perineal body, the area at the posterior aspect of the labia, then the perianal area for evidence of hemorrhoids, sphincter injury, warts, and other lesions
- Examination of the urethra: by inserting the index finger into the vaginal and gently milks it from the inside to the outside. Any tenderness and/or express of exudates should be noted and sample sends for culture.

Examination of the Bartholin's glands: by placing the index finger inside the introitus and the thumb on the outside of the labium majora to feel for an enlargements or

cysts of gland. Repeat the procedure for the opposite side (normally the gland is not palpable).

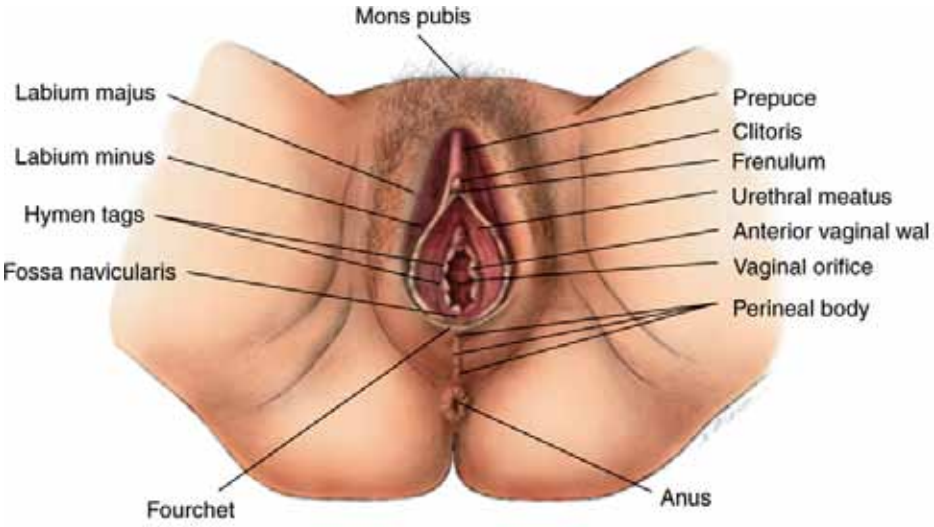

Figure 1-1: External Genitalia

➢ Examination of the vaginal walls: The vaginal walls are examined for abnormalities and/or vaginal wall descent and uterine descent. With the gloved hand holding the labia apart, the patient is asked to bear down (Valsalva's maneuver) or to cough in order to demonstrate stress incontinence and/or signs of descent of lower vaginal wall (cystocele, or rectocele) or upper posterior vaginal wall (enterocele). Also with bearing down the cervix may become visible indicating uterine descent (See Figure 1-2 and 3)

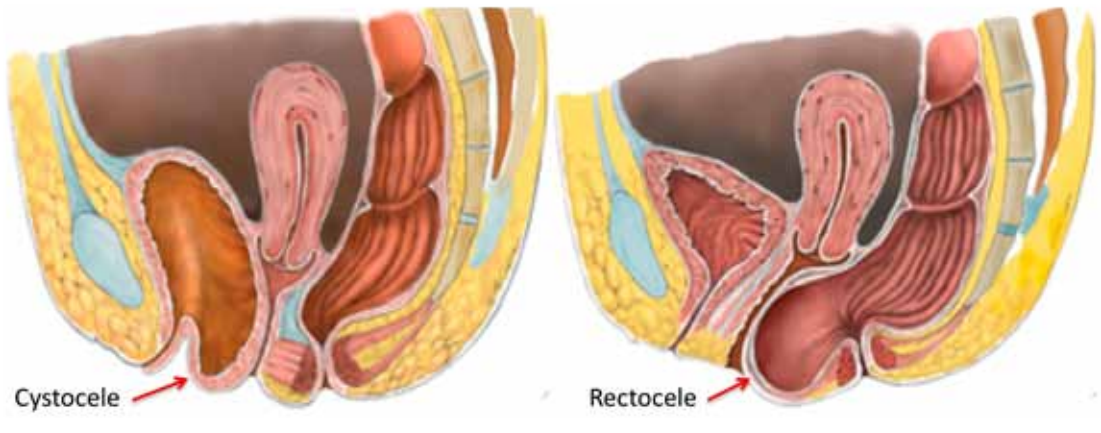

Figure 1-2: Showing side view of cystocele and rectocele. The degree of descent of the vaginal wall should be graded 1+ to 4+, with 1+ being a minimum bulge and 4+ being a bulge through the introitus.

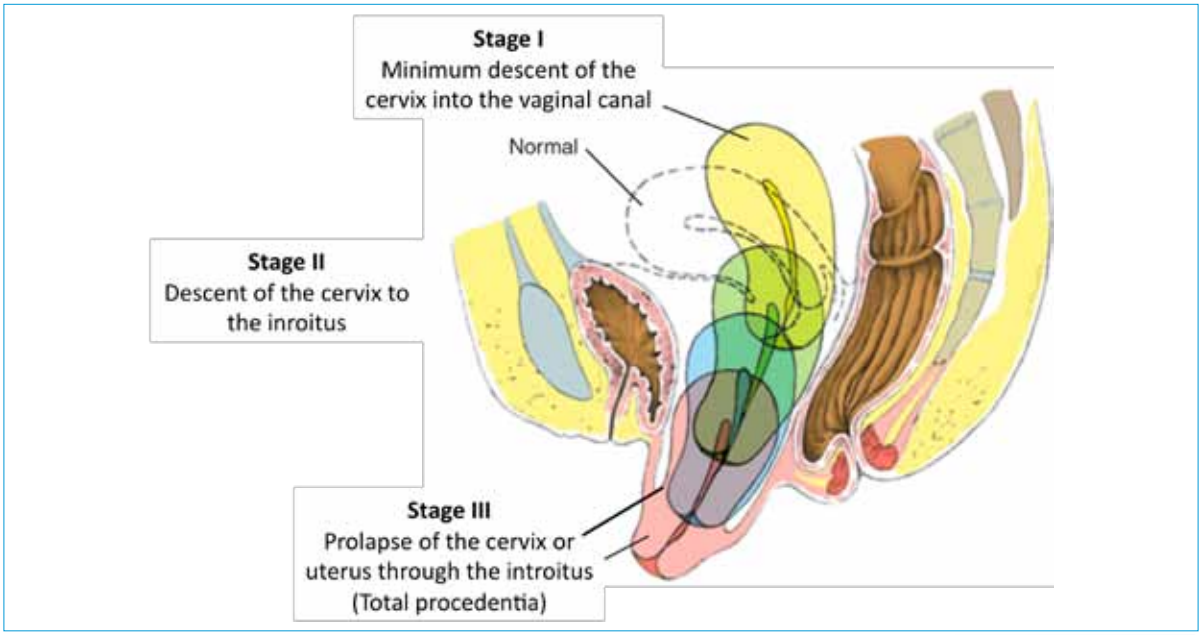

Figure 1-3: Showing the three stages of prolapse of the cervix and uterus.

➢ **Speculum Examination**:

Using a metal or plastic bivalve speculum (Figure 1-4) inspection of the cervix and vaginal walls can be performed. In special cases such as in prolapse a lateral vaginal wall retractor or Sim's speculums are used (the use and application of these special devices are discussed in the chapter on pelvic floor descent).

Figure 1-4: plastic (Left) and metal (right) bivalve Cusco vaginal speculum.

Vaginal speculums come in different sizes. An appropriate size should be chosen. Usually the largest comfortable size is used. The speculum should be first moistened with warm water or other kinds of lubrication (**the latter should be avoided if either cultures or cytology is to be obtained**).

Speculum examination involves three main steps: insertion, opening, and removal

- Insertion: The labia are gently spread aside to expose the introitus, and the closed speculum is inserted obliquely at approximately 30^0 angle from the vertical axis, pointing the speculum directly toward the sacrum. Once the speculum is placed deep in the vagina, the blades are rotated to the horizontal.
- Opening: The speculum is then withdrawn slightly as the blades are slowly opened, allowing the cervix to fall between the two blades. If the cervix is not easily observed, the speculum should be partially withdrawn and redirected (usually more posteriorly). If a patient's uterus is retroflexed, the cervix will often be located more anteriorly.

The cervix is inspected for shape, size, and color, appearance of the squamocolumnar junction, or abnormal discharge, which should be cultured. If indicated a cervical cytology smear (Papanicolaou or Pap smear) is taken.

- Removal: At the end of the examination the speculum lock should be undone and the blades partially kept in the open position with hand pressure and the speculum is gently withdrawn while the examiner inspecting the vaginal mucosa for any signs of masses, ulceration, inflammations and discharge. The blades are allowed to close only when the speculum is free of the introitus.

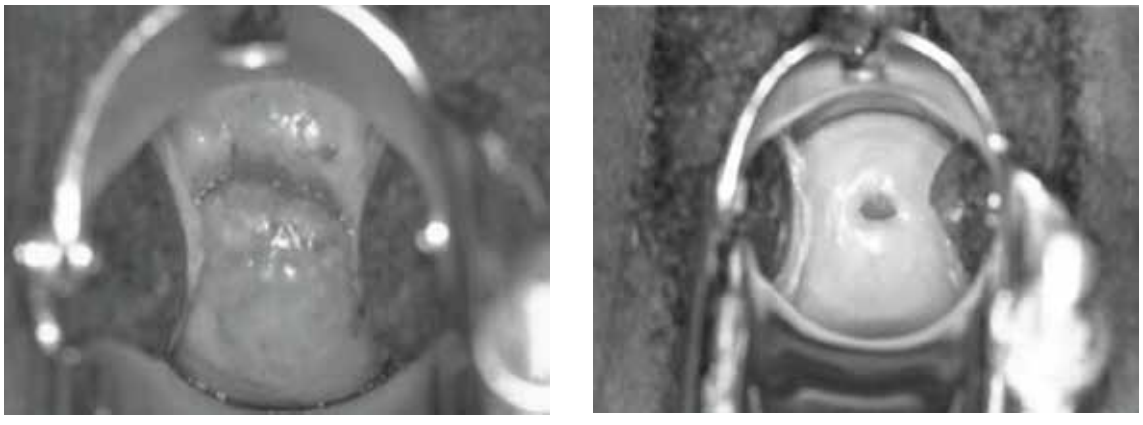

Figure 1-5: Left: nulliparous cervix with smooth round external os. Left: Multiparous cervix, in which childbirth (or abortion) results in more irregular cervix slit like appearance, the squamocolumnar junction easily seen.

➢ **Bimanual examination**:

Bimanual examination provides information about uterus, adnexa and pouch of Douglas. The labia are gently separated with one hand and the gloved, lubricated index and middle fingers of the dominant hand are gently introduced into the vaginal introitus. The other hand, placed on the abdomen, is used to sweep the pelvic organs downward while the vaginal hand is simultaneously elevating them. Using this maneuver, the physician can:

- Determine the size, mobility, position, and consistency of the uterus.
- Feel the adnexal areas for the presence of normal ovaries. The fallopian tubes in health will not usually be palpable.
- Palpate for abnormal masses. Any masses should be described as to location, size, consistency, mobility, and degree of tenderness.
- Finally, the cul-de-sac "the pouch of Douglas" and uterosacral ligaments should be assessed for masses or nodularity.
- Any undue tenderness caused by palpation or movement of the uterus should be noted, since it may imply an inflammatory process.

Normally, the uterus is about 6 cm by 4 cm and tilts anteriorly (anteversion), but it may tilt posteriorly (retroversion). It may also be bent at an angle anteriorly (anteflexion) or posteriorly (retroflexion). The uterus is movable and smooth. Normally, the ovaries are about 2 cm by 3 cm in young women and are not palpable in postmenopausal women. Significant pain when the cervix is gently moved from side to side (cervical motion tenderness) suggests pelvic inflammation.

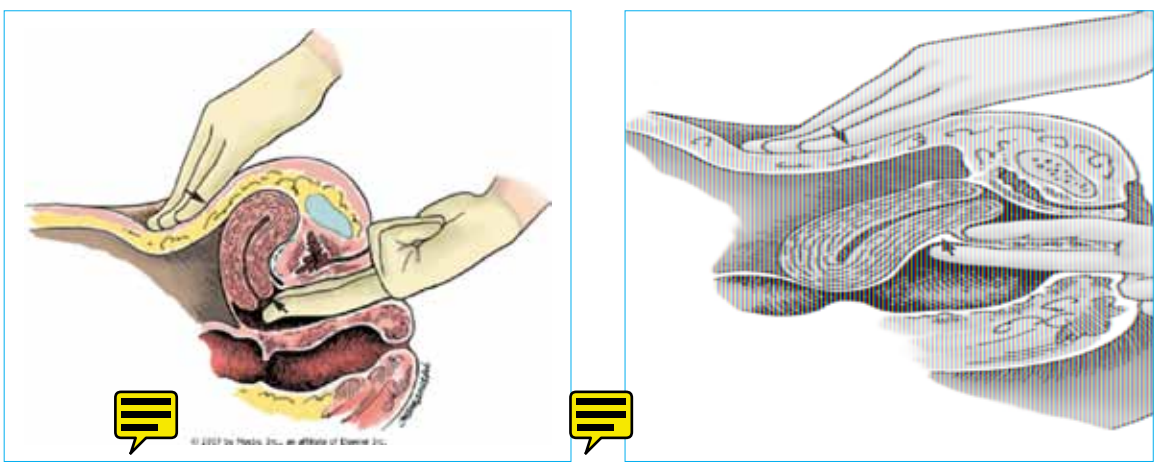

Figure 1-6: Bimanual examination of the uterus. In two thirds of instances uterus is anteflexed so that the abdominal hand is palpating the posterior wall of the uterus and the vaginal fingers the anterior wall.
Rectovatinal examination (Right) not indicted **in all cases but if there is suspected pathology e.g. deposits in the POD.**

- **Rectovaginal and rectal examination**: This not part of the routine gynecological examination, but is performed when indicated.

- It is important that each step of the examination and any abnormal findings should be clearly explained to the patient. It is also useful to use the opportunity of the examination as a vehicle for teaching the patient about her body.

Gynecological examination of children:

- For children the examination should be adjusted according to child psychosexual development and is usually limited to inspection of the external genitals. Young children can be examined on their mother's lap. The perineal area can be inspected vaginal discharge can be collected, examined, and cultured.
- Internal vaginal or cervical examination should be performed by specialist in pediatric gynecology, and may have to be performed under sedation or anesthesia.

Chapter 2

Common Symptoms in Gynecology

In comprehensive gynecological history should addresses detailed menstrual disorder, presence or absence of vaginal discharge, sexual history in addition to the primary presenting complaint.

By the end of this chapter you should be able to:
Define the following terms:
- The normal menstrual cycle
- Dysfunctional uterine bleeding
- Menorrhagia
- Amenorrhea
- Oligomenorrhea
- Polymenorrhea
- Metrorrhagia
- Menometrorrhagia
- Dysmenorrhea
- Dyspareunia
- Vulvodynia

Abnormal uterine bleeding

▶ The normal menstrual cycle:

- The normal menstrual cycle is 28 days but varies from 24 to 35 days, the blood flow lasts from approximately two to seven days, with loss of less than 80 mL per cycle (average normal amount of menstrual blood loss is 30 to 40 mL per cycle).
- Cycle variability is common in the first five to seven years after menarche and for the last ten years before complete cessation of menses. While in between the ages of 20 and 40 the variation is relatively less.
- In ovulatory cycle women often complain of some clinical symptoms include breast

tenderness, bloating or pelvic discomfort, mood changes, and thin vaginal discharge at mid-cycle.

Terminology: there are different terms that are used to describe abnormal frequency, duration, or volume of uterine bleeding. Sometime it can be confusing therefore they can be grouped under the general term "abnormal uterine bleeding" with detailed description is often used instead of the terms described below.

- Dysfunctional uterine bleeding**:** refers to excessive noncyclic endometrial bleeding unrelated to anatomical lesions of the uterus or to systemic disease; thus, it is a diagnosis of exclusion. Sometimes it is referred to as anovulatory bleeding, since this is the primary cause.
- Menorrhagia: Menorrhagia refers to excessive or prolonged menstrual bleeding. It is technically defined as blood loss greater than 80 mL per cycle and/or menstrual periods lasting longer than seven days.

  This is a very common complaint yet it is very subjective because of inaccuracy in determining the amount of blood loss. Therefore another descriptive definition for menorrhagia is "*excessive menstrual blood loss which interferes with the woman's physical, emotional, social and material quality of life, and which can occur alone or in a combination with other symptoms.*"
- Amenorrhea:
  - Primary amenorrhea: is delayed onset of menses beyond age 15 in adolescent who already showing sings of puberty, otherwise is considered as delayed puberty.
  - Secondary Amenorrhea: refers to absence of bleeding for at least three usual cycle lengths
- Oligomenorrhea: refers to bleeding that occurs at an interval greater than 35 days.
- Polymenorrhea: refers to regular bleeding that occurs at an interval less than 24 days.
- Metrorrhagia: refers to light bleeding from the uterus at irregular intervals.
- Menometrorrhagia: refers to heavy bleeding from the uterus at irregular intervals.
- Intermenstrual bleeding: Intermenstrual bleeding refers to bleeding that occurs between menses or in women using some forms of hormonal contraception or postmenopausal hormone therapy.
- Premenstrual spotting: Premenstrual spotting refers to light bleeding preceding regular menses.
- Postcoital bleeding: Postcoital spotting refers to vaginal bleeding that is noted within 24 hours of vaginal intercourse

Dysmenorrhea

Dysmenorrhea is pain during menstruation that interferes with daily activities.

- Primary dysmenorrhea (PD) refers to the presence of recurrent, crampy, lower abdominal pain that occurs during menses in the absence of demonstrable pelvic disease.
- Secondary dysmenorrhea: Dysmenorrhea is pain during menstruation in the presence of pathological lesion.

Vaginal Discharge and Vulvovaginal symptoms

Normal vaginal discharge:

- In reproductive aged women, normal vaginal discharge consists of 1 to 4 mL fluid (per 24 hours), which is white or transparent, thick, and mostly odorless. It increases at certain times such as during pregnancy, use of estrogen-progestin contraceptives, or at midmenstrual cycle close to the time of ovulation.
- This physiologic discharge is formed by mucoid endocervical secretions in combination with sloughing epithelial cells, normal bacteria, and vaginal transudate. It can be somewhat malodorous and accompanied by irritative symptoms
- The pH of the normal vaginal secretions is 4.0 to 4.5; the acidic environment is hostile to growth of pathogens and inhibits adherence of bacteria to vaginal squamous epithelial cells. The microbiology of the vagina is complex. The most abundant normal organisms are lactobacillus, which produce hydrogen peroxide and lactic acid thereby maintaining the normally acidic vaginal pH; diphtheroids; and S. epidermidis.

In premenarchal and postmenopausal women in whom estrogen levels are low, the vaginal epithelium is thin and the pH of the normal vaginal secretions is 4.7 or more. The higher pH is due to reduced colonization of lactobacilli.

- The normal vaginal flora is influenced by factors such as women age, phase of the menstrual cycle, sexual activity, contraceptive choice, pregnancy, presence of necrotic tissue or foreign bodies, and use of hygienic products or antibiotics can disrupt the normal ecosystem.

Dyspareunia

Dyspareunia refers to persistent or recurrent genital pain just before, during, or after sexual intercourse. It is a rather common form of sexual dysfunction. Other forms of sexual dysfunctions include lack of sexual desire, impaired arousal, and inability to achieve orgasm.

Women often do not talk about this complains to the their physician.

Dyspareunia or genital pain may be occasional but becomes a problem when it is persistent and recurrent.

Etiologies: There are many possible etiologies of pain related to sex. The leading cause in women under the age of 50 has been attributed to localized vulvodynia. In women over the age of 50, urogenital atrophy is the leading cause.

Vulvodynia

Vulvar pain syndromes are characterized by unexplained burning or any combination of stinging, irritation, pain, or rawness located anywhere between the mons and the anus and causing physical, sexual, and psychological distress of at least three to six months duration

It is classified into:

- Vulvar pain related to a specific disorder: Infection (eg, candidiasis, trichomoniasis, herpes simplex virus)Neoplasm (eg, Paget disease, squamous cell carcinoma)Neurologic disease, Inflammation (eg, lichen simplex chronicus, lichen sclerosus, lichen planus, atrophic vaginitis, immunobullous disorder)
- Vulvar pain in the absence of visible lesions or a clinically identifiable disorder: This group, termed vulvodynia, refers to several types of vulvar discomfort occurring in the absence of a specific clinically identifiable disorder of any kind (ie, idiopathic).

Chapter 3

Diagnostic Procedures in Gynecology

Over the last few decades' considerable changes in the practice of gynecology have taken place. Many procedures that used to require hospital admission for surgical intervention under general anesthesia can now be performed in the setting of outpatient clinics. This is due to advances in diagnostic and therapeutic measures in imaging including transvaginal ultrasound and minimal invasive surgery such as hysteroscopy, and colposcopy.

Compared to traditional surgical procedures minimal diagnostic and invasive procedures are not only more convenient and safer to the patient but it also involves considerable reduction in overall cost.

By the end of this chapter you should be able to:

- **List** the indications, contra-indications and potential complications of each of the following measures:
    - Endometrial sampling procedures
    - Hysteroscopy
    - Colposcopy

Endometrial sampling procedures

Indications:

Office diagnostic endometrial samplings have replaced the formal dilatation and curettage surgery in many indications such as:

- Abnormal uterine bleeding: e.g. pre or post menopausal bleeding
- Pelvic pain: e.g. endometritis
- Infertility: e.g. secretory changes for evidence of ovulation

Contraindication:

Absolute contraindication:

- Pregnancy

Relative contraindications:

- Cervical stenosis
- Acute infection
- Cervical cancer
- Bleeding diathesis.

Methods and techniques:

Several devices are available for endometrial sampling procedures. The most popular one is the endometrial suction curette e.g. Pipelle endometrial sampling device (Figure 3-1). The main steps of the procedure are:

With the patient in the lithotomy position a bimanual examination is performed to evaluate the size, shape, and orientation of the uterus.

- A speculum is inserted to visualize the cervix, which is then cleaned with antiseptic solution (e.g., povidone-iodine).
- The sampling catheter is then carefully inserted e.g. the 3 mm endometrial suction curette if possible without using a tenaculum forceps in order to avoid pain and discomfort. However if the device will not pass through the cervix because for example uterus is not close to axial position, a tenaculum forces may be used to straighten the cervicouterine angle and reduce the risk of perforation.
- Endometrial sampling is then performed. The entire uterine cavity can generally be sampled with at least four complete back and forth passes from fundus to internal os.
- At the end the device is removed when the entire cavity has been sampled and the catheter is visibly filled with tissue.
- The specimen is then expelled into a formalin container.

Side effects and Complications:

- The most common procedural side effects are cramping and vasovagal reactions (hypotension dizziness, nausea, bradycardia, pallor)
- Uterine perforation is the most serious complication but is very rare as long as one avoid unnecessary force.

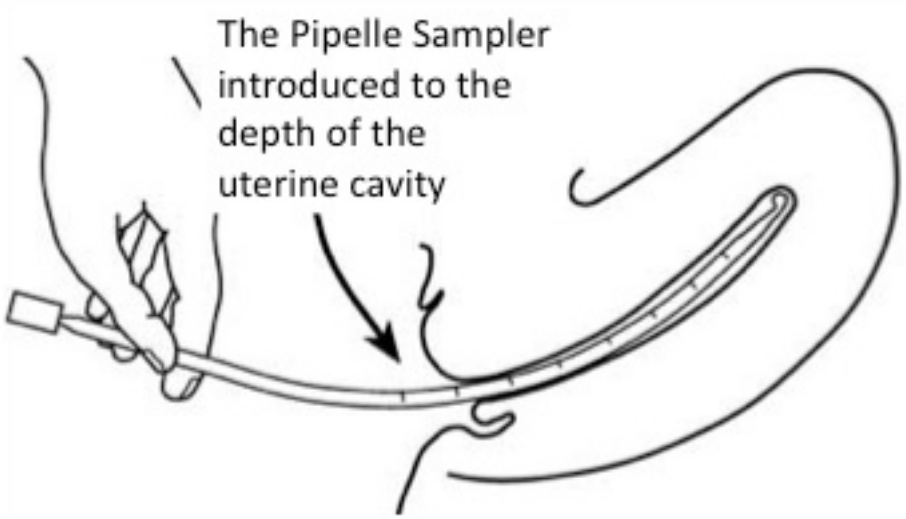

Figure 3-1: Pipelle endometrial sampling catheter

Hysteroscopy

A hysteroscope is a telescope that is inserted into the uterus via the vagina and cervix to visualize the endometrial cavity, as well as the tubal ostia, endocervical canal, cervix, and vagina.

Indications: Hysteroscopy can be performed for diagnostic or therapeutic indications of many conditions in endometrial cavity, tubal ostia, or endocervical canal such as:

- Abnormal premenopausal or postmenopausal uterine bleeding: either for diagnosis or therapeutic intervention by endometrial ablation.
- Endometrial thickening or polyps
- Submucosal, and some intramural, fibroids
- Intrauterine adhesions (e.g. lyses of adhesions)
- Müllerian anomalies (e.g., resection of uterine septum)
- Retained intrauterine contraceptives or other foreign bodies

- Retained products of conception
- Desire for sterilization
- Endocervical lesions

Hysteroscopy has the advantages over other diagnostic methods such as (pelvic sonography, saline infusion sonography, endometrial sampling, hysterosalpingography) because it can offer both diagnosis and treatment. Also, hysteroscopy avoids the risk of missing focal pathology, as may occur with blind endometrial sampling.

However hysteroscopy cannot assess myometrial disease (e.g., adenomyosis), tubal pathology, or the external uterine contour (pelvic adhesions or endometriosis). If such lesions are suspected additional procedures (e.g. laparoscopy or hysterosalpingography) are necessary.

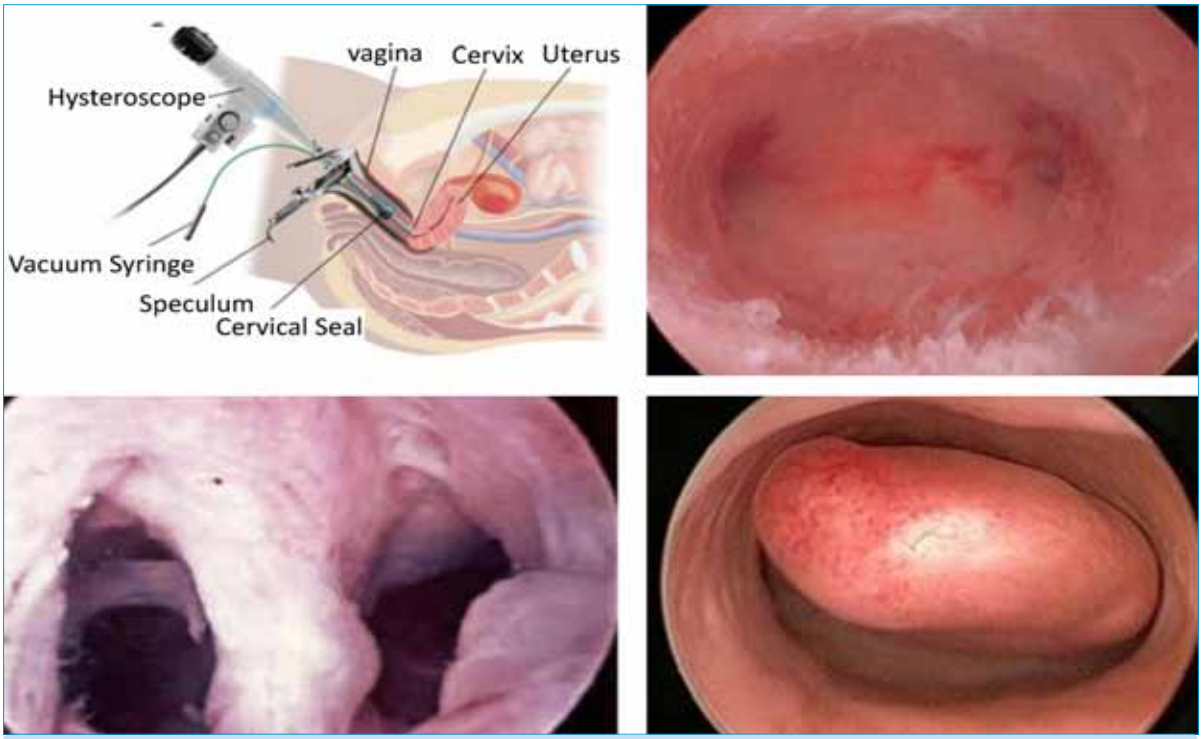

Figure 3-2: Upper Left: A flexible hysteroscope being introduced. Upper right: hysteroscopic view of normal uterine cavity with both tubal ostia. Lower Left: hysteroscopic view of uterine septum. Lower Right: hysteroscopic view of submucus myoma

Contraindications:

Contraindications to hysteroscopy are:

- Viable intrauterine pregnancy (postpartum or post-abortal hysteroscopy is

sometimes useful for evaluation and treatment of retained products of conception)

- Active pelvic infection (including genital herpes infection).
- Known cervical or uterine cancer (since it may cause dissemination of cells)
- Excessive uterine bleeding may limit visualization during hysteroscopy, but it is not a contraindication.

Equipments and basic technique:

There are many different sizes and type of hysteroscopes. Some are better suited for diagnostic versus operative procedures, or for outpatient rather than operating room procedures. There are also rigid and flexible hysteroscopes.

The basic component of a hysteroscopy set includes:

- Outer sheath (diameter range 3.1 to 10 mm)
- The telescope (range from 160 to 302 mm in length), which is introduced through the sheath.
- Distending media inflow and outflow
- Operative instruments e.g. forceps, scissors, resectoscopes (cutting knifes) …etc.
- Additional equipment is needed for infusing and monitoring uterine distending media.
- A video monitor: although is not requisite, but it greatly benefits the surgeon, trainees, and scrub and nursing personnel throughout the case.

Different types of sheaths are available.
Simple one where the distending media channel is also used for insertion of instruments. It allows the use of a small-diameter sheath, but leaks of media are common.
Advanced operative sheaths with three channels: two for operative instruments and one for instilling distending media.
Other operative sheaths contain permanently attached operative tools, such as biopsy instruments, forceps, or scissors.

Rigid versus flexible:

Most hysteroscopes are rigid, but narrow caliber scopes (<5 mm) may also be semi-rigid or flexible.

Rigid hysteroscopes cause more intraoperative pain, but offer better optical quality and are less costly.

Flexible hysteroscopy is especially useful for diagnostic or operative procedures in women with an irregularly shaped uterus.

Distending media: Hysteroscopy is performed using a distending medium to provide a global view of the endometrial cavity.

The most commonly used distending media are low viscosity fluids and carbon dioxide. Carbon dioxide is used for diagnostic procedures.

Preoperative evaluation and preparation:

Complete history and examination should be taken in addition to informed consent.

Timing and endometrial preparation:

For premenopausal women with regular menstrual cycles, the proliferative phase is best for visualization of the uterine cavity. During the secretory phase, the thick endometrium can mimic endometrial polyps and lead to inaccurate diagnoses. Also, during menstruation, blood may interfere with visualization.

Thinning of the endometrium: For operative procedures such as resection of a leiomyomas or endometrial ablation it is better to induce thinning of the endometrium.

The most commonly used method is estrogen-progestin contraceptives or progestins alone (eg, oral medroxyprogesterone acetate 10 mg daily on cycle days 15 to 26). Gonadotropin releasing hormone agonists and danazol are also effective, but are used infrequently due to adverse effects.

For postmenopausal women, hysteroscopy may be performed at any time.

Cervical preparation and dilation: Narrow caliber hysteroscopes (≤5 mm) usually do not require cervical dilation, particularly in premenopausal women.

For patients who do require cervical dilation, cervical preparation with a prostaglandin (e.g., misoprostol) (200 to 400 mcg vaginally the night before the procedure) will facilitate mechanical dilation.

Prophylactic antibiotics: Antibiotics are not routinely administered during hysteroscopy for prevention of surgical site infection or endocarditis since posthysteroscopy infection occurs in less than 1 percent of women.

Sterile preparation: Povidone iodine solution is used for sterile vaginal preparation.

Anesthesia: Most diagnostic and brief or minor operative procedures can be performed without anesthetic or with a local anesthetic.

Regional or general anesthesia is reserved for patients who cannot tolerate a procedure under local anesthesia, extensive operative procedures, or patients with comorbidities that necessitate intensive monitoring.

Local anesthesia for hysteroscopy can be administered topically (cervical or intrauterine [transcervical]) or by injection (intracervical, paracervical, or uterosacral).

Procedure:

- The initial steps for all hysteroscopic procedures are the same as for other transcervical procedures (patient in dorsal lithotomy position, placement of speculum, use of tenaculum or mechanical dilation as needed).
- A Foley urethral catheter is not necessary unless intensive monitoring of urine output is necessary (eg, prolonged procedure, excessive fluid absorption, or need to diuresis patient).
- Entry and cervical dilation: The cervix should not be dilated beyond the size of the hysteroscope, since this may cause leakage of distending medium.
- The hysteroscope is introduced under direct visualization navigate through the cervical canal.
- Evaluating the endocervix: The endocervix can be easily inspected during insertion of the hysteroscope.
- Evaluating the uterine cavity: Once the hysteroscope is within the endometrial cavity, the uterine cavity is distended. The entire cavity is inspected, including the tubal ostia and any pathology.
- Management of distending media: this include both maintenance of a clear operative field and balance of inflow and outflow of fluid to protect against the potential compilations of fluid overload.

Complications:

Complications from hysteroscopy are rare more common in operative than diagnostic hystorscopy, but some are potentially life threatening. The most common complicatons :

- Uterine perforation: **Uterine perforation is the most common complication** of hysteroscopy. It can occur during mechanical cervical dilation or insertion of the hysteroscope. If a uterine perforation occurs, all instruments should be removed from the uterus and the hemodynamic status of the patient should be assessed.
- Urinary tract or bowel injury: **may** occur in association with uterine perforation or as a result of use of electrical current.

Perforation is suspected:

- An instrument passes beyond depth of the uterine fundus.
- sudden loss of visualization.
- omentum or bowel or peritoneal structures are visualized at the uterine fundus.
- There is a sudden increase in the fluid deficit.

- Cervical laceration:
- Excessive fluid absorption: Complications related to distending media vary according to the patient population and the media used.
- Embolism: Embolism (air or carbon dioxide) can occur with any hysteroscopic technique and can cause cardiovascular collapse.
- Hemorrhage: Potential sources of intraoperative bleeding include operative sites, uterine perforation, and cervical laceration.
- Electrosurgical injury: Thermal effects of electrical (or laser) energy can cause injuries to the uterine cavity, as well as bowel, urinary bladder, and large pelvic vessels
- Sepsis: generally results from unrecognized thermal bowel injury; fistulae or urinary ascites can occur from an unrecognized bladder injury. Such complications require consultation with a colorectal surgeon, urologist, or infectious disease specialist.
- Infection: The risk of infection after operative hysteroscopy is low.
- Dissemination of tumor: Concerns regarding the dissemination of malignant cells during hysteroscopy are discussed separately.

Colposcopy

Colposcopy is a diagnostic procedure in which a colposcope (a dissecting microscope with various magnification lenses) is used to provide an illuminated, magnified view of the cervix, vagina, and vulva.

The primary goal of colposcopy is to identify precancerous and cancerous lesions so that they may be treated early.

Colposcopic evaluation of the cervix and vagina is based on ability to distinguish normal from abnormal areas by its macroscopic characteristics relating to contour, color, and vascular pattern (Figure 3-3).

Indications:

- For evaluation of abnormal cervical smear (Pap test) results (see chapter on cancer cervix) and obtaining tissue biopsy under direct colposcopic visualization of abnormal area.
- Assessment of women exposed to diethylstilbestrol (DES) exposure in utero.
- Evaluation of a palpably or visually abnormal cervix, vagina, or vulva.

- In conjunction with laser or other treatment modalities to ensure that known lesions are completely removed or treated.
- For post treatment surveillance.
- Vulvar colposcopy is indicated in women with: Visible abnormalities of the vulva and no abnormalities of the cervix or vagina that can account for the abnormal cervical cytology
- Focal vulvar itch without a clear etiology.

Contraindications:

There are no absolute contraindications to colposcopy.

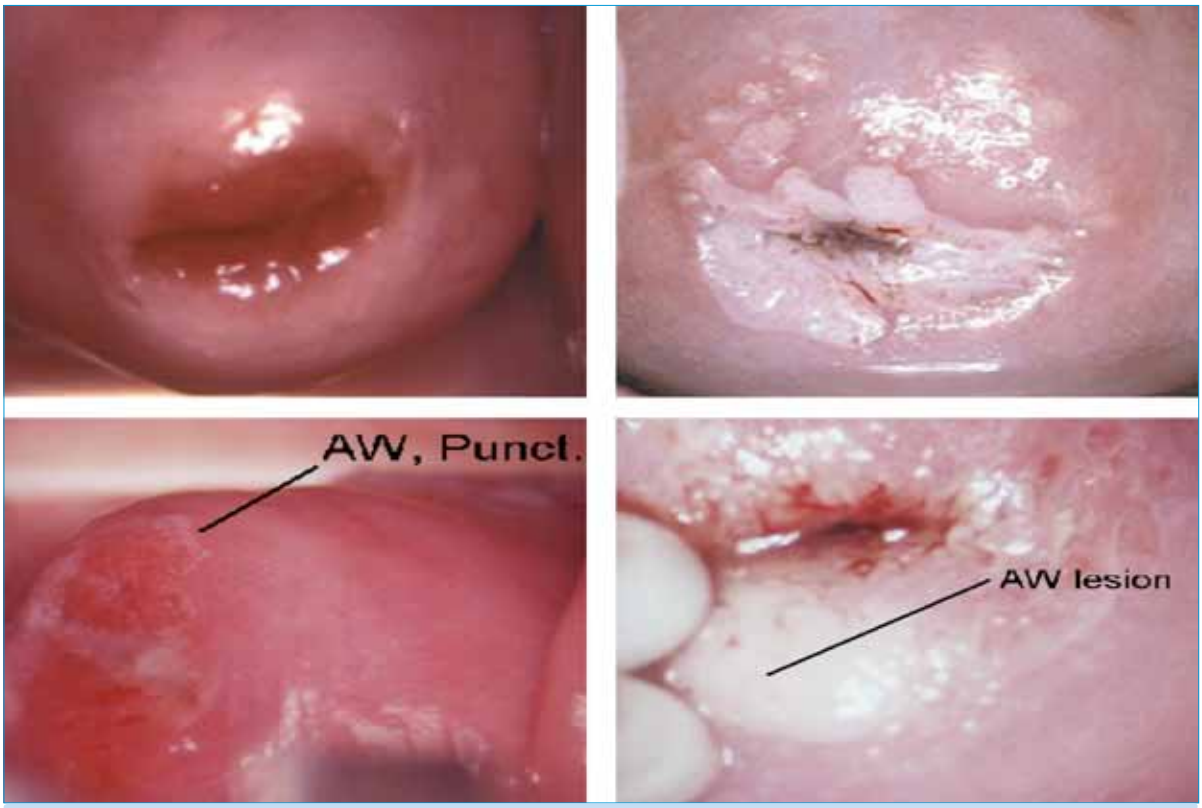

Figure 3-3:
Upper Left: Colposcopic appearance of normal cervix.
Upper right: dense acetowhite changes and sharp margins. The image represents unsatisfactory colposcopy (i.e., the entire squamocolumnar junction is not visualized - see text).
Lower Left: Blood vessel changes (Fine punctation or mosaicism) Changes associated with Low Grade SIL
Lower Right: Blood Vessel changes (Coarse punctation or mosaicism) Changes Associated with High Grade SIL

Equipment and Technique:

The colposcope functions as a lighted binocular microscope, which magnifies the tissue of interest (e.g., cervical, vaginal, or vulvar epithelium), thereby helping to identify features suggestive of abnormal tissue. Colposcope differ by manufacturer which makes different magnification can range from 7.5 to 30. (Figure 3-4)

Procedure: Colposcopy is performed with the patient in the dorsal lithotomy position. After visually examining the vulva and determining if there are any suspicious areas, a speculum is placed in the vagina. It is best to use the largest speculum possible so that the entire cervix and vaginal fornices may be visualized.

Examination: The cervix and vagina are examined with a bright light, and then with the colposcope. Cotton soaked in saline may be used to cleanse a cervix that is covered with mucus, blood, discharge, or debris, to facilitate viewing.

The cervix is first viewed before application of additional solutions, to look for areas of erosion, true leukoplakia, pigmented lesions, or areas of obvious ulceration or exophytic growth.

Acetic acid solution is used to improve visualization of abnormal areas. Three to 5 percent acetic acid is applied to the cervix using cotton swabs to enhance definition of the squamocolumnar junction. After 30 to 60 seconds, the acidic solution dehydrates cells so that squamous cells with relatively large or dense nuclei (eg, metaplastic cells, dysplastic cells, cells infected with human papilloma virus) reflect light and thus appear white.

Blood vessels and columnar cells are not affected, but become easier to visualize against the white background. The acetic acid should be reapplied, as needed, after three to five minutes.

Figure 3-4: Above: a colposcope. Lower: diagram of colposcopic examination

Lugol's or Schiller's solution: If no lesions are seen, a dilute Lugol's or Schiller's solution may be applied to the cervix and vagina to aid in detection. Lugol's iodine consists of 5 g of iodine and 10 g of potassium iodide in 100

mL distilled water. Uniform uptake of stain would confirm the colposcopist's impression that no lesion is present. Glycogen containing cells will take up iodine and become dark brown. Nonglycogenated cells, such as normal columnar or glandular cells, high-grade lesions, and many low-grade lesions, will not take up iodine and remain light yellow. Thus, they can be easily differentiated from normal tissue for sampling or treatment purposes. Iodine staining should not reveal any lesions the examiner has not previously identified with saline or acetic acid.

The squamocolumnar junction, and the cervical transformation zone (figure 3-6):

The squamo-columnar junction is located at the point where the squamous epithelium of the exocervix meets the columnar epithelium of the enodcerix. From birth until puberty this point is termed the original squamocolumnar junction. However the location varies throughout a woman's life due to metaplastic change:

- After puberty and at the first pregnancy the cervix increases in volume in response to hormonal changes. The endocervical epithelium everts onto the ectocervix (portio vaginalis) exposing it to the acid pH of the vagina. This provides a stimulus for metaplastic change of the columnar epithelium. Eventually the whole of the everted endocervical epithelium may be replaced by squamous epithelium creating a new squamocolumnar junction. This area of metaplastic changes, that is between the original and new squamocolumnar junction is termed the transformation zone.

The transformation zone represents the region of active cell division and therefore it is the region most likely to display abnormal growth. **It is the area between an older squamocolumnar junction and the current one.**

The location of this region is altered by age, hormonal conditions such as menopause, hormonal contraception and pregnancy, prior cervical treatments and vaginal pH.

- After menopause as the cervix atrophy the squamo-columnar junction recedes back into the cervical canal.

The metaplastic cells of the transformation zone are the most susceptible areas to carcinogen and most, if not all, cervical cancers arise here.

Satisfactory colposcopic examination:

For complete satisfactory colposcopic examination the clinician first identifies the squamocolumnar junction or transformation (TZ) zone. The differential absorption of light between squamous epithelial cells and columnar cells allows the clinician to differentiate between the smooth grey-pink appearing ectocervix and the pink-red

cobblestone appearing endocervix. The region where the two cell types meet, defines the "transformation" zone i.e. where the columnar cells become squamous epithelium.

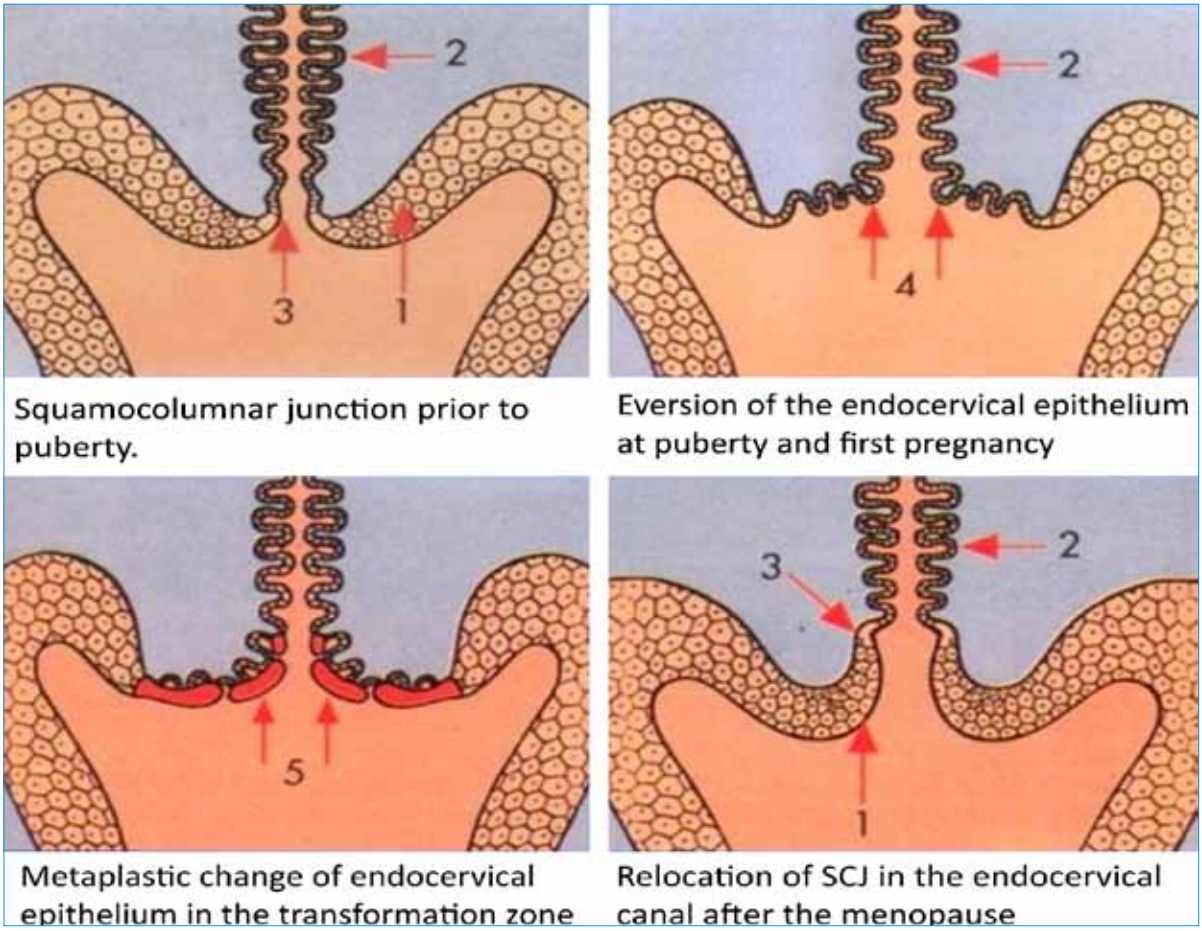

Figure 3-6: Diagram showing the changes in the transformation zone throughout the female reproductive life. 1: native squamous epithelium. 2: columnar epithelium of endocervix. 3: squamocolumnar junction (SCJ). 4: Eversion of endocervical epithelium. 5: Metaplastic change in transformation zone

Documentation: During colposcopic examination the following points should be documented:

- Whether or not the entire the entire squamocolumnar junction (transformation zone) is visible circumferentially around the os.
- Areas of acetowhite epithelium and abnormal vascular patterns are noted and documented. Areas of white epithelium are further evaluated for abnormal vascular patterns such as punctation, mosaicism, or abnormal appearing vessels. Punctate and mosaic vessels in a field of acetowhite epithelium in the transformation zone are suggestive of CIN, (Figure 3-3)

- Accurate diagnosis can only be established definitively by pathologic examination of suspicious areas. Local anesthesia is not routinely used for biopsies of the cervix and upper vagina.
- The upper one-third of the vagina, in particular the lateral fornices, is also inspected. Abnormal vaginal findings include adenosis, polyps, cysts, DES morphology, condyloma, and changes suggestive of preinvasive or invasive disease.

Complications:

Complications include bleeding, infection at the biopsy site or endometrium, and failure to identify the lesion. Significant bleeding and infection are rare. .

Follow-up: Patients should avoid coitus for several days after biopsies are taken to minimize trauma to the cervix, which may result in bleeding. .

References and Further readings:

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Chapter 4

Ovulation, Fertilization, and Early Embryogenesis

Advances in in-vitro fertilization have enabled us to understand many aspects related to ovulation, fertilization and the early implantation period. At the same time it raised many more questions than we previously had.

By the end of this chapter you should be able to:

- **Describe:** the fundamental differences between Oogenesis and Spermatogenesis.
- **Describe:** the difference between mitotic and miotic divisions and the outcome of miotic division.
- **Describe:** the process of fertilization and its outcome.
- **Describe:** the early cleavage, morula and blastocyst stages until hatching " the first birth"
- **Describe:** the process of implantation.
- **Describe:** placentation and early embryonic plate development.
- **Realize important clinical implications in relation to Ovulation, Fertilization, and Early Embryogenesis:**
  - Contraception, increased rate of trisomies with advanced maternal age.
  - The development of stem cell therapy and research.
  - The monochorionic twins and PGD.
  - The effects of teratogen exposure in early phases after fertilization
  - Abnormal placentation and relation to fetal growth restriction and pre-eclampsia.

Oogenesis and Spermatogenesis

➢ **Oogenesis:** refers to the process of formation of the female gametes (oocytes). In human, oogenesis begins during embryonic life, and is completed at puberty when ovulation begins. But the final maturation of the ovum does not take place unless fertilization occur.

The process of oogenesis begins with mitotic division, followed by two cycles of meiotic division:

Through mitotic division the number of primary oocytes reach its peak of 6 to 7 million at around 20 weeks of gestation. From there on it continue to decline, so that at birth it is about 2 to 4 million, and approximately 400,000 at menarche until it completely vanish at menopause.

- **The mitotic division**: involve multiplication of the diploid "oogonia" through rounds of mitosis, during the first 8-10 weeks of embryonic life. It become surrounded by precursors of granulosa cells and called "primordial follicle" which further mature to produce "primary oocytes" as the granulosa cell proliferates.
- **The First Meiotic division "meiosis I"**: the first meiotic division of primary oocytes begins at about 12 weeks. However the process of meiosis is arrested at the prophase "dictyotene stage" and remain at this stage for many years until puberty. At puberty under the influence of the pituitary gonadotropins, **Meiosis I** is resumed again.
- With each menstrual cycle about 4 to 10 follicles resume "meiotic I" division to complete just before ovulation (before the LH peak). The result is the production of two cells; secondary oocytes (contain most of the cytoplasm) and the first polar bodies (which serves no known function). Each cell contains 23 chromosomes. This process continues throughout the women reproductive life.

  - **The second Meiotic division "Meiosis II":** It begins immediately after ovulation. But again will be arrested at the second metaphase and no further maturation occurs unless fertilization takes place.

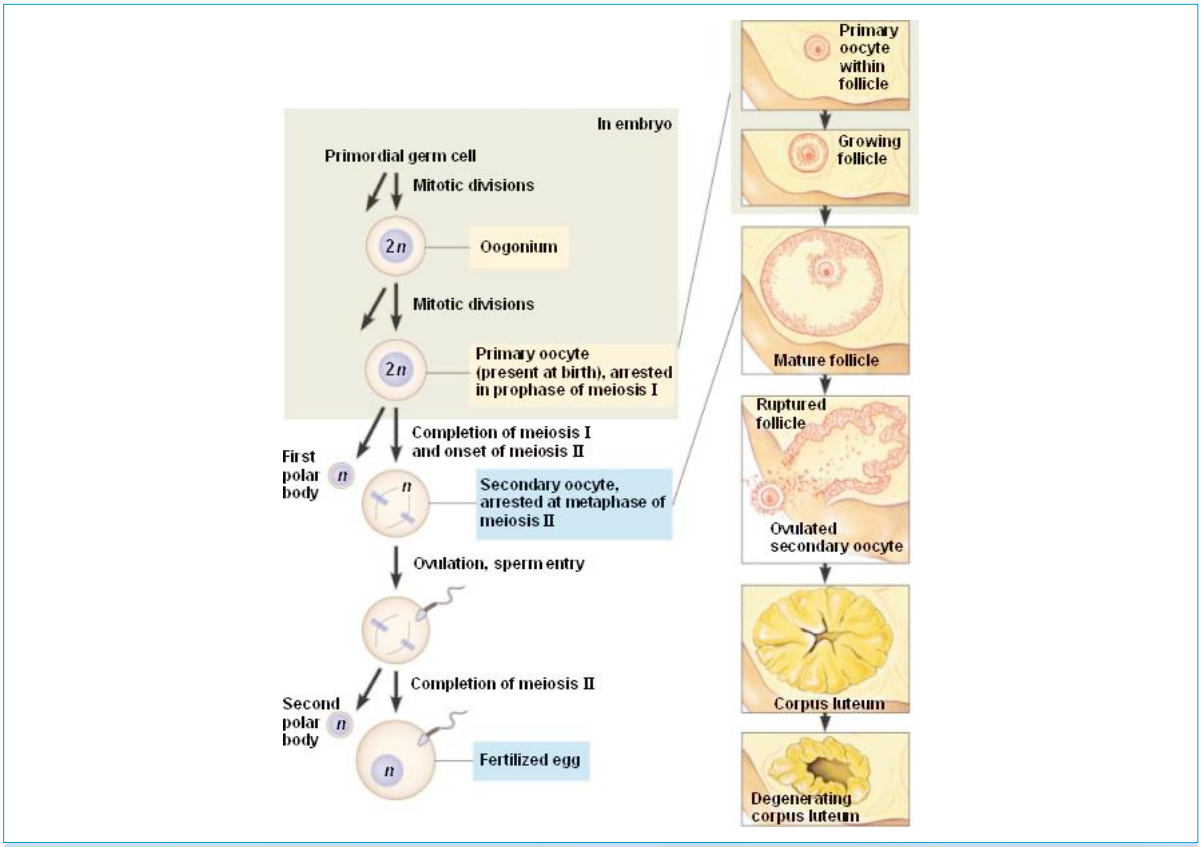


Figure 4-1: Oogonia divide by mitosis, and mature into primary oocytes. Primary oocytes begin their first meiosis. By the 7th month, the primary oocytes are surrounded by a layer of flattened cells and become known as primordial follicles. No further development of the follicle occurs until puberty the oocytes become suspended in prophase some for up to 40 years.

At puberty, periodic secretion of FSH triggers meiosis I, producing a polar body and a haploid secondary oocyte. At ovulation the mature follicle ruptures and releases the secondary oocyte from the ovary, leaving behind the corpus luteum.

Meiosis II does not take place unless fertilization occurs. It produces a second polar body and the fertilized egg, zygote.

Spermatogenesis: Refers to the process by which male spermatogonia develop into mature spermatozoa. Unlike oogenesis the maturation of spermatogonia does not occur in utero but begins at puberty and continues throughout life.

Like oogenesis spermatogenesis involve two meiotic divisions. But no polar bodies are produced therefore a single spermatogonium, produce 4 spermatids, which undergo maturation to form 4 sperm cells, or spermatozoa.

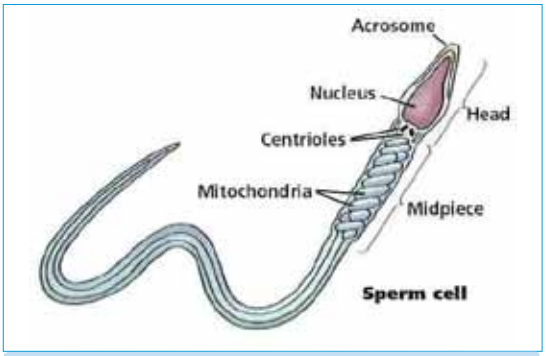


Figure 4-2: Anatomy of the mature sperm

Once sperm are formed they move into the epididymis, where they are stored and undergoes further maturation. In humans it takes about a total of 3 months before sperm are ejaculated.

Each mature sperm cell is formed of head and tail. The head is almost a packed DNA (has very little or no cytoplasm) with acrosome layer over the head. The acrosome contains lysosome enzymes that enable the sperm to penetrate into the oocyte wall.

Speramtogenesis	***Oogenesis***
Number of gametes	
Continuous production from puberty to old age	The stock of ovum is determined at birth Decline in number of oocytes begins from approximately 20 weeks The stock is exhausted at menopause
Meiotic output	
Results in Four functioning motile spermatozoids	Results in one large, immotile oocyte and three polar bodies.
Fetal Period	
No meiotic divisions	Production of the entire supply of germ cells Entering into meiosis (arrested in the dictyotene stage)

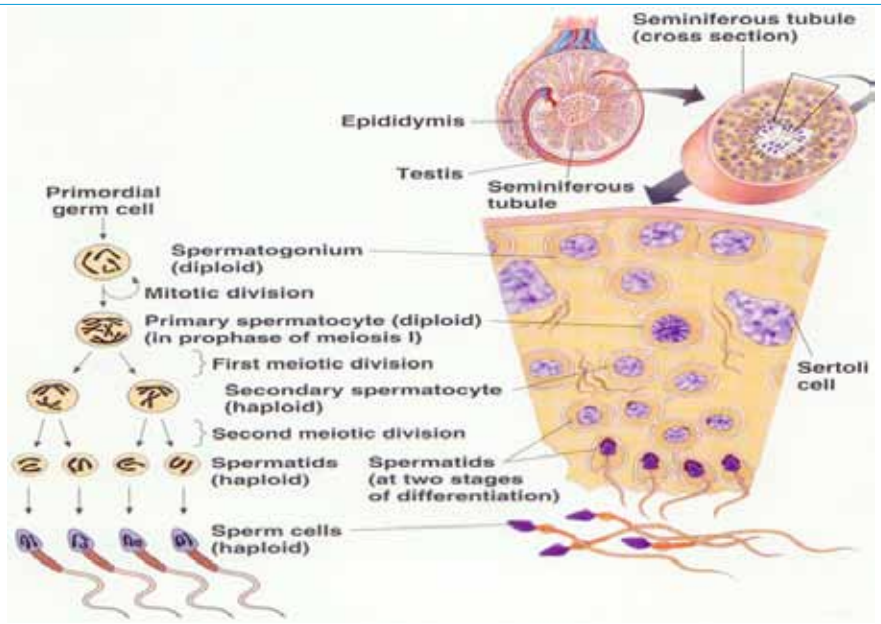


Figure 4-3: The production of sperm occurs in the seminiferous tubules.
The basement membrane of the seminiferous tubules is lined with epithelium and is occupied by spermatogonia as well as Sertoli cells.
Spermatagonia divide mitotically into spermatocytes.
The spermatocytes undergo meiotic divisions to form spermatids that develop into spermatozoa, the mature sperm cells.
The maturing cells move upwards towards the lumen of the testes where the spermatozoa are released

Outcome of first meiotic division

- The chromosome is reduced from 46 chromosomes (or 23 pairs) to 23 chromosome structures in the gamete.
- Exchange of genetic material is completed through chiasma formation and crossing over between homologous chromosome pairs.
- In the primary oocytes the first meiotic division is arrested for variable period from 12 to more than 40 years. It is very possible that mistakes in chromosomal movement and cell division can occur. This could explain increased rate of trisomy with advanced age.
- Spermatogenesis, with its many more cell divisions is more prone to single gene mutations than is oogenesis. There may be as much as a four or five fold increase in the mutation rate for some Mendelian traits in the sperm of older men.

Fertilization

Fertilization refers to the union of male and female pronuclei.

- Following ovulation, with ovum in metaphase II surrounded with cumulus oophorus cells is picked up by the fimbria of the fallopian tube.
- It remains viable in the ampulla of the tube for about 18 to 24 hours. If fertilization does not occur, the ovum disintegrates and is destroyed by the tube.
- Meanwhile, spermatozoa are transported through the cervical mucus and the uterus and into the fallopian tubes.
- During this transport period the sperm undergo two changes: capacitation and acrosome reaction. These changes activate enzyme systems within the sperm head that is necessary for penetration of the cumulus oophorus and the zona pellucida. Sperms

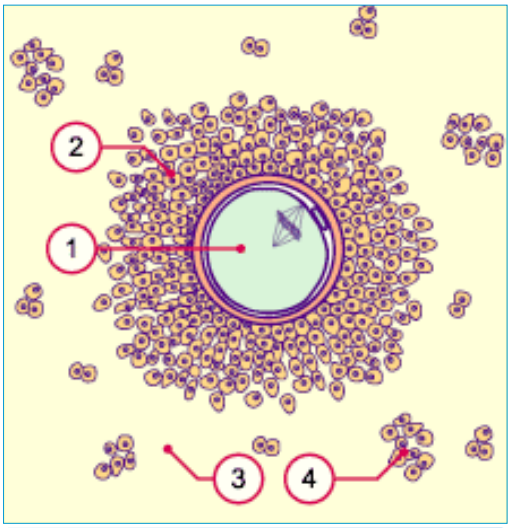


Figure 4-4: 1. Secondary Oocyte and polar body arrested in the metaphase of the 2nd meiosis. surrounded by zona pellucida and a cumulus of granulosa cells (cumulus oophorus). Within the zona pellucida are both the egg and the first polar body. 2: Corona radiata. 3: follicular fluid. 4 scarttered cumulus cells

remain viable in the female reproductive tract for about 48 hours.

- When the sperm reach the ampulla, where fertilization normally occurs, it gets attached to the cumulus oophorus mass and begins to penetrate it by chemical and mechanical means to reach the zona pellucida.
- It then penetrates the zona pellucida, and attaches to the cell membrane of the egg and enters the cytoplasm. Inside the egg cytoplasm, the sperm nucleus (head) swells and forms the male pronucleus.
- At the same time the egg completes its second meiotic division, casting off the second polar body to a position also beneath the zona pellucida to form the female pronucleus.
- The pronuclei membranes disappear and the chromosomes contained within each pronucleus fuses together and a genetically new cell or "zygote" that has diploid complement of chromosomes (n=46) is formed.

Figure 4-5: The two pronuclei and the polar bodies

Outcome of Fertilization

1. Triggers the completion of the second meiotic division in the oocyte.
2. Restore the diploid number of chromosome.
3. Determine the sex of the zygote

Early Cleavage, Morula and Blastula Stage

The fertilized egg (zygote) starts 3-4 days journey in the fallopian tube before it reach the uterine cavity, where it remains free for another 3 days before implantation begins at approximately the 6th day. The important changes that take place during this journey are:

Cleavage stage and Morula formation: The first cleavage (two cell) occurs approximately 20 hours after fertilization; it marks the beginning of the early cleavage phase.

After repeated divisions a "Morula" is formed which consists of roughly 16 to 32 cells (known as blastomeres – embryonic stem cells).

Figure 4-6: Cleavage to morula stage

Blastocyst formation: On the 4th day after repeated cleavage a blastocyst is formed of now hundred of cells. Small fluid cavities appear (initially secreted by the blastomeres) which coalesce to form the so-called blastocyst cavity (figure 4-7)

Up until this point despite repeated divisions there is no increase in the size of the embryo because the cells are still contained within the zona pellucida so that every new cell is only half as large as the cell from which it derives.

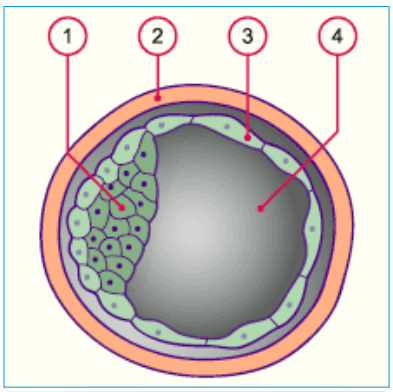


Figure 4-7: Blastocyst. Inner cell mass consists of roughly 12 cells (1), the enveloping trophoblast (3), made of around a hundred cells. (2) Zona pellucisa, (4) Blastocyst cavity.

Hatching (the first birth): Around the end of the fifth day the embryo frees itself from the enveloping pellucid zone. Hatching of the blastocyst or the "the first birth" occurs by enzymatic action and a series of expansion-contraction cycles. (Figure 4-8)

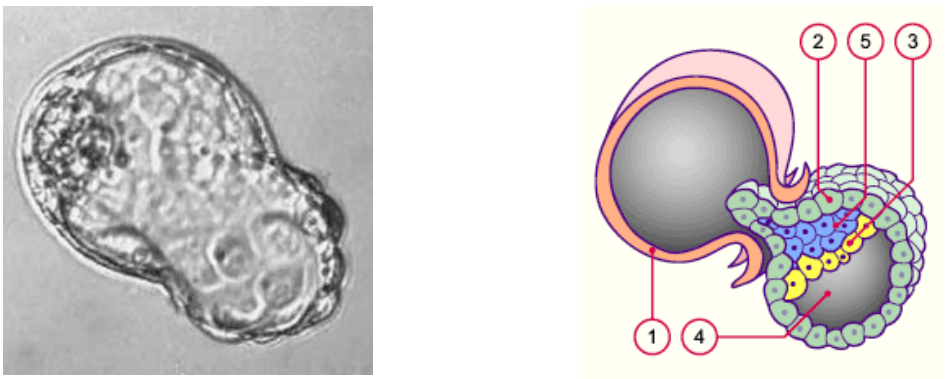


Figure 4-8: Left: a Microscopic picture of hatching. Right: diagram of hatching showing: 1 Pellucid zone 2 Trophoblast (outer cell mass) 3 inner cell mass (Hypoblast) 4 Blastocyst cavity 5 Epiblast (part of the inner cell mass)

Implantation

After hatching the blastocyst adheres to the uterine mucosa in preparation for implantation which generally takes place 3 days after the embryo reaches the uterus. The implantation normally occurs in the **superior and posterior walls of the uterine body** (corpus uteri) in the functional layer of the endometrium during the secretory phase of the cycle. During these days the trophoblast differentiates into **two different types of cell masses:**

- The outer syncytiotrophoblast (ST): forms a **syncytium**, i.e., a multi-nucleic layer without cell boundaries that arises from the fusion of cytotrophoblast cells.
- The inner cytotrophoblast (CT)

At the same time the uterine mucosa between day 20th – 23rd, or 6 days after the LH peak under the influence of rising progesterone becomes ready for implantation of the blastocyst (This phase sometime termed the "implantation window").

The mechanism of endometrial invasion is a complex one, controlled by many factors that are not fully understood **including lytic enzymes** that cause apoptosis of the endometrial epithelial cells.

With completion of implantation the syncytiotrophoblast develops quickly and entirely surround the embryo.

The syncytiotrophoblast cells phagocytize the apoptotic decidual cells of the endometrium and resorb the proteins, sugars and lipids that have been formed there. They also erode the canals of the endometrial glands and the capillaries of the stroma.

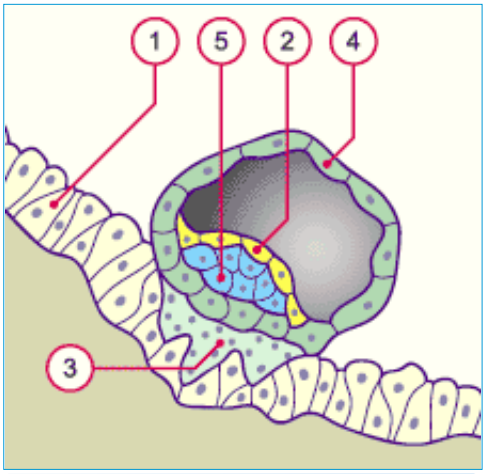


Figure 4-9: Implantation 6-7 days.
1: endometrium,
2: Inner cell mass (hypoblast),
3: Syncytiotrophoblast.
4: Cytotrophoblat.
5: Epoblast

In the middle of the 2nd week extracellular vacuoles appear in the syncytiotrophoblast. They join together forming **lacunae**. Initially filled with tissue fluids but following erosion of the maternal capillaries, becomes filled with maternal blood. They form the future intervillous spaces. At around the 13th day the **primitive utero-placental circulatory system** arises.

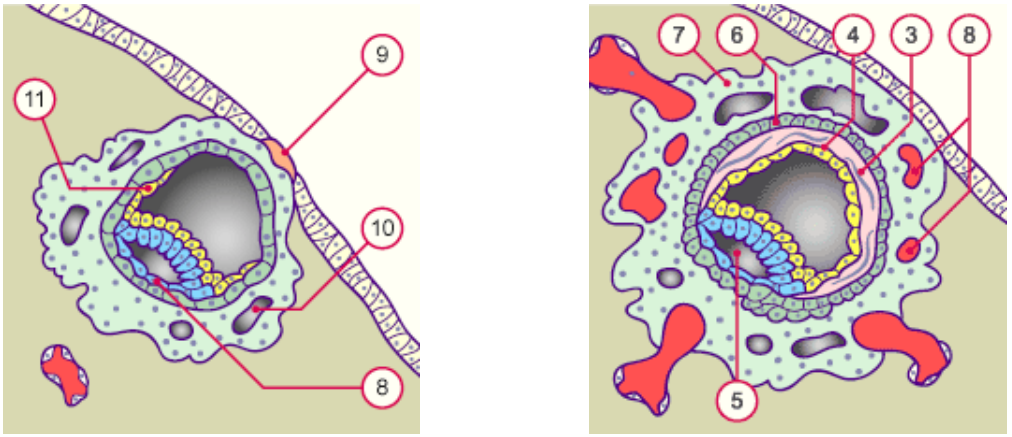


Figure 4-10: Complete implantation of the embryo into the endometrium. On the Right: implantation 8th day, left implantation 9th day. The amniotic cavity begins to form (5) and expands. Extracellular vacuoles appear in the syncitiotrophoblast and join to form lacunae. On the Left: the capillaries in the endometrium have been invaded and maternal blood flows into the lacunae, an arterial inflow and a venous outflow system begins.
6: Cytotrophoblast, 7: Syncytiotrophoblast, 8 Lacunae

The decidua: In pregnancy under the influence of progesterone the endometrium undergoes decidual reaction, which is more prominent at the side of implantation. The feature of this reaction is shown in Figure 4-11.

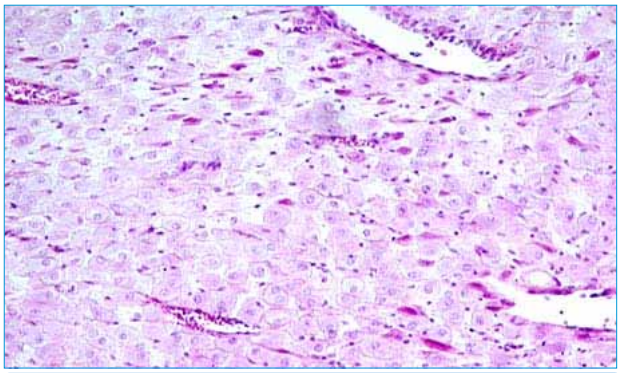


Figure 4-11: Deicidual reaction affect stromal cells, which change into large polygonal cells that store glycogen and lipids. There is also leukocyte infiltration. Not only the cells change their shape, the extracellular matrix is also modified.

The implantation process divides the decidua into three parts depending on its relationship with the embryo:

- Decidua basalis: where the implantation takes place and the basal plate is formed.
- Decidua capsularis: form a capsule around the chorion
- Decidua parietalis: on the opposite uterus wall.

At around the 4th month, as the fetus enlarge the space between the decidua capsularis and decidua parietalis is obliterated by merging of the two deciduae.

The decidua basalis takes part in the formation of the placenta and is heavily invaded by the trophoblast. A zone of fibrinoid degeneration known as the **Nitbuch's layer** has been defined where the trophoblast meets the decidua, it was noted to be absent in cases of

acenta accreta.

Embryonic Disk Differentiation and Placentation

Embryonic Disc Differentiation: The embryo arises from the **inner cells** (also called the embryoblast) in two stages:

- The bilaminar stage: in the second week the embryo is formed of two layers the dorsal germinal layers (epiblast) and a ventral layer (hypblst)
- The trilaminar stage: during the third week as a **third embryonic germinal layer** (mesoblast/derm) appears when cells flow in between the two already existing germinal layers. Now the three layers **ectoblast (ectoderm)**, intermediate **mesoblast (mesoderm)**, and the ventrally lying **endoblast (endoderm)** are formed.

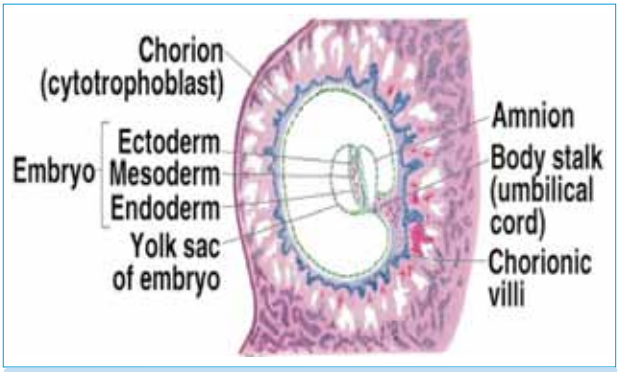


Figure 4-12: the early trilaminar embryonic disc appears in the third week. Further differentiation proceeds at very fast rate.

Placental development

As the trophoblast is implanted deeper in the endometrium it gives out the primary villi. Initially the villi surround the entire surface of the blastocyst. Latter it disappears except from the site of implantation that will be the future placenta.

- By the 15th day maternal blood vessels are invaded by the syncytiotrophoblast and blood lacunae that stem from the spiral arteries are formed.
- The feto-placental circulation begins in the 3rd week; when the fetal vessels develop within the villi. It connects the placenta with the tissues of the embryonic body.
- By the third week the chorion is now divided into: chorion leave (smooth chorion), which is the area, denuded of chorion and chorion frondosum which include the villi adjacent to the decidua basalis and will form the future placenta. The villi will further branches into secondary and tertiary villi adapting itself to the needs of the growing embryo.
- The chorion remains separated from the amnion until the end of the 3rd month by the extraembryonic celomic cavity.
- By 16 to 20 weeks the chorion leave fuses with the decidua vera (capsularis) thus obliterating most of the uterine cavity.

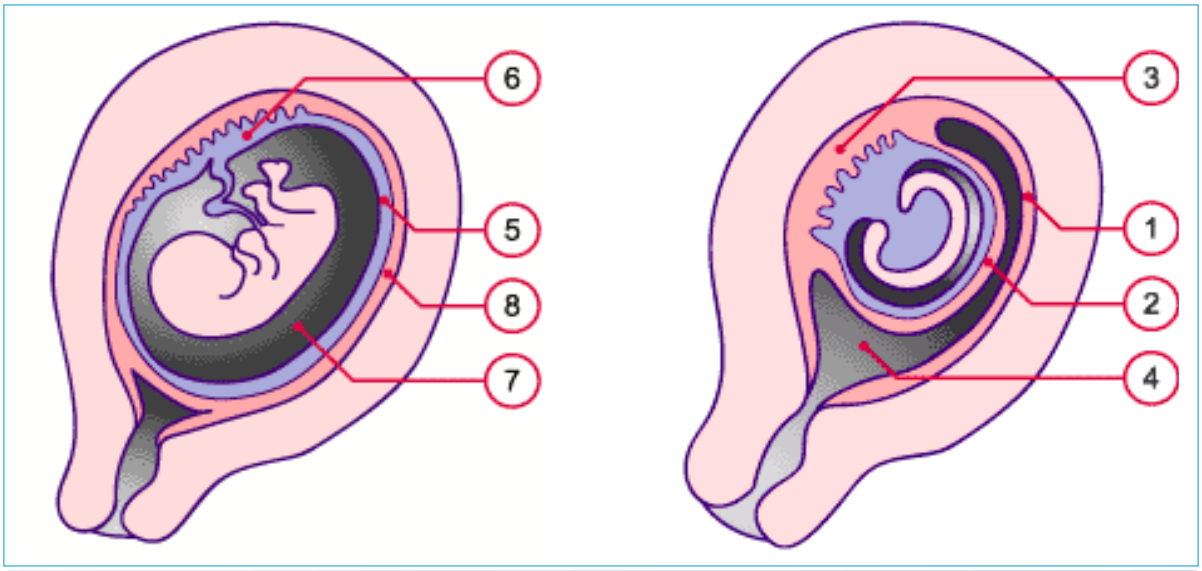
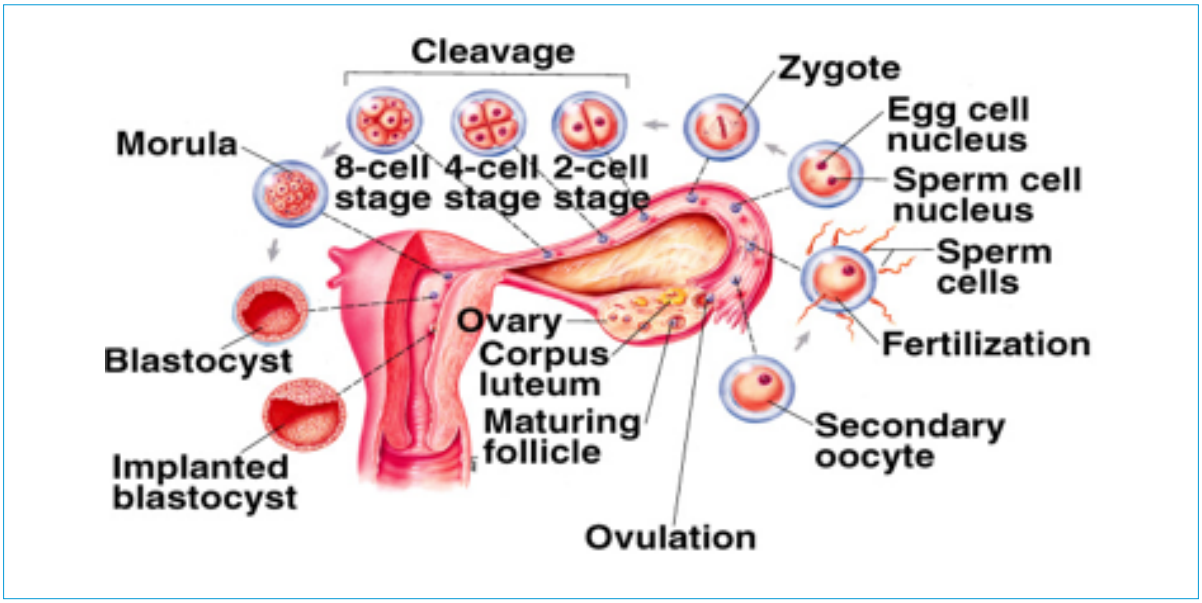


Figure 4-13: The three deciduae in the second month of pregnancy. After the 4th month the growing fetus brings the decidua capsularis into contact with the decidua parietalis. The fusion of the two deciduae leads to the obliteration of the uterine cavity.1: Decidua parietalis, 2: Decidua capsularis, 3: decidual basalis, 4: uterine cavity, 5: Smooth chorion (leave), 6:Chorion villi, 7: Amniotic cavity, 8: Decidual capsularis and parietalis together.

Clinical implications

Understanding the mechanism and control of oogenesis, early process of fertilization, embryonic cleavage and implantation has important clinical implications.



Contraception:

- Can be achieved by suppression of pituitary gonadotropin secretion, which normally trigger resumption of meiotic division and ovarian maturation.

Increased rate of trisomies with advanced maternal age:

- The increased rate of trisomies and miscarriages in older women can be explained by the very prolonged period of arrest of the oocytes in the meiotic phase I that increases the chances of chromosomal breakage and abnormality of cell division.

Stem cells, monochorionic twins and PGD:

- The totipotent nature of blastomeres cells make it important source of embryonic "stem cells" for therapy and research.
- It also explains the phenomenon of monochorionic twins if early division at the morula stage or before that takes place.
- The fact that blastomeres can replace each other enabled the application of preimplantation genetic diagnosis i.e. isolation of one or more blastomeres without adverse effect on further embryonic development.
- It also explain that exposure to teratogen in the first few days after fertilization may result in either loss of the whole embryo or no effect since loss of one or more blastomeres can be replaced by the rapidly dividing remaining ones.

Implantation and placental development:

- Implantation of the blastocyst in the lower part of the uterus explains the occurrence placenta previa.
- Also deep invasion of the trophoblast within the uterine wall and absence or abnormal development of the Nitbuch's layer is associated with placenta accreta.
- Failure of invasion of the trophoblast to the muscle walls of the spiral arteries is associated with increased resistance of placental blood flow and risk of placental insufficiency and/or development of preeclampsia.

Chapter 5

Clinical Anatomy of the Female Genital Tract

In this chapter, the anatomy of the internal and external genital organs of the female pelvis from clinical applied perspective will be described.

By the end of this chapter your should be able to describe:

- **Anatomy of the female external genital organs:**
- **Detailed anatomy of the internal genital organs:**
- **The Vagina**: Basic anatomy / Clinical application
- **The Uterus:** Basic anatomy / Clinical application
- **The Tubes:** Basic anatomy / Clinical application
- **The Ovaries:** Basic anatomy / Clinical application
- **The components and function of the pelvic diaphragm:**
- **Innervations of the pelvis**: and its clinical application
- **Pelvic Blood Supply**: and its clinical application
- **Basic anatomy of non-genital organs**: Ureter, Bladder and Rectum and clinical correlation

The External Female Genitalia

The Vulva:

A collective term that describes the mons pubis, labia minora, labia majora, hymen, clitoris, vestibule, urethra, Skene's glands, Bartholin's glands and vestibular bulbs (Figure 5-1).

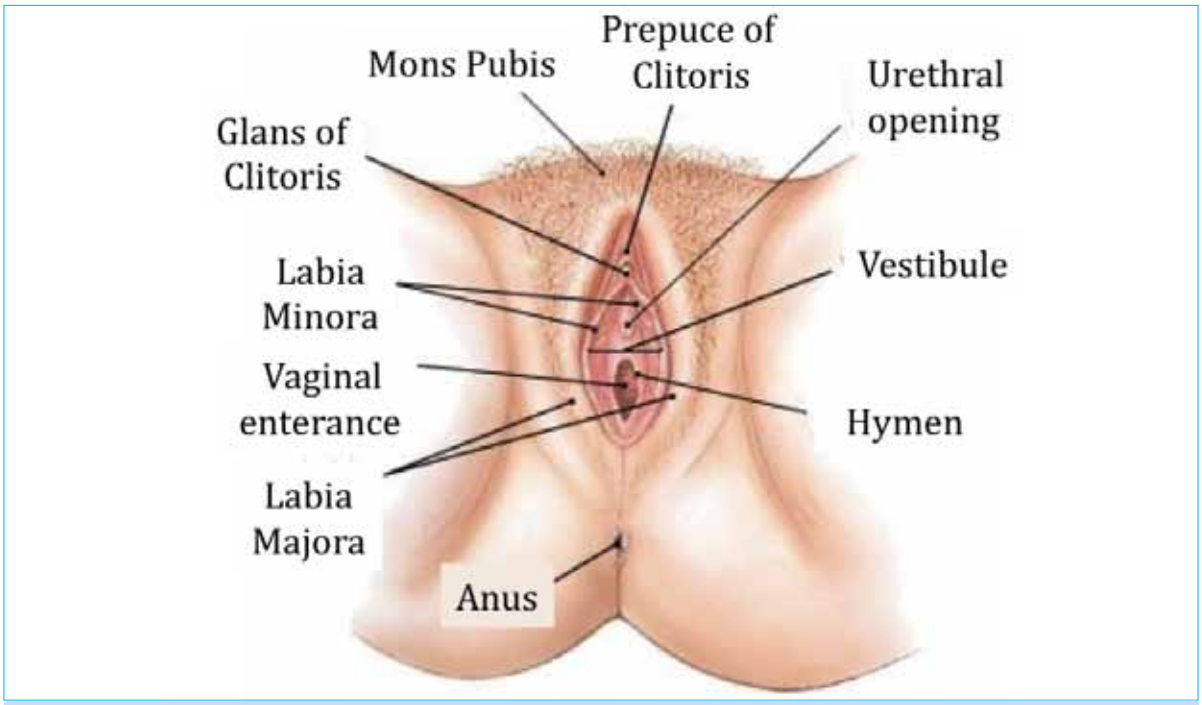


Figure 5-1:External Female Genitalia

Skene's Glands: Branched paraurethral tubular glands that run parallel to the distal one third of the urethra. It opens either at or just outside the urethral orifice.

Bartholin's Glands; Are two lobulated racemes glands, each one about the size of a pea. Located at approx 4 and 8 o'clock at the posterolateral aspect of the vaginal orifice. Histologically, the gland is composed of cuboidal epithelium, whilst the duct is lined by transitional epithelium and is approximately 2 cm in length. The ducts open into a groove between the hymen and the labia minora. Bartholin's glands are homologous to Cowper's gland in the male.

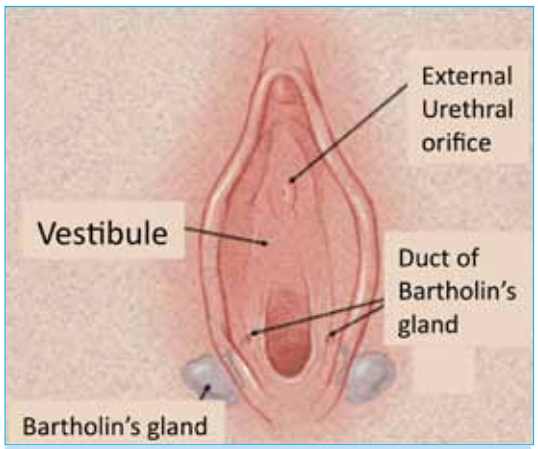


Figure 5-2: Diagram of the urethra relation to the vagina and the Skene's Gland

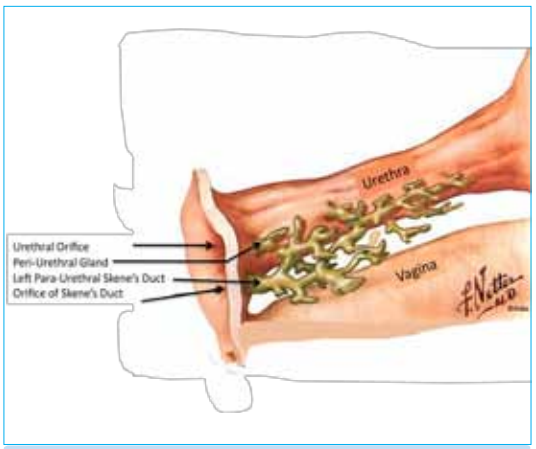


Figure 5-3: Diagram of location of Bartholin's gland and duct

Clinical Correlation

The Vulvar skin: The skin of the vulva is subject to both local and general dermatologic conditions. The vulvar skin of postmenopausal women is sensitive to steroids and testosterone but not topical estrogen.

Vulvar Cysts: The most common large cystic structure of the vulva is the Bartholin cyst, becomes very painful if it develops into abscess.

The Skene's "periuretheral glands" if it becomes chronically infected can results in uretheral diverticual giving symptoms of cystitis.

Blood supply of the vulva: The vulva is very rich in blood supply and the veins are devoid of valves hence trauma can results in large hematomas or profuse bleeding. On the other hand it promotes healing and reduce rate of infection after episiotomies or tears.

The subcutaneous fatty tissue of the labia majora and mons pubis are in continuity with the fatty tissue of the anterior abdominal wall. Infections in this space such as cellulites and necrotizing fasciitis are poorly contained, and may extend cephaladly in rapid fashion

The Internal Genital Organs

The Vagina:

Is a distensible fibromuscular tubular structure, extending from the vestibule of the vulva to the uterine cervix. Its anterior and posterior walls are normally in apposition i.e. it is like an H shape on cross section. The cervix extends into the upper part of the vagina dividing it into four **fornices** (the spaces that surround the cervix) the anterior, posterior, and two laterals.

The anterior vaginal wall is about 6-9 cm in length compared to the posterior vaginal wall, which is about 8-12 cm. The upper half of the vagina lies above the pelvic floor whereas the lower half lies within the perineum.

Important Relations:

- Anteriorly it is related to the bladder above and the urethra below.
- Posteriorly its upper third is related to the rectouterine pouch (pouch of Douglas), the middle third is related to the ampulla of the rectum and the lower third is related to the perineal body.
- Laterally in its upper third it is related to the ureter.

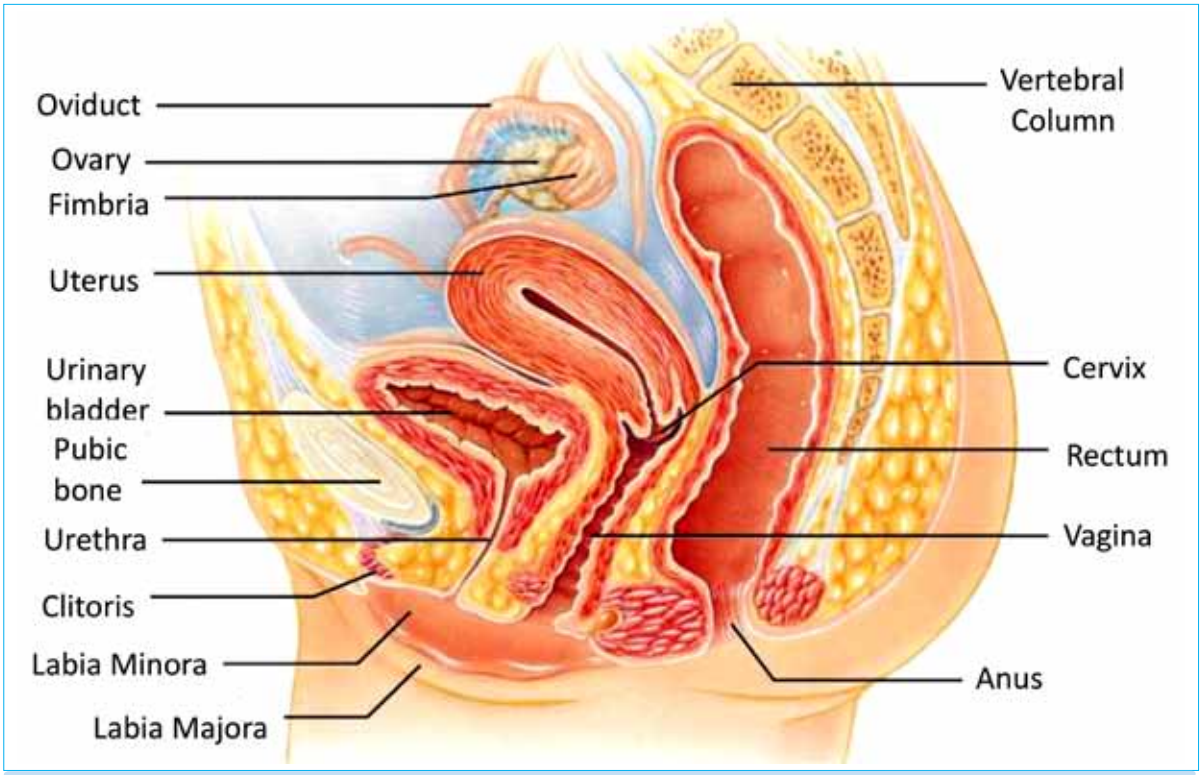


Figure 5-4: Diagram demonstrating the anatomical relation of the vagina. Note the long posterior wall and shorter anterior wall.

Support of the vagina:

The vagina is held in position by the surrounding endopelvic fascia and ligaments namely the following structures:

- The upper third is supported by the cardinal, pubcervical and sacrocervical ligaments.
- The middle third is supported by the levator ani muscles.
- The lower third is supported by the pelvic diaphragm (the urogenital diaphragm) and the perineal body.

The Histology and Lymphatic drainage of the vagina: is shown in figure 6-3:

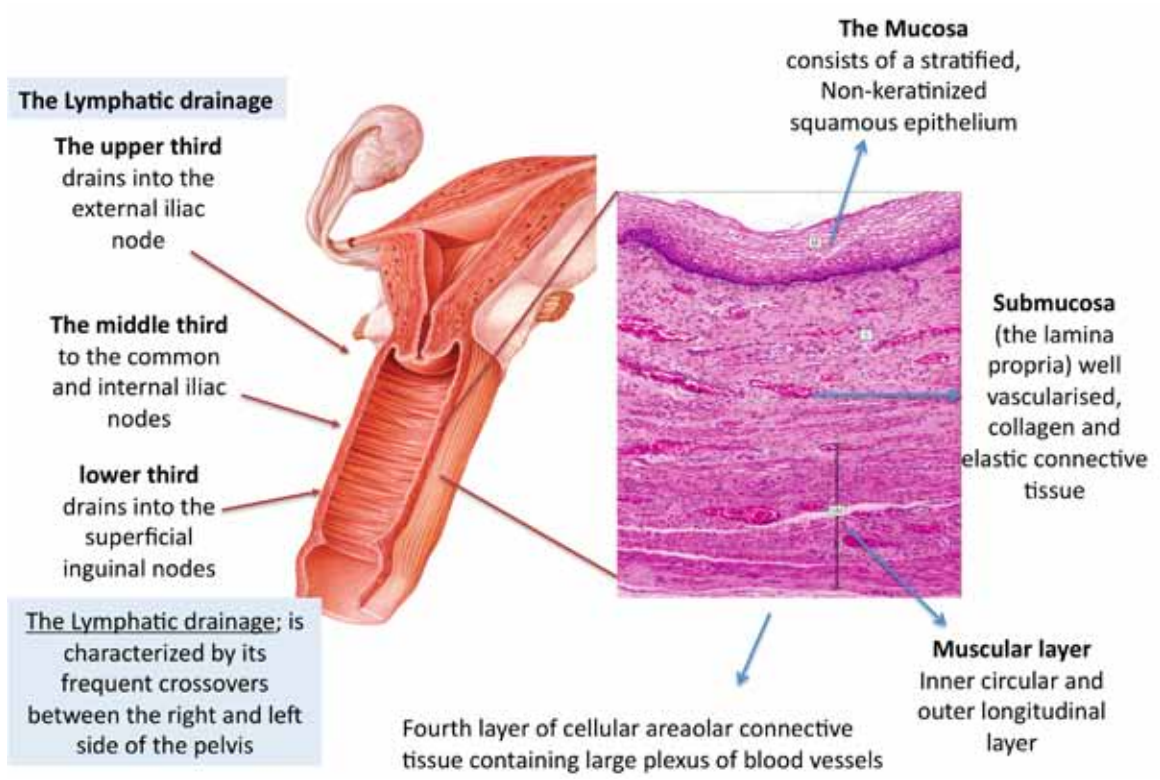


Figure 5-5: The vagina, its histology, its lymphatic drainage

The Vagina - Clinical Correlation

The Vaginal Mucosa: It has no glands but vaginal lubrication comes from the transudate produced by engorgement of the vascular plexuses that encircle the vagina and cervical glands secretion.

Anatomical Relation: The distal course of the ureter is related to the vaginal fornix. Ureteral injury can occur as a result of vaginally placed sutures to obtain hemostasis during repair of vaginal lacerations.

The posterior fornix is an important surgical landmark, since it provides direct access to the cul-de-sac of Douglas.

Vaginal support: Atrophy or weakness of the endopelvic fascia (ligaments) and muscles supporting the vagina may result in the development of a cystocele, rectocele, or enterocele.

Gartner's duct cyst: is a cystic dilation of the embryonic mesonephros is usually present on the lateral wall of the vagina.

The vascular and lymphatic networks: of the bladder and vagina are in close proximity and interrelationships so that inflammation of one organ can produce symptoms in the other. For example, vaginitis sometimes produces urinary tract symptoms, such as frequency and dysuria.

The Cervix: Forms the narrow lower portion of the uterus. It predominantly consists of collagenous connective tissue and mucopolysaccaride ground substances, while smooth muscle fibers form about 15% of the tissue of the cervix. The attachment of the vagina to the cervix divides it into two portions:

1. Upper supravaginal portion "supra-vaginalis".
2. Lower portion called portio-vaginalis (exocervix) within the vagina.

The endocervical canal: is fusiform in shape, about 2.5 to 3 cm in length. It is lined by a single layer of specialized columnar epithelium and secretes mucus to facilitate sperm transport. The exocervix, (the external part of the cervix) is lined by non-keratinized stratified epithelium. The area of transition from the endocervical columnar epithelium of the endocervical canal , to the non-keratinized stratified epithelium of the exocervix, is known as the 'transformation zone'.

Nerve supply of the cervix: The endocervix is rich in pain nerve fibers that accompany the parasympathetic fibers to the 2nd, 3rd, and 4th sacral segments.

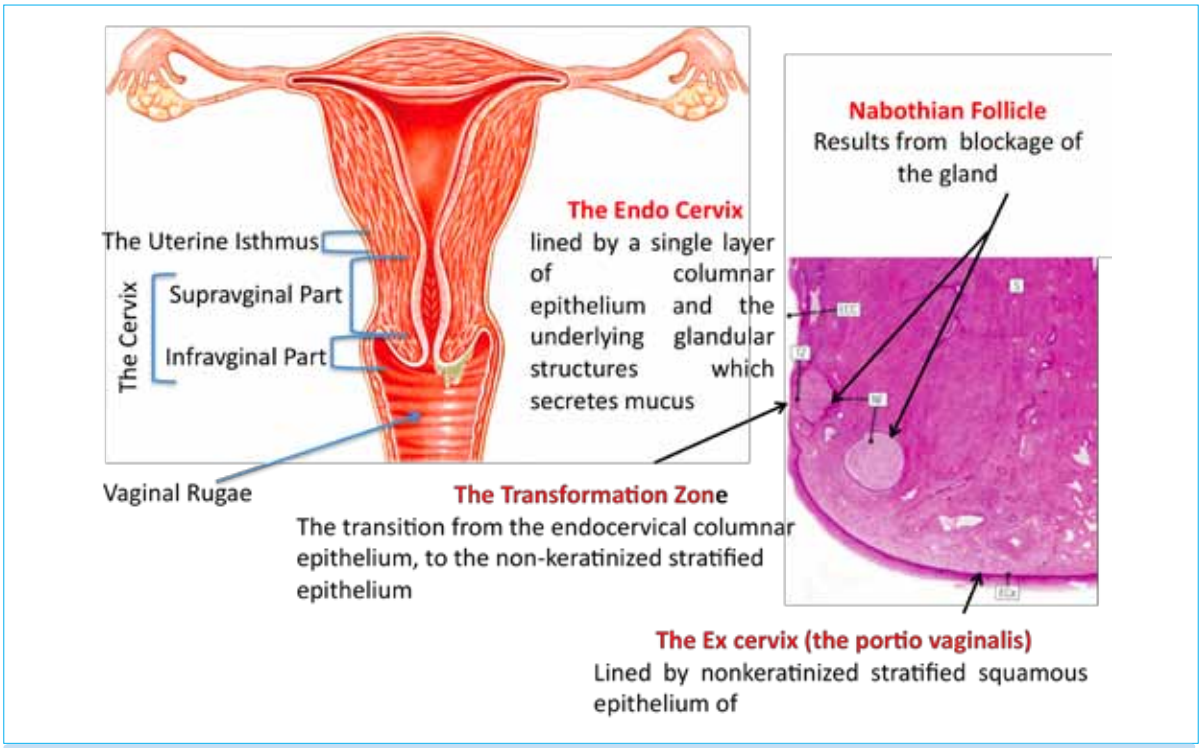


Figure 5-6: The Cervix

The Cervix - Clinical Correlation

Transformation zone: Its position depends on the age of the woman and hormonal status. In term of cellular turnover it is a very active zone hence it is the most likely site for development of dysplasia (cervical cancer)

The Nerve supply: The rich nerve supply of the Endocervix makes transcervical instrumentation painful, and may result in vasovagal response. In contrast to the scarce sensory nerve supply of the Exocervix therefore procedures like cauterization (by cold or heat) may be undertaken with only minor discomfort.

Nabothian's Follicle or Cysts: Are the result of blockage of an endocervical glands which then become filled with mucus secretions. It is not uncommon and considered normal finding in women of the reproductive age .

Ectropion: When the Endocervical epithelium becomes exposed externally it appears as read areas which used to be misnamed as "erosion" this is normal in parous women and women on pills.

The Uterus:

The uterus is a pear shaped, thick walled, hollow muscular organ located centrally in the female pelvis between the bladder and the rectum, attached to the lateral sidewalls of the pelvis by the broad ligaments. The uterine cavity is flattened and triangular in shape. The uterus is formed of the following major parts;

- The fundus is the dome of the uterus above the level of the tubal ostia.
- The body is the part of the uterus that lies below the entrance of the oviducts into the uterus. The uterine cornua are the parts of the body where the tubes join the uterine body.
- The Isthmus is the short constricted area that marks the junction of the uterine body with the cervix. It is the part which forms the lower segment of the uterus in pregnancy.
- The Cervix pierces the anterior wall of the vagina, it communicates with the uterine cavity through the internal os and with the vaginal canal through the external os.

The size and weight of the uterus depends on the hormonal status of the individual and parity. In nulliparous women it is approximately 8 cm long by 5 cm wide and 2.5 cm thick and weighs about 40-50 g. In multiparous women these measurements are about 2.5 cm larger and weighing 20-30 g more. After menopause the uterus atrophies in both size and weight.

The uterus in the majority of women, is anteverted i.e. the long axis of the uterus is bent forward on the long axis of the vagina forming an angle of at least 90 degrees and anteflexed i.e. the long axis of the body of the uterus is bent forward at the level of the internal os with the long axis of the cervix. However, the reverse i.e. a retroverted and retroflexed position of the uterus is a normal variant in approximately 25% of women.

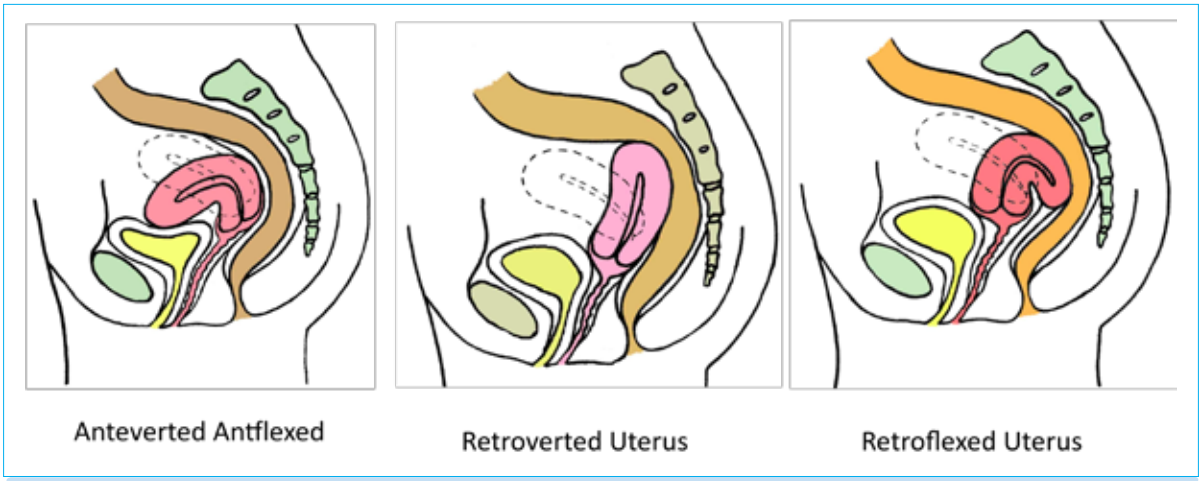


Figure 5-7: In approximately 70 % of women the uterus is anteverted anteflexed. Cervix

Histological considerations: The uterine wall is formed of three layers:

1. External serosal layer which is a continuation of the visceral peritoneum. It is firmly attached to the uterus in all areas except anteriorly at the level of the internal os of the cervix, where it loosens up to reflect on the superior surface of the bladder.

2. A middle thick muscular layer which is composed of three indistinct layers of smooth muscle. An outer longitudinal which is continuous with the muscle layer of the oviduct and the vagina. A middle layer formed of interlacing oblique and spiral bundles of smooth muscle, and an inner longitudinal muscle layer. *This arrangement gives the uterine muscle an optimum mechanical haemostatic power.*

3. The mucus membrane lining the endometrium is formed of the endometrial glands and stroma. The endometrial glands are tubular glands formed of tall columnar epithelium. Functionally the endometrium is divided into a basal layer (stratum basale) and an outer functional layer (stratum functionale). Only the functional layer responds to fluctuating hormonal level.

Blood supply:

Provided by the uterine and ovarian arteries, the role of the ovarian arteries blood supply to the uterus becomes more prominent during pregnancy.

The lymphatic drainage: The lymph vessels from the uterine fundus accompany the ovarian artery and drain into the para-aortic nodes at the level of the first lumber vertebra. The vessels from the body and cervix drain into the internal and external iliac lymph nodes. A few lymph vessels follow the round ligament of the uterus through the inguinal canal and drain into the superficial inguinal lymph nodes.

Nerve supply: Afferent sensory fibers from the uterus are in close proximity to the sympathetic nerves. Entering the spinal cord at the eleventh and twelfth thoracic segments, the sympathetic nerve supply to the uterus comes from the hypogastric and ovarian plexus. The parasympathetic fibers are largely derived from the pelvic nerve and from the second to the fourth sacral segments.

The Uterus - Clinical Correlation

Position and Relation to Vagina: On rare occasion a retro-verted gravid uterus may get entrapped within the pelvis and beneath the sacral promontory, giving rise to anterior sacculatoin of the uterus. Clinically patients presents with acute retention of urine.

The Nerve supply: Pain from uterine ischemia or contractions follow the line of distribution of the afferent sensory fibers. Hence it is often felt in the back around lower thoracic and lumber regions.

The Blood Supply: The uterus receives dual blood supply from the uterine and ovarian vessels on both sides. Therefore internal artery or uterine artery ligation on one or both sides does not induce complete hemostasis unless all four vessels are tied.

The Endometrium: The cyclic shedding of the endometrium is one of the most important mechanisms of protection against chronic endometritis. Acute endometritis can occur if pathogens gets access to areas of row endometrial mucosa e.g. after delivery, abortion or during menstruation. Hence in Islamic teaching intercourse is prohibited during menstruation.

The Muscle wall (the myometrium): The different pattern of orientation of the uterine muscle fibers provide natural "ligature" particularly after delivery.

Oviducts or Fallopian Tubes:

Each oviduct is about 10 cm in length and contained into the mesosalpinx which is the peritoneal reflection formed of the free edge of the superior portion of the broad ligament. The tubes connect the cornua of the uterine cavity and the peritoneal cavity. The ostia of the tubes vary in diameter from about 1.5 mm at the uterine end to about 3 mm at the peritoneal end.

Each tube is divided into four anatomic parts:

1. Uterine intramural or interstitial part; about 1-2 cm in length surrounded by the myometrium.
2. The isthmus; about 4 cm in length with an inside diameter of about 1-2 mm.
3. The ampulla; about 4-6 cm in length with an approximate 6 mm inside diameter. *Fertilization normally occurs in the ampulla.*
4. The infundibulum; the distal funnel shaped lateral portion of the oviduct. It projects beyond the broad ligament. Its abdominal ostia are surrounded by 20-25 fingerlike projections termed fimbriae. One of the large fimbriae is attached to the ovary known as the fimbria ovarica.

Histology of the Tube: Each tube contains numerous longitudinal folds (plicae) formed of mucosa and the underlying stroma. The mucosal lining is made up of three different types of cells in various proportions (Figure 5-6).

The tubal muscle wall is arranged in two layers, an inner circular and an outer longitudinal. Finally, between the peritoneal surface of the tube and the muscle layer, is an adventitial layer that contains blood vessels and nerves.

The Ovaries:

Almond shaped structures; their size depends on the woman's age and parity. During reproductive years each ovary measures approximately 1.5 cm 2.5 cm 4 cm. In older women it becomes firmer and smaller.

The ovaries lie against the lateral wall of the pelvis in the ovarian fossa. This angle is bounded by the external iliac vessels above, internal iliac vessels and the ureter behind as it passes the bifurcation of the common iliac artery. The obturator nerve crosses the floor of the fossa.

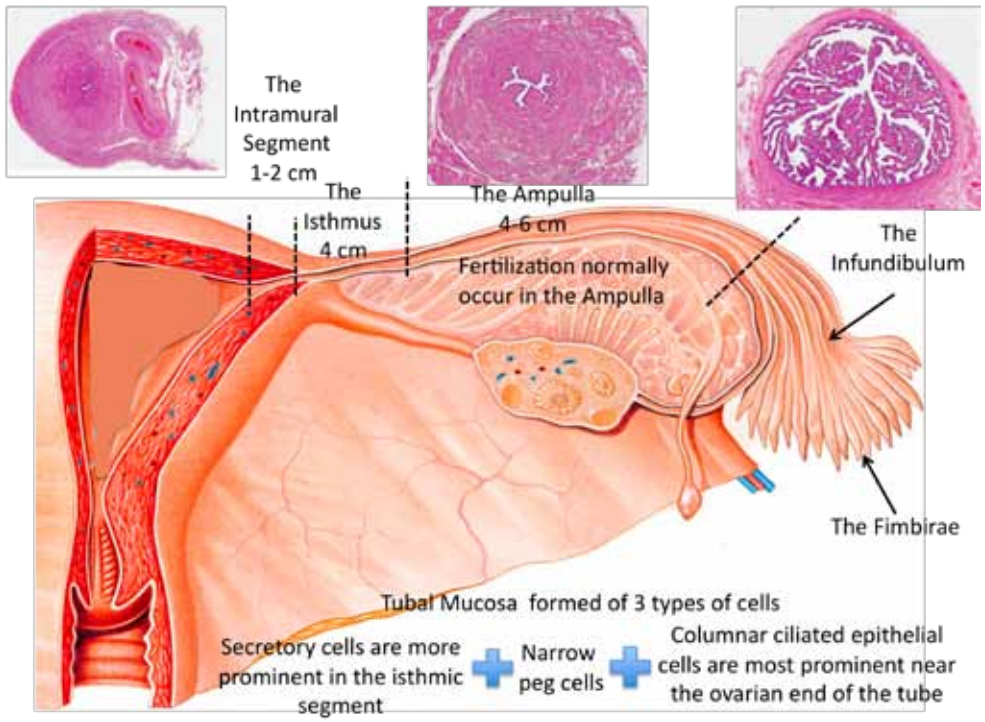


Figure 5-8: Schematic representation. Note the difference in tubal muscle wall thickness and mucosal lining. The peg cells are variant of secretory cells (see text)

The Tubes - Clinical Correlation

Ectopic Pregnancy: The oviduct is the most common site of ectopic pregnancies. The most severe bleeding occurs when the implantation site is in the intramural segment of the tube.

Surgical Procedures: The isthmic segment of the oviduct is the thinnest site therefore it is the preferred site for surgical sterilization (e.g. application of clip) or fitting an occlusive device.

Anatomical Relation: The right oviduct and appendix are often adjacent. Clinically it may be difficult to differentiate inflammation of the tube from acute appendicitis.

Tubal Torsion: Ampullary segment torsion and ischemic atrophy can occur because of the wide mesosalpinx.

Paratubal or paraovarian cysts: can reach 5 to 10 cm in diameter and occasionally are confused with ovarian cysts before surgery.

Uterotubal junction spasm: can occur due to the thick muscle layer and causes temporary physiologic obstruction during hysterosalpingography. It may be relieved by intravenous sedation, a paracervical block.

The ovary has three ligaments: which ensure free ovarian mobility but guard against torsion. These ligaments are:

- The mesovarium: is a peritoneal reflection arising from the posterior leaf of the broad ligament. The blood vessels and nerves supply cross through it.
- The ovarian ligament: extends from the lower pole of the ovary to the lateral wall of the uterus.
- The infundibular pelvic ligament: (suspensory ligament) is the part of the broad ligament that attaches the upper pole of the ovary to the lateral pelvic wall. It contains the ovarian artery, veins and accompanying nerves.

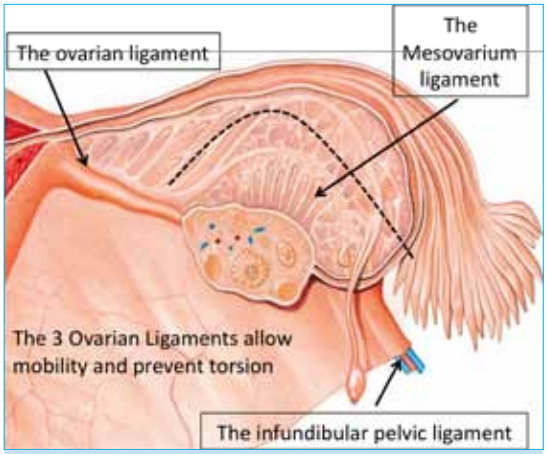


Figure 5-9: The ovarian ligaments

Blood Supply: The ovarian arteries originate directly from the aorta, just below the renal arteries at the level of the first lumbar vertebra. They enter the infundibulopelvic ligaments reaching the mesovarium ligament. They unite with the ascending branch of the uterine artery in the mesovarium just under the suspensory ligament of the ovary. Thus the ovary receives dual blood supply, from the ovarian and the terminal branch of the uterine arteries.

Venous drainage: Accompanies the arteries, however the left ovarian vein drains into the left renal vein, whereas the right ovarian vein drains directly into the inferior vena cava.

The lymphatic drainage of the ovaries follows the ovarian arteries and drain into the aortic nodes at the level of the renal veins.

Vascular System of the Pelvis

The vascular supply of the pelvis and internal pelvic organs are derived from three major sources: The internal iliac, middle sacral, and superior rectal (hemorrhoidal) arteries.

➢ Common iliac arteries:

Originate from the bifurcation of the aorta at the level of the fourth lumber vertebra. Each common iliac artery is approximately 5 cm in length before it divides into the External and Internal (hypogastric arteries).

The Internal Iliac (hypogastric) arteries:

They arise approximately at the level of the lumbosacral joint. They are short vessels (3-4 cm in length) running downwards in the pelvis anteriorly to (crossing) the hypogastric veins and posteriorly to the ureter. Each artery divides into an anterior and posterior division (trunk).

- The posterior division: gives off three (somatic) branches the ilieolumbar, lateral sacral and superior gluteal arteries.
- The anterior division has nine branches:
    - Three parietal: namely the obturator, internal pudendal and inferior gluteal arteries.
    - Six visceral branches: namely the umbilical, middle vesical, inferior vesical, middle hemorrhoidal, uterine and vaginal arteries. The superior vesical artery usually arises from the umbilical artery.

The uterine artery:

Arises from the anterior division of the hypogastric artery and runs medially towards the isthmus of the uterus. At the base of the broad ligament it makes an abrupt turn towards the internal cervical os. At this point, the uterine artery **crosses over the ureter** and reaches the lateral side of the uterus, where it divides into large ascending and smaller descending branches. The ascending branch runs in the broad ligament to finally anastamoses with the ovarian artery in the mesovarium.

Throughout its course it gives off 'arcuate' branches to supply the myometrium and unite with the arcuate branches from the opposite side. These series of arcuate arteries develop radial branches that supply the myometrium and the basalis layer of the endometrium. They then give rise to the spiral arteries of the functional layer of the endometrium.

The descending branches of the uterine artery produce branches that supply the cervix and the vagina and anastamoses with the vessel from the other side.

Vaginal Artery:

It may arise either from the anterior division of the internal iliac artery or from the uterine artery.

Internal Pudendal artery:

This artery is the terminal branch of the hypogastric artery and supplies branches to the rectum, labia, clitoris and perineum.

Veins:

There is a rich and extensive plexus of veins that drain the female pelvic organs. In general, the veins of the female pelvis and perineum are thin walled and have few valves.

The draining veins follow the course of the arterial supply.

Middle sacral artery and veins: are found in the midline of the pelvis. The artery is a direct branch of the aorta passing down the front of the sacrum. It is liable to surgical damage during procedures such as presacral neurectomy or sacrospinous vault fixation.

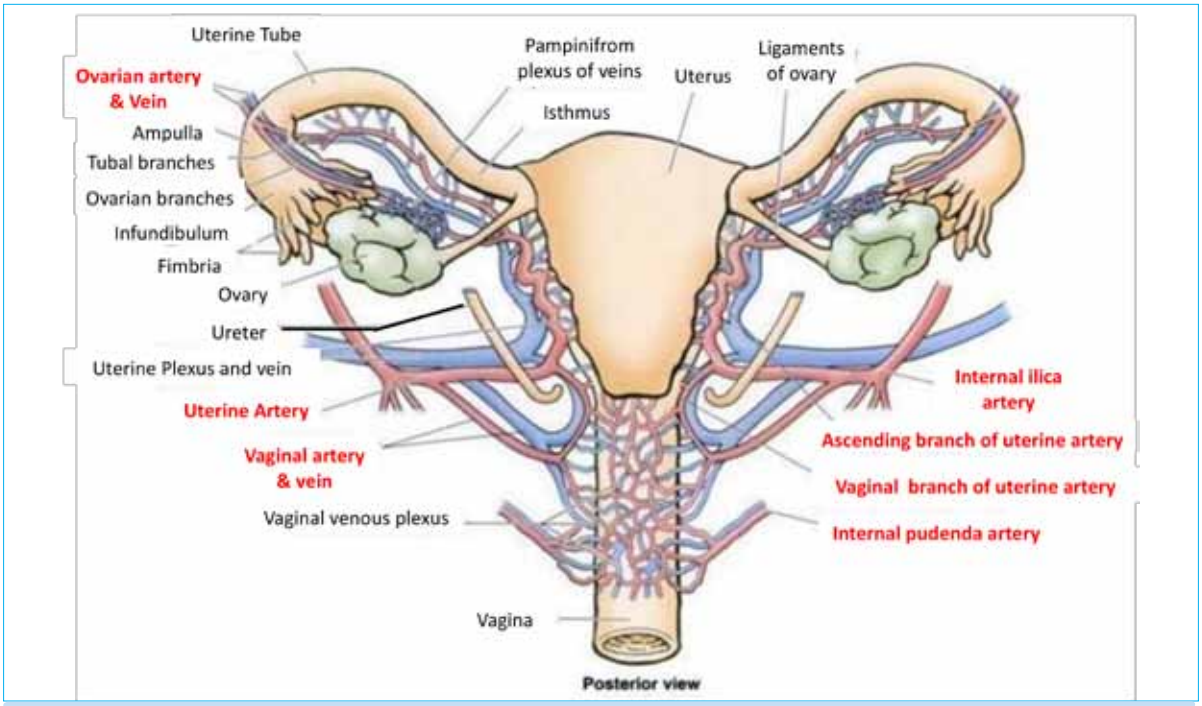


Figure 5-10: Blood supply and venous drainage of uterus, vagina and ovaries. The broad ligament of the uterus is removed to show:

The uterine artery crosses over the ureter (water under the bridge)
The uterine artery near the uterus gives off the vaginal branch and the ascending branch which runs alongside the body of the uterus (see text)
The anastomosing branches of the ovarian artery as they supply the ovary, uterine tube and uterus.
The veins follow similar pattern, but are more plexiform, including a pampiniform plexus related to the ovary and continuous uterine and vaginal plexuses.

The Pelvic Blood Supply - Clinical Correlation

Uterine Blood supply: longitudinal incision in the middle of the uterus produces less bleeding than a transverse one because of arcuate arteries (branching from the uterine) reaches the uterus from its lateral borders.

Anatomic variation: There is wide anatomic variation in the pelvic vasculature e.g. The origin of the uterine artery from the internal iliac vessel is variable. It may arise as an independent vessel from the internal iliac or as a branch from the inferior gluteal, internal pudendal, umbilical and obturator arteries.

Collateral circulation: There is wide collateral circulation that always ensures adequate blood supply. E.g. bilateral hypogastric arteries ligation a procedure that may be performed in intractable postpartum hemorrhage may not be enough to stop the bleeding. It may be necessary to supplement it with ligation of the anastomotic sites between the ovarian and uterine vessels.

Trophoblastic emboli: The anastomosis of the pelvic veins with the presacral and lumber veins may lead to the direct migration of trophoblastic emboli to the brain bypassing the capillary system in the lungs.

Innervations of the Pelvis

Internal genitalia; are supplied primarily from the autonomic nervous system. The sympathetic fibers originate from the thoracic and lumber portions of the spinal cord, its ganglion lie adjacent to the central nervous system.

The parasympathetic fibers originate in cranial nerves and the middle three sacral segments of the cord, the ganglions are located near the visceral organs.

In broad terms the actions of these two systems are antagonistic. Sympathetic fibers produce muscular contractions and vasoconstriction, whereas parasympathetic fibers cause the opposite effect on muscle and vasodilatation. However, both fibers of both divisions of the autonomic nervous system are frequently intermingled together in the same peripheral nerves.

Sensory fibers from the uterus accompany the sympathetic nerves, which enter the nerve roots of the spinal cord at T11 and T12. Hence referred uterine pain is often felt in the lower abdomen. Afferent sensory fibers from the cervix and upper end of the vagina enter

the spinal cord in nerve roots of S2, S3 and S4. The pudendal nerve also innervates the lower end of the vagina however the exact line of demarcation between the upper and lower part of the vaginal is ill defined.

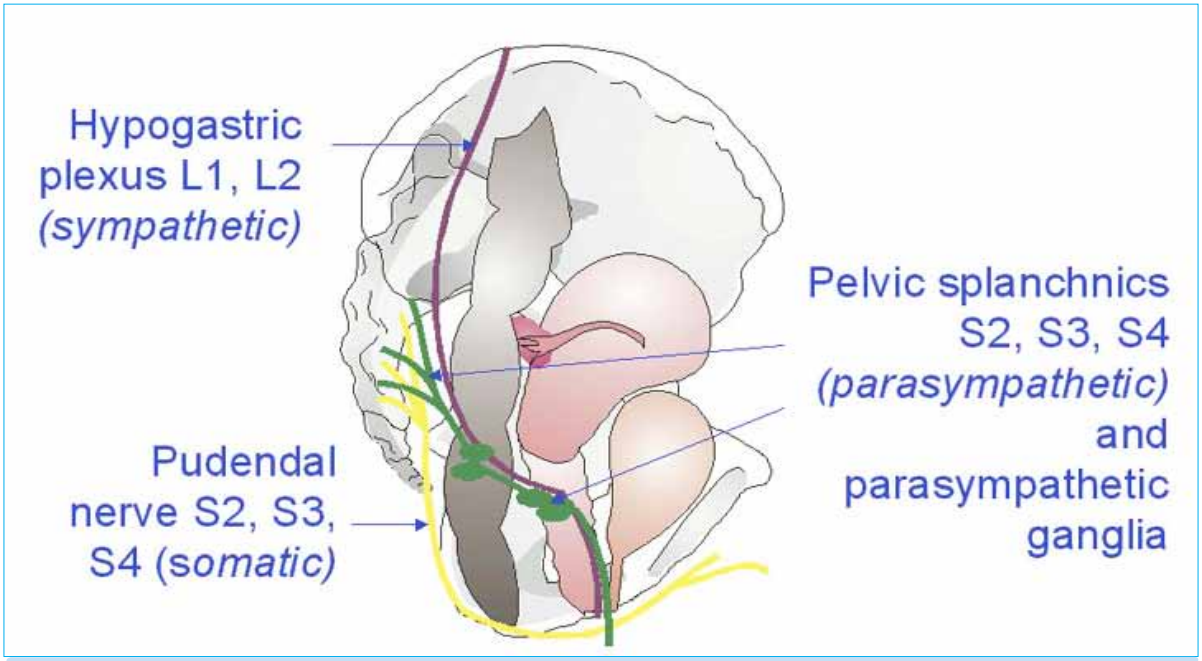


Figure 5-11: Innervations of the pelvic

Pelvic Nerves - Clinical Correlation

Femoral nerve injury: may occur during abdominal hysterectomy. This is due to pressure from the self retaining retractor lateral blade in the area adjacent to where the femoral nerve penetrates the psoas muscle.

This also may occur during vaginal hysterectomy from exaggerated hyper flexion of the legs in the lithotomy position.

Pudendal nerve block: During pudendal nerve block care should be taken not to injure the pudendal vessels

Cervicitis (cervical inflammation): gives referred pain at the lower back, in the lumbosacral region (S2, S3 and S4).

Vaginal nerve supply: The upper two thirds of the vagina are poor in nerve supply; hence foreign bodies and tampons may be forgotten until they produce symptoms.

Pelvic Diaphragm and Ligaments

Pelvic Diaphragm:

The pelvic diaphragm is a term that describes the thin muscular layer of tissues that forms the inferior border of the abdominal cavity (The superior border is formed of the thoracic diaphragm). It extends from the symphysis pubis to the coccyx and from one lateral pelvic side wall to the other. The two main muscles that form the pelvic diaphragm are the levator ani and the coccygeus muscles.

- **The levator ani:** is divided into three components: pubococcygeus, puborectalis, and iliococcygeus.
  - The Pubococcygeus is the more anterior portion of the levator ani. It arises from the posterior surface of the pubis and arcus tendineus. The medial fibers sweep around the vagina and urethra and insert into the perineal body.
  - The puborectalis arises in continuity with the most anterior portions of the Pubococcygeus and inferior surface of the pubes. It crosses posteriorly to fuse with its counterpart fibers from the opposite side and encircles the rectum at its junction with the anal canal producing an abrupt angle that reinforces fecal continence.
  - The iliococcygeus forms the most broad and posterior portion of the levator ani. It arises from the ischial spine and arcuate tendon and enters into the side and tip of the coccyx, while its more anterior fibers fuse in the midline with fibers from the opposite side to form the anococcygeal ligament that extends between the anus and the coccyx.

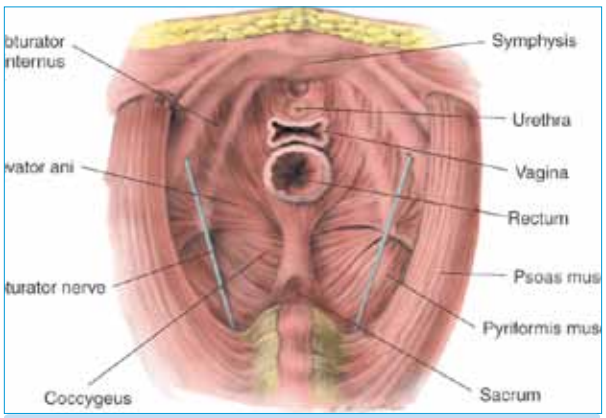


Figure 5-12: Superior view of the pelvic diaphragm

- **The coccygeus:** is a triangular muscle that occupies the area between the ischial spine and the coccyx. It arises from the ischial spine and inserts into the sacrum and coccyx.

The inferior surface of the levator ani forms the superior or upper boundary of the perineum.

The Perineum

The perineum anatomically is divided into two distinct parts (or triangles), an anterior or **urogenital triangle** and a **posterior or anal triangle**. Both triangles have a common sagittal midline attachment for its respective muscles. The midline attachment forms a fibromuscular mass called the perineal body (for gynecologists and obstetricians this fibromuscular structure is considered the perineum). The perineal body is an important structure between the anal canal and the vagina.

The urogenital triangle is further subdivided into superficial and deep perineal spaces by a fibromuscular septum called the urogenital diaphragm.

- The superficial perineal space is triangular in shape, bounded by three sets of muscles, the ischiocavernosus, bulbocavernosus, and superficial transverse perinei. It also includes the Bartholin glands and the vestibular bulbs.
  - The Ischiocavernosus muscles arise from the medial surface of the ischial tuberosities, traverse the medial surface of the pubic rami, and insert into the pubic arch on each side of the crus of the clitoris.
  - The bulbospongiosus muscle (bulbocavernosus, also known as the sphincter of the vagina) forms the most medial boundary of the superficial perineal space. It arises from the central tendon of the perineum, runs forward surrounding the vagina on each side to be inserted into the dorsum of the clitoris.

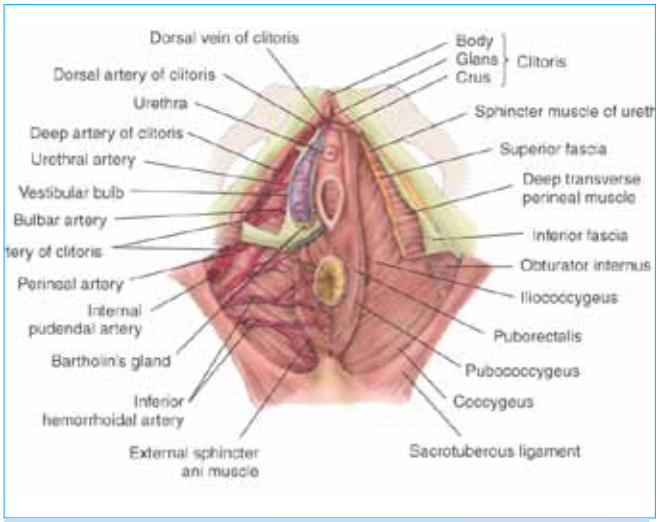


Figure 5-13: Inferior view of the Perineum

  - The superficial transverse perinei muscles arise from the anterior portion of the ischial tuberosities and run transversely across the perineum to insert into the central tendon. During episiotomy it is important to recognize this muscle in order to ensure proper cooptation.

Underneath the bulbocavernosus muscles are the vestibular bulbs, which are the female homologue of the erectile components of the penile bulb in the male. They become engorged during sexual arousal.

Immediately behind the vestibular bulb and under cover of the bulbospongiosus muscles are the greater vestibular glands (Bartholin's Glands). These are homologous of the bulbouretheral glands in males. They have a long slender duct that opens into the vaginal vestibule.

- The deep perineal space has boundaries, inferiorly fascia of the urogenital diaphragm, superiorly fascia of the pelvic diaphragm, and laterally by the fascia of the ischiopubic rami. This space contains the deep transverse perineal muscles and the sphincter urethra. The sphincter urethra arises from the rami of the ischium and pubis, sends some fibers medially that surround the distal urethra and anterior portion of the vagina. The deep transverse perinei as the name implies, runs transversely and inserts into the central tendon of the perineum.

The anal triangle: It is the area of the perineum behind an imaginary line that extends between the ischial tuberosities. It is traversed by the terminal portion of the anal canal with its surrounding external sphincter muscle. On both sides of the anal canal are the ischiorectal fossae. The ischiorectal fossa is a potential cone shaped space, filled with fat. It lies between the skin and levator ani on each side of the anal canal. Together the two fossae make a horseshoe shape; since they connect posteriorly with each other, anteriorly they are separated by the perineal body. The boundaries of each fossa are made laterally by the obturator internus muscle and fascia, medially and superiorly by the sloping inferior surface of the levator ani, as it descends to surround the anal canal. The apical part of the coned shaped fossa is the point of origin of the levator ani from the obturator fascia.

The ischiorectal fossa is not confined to the anal triangle, but rather it extends posteriorly below the lower edge of the gluteus maximums as far as the sacrotuberous ligament and anteriorly above the superior fascia of the urogenital diaphragm to the inferior surface of the levator ani.

The fatty tissue of the ischiorectal fossa is strengthened by connective tissue septa, derived from the fascia lining the lateral walls of the fossa, as well as from Cole's fascia. These septa penetrate the fossa fat providing support and shape to the adipose tissue.

The potential space of the fossae allows distention of the rectum during defecation and the vaginal wall during second stage of labor. It is also a potential space for huge (up to one liter) hematoma collection and abscess formation.

The obturator nerve and internal pudendal vessels run alongside the lateral wall of the ischiorectal fossa in the pudendal or Alcock's canal. This canal is formed from the splitting of the fascia on the lateral wall of the ischiorectal fossa together with the obturator fascia itself.

The external anal sphincter:

The voluntary muscle, which is responsible for fecal continence, is located within the anal triangle. It takes the shape of a muscular tube that surrounds the anal canal and lower rectum. Its total length is about 2 cm, and composed of three components; the subcutaneous, superficial and deep components. The superficial and deep components running on top of each other originate posteriorly from the coccyx and are inserted anteriorly into the perineal body. In between, they diverge to surround the anal canal. During its course they often get attached to the overlying perineal skin. The third component, the subcutaneous part, surrounds the anal canal and runs circumferentially around it.

Innervations of the perineum:

The major nerves supplying the skin of the perineum are:

- **The pudendal nerve (S2-4)** carrying both motor fibers to the perineal pelvic floor muscles and sensory fibers to most of the perineal skin, vulva and clitoris. As it traverses the perineum, it gives several branches along its course in the pudendal canal. Eventually it terminates as the dorsal nerve of the clitoris.
- **Coccygeal and last sacral nerves (S4, 5):** supply skin posterior to the anus and over the tip of the coccyx.
- **Perineal branch of posterior femoral cutaneous nerve:** supply skin lateral to the anus and the most posterior and lateral portions of the labia majora.
- **Ilioinguinal nerve (L1) and genitofemoral nerve (L1, 2):** These nerves descend from the anterior abdominal wall to supply the skin of the mons pubis and most of the anterior portion of the labia majora (except the clitoris).

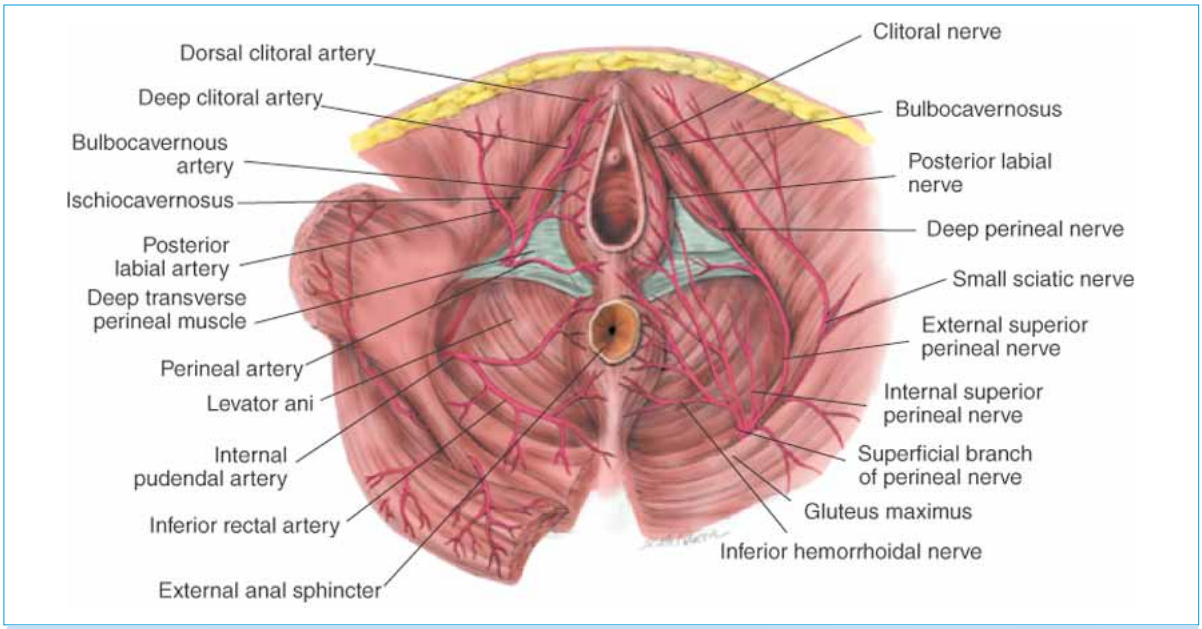


Figure 5-14: A posterior view of the female perineum demonstrating the pudendal nerve emerging externally. The nerve divides into three segments as it passes out of the pelvis: the inferior hemorrhoidal nerve and the deep and superficial perineal nerves. The clitoral nerve is the terminal branch of the deep perineal nerve.

Pelvic Ligaments

The pelvic ligaments are usually formed by thickening of the retroperitoneal fascia. The most important ligaments are:

- **The broad ligament:** Is a mesenteric-like folds of peritoneum stretching from one lateral pelvic sidewall to the other. Enclosed within the folds are loose fatty connective tissues, known as the parametrium. The uterus is contained within its folds with the uterine mucosa contiguous with its folds. Within the leafs of the broad ligaments run important structures: oviducts, ovarian and round ligaments, ureters, ovarian and uterine arteries and veins, embryonic remnants of the mesonephric duct and Wolffian body, and secondary ligaments mesovarium and mesosalpinx.

Between the two leaves of the broad ligaments, particularly near its base, is perivascular connective tissue. This connective tissue thickens to forms two important ligaments; the uterosacral and cardinal (or lateral cervical) ligaments.

- **The round ligament:** Is a fibromuscular tissue ligament that attaches to the superior-anterior aspect of the uterus, anterior and caudal to the oviduct, and runs within the leaves of the broad ligament to the lateral pelvic wall. It crosses the external iliac vessels and enters the inguinal canal where it gets inserted in a fanlike fashion into the labia majora . On entering the inguinal canal it may be accompanied by a peritoneal diverticulum termed the processus vaginalis or canal of Nuck. Cyst formation in the canal of Nuck may be confused with indirect inguinal hernia. The round ligament offers very little support to the uterus.

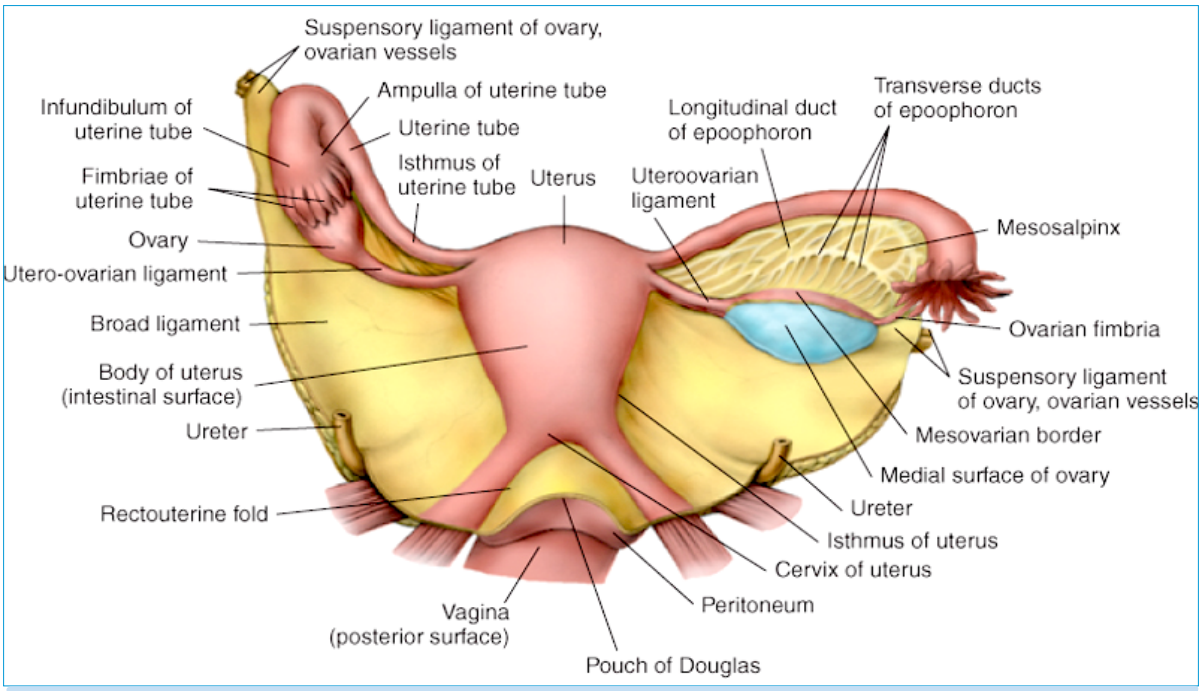


Figure 5-15: Posterior aspect of broad ligament. Showing the structure within the ligaments leafs

- **Cardinal ligaments**: Also know as Mackenrodt's ligaments, is a thickened condensation of the parametrial tissue that extends from the lateral aspect of the upper part of the cervix and the vagina to the pelvic wall. It forms the base of the broad ligaments. Its connective tissue is continuous with the connective tissue of the parametrium and the superior fascia of the levator ani. This continuity gives the support of the vagina and uterus to the pelvic sidewall.

- **Uterosacral ligaments**: Extends from the upper posterior portion of the cervix and is inserted into the region of the 2nd, 3rd, and 4th, foramina of the sacral vertebra.

They are thickened near the cervix while posteriorly they thin out, and split to surround the rectum. The middle of the uterosacral ligament is composed primarily of nerve bundles. The lateral aspect of the uterosacral ligaments merge with the cardinal ligaments. Its role in supporting the uterus is secondary to the cardinal ligaments

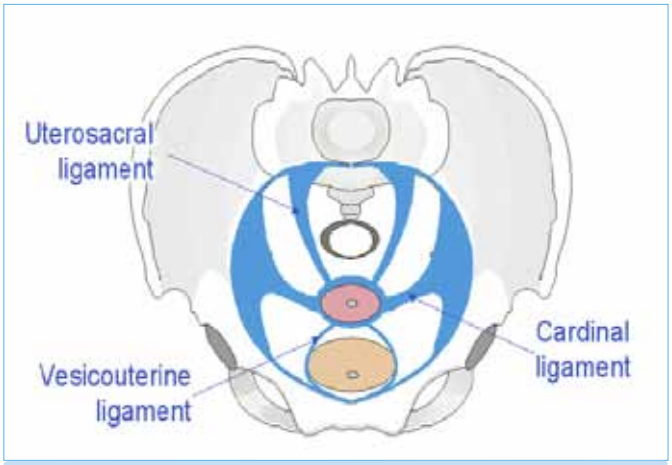


Figure 5-16: Diagram of the pelvic ligaments. Together with the pelvic muscles they keep the uterus in place

Pelvic Ligaments – Clinical Correlation

Pelvic organ prolapse: Normal position of the female pelvic organs in the pelvis depends on mechanical support from both fascia (Cardinal ligaments and uterosacral ligaments) and muscles (pelvic floor muscles).

The round ligament is an important surgical landmark in making the initial incision into the parietal peritoneum to gain access to the retroperitoneal space.

A cyst of Nuck's canal: may be confused with an indirect inguinal hernia.

Non-genital pelvic organs

The Ureters:

Runs in the retroperitoneal potential space extending from the renal pelvis to the urinary bladder. They are about 28-34 cm in length. Anatomically they may be divided into abdominal and pelvic segments. The diameter of the abdominal segment is about 8-10 mm while the pelvic one is about 4-6 mm in diameter.

- The abdominal part of the ureters runs downwards and medially along the anterior surface of the psoas major muscle. Four arteries and their accompanying veins cross anteriorly to the right ureter, namely the right colic artery, the ovarian vessels, the ileocolic artery and the superior mesenteric artery.

- The pelvic part of the ureters begins at the point of the iliopectineal line. In the pelvis the ureters run along the common iliac artery. The right ureter will then cross at the bifurcation of the common iliac artery, whilst the left one make the crossing about 1-2 cm above the bifurcation.

  It then runs, retroperitoneally downwards along the pelvic wall, in close proximity to the ovarian, uterine, obturator, and superior vesical arteries. It then changes its course, at approximately the level of the ischial spines, and runs forward and medially at the base of the broad ligament. It then enters the cardinal ligaments. In this location it is approximately 1 to 2 cm lateral to the uterine cervix surrounded by a plexus of veins. It then runs upward and medially in the vesical uterine ligaments. At this point it is in close contact with the anterior vaginal wall.

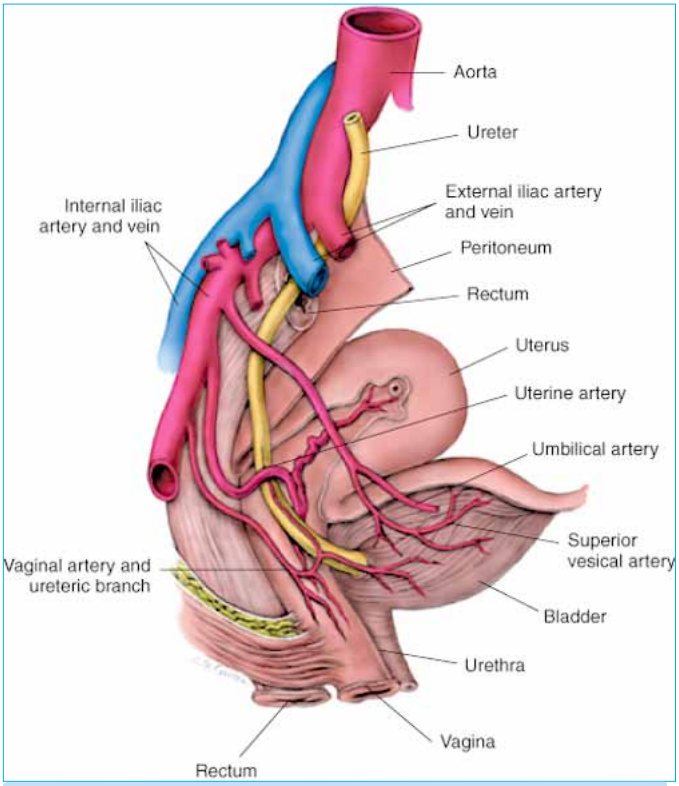


Figure5-17: Schematic presentation of the pelvic course of the ureter and its relation to the pelvic vessels

The ureter has a rich arterial supply, from almost all vessels that it crosses or is near by its course. It forms a longitudinal plexus within its adventitia. This renders the ureter resistant to injury resulting from devascularisation unless the surgeon strips the adventitia from its muscular conduit.

The Bladder:

The bladder is a hollow muscular organ. Its shape, size and anatomic relation to surrounding organs depend on whether the bladder is full or empty. Its superior surface is the only surface covered by peritoneum. At the apical part of the bladder is the urachus, which is the adult remnant of the embryonic allantois. It is occasionally patent for part of its length. Inferiorly it is immediately adjacent to the uterus. Its base is related directly to the anterior vaginal wall. The bladder neck and urethra are attached to the symphysis pubis by fibrous ligaments.

The space of Retzius is the area between the bladder and symphysis pubis, bounded

laterally by the obliterated hypogastric arteries. It extends from the fascia covering the pelvic diaphragm to the umbilicus between the peritoneum and transversals fascia.

Histology of the bladder: The bladder is lined by transitional epithelium. The trigone is the triangle shape area in the bladder bounded by the two ureteral orifices and the urethral orifice. Its mucosa is darker red than the rest of the bladder and free of mucus folds.

The detrusor muscle forms the muscular wall of the bladder, and is arranged in three layers.

Rectum:

Starts at the level of the second or third sacral vertebra, where the sigmoid colon no longer has a mesentery. It is 12 - 14 cm in length. Its upper two thirds are covered with peritoneum anteriorly. The lower one third is below the peritoneal reflection, and is in close proximity to the vagina.

The rectum empties into the anal canal which is 2-4 cm in length. Approximately 10% of carcinoma of the large bowel occurs within the rectum.

Non-Genital Pelvic Organs-Clinical Correlation

Because of close anatomic proximity, operative injuries to the bladder or ureter occur in approximately 1 out of 100 major gynecologic operations. Bladder injuries are approximately five times more common than ureteral injuries

Ureteric injury: Injury to the ureter may occur during clamping or ligating of the infundibulopelvic vessels, clamping or ligating of the cardinal ligaments, or wide suturing in the endopelvic fascia during pelvic reperitonealization after hysterectomy.

The ureter can be identified from a pelvic vessel by (1) visualization of peristalsis after stimulation by a surgical instrument and (2) visualization of Auerbach's plexuses, which are numerous, wavy, small vessels that anastomose over the surface of the ureter.

Ureteric injury during Vaginal Surgery: During vaginal surgery the ureter may be injured during placemen of deep sutures at the vaginal fornix.

"water flows under the bridge." A sentence that is often cauted to remind one with the relation of the uterine artery (bridge) as it crosses over the ureter (water) at the the base of the broad ligament near the cervix.

Rectal injury: In the middle third of the vagina the distance between vaginal and rectal mucosa is only a few millimeters, and usually the connective tissue is densely adherent and should be separated by sharp dissection. Also the rectum bulges anteriorly into the vagina in this area, producing a further challenge during vaginal operative procedure e.g. vaginal hysterectomy with associated posterior colporrhaphy.

Other structures:

Cul-de-sac of Douglas:

Is a potential space that separates the uterus from the rectum. Lined by peritoneal folds, anteriorly it covers the cervix and the upper part of the posterior vaginal wall, it then reflects to cover the anterior wall of the rectum.

The pouch of Douglas is easily accessible in performing transvaginal surgical procedures. Posterior colpotomy is often chosen for drainage of abscess in the cul-de-sac of Douglas.

Parametria:

Parametria is the term that describe the extraperitoneal fibro fatty tissues adjacent to the uterus. It lies between the leaves of the broad ligament but is in a contiguous area anteriorly between the cervix and the bladder. It becomes dense and thicker near the cervix and vagina and also thickens in response to radiation, pelvic cancer, infection or endometriosis.

Parametria and cul-de-sac of Douglas Clinical Correlation

The parametria and cul-de-sac of Douglas are important anatomic landmarks in advanced pelvic infection and neoplasia. Intrauterine infection, cervical carcinoma, and endometrial carcinoma may penetrate the endocervical stroma or the myometrium and secondarily may invade the loose connective tissue of the parametria. Occasionally the cul-de-sac of Douglas is obliterated by the inflammatory process associated with either endometriosis or advanced malignancy.

The pouch of Douglas is easily accessible in performing transvaginal surgical procedures. Vaginal tubal ligation may be the procedure of choice in massively obese women. Posterior colpotomy is frequently chosen for drainage of a pelvic abscess occurring in the cul-de-sac of Douglas.

Enterocele: Many women with uterine prolapse have an associated enterocele, which is a hernia that protrudes between the uterosacral ligaments.

Chapter 6

Normal Sexual Differentiation of the Female Genital Tract

Gender determination of the mammalian species is a complex process. It takes place at least at three levels:

- **The chromosomal sex (XX or XY) established at the time of fertilization.**
- **The gonadal sex, involve gonadal differentiation into testes or ovaries, depends primarily on the presence of a testicular determining gene on Y chromosome.**
- **The Phenotypic sex involves the development of the urogenital tracts (internal genitalia) and differentiation of the sexually indifferent external genitalia into male or female structures.**
- **The final gender identity at adulthood is determined not only by the phenotypic appearance of the individual but also by the brain's prenatal and postnatal development as influenced by the environment and sex of rearing.**

By the end of this chapter you should be able to:

- **Realize that sexual determination**: is established at time of conception according to the presence or absence of X or Y chromosome.
- **Realize that sexual differentiation**: involve:
  - **Gonadal Differentiation**: Y chromosome that carries intact SRY gene direct the gonad to testicular development.
  - The gonad produces Testosterone and Müllerian inhibiting factor. They determine the rest of differentiation.
  - **Internal organ differentiation**:
  - **External organ differentiation**: The role of 5 alpha reductase in converting Testosterone to its active produce Dihydrotestosterone (DHT)
  - Each of the above genital system (gonads, internal and external) goes into two phases: un-differentiation followed by differentiation.

The genetic sex (Genetic Sex Determination)

- The genetic (chromosomal) sex is determined at the time of conception (XX or XY). The genetic sex will then determine the differentiation of the "indifferent" gonads into either testes or ovaries .

- **Testicular differentiation**: differentiation into testes depends primarily on the presence of a small gene (*SRY* gene) sometimes known as the testicular determining factor on the short arm (Yp) of the Y chromosome

  Other important functions of the SRY gene are to suppress ovarian development as well as activation of other genes responsible for development of the Leydig cells, Sertoli cells, and the spermatogenic tubules.

- **Ovarian differentiation**: ovarian differentiation used to be considered as a default process that spontaneously takes place in the absence of *SRY* chromosome. Now it is known that normal ovarian differentiation is not simply a default process but involves an active genetic pathway (including R spondin 1 (Rspo1)/Wnt-4/beta-catenin signaling that is repressed by the presence of SRY).

Figure 6-1: Y Chromosome with SRY region on short the short arm

The *SRY* gene acts as a switch or master gene for testis differentiation since it controls a whole number of other genes on the autosomes as well as on the X chromosome (DAX, WT1, and SOX9".

Gonadal Sex (Gonadal Differentiation)

Differentiation of the gonads goes through two phases: undifferentiated and differentiated phase.

⇒ **The phase of indifferent gonads:** (Up to 6 weeks)

About two weeks after fertilization the germ cells "primordial germ cells PGC" begin to migrate by amoeboid movements along the dorsal mesentery of the hindgut to invade the "genital ridges**".** At this point the genital ridges are formed of elevations of mesenchye tissue on both sides of the midline between the lateral mesoderm and the root of the dorsal mesentery.

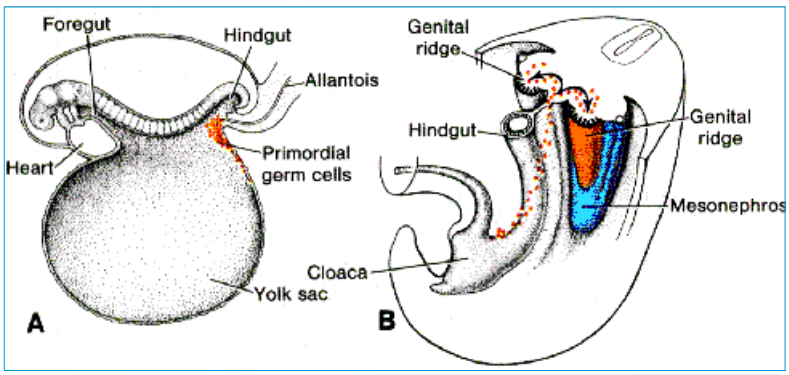


Figure 6-2: ìAî The PGC at the Gastrula stage at wall of the yolk sac GC close to the allantois. ìBî Migration of the PGC along the dorsal mesentery of the hindgut to invade the genital ridges

During their migration, which takes place between the 4th and 6th weeks they multiply by mitosis.

With the arrival of the germ cells the covering epithelium of the genital ridge proliferates and sends cluster of cells into the underlying mesoderm known as the cells of the sex cords, which surround the primordial germ cells.

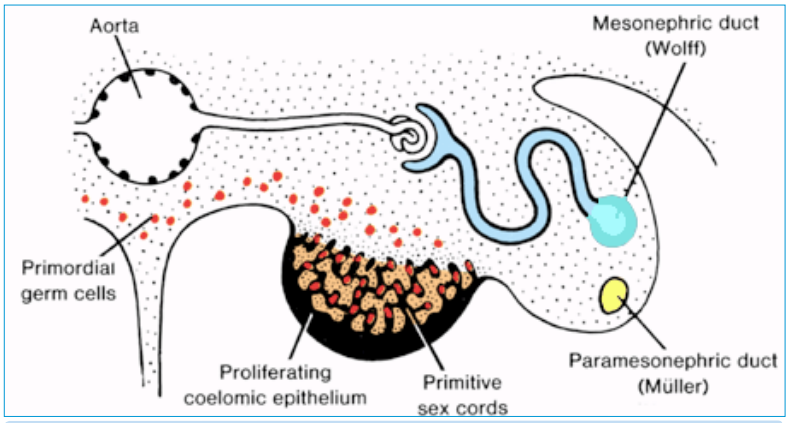


Figure 6-3: The indifferent gonads at 6 weeks show PGC surrounded by cells of the primitive sex cords, proliferation of the mesenchyme and the covering epithelium

Up till this pint, (6 weeks, 42 days) the gonads are "indifferent," i.e. since morphologically the gonadal cords (sex cords) and the PGC can be found both in the cortical as well as in the medullar zones of the future gonads (Figure 6-2, 3)

⇒ **The phase of gonadal differentiation:**

- **Testicular differentiation:** begins during the course of the seventh week **if there is a healthy Y chromosome that carries normal "SRY" gene.**

  The process of testicular differentiation is characterized by:

  - Proliferation of primitive sex cords and their penetration deep into the gonadal medulla. It remain solid until puberty when it canalizes and become the seminiferous tubules.
  - Formation of the dense fibrous connective tissue *"tunica albuginea"* from the cortical region (the surface)
  - The germ cells multiply only by mitosis because meiosis begins only with puberty (unlike the oogonia in female gonads).

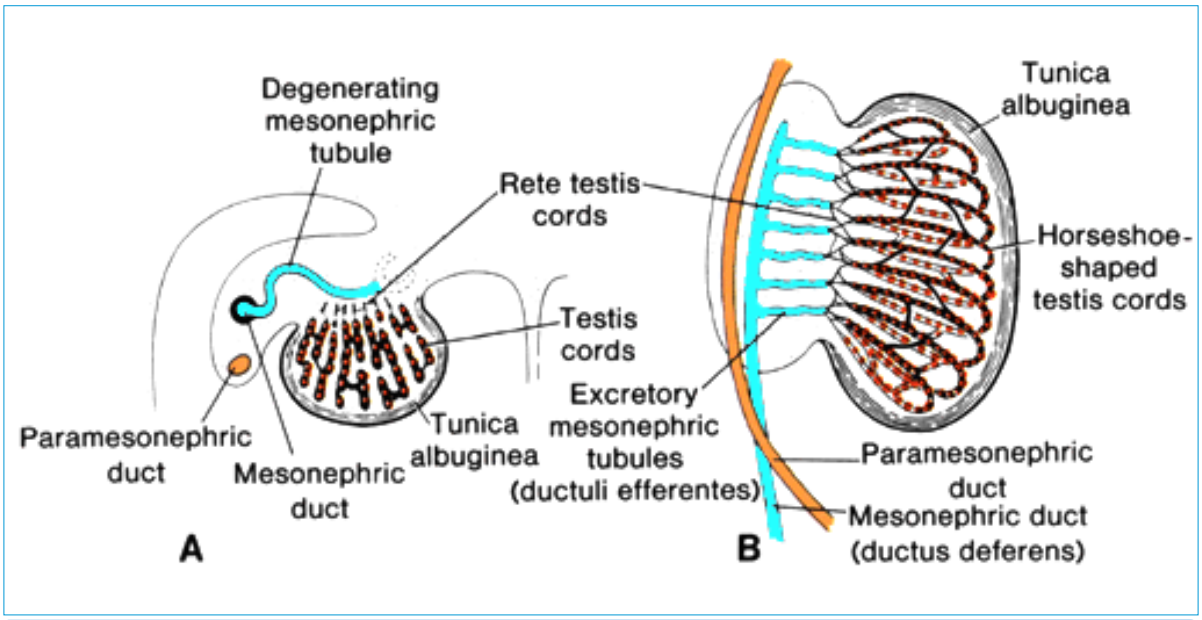


Figure 6-4: In the male the primitive sex cords form the testis and the rete testis cords. The latter communicate with tubules of the mesonephric system, thus linking the testis to the mesonephric duct. The mesonephric duct becomes the ductus deferens

- **Ovarian differentiation:** Begin at the 8th week (2 weeks after testicular differentiation) in the absence of Y chromosome and SRY gene. Ovarian differentiation is characterized by:

  - Differentiation of the gonads into cortex and medulla: In the cortex the primitive sex cords (gonadal cords) attached to the surface remains intact. But in the medulla the primitive sex cords degenerate.

- In the mean time there is rapid multiplication of the germ cells by mitotic division.
- The formation of ovarian mesothelium which arises from the coelomic epithelium (Figure 6-5)
- By the fourth month, the cortical sex cords dissolve and each germ cell become surrounded by a single layer of epithelial cells (later forms the granulosa cells) to be known as Oogonia that soon begins the first meiotic division (see chapter 4) forming primary oocytes.
- By the fifth month the primary oocytes already have completed the prophase of the first meiotic division and become surrounded by monolayer of cells that have differentiated out of the gonadal cord cells and are now called granulosa cells. The primary oocytes that are enveloped by granulosa cells are called "primordial follicles". It remains in the stage of the first meiosis (dictyotene stage) until puberty and beginning of ovulation.

The number of oogonia reaches its maximum peak of about 7 million germ cells around the 20th week of gestation. Following that, a process of atresia commences so that at birth the numbers decline to approximately 2 million germ cells, and to about 400,000 at puberty (Figure 6-6). This process continues throughout women reproductive life till the menopause.

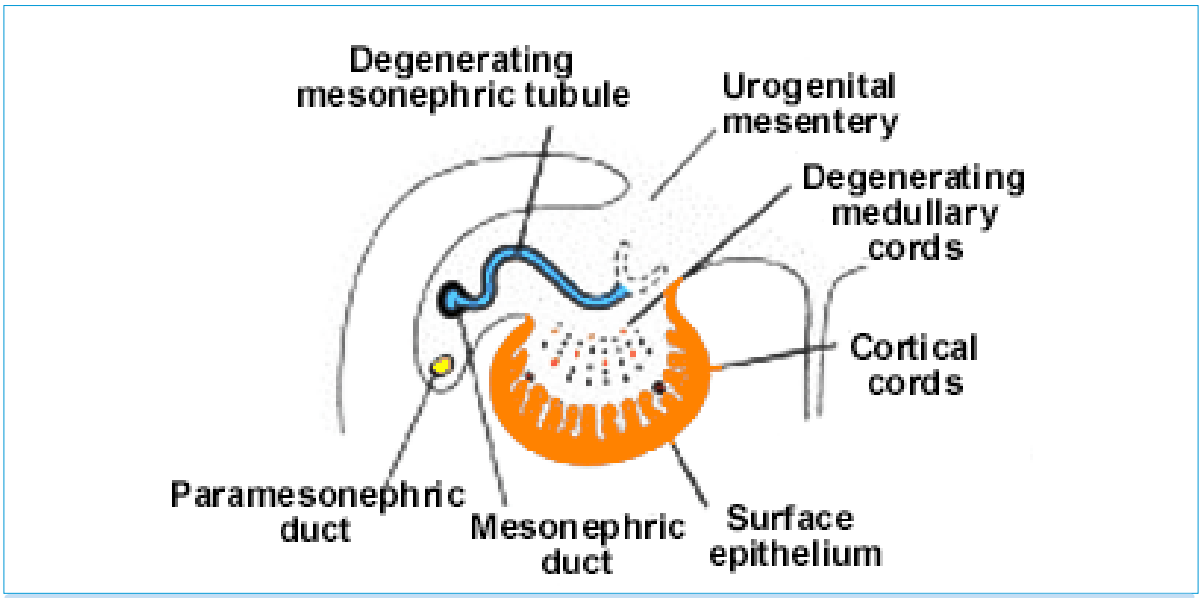


Figure 6-5: Ovarian differentiation. The primitive sex cords degenerate. There is no communication between the gonad and the mesonephros.

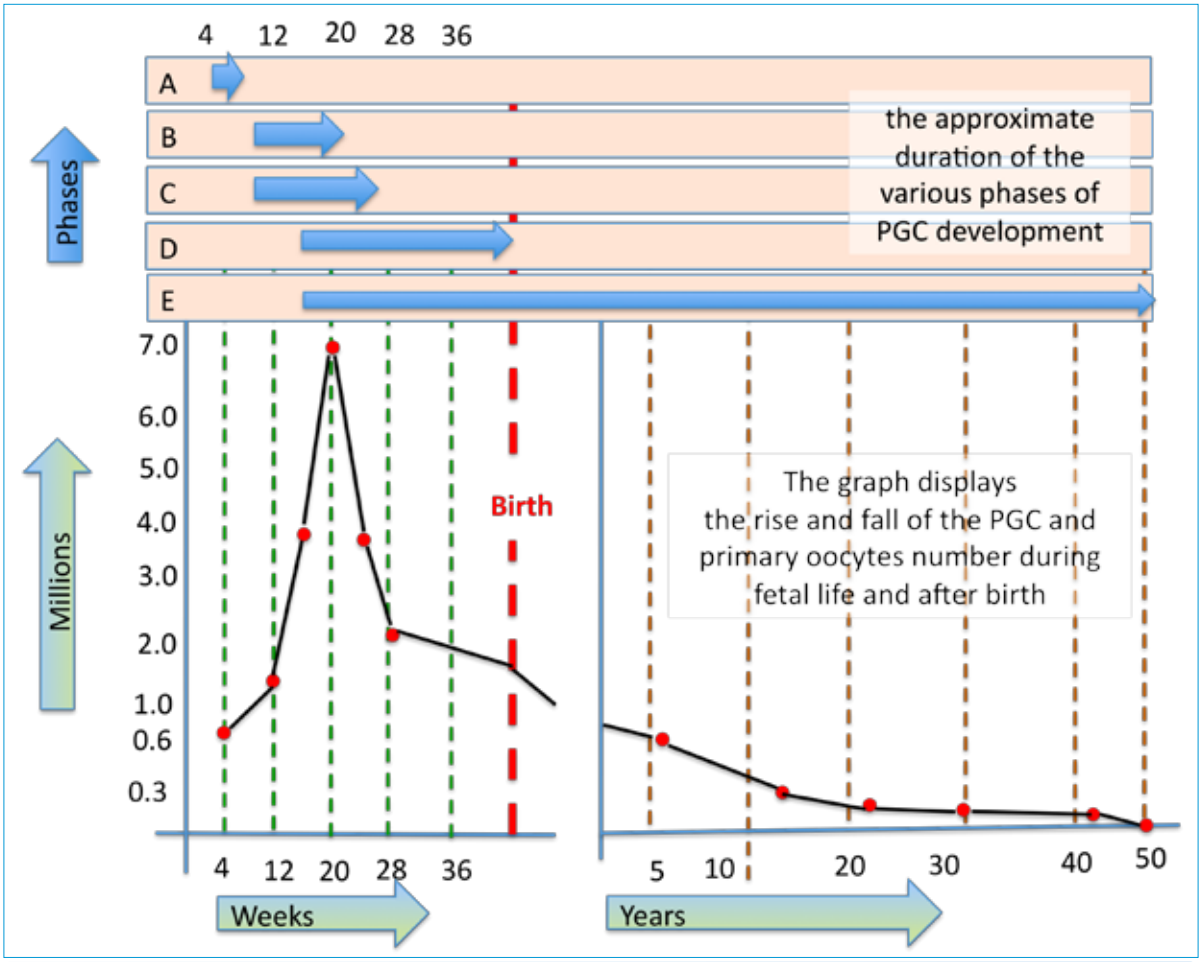


Figure 6-6: Development of PGC (primary gonadal cells), Oogonia, Primary Oocytes and Primoridial follicles during phases of life from conception to menopause.

Phase A: migration of the PGC into the genital ridge and multiplication by mitotic division.

Phase B: (weeks 9 - 22). Active proliferation phase of the PGC and differentiation into oogonia. The maximal number of PGC (7 million) is attained with 20 weeks.

Phase C: (weeks 12-25)The oogonia enter spontaneously into meiosis and become arrested in the diplotene of the prophase of the first meiosis (primary oocytes).

Phase D: (weeks 16 -29) Formation of primordial follicles

Phase E: Progressing follicular atresia from approximately the 20th week. Between 400,000 and 2 million primordial follicles remain at birth. The number at puberty is approximately 300 primordial follicles which then develop further between puberty and menopause.

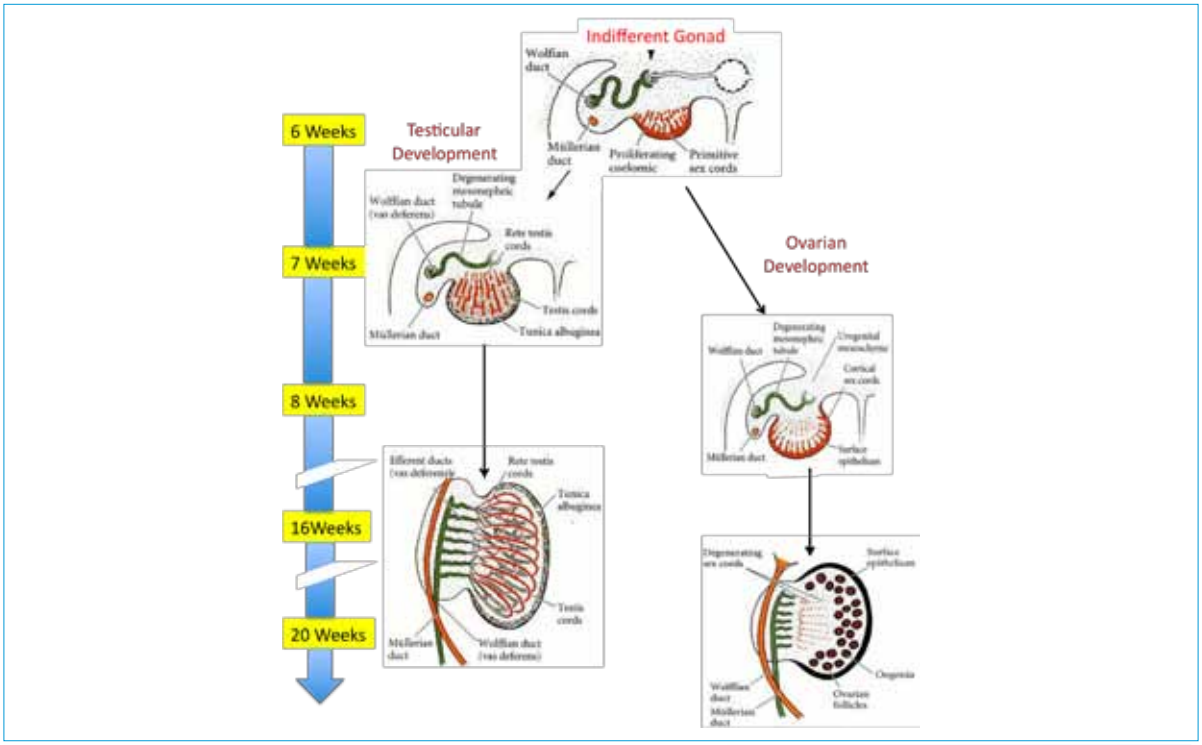


Figure 6-7: summary of gonadal differentiation

Differentiation of the genital ducts - The internal genital organs sex

⇒ The **Indifferent** stage:

Up to the 7th week the internal genital organs in both sexes consists of two pairs of canal on each side:

- The mesonephric (Wolffian) ducts: run on either side of the primitive gut as a longitudinal ridge, covered by the coelomic epithelium.
- The Paramesonephric ducts (Müllerian ducts): run lateral to the mesonephric ducts. It arises as a longitudinal invagination of coelomic epithelium that runs caudally. Initially it is like a solid cords, cranially opening into the coelomic cavity with a funnel-like structure (future ampulla of the fallopian tube). At its caudal part the Müllerian ducts pass medially across the front of the Wolffian ducts. Müllerian ducts from each side meet and fuse

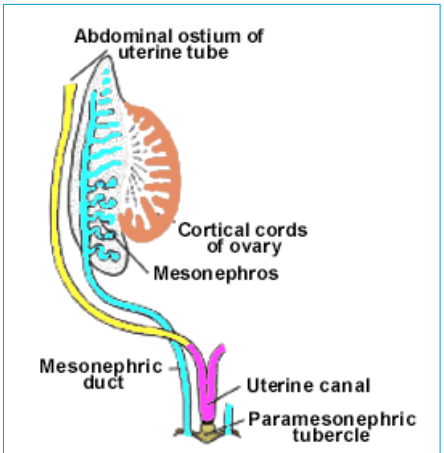


Figure 6-8: Stage of indifferent internal genital organs. In the female, the mesonephric ducts degenerate, while the paramesonephric ducts form the fallopian tubes and uterus.

as a single solid rod of cells. They further extend caudally until they make contact with the urogenital sinus producing a prominent elevation in its posterior wall, known as the Müllerian tubercle.

- At the point where the Müllerian tubercle reaches the urogenital sinus, a solid cord of epithelial cells derived from the urogenital sinus grows upwards (sinovaginal bulbs) increasing the distance between the tubercle and the urogenital sinus.

⇒ **Stage of ductal differentiation:**

Shortly following gonadal determination (8 weeks of intrauterine life) begins the process of ductal differentiation.

- **Differentiation of male internal organs**

The differentiation of the male ductal system begins around the 8th week and is controlled by two factors:

- The Müllerian inhibiting substance: a glycoprotein produced by the Sertoli cells. It is responsible for regression of the ipsilateral paramesonephric (Müllerian) ducts.
- The testosterone hormone: produced by Leydig's cells. It is responsible for the development and differentiation of the mesonephric duct (Wolffian) duct into the internal male genitalia (vas deference, epididymis, and seminal vesicles).

Both the MIS and testosterone acts on the ductal system on the ipsilateral side (the same side of its secretion) an example for local paracrain effect.

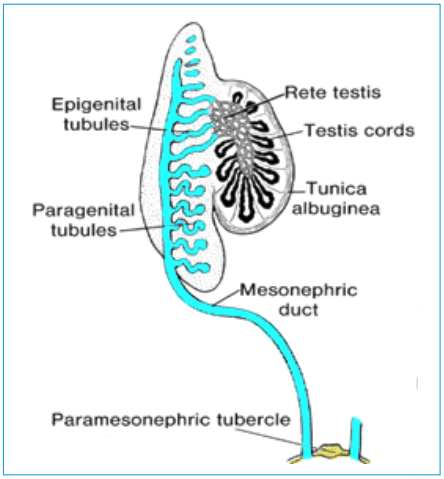


Figure 6-9: Differentiation of the male internal ductal system.

- Differentiation of Female Internal Organs:

During the **7th week** and in the absence of testes (i.e. absence of both MIH and testosterone) the **mesonephric duct** and its tubules atrophy and the **paramesonephric ducts** (Müllerian ducts) develop into the fallopian tubes, the uterus and the upper part of the vagina as follow:

- The fallopian tubes, and uterus:

- The solid core of the Müllerian ducts canalizes to form the fallopian tubes in its upper part. In its caudal part the two tubes meet and canalize, anterior to the mesonephric duct, to form the corpus of the uterus and the cervix and upper 1/3 of the vagina (The lower 2/3 of the vagina is derived from the urogenital sinus).

- By approximately the fifth month, the central core of this cord breaks down to form the vaginal canal.
- Remnants of the Wolffian duct: Sometimes the remnants of the Wolffian ducts form tubule like structures known as the epoöphorons, paroophorons and Gartner's duct. In adulthood these remnants may present as paraovarian, broad ligaments or vaginal cyst.

Thus the vagina has a dual origin; its upper 1/3 derived from the Müllerian tubes while its lower 2/3 is derived from the urogenital sinus.

The hymen marks the site from which the upward growth of cells from the urogenital sinus began. Thus its epithelium is derived from the urogenital sinus.

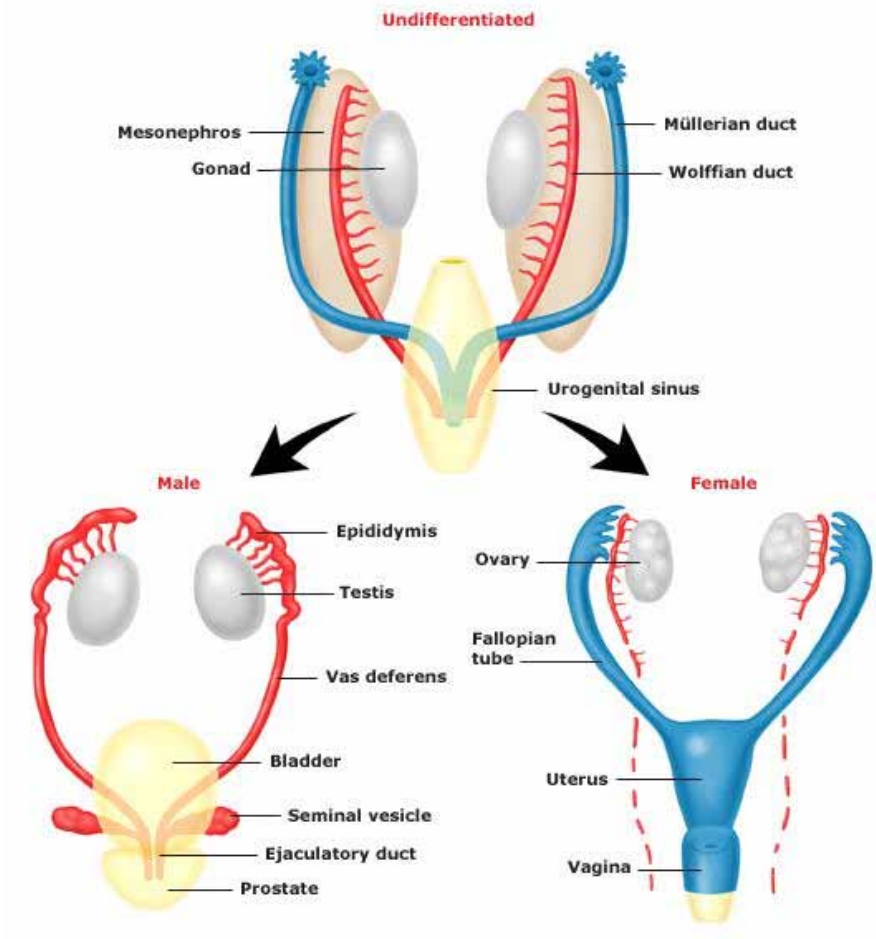


Figure 6-10: Summary of the differentiation of the tubal system in male and female

Differentiation of the External Genitalia

The indifferent stage:

In the indifferent stage both the urogenital sinus and the hind gut open into a common opening known as the Cloaca. On either side of the cloaca develops a pair of slightly elevated folds of mesenchymal cells known as the **cloacal folds**. Anteriorly the cloacal folds unite to form the **genital tubercle**.

In the mean time, another pair of elevated **genital swellings** appears on each side of the urogenital membrane. During the seventh week, a septum of mesodermal cells appears to divide the cloaca into an anterior part (the urogenital membrane) and a posterior part. Also during the 7th weeks the urogenital membrane dissolve and the urogenital sinus communicates freely with the amniotic cavity.

Unlike the internal genitalia where there are two duct systems, one for male and one for female, the external genitalia are derived from common anlagen, these are: the genital tubercle, the genital swellings, and the genital folds that are capable of development into male or female genitalia depending on the absence or presence of testosterone and its activation by 5 alpha reductase enzyme to the Dihydrotestosterone.

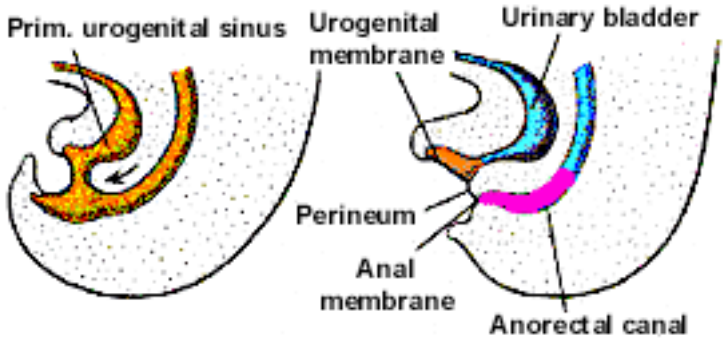


Figure 6-11: The cloaca is divided into the anorectal and urogenital regions as the urorectal septum contacts the cloacal membrane. The urogenital membrane and anal membrane then begin to break down. 50th days of gestation

⇒ The differentiation stage:

- Differentiation to male phenotype:

Under the influence of testosterone, masculinization of the genitalia begins to occur, and is completed by approximately the 14th week.

However, testosterone must first be converted to the active product Dihydrotestosterone (DHT) by the intracellular enzyme 5 alpha reductase.

- **Differentiation to female phenotype:**

In the absence of DHT (even if there is testosterone) the bipotential external genitalia differentiate into female. The genital tubercle elongates slightly to form the clitoris. The inner genital folds (urethral folds) develop into the labia minora. The labia majora develop from the genital swellings. Finally the urogenital membrane disappears, so that the vestibule communicates with the exterior through the vulva.

Ambiguous (masculinised) female genitalia may develop from abnormal sources of androgenic hormones. This may come from the adrenal (as in congenital adrenal hyperplasia) or if in pregnancy a mother was prescribed androgenic hormones during the critical time of external gonadal differentiation.

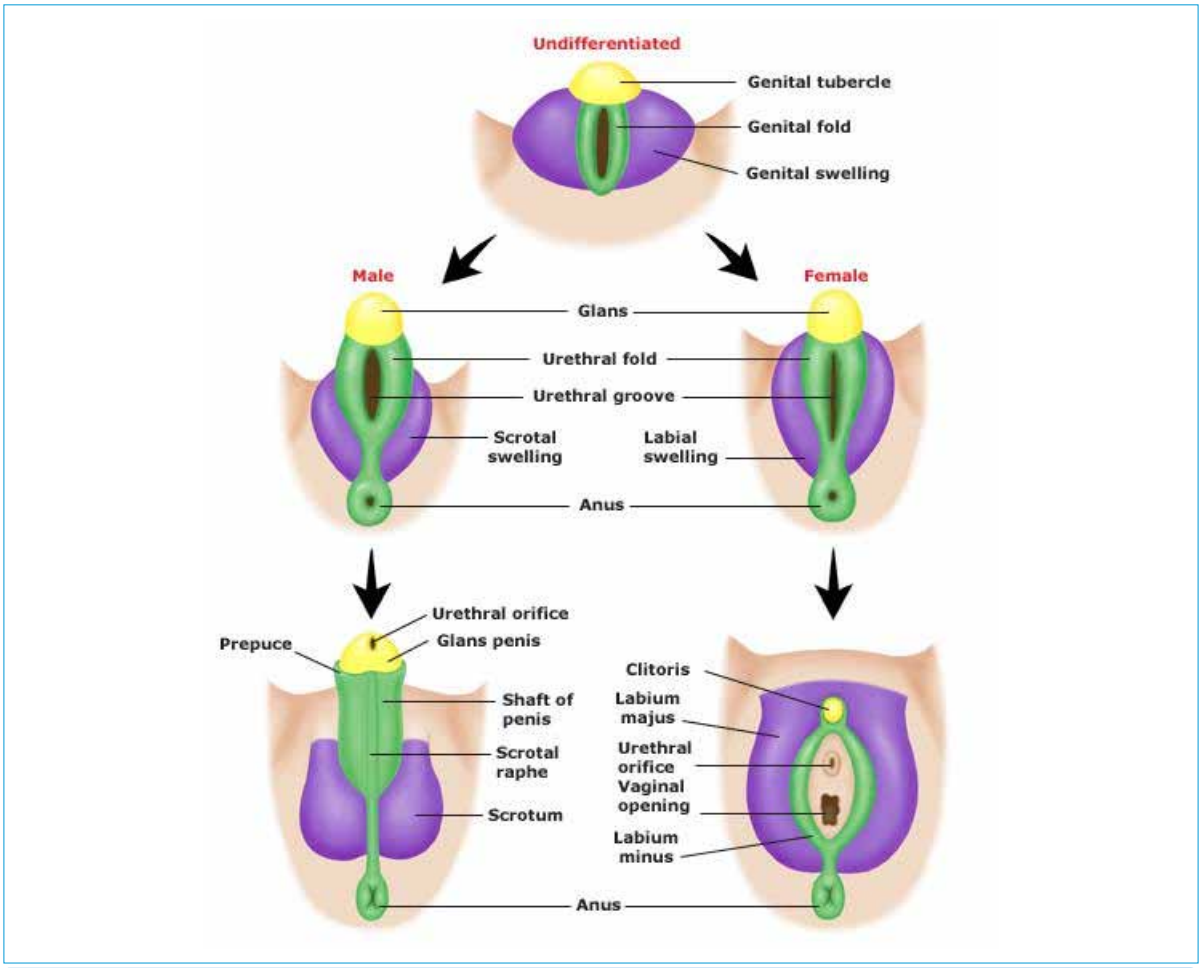


Figure 6-12: Summary of the differentiation of the external genitalia. In the female, the urethral folds remain unfused and will form the labia minora, while the genital swellings become the labia majora.

Clinical implications of abnormal sexual differentiation:

Understanding the sequence of normal sexual differentiation and the factors, which control it, is fundamental to proper management of its abnormalities. The clinical implications of abnormal sexual differentiation including clinical presentation and management are discussed in details in the following two chapters (chapters 7 and 8).

References and Further readings:

- Brennan J, Capel B. One tissue, two fates: molecular genetic events that underlie testis versus ovary development. Nat Rev Genet 2004; 5:509.
- MacLaughlin DT, Donahoe PK. Sex determination and differentiation. N Engl J Med 2004; 350:367.

Chapter 7

Abnormal Sexual Differentiation of the Female Genital Tract

Abnormal differentiation of the genital tract may occur as a result of defect in any one or more of the factors responsible for determination of sex i.e. chromosomal sex, gonadal sex, internal genital sex, and external genital sex. The condition may be recognized immediately at birth as Ambiguous Genitalia. Alternatively, it may not be diagnosed until later on at puberty as in some cases of primary amenorrhea (e.g. the XY female) or even as obstetric complications (e.g. recurrent miscarriage)

By the end of this chapter you should be able to:

- **Describe**: anomalies of the external genital organs (ambiguous genitalia) and its most common causes.
- **Describe**: anomalies of the internal genital organs (Müllerian Ducts Anomalies),its classification, clinical presentation and options of management
  - Obstructive anomalies: Imperforate hymen, cervical atresia, vaginal agenesis and vaginal septum.
  - Anomalies due to defect in Müllerian duct fusion:
    - Complete failure of fusion:
    - Partial failure of fusion:
  - Anomalies due to unilateral failure of Müllerian duct development: (associated with high rate of renal anomalies)
    - Unicorn ate uterus
  - Diethylstilbestrol Associated anomalies "DES"
- **Describe the Complications and Clinical Presentations of Uterine Anomalies:** in Gynaecology and in Obstetric patients

Anomalies of the external genital organs

Ambiguous Genitalia:

The term ambiguous genitalia describe genitalia with unrecognizable sexual features. In case of female fetuses, ambiguous genitalia result from in utero exposure to androgen

hormones during critical time of development of the external genital tract. This could result in variable degree of virilisation ranges from simple one with elongation of the clitoris and/or labial fusion to severe form in which a female newborn may be assigned to male gender.

In clinical practice the condition is most commonly associated with the genetic syndrome "congenital adrenal hyperplasia". This is an inherited autosomal recessive syndrome. It is characterized by deficiency of some of the enzymes involved in the biosynthesis of cortisol, the most common one is the 21-hydroxylase enzyme (the condition is discussed chapter 8).

In rare occasions the fetal exposure to androgen is due to administration of androgenic substances to pregnant mothers during the early weeks of embryogenesis.

Anomalies of the internal genital tract "Müllerian anomalies"

Normal development of the internal female genital tract (fallopian tubes, uterus, cervix, and the upper two thirds of the vagina) depends on three consecutive embryologic processes: first the differentiation of two paired mullerian ducts, second, lateral fusion of the lower segment of the mullerian ducts in the midline to form the uterus, cervix and upper two third of the vagina and finally resorption of the central septum between the two mullerian ducts in order to form a single uterine cavity and cervix.

The lower third of the vagina embryologically originates from the sinovaginal bulb. A normal patent vagina depends on complete fusion of the ascending sinovaginal bulb with the descending müllerian tubercle.

Failure of one or more of these processes will result in some form of anomaly of the genital tract.

Etiology of Mullerian Duct anomalies:

The pathogenesis of mullerian anomalies is not very well understood but in some cases there may be a genetic linkage as evident by the occasional association with other somatic anomalies and familial recurrence in some cases. In utero exposure of the fetus to teratogenic substances during a critical period of its development such as in case of exposure to diethylstilbestrol is also a recognized factor.

Frequency of Mullerian Ducts Anomalies:

The actual prevalence of müllerian anomalies varies depending on the source of data.

Among the general population it is around 2-3 % while it may be reach up to 8 or 10% among patients with recurrent pregnancy loss and/or preterm deliveries.

Classification of mullerian anomalies

Classification of mullerian anomalies is based on its embryological origin as well as its anatomical type(table 7-1).. Four classes of anomalies can be identified:

- Obstructive Mullerian anomalies.
- Fusion Mullerian anomalies.
- Agenesis / hypoplasia.
- Miscellaneous anomalies (difficult to classify).

The vaginal anomalies are usually considered separately since it is mostly obstructive in nature and the uterus is usually present

- **Obstructive Müllerian anomalies**: Obstructive Müllerian anomalies preclude the outflow of menstruation and allow the collection of blood in the uterus and the vagina. Patients usually presents with primary amenorrhea and/or pain due to accumulated menstrual flow. Management goals are to relief symptoms such as pain, as well as preservation of sexual and reproductive function.

The true incidence of obstructive Müllerian anomalies is unknown, but studies reports an incidence of between 0.1% and 3.8%.

a) Imperforate Hymen:

The hymen is present at the junction of the sinovaginal bulbs with the urogenital sinus; hence it is formed from the endoderm of the urogenital sinus epithelium. Normally it is perforated during embryonic life. The incidence of imperforate hymen is estimated around 1 in 2,000 girls or even less.

Clinical presentation and diagnosis:

Rarely an imperforate hymen may be discovered at birth because of the presence of a suprapubic mass "mucocolpos or hydrocolpos" which is formed by retention of fluid secretion behind the imperforate hymen. This fluid results from maternal estrogen effect on the vaginal epithelium and/or cervical glands. It may cause urinary obstruction due to pressure on the anterior urethra.

More commonly however an imperforate hymen remains undetected until puberty when repeated accumulation of menstrual flow in the vagina produce a condition known as "hematocolpos". The fluid component of the menstrual flow gets absorbed

and the remaining blood and debris acquire an altered "chocolate" thick appearance. In more advanced cases the uterus and the fallopian tubes become distended with retained menstrual blood resulting in "hematometra" and "hematosalpinx", respectively. Eventually the retained menstrual flow may trickle back, into the pelvic peritoneal cavity, with the risk of development of endometriosis.

Symptoms: Typically patients with imperforate hymen presents at puberty with primary amenorrhea despite apparently normal pubertal development. They often gave history of recurrent cyclic pelvic pain in the absence of menstrual flow. Another additional presentation is as an emergency case of acute urinary retention.

On abdominal examination, a suprapubic mass is rarely felt and if present it usually reflects a distended bladder rather than a hematocolpos.

On local inspection the accumulation of menstrual blood behind the hymen gives the blue bulging appearance pathognomonic of imperforate hymen (Figure 1).

Figure 7-1: A typical picture of imperforate hymen with the typical "bluish" bulge. The abdominal swelling is more likely a distended bladder

DD of Imperforate hymen: The differential diagnosis of imperforate hymen includes other obstructive conditions, some rare and others relatively common such as: Low transverse vaginal septum, Labial adhesions and vaginal atresia or agenesis (Figure 7-2)

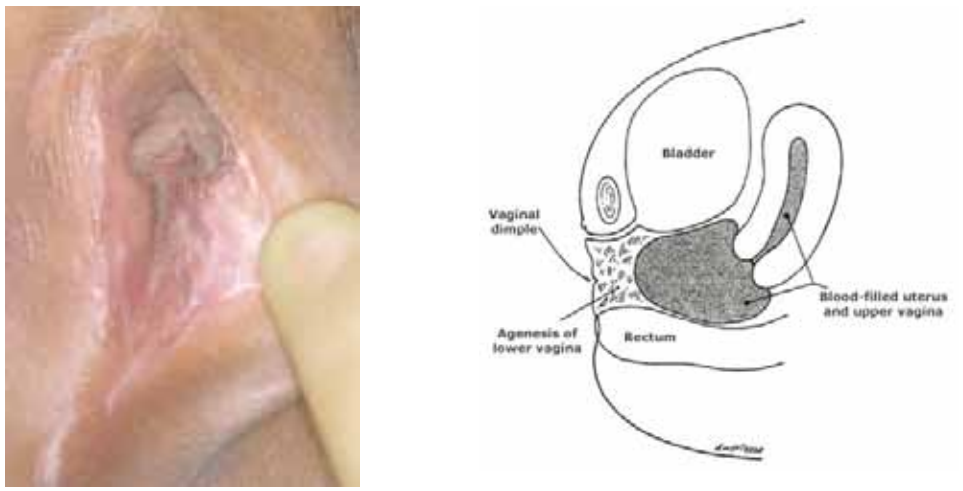


Figure 7-2: (left) Agenesis (atresia) of the lower vagina with a thick transverse septum. (Right) labial adhesions in young adolescent.

Diagnosis and investigations: Carful examination is important to distinguish between acquired conditions (labial adhesions) or imperforate hymen and other congenital obstructive conditions of the lower genital tract. A pelvic ultrasound scan or sometimes MRI may be required to confirm the diagnosis and demonstrate normal internal anatomy.

The treatment of imperforate hymen:

- The treatment is by surgical drainage of the retained contents "the hematocolpos". The operation involves making a cruciate incision in the hymen extending between 2, 10 and 6 o'clock. Because of the viscosity of this material, a double suction apparatus is sometimes required to drain it.
- The components of the hematocolpos are a very receptive medium for bacterial growth. Thus complete antiseptic measures should be undertaken and prophylactic antibiotics have been recommended. Most importantly NO vaginal examination or mopping inside the vagina should be made during or after the operation.
- The prognosis is generally good since long-term follow-up of patients with imperforate hymen reveals normal fertility rates. Imperforate hymen is usually not associated with any other Müllerian abnormalities.

b) Cervical Atresia:

Congenital atresia of the cervix is a relatively rare mullerian developmental disorder less than 100 cases have been reported in the literature. Patients present with primary amenorrhea

and cyclic pelvic pain, and the condition is often associated with absence of all or part of the vagina. Some cases are also associated with uterine anomalies. Endometriotic implants have commonly been described at the time of laparoscopy or laparotomy.

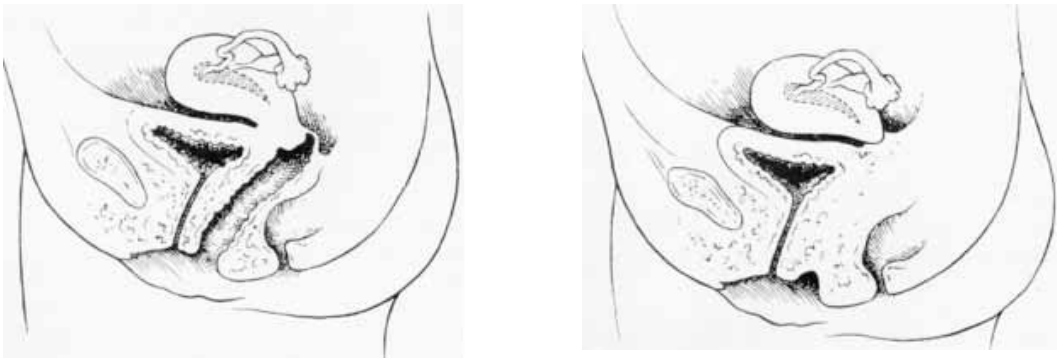


Figure 7-3: (Right) isolated cervical genesis, (left) vaginal and cervical agenesis

The optimum management of cervical atresia remains controversial. The options are between either conservative management in which a surgical canalization is performed in order to provide patients some potential (albeit limited) opportunity for fertility or hystrectomy. The choice depends on whether the vagina is present or absent and if the there are associated uterine anomalies.

C) Vaginal Agenesis:

As an isolated developmental defect there are two varieties of vaginal agenesis either complete or incomplete.

- Complete vaginal agenesis (Müllerian agenesis), the most common one (80%-90%) is the Rokitansky-Mayer-Küster-Hauser (RMKH) syndrome in which there is absence of most or all the entire vagina, all or almost all of the uterus and cervix. Ovarian function is normal thus growth and development are normal.
- Incomplete or partial vaginal agenesis is due to failure of canalization of the lower fifth to one third of vagina (the part made by urogenital sinus). Above which lie a well-differentiated upper vagina, cervix, uterine corpus, and fallopian tubes. This variant is due to different pathophysiologic events and more correctly classified as a variant of transverse vaginal septum.

Clinical Presentation:

- Symptoms: The condition usually presents at puberty with primary amenorrhea. In the rare cases the endometrium in rudimentary uterus may function causing cyclic abdominal or cramping pain.
- Signs: On examination the appearance of the vagina can be diverse; it can be completely absent, a short vaginal pouch, or a short vaginal dimple 12- cm superior to the hymenal ring.
- On rectal examination: the uterus is either absent or replaced by rudimentary structure.
- DD: The main differential diagnosis is from cases of androgen resistance syndrome or the XY female.
- Investigations: include karyotyping to exclude cases of androgen resistant syndrome (XY female), an ultrasound examination or if necessary magnetic resonance imaging examination for defining the uterus and detailed anatomy of the pelvic organs. Rarely if MRI cannot define the degree of uterine development, laparoscopy may be necessary to define the uterus and the ovaries.

Approximately one third of cases of mullerian aplasia are associated with renal anomalies. The most frequent renal anomalies are pelvic kidney, renal ectopia and unilateral aplasia. Skeletal anomalies, especially vertebral anomalies, are also not uncommon.

Treatment of vaginal atresia:

- The timing of treatment: The timing of treatment whether it is surgical or non-surgical requires certain level of psychological and sexual maturity. Surgical treatment is better planned to coincide with subsequent opportunity for intercourse in order to maintain vaginal patentcy. However it may be instituted sooner if a patient presents with vaginal outflow obstruction, abdominal or pelvic pain, or is at risk for secondary endometriosis.

- The objective of treatment: is to creat a functioning vagina. In the rare instances in which a well formed uterus and cervix are present it may be possible to restore potential fertility function through recanalization. Each case should be assessed carefully. Preoperative MRI is very helpful in assessing the status of the cervix. In

some cases laparotomy should be performed and if the cervix is atretic the uterus should be removed. In the majority of cases of mullerian aplasia it is hardly necessary to remove rudimentary uteri unless it is a functioning one.

- Non-surgical treatment (Frank technique or perineal dilation): The technique involves the forceful dilation of a shallow rudimentary vaginal pit with the sequential application of progressively wider and longer dilators. The goal is to create a blind-ending vaginal pouch. The technique requires patient motivation and compliance and has been successful in creating an adequate vagina for normal sexual activity.
- Surgical treatment of vaginal agenesis "vaginoplasty": Surgical treatment should be considered only when the patient wishes to become sexually active. The aim of surgical treatment is to create a neovagina. Various methods of vaginal reconstruction are described, the principle is dissection and creation of a space between the rectum posteriorly and the urethra anteriorly. This new "vaginal" space is maintained by using epithelial tissue obtained either from partial skin graft (as in McIndoe technique), an ileal loop or amniotic membrane. Any of these tissues may be stretched over a formed mould and should be kept in place until the epithelial graft is well taken after about 7-10 days. Subsequently the patient needs to reinsert the mould into the neovagina every day and night for 3 months, followed by nightly insertion for 3 more months to prevent contraction

Another simpler technique is William's vaginoplasty. In this operation vulval flap is used to make a vaginal tube. Still dilation is needed for a lengthy period, and the neovagina has a physiologically abnormal angle.

More recently a new technique using laparoscopic approach to create a neovagina have been described.

d) Transverse Vaginal Septum:

A transverse vaginal septum results from failure of fusion and/or complete canalization of the urogenital sinus and müllerian ducts. It is a very rare anomaly occurs in approximately 1 in 30,000 to 1 in 80,000 women. These septa may occur at any level in the vagina with the following frequencies: 46%, upper vagina; 40%, mid vagina; and 14%, lower vagina. Vaginal septa may be complete or incomplete with a small central or eccentric perforation, which is not adequate to drainage of the menstrual flow.

Complete vaginal septa have a similar presentation to cases of imperforate hymen. Except that on local examination the sign of a bulging bluish hymen is not present. Instead the vagina appears as a closed short pouch.

Patient with incomplete transverse septum may have little bleeding, however over time

they develop hematocolpos and hematometra and may complain of foul-smelling vaginal discharge. Ultrasonographic or magnetic resonance (MR) imaging helps to define the location and thickness of the septum and to differentiate between a high septum and congenital absence of the cervix.

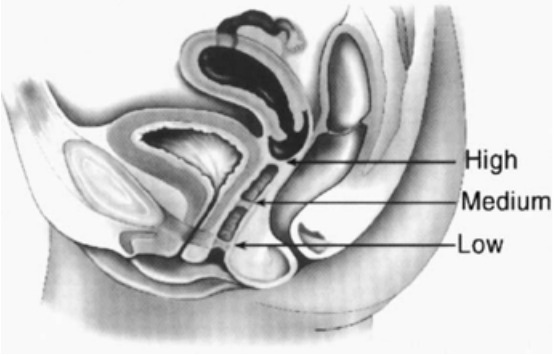


Figure 7-4: Transverse vaginal septum at different levels

The treatment depends on the thickness of the vaginal septum. Usually the septum is thin (< 1cm) and is treated more or less similar to cases of imperforate hymen. However, a thick septum requires referral to a tertiary centre for formal dissection in order to remove the septum. The vaginal skin in the upper and lower parts of the vagina should then be undermined, mobilized and stitched together with interrupted absorbable sutures. Subsequent utilization of the vagina is also necessary in order to prevent stenosis. In more advanced cases, split thickness skin graft may be required to join the two ends of the vagina. Transverse vaginal septum has been reported in diethylstilbestrol (DES) exposed females.

➢ Defects of Mullerian Duct fusion:

Non-obstructive anomalies of the mullerian ducts are relatively common (2-3%). Unlike obstructive anomalies that usually presents with primary amenorrhea, fusion anomalies are often associated with gynecological as well as obstetrics complications such as infertility, recurrent pregnancy loss and poor obstetrics outcome in pregnancy. Some case where there is partial obstruction e.g. a unilateral rudimentary horn, may present with primary cyclic dysmenorrhea.

Anomalies of lateral fusion of the mullerian ducts

This may be partial or complete failure of fusion.

- **Complete failure of fusion of mullerian ducts**: "**didelphic uteri:**

This condition is characterized by duplication of the vagina, uterus and cervix.

- Symptoms: usually asymptomatic until menarche. The most frequent complaint is failure of a tampon to obstruct menstrual flow.

  Occasionally one side may be obstructed. A patient with such anomaly may have cyclic pelvic pain, despite the presence of normal menstrual flow. In those cases there is often ipsilateral renal agenesis. Early diagnosis and excision of the obstructing vaginal septum preserve fertility and prevent development of endometriosis.

  Effect on fertility and pregnancy: The fertility is usually not affected but patients has high spontaneous abortion rate (40%).

  The treatment Surgical treatment is only indicated if there is vaginal obstruction in order to preserve reproductive capacity and prevent impairment of the uterus and tubes on the obstructed side, reduce the risk of development of endometriosis and pelvic adhesions.

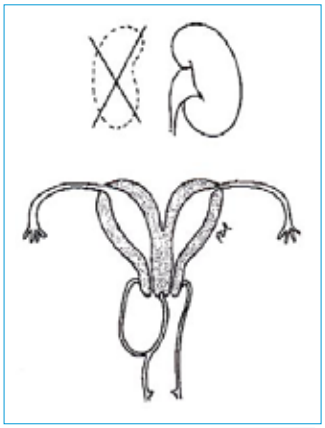


Figure 7-5: Uterus didelphys with obstructed hemivagina with ipsilateral renal agenesis

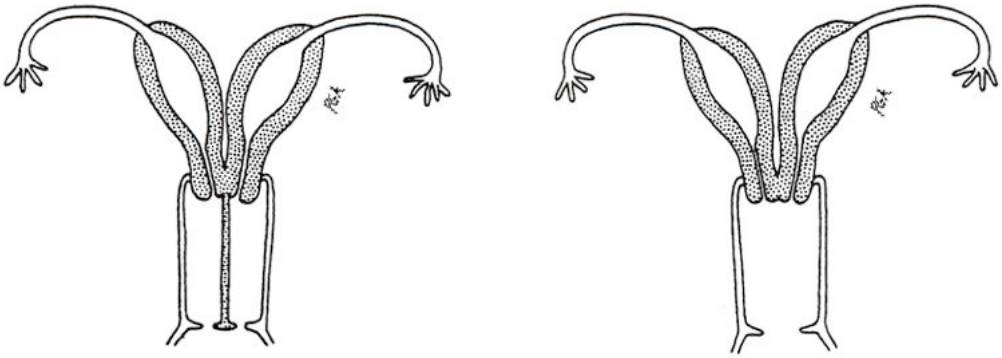


Figure 7-5: Left: Uterus didelphys with vaginal septum. Rt: wit normal vaginal

- **Partial failure of Mullerian tubes fusion:**
  - **Bicornuate Uterus**: In this anomaly, the lower uterus and cervix are normally fused, but the uterine chamber is divided into 2 separate but communicating endometrial cavities with a muscular uterine septum which varies in length, either partial or complete septum (the septum reach down to the cervix). The complete verity could be "**bicornuate unicollis**" if the septum extends to the internal os, or **"bicornuate bicollis"** if the septum reach down to the external os. Externally, the uterus appears as formed of two horns and not single uterine body.

- Obstetric complications of Bicornuate uterus: The potential complications include e.g. early miscarriage, preterm labor and breech presentation. The rate of this complications depends on whether the bicornate uterus is partial or complete.
- **Septate Uterus:** Septate uterus is the most common structural abnormality of all müllerian duct defects. In this condition the two mullerian ducts have completely fused together but there is variable degrees of failure of resorption of the intervening fibromuscular septum. A total failure in resorption can leave a longitudinal vaginal septum (a double vagina). An important feature that differentiates septate from bicornuate uterus is that in the former the uterus externally appears as a normal single uterine body.

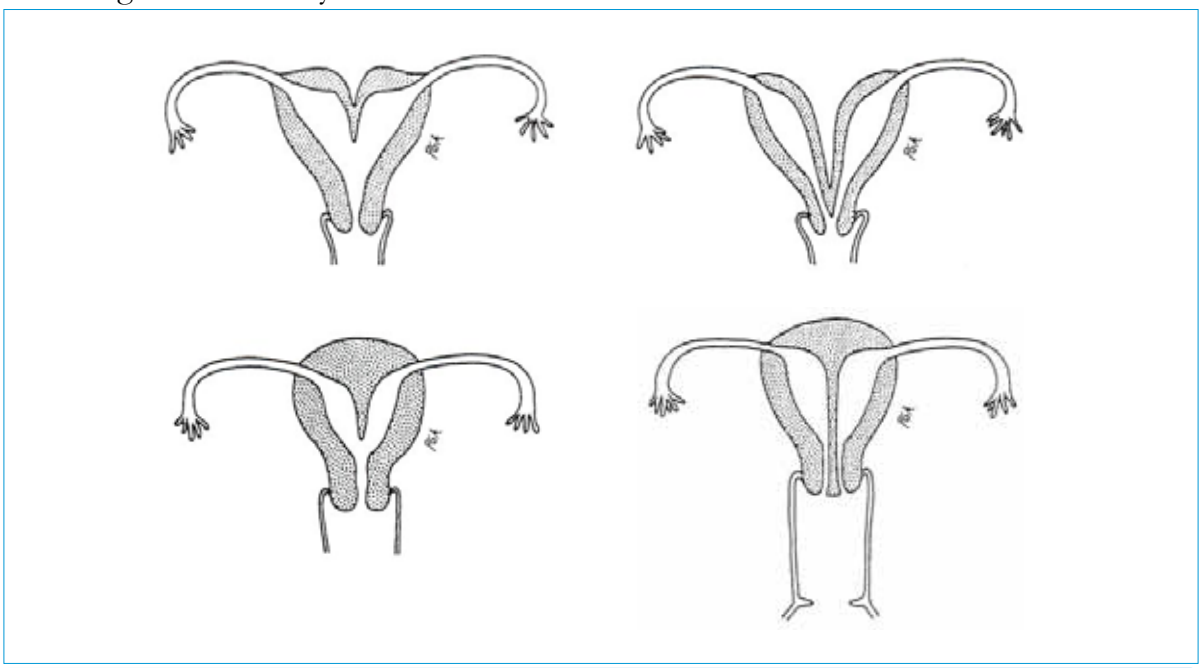


Figure 7-6: The upper row: partial (left) and complete (right) bicornuate uterus
Septet uterus:
Lower row: septat uterus (Left) partial septum and (Right) complete septum reaching external os "bicornuate bicollis"

The differentiation of a bicornuate uterus from a septate uterus is crucial for several important reasons; a bicornuate uterus is associated with much lesser reproductive problems, but septate uterus has a high association with reproductive failure. Additionally, the corrective surgical approaches markedly differ in the two cases.

- For bicornuate uterus the aim of surgical correction is unification of the two cavities. Strassman procedure and its modified approach is the surgical treatment of choice for bicornuate uterus and didelphys uterus. It involves the removal of the septum by wedge resection, with subsequent unification of the 2 cavities. It is

a major surgery that is only reserved for women who have experienced recurrent spontaneous abortion, midtrimester loss, premature birth, and in whom no other etiologic factor has been identified.

- Septate uterus is not a cause of infertility but associated with the poorest reproductive outcomes of all mullerian duct anomalies, in the form of recurrent spontaneous abortion, second-trimester loss, or preterm delivery. Patients with such history in whom no other cause(s) is identified will benefit most from surgical excision of the septum. Treatment by hysteroscopic resection, a day case surgery, and it yield excellent results. The reported post surgery miscarriage rate around 10% compared with a rate 80% without surgery.

- **The Arcuate Uterus:** In this anomaly there is a small indentation at the uterine fundus. It is the most commonly observed uterine anomaly detected on hysterosalpingography findings. Arcuate uterus is benign condition with probably has no consequences and require no treatment.

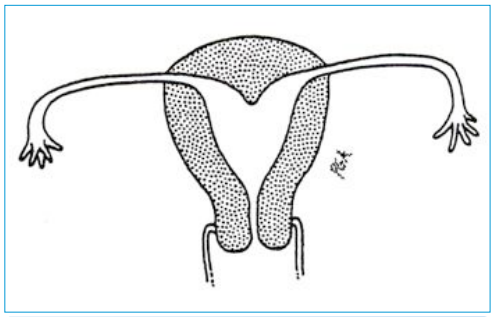


Figure 7-7: The Arcuate uters

Anomalies due to unilateral defects of Mullerian duct development

- **Unicornuate uterus:** Failure of development of one mullerian duct results in **"unicornuate uterus**" where there is a single uterine horn, single cervix and vagina. There is almost always a missing kidney and ureter on the same side. Such a uterus can support a pregnancy but there is an increased rate of obstetric complications.

- In a rare type, there may be a unilateral non-functioning rudimentary horn. If it is a functioning one it may be the site of pregnancy with subsequent high risk of obstetric complications. Most complications occur within the first 20 weeks of gestation and can result in abortion, uterine rupture, and maternal death.

- A non-communicating functioning horn can be a cause of chronic pain and surgical exesion is indicated. Excision of a rudimentary horn can now be accomplished through laparoscopic hemi-hysterectomy.

- Cases of unicornuate uterus should undergo urological assessment because of high rate of associated urological anomalies (44%). Associated urological anomalies include ipsilateral renal agenesis at a rate of 67%, horseshoe kidneys, and ipsilateral pelvic kidney at a rate of 15%.

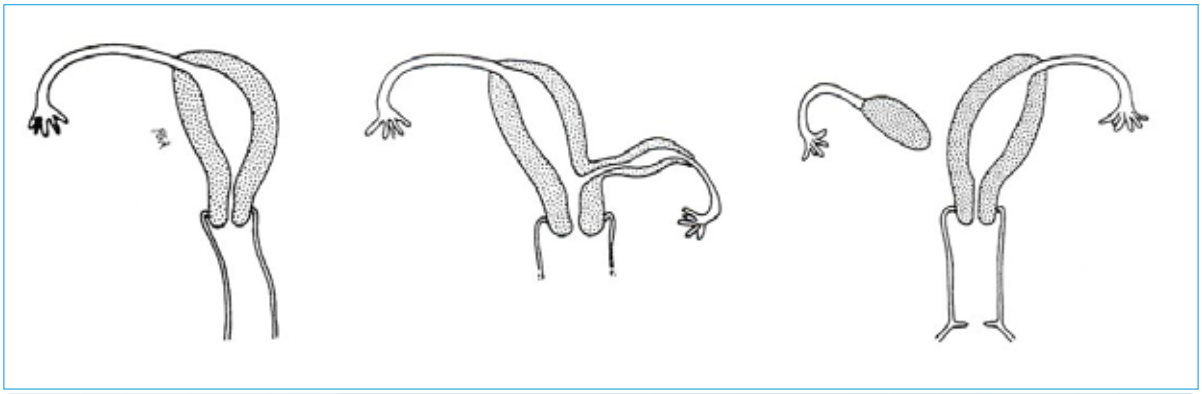


Figure 7-8: Left: Unicornuate uterus, Middle: horn communicating with the uterus, Right: horn not communicating with the uterus.

Diethylstilbestrol Associated anomalies "DES"

DES is a synthetic estrogen that was prescribed to women for recurrent pregnancy loss, premature delivery, and other pregnancy complications during the late 1940s and early 1970s. Latter it was realized that the exposure to high level of estrogen during mullerian development was associated with increased rate of vaginal clear cell adenocarcinoma and various benign vaginal, cervical and uterine abnormalities.

DES-related uterine anomalies are quite common in women with a history of in utero DES exposure. Uterine anomalies associated with in utero DES exposure include a T-shaped endometrial cavity, a widened lower uterine segment, mid-fundal constrictions, endometrial filling defects, irregular margins, and a hypoplastic uterus.

Cervical structural abnormalities were also detected in 44% of these women. These anomalies included hypoplasia, an anterior ridge, a collar, and pseudopolyps. Vaginal adenosis and vaginal constrictions are associated abnormalities.

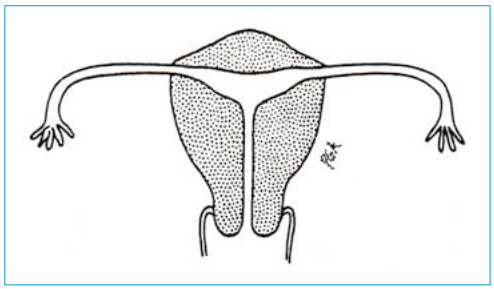


Figure 7-9: T-shaped Uterus

This group of anomalies are probably associated with high rate of obstetric complications although no specific anomaly has been associated with any form of adverse obstetric outcome. However cervical incompetence may be an associated factor in these women and cervical cerclage is the only prophylactic treatment that can be offered.

Complications and Clinical Presentations of Uterine Anomalies

Müllerian duct anomalies (MDAs) are often recognized after the onset of puberty.

- Gynecological complications: At puberty, young women with müllerian anomalies often present with menstrual disorders (e.g. primary amenorrhea, or dysmenorrhea in unilateral functioning rudimentary horn, which fails to communicate with the other horn). Later presentations include infertility and obstetric complications.

- Obstetric complications include: repeated miscarriages, premature labor intrauterine growth restriction, malpresentation, or retained placenta.
  - Recurrent miscarriages: due to uterine anomalies result from failure of the uterus to accommodate the growing pregnancy.
  - The timing of miscarriage is usually in second trimester. The duration of gestation before miscarriage occurs tends to increase with repeated pregnancies. Hence, conservative management may eventually lead to the achievement of a successful pregnancy.
  - Early first trimester miscarriage is more common in cases of septet uterus if the developing embryo gets implanted on the septum where there is often deficient vascular development.

  - Delayed obstetric complications: in the form of malpresentation, breech or transverse lie occurs at a high rate in cases of uterine anomaly due to loss of the normal pear-shaped uterine cavity, which is important for the normal presentation.

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Chapter 8

Disorders of Sexual Differentiation

Gynecologists and obstetricians are likely to encounter cases associated with disorders of sexual differentiation at several occasions. A typical although rare occasion is the birth of a newborn with ambiguous genitalia. But more commonly when dealing with young adolescent presenting with primary amenorrhea, or delayed puberty. Lastly disorders of sexual differentiation may be responsible for some cases of menstrual disorders usually oligomenorrea or infertility.

This chapter describes the most common causes of disorders of sexual differentiation and the approach to the diagnosis and principle of management of ambiguous genitalia at birth.

By the end of this chapter you should be able to:

- **Define Disorders of sexual differentiation "DSD":**
- **List the classification of the main categories and causes of DSD:**
  1. **DSD due to Sex Chromosome disorders**:
     - Klinefelter's Syndrome (47 XXY male
     - XX Male
     - Turner Syndrome 45XO
     - XX, 46 gonadal dysgenesis
     - Ovotestes (pure hermaphrodite)
  2. **46, XX Disorder**
     - CAH (congenital adrenal hyperplasia)
     - Maternal androgen intake, maternal virilising tumor
     - Placental Aromatase enzyme deficiency
  3. **46, XY Disorder:**
     - Inadequate secretion of testosterone: Leydig Cell aplasia or abnormality in Luteinizing Hormone Receptors.
     - Disorder of testosterone synthesis.
     - Inability of target tissue to respond to androgen appropriately: Androgen insensitivity syndrome.
     - 5α-Reductase Deficiency:
     - Persistent Müllerian duct syndrome.
     - The Vanishing testes syndrome
     - Gonadal dysgenesis syndrome
  4. **Unclassified group of DSD:**
     - Mayer-Rokitansky-Küster-Hauser Syndrome
- **Describe the Evaluation And Management Of The Newborn With Ambiguous Genitalia:**
  - Definition
  - DD of Ambiguous genitalia
  - Principle of management

Definition:

Disorders of sexual differentiation refer to abnormality in one of the elements of sex determination i.e. chromosomal, gonadal, or anatomic sex, so that it becomes incompatible with each other (e.g. XY female).

Disorder of sexual differentiation "DSD" covers wide spectrum of clinical presentations. Some of the disorders may present at birth as in cases with ambiguous genitalia others may not be diagnosed until puberty as in some cases of primary amenorrhea with or without virilisation or during investigation for infertility.

Classification of the causes of disorders of sexual development (DSD):

The term "Disorders of sexual Differentiation" has replaced many of the pervious terminologies such as intersex, hermaphroditism, XY female...etc. current classification is more appropriately based on chromosomal sex. Accordingly four major categories of DSD have been identified within each category specific diagnoses can be made (table 9-1).

1. DSD due to Sex Chromosome disorders.
2. DSD with "normal" 46, XX : In this category the ovaries are present but external genitalia exhibiting evidence of masculinization (previously known as female pseudohermaphroditism).
3. DSD with "normal" 46, XY: In this category testes are present but genital ducts and/or external genitalia incompletely masculinized (previously known as male pseudohermaphroditism).
4. Unclassified group of DSD.

Disorders of Sexual Differentiation due to Sex Chromosome disorders

➢ Klinefelter's Syndrome (47 XXY male):

It is the most common major abnormality of sexual diffe rentiation occurs in 1 of 1000 to 500 live born males. The classic 47,XXY complement arises as a result of nondisjunction of the sex chromosomes during the first or second meiotic division in either parent, or less commonly, through mitotic nondisjunction in the zygote at or after fertilization.

Clinically the syndrome is characterized by, eunuchoidism (hypgonadism), gynecomastia, azoospermia, increased level of gonadotropin (FSH and LH), .and small, firm testes

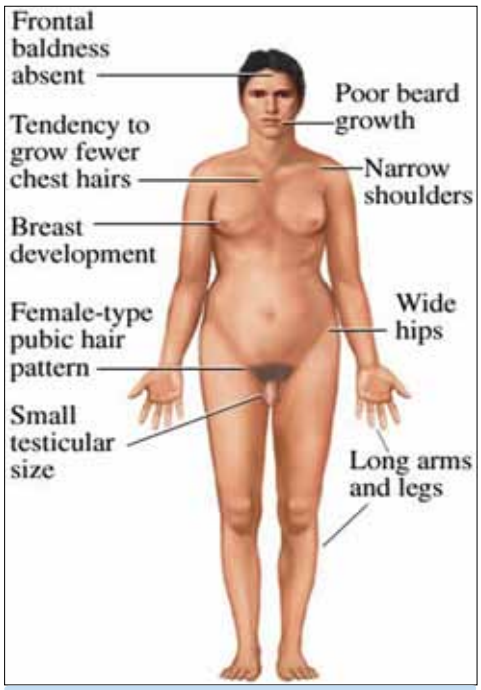

Figure 8-1: Klinefelter's Syndrome (47 XXY male):

➢ 46 XX Males:

In the XX male syndrome the affected individual appears as a normal male, but has a female genotype (two X chromosomes) due to translocation of the SRY gene.

Although patients with XX male have no genital abnormalities, but they have phenotypic features of Klinefelter's syndrome, including hypogonadism, gynecomastia, azoospermia, and hyalinization of seminiferous tubules with altered hormonal levels at puberty (low testosterone, increased level of gonadotropin).

➢ Turner Syndrome "45 X0":

In Turner's syndrome there is only one normally functioning X chromosome the other one is lost through non-disjunction in gametogenesis or an error in mitosis. The syndrome is characterized by premature attrition of oocytes due to apoptosis so that at birth few or no oocytes remain in the ovaries, which become streaked white, fibrous tissue. Turner syndrome affects approximately 1 out of every 2,500 female live births worldwide.

Clinical features: Clinically the syndrome is associated with four classic features: female phenotype, short stature, lack of secondary sexual characteristics, and a variety of other somatic abnormalities (Figure 8-2). Nevertheless the two most pathognomonic features of Turner syndrome are short stature and sexual infantilism (i.e. absent secondary sexual character) due to loss of ovarian function.

Patients usually presents with primary amenorrhea and delayed puberty. However in 2% to 5% of Turner patients, spontaneous menses may occur with a potential to achieve pregnancy independently. This can happen in women with mosaicism for a normal 46,XX cell line, a 47,XXX cell line, or distal Xp deletion.

Hormonal Studies: Both estrogen and androgen are decreased, and levels of FSH and LH are increased.

Prenatal diagnosis: During prenatal ultrasound scanning some ultrasound markers (increased nuchal translucency, lymphedema, cystic hygroma, coarctation of the aorta, renal anomalies) may suggest the presence of turner syndrome and prompt genetic amniocentesis. Most conceptions with 45X0 abort spontaneously in early pregnancy.

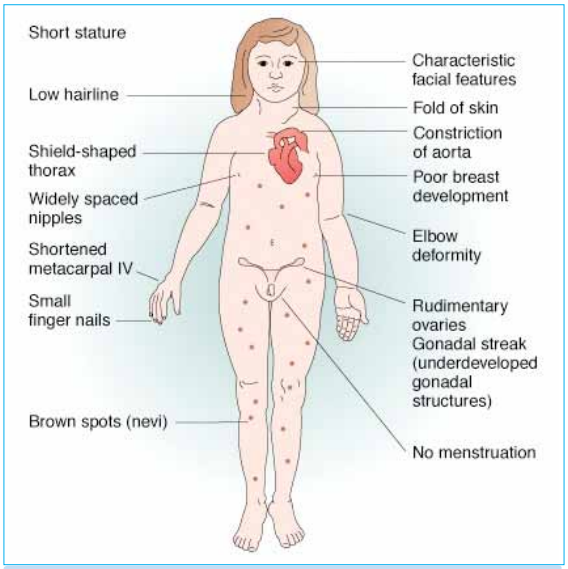

Figure 8-2: Spectrum of features of Turner syndrome

Management: the principle of management of patients with Turner syndrome includes:

- Hormonal replacement therapy (estrogen and progesterone) starting around 12 years of age.
- Administration of growth hormone to achieve increased adult height.
- Ultrasound screening for renal and cardiac abnormalities.
- Genetic studies for possible occult Y chromosomal material (45,X/46,XY mosaicism). Cases with occult Y chromosome should be advised for prophylactic gonadectomy because risk of gonadoblastoma, an in-situ germ cell cancer, is 7% to 30%. Gonadoblastoma is associated with dysgerminoma or other germ cell neoplasms in 50% to 60% of cases, sometimes associated with virilisation.
- Typical cases of Turner syndrome are sterile. However reproduction has been achieved using assisted reproductive technology through ovum donation. Ethically this approach is not universally acceptable and it is prohibited on Islamic ethical principles.

➢ **46,XX "Pure" Gonadal Dysgenesis**:

Patients with 46,XX "pure" gonadal dysgenesis are clinically and hormonally similar to those with Turner's syndrome but with out the physical stigma of Turner syndrome.

The condition may be familial with an autosomal recessive transmission.

The treatment involves only cyclic estrogen and progesterone replacement therapy.

➢ **Ovotesticular disorder or True Hermaphroditism**

True hermaphrodites are individuals who have both ovarian and testicular tissue either one on each side or both tissues on both sides. The most common karyotype is 46,XX which is approximately 60%; 33% are mosaics with a second cell line containing a Y chromosome (46,XX/46,XY; 46,XX/46,XXY), and 7% are 46,XY.

On examination both the external genitalia and internal duct structures of true hermaphrodites display gradations between male and female. In most patients, the external genitalia are ambiguous.

The most important aspect in the management of true hermaphroditism is the decision on gender assignment, which should take in consideration, among other factors, the functional potential of the chosen gender.

46, XX Disorder of Sex Differentiation

Masculinized Female (Female Pseudohermaphroditism)

This category constitutes the most common type of DSD. In this category patients have 46,XX karyotype with normal ovaries and Mullerian development, but variable degree of masculinization of the external genitalia. The most common causes of masculinized female include:

- Congenital Adrenal hyperplasia "CAH": which constitute 60% of the causes of ambiguous genitalia in the newborn.

- Other rare causes: include maternal ingestion of androgens and virilizing tumors in the mother.

➢ Congenital adrenal hyperplasia "CAH":

CAH is an autosomal recessive disorders resulting from deficiency of one of the five enzymes required for the synthesis of cortisol in the adre-.(nal cortex (Figure 8-3

Clinical manifestation of CAH depends on which enzymatic defect is present. Only deficiencies in 21-hydroxylase, *CYP21* and 11-hydroxylase, *CYP11* result in masculinizing disorders (to a lesser extent *3β2HSD)*. Of those the most common is deficiency of 21-hydroxylase (*CYP21)*, accounting for more than 90 percent of cases.

CAH in Male

Deficiencies in the other enzymes namely *3β2HSD*, *CYP17,* and *StAR* block cortisol synthesis as well as gonadal steroid production.

Thus, in boys it causes variable degrees of undermasculinization, whereas girls generally have normal external genitalia.

Pathogenesis: Deficiency in cortisol trigger the production corticotropin-releasing hormone and ACTH by the hypothalamus and pituitary respectively. Consequently, the adrenal glands become hyperplastic, but because of the block at 21-hydroxylase *"CYP21",* steroid precursors namely 17-hydroxyprogesterone accumulate proximal to the blocked pathway. This leads to two problems:

- The excess amount of 17-hydroxyprogesterone *is converted to androgens including testosterone and dihydrotestosterone which is responsible for virilisation of female fetuses.*
- Deficiency in production of Aldosterone*: which is necessary for normal retention of sodium by the kidney, and in its absence, a "salt wasting" disorder occurs* with consequent failure to thrive, dehydration, hyponatremia, and hyperkalemia typically at 7 to 14 days of life

The clinical features in CAH:

Two types of clinical presentation associated with CAH due to 21α-hydroxylase deficiency have been described:

- Classic presentation: which comprises two forms; the salt-wasting type that occur in 75% of cases and a simple, virilizing type with normal aldosterone synthesis (non salt wasting type).
- Non-classic presentation: A mild verity that initially may be asymptomatic but become associated with signs of late onset androgen excess. In such cases untreated male and female neonates progressively shows virilisation, experience rapid somatic growth and skeletal maturation leading ultimately to short stature at school age

  Other late consequences of CAH include reproductive abnormalities in adult females and male such as anovulatory menstrual cycles in females and in males testicular masses (adrenal rests), Leydig cell dysfunction, and abnormal semen analyses may be seen.

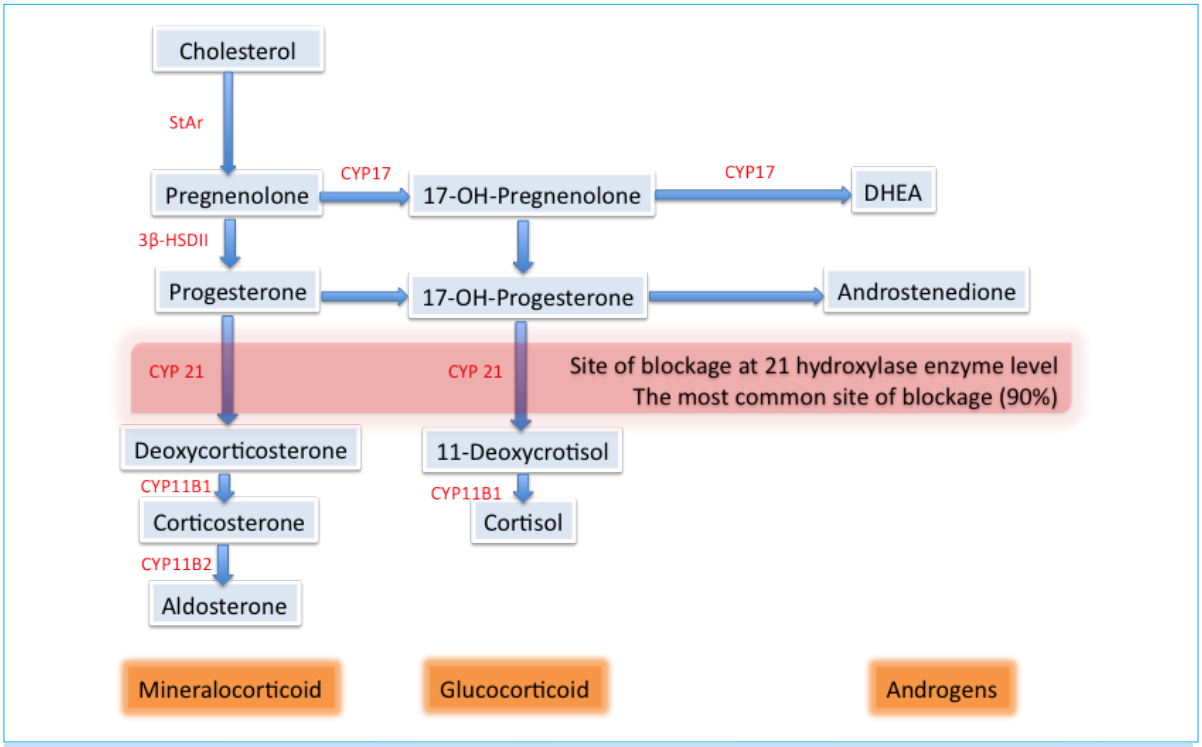

Figure 9 - 2: The steroid biosynthetic pathway. The five genes and the enzymes they encode are include CYP21: 21-hydroxylase; CYP11: 11β-hydroxylase, 18-hydroxylase and 18-oxidase; CYP 17: 17α-hydroxylase and 17,20 lyase; 3β2HSD: 3β–hydroxysteroid dehydrogenase; and StAR: side chain cleavage enzyme.

Principle of Management of CAH:

- Emergency treatment: CAH with salt-wasting complication is a life-threatening emergency that requires immediate intervention by specialized pediatric endocrinologist.
- Cases with ambiguous genitalia require referral to tertiary center for multidisciplinary management (see management of ambiguous genitalia). In those cases the internal genital tracts in female is intact and normal.
- Management of future pregnancies: patients at risk of giving birth to child with CAH because of previous history of affected offspring or known family history of carriers should be referred for specialized center with experience in genetic counseling prenatal diagnosis and treatment of such cases.

Genetic counseling, prenatal therapy and Prenatal Diagnosis of 21OHD:

CAH is one of the few genetic disorders that are amenable to transplacental therapy with the objective of ameliorating adverse effects of excess androgen on the fetus.

The principle of prenatal therapy is based on administration of steroid before the 8th week of gestation, prior to the onset of adrenal androgen secretion in order to suppresses fetal pituitary ACTH output therefore decreases the stimulation of fetal adrenal secretion of cortisol and the accumulation of androgenic substances.

However administration of steroid to all at risk women means that 7 out of 8 fetuses will unnecessary receive steroid until term (*The risk of inheritance of autosomal diseases when both parents are carrier is 25% (1 in 4). Since ½ of the fetuses are males then 7 out of 8 fetuses do not require treatment*). This involves ethical and medical issues. Therefore it is important to employ prenatal diagnosis to identify the affected fetus that benefit from steroid therapy.

Choice of Steroid Therapy

Dexamethasone: is the steroid of choice because it binds minimally to cortisol-binding globulin in the maternal blood, and is not inactivated by placental 11β-hydroxysteroid dehydrogenase enzyme. Thus, it crosses the placenta and suppresses fetal ACTH secretion with a longer half-life than other synthetic steroids.

The optimal dosage and timing 20 μg/kg/day of dexamethasone per maternal pre-pregnancy body weight, in three divided doses, starting as soon as pregnancy is confirmed, and no later than 9 weeks after the last menstrual period.

Prenatal diagnosis: Recently the advances in DNA analysis have enabled prenatal molecular genetic diagnosis of 21CAH from fetal DNA, which can be obtained by chorionic villus sampling "CVS" or Amniocentesis. The latter is performed if CVS is unavailable and in such instances, the supernatant is used for hormonal measurement (17-hydroxyprogesterone) and the cells are cultured to obtain a genotype through DNA analysis.

If the fetus is determined upon karyotype to be a male, or an unaffected female upon DNA analysis, treatment is discontinued. Otherwise, treatment is continued to term.

More recently it is possible using molecular biology studies not only to predict the risk of a couple having an affected child, but also the likely clinical form of the disease. Therefore, genotypes of severe mutations would motivate prenatal treatment, whereas genotypes of less severe mutations would not. Furthermore a less severe genotypes in the newborn would allow for modification of steroid treatment to minimize side effects

- **Maternal androgens**: virilisation of female fetus from maternal source of androgens may be through:

- Maternal intake of drugs with androgenic effects: The typical example is the use of progestational agents that might have androgenic effect during the first trimester of pregnancy. These drugs were thought to avoid spontaneous miscarriages in patients with history of habitual abortion.
- Functioning tumors: various ovarian tumors (e.g., arrhenoblastomas, Krukenberg tumors, luteomas, lipoid tumors of the ovary, stromal cell tumors) can be associated with virilisation of a female fetus. However this is even more rare than androgenic drug intake because patients with such abnormalities will usually not conceive.
- Placental Aromatase enzyme deficiency (cytochrome P450 aromatase enzyme): Normally, weak androgens produced by the fetal adrenal gland are converted to estrogens by placental aromatase and pass to the maternal circulation. Deficiency of this enzyme due to mutations of the *CYP19* aromatase gene can result in profound virilisation of the female fetus and mother during pregnancy.

46, XY Disorder of Sex Differentiation

Undermasculinized Male (Male Pseudohermaphroditism)

46, XY DSD (previously known *male pseudohermaphroditism)* refers to heterogeneous disorders in which testes are present but the internal duct system or the external genitalia exhibit varying degrees of phenotypic feminization (incompletely masculinized).

Impaired male differentiation in these patients is secondary to:

- Inadequate secretion of testosterone by the testes at the necessary period of embryonic development.
- Inability of target tissue to respond to androgen appropriately.
- Impaired production or action of MIS (Mullarian inhibiting substances).

➢ **Inadequate secretion of testosterone by the testes:** Inadequate secretion of testosterone is often an autosomal recessive disorders that may be due to:

- Leydig Cell failure either due to aplasia or abnormality in Luteinizing Hormone Receptors. or
- Disorders of Testosterone enzyme Biosynthesis.

The result is variable degrees of failure in testosterone production with consequent failure of virilisation of the external genitalia of male fetuses.

The clinical presentation at birth ranges from a normal appearing female, typically with testes palpable in the inguinal canal or labia majora to male with genital ambiguity (variable degree of hypospadias, cryptorchidism, penoscrotal transposition and a bind vagina pouch).

On examination: there are no Müllerian structures and the vagina is short. Hormonal assay shows low testosterone level and elevated LH concentration.

In cases with apparent normal female genitalia at birth a palpable gonads may be noted in the inguinal canal or labia on physical examination. Alternatively the presentation is usually at the age of puberty with sexual infantilism (absence of secondary sexual characteristics).

- **Androgen insensitivity syndrome "Inability of target tissue to respond to androgen appropriately"**

Disorders of androgen receptor function represent the most common definable cause of the undervirilized male. These patients characteristically have a 46,XY karyotype, testes and absent mullarian structures. It presents with a spectrum of phenotypic abnormalities that vary from complete external feminization (syndrome of complete androgen insensitivity or testicular feminization syndrome), to ambiguous genitalia (partial androgen insensitivity), to the phenotypically male that present at puberty with infertility, some gynecomastia, and small phallus.

This condition has an incidence of 1 in 20,000 to 1 in 60,000 males, with a maternal inheritance pattern, because the androgen inheritance gene is located on the long arm of the X chromosome.

Clinically: Patients usually presents with primary amenorrhea or the finding of a testis at inguinal herniorrhaphy. Fifty percent of patients with complete (severe) androgen insensitivity syndrome have an inguinal hernia.

On Examination: In the complete androgen insensitivity form, patients have a normal female phenotype with the exception of diminished axillary and pubic hair; the vagina is short and blind-ending. Because the fetal testes secrete MIS, müllerian structures are absent. The testes may be found in the labia, inguinal canal, or abdomen.

Management:

- Patients with complete androgen insensitivity (testicular feminisation syndrome) are

almost always raised as female. The management entails gonadectomy after puberty because of 2% to 5% risk of development of testicular tumor (usually seminoma or gonadoblastoma). After gonadectomy estrogen replacement hormonal therapy should be commenced.

- Patients with incomplete form require decision regarding gender assignment. Those raised as male will need surgical treatment in the form of genitalia reconstruction, treatment of their cryptorchidism, and reduction of gynecomastia.

➢ 5α-Reductase Deficiency:

5α-Reductase is a microsomal enzyme that catalyzes the conversion of testosterone to Dihydrotestosterone "DHT", the active androgen hormone responsible for the differentiation of the external male genitalia. The condition an autosomal recessive disorder, and only homozygous males are affected.

- At birth: Patients with this disorder present as newborns with a 46,XY karyotype, ambiguous genitalia, normally differentiated testes with male internal ducts. Endocrine evaluation reveals elevated mean plasma testosterone but low DHT levels.
- At puberty: normal partial masculinization occurs due to the normal increase in testosterone level. Some secondary sexual characteristics, including enlargement of the prostate and hairline recession does not develop.

➢ Persistent Müllerian Duct Syndrome:

Persistent Müllerian duct structure may occur sporadically or as inherited X-linked (or autosomal dominant, sex-limited) trait due to defect in the gene for MIS.

Patients with PMDS are phenotypic male with 46,XY karyotype but persistent internal müllerian duct structures. Typically, they have unilateral or bilateral undescended testes, bilateral fallopian tubes, a uterus, and an upper vagina draining into a prostatic utricle.

This condition is often discovered during repair of inguinal hernia hence sometimes it is referred to as the *"hernia uteri inguinale"* syndrome.

➢ Embryonic Testicular Regression and Bilateral Vanishing Testes Syndromes:

The syndrome entails the presence of testes that "vanish or cease to function" at some point during embryogenesis. This could be due to genetic mutation, a teratogen, or bilateral testicular torsion.

Clinically, the syndromes has a spectrum of phenotypic presentation depends on the time of cessation of testicular function.

- Before 8-weeks gestation loss of testicular function causes 46,XY patient with female external and internal genitalia and either no gonads or streak gonads.
- A loss of testes between 8-10 weeks of development leads to ambiguous genitalia and variable ductal development.
- A loss of testes function after the critical male differentiation period, which is at 12- to 14-weeks gestation, results in a normal male phenotype externally along with anorchia (absent testes) internally.

➢ Gonadal Dysgenesis:

Dysgenetic testes can result from mutations or deletions of any of the genes involved in testicular determination, namely SRY, DAX, WT1, and SOX9. Gonadal dysgenesis can take different forms:

- Pure (complete) 46, XY gonadal dysgenesis "Swyer syndrome": Patient with this condition presents with primary amenorrhea and sexual infantilism. On examination they have female external genitalia and mullarian structures (uterus and fallopian tubes) but bilateral streaked gonads (DD from Turner syndrome).
- Partial or Mixed forms of gonadal dysgenesis syndromes: In the "Mixed gonadal dysgenesis" variety there is unilateral dysgenetic testis on one side and contralateral streak gonad on the other side. In contrast to "Partial gonadal dysgenesis" where there are two dysgenetic testes rather than one dysgenetic testis and a streak gonad. In both conditions the karyotype is either 45,X0/46,XY or 46,XY.

  Clinically: The phenotypic spectrum of patients with XO/XY mosaicism extends from phenotypic females with Turner's syndrome (25%), to those with ambiguous genitalia, to, rarely, those appearing as normal males. This depends on the embryonic stage at which the dysgenetic testes stopped producing MIF and /or testosterone.

Patients with a Y chromosome in the karyotype are at a higher risk than the general population to develop a tumor in the streak or dysgenetic gonad. Gonadoblastoma, a benign growth, is the most common tumor. Because of the 20% to 25% risk for malignant transformation into a dysgerminoma, surgical removal of the gonad is recommended.

Unclassified Forms of Sex Development (DSD)

Mayer-Rokitansky-Küster-Hauser Syndrome:

This is a rare disorder entailing congenital absence of the uterus and vagina. It occurs in approximately 1 of every 4000 to 5000 female births. Patients with MRKH syndrome have a 46,XX karyotype and are normal-appearing females with normal secondary sex characteristics. The external genitalia appear normal, but only a shallow vaginal pouch is present. In the typical form of the syndrome, there is symmetrical anatomy with absence of both vagina and uterus. Normal ovaries and fallopian tubes are present, and ovarian function is normal, but only symmetrical uterine remnants are found

The most common clinical presentation for MRKH syndrome is primary amenorrhea, but patients may present with infertility or dyspareunia. Upper urinary tract anomalies occur in approximately one third of patients and include renal agenesis, pelvic kidney, and horseshoe kidney.

Principle of Evaluation And Management of The Newborn With Ambiguous Genitalia

Ambiguous genitalia are DSD in which the outer genitals do not have the typical appearance of either a boy or a girl. This is a very rare event occurs in approximately 1 in 14,000.

Although obstetricians are not primary responsible for the management of the newborn but he/she is still involved in of the counseling process making sure that the parents understand the problem and able to cope with its psycho-social consequences. Hence the role of an obstetrician does not stop only at the recognition of DSD at birth but should also be aware of the important issues in examination and diagnostic procedures and potential of long-term outcome and consequences.

> For obstetricians attending childbirth any newborn with bilaterally impalpable testes or a unilaterally impalpable testis should be regarded as having DSD until proven otherwise, whether or not the genitalia appear ambiguous.

The initial evaluation and management of such cases must be regarded as; medical emergency because congenital adrenal hyperplasia, the most common cause of DSD, is both a potentially life threatening condition, as well as a psychosocial emergency since the first question parents expect to ask " is it a boy or girl?"

Management of DSD requires experienced multidisciplinary team of pediatric endocrinologist, pediatric surgeon/urologist, and psychologist. The team has to work in close contact with the family making sure that they understand the problem and participate positively in the long-term management plan.

The goals of management are:

- To make a precise diagnosis of the intersex disorder and exclude CAH not only because it is the most common cause of DSD but because of its potential life threatening complication.
- To assign a proper sex of rearing based on the diagnosis, the status of the child's anatomy, and the functional potential of the genitalia and reproductive tract.

To achieve these goals a systematic approach begins with history, examination, and investigations is adopted:

History: should include the following information:

- Prenatal exposure to androgens (e.g. progesterone, danazol, testosterone) steroids or contraceptives.
- Maternal virilisation in pregnancy (suggest placental aromatase deficiency, luteoma).
- Infertility, amenorrhea, or hirsutism might also suggest possible familial patterns of intersex states (adult onset CAH)
- Family history of females who are childless or have amenorrhea (androgen insensitivity).
- Family history of unexplained infant deaths (congenital adrenal hyperplasia).
- History of consanguinity (recessive disorders, e.g. CAH, or disorders of androgen biosynthesis).

Examination: complete physical examination that includes the genital and extra-genital examination for other dysmorphic features (e.g. feature of Turner syndrome) should be performed. On genital examination the following points should be documented:

- Examination of the gonads**:** This is critical for DD and treatment. Palpable Gonads (in the inguinal canal, labioinguinal region, or labioscrotal folds are almost always testes) implies a male with ambiguous genitalia. Conversely, an infant with ambiguous genitalia but without palpable testes in the scrotum is likely to be a virilized female, most often the result of congenital adrenal hyperplasia.

- Examination of clitoris or penile size should be assessed and an accurate measure of stretched penile length recorded.
- The urethral opening should be identified and in female fetuses the labia should be gently separated to see if the vaginal introitus can be visualized
- Examination for the presence of a uterus, which can be performed by digital rectal examination.
- Serum studies should be immediately sent to rule out a salt-wasting form of CAH most importantly, 17-OH progesterone in addition to serum and urine electrolytes.
- Imaging studies: for examination of the internal genital system. This includes pelvic ultrasound, and MRI to look for the uterus and gonads, and exclude renal anomalies.
- Genetic studies: FISH (florescent insitu hybridization) can give quick results as to presence of Y and X chromosome. Detailed karyotyping and other genetic tests are normally requested as appropriate.
- Invasive tests: including endoscopy or laparoscopy may be necessary. On the rare occasions when the physician needs to examine the vagina or see the cervix of the newborn, an endoscope, such as a pediatric cystoscope, may be used. The hymen is generally perforate and will accept this instrument. Tissue biopsy may be necessary in some cases of DSD with suspected ovotestes, streak or dysgenetic gonads.

Gender Assignment: gender assignment sometimes becomes the most challenging issue in the management of newborns with ambiguous genitalia. It should be also noted that in Islam gender assignment is a important issue since there are crucial difference between religious responsibilities, inheritance and social obligations between female and male.

However a decision on gender assignment should be reached as soon as possible, the family should understand and support the decision. The following parameters of optimal gender policy assignment had been proposed:

- Reproductive potential
- Good Sexual function
- Minimal medical procedures
- An overall gender-appropriate appearance
- A stable gender identity
- Psychosocial well-being.

References and Further reading

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Chapter 9

Family Planning

Throughout the history of mankind the search for a fertility control method to avoid unintended pregnancy have never stopped. However there is no doubt that the real history of effective contraception began after the discovery of hormonal contraceptive pills, which is considered a landmark in the history of medicine. It did not only fulfill humans desire at personal level but also has greatly contributed to the reduction in maternal mortality and morbidity from unplanned and/or unintended pregnancy.

Obstetricians and Gynecologists are responsible to help women to chose the method that is best for them after full evaluation of their medical history, future reproduction plans and lifestyle.

By the end of this chapter you should be able to:

- Realize the importance of fertility control at global, national and family levels.
- List the major classes of contraceptive measures
- Realize the Islamic ethical view in relation to contraception
- Realize the factors that determine choice of contraception
- Describe effectiveness of contraception under perfect and typical use and the Pearl index

The hormonal contraceptives:

- Describe the pharmacology of hormonal contraceptive
- Enumerate the different types of hormonal contraceptive, its methods of administration.
- Describe the mechanism of actions: for combined and progestogen only measures.
- Discuss the side effects of hormonal contraceptives (minor and major ones)
- Discuss the categories of precaution and contraindication for hormonal contraceptives.
- Describe the elements of patient counseling: screening history and examination, non-contraceptive benefits, the efficacy of hormonal contraception.

The Intrauterine Contraceptive Device (IUCD):

- Describe the main types and its mechanism of action
- Describe the minor side effects
- Describe contraindications for IUD
- Describe complications and principle of management of IUD

Barrier method, Spermicidal

Describe its efficacy and potential benefits

Natural methods: Describe the principle and the limitation of each:

- Fertility awareness method: The standard day method, the ovulation method, the Twodays method, and the symptothermal method.
- Withdrawal methods: coitus interruptus
- Lactation: criteria for use as contraception

Surgical Sterilization: for male and female: describe its place and principle.

Emergency contraception:

- Describe the methods, the potential mode of action and side effects.
- The indications for each
- Effectiveness and follow up of each method

⇒ **Importance of family planning Family planning:**

At the global level the importance of family planning in relation to women health cannot be overemphasized. The World Health Organization reports indicates that more than half a million women die every year from pregnancy related complications. Family planning and proper use of contraception for spacing of childbirth can plays a major role in reducing the maternal mortality and morbidity from pregnancy complications.

At national levels the population explosion is a major stumble in its economic growth. In Saudi Arabia the situation is different since family planning is not yet a national policy but rather a personal choice. Increasing number of married couples, especially among the high income and more educated women, are requesting family planning and would like to avoid unintended pregnancy for social and occasionally for economic reasons.

⇒ **Types of contraception:** The types of contraception may be considered as two major types:

- **Medical or reversible method: hormonal methods, contraceptive device, barrier methods, Spermicidal, fertility awareness methods, withdrawal method, and lactation.**
- **Surgical or irreversible methods: tubal ligation or blockage, and vasectomy.**

⇒ **Ethical View on Contraception:**

The use of contraception for purpose of family planning is ethically accepted by the Islamic jurisdiction. However it is important that both the husband and the wife should be aware and agreeing on the chosen method.

Surgical sterilization (being a permanent contraception) either for the husband or the wife is generally not permitted except for strong medical reasons and again with the approval of both parties the husband and the wife.

⇒ **Choices of contraceptive methods:**

There is no perfect contraception method (i.e. effective, reversible and totally safe ...etc). Therefore the gynecologist has an important role to counsel woman regarding the prose and cones of each method and balance the risks and benefits of each one for each individual patient. At the end a healthy non-smoker woman should be the one to make her choice of a contraception method.

The factors that may be considered when making a choice include:

- Efficacy:
- Convenience:
- Duration of action:

- Reversibility and time to return of fertility:
- Effect on uterine bleeding: this particularly important for Moslem women.
- Frequency of side effects and adverse events:
- Cost:
- Protection against sexually transmitted diseases: important in some cases as in carriers of HIV.

Choice of contraception for women with medical issues: The situation is different in women who have some diseases or on certain medications since in such cases some types of contraception's may be contraindicated.

The World Health Organization has published comprehensive tables of medical conditions (such as cardiovascular diseases, diabetes, rheumatoid diseases… etc) and personal characteristics (e.g. depression) that may affect contraceptive choice. These tables can be accessed on line (www.who.int/topics/contraception/en). In some cases such as cancer or severe cardiac diseases surgical sterilization may be recommended.

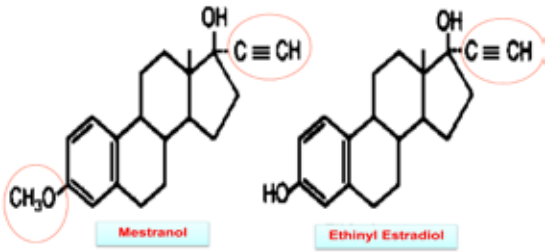
⇒ **Effectiveness of contraceptives:** The effectiveness of a contraceptive method is usually expressed as theoretical (perfect use) efficacy and the actual (typical use) efficacy.

- Theoretical or perfect efficacy: refers to the failure rate (or pregnancy rate) when the method is correctly used on every occasion.
- Actual or "typical" efficacy: refers to the failure rate in "real" circumstance. The actual efficacy is usually lower due to inconsistent or incorrect use. It is also influenced by frequency of intercourse, age, and regularity of menstrual cycles. (table 9-1)

The Pearl Index: is a quantitative estimation of the effectiveness of contraceptive method. It is defined as the number of unintended pregnancies per hundred women per year (i.e., the number of pregnancies in 1200 observed months of use).

Hormonal Contraception

Pharmacology: Hormonal contraceptives contain estrogen plus progestin or progestin alone



The Two Estrogens Used In Combination Oral Contraceptives. Ethinyl Estradiol Is The Active Estrogen For Both Synthetic Compounds.

- **The Estrogens:**

  The natural estrogens (estradiol, estrone, and estriol) were first isolated in the late 1920s and 1930s. These estrogens are inactive if given orally. Therefore biochemical modification was introduced to produce the orally active compound **Ethinyl Estradiol** that is currently the most common estrogen preparation in OC pills. The other type of orally active synthetic estrogen is Mestranol, however in the body Mestranol must first be converted to Ethinyl Estradiol to be active.

- **Progestogen or progesterone like compounds:**

  The term "progestogen" refers to any natural or synthetic substance that produces effects similar to natural progesterone.

  However in contrast to natural progesterone the synthetic progestogens have, in addition to its progestational effects, other effects including estrogenic, anti-estrogenic, androgenic, and anti-androgenic effects.

The androgenic effects of progestogen
Explains some of the adverse metabolic effects of OCs, such as acne and seborrhea, weight gain, rise in blood pressure and increase in the low-density lipoprotein (LDL) to high-density lipoprotein (HDL) ratio

There are four major groups of progestational compounds (table 9-2) as follow:

1. **Natural progestogens**: it is not really natural but is synthetic progestogens that are similar biochemically to the natural progesterone. They are not used for contraception but have other utilization.
2. **Synthetic progestogens:** include
    1. **19-nortestosterone derivatives**: are subdivided into Estrane and the Gonane subgroups. They are the ones used in the majority of oral contraceptive pills.
    2. **The 17-hydroxyprogesterone**: Used mostly in injectable forms of contraceptives.
3. **Drospirenone (DRSP):** Is a spirolactone analogue.

Classes of the Progestogens in clinical use and their origin			Example of compounds
Natural Progesterone Not really natural but chemically identical to ovarian progesterone	- Oil based IM Injection - Transdermal Cream - Suppositories (PR/PV)\ - Orally in Micronised forms - Vaginal Gel		Primolut Dept
Synthetic Progestin Include two major groups: **19-noretestosterone:** derived from testosterone **17 hydroxyprogesterone** derived from acetylation of the 17-hydroxy group of hydroxyprogesterone	19 noretestosterone (Include 2 groups)	**Estranes** 1st generation	Norethindrone. Norethynodrel Lynestreanol.
		Gonanes 2nd & 3rd generation	Levonorgestrel Desogestrel. Norgestimate Gestodene
	C-17 derivatives		MPA Chlormadinone Acetate Megestrol Acetate. Cyproterone Acetate.
Drospirenone (Spironolactone analogues) Derived from 17a-spirolactone	Pharmacologically and biologically similar to spironolactone Has both progestogenic and anti-mineralocorticoid activity		Drospirenone
MPA: medoxyprogesterone acetate (provera) only used as injectable			

Table 9-2: The groups of progestational compounds and its main uses

Types of Hormonal Contraceptive Methods:

- **Combined contraceptive method: (contain estrogen "Ethinyl Estradiol and a progestogen):** Includes combined oral contraceptive pills, combined injectable contraceptives, the contraceptive vaginal ring and the transdermal contraceptive system. They all have similar mechanism of action, physiologic effects and prescribing precautions (see later).
  - **Low-dose combined oral contraceptives pills (COCs):** usually administered cyclically (traditionally 21 active pills followed by 7 hormone-free pills). Most of the currently used pills contain 30 to 35µg Ethinyl Estradiol. The older versions that used to contain 50µg ethinyl estradiol are only used for special indications such as in emergency contraception (see later).

- **Combined injectable contraceptive (CICs):** It provides slow release of estrogen plus progestogen over four weeks. Hence and injection is given at four weeks interval.

- **Combined contraceptive patch (P) and combined contraceptive vaginal ring (R):** are alternative options for administration of combined hormonal contraception. One patch that contains estrogen and progestogen is applied to the skin once a week for three out of four weeks.

  In case of the ring the combined hormones are administered through a small flexible ring. Each month a woman inserts a new ring deep into the vagina, leaving it in place for three out of four weeks.

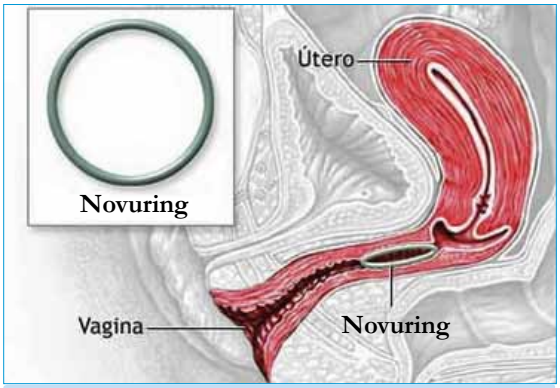


Figure 9-1: The contraceptive ring "Novuring" in place.

➢ Progestin-Only Methods:

Progestin only contraceptive methods should be considered for:

- Women in whom estrogen is contraindicated e.g. history of thromboembolic diseases, sickle cell anemia, congenital heart diseases, and hypertensive women.
- Women in the premenopausal years.
- Women who experienced adverse side effects with estrogen.
- Breast-feeding women.

The Progestin only method includes:

- **Progestin only pills**: (also referred to as the "mini-pill) It contains about 25% of the dose of progestin in combined pills. The pills must be taken at almost the same time each day because it is eliminated from the body within 24 hours. Therefore it has a high failure rate up to 5% with typical use (0.5% with perfect use) (Table..). It is also associated with more breakthroughs bleeding than combination pills. It is rarely prescribed except in lactating women.
- **Injectable agents (Depo-Provera or Medroxyprogesterone acetate 150 mg DMPA):** it comes in both intramuscular, and subcutaneous injections formula. The injection is effective for three months period.

- **Sub-dermal implants:** In this method a rod (single or double rods) that contains progestogen (e.g. etonogestrel or levonorgestrel) are inserted subdermally. The contraceptive effect is due to slow release of the progestogen, which is effective for up to five years.
- **The levonorgestrel intrauterine device** (IUD "see later").

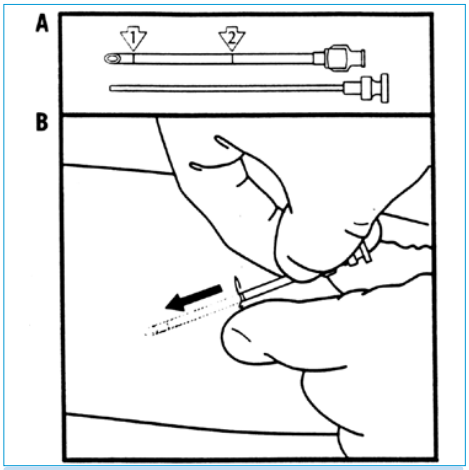


Figure 9-2: The subdermal implants. A: showing the trocar. B: the implants being inserted subdermally under local anesthetic.

- **Mechanism of Action of hormonal contraception:**
  - **The combined contraceptive hormones:** (oral pills, patches or rings):
    - The primary mechanism of action is through inhibition of ovulation, which is mediated by the progestogen component that suppresses the LH surge. Progestogen also causes cervical mucus thickening and atrophy of the endometrial glandular epithelium.
    - The estrogen component main function is to stabilize the atrophic endometrium and prevent breakthrough bleeding. It also potentiates the action of progestogen by suppressing the rise in FSH thus prevent growth of the dominant follicle.
  - **The progestogen only methods**: (minipills, injectable and implants) Prevent conception through combination of mechanisms:
    - Progesterone increases thickening of the cervical mucus, which interferes with sperm migration and movements.
    - It also induces atrophy of the uterine lining, which inhibits implantation of fertilized eggs.
    - Reduced tubal ciliary function. This alters the rate at which the egg moves through the fallopian tubes and prevent sperm from meeting the egg.
    - Ovulation suppression in some cycles.

- **Adverse Effects of combined hormonal contraception:**

Side effects of combined hormonal contraceptives can be caused by estrogen or progestin components.

– Estrogen related side effects:

Include minor not uncommon side effects such as nausea, bloating, increased breast size, leukorrhea and break through bleeding. It can also include rise in cholesterol concentration in gallbladder bile, and growth of leiomyomas.

Most of the minor effects disappear after 2-3 cycles and patient should be reassured and encouraged to continue for that period of time.

More serious effects include hypertension, hepatocellular adenomas, arterial vascular diseases (myocardial infarction, and stroke) venous thromboembolism and stimulation of breast neoplasia are discussed below.

– Progestogen related side effects: its side effects are mainly due to its "androgenic effects" which include headache, emotional liability, depression, fatigue, nausea, acne, weight gain, decreased libido, breast tenderness and increased LDL and decreased HDL levels.

The serious side effects of hormonal contraceptives: The major side effects of hormonal contraceptive have and still the subject of most epidemiological studies. The current consensus regarding the potential serious effects of hormonal contraceptive are:

- **Cardiovascular** (myocardial infarction and stroke), complications are very low with current low dose pills and in low risk women (non obese and non-smoker).
- **Venous thromboembolic disease (DVT and Pulmonary embolism)**: is the most common serious cardiovascular event among women who use oral contraceptive pills. Despite a low absolute risk (15 cases per 100,000 cardiovascular events per year), women who are taking oral contraceptive pills have a three to six times greater risk of VTE than women who do not use this contraceptive method. The risk is highest during the first year of use. It also increases with age, obesity, recent surgery and some forms of thrombophilia.
- **Cerebral vein thrombosis**: Carriers of hereditary thrombophilias (factor V Leiden, the prothrombin gene mutation, and deficiencies of protein S, protein, C, and antithrombin) and subjects with hyperhomocysteinemia who take an OC are at higher risk of cerebral vein thrombosis.
- **Effect on BP**: early studies had shown slight increase in BP but current preparation with lower dose estrogen do not result in significant rise in BP with the use of PCP.

- **Carbohydrate and lipid metabolism:**

Glucose Metabolism: combined hormonal contraceptive causes some mild insulin resistance but not to the extent of inducing glucose resistance in normal women. However diabetic women taking hormonal contraceptive require follow up of glucose control.

Lipid Metabolism: The estrogen component of the hormonal contraception has beneficial effect on lipid metabolism. It increases serum triglycerides and HDL concentrations, and lowers serum LDL cholesterol concentrations. But the progestin, because of its androgenic effect, it usually increases serum LDL cholesterol and lowers serum HDL cholesterol concentrations.

- **Risk of Cancer**: There have been concerns that the use of OC might be associated with an increase in the risk of cancer. However epidemiological data are reassuring that the pill is not associated with oncogenic risk.
  - Breast cancer**:** Epidemiologic studies have not demonstrated an association between OC use and the risk of breast cancer later in life.
  - Cervical cancer: Most studies indicate that in HPV-negative OC users do not have an increased risk of cervical cancer. Studies that have shown that an increased risk have many confounding variables related e.g. early encounter with multiple partners and HPV infection.
  - Ovarian cancer**:** The pills are associated with a **decrease** in the risk of non-hereditary forms of ovarian cancer.
  - Endometrial cancer**:** the use of oral contraceptive pills is associated with **decreased risk** of endometrial cancer by approximately 40%. The protective effect of oral contraceptives persists for at least 15 years after cessation of use. This benefit is likely related to the progestin effect of oral contraceptives, which suppresses endometrial proliferation.

Precaution and Contraindications for hormonal contraception:

Contraceptives unlike other medications are prescribed for healthy women usually for long periods of time. Hence the balance should always be in favor of the benefits rather than any potential risks related to the contraception.

In a small proportion of women hormonal contraception are contraindicated

In the remaining majority a graded scheme of "precautions" based on specific risk

factors have been recommended by the WHO and other international bodies (Table 9-3). Accordingly four categories are identified:

- Category 4: women who should not be given oral contraceptive pills (absolute contraindications).
- Category 3: women whom should "exercise caution" in prescribing oral contraceptive pills "and carefully monitor for adverse effects".
- Category 2: women in whom the "advantages of oral contraceptive pills generally outweigh theoretical or proven disadvantages.
- Category 1: women with conditions, which are essentially unrelated to the metabolism of oral contraceptive agents. Women with these conditions have no restrictions on the use of oral contraceptive pills.

⇒ **Counselling patients for hormonal contraception**:

Counseling patients for hormonal contraceptive is important step to help the women making an informed choice according to her preference. It requires undertaking screening history and examination in order to identify any potential risks or contraindications. In addition to explaining to the patient the potential side effects, benefits, and efficacy of each method.

- **Screening requirements**: A careful medical history and examination including blood pressure, BM should be taken paying attention to the important conditions highlighted in table 9-2.
- **Non-contraceptive benefits of OCs pills:** This include**:**
  - Regulation of menstrual cycles and treatment of some menstrual disorders e.g. dysmenorrhea, menorrhagia, and sometimes-in premenstrual syndrome.
  - Reduce the frequency of some benign tumors including leiomyomas, benign breast masses and fibrocystic diseases.
  - Reduce formation of ovarian cysts
  - On long term it reduces risk of ovarian, endometrial and possibly colon cancers.
  - Oral contraceptives with a low androgenic progestin may be useful in some women with acne.
  - Reduce the risk of PID (pelvic inflammatory disease) probably through

While breast exams, pap smears, and screening for sexually transmitted diseases are important, most groups, including the ACOG, the WHO, and the RCOG agree that these procedures are not necessary before a first prescription for OCs.

thickening cervical mucus but do not protect against STD.

- **Efficacy of hormonal contraceptive and potential drug interactions:**

It is important that the patient understand the efficacy of the hormonal contraceptive under perfect and typical uses (see table 9-1).

Under some circumstances the contraceptive efficacy of OCs is decreased for example:

- Women taking drugs that increases liver microsomal enzyme activity hence it accelerate the metabolism of OCs (such as antiepileptic or rifampin)
- Also some antibiotics such as tetracycline, penicillin derivatives, and cephalosporin's.

Intrauterine contraceptive Device (IUCD)

The **intrauterine device** (**IUD**) refers to the use of intrauterine object placed in the uterus, to prevent pregnancy. Intrauterine devices are one of the oldest methods of contraception. Currently there are of two types of medicated IUCDs; copper-containing devices that release copper, and a hormone-containing device that releases a progestogen. A third non-medicated inert device is also available but very rarely used.

- Copper IUDs: consisting of fine copper wire wound around a vertical stem and copper collars. The copper device is effective for up to 10-12 years. With perfect use (in which the user checks the strings regularly to detect expulsion), the probability of pregnancy in the first year is 0.6 percent; with typical use, the first-year pregnancy rate is 0.5 to 0.8 percent
- Hormone-releasing IUDs: is composed of a T-shaped polyethylene frame with a collar containing 52 mg of levonorgestrel dispersed in polydimethylsiloxane attached to the vertical stem. It release approximately 15 mcg of levonorgestrel daily. It works for up to 5 years.
- Unmedicated (inert) IUDs: composed of inert materials such as stainless steel or plastic. Its main advantage is that they never need to be replaced.

⇒ **Mechanism of action:** The precise mechanism of the IUDs' contraceptive action is not known; it is likely that it involve several factors:

1. The presence of the IUD induces sterile inflammatory reaction with the

It is important to emphasis that the IUCDs primary mechanism of action is by prevention of fertilization and it does not act as abortifacient (interruption of implantation).

reseals of substances that are toxic to sperm and ova and also could prevents implantation.

2. The copper containing IUCD release free copper and copper salts which enhance the inflammatory reaction.
3. The progesterone loaded IUCD: The progestin secreted by hormone-releasing IUDs causes endometrial decidualization and glandular atrophy, and thickening of the cervical mucus, which serves as a barrier to sperm penetration.
4. In addition the serum concentrations of progestin lead to partial inhibition of ovarian follicular development and ovulation; although at least 75 percent of women have ovulatory cycles.

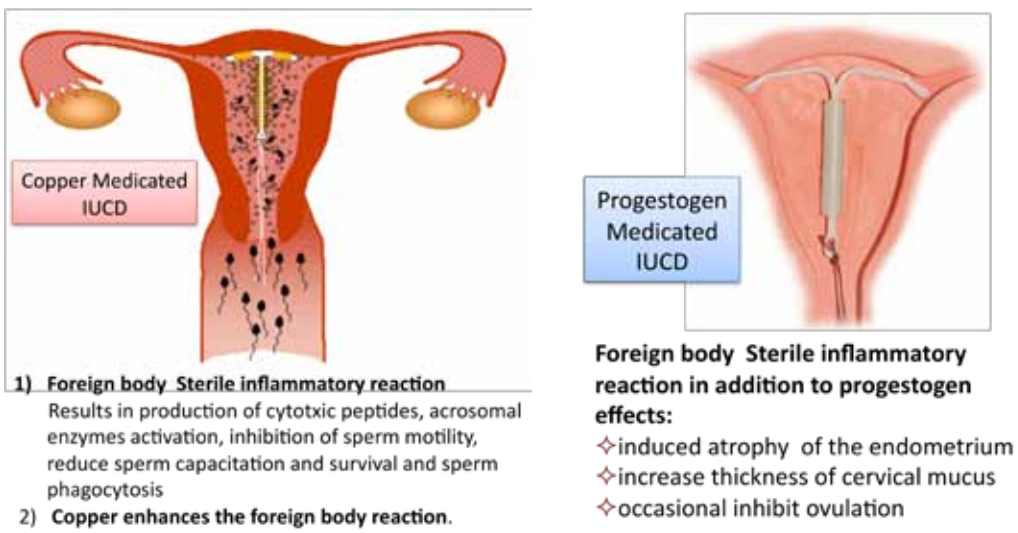


Figure 9-3: A diagram showing the mechanisms of action of a copper and progestogen loaded IUCD (see text for details). It is clear that the primary mechanism of IUD is by prevention of fertilization.

Advantages and non-contraceptive benefits of IUDs:

- IUDs are safety, cost-effective, long-acting (the copper IUD can be used up to 10-12 years and the Levonorgestrel IUD to 5 years), and rapidly reversible method of contraception with few side effects.

- It is a private and convenient method of contraception, does not interfere with the spontaneity of sex.
- High rate of efficacy: the failure rate of copper IUD is < 1 per 100 women per year and the progestogen "Levonorgesrel" medicated IUD is comparable in efficacy to tubal ligation (failure rate with typical use is 0.1-0.2%).
- No contraceptive health benefits: The progestogen-medicated system (IUS) significantly reduces menstrual blood loss, and dysmenorrhea. It is a recognized alternative treatment to surgical management of menorrhagia.
- The progestin-releasing contraceptives (IUS) are associated with decrease in the risk of pelvic inflammatory disease (PID).

⇒ **Contraindications and precautions:** There are very few absolute contraindications for use of IUCDs. But there are some relative contraindications and some concerns that should be considered in individual cases

- **Severe uterine distortion**: e.g. bicornuate uterus, cervical stenosis, or distorting leiomyomata are associated with increased difficulty of insertion and increased risk of expulsion.
- **Active, recent, or recurrent pelvic infection**: In such cases IUD increases the risk of upper genital tract infection.
- **Known or suspected pregnancy**:
- **Undiagnosed abnormal uterine bleeding:** since an irregular bleeding may be erroneously attributed to the IUD. Cervical dysplasia or cervical ectropion are not contraindications to IUD use.
- **Wilson's disease or copper allergy**: Although no adverse event related to copper allergy or Wilson's disease has ever been reported with a copper IUD, it is recommended that hormone-releasing IUDs be used in these patients.
- **Immunocompromised Women**: such patients may be at increased risk of pelvic inflammatory disease "PID" with the IUD e.g. women at risk for HIV or with HIV or AIDS
- **Previous problems with the IUD:** including pregnancy, expulsion, perforation, pain, and previous ectopic or heavy bleeding, are not contraindications to use but are precautions that should be taken in consideration.
- **Nulliparous women:** There are often concerns about infertility risk, particularly in women who have never been pregnant. However, there are no evidence that the

previous use of a copper IUD increase the risk of tubal infertility in nulligravid women.

- **Valvular heart disease**: There is no contraindication to use of the IUD among women with uncomplicated valvular heart disease (including mitral valve prolapse and aortic stenosis) or in women with complicated valvular heart disease (e.g. pulmonary hypertension, high risk of atrial fibrillation, history of subacute bacterial endocarditis, or on anticoagulant treatment). The advantages of the IUD generally outweigh the theoretical or proven risks (avoidance of pregnancy risks and avoidance of the risks associated with hormonal contraceptives).
- **Other Chronic Medical Conditions**: There is no contraindication to use of the copper IUD in women with diabetes mellitus, cardiovascular disease, migraine headaches, breast cancer or benign breast disease, smoking, obesity, epilepsy, or liver, gallbladder or thyroid disease.

⇒ **Adverse Effects and Problems Management:**

- Systemic Side Effects: Generally there are no systemic side effects with copper or unmedicated IUDs. Occasionally systemic effects may occur with levonorgestrel loaded IUS e.g. hirsutism, acne, weight change, nausea, headache, mood changes, and breast tenderness.
- Pain: Cramping pain at the time of IUD insertion and for up to 15 minutes following insertion is normal. In severe cases it might leads to vasovagal hypotension. If a vasovagal reaction is anticipated by prior history, a paracervical block with local anesthesia (5 mL of 1 percent Lidocaine or chlorprocaine injected bilaterally into the posterior vaginal fornices at the 5 and 7 o'clock positions at a depth of 2 to 3 mm)
- Menorrhagia, Dysmenorrhea and/or irregular bleeding: are often greatest in the first few cycles after IUD insertion. It the most common causes of discontinuation of IUD within the first year after insertion. Most of those symptoms decrease considerably in subsequent years.
- Expulsion: expulsion occurs in 3 to 10 percent of women in the first year. Risk factors for expulsion include: Nulliparity, menorrhagia, severe dysmenorrheal, prior expulsion (30 percent chance of repeat expulsion), age less than 20 years, insertion immediately after second trimester abortion or postpartum.
- Infection: the risk of pelvic inflammatory diseases (PID) with IUD use is most strongly associated with the insertion process such as the presence of bacterial vaginosis (BV), cervicitis, and contamination at insertion.

Infection risk is highest in the first 20 days after insertion (9.6 per 1000 women) and is rare thereafter (1.4 per 1000 women) and does not increase with prolonged IUD use.

Management of Infection associated with IUCD

If a woman is suspected of having PID, standard antibiotic treatment should be initiated followed by removal of the IUD. Asymptomatic women with cervical culture results positive for gonorrhea or chlamydia and women with trichomoniasis should receive standard treatment. Women with BV and candidiasis should receive standard treatment without IUD removal.

- Perforation: Uterine perforation occurs in one in 1000 IUD insertions, almost always at the time of insertion. Risk factors include an inexperienced clinician and an immobile and retroverted uterus. Perforation also can be asymptomatic and may not be noted at the time of insertion. It is important, therefore, to check the strings within a few weeks of placement. Ultrasound or, if not available, x-ray can be used to detect the location of a suspected perforating IUD. It should then be removed either by operative laparoscopy or operative hysteroscopy.
- Pregnancy complications: If a woman becomes pregnant with an IUD in place, an ectopic pregnancy should first be ruled out. If the pregnancy is intrauterine, within the first trimester, and the IUD string is visible on speculum exam: the IUD should be removed to decrease the risk of late miscarriage, preterm labor and infection.
- Ectopic pregnancy: Pregnancy is very rare in women using IUCD however, if it occurs the risk of ectopic is higher that in women using other forms of contraception. Approximately 3 to 5 percent of all contraception failures with an IUD are ectopic.
- Actinomyces: Actinomyces, a Gram positive bacillus, is part of the normal flora of the gastrointestinal tract and is commonly present in normal vaginal flora. There are several case reports of endometritis, PID, and pelvic abscesses due to Actinomyces in IUD users.

Barrier Contraceptive Methods

Barrier methods include condoms (male and female), diaphragm, cervical cap, and contraceptive sponge. Its efficacy can be made to increase significantly if combined methods are uses (e.g. condom and vaginal spermicide, diaphragm and condom). A male

or female condom should only be used once and then discarded immediately.

The efficacy of all barrier methods is highly user-dependent (Table 9-1).

Protection against STDs and HIV infection: A major advantage of barrier contraceptives, especially male and female condoms, is their efficacy in protecting against sexually transmitted diseases (STDs). However its efficacy protection against transmission of infection varies. For example female condom are effective in prevention of HIV/AIDS and other sexually transmitted infections. This does not apply to other barrier methods such as the diaphragms and cervical caps.

Also studies have demonstrated a decreased risk of transmission of HIV, gonorrhea, chlamydia, trichomoniasis, and hepatitis when the male partner consistently uses a latex condom.

Spermicidal

Spermicidal comes in a variety of forms including gel, foam, cream, film, suppository, and tablet. They are not a highly effective method of contraception when used alone (without a barrier method).

Its effectiveness is reduced if the patient does not wait long enough for the spermicide to disperse before having intercourse, if intercourse is delayed for more than one hour after administration, or if a repeat dose is not applied before each additional act of intercourse.

Women can be assured that there is no evidence of spermicides association with adverse fetal outcomes, including congenital malformations.

Natural methods of family planning

Natural methods of family planning are alternative methods of family planning for women who prefer non-hormonal, nonsurgical form of contraception it include:

- Fertility awareness method.
- Withdrawal methods.
- Lactation.

➢ Fertility awareness methods "FAM":

These methods depend on using predictor of ovulation and avoiding intercourse or using barrier methods during the fertile days "window" of the menstrual cycle.

Studies have shown that the probability of pregnancy from unprotected intercourse reaches a peak 2 days before the time of ovulation (Figure 9-4 and 5). Given the short and even shorter life span of sperm and ovum (5 and < 24 hours respectively) the fertility window in women is approximately 6 days (five days before ovulation plus the 24 hours after ovulation).

Successful use of FAB methods depends upon several factors including: accuracy in identifying fertile days, the woman's ability to adhere to method instructions, the ability of the woman and her husband to avoid unprotected intercourse on her fertile days.

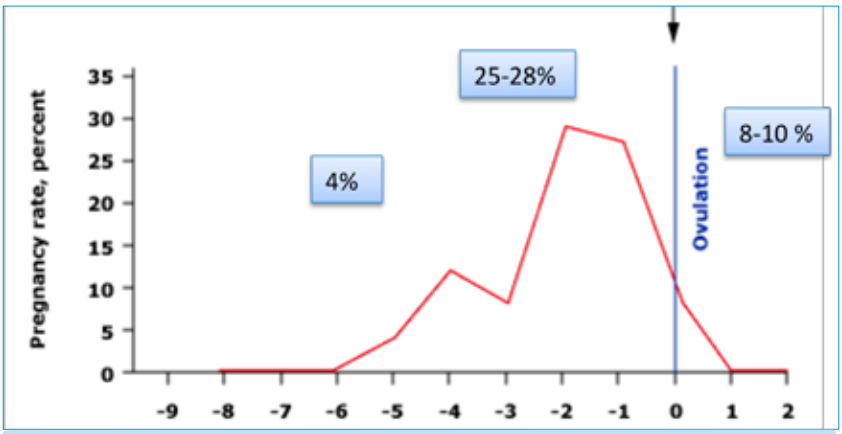


Figure 9-4: Possibility of pregnancy relative to ovulation: 4% five days before ovulation, 25 to 28 days two days preceding ovulation and 8 to 10 % during 24 hours after ovulation (i.e. 6 days is the fertile window)

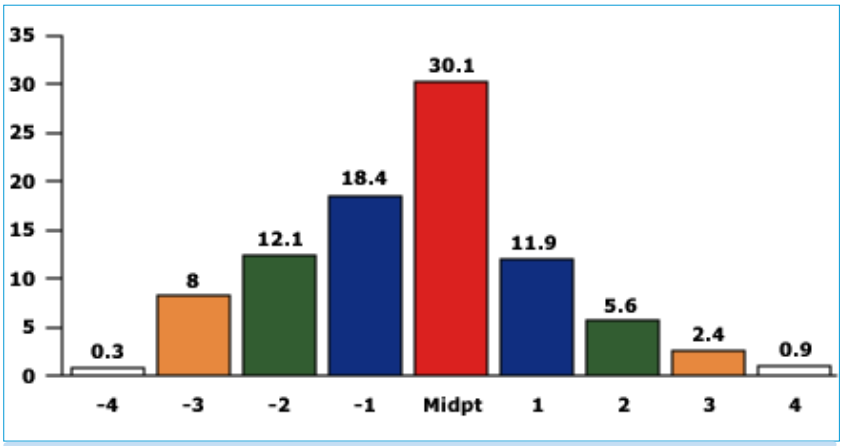


Figure 9-5: Probability of ovulation relative to midpoint of the cycle. In approximately 30 percent of cycles, ovulation occurs at the mid-point in 28 days cycle. And in 95 percent of cycles ovulation occurs within four days before or after the mid-point

Predicting ovulation:

- By calendar method: In women with regular monthly cycle (26-32 days) ovulation occur at the mid point (day 14) or within four days around it (figure …..).
- By changes in cervical secretion: ovulation may be predicted based on the physiological effect of estrogen and progesterone on the characteristics of cervical secretions. The pattern of secretion in typical menstrual cycle is as follows:
  - No noticeable secretions immediately following menses (duration usually three to four days)
  - Scanty, cloudy, sticky secretions for the next few days (duration usually three to five days): stimulated by increasing estrogen level. The cervical secretion helps to capacitate sperms and allows its travel through the cervix, uterus and fallopian tubes to the ovum.
  - Abundant, clear, wet secretions immediately before, during, and right after ovulation (duration usually three to four days)
  - Absence of secretions until after the next menses (duration usually 11 to 14 days): this occurs following ovulation, when the progesterone produced by the corpus luteum causes an abrupt change in secretions, which then inhibit sperm capacitation and transport

Observable changes in cervical secretions accurately predict and detect ovulation. However the duration of these phases varies with cycle length and with individual women.

- By change in basal body temperature (BBT): In a normal cycle, BBT is approximately 0.5 degrees Fahrenheit or 0.3 degrees Celsius higher in the luteal phase than in the follicular phase. The temperature rise begins one or two days after the surge in luteinizing hormone and the rise in progesterone concentrations, and persists for at least 10 days. Thus, the temperature change allows identification of ovulation retrospectively.

Based on the above information the current fertility awareness methods that is used in clinical practice are the following ones:

1. **The standard day method "Counting method"**: is the most commonly and easier method to teach. A woman who adopts this method should have regular monthly cycles that range between 26 and 32 days. In such cases ovulation occurs very close to the middle of the cycle, and abstinence or use of other precaution should be applied from the 8th through the 19th day of the cycle.

2. **Ovulation method "Observing cervical secretions"**: The ovulation method requires women to observe and evaluate their cervical secretions several times each day and avoid unprotected intercourse based on their findings. Women with cycles of any length, as well as those with irregular cycles may use this method. Based on the rules of the ovulation method, the user avoids unprotected intercourse for approximately 15 days each cycle.

3. **Two days method**: women using this method should avoid unprotected intercourse on all days when they note the presence of secretions and on the first day following a day with secretions. It is the easiest cervical secretion method to learn and apply. Women with any cycle length, as well as irregular cycles can use the "Two Day" method. Users of the Two Day Method avoid unprotected intercourse for approximately 10 to 14 days each cycle.

4. **Combination of cervical secretion and BBT "The symptothermal method":** requires women to observe and evaluate their cervical secretions several times each day and take their temperature with a BBT thermometer each morning before rising. Women with cycles of any length, including irregular cycles, can use this method. Users of the symptothermal method avoid unprotected intercourse for approximately 12 to 15 days each cycle.

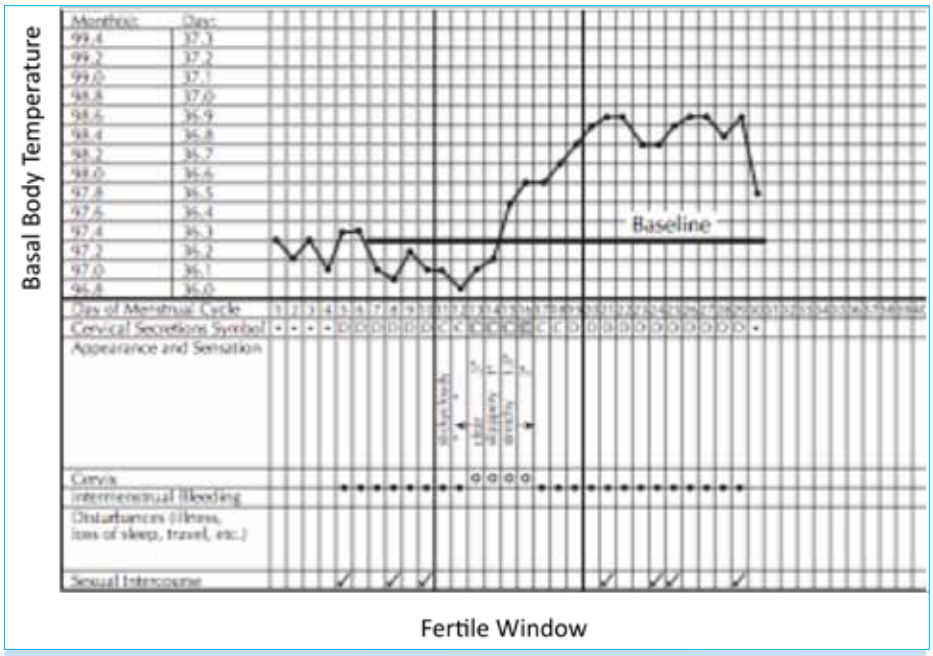


Figure 9-5: The fertile window in a normal menstrual cycle. Notice change in BBT and Cervical secretion

- **Withdrawal (coitus interruptus):** The withdrawal method requires men to withdraw from the vagina before ejaculation. Failure occurs if withdrawal is not timed accurately or if the preejaculatory fluid contains sperm. Failure rates as high as 18 to 20 percent have been reported.

- **Lactation:** Women who breastfeed have a delay in resumption of ovulation postpartum due to prolactin-induced inhibition of pulsatile gonadotropin-releasing hormone release from the hypothalamus. While breastfeeding is associated with subfertility, it only can be relied upon to prevent pregnancy when specific conditions are met namely: within the first six months after childbirth, if breastfeeding is the only source of infants feeding, and if the woman remains amenorrheic. If these conditions are not met, the risk of unintended pregnancy while breastfeeding is high.

Surgical Sterilization

Sterilization by tubal ligation/obstruction and vasectomy are effective forms of contraception that requires no further contraceptive actions after the procedure is performed. While these procedures should be considered permanent, and therefore performed only after thorough patient counseling, reversal of sterilization is possible in selected cases.

- **Tubal obstruction or ligation**: refers to any procedure that prevents pregnancy by occluding or disrupting tubal patency. Various techniques have been described including include ligating or removing a section of the fallopian tubes; mechanical blockade using clips, rings, coils, or plugs; and coagulation-induced blockage using electrical current or chemical agents.

  Currently the procedures are performed via a laparoscope under general or regional anesthesia in outpatients. Hysteroscopic procedures (tubal obstruction) are often performed under local anesthesia. In postpartum women shortly after birth surgical sterilization require a small infraumbilical incision.

  While pregnancy is rare after surgical sterilization but if pregnancy does occur, the risk that it will be an ectopic pregnancy is increased, with approximately 33 percent of pregnancies being ectopic and almost always tubal.

- **Vasectomy**: Vasectomy (ligation of the vas deferens) can be performed under local anesthesia. It is a safe, highly effective sterilization procedure. Although men should

be counseled before vasectomy that the procedure is permanent, the procedure can often be reversed with a return of fertility.

Emergency contraception

Emergency contraction (postcoital contraception and the morning-after pill) are terms that refers to the use of drugs or a device as an emergency measure to prevent pregnancy

⇒ **Indications:**

- When there is a contraceptive failure or incorrect use of a contraceptive within the previous 120 hours, including: a condom ruptures; a diaphragm or cervical cap dislodges; an intrauterine device (IUD) is expelled; or birth control pills are missed (>3 days), or poorly absorbed in the presence of gastrointestinal hypermotility.
- Other indications: e.g. follow rape or incestual coitus.

⇒ **Methods:**

- o Hormonal emergency contraception: involves taking high-dose estrogen, estrogen plus a progestin, or a progestin alone, or antiprogestins (mifepristone) as soon as possible after unprotected intercourse.
- o Cupper IUCD: usually within 5-7 days of coitus. (Table 19-4)

Method	Dose	Reported Efficacy
Levonorgestrel	0.75 mg given twice, 12 hours apart, or 1.5 mg single dose (not FDA approved)	89 percent of pregnancies prevented
Estrogen plus progesterone (Yuzpe regimen)	100 microgram ethinyl estradiol plus 0.5 mg levonorgestrel, each given twice, 12 hours apart	75 to 80 percent of pregnancies prevented
Antiprogestins e.g. Mifepristone	Single 600 mg dose	100 percent
Copper intrauterine device	Inserted within 120 hours after intercourse	Over 90 percent

Mechanism of Action: The mechanism of action of oral emergency contraception is

Table 9-4: Post coital contraceptives.

uncertain and may vary depending upon the day of the cycle the drug is administered, it include:

1. Inhibiting or delaying ovulation
2. Interfering with fertilization
3. Interfering with tubal transport
4. Preventing implantation by altering endometrial receptivity
5. Causing regression of the corpus luteum.

Important Ethical Consideration

Direct laboratory evidence supports the hypothesis that emergency contraceptives work by mechanisms that do not include post-fertilization events.

Since these drugs are administered within hours of intercourse and implantation does not occur until approximately five to seven days after ovulation, use of emergency contraception does not interrupt pregnancy and is ineffective after pregnancy has occurred.

Timing:

The efficacy of emergency contraception decreases with time since intercourse. It should be administered within 72 hours; its efficacy after 120 hours has not been established.

If emergency contraception is required after more than 120 hours of unprotected intercourse; insertion of a copper intrauterine contraceptive may be effective because of secondary post-fertilization mechanisms of contraception.

Contraindications:

There is no contraindication for emergency contraception. The precautions for regular administration of hormonal contraception do not apply for the emergency contraception. Neither specific physical examination nor any laboratory tests are needed before providing oral emergency contraception

Side Effects:

Include nausea and vomiting. It is helpful to administer an antiemetic drug 60 minutes before the initial dose of oral contraceptive.

Follow up:

Administration of postcoital oral contraceptives may affect the onset of the woman's next menstrual period. Pregnancy test should be performed if the period is delayed by more than 3-4 weeks.

Pregnancy rate (percent) during first year of use		
	Typical use	Correct use
Cervical cap		
Previous births	32	26
No previous birth	16	9
Condom with out spermicide		
Male	15	2
Female	21	5
Diaphragm with spermicide	16	6
Sponge		
Previous births	32	20
No previous birth	16	9
Fertility Awareness		
Ovulation	23	3
Sympatothermal	13-20	2
TwoDay	14	4
Standard days	12	5
Lactational amenorrhea	5	<2
Withdrawal	27	4
Intrauterine Devices (IUD)		
Copper or Mirena	<1	<1
Hormonal Contraception		
Depot-provera (injections)	3	<1
Patch (Transdermal)	8	<1
PCPs Progestin only or combined estrogen-progestin	<1	<1
Ring	<1	<1
Surgical		
Female sterilization	<1	<1
Vasectomy	<1	<1
Emergency contraception		
Pills	Pregnancy rate decreased by 75 to 89 percent, depending on the regimen used (higher pregnancy rate is for combined estrogen-progestin pills, lower pregnancy rate is for levonorgetrel alone)	
IUD	Pregnancy rate decreased by 99 percent	
Implants	<1	<1
Spermicides	29	18
No Method	85	85

Table 9-1: Data refer to number of pregnancies per 100 women during first year of use

Typical Use: failure rates for women and men whose use is not consistent or always correct.

Correct Use: refers to failure rates for those whose use is consistent and always correct.

* Rate reflects cumulative pregnancy rate in the first 6 months.

Data adapted from: Contraceptive Technology, 19th edition, 2007

Category 4 (refrain from use)	Category 3 (Exercise caution)	Category 2 (advantages outweigh risks)	Category 1 (No restrictions)
Venous thromboembolism	Postpartum <21 days	Severe headaches after initiation of OC	Postpartum >=21 days
Cerbrovascular or coronary artery diseases	Lactation (6 weeks to 6 months)	Diabetes mellitus	Post-abortion, with abortion performed in 1st or 2nd trimester
Coronary artery disease	Undiagnosed	Major surgery without prolonged immobilization	History of gestational diabetes
Structural heart disease	Vaginal or uterine bleeding	Sickle-cell disease or sickle-cell hemoglobin C disease	Varicose veins
Diabetes with complications	Age >35 years and smoke fewer than 20 cigarettes per day	Blood pressure of 140/100 to 159/109 mm Hg	Mild headaches
Breast cancer	History of breast cancer but no recurrence in past 5 years	Undiagnosed breast mass	Irregular vaginal bleeding patterns without anemia
Pregnancy	Interacting drugs	Cervical cancer	Past history of PID
Lactation (<6 weeks postpartum)	Gallbladder disease	Age >50 years	Current or recent history of PID
Liver disease		Conditions predisposing to medication noncompliance	Current or recent history of STD
Headaches with focal neurologic symptom		Family history of lipid disorders	Vaginitis without purulent cervicitis
Major surgery with prolonged immobilization		Family history of premature myocardial infarction	Increased risk of STD
Age >35 years and smoke 20 cigarettes or more per day			HIV-positive or at high risk for HIV infection or AIDS
Blood pressure of >160/100 mm Hg or with concomitant vascular disease			Benign breast disease
			Family history of breast, endometrial or ovarian cancer
			Cervical ectropion
			Viral hepatitis carrier
			Uterine fibroids
			Past ectopic pregnancy
			Obesity
			Thyroid conditions

Table 9-3: World Health Organization Precautions for the Use of OCs Pills

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Chapter 10

Breast Diseases
Gynecologist Perspective

For many women gynecologists are their primary health care physicians. Therefore it is not uncommon that a woman will consult her gynecologist whenever she is concerned about breast problem. On the other hand gynecologist and obstetrician routinely see their patients on several occasions for annual check up examination and in pre- and postnatal visits. In this respect they have an important role to play in the prevention and early detection of breast cancer. Hence gynecologist must be familiar with the epidemiology of the common breast diseases, its symptoms, signs and the screening and diagnostic techniques for breast cancer.

By the end of this chapter you should be able to:

- **Describe:** the basic anatomy of the breast..
- **Describe:** approach to routine history and examination of female breast.
- **Realize:** the important role of gynecologist in breast care and in prevention of breast cancer.
- **Describe:** the major types of benign breast diseases: Fibrocystic breast changes, fibroadenoma, inflammatory breast diseases.
- **Describe the approach to:** diagnosis and outline the management of common breast complaints: Mastalgia, Breast lumps, Nipple discharge and inflammatory lesions.
- **Identify:** patients at higher than average risk of developing breast cancer.
- **Describe:** the principle of breast screening and its role: manual examination and mammography.

Anatomy of the Breast:

The breast is a mass of glandular, fatty, and fibrous tissues positioned over the pectoral muscles of the chest wall and attached to the chest wall by fibrous strands called Cooper's ligaments. A layer of fatty tissue surrounds the breast glands and extends throughout the breast. The fatty tissue gives the breast its soft consistency.

Each breast has 15 to 20 lobes. Each lobe has many smaller lobules, which end in dozens of tiny bulbs that can produce milk. Toward the nipple, each duct widens to form a sac (ampulla). During lactation, the bulbs on the ends of the lobules produce milk. Once milk is produced, it is transferred through the ducts to the nipple.

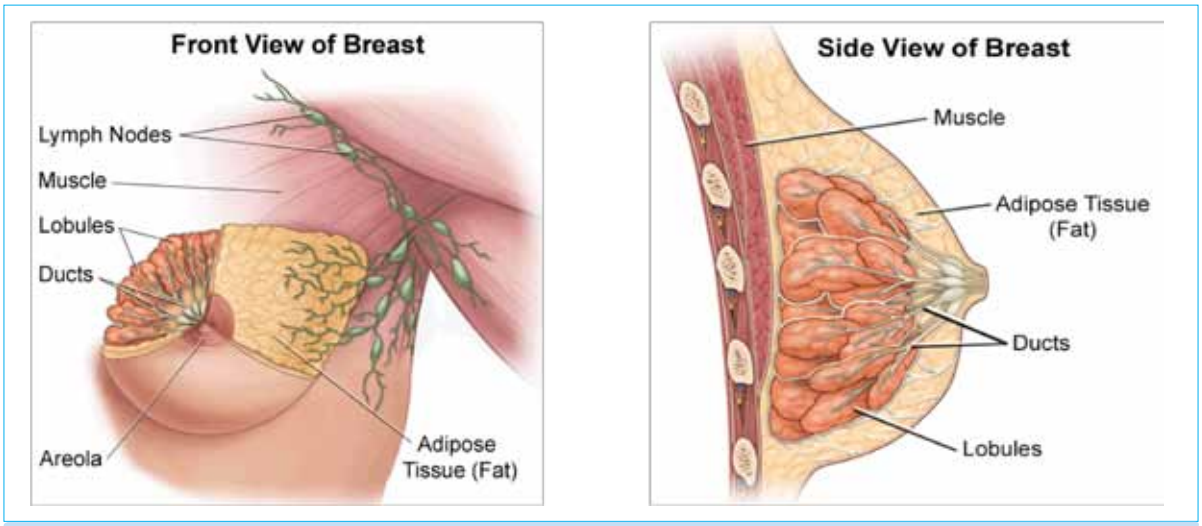

Figure 10-1: Diagram showing the basic anatomy of the breast from front and side views. Note the primary lymphatic drainage of the breast.

Approach to routine history and examination of the breasts: The goal of history and breast examination is to determine if the breasts are normal or abnormal.

- History: begins with special emphasis on breast related symptoms, if there is any then enquiry should be made on its duration whether there has been any change, if it is unilateral or bilateral, and if there is any relation to menstruation particularly if the symptoms increase in premenstrual period and abate after menses.

  It is very important that this should be assessed in context of patient background risk factors most importantly age, family history of breast cancer, hormonal therapy...Etc (see later for risk factors of breast cancer)

- Examination: Systematic and careful examination is essential and presents a good

opportunity for teaching patient the proper method of self-examination of the breasts.

- Inspection: is performed while patient is in the sitting position and under good light. The breasts are inspected for areas of dimpling, skin retraction, redness, ecchymosis, asymmetric characteristics of the breast, or changes in the nipple, particularly surface change, excoriation or importantly, retraction. The presence of a spontaneous nipple discharge should be noted.
- Palpation: After the visual examination has been completed, each breast is palpated in a methodical fashion, utilizing a circumferential technique evaluating each breast quadrant (Figure 10-2)

The areolar area should be compressed to determine if there is nipple discharge and to detect the possibility of small subareolar masses. The axilla should be examined with care taken to completely examine all areas posterior to the lateral edge of the pectoralis major. Gentle compression should be used but of sufficient pressure to be able to feel the upper portion of the rib cage. After the patient has been examined in the sitting position, she should be placed in the supine position and the examination repeated.

Figure 10-2: Diagram demonstrating the steps of routine palpation of the breasts

Benign Breast Diseases

Benign breast diseases constitute the majority of breast lesions seen by gynecologist. Fibrocystic changes (FCCs) constitute the most frequent benign disorder of the breast (Figure 10-3). It generally affects premenopausal women between 20 and 50 years of age (see later).

On histological bases benign breast lesions can be divided into three categories:

- Non-proliferative lesions: include simple cysts. It usually requires no intervention. Non-simple or complex cyst (contain solid and fluid) require referral to breast specialist.
- Proliferative lesions without atypia: the most common is fibro adenoma. There is slight increase in the risk of development of breast cancer estimated as 1-2 times greater than the general population.

  Other types are the ductal hyperplasia with out atypia: in this category the cells retain its benign cytological features.
- Atypical hyperplasia: Usually found accidentally on histological examination of excised breast lesions e.g. atypical ductal hyperplasia and atypical lobular hyperplasia and is associated with a moderate increase in risk of subsequent breast cancer
- Miscellaneous lesions:
  - Inflammatory lesions: Lactational and non-Lactational mastitis.
  - Fat necrosis
  - Lipoma

The following section discusses the features of the most common benign breast diseases.

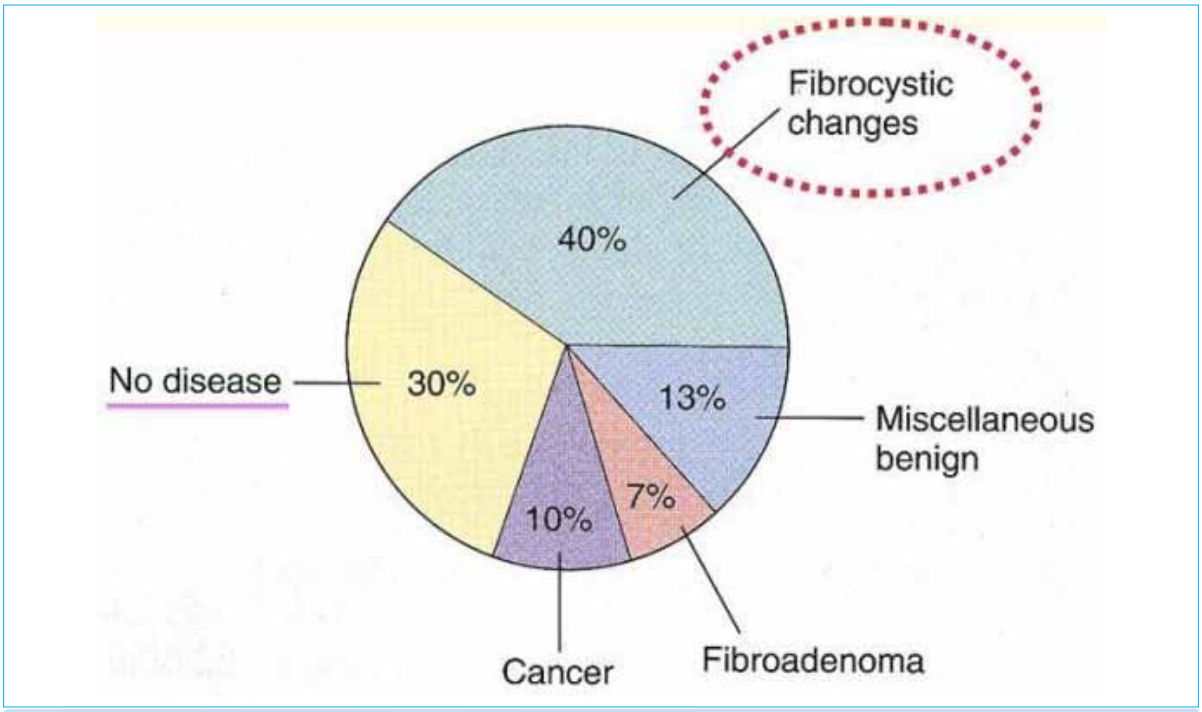

Figure 10-3: Incidence of distribution of breast diseases source http://ocw.tufts.edu/Content/51/lecturenotes

Fibrocystic changes

Fibrocystic breast "changes" are not a disease. It describes histological microscopic changes that are commonly observed throughout women reproductive life with increasing frequency from teenage to the premenopausal period.

- Incidence: Its exact incidence is difficult to determine. Clinically, approximately 10% of women under the age of 20 are noted to have fibrocystic changes while the figure reaches up to 60-70% in the premenopausal years. Such changes are unusual after the menopause unless associated with exogenous hormones.
- Histopathology: as the term implies the microscopic features include fibrosis, and cystic changes either non proliferative or proliferative (including hyperplastic ductal epithelium, adenosis and occasional papilloma formation). The nature and type of predominate changes seems to correlates with age.

Fibrocystic changes are not associated with increased risk of breast cancer.

-Symptoms: Typically fibrocystic breast changes cause cyclic premenstrual breast pain,

commonly bilateral and mostly located in the upper outer quadrant of the breast.

- Sings: On examination there is identifiable tenderness and ill-defined nodularity that are rubbery in consistency. Larger cysts, if present, are felt as balloon filled with water.

- Investigations: are rarely required. There is no specific mammographic sings and the breasts are too radiodense in young women to allow adequate visualization. An ultrasound may be requested for differentiating a solid from a cystic mass.

-The etiologic factors: are unknown. No hormonal abnormalities have been found. Dietary factors with excessive consumption of methylxanthines containing foods (coffee, tea, chocolate and cola drinks) have also been described as precipitating factors.

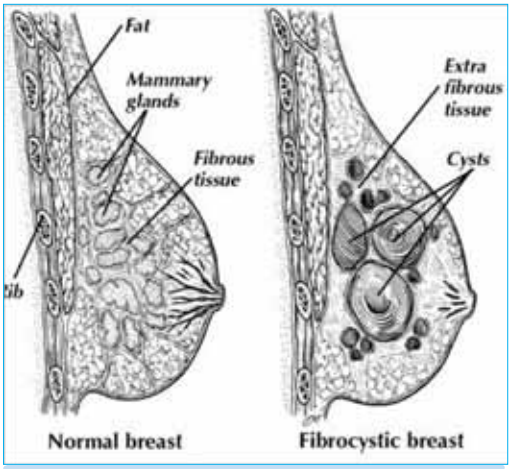

Figure 10-4: Diagram of normal breast (Left) and the histopathological fibrocystic changes (Right): Extra-fibrous tissue (fibrosis) and proliferative ductal epithelial changes with cyst formation.

The management: There is no specific treatment.

- Reassurance is of key importance since many women are primarily worried about cancer.
- Non-pharmacological treatment includes:
  - Wearing firm bra for breast support.
  - Avoid caffeine and chocolate.
  - Eliminate excessive dietary fat and limit salt intake.
  - Analgesics for pain relieve.
  - Vitamin E or γ-linolenic acid a polyunsaturated fatty (evening primorose oil) supplementation.
- Pharmacologic treatments: may be required in some cases this includes, short-term use of diuretics for 2-3 days in the premenstrual days. Low estrogen contraceptive pills are also effective in relieving symptoms in 60%-70% of cases. Progesterone administration (e.g. medroxyprogesterone acetate 5-10 mg) as supplementation during the secretory phase was found to be effective in reducing the symptoms in some cases. Danazol (100 up to 400 mg/day) continuously for 4-6 months is the drug of choice in severe cases. Its relieving effect can last for several months after

discontinuation however it is not commonly used because of its side effects. Other agents that can be tried and can be effective are bromocriptine (5 mg /day) and Tamoxifen.

- Surgical intervention is rarely indicated. If a dominant mass is present it merits thorough evaluation that may include biopsy. If a cyst is aspirated and disappears it is prudent to perform follow up examination in 3 months.

Fibroadenoma

Incidence: Fibroadenoma is the second most common benign breast lesion. It affects women in their early twenties. It is considered as aberrant growth of normal tissue rather than neoplasm.

Symptoms and signs: Clinically it is usually discovered accidentally as painless solid mass which is mobile, non tender and rubbery in consistency (hence the name breast mouse). There may be slight cyclic discomfort.

Investigations: Ultrasound examination may be required in some cases to differentiate between a cyst and fibroadenoma.

Treatment: Once confirmed, fibroadenomas don't usually require medical treatment, although in some cases they may be biopsied or removed (excision biopsy) especially in women above thirties or if it increases in size. Otherwise, and in young girls (<25 years) conservative treatment and assurance is appropriate. Around one-third of these lumps gets smaller or disappears without treatment within a few months or years.

Fat Necrosis

Fact necrosis is a condition that can clinically be confused with breast carcinoma. It usually follows trauma but patients cannot often recall the incident . The lesion is felt as a tender, firm, irregular mass that may be associated with area of ecchymosis and even skin retraction. The diagnosis is determined after excision biopsy.

Inflammatory Breast Conditions

Mastitis: Mastitis is the most common inflammatory condition of the breasts. It is seen most commonly, but not always, among nursing mothers "lactational mastitis". The

causative organisms are Staphylococcus aureus and Streptococcus species.

Non-lactational mastitis may occur in women following surgical lumpectomies or in women with diabetes, or depressed immune system.

- Clinically: Initial presentation is fever, erythema, indurations and tenderness. The condition should not be neglected otherwise it may progress to form a breast abscess.
- Treatment: Early treatment with broad spectrum antibiotics or penicillin such as e.g. Dicloxacillin can abort the progression of the infection. In nursing mothers it is important to prevent milk engorgement. Therefore the mother may continue lactation from the unaffected breast while expressing the affected one.

Subareolar abscess: results from sebaceous gland infection. If the infection is detected early, before the abscess forms, it can often be treated with antibiotics. Abscess formation requires surgical drainage.

Superficial thrombophlebitis (Monor's disease):

This is an uncommon inflammatory condition presents as acute pain or erythema in the upper lateral portion of the breast usually caused by an inflammation of the superficial veins. It may be associated with pregnancy, breast trauma, or surgical plastic breast procedures. The treatment is conservative with symptomatic treatment similar to superficial thrombophlebitis in any other location.

Common Presentation of Breast Problems

Non-pregnant women may present with a variety of complaints the most common are breast pain or mastalgia, breast lumps and nipple discharge.

Breast Pain "Mastalgia"

Mastalgia is defined as pain originating in the breasts. It may be localized in the breast; in severe cases it radiate to the axillae. Mastalgia should be differentiated from premenstrual breast discomfort, which is a not uncommon symptom.

Mastalgia varies in severity, sometimes the pain is severe enough to disturb daily activities, sex life and even sleep.

Etiology of breast pain:

In the majority of cases no definite cause can be found. The most common cause is fibrocystic changes, which is often gives cyclic pain. Other causes of pain should be excluded such as pain originating from costochondritis junction (Tietze's syndrome), mastitis or breast abscess. Cancer infrequently presents with pain (Figure 10-5)

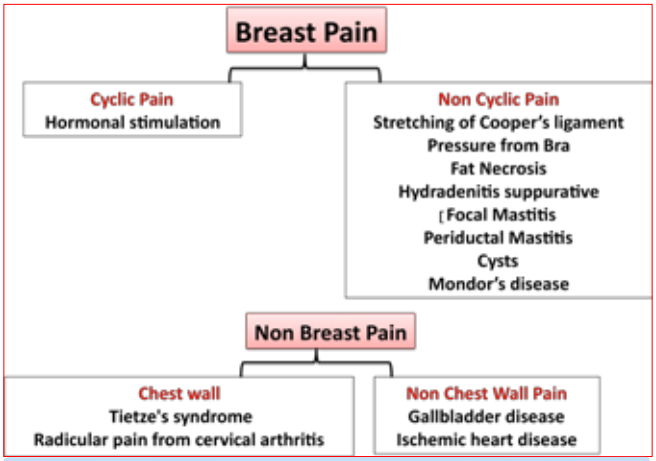

Figure 10-5: Algorithm of diagnosis of Mastalgia. Non-breast pain should be excluded.

Management of Mastalgia:

- Careful history to exclude causes of pain other than the breast (e.g. chest wall) should be undertaken. Most importantly the pattern of pain and its relation to menses should be explored.
- Any risk factors for breast cancer should be identified (see risk factors for breasts cancer) including use of hormones.
- Physical examination should then be performed in systematic fashion as discussed before.

Investigations: In low risk patients usually no further investigations are required, whereas in high-risk women (>40 years) mammography and ultrasound examination should be performed.

In most cases the corner stone of management is reassurance that there is no cancer. The majority of patient will feel comfortable with such reassurance. Additional therapy whether non pharmacologic or pharmacologic is individualized and depends on the severity of the condition and patient response and understanding (see management of fibrocystic changes).

Patients with a breast lump or who fail to respond to medication or unilateral persistent pain in post-menopausal women should be referred for further evaluation in a center with facilities for imaging and cytology.

Breast Lump

Breast Lump whether discrete or multiple is a common presentation and perhaps one of the most worrying for women. The differential diagnosis of breast lump includes a variety of conditions.

The approach to the differential diagnosis of breast lumps should take in consideration the patient's age, nature of the lump if uni or bilateral, patient's history and risk factors. Figure 10-6 shows the differential diagnosis and the algorithm of management of low risk cases as opposed to cases with high-risk cases.

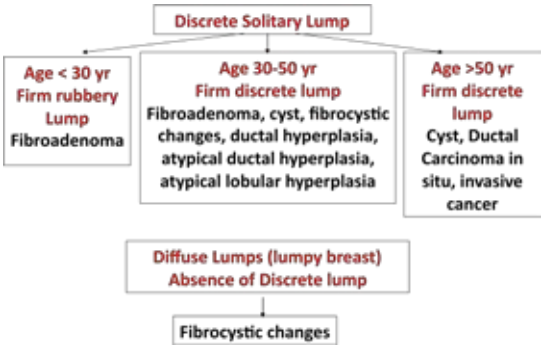

Figure 10-6: Algorithm of management of patients with breast lump

Nipple Discharge

Spontaneous, persistent discharge in non-lactating women can be due to a variety of causes (Figure 10-7). Although in only approximately 3% nipple discharge is associated with breast carcinoma each case should be carefully evaluated. The main objective is to rule out underlying malignancy.

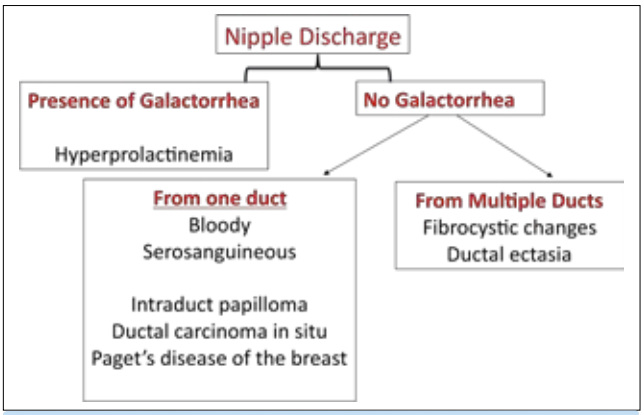

Figure 10-7: Algorithm of DD of breast discharge

The diagnosis of the underlying cause of nipple discharge requires careful evaluation, mammographic examination and eventually excision biopsy. It is to be noted that the color of the discharge does not differentiate a benign from a malignant process. Furthermore while cytology of the discharge is important it may yield false negative results in up to 20% of cases.

Breast Cancer:

Breast cancer is the most common malignant neoplasm in women and comprises 18% of all female cancers. There is about one million new cases in the world each year, with about 14 000 deaths.

The role of gynecologist in the overall fight and / or management of breast cancer cannot be over emphasized. Usually women will seek the advice of their gynecologist regarding potential risks of hormonal therapy whether in the form of hormonal replacement or contraceptive pills in relation to the development of breast cancer. He or she should be able to provide the patient with the basic counseling principles about screening and measures for early detection of breast cancer.

Risk Factors:

It is important to recall that breast cancer is a disease of aging i.e. female gender and age are the most common risk factors (table 10-1).

While it is estimated that one in eight women will develop breast cancer during her lifetime this risk is largely aggregate in the peri-menopausal and postmenopausal years (see sharp increase in risk at age 45). In addition there is a noticeable geographical and ethnic variation in the incidence of breast cancer. In Sauida Arabia recent data shows increased incidence of breast cancer at a rather young age than among Western women.

By age 25	1 in 19609
30	1 in 2525
35	1 in 622
40	1 in 217
45	1 in 93
50	1 in 50
55	1 in 33
60	1 in 24
65	1 in 17
70	1 in 14
75	1 in 11
80	1 in 10
85	1 in 9
Ever	1 in 8

Table 10-1: Risk By Age: A Woman's Risk of Developing Breast Cancer Data from National Cancer Institute. Painter K: Factoring in cost of mammograms, USA Today, 1996

Other specific risk factors for breast cancer fall can be considered under four main categories namely: reproductive factors, particular histological features, and family history and life style factors (Table 10-2):

Risk factor	High Risk Feature	Relative Risk
Reproductive Factor		
Menarche onset	<12 yr old	1.3
Menopause onset	>55 yr old	1.5
Age at birth of first child	Nulliparous or >30	1.9
Histological pattern		
Benign breast condition		1.5
Proliferative disease		2.0
Atypical Hyperplasia		4.0
Family history / Genetic Causes		
Family history of breast cancer	Mother affected	1.7
	Two 1st degree relatives	5.0
Life style and environmental factor		
Obesity	90th percentile	1.7
Alcohol use	Moderate drinker	1.7
HRT	Current use, age 50-59	1.5

Table 10-2: Major categories of breast cancer risk and the estimated risk for each factor.

Genetic risk of breast:

Approximately 10% of breast cancers occur in families in which there are many women with the disease. In about half of these cases there appears to be an autosomal dominant pattern of inheritance.

- Two highly penetrance breast-ovarian cancer genes have been identified BRCA1 and BRCA2, located on the long arms of chromosomes 17 and 13 respectively. Both are tumour suppressor genes inherited as an autosomal dominant with limited penetrance. Together they account for about 5% to 7% of all cases of breast and ovarian cancer and for 50% to 70% of hereditary cases of breast cancer.
- Genetic Counseling and testing:

  Genetic testing should be reserved for individuals who appear to have an increased likelihood of carrying a mutation. It should however be realized that the interpretation of test results whether negative or positive and recommendation for specific prophylactic measure(s) is a complex matter. Many units now have dedicated caner genetics team for that purpose.

Estimation of women specific risk: Different methods have been employed in order to estimate an individual woman specific risk for development of breast cancer. The most common one is the Breast Cancer Risk Assessment Tool (Gail model) (the model is available online at www.cancer.gov/bcrisktool/)

Screening for breast cancer

The aim of screening is to decrease mortality from breast cancer by detecting the disease at an early stage.

The approach to breast cancer screening, in term of the method and the age at initiation of screening should take in account the incidence of screening in the given population and risk factors other than the age.

The methods most commonly used for screening for breast cancer are:

- **Mammography**: So far mammography is the only screening tool of proven effectiveness in reducing mortality from breast cancer by almost 50%. It involve using low-dose amplitude-X-rays to examine the human breast (Figure 10-7). There is however some uncertainties in relation to the age at which screening should begin (from 40 or from 50 years of age) and the frequency of doing mammographic examination.

  Studies have shown a reduction by 29% in mortality when mammography starts after the age of 50. Initiating screening at earlier age (between 40 and 49 years) still can result in reduction of mortality but the yield is too small to be cost effective. However among the local population in Saudi Arabia because of tendency for breast cancer to appear at younger age, the local recommendation is to start mammography screening at age of 40 years, continue at two yearly intervals until 49 years and yearly thereafter.

- **Clinical Breast examination**: refers to the examination performed by the doctor at regular check up visits (every two years before and annually after the age of forty). However clinical breast examination should not replace screening by mammography.

- **Breast self examination "BSE":** The views differ about the benefit of teaching women on self-breast examination in term of reduction of mortality from breast cancer. For example while body like the American College of Obstetricians and Gynecologists recommends routine teaching of BSE, the World Health Organization recommends against BSE. However if BSE is recommended it should not be performed except by women who express a desire to do so and who have received careful instruction to differentiate normal tissue from suspicious lumps

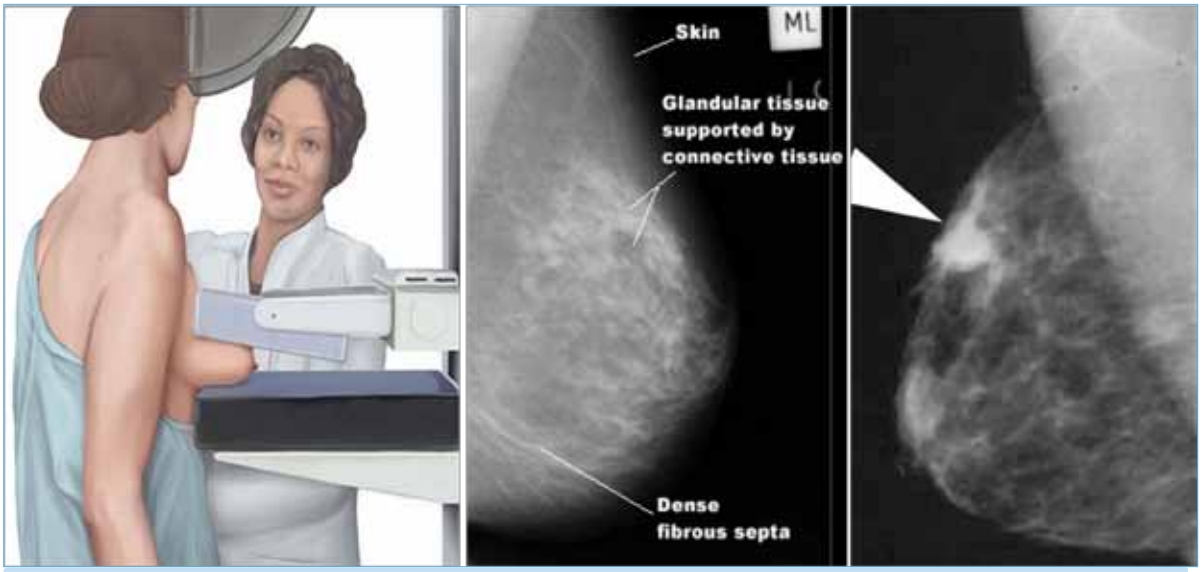

Figure 10-8:Left shows technique of breast mammography, Middle: shows normal mammography, Right: mammography shows early breast cancer detection of breast cancer

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Chapter 11

Ectopic pregnancy

Over the last few years the approach to the diagnosis and management of ectopic pregnancy has dramatically changed. For many years the diagnosis of ectopic pregnancy was only made after its rupture. In such cases the only option of management was surgical removal of the tube. Now with the use of ultrasound and sensitive pregnancy tests ectopic pregnancies are being diagnosed before it rupture or even in asymptomatic women. This permits other options of management either via laparoscopy or by medical and occasionally conservative treatment.

However, despite this development, ectopic pregnancy is still an acute emergency and hemorrhage from ectopic pregnancy is a leading cause of pregnancy related maternal death in the first trimester and accounts for 4 to 10 percent of all pregnancy related deaths.

By the end of this chapter you should be able to:

- **Define** the meaning of ectopic pregnancy.
- **Describe the pathology of ectopic pregnancy:** its location, and natural history.
- **Realizes** the difficulties in defining true incidence of ectopic pregnancies and the factors that changes the incidence.
- **Describe:** the risk factors for ectopic pregnancy.
- **Describe the DD and its different clinical presentations:** Ruptured, Impending ruptured and Un-ruptured ectopic.
- **Describe**: the role of combined Ultrasound and BHCG hormone assay in the diagnosis of ectopic pregnancy.
- **Describe the available options for management of ectopic pregnancy:** Surgical, medical, conservative, the place of each one, its prose and conse.
- **Describe** the principle of medial treatment regiments, including selection of patients, and plan for follow up.
- **Counsel patient:** regarding the different options for management of "stable" ectopic pregnancy, and offer advice on prognosis.

Definition: Ectopic pregnancy occurs when the developing blastocyst becomes implanted at a site other than the endometrium of the uterine cavity.

Pathology and natural history:

Pathogenesis: following fertilization the conceptus spent the first 3 days in the tube before it reaches the uterine cavity. Ectopic pregnancy " i.e. implantation" may occur if the period of transition is delayed or halted because of either tubal factor (e.g. in case of unhealthy tube) or intrinsic factor in the embryo itself.

Location: In about 98% of cases ectopic pregnancy occurs in the fallopian tubes, most commonly in the ampulla followed by the isthmus, and the fimbria (figure 11-1)

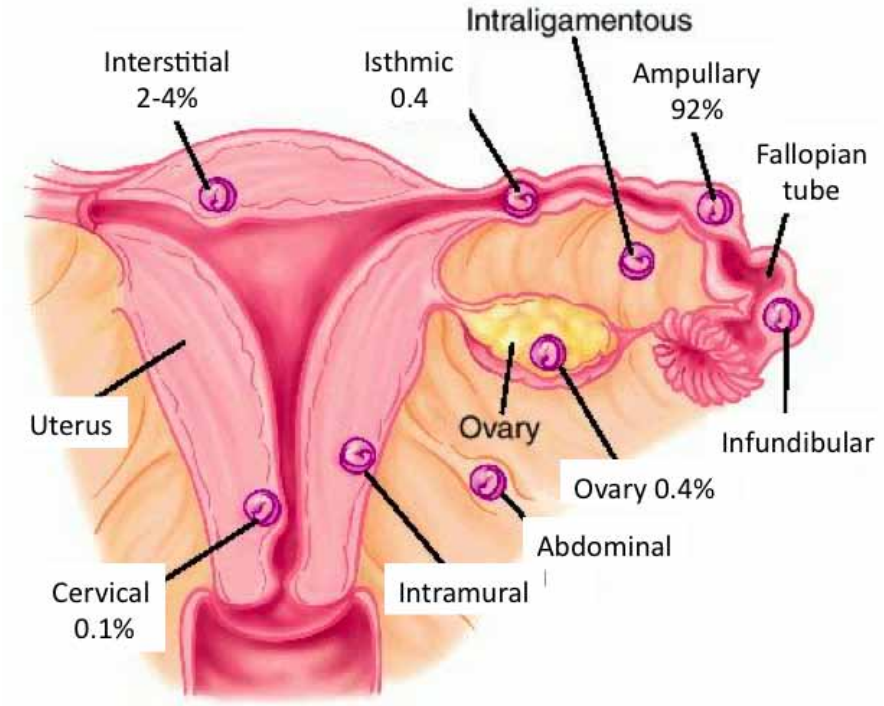

Figure 11-1: Potential sites of ectopic pregnancy and rate of distribution.

Other uncommon sites of ectopic pregnancy:

In the remaining 2% the pregnancy may occur in ovary (ovarian ectopic), or the cervix (cervical ectopic) or the peritoneal cavity (abdominal pregnancy).

- Cervical pregnancy: accounts for 1 percent of ectopic pregnancies. The most common symptom of cervical pregnancy is vaginal bleeding, which is often profuse and painless.

- Ovarian pregnancy occurs in 1 to 3 percent of ectopic pregnancies. The diagnosis is rarely suspected preoperatively. Ovarian ectopic pregnancy may be either primary or secondary. In the primary one the ovum is fertilized in the peritoneal cavity and then implants onto the ovary. In the secondary type, fertilization occurs in the tube followed by tubal abortion with secondary implantation of the embryo on the ovarian surface.

The criteria for diagnosis of ovarian pregnancy

- The fallopian tube with its fimbria should be intact and separate from the ovary.
- The gestational sac should occupy the normal position of the ovary.
- The gestational sac should be connected to the uterus by the ovarian ligament.
- Ovarian tissue must be present in the specimen attached to the gestational sac.

- Interstitial pregnancy accounts for up to 1 to 3 percent of ectopic pregnancies. The problem of interstitial pregnancy is that it is difficult to be differentiated, by ultrasound, from an intrauterine pregnancy that is eccentrically positioned. Therefore delayed rupture of the uterus is a common presentation with high risk of maternal mortality.
- Abdominal pregnancy accounts for up to 1.4 percent of ectopic pregnancies. These pregnancies can go undetected until an advanced gestational week. It is however associated with high rate of maternal mortality (up to 20%) and morbidity.

Natural history of ectopic pregnancy: Once an ectopic pregnancy occurs it takes one of the following courses:

- Tubal rupture: leading to severe hemorrhage and fatal consequences if not promptly treated.
- Tubal abortion: which is expulsion of the products of conception through the fimbria. This can be followed by resorption of the tissue or by reimplantation of the trophoblasts in the abdominal cavity (leading to abdominal pregnancy) or on the ovary (leading to secondary ovarian pregnancy). Tubal abortion may be accompanied by severe intraabdominal bleeding, necessitating surgical intervention, or by minimal bleeding, not requiring further treatment.
- Spontaneous resolution: It is not unknown how many pregnancy undergoes spontaneous resolution (resorption). It is also difficult to predict which patients will experience uncomplicated spontaneous resolution.

Incidence of ectopic pregnancy:

The incidence of ectopic pregnancy is commonly reported as 1.5- 2 per 100 pregnancies. It is probably higher in societies with increased prevalence of pelvic inflammatory disease and among specific patients population with other risk factors such as infertile patients and patients undergoing assisted reproductive technique.

However the true incidence ectopic pregnancy is difficult to know because:

- Many "ectopic pregnancies" vanishes at a very early stage with or without brief presentation by pelvic pain and some vaginal bleeding.
- Furthermore since in most reports the incidence of ectopic pregnancies is often expressed as the number of ectopic per /1000 pregnancies the denominator does not usually include early pregnancy losses that do not result in delivery.
- Currently with an increasing trend for medical treatment of ectopic pregnancies on outpatient bases such cases are not usually included in hospital records as ectopic pregnancies.

Risk Factors for Ectopic pregnancies:

Over 50 percent of cases ectopic pregnancy occur in women who do not have identifiable risk factor. However some women are at higher risk of having ectopic pregnancy than others. Those women should be advised to be screened for ectopic pregnancy as soon they miss a period or have a positive pregnancy test. The risk factors of ectopic pregnancy include:

- Previous ectopic: Women who had previous conservative treatment for ectopic pregnancy are at high risk for recurrence (up to 15 %)
- Tubal pathology: this may be due to previous infection, surgery, congenital anomalies, or tumors.
- Sterilization: If sterilization fails and pregnancy occurs there is high risk of it being ectopic. The risk varies depends on factors such as the technique used for sterilization and patients age.
- Use of intrauterine contraceptive device (IUD): IUD is not a cause of ectopic pregnancy, but like all contraceptive methods, reduces the risks of both ectopic and intrauterine pregnancy (The rate of ectopic pregnancy in women using an IUD is 1/10 of those not using any contraception). However, if a woman with an IUD becomes pregnant, she is at a higher risk of ectopic pregnancy than other pregnant women

- Previous genital infections: Pelvic infection (e.g. nonspecific salpingitis, chlamydia, gonorrhea), especially recurrent infection
- Infertility: The incidence of ectopic pregnancy is higher among infertile population. This could reflect the increased incidence of tubal abnormality in this group of women.
- Other risk factors: include smoking, multiple sexual partner, the extreme of reproductive age (ectopic is more common among young women (i.e. less than age 18) women and women in the older age groups)

Clinical presentation of ectopic pregnancy:

➢ **History and symptoms:**

➢ **Symptoms**: There are no specific diagnostic symptoms for ectopic pregnancy hence a high index of suspicion.

The usual classic triads of symptoms of ectopic pregnancy are: abdominal pain, amenorrhea and vaginal bleeding.

- Abdominal pain: occurs in more than 90% of cases of ruptured or un-ruptured ectopic.
- Amenorrhea: usually of 6-8 weeks with or without pregnancy symptoms e.g. breast tenderness, frequent urination, and nausea. Longer period of amenorrhea may occur in cases of ovarian or cornual pregnancy. However in some cases there may be no history of amenorrhea.
- Vaginal bleeding: if present it is usually scanty and not heavy.

DD of Ectopic pregnancy

From other early pregnancy complications:
- Miscarriage.
- Trophoblastic diseases.
- Ruptured luteal or follicular cyst.
- Complications of ovarian neoplasm e.g. torsion.
- Degenerative fibroid
- Appendicitis
- Cystitis or ureteric pain

It is obvious that those symptoms are not diagnostic for ectopic and are more commonly seen with complicated intrauterine pregnancy (see blue box). Therefore a high index of suspicion is required for early diagnosis of ectopic pregnancy.

➢ **Sings**: the findings on examination varies according to whether the ectopic is ruptured, impends to rupture, or un-ruptured:

◆ Un-ruptured ectopic pregnancy: there is usually tenderness in lower abdomen, may be toward one side more than the other.

On pelvic examination the uterus may be enlarged, and an adnexal fullness may be palpable. An important sign is positive cervical motion sign (i.e. elicitation of tenderness on moving the cervix during examination). In some cases the examination is unremarkable.

- Impending rupture or leaking ectopic pregnancy: The condition should be suspected if there are associated systemic symptoms and signs of impending shock e.g. lightheadedness, tachycardia and tachypnea. The patient may also have shoulder pain due to blood leaking out of the fallopian tube, causing irritation of the diaphragm and/or urge to defecate due to blood pooling in the posterior cul-de-sac (pouch of Douglas).
- Ruptured ectopic pregnancy: this is an acute emergency. Patients usually present with picture of hemorrhagic shock namely pallor, sweating, tachycardia, weak pulse, tachypnea, and hypotension. In addition there are sings of acute abdomen (tenderness, guarding and rigidity) secondary to intraabdominal hemorrhage and peritoneal irritation.

Diagnosis of ectopic pregnancy: early "un-ruptured" ectopic pregnancy should be suspected in all cases that presents with any one or more of the classical triad of pain, bleeding or amenorrhea particularly if the patient has risk factor(s) for ectopic pregnancy. The diagnosis is then made clinically based on the combined results of ultrasound and laboratory tests (hCG).

Transvaginal Ultrasound Examination (TV-US): It is the primary tool in the work up procedures for the diagnosis of ectopic pregnancy. The findings of TV-US are usually one of following:

- A definite intrauterine pregnancy (IUP): This practically excludes tubal pregnancy except in the very rare cases of heterotropic pregnancy (combined intrauterine and tubal pregnancy). By TV-US an intrauterine pregnancy can be visualized by approximately 38 days (5 ½ weeks), which is about 1 week earlier than when using transabdominal US.
- A definite extrauterine pregnancy: in few cases the TV-US may reveal embryonic cardiac activity or a gestational sac with a definite yolk sac or embryo in an extrauterine location.
- A complex adnexal mass: This is the more common finding on US examination.
- Empty uterus: This could be due to either an intrauterine pregnancy, that is too early to be visualized on ultrasound, or an extra uterine pregnancy. The discrimination

Heterotropic pregnancy

Occur in 1 in 4000 - 30,000 spontaneous pregnancy, but about 10 times more in pregnancies following assisted reproduction.

It should be suspected in all women who after an IVF continue to have abdominal or pelvic pain

between the two possibilities can be made by correlating the US findings with the serum human chorionic gonadotropin (hCG) concentration (see below). The combined use of TV-US and hCG permits a definitive diagnosis in almost all cases at a very early stage of pregnancy.

Serum hCG measurements: Both single as well as serial measurements of hCG have important role in the early diagnosis of ectopic pregnancy.

- Single measurement of hCG "**the hCG discrimination zone**": the term hCG discriminatory zone refers to the level of hCG, at which all intrauterine pregnancies should be visible on US. Normally an intrauterine pregnancy should be visualized by transabdominal US at hCG serum level above 6000-6500 mIU/mL and by transvaginal US at hCG level of approximately 1500-1800 mIU/mL (using the Third International Standard for quantitative bhCG).

The "discrimination zone"

Varies between institutions depending on the sonographer expertise, the quality of the ultrasound scan and the presence of physical factors (e.g. fibroids, multiple gestation), and the laboratory characteristics of the hCG assay used.

- Serial hCG assay: in normal pregnancy the level of serum hCG almost double every two days until about 11-12 weeks (figure 11-2), Therefore serial assay of hCG e.g. every 2 or 3 days can helps in the early diagnosis of ectopic pregnancy in the following situations:
  - In cases of "pregnancy of unknown location". This term refers to cases in which the US examination is negative and the hCG levels is still below the discriminatory zone.
  - Also in screening of patients with high-risk factors for ectopic.

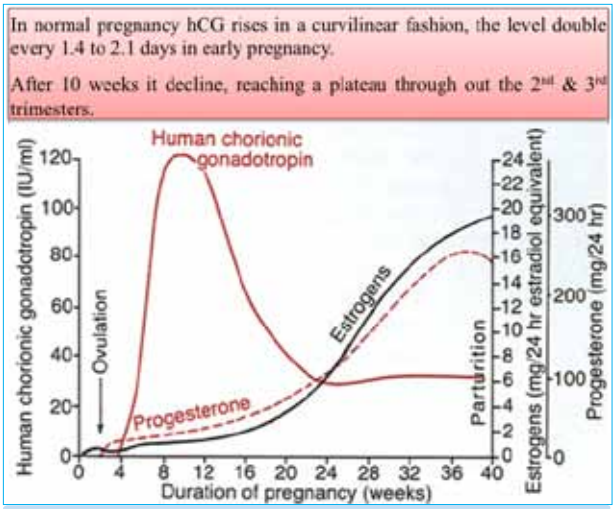

Figure 11-2: Pattern of hCG, progesterone, Estrogen during pregnancy.

In both situations a serum hCG that fails to rise along the normal pattern suggest a failed pregnancy (e.g., arrested pregnancy, anembryonic pregnancy, tubal abortion, spontaneously resolving ectopic pregnancy, complete or incomplete abortion).

Other diagnostic tests for ectopic pregnancy:

- Serum progesterone: A high progesterone level (>20 ng/ml (3.6 mmol/L) usually exclude ectopic pregnancy. However a lower progesterone level does not differentiate between intrauterine pregnancies that are destined to abort or ectopic pregnancy. For this reason measurement of serum progesterone is not commonly used in the diagnostic workup of suspected ectopic pregnancy.

- Curettage / Pipelle endometrial biopsy: It has no place if there is normal rise in hCG levels or if the level is above the discriminatory zone since in such cases the procedure may disrupt a viable intrauterine pregnancy. Curettage or endometrial sampling may however be indicated in cases with declining or plateau hCG levels below the discriminatory zone. Such cases may be due to ectopic pregnancy that would require medical treatment but more likely (70-80% of cases) it is associated with non-viable intrauterine pregnancy and thus would be saved from MTX therapy. It should be remembered that while the presence of chorionic villie is a positive sign of intrauterine pregnancy it could still be absent in up to 20-30 % of intrauterine pregnancy.

- Laparoscopy: Laparoscopy is rarely required for diagnostic purposes. If performed it should be both diagnostic and therapeutic i.e. if ectopic pregnancy is detected it should be treated immediately by surgery.

- Culdocentesis: Is a historical procedure in which a clinical suspicion of ectopic is confirmed if blood can be aspirated from the cul-de-sac by needle insertion through the posterior vaginal fornix. The procedure is rarely used these days because blood in the cul-de-sac can be easily demonstrated by transvaginal ultrasound. In addition it is not necessarily diagnostic for ectopic because it may also be the result of a ruptured ovarian cyst.

Treatment of Ectopic pregnancy:

For many years the only option for treatment of ectopic pregnancy was surgical, usually by laparotomy and salpingectomy. However recent advances in the early diagnosis of undisturbed ectopic pregnancy has increased the management options. Ectopic pregnancy can now be treated by laparotomy, operative laparoscopy, medical treatment, and occasionally by observation alone. The choice depends on the patient clinical condition, her future fertility requirements and her choice after carful counseling.

⇒ Surgical Treatment:

The approach to surgical treatment of ectopic pregnancy may be either through open laparotomy or ideally via the laparoscopic route.

Open laparotomy: The indications for open laparotomy include:

- A hemodynamicaly unstable patient: in such cases the priority is to arrest the bleeding. The procedure most commonly performed is salpingectomy.
- Previous multiple prior surgeries with pelvic adhesions, or lack of laparoscopic surgical skill or proper endoscopic equipments.

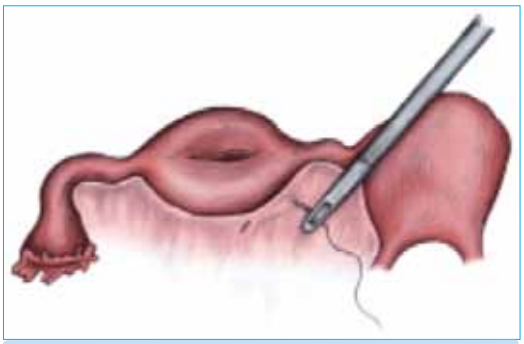

Figure 11-3:In salpingectomy. The tube is clamped and removed

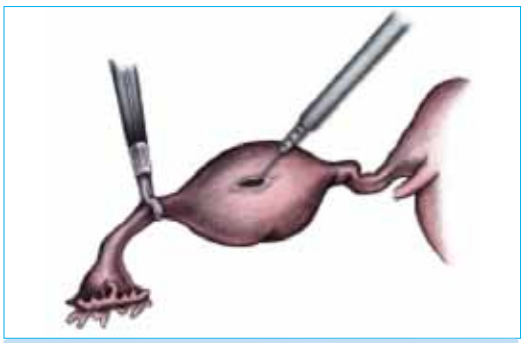

Figure 11-4: linear salpingotomy the ectopic is removed and tube is preserved

Laparoscopic approach: Is considered the ideal surgical approach. The procedures most commonly performed are either salpingectomy, linear salpingotomy or in some cases of fimbrial ectopic pregnancy the gestational tissue can be evacuated "or milked" out of the tube.

Post surgical follow up: All procedures other than salpingectomy run a small risk of proliferation of residual trophoblastic disease "i.e. persistent ectopic pregnancy". Therefore it is recommended that patients who had surgical intervention other than salpingectomy should be followed up by weekly measurement of hCG levels until it returns to nonpregnant values.

In addition patients should be advised to use some form of effective contraception at least until their hCG levels have returned to nonpregnant levels.

⇒ Medical treatment of ectopic pregnancy:

In properly selected cases medical treatment of ectopic pregnancy using methotrexate (MTX) can be successful in nearly 90 percent of cases. It has the advantage of overall lower cost of treatment in addition it save the patient the potential morbidity of anesthesia and surgery.

Units that provide medical treatment should have clear

MTX

It is a folate antagonist, it inhibits DNA synthesis and cell reproduction, in actively proliferating cells such as malignant cells, trophoblasts, and fetal cells.

protocols for patient selection, indications, contraindications, and follow up plan:

Contraindication for medical treatment:

- Hemodynamic instability (*because it usually indicate ruptured ectopic*)
- Impending or ongoing ectopic rupture (*this should be suspected in patients with severe or persistent abdominal pain or >300 mL of free peritoneal fluid outside the pelvic cavity*)
- Patient who is unable or not willing to comply with medical therapy post-treatment follow-up.
- The presence of important abnormalities in baseline hematologic, renal or hepatic laboratory values (*since MXT is metabolized in the liver and excreted by the kidneys*)
- Immunodeficiency, active pulmonary disease, peptic ulcer disease
- Hypersensitivity to MTX
- Coexistent viable intrauterine pregnancy (*cases of Heterotropic pregnancy*)
- Breastfeeding

Precautions during MTX therapy

- Avoid intercourse.
- Avoid pelvic examination.
- Avoid sun exposure to limit risk of MTX dermatitis
- Avoid foods and vitamins containing folic acid
- Avoid non-steroidal anti-inflammatory drugs, as the interaction with MTX may cause bone marrow suppression, aplastic anemia, or gastrointestinal toxicity.

Other relative contraindications include:

- High hCG concentration: the chances of success of medical treatment was shown to be inversely associated with the level of serum hCG concentration (table 11-1). A level of serum hCG greater than 5000 mIU/mL is relative contraindications for medical treatment because of the high risk of treatment failure.
- Fetal cardiac activity: which indicate advanced pregnancy and higher risk of treatment failure.

hCG concentration (IU/L)	% of women treated successfully
< 1000	99
1000 to 1999	94
2000 to 1999	96
5000 to 9999	86
10,000 to 150,000	82

Table 11-1: Success of single dose methotrexate according to hCG concentration.

- Large ectopic size: similarly the chance of successful medical treatment is low if the size of the ectopic pregnancy ≥3.5 cm.
- Large amount of fluid collection in the cul de sac (*could indicate intraperitoneal bleeding*)

Pretreatment counseling: Patients should be counseled regarding the chances of success

of MTX therapy, the potential side effects of the drug, the precautions during the medial therapy in addition to the importance of adherence to the follow up protocol. All instructions should be written down and consented for after careful explanation. This is particularly important for patient who may be treated as out patients.

Pretreatment testing: Prior to medial treatment the following tests should be undertaken:

- HCG level.
- Blood type, complete blood count (*Rh(D) immune globulin should be administered if the woman is Rh(D)-negative*).
- Renal and liver function tests

MTX dose regiments and follow up after treatment:

Several regiments of MTX have been described. Table 11-2 shows the dose and the follow up program for the single and multiple doses regiments of MTX. Currently the single dose regiments is the most widely used one.

Side effects and complications of MTX therapy: Adverse reactions to MTX occur in about 30% of cases. It is usually mild and self-limited. The most common are stomatitis and conjunctivitis. Rare side effects include gastritis, enteritis, dermatitis, pneumonitis, alopecia, elevated liver enzymes, and bone marrow suppression.

Post-treatment laboratory monitoring: The level of hCG usually rises in the first several days (until day 4) due to continued production of hCG by syncytiotrophoblast despite cessation of production by cytotrophoblast. Subsequently by day 7 the hCG is expected to decline by almost <25% from day 1.

⇒ Expectant management:

Expectant management of ectopic pregnancy has very limited place. It may be offered under the following conditions:

- In cases of pregnancy of unknown location: which refers to cases in which the serum hCG levels are below the discriminatory zone (<1000 iu) and there is no pregnancy (intra- or extrauterine) visible on transvaginal ultrasound scan
- In asymptomatic women with an ultrasound diagnosis of ectopic pregnancy, with no evidence of blood in the pouch of Douglas and decreasing hCG levels that are less than hCG 1000 iu/l at initial presentation and less than 100 ml fluid in the pouch of Douglas

The principles of conservative management are:

- Serial measurements of serum hCG every 48–72 hours until the levels are less than 20 iu/l and weekly TV ultrasound examination.

- Active intervention should be considered if symptoms of ectopic pregnancy occur, serum hCG levels rise above the discriminatory level (1000 iu/l) or levels start to plateau.
- Most importantly the patient should be aware of the importance of compliance with follow up and should live within easy access to the hospital treating them.

Prognosis of Ectopic pregnancy:

The prognosis for patients with an ectopic pregnancy is good for those with an early diagnosis.

Fertility may be conserved in those patients diagnosed with an ectopic pregnancy. The earlier the diagnosis is made and treatment administered, the higher the likelihood of subsequent fertility.

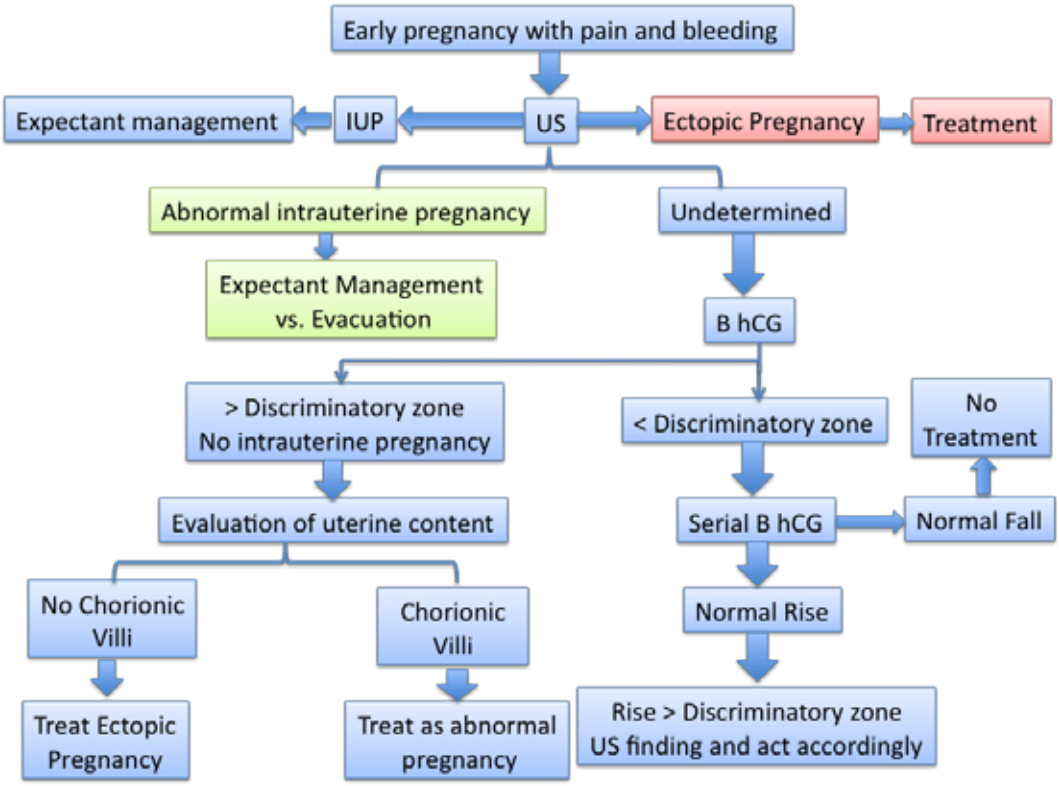

Figure 11-5: Algorithm for treatment of patient's presents with symptoms suggestive of ectopic pregnancy. IUP=intrauterine pregnancy,

Treatment day	Single dose protocol	Multiple dose Protocol
1	hCG Concentration	hCG concentration
	MTX 50 mg/M2 body surface area IM	MTX 1 mg/kg body weight IM
2		LEU 0.1 Mg/kg PO
3		hCG
		If <15 percent hCG decline from day 1 to 3 give MTX 1 mg/kg IM
		If ≥ 15 percent decline from day 1 to 3 begin weekly hCG
4	hCG (protocols vary, see day 7)	LEU 0.1 mg/kg PO*
5		hCG
		If < 15 percent decline from 3 to 5 MTX, give MTX 1 mg/kg IM
		If ≥15 percent decline from day 3 to 5, begin weekly hCG
6		LEU 0.1 mg/kg PO*
7	hCG	hCG
	If < 15 Percent hCG decline from day 4 to 7 (OR < 25 percent decline from day 1 to 7), give additional dose of MTX 50 mg/m2 IM	If <15 percent decline from day 5 to 7 MTX, give MTX 1 mg/kg IM
	If ≥ 15 percent hCG decline from day 4 to 7 (OR ≥ 25 percent decline from day 1 to 7), draw hCG concentration weekly until hCG is undetectable	If ≥15 percent decline from day 5 to 7, begin weekly hCG
8		LEU 0.1 mg/kg PO*
14	hCG	hCG
	If <15 percent hCG decline from day 7 to 14, give additional dose of MTX 50 mg/m2 IM	If <15 percent hCG decline from day 7 to 14, give additional dose of MTX 1 mg/kg IM (give LEU 0.1 mg/kg PO on day 15)
	If ≥15 percent hCG decline from day 7 to 14, check hCG weekly until undetectable	If ≥15 percent hCG decline from day 7 to 14, check hCG weekly until undetectable
21 and 28	If 3 doses have been given and there is a <15 percent hCG decline from day 21 to 28, proceed with laparocopic surgery	If 5 doses have been given and there is a <15 percent hCG decline from day 14 to 21, proceed with laparoscopic surgery
Laparoscopy		
If severe abdominal pain or an acute abdomen suggestive of tubal rupture occurs		
If ultrasonography reveals greater than 300 mL pelvic or other intraperitoneal fluid		

Table 11-2: Chemical Treatment of Ectopic pregnancy

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Chapter 12

Benign Gynecologic Lesions "Vulva, Vagina, Cervix, Uterus"

Benign lesions constitute the majority of gynecological problems seen by general medical practitioners and gynecologists. Proper diagnosis is important not only for treating the patient's symptoms but also to differentiate between malignant and benign lesions. The clinical approach begins with detailed history, general and local examination.

By the end of this chapter you should be able to:

List the most common benign lesions of the vulva: Dermatological lesions, cysts, ulcers, and warts.

Realize the importance of differentiating malignant from benign lesions: plans follow up, indications for further tests and biopsy.

List the most common vaginal lesions: DD of vaginal cysts.

List the most common cervical lesions:

- The pathology and significance of Nabothian follicles
- The pathology and significance of cervical polyps
- Differentiate between ectropion and erosion
- Describe the causes of cervicitis, cardinal signs and symptoms

List the most common benign lesions of the uterus:

- Uterine leiomyomas:
- Its pathology, different types and frequency
- The symptoms: bleeding, pressure and pain and diagnosis
- The obstetrics and gynecological complications of uterine leiomyomas
- Counsel patients on the different options of manamgene

This chapter is not comprehensive review of all lesions but rather the clinically important ones. (table 12-1).

Benign vulvar lesions

The vulva is comprised of the mons pubis, the vulvovaginal cleft, the labia majora, labia minora, clitoris, vaginal introitus, uretha, and vestibule of the vagina. It is thus comprised of dray squamous epithelium and moist mucous membrane, which similar to other skin areas can by affected by spectrum of benign, premalignant and malignant lesions that fall within the realm of various specialties including dermatologists and gynecologists.

The challenge to the clinician is to differentiate between normal variants, benign findings, and potentially serious disease, and this is not always easy.

General approach to evaluation of vulvar lesions: Should include history, physical examination, and diagnostic studies including vulvar biopsies.

The indications of vulvar biopsy include: **(1)** clinically suspicious lesions (*e.g. asymmetry, border irregularity, color variation, rapid change in size or color, bleeding, non-healing*). **(2)** If a diagnosis cannot be made confidently by visual inspection or noninvasive methods **(3)** if the lesion does not resolve after standard therapy.

Vulvar, vaginal Cervical and Uterine benign lesions "Clinically important lesions"		
Vulvar diseases	Cysts and masses	- Urethral Caruncle - Cysts - Nevus - Hemangioma - Fibroma - Lipoma - Hidradenoma - Endometriosis
	Dermatologic diseases	- Pruritus - Vulvar pain Syndrome - Contact dermatitis - Seborrheic dermatitis - Lichen Planus - Hidradenitis Suppurativa
Vagina	- Urethral Diverticulum - Inclusion cyst - Tampon problem - Local trauma	
Cervix	- Endocervical and cervical polyp - Nabothian cysts - Lacerations	
Uterus	- Uterine leiomyomas - Endometrial Polyps	

Table 12-1: Common benign lesions of the vulva, vagina, cervix, and uterus

Dermatologic diseases:

- **Pruritus**: Is the most common gynecologic problems. It is a non specific symptoms the differential diagnosis includes a wide range of vulvar diseases including skin infections, sexually transmitted diseases, specific dermatosis...etc. in addition to psychological causes. In some women pruritus become too severe. Repetitive "itch-scratch" cycles (itching leading to scratching, producing excoriation and then healing) sometimes develop and becomes a real problem.

  The treatment involves treating the cause and interruption of the itch-scratch cycle before it becomes chronic.

- **Vulvar Pain and vulvodynia:** are common gynecological complaints. The differential diagnosis of vulvar pain includes a wide spectrum of causes such as inflammatory conditions, vulvar vestibulities, herpes simplex, neurologic diseases especially of nerve root and psychological causes.

  Vulvodynia is a term that refers to chronic vulvar pain in the absence of clear cause. Treatment is difficult but all possible sources or irritants must be removed. In some cases trial with low dose tricyclic antidepressants may be helpful.

- **Contact dermatosis:** Either contact dermatitis or primary irritant dermatitis. Clinically there is diffuse reddening of the involved skin with possible excoriation and ulceration. Common causes are local irritants such as perfumed soap, deodorant, bubbles baths, tight clothing and urine often induce the condition. Treatment by removing the irritants, applying wet compresses and sometimes using hydrocorticosone 0.5 to 0.1%.

- **Seborrheic dermatitis**: Occurs in areas of skin where sebaceous glands are active, such as the face, body folds and less commonly in the genitalia usually the labia majora and mons pubis.

- **Hidradenitis Suppurativa**: Is a chronic, unrelenting, refractory infection of the skin and subcutaneous tissue primarily the apocrine glands.

- **Lichen sclerosis:**

  Pathology: Is characterized by epithelial thinning, atrophy and dryness of the affected area. The condition typically found in postmenopausal women in the anogenital region but can affects both sexes, at any age.

  Symptoms: common presentation includes: intractable itching (pruritus vulvae), vaginal

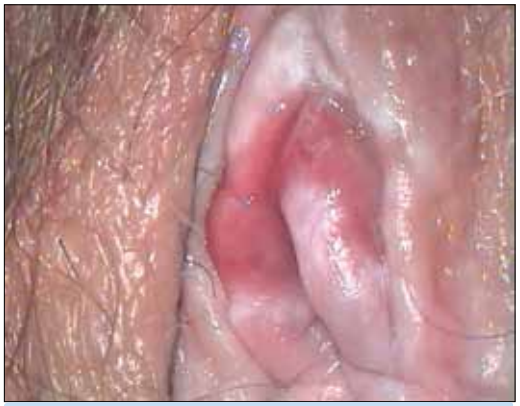

Figure 12-1: Lichen sclerosis

soreness and dypareunia but can be asymptomatic.

Management: include symptomatic treatment by potent topical corticosteroid ointment and close follow .up for signs suggestive of malignant changes

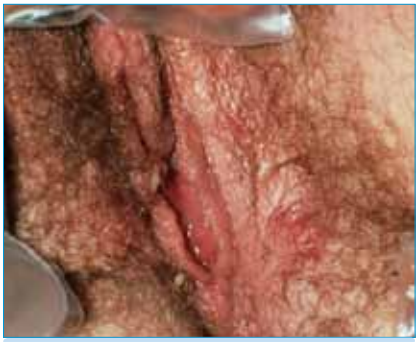

Figure 12-2: HSV Lesions

:(Herpes Simplex (HSV

Causes: Herpes simplex virus: appears as vesicles then ulceration.

Syphilis: appears as papules then ulcerate.

- **Chancroid, granluma inguinale, and lymphgranulma venerum**:.

Treatment: according to the cause

:(Genital warts (condylomata accuminata

Etiology: Human papilloma virus "HPV" can affect the vulva, vagina and cervix. There are more than 50 types of HPV the most important type 6, 11, 18. Tends to increase in pregnancy and in women using OCP.

It is a sexually transmitted disease

Treatment: HPV is a chronic disease, but the Genital warts can be treated by topical application of 25% podophyllin at weekly intervals (should not be used in pregnancy). Other measures include: freezing liquid nitrogen application, cryosurgery, electro diathermy, and carbon dioxide laser.

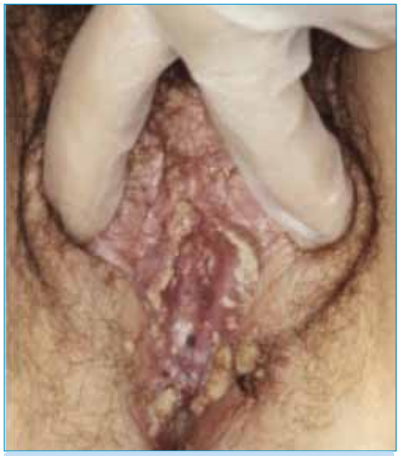

Figure 12-3: Vulvar condylomas appear as painless, cauliflower-like growths

Cysts of the vulva:

The most common conditions in the DD of vulvar cysts are Bartholin's cyst, epidermoid (inclusion) cyst, Gartner cyst, and mucous cysts.

Bartholin Gland:

The Bartholin's glands is approximately 0.5 cm with a duct (2.5 cm long) that open onto the vestibule at the four and eight o'clock positions on each side of the vaginal orifice, just below the hymenal ring (Figure 12-4). Normally it is not palpable.

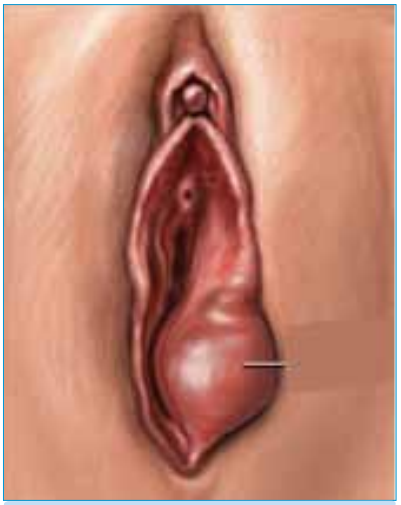

Figure 12-4: Diagram of Bartholin cyst

Disorders of Bartholin's glands: Cysts and abscesses are the most common disorders of the Bartholin's glands, occurring in 2 percent of women; carcinoma and benign tumors are rare.

Bartholin cyst: develops secondary to obstruction of the duct and accumulation of the mucus gland secretion. Bartholin's cyst is usually small in size and asymptomatic. It may be detected during a routine pelvic examination or by the woman herself. Larger cysts may cause discomfort, typically during sexual intercourse, sitting, or ambulating.

Management: No intervention is necessary for asymptomatic Bartholin's cysts, except in women over age 40 in whom drainage and a biopsy should be performed to exclude carcinoma. Cysts that are disfiguring or symptomatic may require surgical drainage or excision.

Bartholin's Abscess: It results from infection of a Bartholin's cyst

Microbiology: usually polymicrobial infection

Clinical manifestation and diagnosis: Women usually present with severe pain and swelling that they are unable to walk, sit, or have sexual intercourse. On examination, the abscess appears as a warm, tender, soft or fluctuant mass in the lower medial labia majora or lower vestibular area, occasionally surrounded by erythema (cellulitis) and edema (lymphangitis).

Treatment: is by surgical drainage. Although excision of Bartholin's gland is a definitive treatment but is associated with high risk of complications, particularly excessive bleeding, hematoma formation, cellulitis, scarring, disfigurement, and dyspareunia. A swab should always be send for culture.

Urethral caruncle:

Pathology: Urethral caruncle is a benign, fleshy outgrowth of the distal edge of the urethra not infrequently seen in postmenopausal women. Appear small, single and sessile but may be pedunculated and grow to be 1 to 2 cm in diameter.

Diagnosis: Most urethral caruncles are asymptomatic and are incidentally noted on pelvic examination; however, some may be painful, and others may be associated with dysuria. Common clinical presentation is by bleeding or blood on the undergarments.

DD: include uretheral proplapse, urethral carcinoma

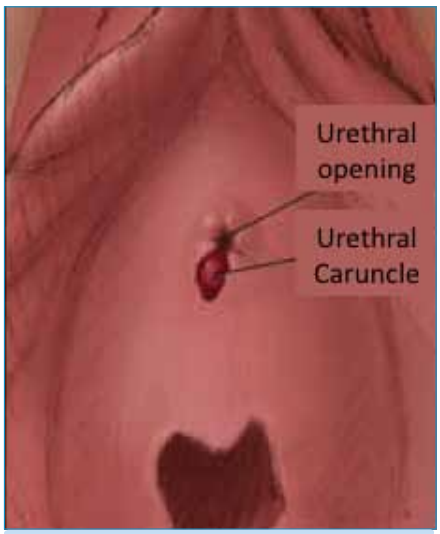

Figure 12-5: Diagram of urethral caruncle

and urethral diverticulum or abscess of periuretheral glands .

Treatment: Conservative therapy is usually the first choice (e.g. warm sitz baths, topical estrogen creams, topical anti-inflammatory drugs). Surgical intervention should be reserved for patients with larger symptomatic lesions, for those in whom conservative therapy fails to elicit a response, and .for those with uncertain diagnoses

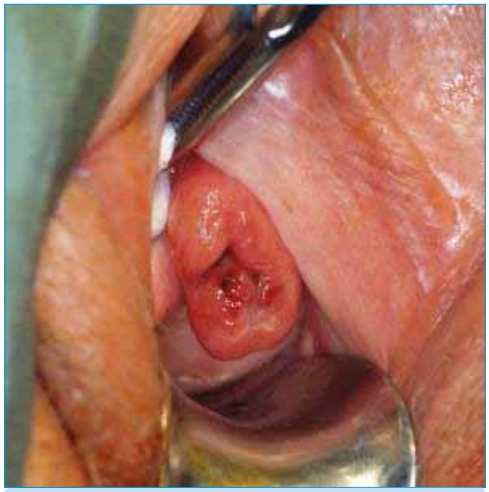

Figure 12-6: Urethral prolapse

Urethra prolapse:

Pathology: Urethral prolapse is defined as the complete eversion of the terminal urethra from the external meatus. It occurs at the extremes of ages among postmenopausal women and prepubertal girls.

Diagnosis: urethral prolapse is predominantly asymptomatic especially in children. On examination, the mucosa is protruding from the urethral opening in a complete rounded doughnut-shape.

In children symptomatic prolapse present with bloody spotting on their underwear or diapers. Voiding disturbances are typically rare in the pediatric population.

In postmenopausal urethral prolapse are often symptomatic presents with vaginal bleeding, dysuria, urinary frequency or urgency, and nocturia.

DD: Urethral prolapse, in which there is complete eversion of the urethra, must be distinguished from urethral caruncle, in which one quarter of the urethral mucosa protrudes.

Treatment: ranges from medical therapy that consists of topical estrogen use to conservative surgical excision when medical therapies fail.

Benign lesions of the cervix

Benign lesions of the cervix (cervix is Latin for neck) are common gynecological problems it includes premalignant, malignant, infection-related, and benign neoplasms. In this section only the common benign cervical lesions will be discussed.

Cervical Ectropion: Is a condition in which the endocervical columnar epithelium everts and becomes exposed to the vaginal milieu.

The condition is commonly seen in adolescents, among women taking hormonal contraceptive pills, and in pregnant women.

It may also be seen in parous women in whom the external os is wide and patulous as a result of tears from prior labor and delivery. Previously the condition used to be described as erosion. Now this term is abandoned.

Ectropion Vs. Erosion

Erosion is a term that implies that the superficial squamous cells have eroded away to expose underlying tissue. Although this can occur, most "erosions" represent areas on the portio of the cervix where squamous cells have been replaced by overgrowth of columnar epithelium.

Symptoms: usually asymptomatic but in some cases a woman may complain of excessive vaginal secretion from the exposed endocervical epithelium, and occasionally postcoital bleeding.

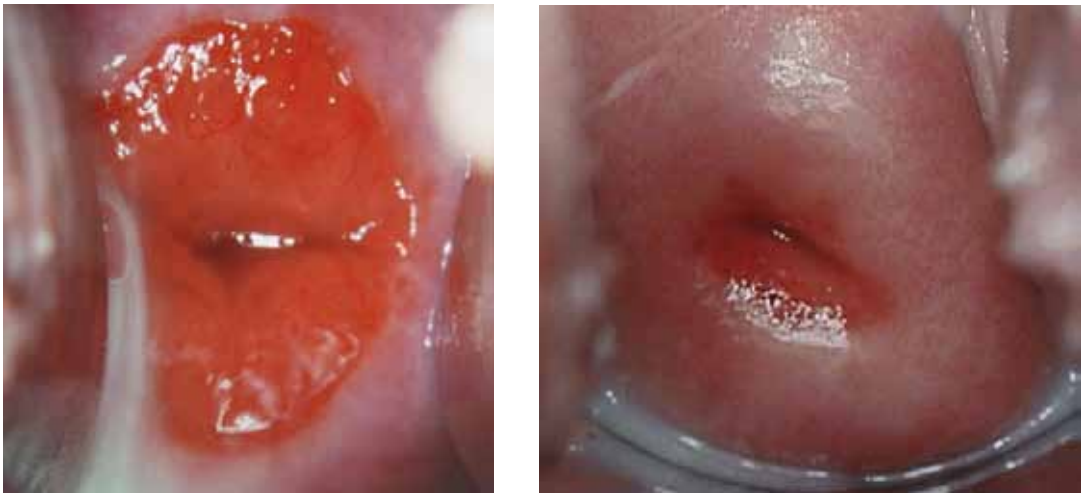

Figure 12-7: Left: normal cervix showing normal squamocolumnar junction. Right cervical ectropion

Treatment: Treatment is only indicated if there are symptoms. In all cases Pap smear should be taken to exclude malignant or premalignant lesions.

Medical: two-week trial of an acidifying agent, such as boric acid suppositories 600 mg vaginally at bedtime or use of deoxyribonucleic acid 5 mg vaginal suppositories.

Ablative treatment: using cryocautery or diathermy. It has the disadvantages of causing copious vaginal discharge until healing is completed and the potential risk of cervical stenosis and scarring on the long term.

Cervicitis: Cervicitis is an inflammatory disorder that primarily affects the endocervical glands it may be acute or chronic.

Etiology: In large proportion of cases no etiology can be found. But some cases are due to sexually transmitted infections such as Chlamydia trachomatis and Neisseria gonorrhoeae, and less common causes include T. vaginalis, Mycoplasma genitalium, bacterial vaginosis, and streptococci (group A and group B).

In some cases the precipitating cause may be trauma from foreign bodies, vaginal douching, pessary, diaphragm, cervical cap or irritation from exposure to latex, vaginal douches, or contraceptive creams.

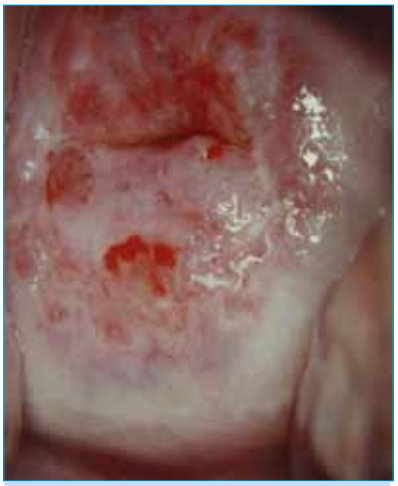

Figure 12-8: Chronic cervicitis

Diagnosis: The cardinal signs are purulent or mucopurulent discharge and friability of the tissue of the ectocervix (i.e. easily induced bleeding). Associated symptoms include abnormal vaginal discharge, dysuria/urinary frequency, and intermenstrual or postcoital bleeding.

Definitive diagnostic evaluation for potential causative organisms includes assays for chlamydia and gonorrhea, as well as evaluation of vaginal fluid for trichomoniasis and bacterial vaginosis.

Treatment: The goals of treatment are relief of symptoms and prevention of ascending infection of the upper genital tract. In most cases the treatment is empirical with antibiotic therapy against the most likely causative agent.

Antibiotic Treatment

N. Gonorrhoeae: Oral Cefixime 400 mg as a single dose

Bacterial vaginosis and Trichomonas vaginitis: Metronidazole 500 mg oral twice daily for seven days

Chlamydia: Azithromycin 1 g orally once or doxycycline 100 mg orally twice daily for seven days

Nabothian cysts: (also called mucinous retention cysts, epithelial inclusion cysts) is the most common cystic lesion of the cervix. It forms when a cleft of columnar epithelium becomes covered with squamous cells and the columnar cells continue to secrete mucoid material. The cysts vary from microscopic to several centimeters in size.

Treatment: is not indicated unless it becomes symptomatic e.g. causing fullness in the vaginal.

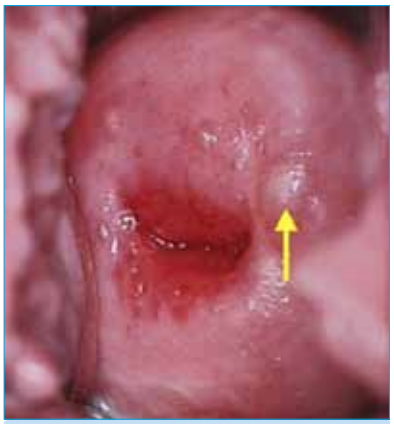

Figure 12-9: Nabothian cyst

Endocervical polyps: are the most common benign neoplasms of the cervix. They are focal hyperplastic protrusions of the endocervical cells, including the epithelium and underlying tissues.

Clinical presentation: Endocervical polyps are usually asymptomatic but may cause profuse leukorrhea or postcoital spotting. Sometimes it is difficult to distinguish from endometrial polyps protruding through the cervix.

Treatment: if the polyp pedicle is slender it can be removal, by simply twisting the polyp with ring forceps. Smaller polyps may be removed with punch biopsy forceps. Polyps with a thick stalk require surgical removal.

Figure 12-10: Endocervical polyp. Sagital view.

Benign lesions of the vagina

Vaginal discharge and vaginitis: Bacterial vaginosis, vulvovaginal candidiasis, and trichomonas vaginitis are the most common causes of vaginal discharge in premenopausal women. However other causes should be considered. The subject is addressed in chapter 15.

Vaginal congenital anomalies: include obstructive and non-obstructive anomalies, partial and complete vaginal agenesis (see chapter 7)

Vaginal cysts: The DD of cysts in the vagina includes:

- Epidermal inclusions cysts: These cysts result from trauma (e.g. laceration, episiotomy repair) that entraps viable epithelial tissue below the vaginal epithelial surface.
- Gartner's duct (a remnant of Wolffian duct): This is usually located on the lateral or posterior vaginal walls.
- Urethral diverticulum cysts: are usually located on the anterior vaginal.

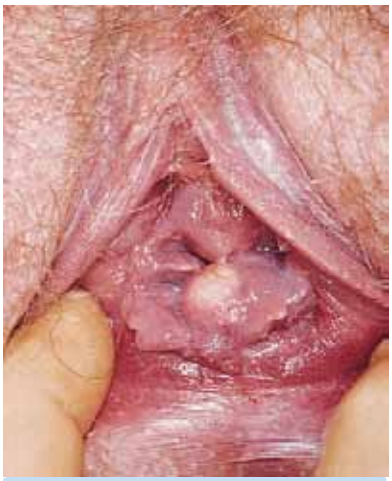

Figure 12-11: vaginal inclusion cyst

Symptoms: Apart from uretheral diverticulum cysts, vaginal cysts are usually asymptomatic. It may be discovered accidentally during gynecologic examination or the patient herself may feel it during self-examination, while inserting a tampon or because of dyspareunia.

Treatment: asymptomatic cysts may be treated conservatively. If symptomatic it can be treated by excision, or marsupialization, which is safer in cases of deep cysts in order to avoid significant bleeding. Also in rare cases a Gartner's duct cyst may communicate with an ectopic ureter. For this reason, imaging of the urinary tract is indicated prior to its excision.

Urethral diverticulum:

Pathology: Is a protrusion of the urethra into the potential space between the periurethral fascia and anterior vaginal wall. Most probably it results from repeated infection of the periurethral glands.

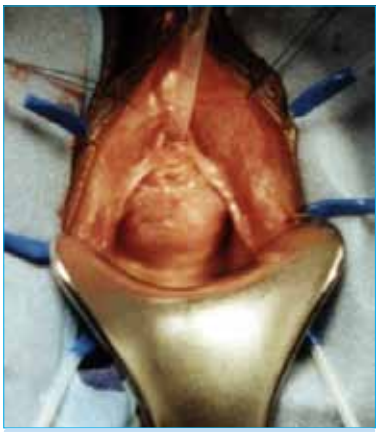

Figure 12-11: urethral diverticulum showing as anterior wall vaginal bulge

Diagnosis: Typically patients presents with triad of symptoms: Dysuria, Post void dribbling, Dyspareunia. On examination a fullness, or tenderness mass may be felt and urine or purulent discharge can be expressed. Investigations using imaging studies e.g. MRI and US is required to confirm the diagnosis.

Treatment: Asymptomatic urethral diverticulum do not require treatment. Mildly symptomatic patients may be managed conservatively with digital decompression after voiding or periodic needle aspiration, and antibiotic prophylaxis. Patients who have significant symptoms are best managed by a surgical approach.

Benign lesions of the uterus

Uterine leiomyomas

Pathology: Uterine leiomyomas (fibroids or myomas) are the most common benign uterine tumors. It arises from the smooth muscle cells of the myometrium, and contains a large amount of extracellular matrix. It is usually surrounded by pseudocapsule made of the surrounding compressed areolar tissue and muscle fibers. Myomas can occur as single or multiple tumors and range in size from microscopic to tens of centimeters.

Types: Fibroids are often described according to their location in the uterus into:

- **Intramural fibroids**: develop from within the uterine wall. They however may enlarge sufficiently to distort the uterine cavity or serosal surface.
- **Submucosal myomas**: originate from the myometrial cells just below the endometrium. These neoplasms often protrude to a variable degree into the uterine cavity. Sometimes develop a long pedicle and presents as prolapsed pedunculated fibroid.
- **Subserosal myomas**: originate from the serosal surface of the uterus. They can have a broad or pedunculated base, or may grow between the folds of the broad ligament (intraligamentary).
- **Cervical fibroids:** are located in the cervix, rather than the uterine corpus.

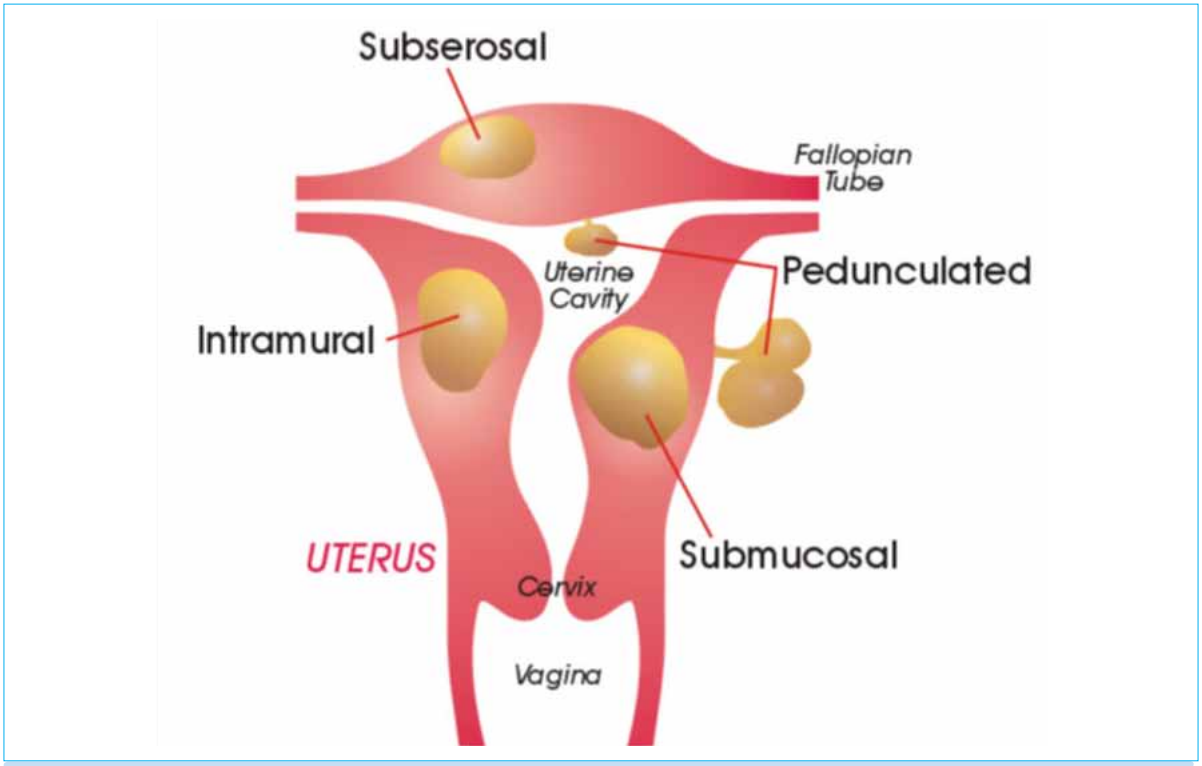

Figure 12-12: illustration-showing types of fibroids. According to its location

Prevalence:

The true prevalence of fibroids is not exactly known because many women have fibroids that remain asymptomatic. It is estimated that about 70% of women have fibroids but in approximately only 25% it becomes symptomatic.

Risk factors for fibroids: Epidemiological studies have shown that the following factors are associated with increased rate of fibroids:

- Racial factors: fibroids are more common in African women, in whom it tends to appear at younger age and reach larger size.
- Parity: fibroids are more common among nulliparous women. Having one or more pregnancies extending beyond 20 weeks decreases the chance of fibroid formation.
- Age: Fibroids usually affect women over age 30. They are rare in women under 20, and often shrink and cause no symptoms in women as they approach menopause.
- Familial: Studies have shown familial predisposition to developing fibroids.

Clinical manifestations (complications of fibroid):

Symptoms of fibroids: The symptoms are related to the number, size, and location of the fibroids. Symptoms attributable to uterine myomas can generally be classified into three distinct categories:

1. **Increased uterine bleeding**: is the most common symptom usually in the form of heavy and/or prolonged menses (menorrhagia or hypermenorrhea). The mechanism(s) of profuse menses can be explained by increased uterine vasculature, increased endometrial surface area and impaired endometrial hemostasis.

   The presence and degree of uterine bleeding is determined, in large part, by the location of the fibroid e.g. Subserosal fibroid may not be associated with abnormal uterine bleeding. Also pedunculated submucosal fibroids are associated with metrorrhagia and inter-menstrual bleeding, spotting and blood stained discharge.

2. **Pelvic pressure "bulk-related" symptoms**: The extent and nature of pressure symptoms depends on the size and location of the fibroid.

   - Urinary pressure symptoms: e.g. urinary frequency, difficulty emptying the bladder, and, in rare occasion urinary obstruction. Silent prolonged pressure can occasionally cause ureteric compression and leads to renal hydronephrosis.
   - Pressure on the rectum: can result in constipation.

3. **Pain**: fibroids can cause different types of pain:

   - Acute pain: can results from torsion of a pedunculated tumor or degeneration namely red degeneration (most commonly occur in pregnancy)

- Pressure pain: chronic pelvic pressure due to increased size.
- Dysmenorrhea: can also be caused by fibroids. This pain, at least in some cases, is related to heavy menstrual flow.

The pain resulting from degenerating fibroids is self-limited, lasting from days to a few weeks, and usually responds to nonsteroidal anti-inflammatory drugs.

Complications of fibroids:

1. **Reproductive complications**: include gynecological and obstetrical complications
   - Gynecological complications:

     Infertility: fibroids do not interfere with ovulation and are not direct causes of infertility. However it can affect fertility by being a cause of miscarriage due to multiple reasons e.g. distortion of the endometrial cavity that interferes with implantation or placental growth over the myoma site, and /or increased uterine contractility .
   - Obstetrical complications:

     The presence of fibroids increases the risk of some pregnancy complications, including first trimester bleeding, placental abruption, abnormal fetal presentation, dysfunctional labor and an increased risk of cesarean delivery. These complications appear to be related to the size and location of the leiomyomas as well as the position of the placenta, with the highest risk when the placenta implanted over the myoma.
2. **Degenerative changes of fibroid:** The most common degenerative changes are hyaline changes in which the fibrous and muscle tissues are replaced with hyaline tissue. Further reduction in blood supply leads to cystic changes "cystic degeneration". Other degenerative changes include calcification, fatty degeneration, and red degeneration. Red degeneration occurs mostly in pregnancy in 5% to 10% of cases with fibroids. Red degeneration occurs due to hemorrhage into the center of tumor. It is one of the DD of acute abdominal pain in pregnancy. The treatment is conservative with analgesics, and hydration.
3. **Uterine fibroid and leiomyosarcomas**: The risk that a leiomyomas development into leimyosarcoma is extremely small. Genetic studies of fibroids and uterine muscle cancer (sarcoma) show that they have very different genetic mutations and that sarcomas do not develop from fibroids. Most premenopausal women with a uterine mass, even those with a rapidly enlarging mass, do NOT have a sarcoma. However the risk of sarcoma is higher (1-2%) among postmenopausal women with a new or enlarging pelvic mass, abnormal bleeding, and pelvic pain.

Diagnosis of fibroids:

Clinically: Majority of fibroids are asymptomatic and frequently detected during a routine pelvic examination especially with the current widespread use of ultrasound in gynecological examination. The diagnosis is suspected on the bases of the finding of an enlarged, mobile uterus with an irregular contour on abdominal and bimanual examination.

Investigations: Although a pelvic exam detects fibroids, the possibility of other conditions such as ovarian masses, adnexal swellings and cysts must be ruled out.

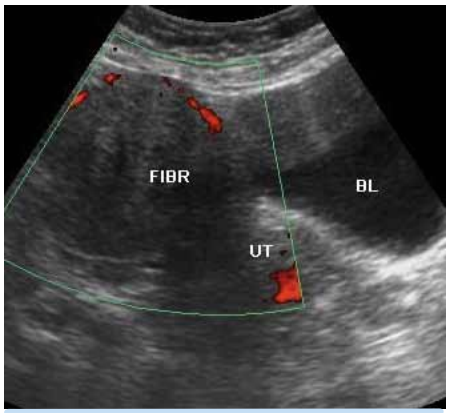

Figure 12-13: US picture showing fundal fibroid. Ut=uterus, Bl=bladder

Ultrasound examination: either abdominal and/or transvaginal is the principle investigation to confirm the diagnosis of fibroid and determine its location. The 3D ultrasound is particularly useful in definining submucus myomas.

Magnetic resonance imaging: is usually reserved when planning surgery for complicated fibroids. MRI is the best modality for visualizing the size and location of uterine myomas, to distinguish between leiomyomas, and adenomyosis. It is also useful in differentiating leiomyomas from leiomyosarcomas.

Other diagnostic tools: in some cases other diagnostic tools such as hysterosalpingogram, hysteroscopy, computed tomography and salinesonography might be required.

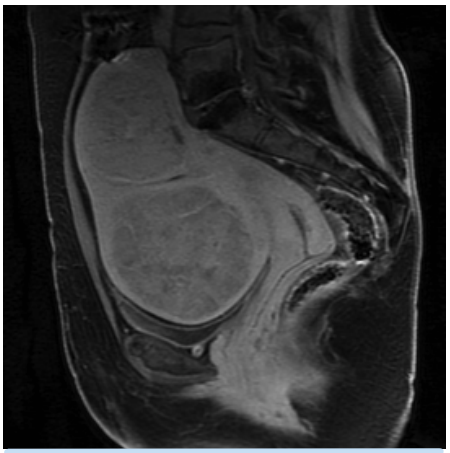

Figure 12-14: MRI picture in case of complicated, impacted fibroid.

Management:

There are several options for treatment of uterine fibroids including conservative medical, radiological and surgical therapies either via laparotomy or minimal access approaches. The choice depends on several factors these are:

- Size of the myoma(s)
- Location of the myoma(s)

Severity of symptoms

- Patient age

- Reproductive plans and obstetrical history

- **Conservative treatment:** no definitive treatment is required for asymptomatic small fibroids (e.g. < 12 weeks in size) especially in patients > 40 years of age. Patient can simply be asked to adhere to her regular visit for annual check up examination including assessment of the fibroid size.
- **Medical Treatment:** aims to treat the of fibroids symptoms namely uterine bleeding:
  - **Combined oral contraceptive pills "OC":** reduce bleeding through enhancing endometrial atrophy.
  - **Levonorgestrel-releasing intrauterine system "IUS" (progestogen loaded IUD - Mirena):** In selected cases the Mirena IUS can be used to reduce the bleeding. It also has the advantage of providing contraception. It is however contraindicated in cases with large submucus leiomyomas amenable to hysteroscopic resection.
  - **Gonadotropin-releasing hormone (GnRH) agonists:** GnRh agonist **inhibits** the secretion of gonadotropins and sex steroids through pituitary desensitisation and down-regulation, thus results in a state of hypoestrogenism that clinically resembles menopause. Treatment with GnRH agonist usually induces amenorrhea and result in decrease in the size of fibroids by up to 50% within three months of therapy. However this reduction is temporary, and cessation of therapy is often associated with prompt re-growth of the fibroids. Another disadvantage of GnRH administration is the potential for irreversible bone loss if given for > 6 months as a result of demineralisation caused by the hypoestrogenic state. Some women may also develop annoying menopausal symptoms of hot flashes and irritability.

    Therefore currently the place of GnRh therapy is for preparing patients for surgery by reversal of preoperative anaemia and perhaps reduction of operative morbidity by reducing the fibroid mass and intra-operative blood loss. It may also facilitate better surgical approach through a transverse (Pfannenstiel- type) rather than a midline incision

- **Surgical treatment:**

The surgical options for treatment of fibroids include:

- Hysterectomy: is the definitive treatment
- Myomectomy: can be achieved either through laparotomy or via laparoscopy

- Less invasive techniques such as uterine artery embolization (UAE), magnetic resonance-guided focused-ultrasound surgery (MRgFUS) and myolysis.
- **Hysterectomy:** is indicated in the following situation:
  (1) Women with acute hemorrhage who do not respond to other therapies.
  (2) Women who have completed childbearing and have current or increased future risk of other diseases (e.g. cervical intraepithelial neoplasia, endometriosis, adenomyosis, endometrial hyperplasia, or increased risk of uterine or ovarian cancer)
  (3) Women who have completed childbearing and have significant symptoms, multiple leiomyomas, and a desire for a definitive end to symptomatology.
- **Myomectomy:** Myomectomy is a surgical procedure that removes visible fibroids from the uterine wall. It is not a definitive treatment. It is an option for women who have not completed childbearing or otherwise wish to retain their uterus.

  It has the disadvantages that in 10 percent to 30 percent of cases fibroids grow back several years after myomectomy from new clones of abnormal myocytes. Myomectomy can be performed in several ways:
  - Through laparotomy.
  - Via minimal invasive laparoscopic or laparoscopy and robotic-assisted surgery.
  - Hysteroscopic Myomectomy: for some cases of submucus fibroids with > 50% protrusion into the uterine cavity.
- **Myolysis:** Myolysis refers to laparoscopic thermal coagulation or cryoablation (cryomyolysis) of leiomyoma tissue. The procedure is usually reserved for women who have completed childbearing because of potential risk of scar dehiscence in future pregnancy.
- **Uterine artery or fibroid embolization:** is a minimally invasive "myomectomy" that aims to primarily treat the leiomyomas-related symptoms. It is not recommended for women who want to maintain future fertility.

Magnetic resonance guided focused ultrasound: is a non-invasive outpatient, procedure that uses high intensity focused ultrasound waves to ablate (destroy) the fibroid tissue. During the procedure, an interventional radiologist uses magnetic resonance

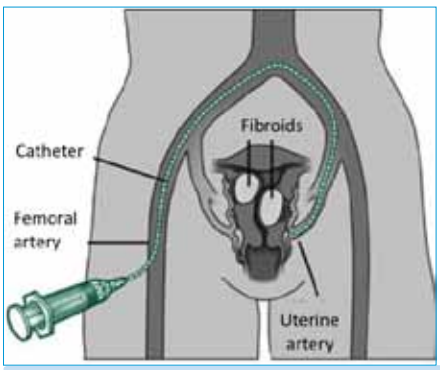

Figure 12-15: Diagram displaying technique of uterine artery embolization

imaging (MRI) to see inside the body to deliver the treatment directly to the fibroid. It is . suitable for premenopausal women who have completed childbearing

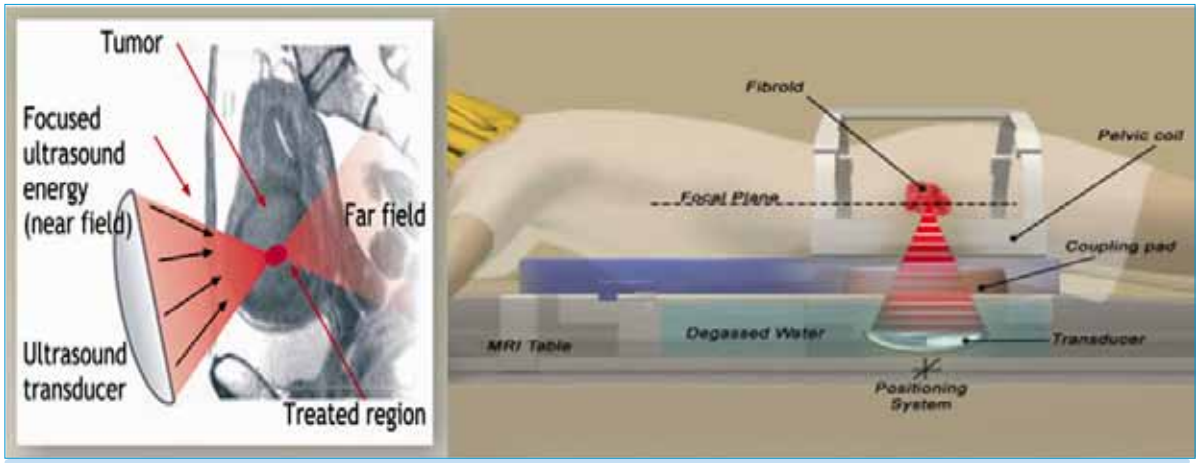

Figure 12-20: Diagrammatic presentation of the use of Magnetic resonance guided focused ultrasound in targeting uterine fibroids. The procedure is performed as outpatient procedure.

Endometrial polyps

Endometrial polyps are a common cause of bleeding in pre- and postmenopausal women. They are usually benign although some may be precancerous or cancerous. No definitive cause of endometrial polyps is known, but they appear to be affected by hormone levels and grow in response to circulating estrogen.

Clinical presentation: symptoms include irregular menstrual bleeding, inter-menstrual bleeding, excessively heavy menstrual bleeding (menorrhagia), and postmenopausal bleeding. Occasionally a pedunculated large polyps can protrude through the cervix into the vagina.

Diagnosis: Endometrial polyps can be detected by vaginal ultrasound, 3D ultrasound, sonohysterography, and hysteroscopy.

Treatment: The ideal treatment is by hysteroscopy resection. Simple curettage often misses endometrial polyps. After removal the specimen should be send for histological examination to exclude malignant changes.

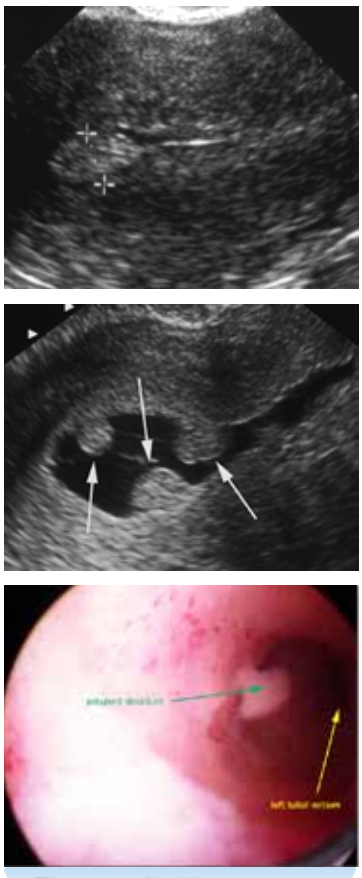

Figure 12-21: Endometrial polyp as seen by US (top), Sonohysterography (middle) and via hysteroscop (bottom)

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Chapter 13

Chronic pelvic pain (CPP) Endometriosis and Adenomyosis

Pain is a serious symptom, if it is chronic it is debilitating, can affects ones family, social, and mental life. Chronic pelvic pain is more common among women, although it can also affects men.

For gynecologist the diagnosis and management of CPP is challenging and often require multidisciplinary approach. This chapter addresses the approach to the diagnosis and management of women with CPP with emphasis on the common gynecological causes namely endometriosis and adenomyosis.

By the end of this chapter you should be able to:

Chronic pelvic pain "CPP" syndrome:

- **Define** the diagnostic criteria of CPP and risk factors for CPP syndrome.
- **Appreciate:** the multidisciplinary nature of CPP: Gastrointestinal, Urological, Gynecological, Psychological, Musculoskeletal and Neurological.
- **List:** the most common gynecological causes
- **Describe:** the approach to the diagnosis and management of CPP

Endometriosis:

- **Describe** the prevalence of endometriosis and its risk factors
- **The pathology and pathogenesis:** of its symptoms
- **List the clinical presentation:** Pain (its different presentation) and infertility. In many occasions it is incidental and asymptomatic.
- **Describe** the approach to the diagnosis
- **Describe the options of management:** Analgesics, hormonal, Surgical. Including the different levels of surgery (conservative, radical, for pain)
- **Counsel patients** on the option of management according to factors: age, primary complains, and patient wishes.

Adenomyosis:

- **Describe the pathology** and risk factors for adenomyosis.
- **Describe the clinical presentation**: pain and abnormal uterine bleeding.
- **List the DD diagnosis of adenomyosis** (DUB and uterine myoma)
- **Appreciate the limitation**: of the diagnostic tools, MRI and US
- **Discuss the management:** of adenomyosis

Chronic pelvic pain Syndrome (CPP)

Refers to pain of at least six months' duration that occurs below the umbilicus and is severe enough to cause functional disability or require treatment. It is a common problem that constitutes approximately 10 percent of all referrals to a gynecologist and is a common indication for diagnostic and therapeutic surgery.

The type, presentation and severity of the pain varies, it can lead to depression, sleeping disorders, family and social problems.

Causes of chronic pelvic pain:

The major sources that should be considered when evaluating women with CPP include:

- **Gastrointestinal:** irritable bowel syndrome, inflammatory bowel disease (e.g. Crohn's disease, Ulcerative colitis…etc), Diverticular colitis, colon cancer, chronic constipation...etc.
- **Urological**: e.g. interstitial cystitis
- **Gynecological:** endometriosis, adenomyosis, chronic pelvic inflammatory disease, leiomyomas, ovarian remnant and residual ovary syndrome, pelvic congestion syndrome.
- **Psychological:** Depression, physical or sexual abuse (past or present)….etc
- **Musculoskeletal**: Fibromyalgia, Coccygodynia, pelvic floor tension myalgia, or pelvic myofascial pain is caused by involuntary spasm of the pelvic floor muscles (e.g. piriformis, levator ani, iliopsoas, obturator internus).
- **Neurological:** Neuralgia, especially of the iliohypogastric, ilioinguinal, genitofemoral, or pudendal nerves. Other neuromuscular lesions include herniated nucleus pulposus, neoplasia neuropathic pain, abdominal epilepsy and abdominal migraine.

The approach to diagnosis and management of patients with CPP:

Identifying the exact cause of CPP syndrome is a challenging exercise. Therefore it requires time, sympathetic and approach in order to develop trust and confidence between the doctor and patient.

History: taking full and detailed history is the first and most important step. The main areas to be reviewed are:

- Historical risk factors of CPP such as:

- A previous pregnancy that has stressed the patient's back and uterus especially if ended by difficult normal or operative delivery.
- Pelvic inflammatory disease, radiation of the uterus, and surgical procedures performed upon the female reproductive system.
- Sexual abuse, alcohol or drug abuses are important risk factor for Pelvic Pain Syndrome.

- Pain history: A complete history of the patient's pain, as well as a thorough review of systems with emphasis on symptoms of urinary tract disease, bowel disease, reproductive tract disease, musculoskeletal disorders, and psycho-neurological disorders, including history of sexual abuse.
- Psychological history: aims to identify potential psychological background or disorders. A tool for assessing psychological status is provided in the International Pelvic Pain Society's patient evaluation form (www.pelvicpain.org)

Physical examination:

- Abdominal examination: the aim is to identify areas of tenderness, surgical scars, hernias, and any masses.
- The pelvic examination: should include a careful inspection and careful internal examination for evaluation of the shape, size, and mobility of the pelvic organs, as well as any areas of tenderness
- The goal is to identify tender areas, correlate these areas with the patient's pain map, and determine whether the pain produced on examination represents her CPP.

Investigations:

Routine investigations:

- Blood tests for hemoglobin, white blood count and sedimentation rate
- Cervical Pap smear
- Vaginal swab and culture from any abnormal discharge
- Urine for microscopy and culture

Special tests:

- Screening to rule out infection and sexually transmitted diseases.
- Ultrasound, MRI and CT scans as appropriate.
- Laparoscopy: not-uncommonly has to be performed. It serves two main purposes first to search for the cause and second to reassure the patient.

Pelvic congestion syndrome: One of the common gynecological diagnoses is pelvic congestion syndrome, which is a rather controversial condition. It can be explained by the unique characteristics of the pelvic veins that make them vulnerable to chronic dilatation with stasis leading to vascular congestion.

The patient often complains of characteristic symptoms of shifting location of pain, deep dyspareunia, post-coital pain, and exacerbation of pain after prolonged standing. Imagining examination shows the pelvic varicosities (dilated uterine and ovarian veins) that display reduced blood flow. However the non specific nature of such findings is that it is not uncommonly found in asymptomatic women.

Treatments:

Successful treatment of CPP depends on indentifying a cause. This requires multidisciplinary approach, sympathy and understanding. Unfortunately the exact cause may not be identified. It is important to differentiate between gynecological and non-gynecological causes.

The most common gynecological causes include endometriosis, adenomyosis, chronic inflammatory diseases, uterine leiomyomas and others…etc.

Endometriosis

Definition: Endometriosis is defined as the presence of endometrial glands and the underlying stroma outside the uterine cavity.

Epidemiology and Prevalence: The prevalence of endometriosis is variably reported with a range from 2-50 % depending on the type of population being studied whether they are symptomatic or asymptomatic:

- Among asymptomatic women undergoing surgical sterilization, about 2 to 5% were found to have endometriosis.
- Whereas among women being investigated for infertility the range is about 20-25% and can be as high as 80% among women with chronic pelvic pain.

Risk factors for endometriosis:

- Age and parity: Endometriosis affects women in their reproductive age between 30-40 years particularly nulliparous. However currently with wide spread utilization of

laparoscopy in the investigation of patients with CPP and infertility many cases of endometriosis are being identified at younger ages.

- Racial and social factors: Endometriosis is more common among white, professional women particularly those described as being perfectionist with strong ego. However this apparent relationship is probably confounded by delayed conception and family formation among such women.
- Genetic predisposition: A first-degree relatives of a woman with endometriosis has an approximately 7% chance of being similarly affected.

Pathogenesis:

Because of a lack of suitable animal model that could replicate the anatomic correlation and natural history of the diseases in humans, the etiology and pathophysiology of endometriosis is not well understood. Several theories have been put forward to explain the pathogenesis of endometriosis the most important ones are:

1. Transplantation theory:

Extrauterine implantation of the endometrial epithelium can be transplanted outside the uterine cavity through one or more of several mechanisms. The most common ones are:

- Retrograde menstruation: this theory was first described in Sampson classic paper in 1927, and still holding as the most likely mechanism particularly for pelvic endometriosis. In support of this theory are clinical observations in humans, which have demonstrated that not only retrograde menstruation is a normal phenomenon in approximately 80% of women but also the endometrial cells in the menstrual fluid remain viable. Another fact in favor of this theory is the recognized high rate of endometriosis in girls with menstrual outflow obstructions. However what is against this theory being the only pathogenic way of endometriosis is that it does not account for cases of extra pelvic endometriosis.
- Lymphatic and vascular dissemination: Dissemination of endometrial cells through the lymphatic and vascular system has been proposed as a mechanism for the presence of endometriosis at distant locations i.e. extra-pelvic sites
- Iatrogenic implantation: iatrogenic implantation of endometrial tissue during surgical procedures is another mechanism for the transplantation theory. It could explain the presence of endometriosis in surgical scars such as laparotomy and episiotomy scars.

2. Caelomeic Metaplasia "Mullerian metaplasia theory":

Based on the fact that the Mullerian and the peritoneal mesothelium have the same embryonic origin. Therefore it is postulated that under yet undefined circumstances e.g. effect of sex hormones, the multipotent mesothelial cells undergoes a process of metaplasia into endometrial cells.

3. The Immune theory:

More recently several studies have suggested an association between endometriosis and abnormalities in cell-mediated and humeral immunity.

4. Genetic Predisposition:

Several studies have demonstrated an increased incidence of endometriosis in first-degree relatives of patients with the disorder. It is postulated that genetic predisposition is transmitted via polygenic or multifactorial pattern of inheritance.

Nevertheless combining all the theories could explain why not all women develop endometriosis despite the near universal phenomenon of retrograde menstruation. Furthermore the nature and degree of immune impairment could account for the variation in severity of endometriosis from asymptomatic accidental findings to severe disabling disease.

Pathology:

- **Pathogenesis of complications of endometriosis**: The endometrial implants behave like the normal endometrial tissue by proliferation in respond to the menstrual hormonal changes (namely estrogen) in cyclic fashion. Repeated cycles of hormonal stimulation and withdrawal results in proliferation and sloughing. The sloughed material induces inflammatory reaction, pain and eventually adhesions.
- **Sites of endometriosis**: The ***most common*** *sites* of endometriosis (about 60%) are the dependant parts of the pelvis: mainly the ovaries (usually bilateral), uterine peritoneal surface, fallopian tubes, anterior and posterior cul-de-sac, and uterosacral ligaments. The pelvic lymph nodes may be affected in about 30% of cases. ***Infrequent sites*** are the rectosigmoid (10-15% of cases), vagina, and other gastrointestinal tract sites (5%). ***Rare sites*** include any distant sites e.g. lungs, arms... etc, in addition to surgical scars (scars of cesarean section).
- ***Gross appearance of endometriosis***: The gross pathology of endometriosis depends on several factors such as the size of lesion, the amount of debris within the lumen of the glands, the extent of peritoneal scarring overlying the lesion, blood supply, duration of the lesions and even the phase of the menstrual cycle

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during examination.

- ***Peritoneal lesions:*** Macroscopic lesions can takes different shapes. Typically appear as black or dark blue spots. Active lesions usually appear red. Light or dark brown lesions are usually larger in size, described as "powder burn". White-opaque plaques are due to fibrosis and represent previously active lesions. Peritoneal defects and other less typical appearances of endometrial lesions have also been described (Figure 31-1).
- ***Ovarian lesions:*** Include superficial implants and cystic lesions contains, altered blood and blood pigments usually described as "chocolate cysts". The cysts can be very similar to that of the hemorrhagic luteal cysts. The cyst often perforates, spilling its highly irritating contents within the peritoneal cavity, which is responsible for the exacerbation of abdominal pain seen in cases of endometriosis. It also results in the development of dense adhesions.
- ***Other sites***: Uncommonly the disease may spread to involve the bladder, ureters, and kidneys (the urinary tract) by invasion, compression or scarring.

It should be noticed that peritoneal lesions might infiltrate deep within the uterosacral ligaments and rectovaginal septum, or invade the muscularis of the rectum or sigmoid wall. Rarely however, does it infiltrate into the bowel lumen. Thus laparoscopic inspection may not be sufficient to realize the depth of lesions in the retroperitoneal tissue.

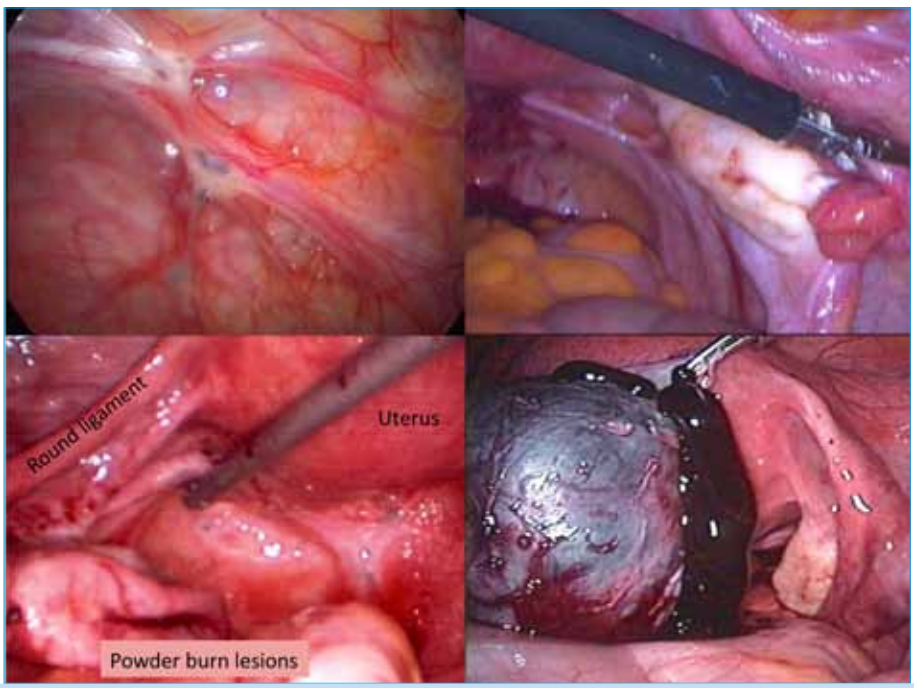

Figure 13-1: Gross pictures of common endometriotic lesions. Top & bottom left: shows a combination of white scar, powder-burn and a peritoneal window, Top & Bottom right shows superficial ovarian lesions and leaking chocolate cyst.

Microscopic appearance: The cardinal histological features of endometriosis are ectopic endometrial glands, ectopic stroma and hemorrhage into the adjacent tissue identified by hemosiderin-laden macrophages near the periphery (Figure 13-2). However in about one third of the cases, endometrial glands and stroma cannot be identified. This is because repeated hemorrhage results in necrobiosis secondary to pressure atrophy or lack of blood supply. The walls of endometrial cysts or endometriomas are often lined with fibrous tissue, containing cuboidal epithelium cells with little evidence of menstrual activity.

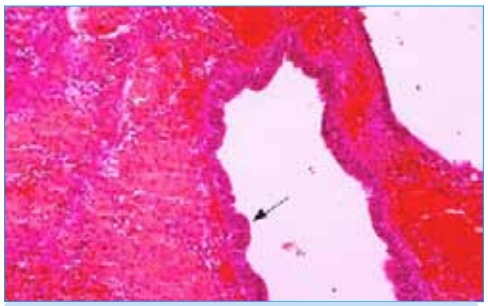

Figure 13-2: Microscopic picture of endometriosis. Arrow endometrial glands with surrounding stroma

Clinical Presentation:

Establishing a diagnosis of endometriosis can be difficult because the presentation is so variable and there is a considerable overlap with other gynecological and non-gynecological conditions.

Furthermore two important facts must be realized. The first is that endometriosis can be asymptomatic and it is commonly discovered accidentally during the course of laparoscopy for other indication.

Secondly several studies have demonstrated that there is no relation between the patient symptoms and extent or severity of endometriotic lesion i.e. patient with extensive lesions may be asymptomatic and vise versa.

Symptoms: The classical two major symptoms of endometriosis are pain, and infertility.

- **Pain:** This is the most common presenting symptom of endometriosis. The mechanism of pain development in endometriosis is not exactly known but could be induced by mechanical as well as chemical factors. Mechanical factors including scarring and fibrosis could result in anatomical distortion, devitalization of pelvic organs from disruption of blood supply, and/or involvement of nerve endings. At the same time chemical inflammatory substances like prostaglandin and histamine could play an important role in inducing or exacerbating pain symptoms. The nature and severity of pain varies depending on the locations and activities of the lesions. Pain could take one or more of the following symptoms:
  - Chronic pain often described by the patient as "swollen pelvic organs" that increase in bouts during the various phases of the menstrual cycle.
  - Secondary Dysmenorrhea that varies in severity, and classically starts one to two days before the onset of flow and continues throughout the menses.

- Dyspareunia usually with deep penetration is often associated with the presence of uterosacral endometriosis and/or vaginal nodules.
- Less common presentations are the gastrointestinal symptoms such as "Dyschezia" in patients with rectosigmoid endometriosis. Cyclical rectal bleeding (hematochezia) is pathognomonic of transluminal bowel involvement.
- Acute pain may occur due to rupture or torsion of endometriomas. But more commonly acute exacerbation of abdominal pain may results from recurrent leakage of the highly irritant chocolate cyst fluid.

➢ **Infertility**: Infertility may be the only presenting symptoms in patients with endometriosis. The pathogenesis of infertility in patient with endometriosis is multifactorial. In advanced endometriosis infertility can be explained by peritubal and periadnexal adhesions or even destruction of ovarian tissue that interferes with normal tubal motility, folliculogenesis and corpus luteum function.

However in minimal and mild cases in which there is only few endometrial implants the association with infertility is not clearly explained and a number of possible mechanisms have been proposed such as the state of chronic inflammatory changes in the peritoneal cavity, increased number and concentration of macrophages, autoantibodies, and prostaglandins all are substances that can affect gamete function, tubal function, and embryo growth.

Signs: The physical sings depends on the nature and extend of the pathology. In mild cases the signs may be very subtle or even non-existent, while in more advanced cases endometriotic lesions may be felt as:

- Palpable tender nodules along the uterosacral ligaments, a retroverted uterus with limited or no mobility, and in some cases thickening along one or both sides of the broad ligaments may be felt.
- If there is ovarian involvement, large endometriomas (> 5 cm) may be palpable; which is usually fixed and tender.
- In rare cases bluish lesions may be visible on the cervix or vagina during speculum examination.
- Implants in distant areas (skin or scar tissue) can usually be visualized as tender dark nodules that often exhibit cyclical changes related to menstrual hormonal activities

Differential Diagnosis: The differential diagnosis includes a variety of gynecological as well as non-gynecological disorders. In cases presenting primarily with menstrual

disorders investigation should role out conditions such as anovulation, thyroid disorders or hyperprolactinemia. While in other cases pelvic inflammatory diseases, degenerating myomas, ovarian malignancy, pelvic adhesions and gastrointestinal dysfunction have to be entertained.

Acute abdominal pain that may be due to rupture of a large endometriomas of the ovary should be differentiated from other causes of acute surgical abdomen such as acute appendicitis, rupture ectopic pregnancy, and complication in corpus luteum cyst.

Investigations:

- ***Laparoscopy:*** In practice laparoscopy preferably with histological biopsy is the gold standard for the diagnosis of endometriosis. Not uncommonly a deep or very subtle appearance of endometriotic implants can be missed during laparoscopic examination. Therefore in doubtful cases biopsy should be obtained. During laparoscopic examination the surgical findings should be carefully recorded using a standard classification (see below classification of endometriosis).
- ***Conscious Pain mapping*:** Is the procedure where minilaparoscopy is performed while the patient is awake. Its value is to accurately locate the areas that cause the maximum pain. Subsequently, the patient is placed under anesthesia and the deposits are ablated.
- ***Imaging Studies*:** Ultrasound, particularly transvaginal, and Magnetic resonance imaging are the two imaging modalities that have been used in endometriosis.

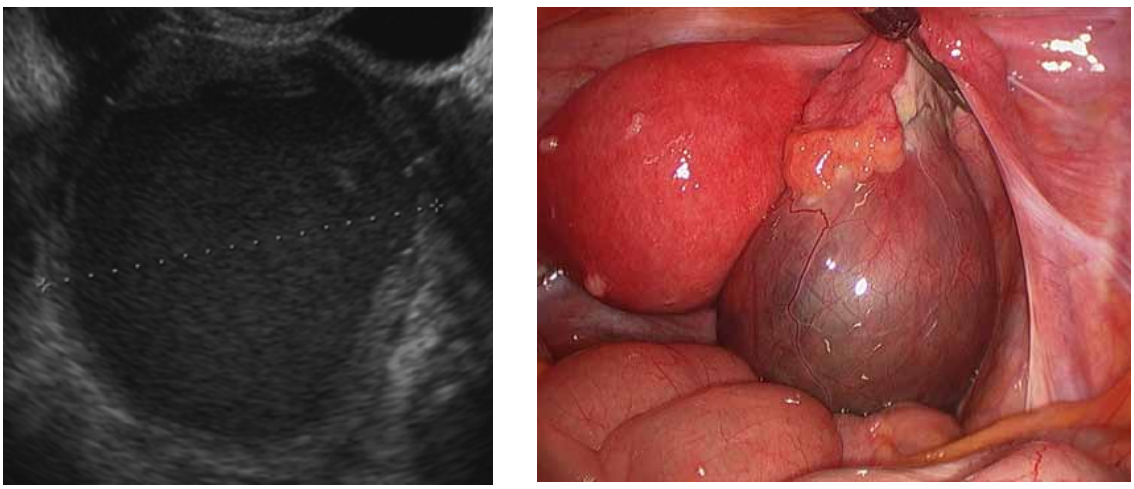

Figure 13-3: Transvaginal US picture of endometrioma (left) showing the typical ground glass appearance. Laparoscopic finding showing the endometrioma (Right).

However their place is only to help in defining the nature of clinically palpable ovarian cysts or undefined adnexal masses not for the detection of endometriotic deposits or implants.

- ***Laboratory Tests*:** Biochemical markers may be used as diagnostic tests, screening tests or follows up of treated cases. The most studied one is the cancer antigen 125 (CA-125). In endometriosis the serum level of CA-125 was found to be elevated and increase incrementally with advanced stages.

Classification of endometriosis: A number of classification systems have been described all aims to allows objective correlation of the volume of the disease with the severity of symptoms mainly fertility, provide reasonable prediction of its course, and guidance in selecting appropriate therapy based on the extent of the diseases. Currently the classification of the American Society for Reproductive Medicine is the most widely used one. In this system points scores are assigned based on lesions number, size and their bilaterality (Figure 13-4). Four stages of the diseases can be identified:

a) Minimal disease is characterized by isolated implants and no significant adhesions.

b) Mild endometriosis consists of superficial implants less than 5 cm in aggregate,

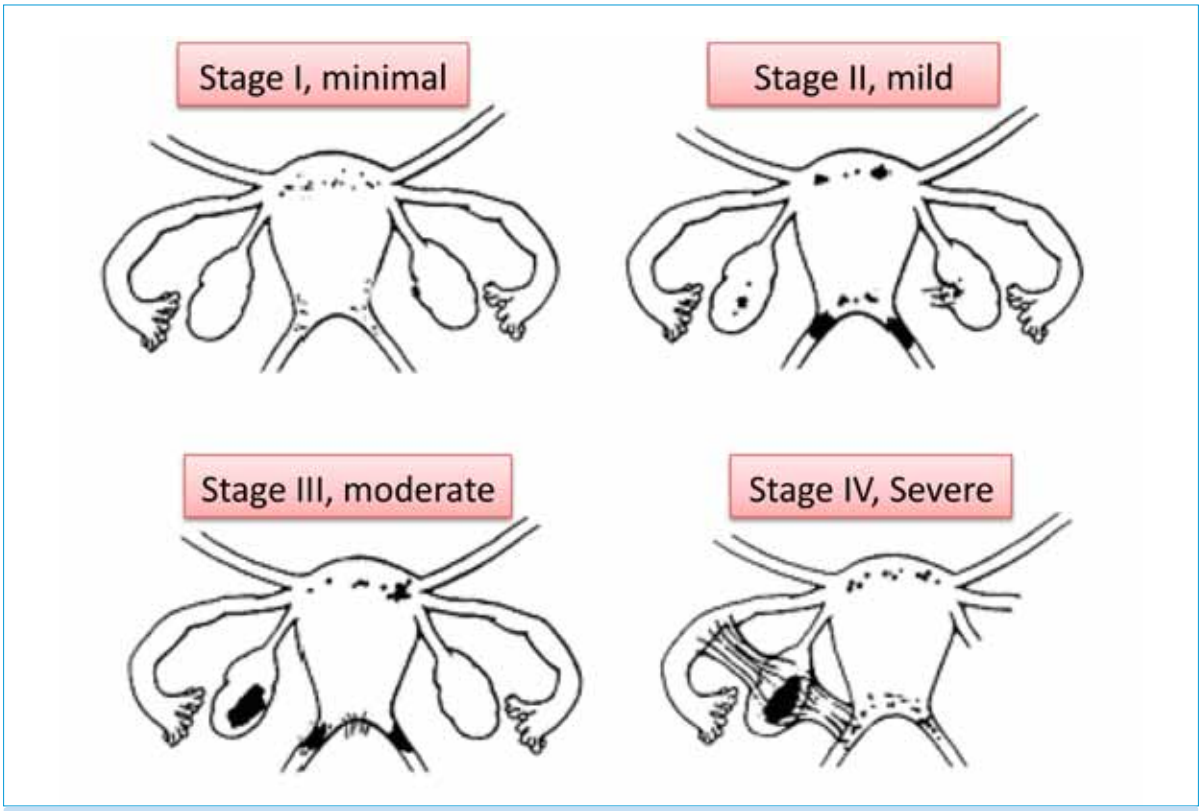

Figure 13-4: Example of classification of endometriosis bases.
The American Fertility society

scattered on the peritoneum and ovaries. No significant adhesions are present.

c) Moderate disease exhibits multiple implants, both superficial and invasive. Peritubal and periovarian adhesions may be evident.

d) Severe disease is characterized by multiple superficial and deep implants, including large ovarian endometriomas. Filmy and dense adhesions are usually present.

Management of Endometriosis:

Although endometriosis is a benign disease, it exhibits characteristics of both malignancy and sterile inflammation (invasion and progression). Its consequences on patients can be very debilitating. The psychological impact of the disease is due to the chronic severe pain and/or the fertility. There are several modalities for the management- a term preferred than treatment- of endometriosis. Each has its pros and cons. The choice is influenced by several factors such as:

- The patient primary concerns whether pain or fertility.
- The age of the patient and her desire to maintain fertility.
- The stage of the disease, its effect on neighboring organs e.g. if causing obstruction to structures such as ureter or bowel, presence of endometriomas in addition to any associated pathology.

Modalities available for treating Endometriosis:

The available treatment modalities range from simple use of analgesics in the form of non-steroidal anti-inflammatory agents, medical hormonal treatment, to surgical management including conservative and radical surgery. Not uncommonly combination of any two or more modalities is employed.

- Non Steroidal anti-inflammatory drugs: Sometimes effective control of symptoms may be obtained with simple analgesics. It can be used in selected patients with mild disease who prefer to avoid hormonal therapy. Most of these drugs (e.g. such as ibuprofen, diclofenac, mefenamic acid) have the side effects of gastric irritation and should not be taken on an empty stomach or if there is already gastric disease.
- Medical Hormonal Treatment:

  The objective of hormonal treatment is to induce atrophy of the endometriosis implants. This is achieved through induction of amenorrhea by suppression of the cyclic ovarian hormonal activities.

- *Combined Oral Contraceptive treatment*: Administration of COC in a continuous fashion (3 to 6 months duration) induces decidual reaction in the functioning endometrium (a state of psuedopregnancy) and eventual atrophy. Additional benefit form the induced amenorrhea is reduction of retrograde menstrual flow. The treatment needs to continue for at least 6-12 months. Exacerbation of symptoms may be encountered in the first 2-3 months due to proliferation of the endometrial implants. Side effects include nausea, weight gain, fluid retention, breast tenderness, mood changes and breakthrough bleeding.

- *Progestins:* The most commonly used agents are Provera (Medroxyprogesterone acetate) 20-40 mg/day; Depo-Provera (depo-medroxyprogesterone acetate) 100 mg IM every 2 weeks, then 200 mg monthly after 8 weeks. Progestins act by promoting decidualization and atrophy of the endometrial tissue. Side effects include breakthrough bleeding (in 38% to 47%), nausea, breast tenderness, fluid retention and depression.

- *Danazol:* is a 17 α-ethinyl testosterone derivative, it acts by suppressing luteinizing (LH) and follicular (FSH) stimulating hormone midcycle surges. Therefore the basal levels of gonadotropins hormones are more or less maintained "a state of pseudo rather than true menopause". This results in chronic anovulation, amenorrhea and hypoestrogenemia. The recommended dose is between 400 mg and to 800 mg/day administered as divided rather that one single dose for approximately six to nine months. For the treatment to be effective amenorrhea should be induced. Danazol is not contraception and women should use mechanical contraception for the first month, as it can cause androgenic changes in female fetuses (female pseudohermaphroditism).

  Side effects of Danazol: the drug has many side effects due mainly to its androgenic and hypoestrogenic activities. Although almost all side effects are reversible some of it such as deepening of voice may not be completely resolved.

- *Gonadotropins-Releasing Hormones Analogues* (GnRH): Administration of GnRH analogues results in a state of "medical oophorectomy" with a consequent dramatic reduction in the level of serum estrone, estradiol, and testosterone and androstenedione levels similar to the hormonal profile levels in castrated women (menopausal state).

  Side effects of GnRH: The potential side effects of GnRH agonist are primarily those associated with estrogen deprivation similar to menopause. The most common short-term side effects are hot flushes, vaginal dryness, and insomnia. Other side effects are depression, fatigue, irritability, headache and decreased libido. On the long term (> 6 months) there is risk of bone demineralization.

Therefore for therapy of longer than 6 months duration an "add-back" therapy using low dose estrogen and progestin combined with GnRH analogue is recommonded in order to minimize the short and long term side effects of hypoestrogenism while maintaining the therapeutic efficacy.

- Surgical Management: Surgery may be performed via laparoscopy or laparotomy. Surgical management of endometriosis may be divided into conservative surgery, semi-conservative surgery and definitive or radical surgery. In addition in selected cases some surgical procedures may be performed for alleviation of pain. Surgery may be combined with hormonal or non-hormonal treatment.

- Conservative surgery: the aim is to remove all active endometrial implants, lysis of adhesions, and reconstruction of reproductive organs with the objective of preserving patient fertility. Removal of endometrial implants is performed either by sharp dissection, electro-cauterization, or laser ablation.

- In radical or definitive surgery: bilateral salpingo-oophorectomy and hysterectomy in addition to removing endometrial implants. Definitive radical surgery is reserved for women who are not keen on future fertility. The administration of estrogen replacement therapy after definitive radical surgery should not be avoided for fear of stimulating recurrent diseases. The risk associated with prolonged estrogen deficiency is far serious than the small risk of endometriosis reactivation.

In women who have completed their childbearing and are too young to undergo premature menopause healthy ovarian tissues are preserved.

- Special surgical procedures for relief of pain:
  - *Presacral Neurectomy*: In this procedure the sympathetic innervations of the uterus are transected at the level of the third sacral vertebra (the hypogastric plexus), and the distal ends are ligated.
  - *Laparoscopic Uterine nerve ablation (LUNA):* the aim is to interrupt pain fibers along the neural pathways via the Lee-Frankenhuser plexus along the uterosacral ligaments.

Management of Ovarian endometriomas: Endometriomas (endometriotic ovarian cyst) is one of the situations where surgical treatment is mandatory. Removal of ovarian endometriomas is best approached via laparoscopic approach.

Adenomyosis

Perhaps the only points of connection between adenomyosis and endometriosis are that in both conditions there is ectopic endometrium. Apart from that there is almost no clinical or pathophysiological similarity between those two conditions, they are two separate diseases.

Definition: Adenomyosis is defined as the presence of endometrial glandular epithelium and stroma within the uterine myometrial tissue, usually at a depth at least 2.5 mm from the basalis layer of the endometrium. Because the epithelium is derived from the basalis layer of the endometrium, it does not usually respond to the hormonal changes of the menstrual cycle.

Epidemiology:

In contrary to endometriosis, adenomyosis is a disease of porous women older than 30 years of age.

Its exact prevalence cannot be determined because adenomyosis is often reported as an incidental finding on histological examination of surgically removed uterine specimens.

Depending on how meticulous a pathologist is in examining the histological sections of uterine specimens the frequency of adenomyosis can reach as high as 70% of women between 40-50 years of age.

Pathogenesis:

The exact pathogenesis of adenomyosis remains unknown. It is hypothesized that invading of the myometrium by endometrial epithelium can occurs following a breach in the barrier between the endometrium and myometrium secondary to some unknown factors such as chronic postpartum endometritis. Some hormonal factors such as high level of estrogen levels may also plays a role in stimulating hyperplasia of the basal layer of the endometrium.

Pathology:

Pathologically there are two distinct types of adenomyosis:

The first and most common type is diffuse involvement of the uterine wall, the posterior wall being more involved than the anterior.

The second type is a focal area of adenomyosis. "adenomyomas" is the name that describes a circumscribed nodular aggregate of the ectopic endometrial glands with compensatory hypertrophy of the smooth muscle of the myometrium surrounding it. Unlike the case of leiomyo-.mas there is no true capsule for such lesion

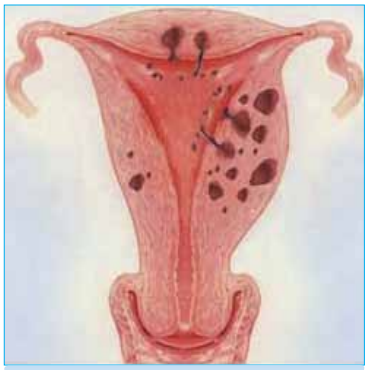

Figure 13-5: diagram for adenomyosis.

Clinical presentation:

- Symptoms: In most of the times adenomyosis is asymptomatic. However the classic symptoms of adenomyosis are:
  - Secondary dysmenorrhea.
  - Menorrhagia and irregular vaginal bleeding that does not respond to hormonal therapy or uterine evacuations.
  - Pelvic pain.

- Signs: on examination the uterus is diffusely enlarged, tender especially if examination is performed in the premenstrual phase. The size of the uterus rarely exceeds 14 weeks, unless there is an associated fibroid. Other findings may be due to coexistent pelvic pathology, most commonly myomas or endometriosis which is expected in about two thirds of women with adenomyosis.

Differential diagnosis: The differential diagnosis of adenomyosis includes other causes of chronic pelvic pain such as endometriosis, ovarian cyst or pelvic inflammatory diseases. However the two most common differential diagnoses are small uterine myomas and dysfunctional uterine bleeding.

Investigations Transvaginal ultrasound and/or magnetic resonance imaging (MRI) are often used to exclude other causes, but they are not very sensitive diagnostic tools, although MRI is more sensitive than US.

However in most instances the diagnosis of adenomyosis is usually confirmed postoperatively following histological examination of the hystrectomy specimen.

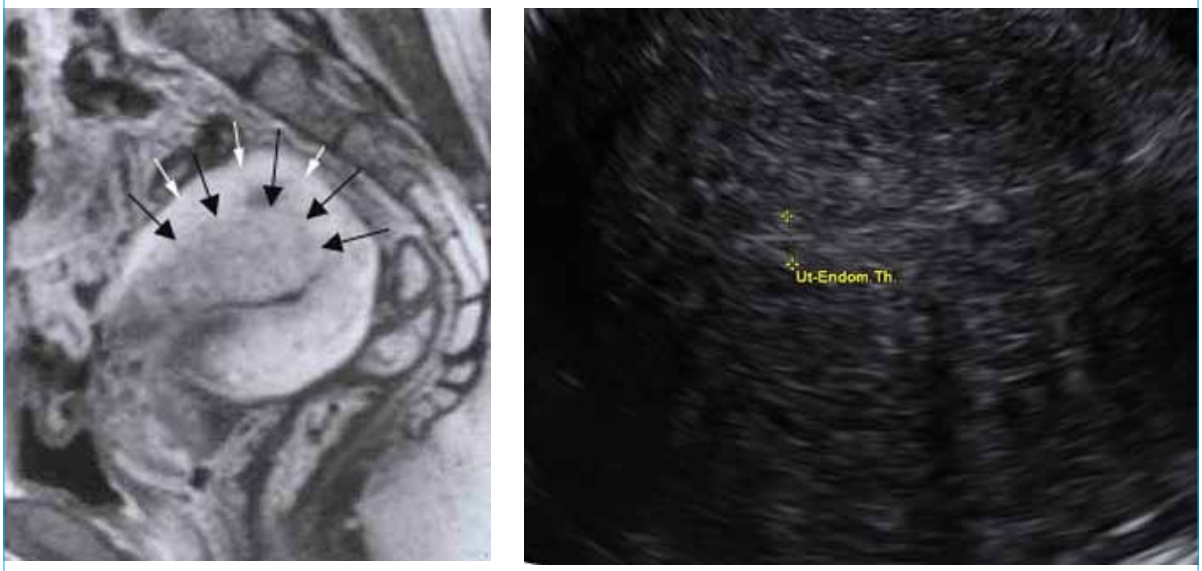

Figure 13-5: Left MRI, Right: Ultrasound images for adenomyosis

Treatment: The only effective treatment for adenomyosis is hysterectomy. The ovaries can be consevered unless there are other indications for its removal.

Hormonal treatment: using IUS (intrauterine loaded progestogen system) such as Mirena IUD and oral contraceptives (continuous regimen for 2-3 months) can be successful to decrease the symptoms of bleeding and pain in some cases.

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Chapter 14

Genitourinary Dysfunction
Pelvic Organ Prolapse, And Urinary Incontinence

The human being spends most of his life in the upright position. Therefore it may not be surprising that eventually the supporting mechanism of their pelvic and/or abdominal organs might fail and hernias ensue. This is more likely to happen if the supporting tissues are inherently weak, exposed to damage, or chronic pressure. This typically occurs in parous aging women. The result is herniation of pelvic organs or "pelvic organ prolapse" POP.

The abnormalities resulting from POP include wide spectrum of defects; urethrocele, cystocele, rectocele, enterocele; uterine prolapse and vaginal vault prolapse if hystrectomy had been performed. However it is unusual to have only one of these conditions. In most cases the failure of the pelvic supporting structures induce combination of those defects.

By the end of this chapter you should be able to:

- **Define** different type of genital prolapse and urinary incontinence
- **Describe** the pathological anatomy of genital prolapse
- **List** the risk factors of prolapse
- **Describe** the symptoms and signs of prolapse: pressure symptoms, low backache, bladder dysfunction, defecation dysfunction, and sexual dysfunction
- **Describe** the examination of prolapse, types and degrees of prolapse:
- **Discuss** the management of prolapse: surgical and non surgical.
- **Define** urinal incontinence its types.
- **Discuss** the mechanism of continence and bladder innervation.
- **List** the differences between SI and UI.
- **Describe** the principle of management of each type of incontinence.
- **Definite** the place of urodynamic studies in patients with urinary incontinence
- **List** the causes of gynecological and obstetrical urogenital fistulae.
- **Describe** the approach to evaluation and management of patient presenting with urinary incontinence

Pelvic Organ Prolapse (POP)

Definition:

Pelvic organ prolapse refers to hernia (or descent) of one of the pelvic organs i.e. uterus, and/or vaginal walls from its normal location. Descent of the vaginal wall may occur without uterine descent but the reverse is not true.

Pathophysiology of pelvic prolapse:

POP results from weakness of the muscles and/or the ligaments, which support the pelvic organs, which include:

- The pelvic floor muscles: include the levator ani and perineal body: These muscles form a shelf of support for the pelvic organs.
- The pelvic ligaments: the main ones are the cardinal, uterosacral and pubourethral ligmaents. These ligaments are formed bilaterally from thickening of the endopelvic fascia, the fascia that invests the pelvic organs. These structures attach the pelvic organs to the bony pelvis.

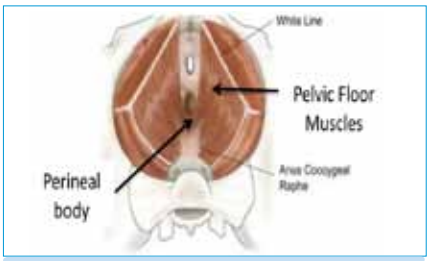

Figure 14-1: The pelvic floor muscles form a sling around the lower pelvic outlet and offers support to the genital tract and the lower urinary tract. These muscles arise from the white line on lateral pelvic side-wall and interdigitate with each other and the anococcygeal raphe in the centre

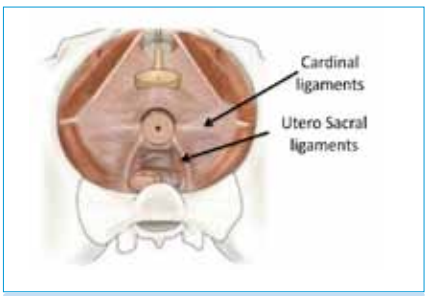

Figure 14-2: The cervix supported by the strong uterosacral ligaments that run from the sacrum to the cervix and to the lateral pelvic side-wall by the strong cardinal ligaments.

Several factors can predispose to weakening of the pelvic support mechanism and development of prolapse. These include:

- Pregnancy: Each pregnancy is associated with stretching and softening of the supporting ligaments and muscles. It will normally recover and regain its strength and tone after childbirth. However if the process of pregnancy is repeated especially with short interval in between it could precipitate permanent damage and weakness of the supporting tissues.
- Labor: repeated and/or difficult labor (e.g. large fetus, instrumental delivery) can cause either direct damage of the levator ani muscle or indirect muscle atrophy secondary to nerve injury.

- Precipitating factors: this include any factor that induces increased intraabdominal pressure: e.g. chronic cough, constipation, obesity, ascites…etc
- Role of menopause: The clinical manifestations of prolapse often develop in the menopausal years. At this time estrogen deficiency precipitate atrophic changes of the already weakened pelvic supporting.
- Inherent weakness: genetic, neurologic and environmental factors could explain racial variation in prevalence of prolapse. Also the occasional development of prolapse in nulliparous women.

Types of prolapse:

The type of prolapse and the prolapsed organ depends on the site at which the muscle or fascia is damaged (Figure 14 -3 q-c),

- **Cystocele:** hernia of the bladder with associated descent of the anterior vaginal segment (figure 14-3 a-c).
- **Cystourethrocele:** a cystocele combined with distal prolapse of the urethra (bladder neck).
- **Uterine prolapse:** descent of the uterus and cervix. It is always associated with vaginal wall prolapse.
- **Vaginal vault prolapse:** descent of the vaginal apex in patients who had hysterectomy.
- **Rectocele:** hernia of the rectum with associated descent of the posterior vaginal segment.
- **Enterocele:** herniation of the small bowel/peritoneum into the vaginal lumen, most commonly presenting following hysterectomy in conjunction with vaginal vault prolapse

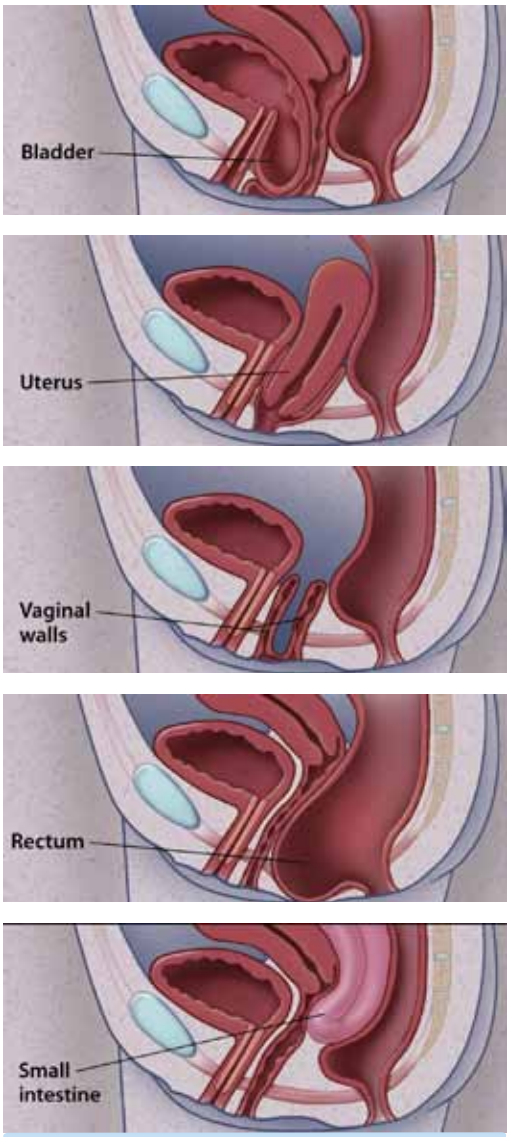

Figure 14-3: (A to E) from top to bottom. Diagrams of different types of prolapse

Classification of prolapse:

According to the degree of descent of the genital tract the International Continence Society recommends classification of prolapse into four grades (table 14-1). This classification helps to standardize patient assessment and development of better treatment .modalities

Stage 0 No prolapse
Stage 1 Most distal portion of the prolapse > 1 cm above the level of hymen
Stage 2 Most distal portion of the prolapse less or equal to 1 cm above or below the level of the hymen
Stage 3 Most distal portion of the prolapse > 1 cm below the level of the hymen but protrudes no farther than 2 cm less than the total vaginal length.
Stage 4 Complete eversion; of the total length of the lower genital tract (total prolapse (i.e., procidentia).

Table 14-1: Stages of genital prolapse

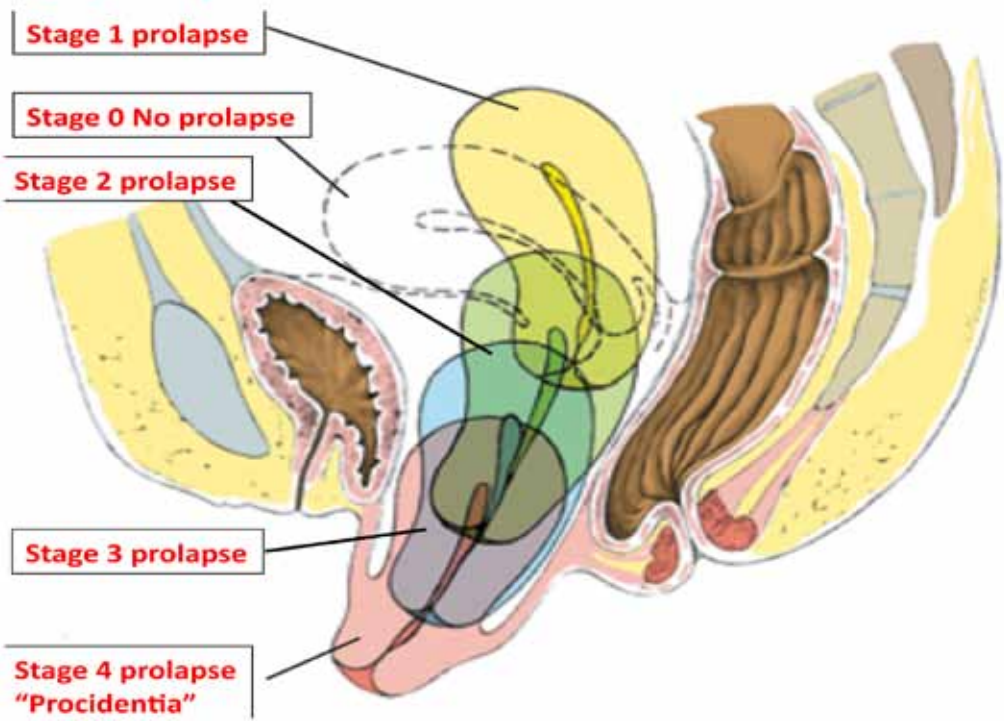

Figure 14-4 Stages of prolapse (see table 14-1)

Clinical manifestation of prolapse:

Symptoms: the symptoms of prolapse are not necessary indicative of its type or severity. In general the patient may present with one or more of the following symptoms:

- **Sensation of pelvic pressure/heaviness or protrusion of a lump from the vagina:** Typically it is less noticeable in the morning and worsens as the day progresses. Laying down usually relieves symptoms, while long periods of physical exertion aggravate them. Excessive discharge "leukorrhea" and or bleeding may occur from congestion or irritation of the protruding vaginal mucosa.
- **Low backache:** is not uncommon and is usually explained by chronic stretch on the uterosacral ligaments.
- **Bladder dysfunction "Urinary symptoms":** range from urinary stress incontinence, to weak stream, to urinary retention or "incomplete emptying of the bladder". Urinary stress incontinence occurs due to loss of anterior vaginal support that leads to a hypermobile bladder neck (see SI). On the other hand urinary retention occurs with large anterior vaginal wall prolapse causing urethral kinking/obstruction. In the later case the patient she has to manually reduce the prolapse to assist in emptying her bladder. This anatomical distortion may mask true stress incontinence.
- **Recurrent Urinary infection**: the presence of residual urine in the prolapsed bladder pouch enhances recurrent bladder infection, presenting as frequency, urgency, or hematuria.
- **Defecatory symptoms:** Anterior protrusion of the rectum into the vaginal canal (rectocele) can cause "difficulty in defecation or complete emptying of rectum". In severe cases, the patient may have to manually splint the posterior vagina in order to defecate.
- **Sexual function:** Impairment to sexual relations may occur with prolapse in any compartment. Multiple causes could contribute to this problem including the weak perineal muscles, excessive discharge or bleeding.

Signs: The purpose of the examination is to confirm the diagnosis of the type of the prolapse and assess its severity which important when planning management.

- In contrast to standard bivalve vaginal examination, evaluation of prolapse is best accomplished by retracting the anterior, posterior, and lateral vaginal walls suing a single-bladed speculum (e.g. Sims speculum).
- Examination should involve the anterior vaginal wall (for cystocele and /or

urethrocele), posterior vaginal wall (for rectocele and/or enterocele) and uterine (or vaginal vault) prolapse should be examined.

- The examination should be performed at both rest and with Valsalva maneuver (to demonstrate the maximum extent of the prolapse).

Examination may have to be performed both in the recumbent (dorsal lithotomy or Sims position). In some occasions if the prolapse is not detected in the recumbent position examination may be necessary in upright positions with one foot elevated on a well-supported footstool.

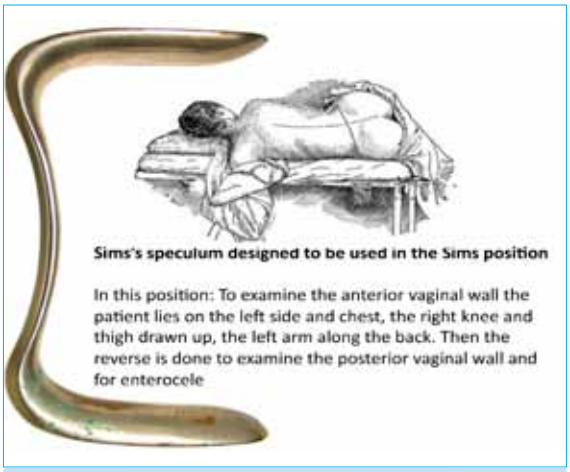

Figure 14-5: Sims' speculum and diagram of patient in Sims's position.

- Bladder function can be evaluated by assessing for leakage when the patient coughs (for stress incontinence) and by measuring the post-void residual (normally it is < 50 mL). It should be noted that patient with cystocele might have "occult stress incontinence" which can only be demonstrated if the cystocele is reduced.
- At the end of the examination the clinician should identify the defect and classify it according to its type and degree using the POP-Q method (see above).

Management:

The treatment of prolapse is either non surgical or surgical. The choice depends on the (1) the severity of symptoms (2) the severity of prolapse (3) patient wishes and/or fitness for surgery.

In all cases any precipitating factor(s) e.g. chronic respiratory diseases, chronic constipation, obesity…etc should be evaluated and managed.

➢ In mild degrees of prolapse: usually with no or mild symptoms the treatment involve:

- Pelvic floor muscle exercises: aims to increase the strength and endurance of the pelvic muscles and therefore improve support for pelvic organs.
- Behavioral modification: e.g., timed voiding/defecation, dietary modifications to improve bowel function.

- In moderate or severe cases: Surgery is the ideal treatment. The aim of surgery is to repair the muscle and facial defect and restore normal visceral function (bladder and/ or rectum) and allow normal coital function.

There are many types of surgical or a "colporrhaphy" procedures that aims to repairs vaginal wall defects and reduce visceral organ prolapse including **A**nterior colporrhaphy for repair of cystocele, or **P**osterior colporrhaphy for repair of rectocele or combined **A/P** repair. All procedures can now be performed vaginally or better via laparoscopy.

For **uterine prolapse**: The treatment of choice is laparoscopic uterine suspension unless there is a pathology involving the uterus, in which case a hysterectomy is necessary.

Manchester repair: is procedure that combines anterior colporrhaphy, amputation of the elongated cervix, posterior colporrhaphy and suturing (shortening) of the cardinal ligament. It is the preferred procedure for women who do not wants to have hystrectomy.

Vaginal pessaries for treatment of prolapse:

Vaginal pessaries are devices inserted into the vagina to support the prolapsed organs. Different types of pessaries are available either supportive (e.g., ring), or space occupying (e.g., doughnut, cube, ring).

Figure 14-6: Different types of pessaries used for support of genital tract prolapse (Right). Middle: Doughnut and Ring pessary pessaries in place (middle and left). Note the pessary it tucked behind the pubic bone

Indications for pessaries: (1) patients unfit or who refuse surgery (2) prolapse during .pregnancy or the postpartum period (3) patient on waiting list for surgery

Disadvantages of pessaries: Although pessaries are formed of medical-graded silicone, but it can causes irritation and ulceration. Therefore it must be removed periodically (every 3-6 months) cleaned and reinserted.

Urinary Incontinence

Urinary incontinence is defined as involuntary leakage of urine that causes physical, functional, and psychological morbidity, and diminished quality of life.

The condition is not uncommon especially in older age. However the actual prevalence of incontinence is not known because many women are reluctant to talk about their incontinence.

Physiology of continence and voiding:

Normally continence (ability to control bladder function) occurs because the intravescial pressure remains lower than the intraurethral pressure at all times during filling (rest) and excretion (e.g. coughing). It is only reversed -voluntarily – at the time of voiding when time and place are convenient (Figure 14-7).

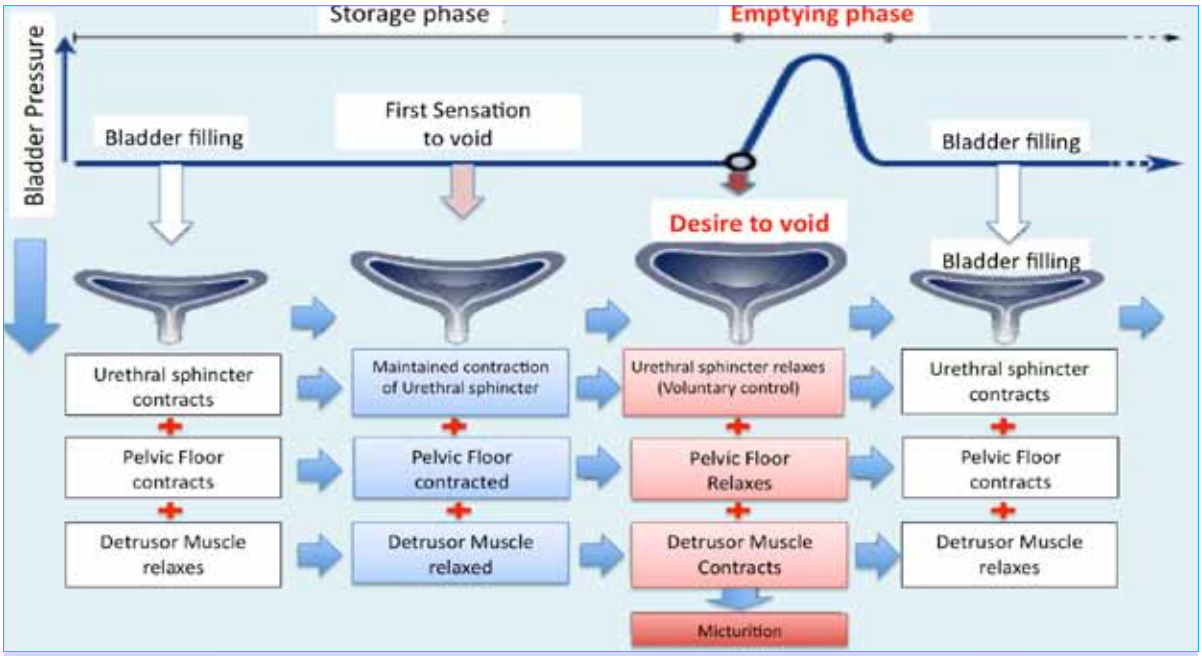

Figure 14-7: Bladder filling and voiding mechanism. The cycle of continence and voiding is learned during infancy. Note that:
The intravescial pressure remains low during urine storage phase due and no leakage occur due to maintained relaxation of detrusor muscle, contractions of urethral sphincter. With the first desire to void an adult person can maintain the same relation.
At certain point when time is convenient this relation can be reversed.

This safe threshold between the intravesical and the intraurethral pressure depends on:

1. **Intact bladder Innervation**: which ensures that the bladder detrusor muscle can expand without increase in pressure (compliance).
2. **Intact urethral sphincter mechanism:** that ensure higher intraurethral pressure both during rest and exertion (e.g. coughing).

Innervation of the bladder: The bladder receives innervation from three sources: the sympathetic, the parasympathetic and somatic nervous system (Figure 14-8).

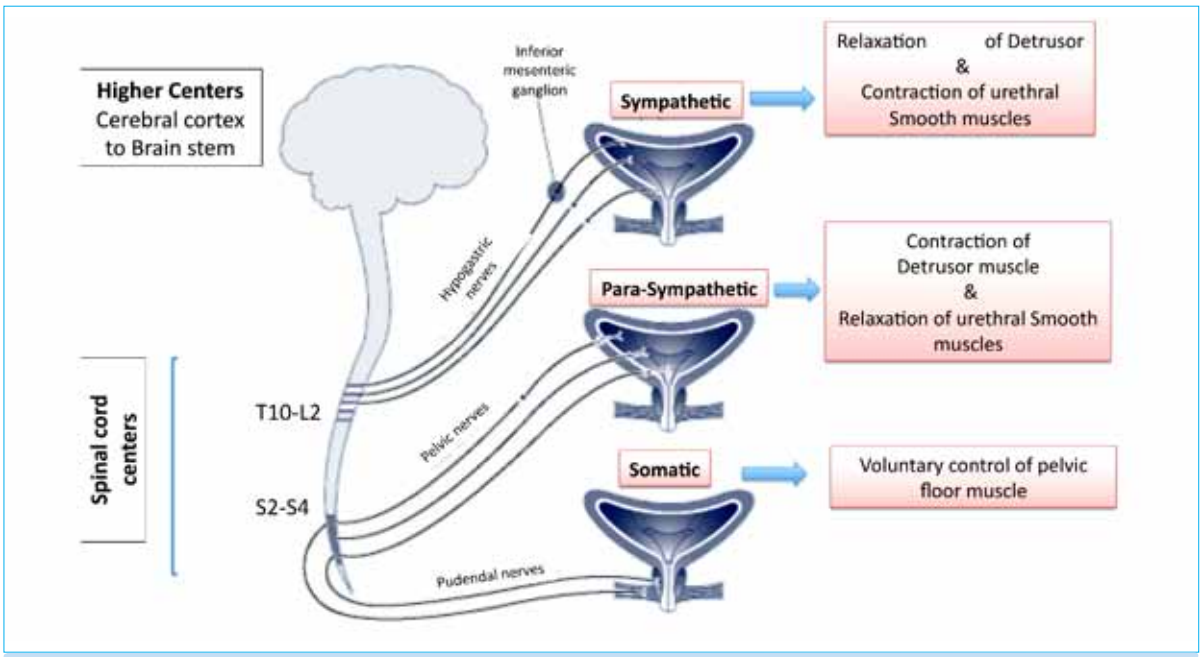

Figure 14-8: Diagram of innervation of the bladder and urethra and control of bladder function

- The sympathetic supply (hypogastric neurons from T10–L2): control urine storage through mediating relaxation of the detrusor muscle and contraction of the urethra.
- The parasympathetic system (S2–S4 segments): controls voiding through mediating contraction of the detrusor muscle.
- The somatic nerves (Pudendal nerve S2–S4): allows some voluntary control over the pelvic floor and external urethral sphincter.

The urethral sphincter (closure) mechanism: although there is no defined anatomical sphincter but there is closure mechanism formed of two components:

- Intrinsic mechanism: formed of the smooth and striated muscle fibers of the urethral wall, the vascular content of the urethral submucosal cavernous plexus, and the

passive elasticity of the urethral wall. These structures are dependent on estrogen for normal function. Hence they become weakened at menopause.

- Extrinsic mechanism: formed of (1) Levator Ani muscles (pelvic diaphragm) particularly the pubourethralis portion form voluntary "external sphincter" (2) The endopelvic fascia which form three important ligaments: pubourethral ligament (stabilizes the urethra), urethropelvic ligament (supports the bladder neck and the urethra) and pubocervical fascia (supports the bladder) (figure 14-9)

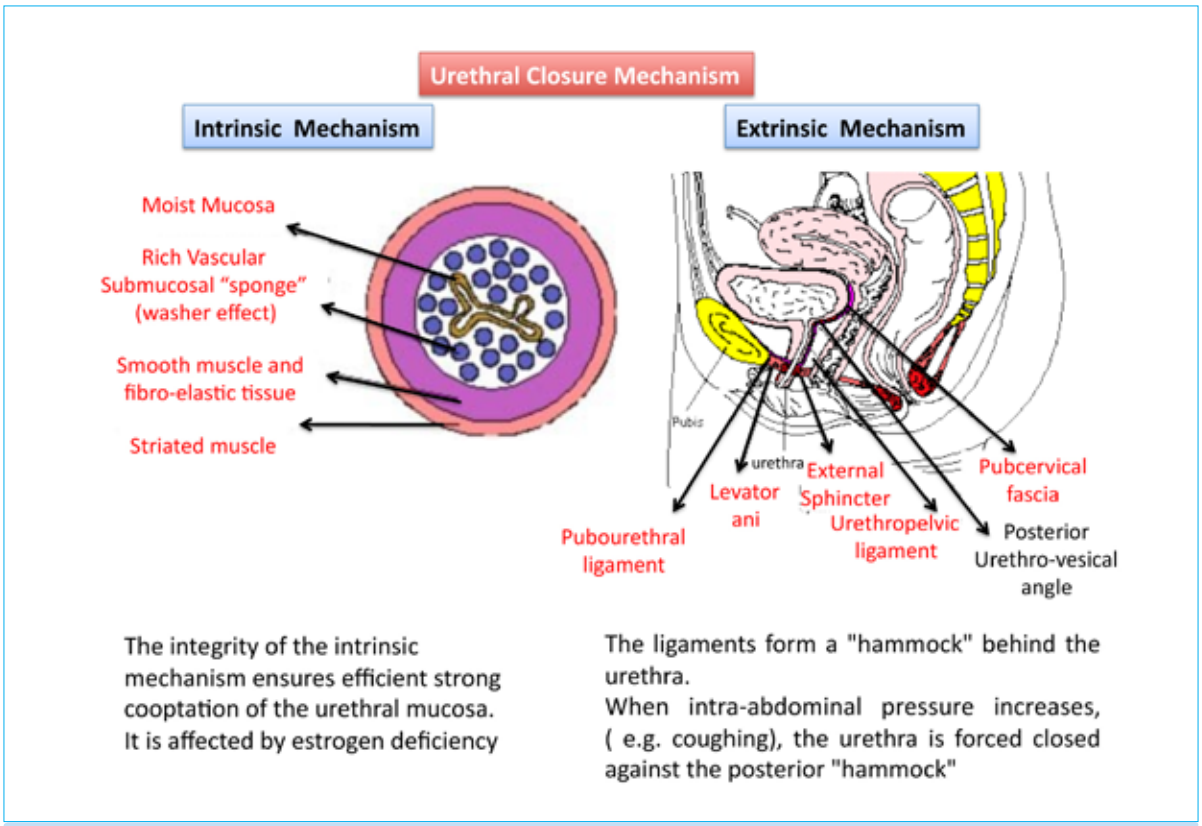

Figure 14-9: Urethral closure mechanism. Left: cross section of the urethra to demonstrate elements of intrinsic mechanism. Right: diagram of elements of the extrinsic mechanism.

➢ Types of urinary incontinence:

There are three major clinical types of urinary incontinence:

- Urge incontinence (UI) is the most common occurs in about 50%.
- Stress incontinence (SI) occur in about 20%
- Mixed incontinence occur in about 30 %

Other less common types of urinary incontinence include:

- Overflow incontinence: refers to involuntary loss of urine due to either obstruction of urine flow or weakness in detrusor contraction.
- Total incontinence: refers to incontinence due to genito-urinary fistula.

Urge incontinence

Urge incontinence (UI) is involuntary loss of urine with a strong urge for micturition (a sudden need or urge to void).

Pathophysiology of urge incontinence: symptoms of urge urinary incontinence are due to defect in the mechanism responsible for relaxation of the bladder during filling, hence the terms uninhibited bladder contractions and detrusor over-activity "DO".

This may occur if there is disruption in the neuro-muscular control of the bladder e.g. loss of the inhibitory impulses from the higher brain centers on the autonomic nerve supply of the bladder. It also may result from local factor(s) causing irritation of the bladder detrusor muscle that prevent its relaxation. The end result is that the bladder becomes unstable (un-inhibited) even with small amount of urine.

Clinically: the patient complains of frequency, nocturia, urgency (strong desire to void) and urge incontinence (strong desire to void but can not hold her bladder). Such symptoms may be triggered by simple activities such as the site of water or change in posture… etc. However urge incontinence should be differentiated from simple urgency (e.g. due to cystitis), which is strong desire to void, but without incontinence (involuntary loss of urine).

Etiology of urge urinary incontinence:

In most cases there is no clear etiology, and the condition is described as idiopathic detrusor muscle instability due to an unidentified dysfunction in muscle or nerve tissue. However some local or systemic diseases may cause or be associated with symptoms of urge incontinence these include:

- Interstitial cystitis: which commonly causes symptoms of urge urinary incontinence in younger women. This condition is characterized by urgency and frequent voiding of small amounts of urine, often with dysuria or pain.
- Local bladder diseases: such as infection, stones, and tumors.
- Factors outside of the lower urinary tract: pressure of pelvic mass or cyst.

- Impaired detrusor contractility, which is common in frail older persons.
- Neurological diseases and disorders associated with a neurogenic bladder e.g. Alzheimer's disease, multiple sclerosis, diabetes..etc

Treatment of urge incontinence:

The objective of treatment is to enable the patient to lead a sociable and physically healthy life. The patient should understand that complete cure may be difficult and a considerable part of the management depends on her active participation in behavior change and bladder drill exercise.

- **Behavior change**: this includes advice regarding fluid intake (not more than 1.5 liter/day), and restricting intake of caffeine, which may help in reducing the symptoms.
- **Bladder drill**: involve instructing the patient to void at predetermined interval depending on the severity of the symptoms (e.g. every hour) regardless whether or not she has the desire to void. The voiding interval is then gradually increased once the initial goal is achieved. The process is continued until voiding can be deferred to every 3-4 hours without urgency or incontinence.
- **Pharmacologic treatment**:
  - **Anti-cholenrgic drugs:** are the most frequently used drugs. It acts by suppressing bladder urges and contractions, and increases the ability of the bladder to hold more urine through inhibiting the cholinergincally innervated detrusor muscle. E.g. of these drugs include oxybutynin (Ditropan), tolterodine (Detrol), and solifenacin (Vesicare).
  - **β –Sympathomimetic agonist:** they have a detrusor-relaxing action on the β-adrenergic receptors.
  - **Tricylcic antideprssants:** These drugs can are helpful for nighttime incontinence or frequency e.g. Imipramine (Tofranil).
  - **Estrogen:** Applying low-dose, topical estrogen in the form of a vaginal cream, ring or patch may help tone and rejuvenate tissues in the urethra and vaginal areas.

Stress incontinence

Stress incontinence (SI) is defined as involuntary loss of urine that coincides with excretion i.e. increased intraabdominal pressure. In contrast to UI, in SI there is absent desire for micturition and absence of detrusor muscle contraction. Stress urinary incontinence is the most common cause of urinary incontinence in younger women, and second most common cause in older women.

Pathophysiology of urinary stress incontinence: SI is due to weakness in the urethral closure pressure. In SI a passive rise in the intravescial pressure, secondary to excretion (e.g. coughing) exceeds and/or not adequately compensated by concomitant increase in intraurethral pressure. The result is involuntary loss of urine descried as SI. The degree of severity of SI depends on the degree of weakness of the urethral closure pressure i.e. the intraurethral pressure.

The resting pressure in the bladder is normally between 20 and 30 cm H_2O. The urethral closure pressure varies along the urethral length; it reaches its maximum value just above the urogenital diaphragm (Figure 14-10).

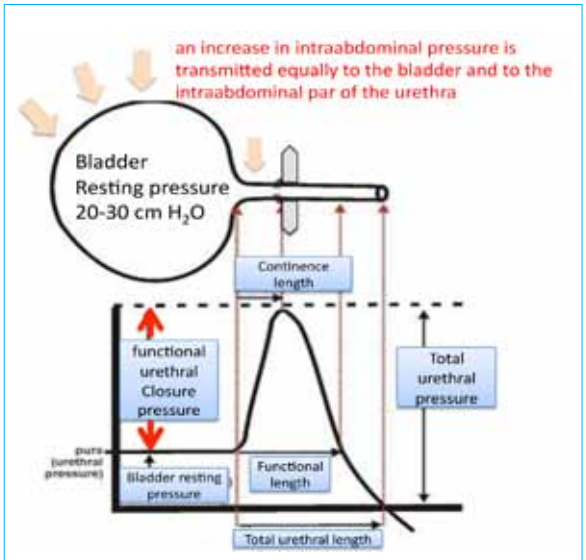

Figure 14-10: diagram showing the location of the maximum urethral pressure in relation to the urogenital diaphragm

The urethral closure pressure varies with age, increasing up to the age of 20 and decreases until menopause due to estrogen deficiency.

If the extrinsic factors is damaged (e.g. with high parity) the urethra becomes hypermobile. In such cases with an increase in intraabdominal pressure the bladder neck descent below the pelvic floor level and the pressure will not be transmitted to the intraabdominal part of the urethra. The result is that the increased intravescial pressure exceeds the intraurethral pressure and leakage of urine occur (Figure 14-11).

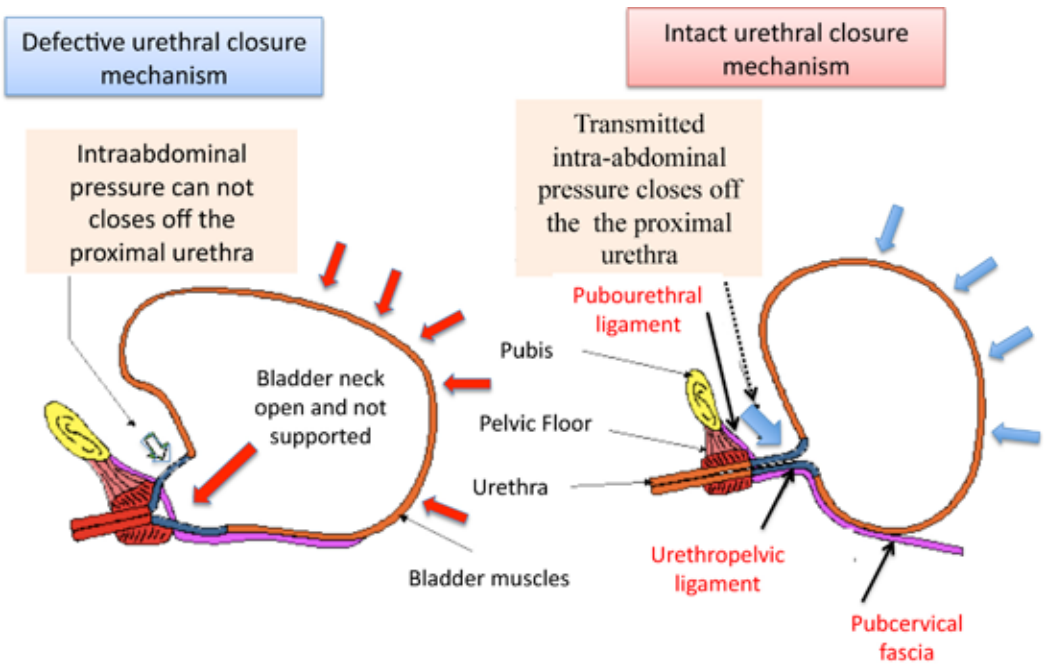

Figure 14-11: Diagram showing the urethral closure mechanism. Hypermobility of the urethra due to pelvic floor defect results in descent of the urethra. Therefore an increase in the intravesical pressure is not transmitted to the proximal urethra and the intravesical pressure may exceed the intraurethral pressure and results on loss of urine

Clinically: the patient complains of involuntary loss of urine, normally small amount, with exertion that induces increases in intraabdominal pressure (e.g. coughing, sneezing). The severity depends on the degree of decline of the intraurethral pressure and hence the decline in the safety threshold between the intravesical and intraurethral pressure. In some cases just any form of rapid movements or walking or simply changing posture could lead to loss of urine.

Etiology of SI:

High parity with repeated deliveries, and perineal tears especially if poorly repaired causes damage and weakness of the extrinsic urethral support mechanism. The weakness becomes symptomatic as the women approach menopause as estrogen deficiency induces atrophic changes in the intrinsic urethral closure elements.

Treatment f SI:

- **Pelvic floor exercise (Kegel exercises):** especial set of muscle exercise, which aims to strengthen the pelvic floor muscle support. It may be helpful in mild cases of SI and particularly in postpartum urinary incontinence.

- **Behavior modification**: that entails regular emptying of the bladder and avoidance of excessive fluid intake.
- **Surgical Repair:** the goal of surgery is repositioning of the bladder neck and urethra to a high retro-pubic position (Bladder Neck Suspension) thereby restores the normal intraabdominal position of the bladder neck and proximal urethra. The approach to such surgery may be vaginal, abdominal or combined.

Mixed incontinence

Mixed incontinence is the most common type of urinary incontinence in women. In this type patient presents with overlapping symptoms of urge and stress incontinence.

Pathophysiology: in such cases there is overlap of two pathologies, detrusor overactivity and impaired urethral sphincter function.

Clinically: table 14-2 describes the distribution of symptoms in each of the major types of urinary incontinence.

Symptoms	Urge Incontinence	Stress Incontinence	Mixed Symptoms
Urgency (sudden desire to void)	yes	No	Yes
Frequency	Yes	No	Yes
Leaking during physical activity	No	yes	Yes
Amount of urine leakage	Large	Small	Variable
Ability to reach toilet in time	Often no	yes	Variable
Waking pass urine at night	Usually	Seldom	May be

Table 14-2: DD of Urge, Stress and mixed symptoms of incontinence

Overflow incontinence

Overflow incontinence is a term that describe the dribbling and/or continuous leakage associated with incomplete bladder emptying. This may be due to: (1) impaired detrusor contractility (2) or bladder outlet obstruction.

- Causes of impaired detrusor contractility: smooth muscle damage, fibrosis, low estrogen, aging, peripheral neuropathy (due to diabetes mellitus, vitamin B12 deficiency, Parkinson disease, alcoholism, tabes dorsalis), and damage to the

spinal detrusor efferents by disc herniation, tumor, or congenital abnormalities.

- Bladder outlet obstruction: uncommon in women but may be caused by scarring from prior anti-incontinence surgery or significant pelvic organ prolapse, when the prolapsed bladder or uterus kinks the urethra.

True / Total incontinence – "Genito-Urinary Fistula"

In this type of urinary incontinence the patient complain depends on location, site, and size of fistula. For example in low vesicovaginal fistula there is continuous vaginal leakage of urine, the bladder never fills up and hence no desire for micturition, while in high fistula or with ureterovaginal fistula the patient may still has some desire to void in a addition to continues vaginal leakage of urine.

Etiology:

- In developed countries most genito-urinary fistulae occur as complications of pelvic surgery (e.g. hystrectomy) or irradiation. In rare cases it can be a complication of advancing cancer.
- Obstetric fistulas: this includes two types:
    - Secondary to surgical trauma e.g. following difficult cesarean section or forceps delivery. In this variety the symptoms of vagina leakage of urine either appears immediately or within short period.
    - Necrotic obstetric fistula: unfortunately this type of fistula is still common in non-developed countries where women do not have ready access to obstetrical care. It develops secondary to neglected obstructed labor. During prolonged/ obstructed labor, the soft tissue of the vagina is trapped between the fetal head and the bony pelvis. If the compression is not relieved, the tissue will become necrotic. Usually between 3 and 10 days postpartum, this necrotic tissue sloughs off and a fistula develops between the bladder and the vagina (vesicovaginal) or the rectum and the vagina (rectovaginal)

Diagnosis:

Careful examination should be undertaken to determine the site and size of the fistula. Examination is best performed using a Sims (or single bladed) speculum with the patient in Sims position.

In difficult cases further investigations will be required such as:

- Installation of methylene blue dye into the bladder while inserting a vaginal pack and looking for discoloration of the pack.
- Injection of intravenous indigo-carmine, which will be excreted in the urine and causes discoloration of the vaginal pack if a vescivaginal or ureterovaingal fistula, is present.
- Cysto-urethroscopy: may be necessary to determine the location of the fistula in the bladder, its relation to ureteric orifices and the condition of the bladder mucosa which is important for the surgical repair.
- Intravenous pyelogam and/or retrograde pyelogram to localize ureterovaginal fistula.

Treatment:

- Non-surgical treatment: The aim of non-surgical treatment is to allow healing of the fistula while ensuring continuous drainage of urine by inserting bladder catheter or ureteric stent (double J) in case of small uretero-vaginal fistula. This is should be the first step to be tried in cases of traumatic surgical fistula (e.g. following hysterectomy or operative delivery). There is usually good chance of spontaneous healing provided the tissues are healthy and continuous urine drainage is secured.
- Surgical repair: is indicated all other cases i.e. failure of spontaneous healing, chronic or old fistula or unhealthy tissues. The approach to fistula repair can be via abdominal or vaginal approach or combined approach.

Approach to patient with Urinary Incontinence

The approach to management of patient with complains of involuntary loss of urine i.e. urinary incontinence depends on reaching the correct diagnosis of the type of incontinence. This begins by taking full history, examination and investigation.

History: Key components of history:

- Analysis of the symptoms looking for type of incontinence. In proportion of cases the history may be typical for symptoms of urge or stress incontinence. In the remaining cases patients may have mixed symptoms or one of the other less types (see above).
- Severity of symptoms: this should be evaluated by enquiring about duration, course, leakage frequency, volume, timing, and to what extend it affects patient social life.
- Symptoms suggestive of cystitis such as dysuria and frequency should be explored. Patient may have urgency i.e. strong desire to void but no incontinence.

- Relevant systemic disease e.g. diabetes, neurological diseases or medications (e.g. diuretics)
- Any previous specific medication or surgery for incontinence.

Examination:

- Should begin with assessment of the patient general health. In abdominal examination the aim is to look for distended bladder or abdominal masses.
- Standard vaginal examination is then performed with special emphasis on changes such as atrophic vaginitis/urethritis, pelvic muscle laxity, bladder neck descent, cystocele, rectocele, uterine/vault prolapse, any pelvic masses. During examination clinical tests can be performed to demonstrate SI and urethral hypermobility:
    - Demonstration of SI: the patient is asked to cough, when the bladder is full, while the physician observes the urethral meatus. In positive cases a small jet of urine escape simultaneously with each cough. If the test is negative it should be repeated while the patient in standing position.
    - Demonstration of urethral mobility "The Q-Tip test": is a diagnostic test for of hypermobility of the urethrovesical junction. With the patient in the supine position, the urethral meatus is cleaned with providone-iodine and a sterile, well-lubricated cotton-tipped swab (Q-tip) is introduced into the urethra to the bladder. The patient is then asked to perform a Valsalva strain. In a normal patient, the angle of the Q-tip is less than 30 degrees from the horizontal, and will remain at this angle when the patient strains. In patients with inadequate bladder neck support and stress incontinence, the Q-tip angle generally exceeds 30 degrees from the horizontal.

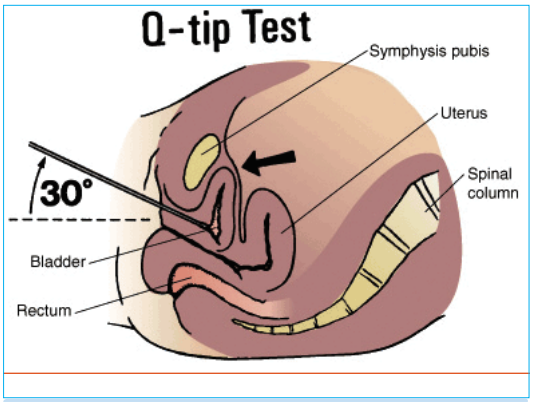

Figure 14-12: Movement of the Q-Tip of more than 30-degrees in the horizontal plane with straining is indicative of urethral hypermobility of the urethrovcesical junction

Investigations:

- General tests: The nature of investigations depends on the diagnosis and the general condition of the patient.

- Tests for general assessment of the patient health: Investigations directed for cardiovascular assessment is warranted in older patients. Also creatinine and electrolytes for renal assessment may be necessary in some cases. Diabetes should be excluded in patient with plyuria. ,
- Urine microscopy and if necessary culture should be performed to exclude urinary infection.

- Specialized tests:
  - Urodynamic tests: are specific tests used to assess the physiological function of the urinary tract during urine filling (storage) and evacuation. They help in improving the accuracy in the differentiation between bladder muscle dysfunction (UI) or urethral sphincter defect (SI). However they are invasive, expensive, and require special equipment and training. Furthermore it has not been found to affect outcome. Therefore routine urodynamic testing is not recommended in the evaluation of all cases of urinary incontinence. It is indicated if the diagnosis is not clinically clear (e.g. mixed incontinence), or if the patient fails to improve with treatment or if surgical intervention is planned.

Figure 14-13: Patient having urodynamic test. Pressure catheters inserted into bladder and, urethra and rectum

The most important urodynamic tests are:

- Cystometry (or cystometrogram): This test aims to assess
  - The compliance and stability of the detrusor muscle bladder during filling.
  - The capacity of the bladder.
  - The transmission of sensation through the neurosensory pathways

The voiding or competence of the bladder outlet

The test is performed by filling the bladder with water through a urethral catheter at a steady rate. A second catheter placed in the rectum or vagina measures intra-abdominal pressure that is then subtracted from the vesical pressure to measure true detrusor pressure during filling and voiding.

- Uroflowmetry test: aims to measure the peak flow rate of urine in ml/sec, and give an idea about the interaction between a detrusor contraction and the urethral resistance (e.g. in cases of suspected bladder outlet obstruction). It may be followed by a *post void*

residual (PVR) ultrasound.

- Leak point pressure test: to determine the bladder or abdominal pressure when leakage occurs due to increased abdominal pressure (Valsalva or cough) to assess urethral resistance.
- Urethral pressure profile (UPP) test: to assess urethral function and its ability to prevent leakage of urine, at rest and during stress through measuring sphincter closure pressure.
- Voiding Cystourethrogram**:** Voiding cystourethrogram allows for radiographic visualization of the lower urinary tract during bladder filling and voiding to determine bladder outlet obstruction, integrity of the bladder sphincter, bladder wall abnormalities, or vesicoureteral reflux. It may be performed after or in conjunction with other urodynamic studies.

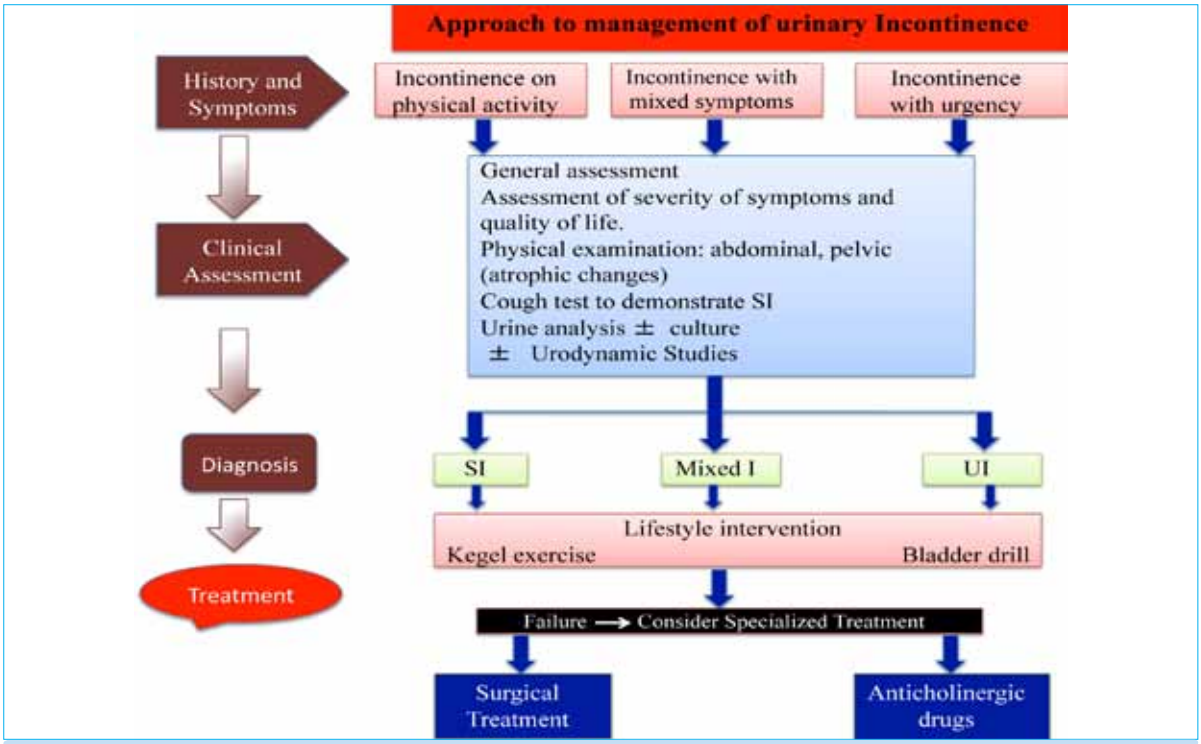

Figure 14-14: Algorithm for approach to dealing with patient presenting with incontinence. The rare types of overflow incontinence and incontinence due to fistula should be excluded from history and examination.

References and further readings:

- Reproduced with permission from Harvey, M-A, Versi, E. Urogynecology and pelvic floor dysfunction. In: Kistner's Gynecology and Women's Health, 7th ed, Ryan, KJ, Berkowitz, RS, Barbieri, RL, Dunaif, A (Eds), St. Louis, Mosby 1999. Copyright © 1999 Elsevier.

Chapter 15

Vulvovaginitis and Sexually Transmitted Infections (STIs) (Infections of the lower genital tract)

Vulvovaginitis is the most common gynecologic condition seen by gynecologists and primary care physicians. It can be due to infective causes or non-infective causes.

The most common causes of infectious vaginitis are bacterial vaginosis (40%), and Candida infection (20-25%). Other causes including sexually transmitted infections i.e. infections primarily transmitted by sexual contact (STIs) should be considered particularly in areas and among at risk population.

Clinical symptoms of vulvovaginitis in many occasions are overlapping include discharge, burning, and pruritus. Signs of vulvar irritation such as erythema and excoriation of the vulvar skin may also be present. The diagnosis can often be made based on clinical presentation, office tests and knowledge of epidemiologic prevalence of specific infections. In some cases confirmation by further laboratory tests such as culture, monoclonal antibody tests, and tests based on nucleic acid amplification techniques (NAAT) must be undertaken.

By the end of this chapter you should be able to:
Describe the difference between STIs and STDs
Describe the impact of STIs on women, and infant health
List the factor that protects against vaginal infection: the nature of the epithelium & the vaginal PH.
Describe: the pathophysiology of vaginal infection throughout women age.
List the causes of vulvovaginitis:
- **Non-infectious causes**: Leukorrhea, Atrophic vaginitis, Vulvovaginitis due to irritants or allergen, Vulvovaginitis secondary to cervical or vaginal lesions.
- **Infectious causes**: Bacterial vaginosis, Candida infection, Trichomonas vaginitis, Foreign body induced infection, Streptococcal, Chlamydia trachomatis, Gonorrhea, Human papiloma virus infection and Herpes genitalia.

Describe: the Microbiology, Pathogenesis, Clinical manifestation and the Treatment for each of the infectious causes.
List the causes "sexually transmitted infections"
Describe: the approach to patient presenting with symptoms of vulvovaginitis.

Sexually Transmitted Infections

The term sexually transmitted infections (STIs) is now preferred to the former terms sexually transmitted diseases (STDs) or Venereal diseases. The reasons are that the term STDs is not very specific since many infections while related to sexual contact (e.g. candida infection, etc) but are not considered sexually transmitted infections. Furthermore the word disease is not appropriate since many individuals are carriers for sexually transmitted infections but not necessarily having symptomatic disease.

Definition: (STIs) are infections that spread primarily through person-to-person sexual contact.

Some STIs such as HIV and syphilis; can also be transmitted from mother to child during pregnancy and childbirth, and through blood products and tissue transfer

The Burden and Clinical significance of STIs:

The burden of STIs is reflected in the WHO (world health organization) report. According to this report it is estimated that 340 million new cases of curable STIs (syphilis, gonorrhea, chlamydia and trichomoniasis) occur annually throughout the world in adults aged 15-49 years. Furthermore in developing countries, STIs and their complications rank in the top five disease categories for which adults seek health care.

Consequences of STIs: STIs have serious consequences in term of both morbidity and mortality.

- They are common causes of PID, infertility, and genital cancer (with HPV infection).
- Furthermore, in pregnancy maternal fetal transmission is associated with high rate of perinatal mortality and morbidity.

Appropriate measures for prevention, diagnosis and treatment are essential to prevent the serious consequences of STIs.

These issues are discussed with individual infections.

Pathophysiology of the lower genital tract protective mechanism:

During the reproductive years the vagina is protected against infection by:

- The non-keratinized stratified squamous epithelium of the vagina, which is devoid of any glands. The thickness of the epithelial layers increase under the effect of estrogen due to increased contents of glycogen storage. With diminishing levels of estrogen, the layers become thin and atrophic.

- The low acidic vaginal ph (3.8 – 4.5): This is due to lactic and acetic acid, which are produced by the action of the normal acidophilic flora of the vagina, namely *Lactobacillus* and *Corynebacterium* on the glycogen stored in the vaginal epithelial cells. The low vaginal ph provide protection against some STI (sexually transmitted infection) including HIV. It also keeps the balance of the "normally" present vaginal aerobic and anaerobic gram-positive and gram-negative bacteria in check.

The vaginal environment during woman life:

The vaginal environment depends on the estrogen level.

- In pre-pubertal years the epithelium is thin, there is hardly any microorganism and the PH is around 7.
- During the reproductive years the thickness of vaginal epithelium increases, and the vagina maintains a moist acidic environment due to low PH. The vagina becomes inhabitant by numerous microorganisms.
- As women approach menopause and the estrogen level declines, the vagina again becomes thin and atrophic, the PH rises and the protective effect of the acidophilic microflora decreases.

Immediately after birth the vagina becomes colonized by aerobic and anerobic bacteria acquired from passing through the birth canal. However as a result of exposure to maternal estrogen the vaginal epithelium becomes rich in glycogen, which support predominance of the protective acidophilic microflora. Therefore the PH is low (<4.7). Soon this situation changes as the level of estrogen declines.

Causes of vaginal discharge: vaginal discharge and or symptoms of vulvovaginitis may be due to non-infectious and infectious causes:

- **Non-Infectious causes of vaginal discharge:** Common causes of non-infectious vaginal discharge and vaginitis include:
  - **Physiological discharge or leukorrhea**: refers to vaginal discharge in the absence of a pathological cause. Physiological leukorrhea is usually due to estrogen-induced changes in cervicovaginal secretions. Therefore its quantity and quality varies during women menstrual cycles (discharge is greatest at midcycle).

    It is generally nonmalodorous, mucousy, white or yellowish and usually not accompanied by other signs and symptoms, such as pruritus, pain, burning or irritation. If it is heavy in amount a slight malodor and irritative symptoms can be normal
  - **Atrophic vaginitis**: Atrophic vaginitis refers to inflammatory reaction secondary to estrogen deficiency.

Atrophic vaginitis typically occurs in menopausal women, but can occur in premenopausal women in associated with hypoestrogenic state e.g. in the postpartum period, lactation, and during administration of antiestrogenic drugs.

- **Irritants and allergens**: Noninfectious vaginitis can be due to irritants (e.g., scented panty liners, spermicides, soaps and perfumes, and some topical drugs) and allergens (e.g., latex condoms, topical antifungal agents, seminal fluid, chemical preservatives) that produce immunologic acute and chronic hypersensitivity reactions, including contact dermatitis.
- **Cervical and vaginal lesions**: Cervical and vaginal lesions e.g. ectropion, polyps, granulation tissue, and neoplasia can also be associated with persistent vaginal discharge. These disorders can be detected by speculum examination.

Clinical presentation: Clinically non-infectious vaginitis may be difficult to be distinguished from infection related vaginitis. In both conditions symptoms of pruritus, irritation, burning, soreness, and vaginal discharge may be present.

Careful history taking, examination and office tests (pH < 4.5, normal findings on microscopy, and negative amine test) can help in making the diagnosis.

If there is doubt about the physiological basis of the discharge, a yeast culture and testing for chlamydia and gonorrhea should be performed.

➢ Infectious causes of vaginal discharge:

The most common causes of infectious vaginitis are bacterial vaginosis (40%), Candida infection (20-25%).

The remaining causes include more than 30 different sexually transmissible bacteria, viruses and parasites. The commonest ones are:

Bacterial infections:

- Neisseria gonorrhoeae.
- Chlamydia trachomatis
- Treponema pallidum
- Haemophilus ducreyi (causes chancroid)
- Klebsiella granulomatis (previously known as Calymmatobacterium granulomatis causes granuloma inguinale or donovanosis).

Viral infections

- Human immunodeficiency virus (causes AIDS)

- Herpes simplex virus type 2 (causes genital herpes)
- Human papillomavirus (causes genital warts and certain subtypes lead to cervical cancer in women)
- Hepatitis B virus (causes hepatitis and chronic cases may lead to cancer of the liver)
- Cytomegalovirus (causes inflammation in a number of organs including the brain, the eye, and the bowel).

Parasitic organisms

- Trichomonas vaginalis (causes vaginal trichomoniasis)
- Candida albicans (*not sexually transmitted infection but can be aggravated by sexual relation*)

o Bacterial Vaginosis "BV":

Bacterial vaginosis (BV) is the most common cause of vaginal discharge in women of childbearing age, accounting for 40 to 50 percent of cases.

Microbiology: BV is NOT an infection by new microorganism but is a disturbance of the balance of the normal vaginal flora characterized by reduction in concentration of the normally dominant lactobacilli and increase in concentration of other organisms, especially anaerobes (*including Gardnerella vaginalis, Mycoplasma hominis, Prevotella species, Porphyromonas species, Bacteroides species, anaerobic Peptostreptococcus species, Fusobacterium species, and Atopobium vaginae*)

Pathogenesis: Disturbance of the normal balance of the vagina microorganisms may occur under certain circumstance e.g. stress, use of vaginal douching, use of IUD for contraception, new or multiple sex partners.

Clinical presentation and diagnosis: Approximately 50 to 75 percent of women with BV are asymptomatic. In symptomatic cases the diagnosis of BV can be made based on the clinical presentation and office tests.

- **Symptoms**: unpleasant, "fishy smelling" discharge that is more noticeable after coitus. The discharge is off-white, thin, and homogeneous. Dysuria and dyspareunia may be present. Pruritus, erythema, and inflammation are typically absent.
- **Diagnostic office tests**: Three of four criteria known, as Amsel criteria are necessary for making the diagnosis of BV. It should be noted however that the first three findings are sometimes present in patients with trichomoniasis.

1. The presence of homogeneous, thin, grayish-white discharge that smoothly coats the vaginal walls.
2. A vaginal pH > 4.5
3. Positive whiff-amine test: a fishy odor is produced when 10 percent potassium hydroxide (KOH) is added to a sample of vaginal discharge.
4. The presence of "Clue cells" on saline wet mount: Clue cells are vaginal epithelial cells studded with adherent coccobacilli at the edge of the cell (Figure 15-1). This is the single most reliable predictor of BV.

Vaginal culture has no role in diagnosis of BV because there are no bacteria that are specific for BV. Furthermore although cultures for G. vaginalis are positive in almost all women with symptomatic infection, the organism is detected in up to 50 to 60 percent of healthy asymptomatic women; thus, its presence alone is not diagnostic of BV.

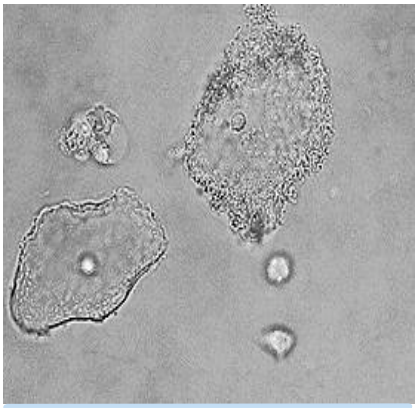

Figure 15-1: Clue cells as seen under the microscope.

Treatment: women with symptomatic BV whether pregnant or non-pregnant should be treated to relieve the symptoms and reduce possible fetal or obstetrical adverse effects namely risk of preterm birth (secondary to Chorioamnionitis) and endometritis after cesarean and vaginal delivery. The choice of treatment include:

- Metronidozole 500 mg orally twice daily for seven days
- Clidamycin 300 mg orally twice daily for seven days.

o Candida infection:

Microbiology: there are several types of candida species; the type most involved in vulvovaginitis is the Candida albicans. However because of inappropriate use of antifungal medications other types particularly C. glabrata and C. parapsilosis are increasing.

Pathogenesis: Candida species are part of the normal commensal of the lower genital tract flora in 20 to 50 percent of healthy asymptomatic women.

Symptomatic infection " i.e. vulvovaginal candidiasis" may occur with no obvious reason. But it often develops under certain circumstances such as when a patient has some alteration in cellular immunity, normal flora or normal physiology such as:

- Diabetes mellitus: especially with poor glycemic control.
- Administration of antibiotics: during or after taking broad-spectrum antibiotics there

is increased risk of developing episode of infection. This apparently occurs because antibiotics disturb the normal balance of vaginal microorganism by inhibiting the normal bacterial flora, which favors growth of potential pathogens such as candida.

- Increased estrogen levels: e.g. pregnancy and use of oral contraceptive (especially when estrogen dose is high).
- Immunosuppression: Candida infections are more common in immunosuppressed patients, such as those taking corticosteroids or with HIV infection.
- Contraceptive devices e.g. vaginal sponges, diaphragms, and intrauterine devices have been associated with vulvovaginal candidiasis, but not consistently.
- Genetic susceptibility: some women are genetically susceptible to recurrent vaginal infection. This explains resistant and recurrent cases of vulvovaginal candidiasis.

Clinical presentation and diagnosis:

- **Symptoms:** The most common symptom is vulvar pruritus. Other symptoms include dysuria (external or vulvar rather than urethral), soreness, irritation, and dyspareunia. There is often little or no discharge, if there is discharge it is typically white and clumpy (curd-like).
- **Signs**: physical examination often reveals erythema of the vulva and vaginal mucosa and vulvar edema. There may be thick, adherent, and "cottage cheese-like" discharge.
- **Diagnostic office tests:** the clinical diagnosis can be confirmed by positive wet mount test using 10 percent potassium hydroxide. In this test the yeast and hyphae can be identified by adding 10% potassium hydroxide to wet mount of the discharge and examine the sample under the microscope.
- **Culture:** doing swab and culture is not necessary for diagnosis except if the wet mount test is negative in a clinically suspected vulvovaginal candidiasis (occur in up to 50 % of patients) and in patients with persistent or recurrent symptoms. In the later cases many of these women have non-albicans infection that is resistant to standard antifungal treatment (i.e. azoles).

Treatment: is indicated in symptomatic cases by administration of antifungal medications either orally (e.g. fluconazole) or as vaginal preparations (e.g. Miconazole).

Treatment is not indicated in asymptomatic cases, which occur in approximately ten to 20 percent of women in reproductive age group.

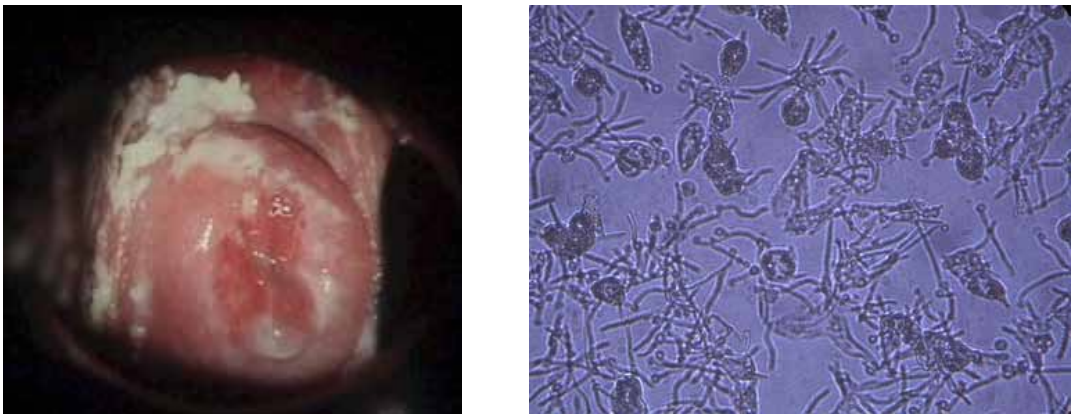

Figure 15-2: Left: Speculum vaginal examination showing the cervix with typical picture of "cottage cheese-like" discharge. Right: Microscopic view of yeast spores and hyph.

- **Trichomonas vaginalis "TV":**

Microbiology: Trichomonas vaginalis is a flagellated protozoan. **Pathogenesis**: TV is a sexually transmitted infection (STI) usually found in the vagina and urethral tissues. Men can also be infected but often asymptomatic. Infection with trichomoniasis is associated with a high prevalence of coinfection with other sexually transmitted diseases. Therefore diagnosis of trichomoniasis usually prompts a search for other sexually transmitted diseases (syphilis, HIV, gonorrhea or chlamydia).

Clinical presentation and diagnosis:

- **Symptoms**: Approximately 50% of infection with trichomoniasis is asymptomatic. Symptomatic cases presents with purulent, malodorous, thin discharge (70 % of cases) with associated burning, pruritus, dysuria, frequency, and dyspareunia.
- **Signs**: erythema of the vulva and vaginal mucosa; the classic green-yellow frothy discharge may be seen in about 10-30% of cases. Punctate hemorrhages may be visible on the vagina and cervix "strawberry cervix".
- **Diagnostic test**: the clinical suspicion should be confirmed by diagnostic one of the following tests.
    - Wet mount test: The presence of motile trichomonads on wet mount is diagnostic of infection, but this occurs in

Complications of Trichomoniasis

In non-pregnant women: post-hysterectomy cellulitis, tubal infertility, and increase risk of HIV infection.

In pregnant women: PROM and preterm delivers: Newborn: fever, respiratory problems, urinary tract infection, nasal discharge, and, in girls, vaginal discharge

only 50 to 70 percent of culture-confirmed cases.

- Culture: Swab and culture test for TV has high sensitivity and specificity (95 percent and >95 percent respectively).
- Rapid antigen and nucleic acid amplification tests: these are rapid tests based on development monoclonal antibodies and specific DNA probes. It is useful for areas with high prevalence of STD.

Treatment: Treatment of TV is indicated in symptomatic and asymptomatic cases because of its potential complications (see blue box). The recommend drug is Metronidazole administered usually as a single oral dose of 2 grams (four 500 mg tablets).

Foreign bodies: A foreign body (e.g. retained tampon, condom or diaphragm) can be associated with chronic vaginal discharge, intermittent bleeding or spotting, and/or a foul smelling odor due to inflammation and infection. Removal of the foreign body is generally adequate treatment. Antibiotics are rarely indicated.

Foreign body vaginitis should also be suspected if a child complains of vulvar itching, infection or bloody vaginal discharge.

- **Streptococcal vulvovaginitis:**

Group A streptococcus: Group A streptococcus (Streptococcus pyogenes GAS) is an uncommon cause of vulvovaginitis.

Clinical features include acute onset of frankly purulent discharge accompanied by pruritus, soreness and irritation, erythema, labial edema, and possibly dysuria from burning of the skin with voiding. Microscopy of the discharge reveals a marked increase in polymorphonuclear leukocytes and Gram's stain shows chains of gram-positive cocci.

Treatment: Penicillin VK 500 mg four times daily for 10 to 14 days or clindamycin cream 2 percent per vaginam for 7 to 10 days.

Group B streptococcus: Group B streptococcus (GBS) commonly colonizes the vagina and causes neonatal sepsis and maternal upper tract infection (endometritis). It is controversial whether GBS is a pathogen in vulvovaginitis hence treatment of asymptomatic non-pregnant women may not be necessary.

- **Chlamydia Trachomatis "CT"**:

Microbiology: C. trachomatis is an obligate intracellular small gram-negative bacterium.

It causes different types of infection depends on its type:

- Genital infection is caused by the C. trachomatis serovars B and D through K.
- The L serovars cause lymphogranuloma venereum, a genital ulcer syndrome.
- Endemic trachoma, an ocular infection is caused by serovars A to C.

Pathogenesis: In Western countries CT are considered the most common sexually transmitted disease (STD). There is no reliable data on its prevalence among local population in Saudi Arabia.

Risk factors for infection with CT include: Adolescents age, multiple sex partners, inconsistent use of barrier contraceptives, cervical ectopy, history of prior STD and lower socioeconomic class.

Infection with CT does not provide long-lived immunity. As a result, reinfection or persistent infection is common.

Clinical Manifestation: In the majority of women with C. trachomatis infection is asymptomatic. Therefore asymptomatic carriers provide ongoing reservoir for spreading of infection. In symptomatic cases the clinical manifestations range from cervicitis to pelvic inflammatory disease (PID).

- **Cervicitis**: manifested as vaginal discharge that may be confused with vaginitis, or poorly differentiated lower abdominal pain. On examination there may be mucopurulent cervical discharge, cervical friability, and edema. In some cases examination is unremarkable.
- **Urethritis:** manifested with typical symptoms of a urinary tract infection (UTI) such as frequency and dysuria, and occasionally lower abdominal pain. Urinalysis reveals pyuria, but no organisms seen on Gram stain or in traditional culture.
- **Perihepatitis (Fitzhugh-Curtis syndrome)**: in 5-15% of women with chlamydia infection, particularly cases complicated with PID develop perihepatitis, an inflammation of the liver capsule and adjacent peritoneal surfaces (Figure 15-3). Perihepatitis may occur either as direct extension of infected material from the cul-

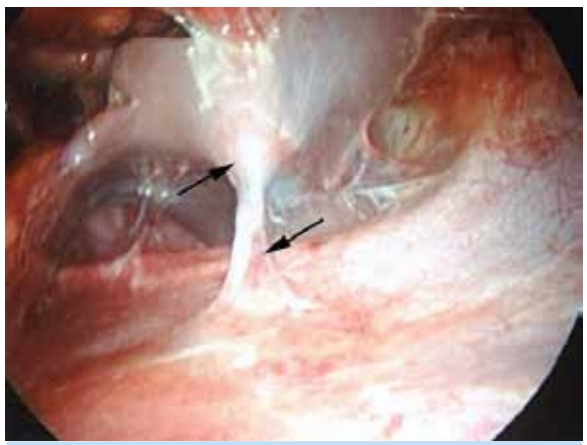

Figure 15-3: Laparoscopic picture of perihepatits "Fitzhugh-Curtis syndrome". About 50% to 75% of cases are caused by Chlamydia trachomatis infection, 10% result from N gonorrhoeae infection, sometimes a complication of PID.

de-sac and/or through lymphatics or an immunologically mediated mechanism. Perihepatitis is manifested as right-upper quadrant pain or pleuritic pain. There are typically no associated liver enzyme abnormalities. Treatment is supportive, usually with nonsteroidal anti-inflammatory agents.

- **Pelvic inflammatory disease**: Approximately 30 percent of women with chlamydia infection will develop PID if left untreated. PID due to C. trachomatis tends to be associated with higher rates of subsequent infertility.
- **Pregnancy and CT infection**: Untreated chlamydia infection can increase the risk for premature rupture of the membranes and low birth weight. If the mother is untreated, 20 to 50 percent of newborns will develop conjunctivitis, and 10 to 20 percent will develop pneumonia.

Diagnosis:

- **Culture:** Culture methods are difficult and expensive since it requires live cells hence its use is limited to research and in cases of forensic investigation (e.g., rape, child abuse).
- **Nucleic acid amplification techniques** (NAAT): based on amplifying C. trachomatis DNA or RNA sequences using new DNA amplification techniques e.g. polymerase chain reaction (PCR), transcription-mediated amplification (TMA) and others. A major advantage of NAATs is that it can be performed on urine as well as urethral and vaginal specimens.
- **Chlamydia rapid testing**: are immunoassay-tests based on monoclonal antibody binding of chlamydial antigens from self-collected vaginal samples. These rapid tests provide results within 30 minutes of testing and are less expensive to perform and simple to interpret since testing results are reflected in a test strip color change.

Treatment:

- The two recommended regimens are azithromycin (1 g PO as a single dose) and doxycycline (100 mg PO BID for 7 days).
- Other measures: include treatment of sexual partners, and evaluation for other STDs (syphilis serology, gonococcal testing).
- Treatment of TV in pregnancy: Azithromycin (1 gram orally in a single dose) or amoxicillin (500 mg orally three times a day for seven days).

○ Gonorrhea:

Microbiology: Neisseria gonorrhea is a gram-negative diplococus bacteria.

Pathogenesis: NG is a sexually transmitted infection. In Western countries, NG is the second most common STI (no available statistics for NG infection in Saudi Arabia). It can involve any portion of the genital tract, the oropharynx or become disseminated.

Clinical Manifestation: Infection in women is often asymptomatic compared to men who are asymptomatic in only 10 percent of the time.

In symptomatic cases the signs and symptoms are similar to Chlamydia trachomatis infection:

- Cervicitis: the cervix is the most common site of mucosal infection. On examination, the cervix appears swollen, red, and friable with contact bleeding. It manifests with vaginal pruritis and/or a mucopurulent discharge.
- Urethritis: results in dysuria, frequency/urgency but culture are usually negative.
- Anorectal infection and proctitis: Anorectal gonococcal infection can be asymptomatic or associated with clinical proctitis. Anorectal infection may results from direct contact or autoinoculation from vaginal secretions.
- Oropharyngeal infection: Gonococcus isolated from the oropharynx typically represents asymptomatic colonization, although symptomatic pharyngitis can also occur.
- Other mucosal sites of infection: Bartholin and Skene's glands. These sites typically are symptomatic and rarely the sole site of infection.
- Pelvic inflammatory disease "PID": Gonorrhea is the causative organism in 40 percent of cases of PID. It complicates approximately 10 to 40 percent of women with cervical gonorrhea. It can be the first presenting complaint. Symptoms of PID include pelvic/abdominal pain, abnormal vaginal bleeding, and dyspareunia Signs of PID on examination include uterine tenderness adnexal or cervical motion tenderness.
- Fitz-Hugh Curtis syndrome or perihepatitis: as in Chlamydia infection the symptoms and signs include right upper quadrant pain and tenderness. Liver function tests are frequently abnormal.

Diagnosis:

- Culture: from endocervical specimens using special media (modified Thayer-Martin medium) are available in most laboratories and have the advantages that it allows determination of antibiotic resistance. However currently it is not the "gold standard" for the diagnosis of NG infection. This is because it takes approximately 24 hours to have a result and its sensitivity is only about but 65 to 85 percent in asymptomatic infection. Current gold standard tests are based on DNA analysis,

which is considered more sensitive, rapid and easier to perform (see below).

- Gram stain: The detection of intracellular gram-negative diplococci using Gram stain is rapid and inexpensive test. However it is only 60 percent sensitive in symptomatic women compared with 95 percent in symptomatic men.
- DNA probe: In this method a DNA probes labeled with a specific marker aims to identify a specific nucleic acid sequence of the organism. The DNA probes for diagnosis of gonorrhea from endocervical swabs are approved by the FDA (Food and Drug Administration).
- DNA amplification techniques "nucleic acid amplification tests "NAATs": NAATs are the most sensitive and specific test for N. gonorrhoeae infection. It offers rapid results (within hours). It is non invasive i.e. can be performed not only on endocervical swabs, but also on liquid PAP specimens, self-collected vaginal swabs (by the patient herself), and urine specimens. The test is highly sensitive but still more expensive than traditional culture methods. The NAATs and other nonculture methods are not approved by the Federal Drug Administration (FDA) for diagnosis of gonorrhea in non-genital sites.

Treatment:

Over the years the emergence of antimicrobial resistance has limited the antibiotic choice for treatment of gonococcal infection. Currently the recommended drug for cervical, urethral and anorectal infection is:

- Ceftriaxone 125 mg IM once OR Cefixime 400 mg orally once.
- Since dual infection with chlamydia is common in persons with gonorrhea all patients should also be empirically treated for presumed concomitant chlamydia infection by administration of Azithromycin (1 g orally once) or doxycycline (100 mg orally two times daily for seven days).
- Penicillin allergic patients: patients with history of penicillin allergy should undergo Penicillin skin testing to confirm the diagnosis. If the test is positive alternative antibiotics include spectinomycin or azithromycin (2 grams as a single oral dose).

o Human Papilloma Virus infection "HPV":

Microbiology: HPV is member of the papillomavirus, deoxyribonucleic acid (DNA) viruses. The HPV is the cause of common warts of skin as well as of lesions of the mucous membranes. HPV infects epithelial tissues of skin and mucous membranes only in humans.

More than 30 to 40 types of HPV are typically transmitted through sexual contact and infect the anogenital region. Some types "the high risk types" are associated with cancerous and precancerous conditions of the cervix, vulva, vagina and anus in women or cancers of the anus and penis in men (table 15-1).

High risk (oncogenic or cancer associated) types
Common types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 69, 82
Low-risk (non-oncogenic) types
Common types: 6, 11, 40, 42, 43, 44, 54, 61, 72, 81

Table 15-1: Risk of cervical cancer with HPV. National Cancer Institute Factsheet. Human papillomavirus and cancer: Available at: www.cancer.gov/cancertopics/factsheet/Risk/HPV.

Pathogenesis: HPV is the most common sexual transmitted infection (SDI). Most HPV infections (90%) are temporary, have little long-term significance and spontaneously disappear within 1-2 years. However persistent infections which occur in 5% to 10% of cases especially with the high risk types of virus is associated with increased risk of development of precancerous lesions of the cervix, which can progress to cervical cancer. It is now known that HPV infection is the cause of nearly all cases of cervical cancer.

Clinical Manifestation:

- Symptoms: Most infections with HPV are asymptomatic. Therefore the diagnosis of infection with HPV virus is usually made when DNA hybridization testing is performed in evaluation of an abnormal pap smear.
- Signs: In symptomatic cases the earliest sign is the development of small, hard spots within 3 weeks to 3 months after exposure. Later it develops into warts "Condyloma acuminata" usually on the lips of the vagina, inside the vagina, or around the anus. The warts vary in size and shape. In some cases it can be difficult to identify by naked eye examination.

  Patient may also complain of vaginal discharge, pruritus, bleeding, burning, tenderness, and pain.

Treatment: The choice of treatment of genital warts depends on factors such as its size and location:

- Chemical treatment: e.g. with topical application of 25 percent podophyllin solution (contraindicated in pregnancy because it is absorbed by the skin and may cause birth defects).

- Surgical treatment: excision by freezing (with liquid nitrogen) or burning (electrodesiccation) or laser vaporization.

○ Genital Herpes Virus infection "HSV":

Microbiology: Herpes simplex is part of a group of other herpes viruses that include herpes zoster (the virus responsible for shingles and chicken pox). There are more than 80 types of herpes viruses. Herpes simplex virus is a common sexually transmitted disease worldwide.

There are two forms of the herpes simplex virus: Herpes simplex virus 1 (HSV-1) and Herpes simplex virus 2 (HSV-2). Previously it was assumed that HSV-1 infections occur in the oral cavity (mouth), while HSV-2 attacks the genital area and is sexually transmitted. It is now widely accepted, however, that either type can be found in either area and at other sites. In fact, HSV-1 is now responsible for up to half of all new cases of genital herpes in developed countries.

Pathogenesis: Transmission of infection occurs through direct contact where the virus passes through body fluids (saliva, semen, fluid in the female genital tract) or in fluid from herpes sores.

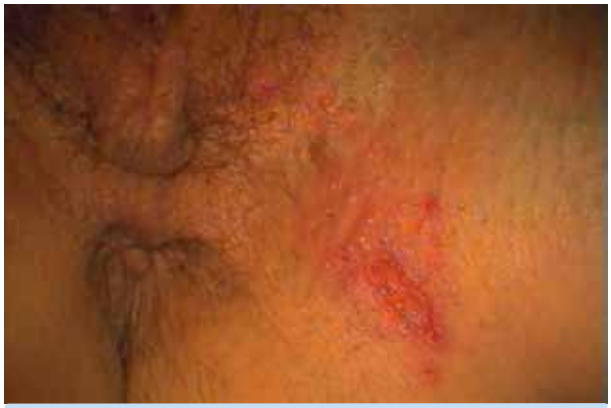

Figure 15-4: Close view of early herpes outbreak shows small, grouped blisters (vesicles), ulcers and lots of inflammation (erythema).

It gets into the body through broken skin or a mucous membrane, where it starts destroying the host cells causing inflammation and fluid-filled blisters or ulcers. Once the fluid is absorbed, scabs form, and the blisters disappear without scarring.

The viral particles are carried from the skin through branches of nerve cells to clusters at the nerve-cell ends (the *dorsal root ganglia*). There, the virus lives in an inactive (*latent*) form.

At unpredictable times, the virus begins multiplying with or without symptoms "subclinical viral shedding" passes through body fluid where it can result in infection of other people. HSV is a strong risk factor for HIV infection in areas with high prevalence of HIV.

Clinical Manifestation: The clinical manifestations of genital HSV vary widely depending upon whether the infection is primary, nonprimary or recurrent:

- Primary infection: the first outbreak usually occurs 1 - 2 weeks after sexual exposure to the virus. The first signs are a tingling sensation in the affected areas (such as genitalia, buttocks, and thighs) and groups of small red bumps that develop into blisters. Over the next 2 - 3 weeks, more blisters can appear and rupture into painful open sores. The lesions eventually dry out, develop a crust, and heal rapidly without leaving a scar. In some cases the infection can be mild, subclinical, or entirely asymptomatic.

  About 40% of men and 70% of women develop other symptoms, such as flu-like discomfort, headache, muscle aches, fever, and swollen glands. (Glands can become swollen in the groin area as well as the neck.) Some patients may have difficulty urinating, and women may experience vaginal discharge.

  - Recurrent infection: refers to reactivation of genital lesions in a seropositive person.
  - Non-primary genital infection: refers to genital HSV-2 lesions in a patient with preexisting antibodies to HSV-1; or genital HSV-1 lesion in a patient with preexisting antibodies to HSV-2.

    In the later two types (non-primary and recurrent infection) the symptoms and signs (lesions) are milder, and often no symptoms at all.

Diagnosis:

Should be confirmed by one the following tests: (1) antibodies specific serology testing of IgG and IgM antibodies for HSV type I and II (2) viral culture: as obtained from active lesions. (3) PCR amplification of viral particle. The choice to testing depends on the clinical presentation.

Treatment:

- In primary infection antiviral treatment "e.g. acyclovir, 400 mg three times a day" should be offered whether the patient is pregnant or not (see HVS in pregnancy in).
- Patient with recurrent lesions can be offered suppressive antiviral treatment.

  For HVS and pregnancy see "Obstetric-the Text Book for Undergraduate".

○ Other Sexually Transmitted Infections:

➢ Chancroid:

- Causative organism: Haemophilus ducreyi
- Pathological lesions: Ulcers are sharply circumscribed or irregular, ragged undermined edges, not indurated, base may have gray or yellow exudate. About 50% of cases have inguinal adenopathy, often unilateral, painful and may suppurate/rupture
- Treatment: Azithromycin 1 g orally in a single dose or Ceftriaxone 250 mg intramuscularly (IM) in a single dose or Ciprofloxacin 500 mg orally twice a day for 3 days (not for pregnancy) or Erythromycin base 500 mg orally three times a day for 7 days

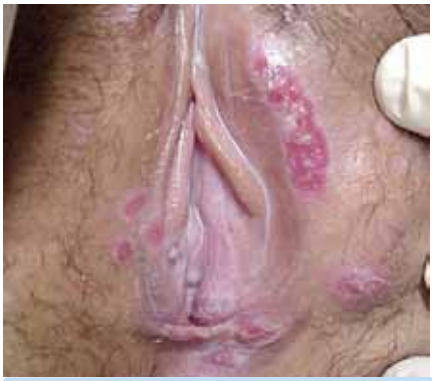

Figure 15-5: Chancroid Ulcer

➢ Granuloma Inguinale (Donovanosis)

- Causative agent: Klebsiella granulomatis intracellular gram-negative bacterium. Difficult to culture, and diagnosis requires visualization of dark-staining Donovan bodies on tissue crush preparation or biopsy
- Clinical picture: Extensive, progressive, granulation-like tissue, rolled edges and usually painless.
- Treatment: Doxycycline 100mg twice a day for a minimum of 3 weeks or erythromycin base 500 mg orally 4 times a day for 21 days

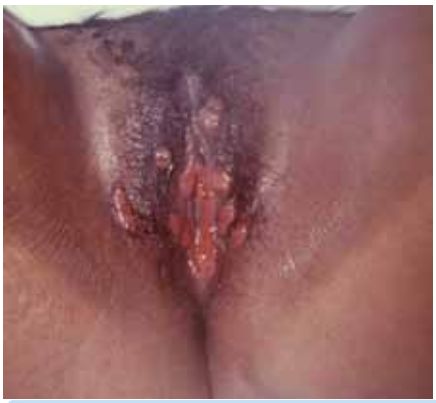

Figure 15-6: Granuloma Inguinale ulcer

➢ Lymphogranuloma venereum:

- Causative agent: Chlamydia trachomatis serovars L1, L2, or L3.
- Clinical picture: The most common clinical manifestation is tender inguinal and/or femoral lymphadenopathy that is typically unilateral. A self-limited genital ulcer or papule sometimes occurs at the site of inoculation. However, by

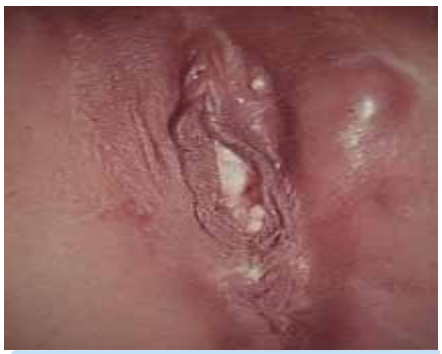

Figure 15-7: Lymphogranuloma veneruem

the time patients seek care, the lesions have often disappeared.

- Treatment: Doxycylcine 100 mg twice/day for 3 weeks

➢ **Syphilis:**

- **Causative agent:** Terponema pallidum
- **Clinical presentation:** classic presentation of primary syphilis with painless, indurated, clean-based ulcer, called a chancre
- **Treatment:** Parenteral penicillin G.

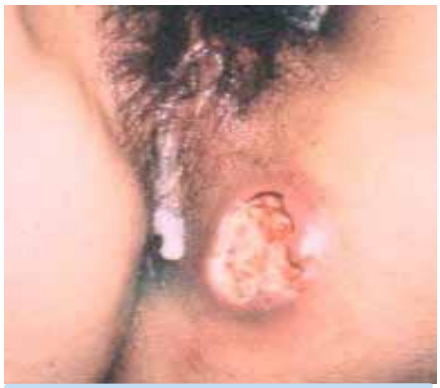

Figure 15-8: Syphilitic ulcer "Chancre"

Approach to the Diagnosis and Management of STIs:

Approach for patients presenting with vaginal discharge begins with attempts to decide whether or not the symptoms are due to infections or non infectious causes. This require detailed history of the nature of the discharge e.g. its color, smell, associated symptoms such as itching, urethritis..etc.

The most common infectious causes are bacterial vaginosis (though not an infection), candida infection and trichomonas vaginalis. The diagnosis of those infections can be confirmed by office test (see above).

Consideration of other STIs e.g. gonorrhea and chlamydia should be included only according to the presence of other signs (see figure 15-9), knowledge and prevalence of risk factors for these pathogens among the population.

All patients with STIs should be screened for other STIs, and HIV.

In clinically suspected cases empirical treatment may be initiated until the diagnosis is confirmed by appropriate laboratory tests.

Patients should be counseled regarding the mode of transmission, the need for screening and treatment of partner and future preventive measures.

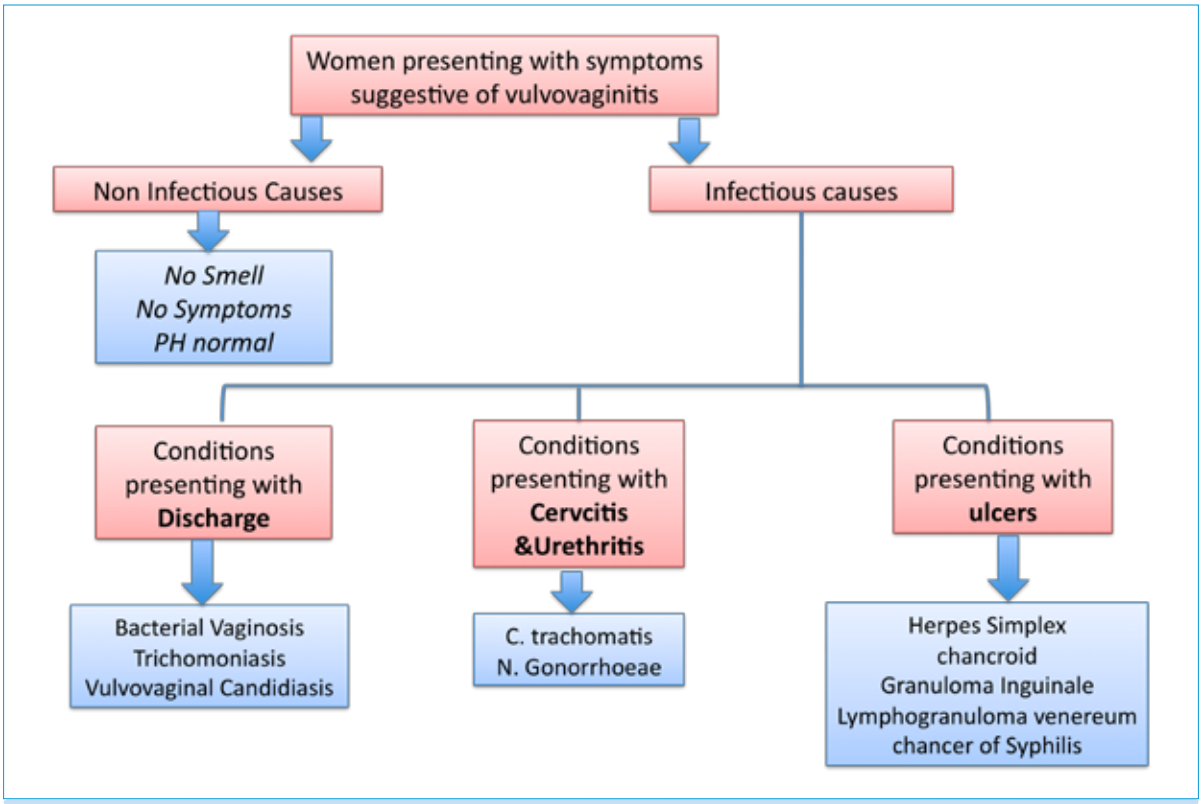

Figure 15-9: Algorithm for management of patient with vulvovaginitis.

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Chapter 16

Infection of the Upper Genital Tract Pelvic Inflammatory Disease PID

Pelvic inflammatory disease (PID) is a community-acquired disease caused primarily by sexually transmitted agents. Clinically PID encompasses a spectrum of presentations range from almost asymptomatic to severe and fatal condition. PID has both short and long term serious consequences on women health and fertility status. Since there is no one single gold standard diagnostic criteria the current guide lines recommends that "health care providers should maintain a low threshold for the diagnosis of PID" and that sexually active young women with the combination of lower abdominal, adnexal, and cervical motion tenderness should receive empiric treatment for PID.

By the end of this chapter you should be able to:

- **Define PID and appreciate**: the clinical and therapeutic difference between pelvic infection as a disease (sexually transmitted) and other causes of pelvic infection.
- **Describe the pathogenesis and risk factors for PID**:
- **Appreciate the spectrum of clinical presentation of PID**: Form mild to fatal condition. Not infrequently PID is discovered during investigation for infertility.
- **List the long-term sequelae of inadequate treatment of PID**:
- **Describe the clinical features of PID:** The cardinal features; lower abdominal, adnexal, and cervical motion tenderness. The role of investigations in the diagnosis of PID.
- **Describe the principle of treatment of PID**: As outpatient and as inpatient.
- **Describe the pathology of Tubo Ovarian Abscess "TOA"**:
- **Appreciate the life threatening potential of TOA:**
- **Describe the approach to treatment of TOA:**

Definition: The term Pelvic inflammatory disease (PID) refers to infection of the upper female reproductive tract, including the uterus "*endometritis*", fallopian tubes "*salpingitis*", the ovaries "*oophoritis*" and adjacent pelvic structures "*parametritis*".

PID is a community-acquired infection caused by a sexually transmitted agent. In this respect it should not be confused with pelvic infection that might develop as post-operative pelvic complications, pregnancy-related pelvic infection, and pelvic infection secondary to spread of another infection (appendicitis, diverticulitis, tumor, tuberculous peritonitis, actinomycosis, others) although the clinical picture can be very similar to PID.

However, this differentiation is important in relation to the pathophysiology, treatment and prevention (see later).

Epidemiology and prevalence: Determining the actual incidence and/or prevalence of PID are difficult because of lack of accurate diagnostic methods, in addition many patients with mild symptoms may not seek medical care. In the US it is estimated that more than 10% of reproductive age women report a history of PID. There is no data as to the prevalence of PID among local population. However since the main risk factor in PID is multiple sexual partners, this make it a major health burden in countries where sexual promiscuity is not prohibited.

Pathophysiology of PID:

Normally the upper genital tract is maintained in a sterile state in comparison to the vagina which has a dynamic microorganisms ecosystem. This has been attributed to the integrity of the endocervical mucus plug.

However at certain times and under certain circumstance this protection may be weakened and/or breached. If there is heavy vaginal infection or disturbance in the normal balance of the vaginal microorganism ascend of organism from the lower to the upper genital tract can take place.

Therefore PID occur over two stages. The first stage is vaginal infection, which is often sexually transmitted and may be asymptomatic. The second stage is direct ascent of microorganisms from the vagina or cervix to the upper genital tract.

Ascend of organisms from the lower to the upper genital tract is enhanced in certain situations such as:

- During menstruation with retrograde menstrual flow.
- During the postmenstrual days when the endocervical mucus is not well formed.
- Intercourse during menstruation (a practice that is prohibited by Islamic regulations).

It is known that bacteria can be carried along with sperm into the uterus and tubes.

- Within the first 2-3 weeks following intervention such as hysterosalpingogram, uterine sampling, IUD insertion particularly if there is already vaginal infection. It should be noted that with modern IUD there is no evidence of increased risk of PID thereafter.

Once infection reaches the the upper tract the extent of tissue reaction and subsequent sequelae such as scarring and adhesions is influenced by several microbial and host factors. This explain the spectrum of clinical presentation of PID from mild, even asymptomatic condition to severe and fatal pelvic infection, tubo-ovarian abscess "TOA" and peritonitis.

Further spread of infection may occur by spillage of purulent materials from the fallopian tubes or via lymphatic spread beyond the pelvis to produce acute peritonitis and acute perihepatitis (Fitz-Hugh Curtis syndrome).

Long-term sequelae of PID include chronic pelvic pain, menstrual disorders, infertility or sterility.

Microbiology of PID:

- Neisseria gonorrhoeae and Chlamydia trachomatis: are the two most important pathogenic organisms either causing or initiating pelvic infection. of the upper tract, in addition to anaerobes, facultative anaerobes, and other bacteria.

  Approximately 15-20 % of inadequately treated cases of N gonorrhoeae and CT go on to develop PID.

- Other initiating pathogens, which are almost certainly sexually transmitted, include Mycoplasma species, such as Mycoplasma hominis, and Bacterial vaginosis (BV), in which anaerobic bacteria assume predominance over the lactobacilli, was shown to be associated with increased risk of PID.

- **However for clinical purpose PID should be viewed and treated as a mixed (facultative and anaerobic) polymicrobial infection.**

Risk factors for PID

- Previous episode of PID
- Sex during menses
- Vaginal douching
- Bacterial vaginosis
- Intrauterine device
- New, multiple, or symptomatic sexual partners
- Age less than 25 years
- Young age at first sex

Clinical presentation and diagnosis:

The clinical presentations of PID range from asymptomatic (subclinical) to seriously ill cases.

- Subclinical or Asymptomatic PID: These cases are usually discovered retrospectively during

investigations for infertility, chronic pelvic discomfort, dyspareunia or abnormal vaginal bleeding.

- Clinically symptomatic cases of PID: varies from mild cases due to endometritis or myometritis to severe and potentially fatal cases of pelvic peritonitis.

The diagnosis of PID especially non-severe cases requires high index of suspicion taking in consideration symptoms, signs and indices of high risk factors (see blue box). Other causes of acute onset of pelvic pain should be sought and excluded (table 16-1).

Differential diagnosis of PID

Gastrointestinal: *Appendicitis, cholecystitis, constipation, gastroenteritis, inflammatory bowel disease*

Renal: *Cystitis, pyelonephritis, nephrolithiasis, urethritis*

Obstetric/Gynecologic: *Dysmenorrhea, ectopic pregnancy, intrauterine pregnancy complication, ovarian cyst, ovarian torsion, ovarian tumor*

Table 16-1: differential diagnosis of lower abdominal pain in a young woman.

Symptoms:

- Lower abdominal pain: is the cardinal symptom.
  Usually, pain is described as dull, aching or crampy, bilateral, and constant; it begins a few days after the onset of the last menstrual period and tends to be accentuated by motion, exercise, or coitus.
- Abnormal uterine bleeding about one third of patients may complain of abnormal uterine bleeding.
- Abnormal vaginal discharge: Abnormal vaginal discharge is present in approximately 75% of cases but not all cases.
- Other non-specific symptoms: such as dysuria, nausea and vomiting are less common. Temperature higher than 38°C (30% of cases) usually manifest late in the clinical course of the disease.

Signs:

- General: about one-half of patients with PID have fever and or chills. Features of general illness and or septicemia depend on the severity of infection.
- Abdominal examination: reveals diffuse tenderness greatest in the lower quadrants, which may or may not be symmetrical. In severe cases there may be rebound tenderness, and/or rigidity. Decreased bowel sounds are common.

  Approximately 10% of cases develop perihepatitis (Fitz-Hugh Curtis syndrome). In such cases there is marked tenderness in the right upper quadrant.

- Pelvic examination: may show purulent endocervical discharge. But the most important signs are elicitation of pain on acute cervical motion "positive cervical excitation" and adnexal tenderness with bimanual examination.

Investigations: There is no single gold standard investigation for PID. Each of the following tests may add valuable information, evaluate severity of the disease or identify other pathology, but the diagnosis of PID remains a clinically based diagnosis.

- **Laboratory tests:**
  - Pregnancy test: important in order to rule out ectopic pregnancy and complications of an intrauterine pregnancy. It should be noted that while PID is rare in pregnancy but it can occur in the first 12 weeks of gestation before the mucus plug and decidua seal off the uterus from ascending bacteria.
  - Test for evidence of cervical infection with *N gonorrhoeae* or *C trachomatis:* this may be obtained either by culture, a positive Gram-negative intracellular diplococci test, or a DNA test (Nucleic acid amplification tests for chlamydia and gonococcus). However while a positive result greatly increases the probability of PID; a negative one is of little use. It has also been shown that the presence of leukocytes on microscopic examination of vaginal discharge is strong evidence of purulent secretion.
  - Complete blood counts "CBC", C-reactive protein and erythrocyte sedimentation rate: positive results support the diagnosis of acute PID. However it should be remembered that CBC have limited value in the diagnosis of PID since less than one-half of PID patients exhibit leukocytosis.
  - Urinalysis: a positive urine analysis may suggest urinary tract infection and lessen the probability of PID.
- **Imaging studies "Transvaginal ultrasonographic scanning or magnetic resonance imaging":**
  - May show thickened, fluid-filled oviducts, with fluid in the cul-de-sac. Such findings support a clinical diagnosis of PID but its absence does not diminish the probability of PID.
  - However imaging studies are important if a pelvic abscess is suspected and to exclude other pelvic pathologies such as ectopic pregnancy, torsion of ovarian cyst.
- **Endometrial biopsy:** an endometrial biopsy showing endometritis as demonstrated by the presence of plasma cells and polymorphonuclear cells is further confirmatory test. Endometrial biopsy is approximately 90% specific and sensitive. The procedure

is performed with an endometrial suction pipette/curette and is well tolerated.

- **Laparoscopy:** Laparoscopy used to be the gold standard for the diagnosis of PID. However it is a major invasive procedure, and was found to have low sensitivity (approximately 50%) in the diagnosis of PID in addition the findings on laparoscopy do not necessarily correlate with the severity of illness, as only the surfaces of structures are visible.

Currently the indications for laparoscopy are limited to:

- A sick patient with high suspicion of a competing diagnosis (usually appendicitis, etc.)
- An acutely ill patient who failed outpatient treatment for PID.
- Any patient not clearly improving after approximately 72 hours of inpatient treatment for PID

Recommendations for the diagnosis of PID:

Because of the wide spectrum of clinical presentation, the lack of gold standard diagnostic test, and the serious consequences of inadequate treatment of PID the current recommendations encourage low threshold for the diagnosis and treatment of PI (the Centers for Disease Control and Prevention). The presences of clinical (namely cervical motion tenderness, uterine tenderness, or adnexal tenderness), and epidemiological features (sexually active young women) are indications for imperial treatment of PID.

Management of patient with PID:

The goals of treatment of pelvic inflammatory disease (PID) are: to relief the acute symptoms, eradicate the current infection, and prevent or minimize long-term sequelae. The following principles are important elements in the management of patients with PID:

- Early diagnosis and treatment is critical for preservation of fertility.
- Medical treatment with antibiotics alone is successful in 33-75% of cases. Surgical intervention is however indicated in cases suspected to have TOA or who failed to respond to medical treatment (see surgical treatment of PID and TOA).
- Antibiotics regiments should include empirical broad-spectrum antibiotics that cover *Chlamydia trachomatis* and *Neisseria gonorrhoeae*, as well as gram-negative facultative organisms, anaerobes, and streptococci (table 16-2).
- Most patients with PID can be managed on outpatients' bases with close follow up within 48-72 hours to assess improvement (i.e. reduction in abdominal tenderness and

reduction in cervical motion tenderness). If the patient has not improved by 72 hours, hospitalization and further evaluation should be considered.

- Some cases require hospitalization from the outset (see blow box).
- All patients should be offered testing for: HIV testing, Hepatitis C, serology testing for syphilis especially if a diagnosis of STI is confirmed.
- For prevention of future infection and society protection patients should be counseled as to the route of acquisition of sexually transmitted infections, the need for partners treatment, and future safe sex practices.

Indications for Hospitalization

- Uncertain diagnosis
- Pelvic abscess on ultrasonographic scanning
- Pregnancy
- Failure to respond to outpatient management after 72 hours of outpatient therapy
- Inability to tolerate outpatient oral antibiotic regimen
- Severe illness or nausea and vomiting precluding outpatient treatment
- Immunodeficiency (e.g., patients with HIV infection, or patients using immunosuppressive medications)

Outpatient treatment
Regimen A:
Ceftriaxone 250 mg IM once as a single dose plus doxycycline 100 mg PO bid for 14 days, with or without metronidazole 500 mg PO bid for 14 days.
Regimen B:
Cefoxitin 2 g IM once as a single dose and probenecid 1 g PO concurrently in a single dose or: Other single-dose parenteral third-generation cephalosporin (ceftizoxime or cefotaxime) plus doxycycline 100 mg PO bid for 14 days with or without metronidazole 500 mg PO bid for 14 days.
Metronidazole can be added if there is evidence or suspicion for vaginitis or gynecologic instrumentation in the past 2-3 weeks.
Inpatient treatment
Regimen A:
Cefoxitin 2 g IV q6h Or Cefotetan 2 g IV q12h Plus doxycycline 100 mg PO/IV q12h.
Continue this regimen for 24 hours after the patient remains clinically improved, and then start doxycycline 100 mg PO bid for a total of 14 days.
If TOA is present, use clindamycin or metronidazole with doxycycline for more effective anaerobic coverage.
Regimen B:
Administer clindamycin 900 mg IV q8h plus Administer gentamicin 2 mg/kg loading dose IV followed by a maintenance dose of 1.5 mg/kg q8h. IV therapy may be discontinued 24 hours after the patient improves clinically, and PO therapy of 100 mg bid of doxycycline should be continued for a total of 14 days.
If TOA is present, use clindamycin or metronidazole with doxycycline for more effective anaerobic coverage.
An alternative parenteral regimen is as follows: Ampicillin/sulbactam 3 g IV every 6 hours plus doxycycline 100 mg orally or IV every 12 hours

Table 16-1: Antibiotics regimens for PID from http://www.cdc.gov/std/treatment/2010/default.htm

Tubo Ovarian Abscess and Surgical treatment of PID

Tubo ovarian abscess "TOA" is an abscess that involves the ovary and fallopian tube. It often arises as a consequence of pelvic inflammatory disease (PID). However, TOA can also develop following pelvic surgery, or as a complication of an intraabdominal process, such as appendicitis or diverticulitis.

TOA is a potentially lethal condition. It is almost the last lines of the host defense attempts to contain spreading of infection in cases of PID. If this attempt fails or if the abscess ruptures it leads to peritonitis, septicemia, and septic shock with mortality rate up to 25%.

Diagnosis:

TOA should be suspected in patients with severe cases of PID, if there is palpable adnexal mass and in cases that do not improve within 72 hours of initiation of therapy. Clinically 90% of patients will have abdominal and/or pelvic pain. However it should be noted that fever and leukocytosis are found in approximately 60 to 80 percent and not in all patients.

Differential diagnosis TOA

DD of TOA includes ectopic pregnancy, all of the pelvic neoplasms, ovarian hematoma or torsion, appendicular and diverticular abscesses, and uterine pyomyoma all must be considered.

Imaging studies: If TOA is suspected imaging study should be undertaken. Transvaginal ultrasound is the modality of choice compared to others such as MRI and CT. An additional advantage of US is that surgical drainage can also be guided by vaginal sonography.

On sonography a pelvic abscesses is seen as complex, adnexal masse with multiple internal echoes (Figure 15-1).

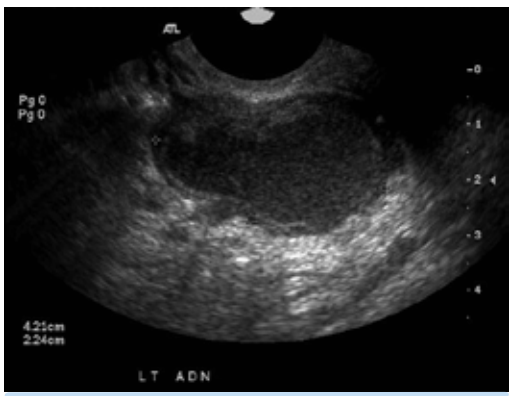

Figure 16-1: Sonographic imaging of left adnexal (LT And) TOM. Showing typical features of complex mass with multiple internal echoes.

Treatment of TOA: TOA is acute life threatening emergency. The management requires evaluation of severity, close monitoring for body system functions in intensive care setting. In only selected cases medical therapy using potent antibiotics regimen may be successful. However surgical intervention should be resorted to without delay if medical patient condition does not show positive improvement, or a large abscess is identified. The surgical techniques include one or more of the following interventions:

- Drainage procedures of the abscess under ultrasound guidance, or via laparoscopy are usually preferred. Success of a drainage procedure is generally defined as recovery from acute infection without need for laparotomy.
- Laparotomy is reserved for severe cases such rupture of TOA or failure of response to medical treatment medical management and laparoscopic drainage. In surgery the principle is conservation of patient fertility as much as possible since most women with tubo-ovarian abscess are in the reproductive age. However in severe life threatening cases radical surgical procedures such as unilateral salpingo-oophorectomy or hysterectomy and bilateral salpingo-oophorectomy may have to be undertaken.

Begin intravenous fluids & Nasogastric tube may have to be inserted
Begin potent broad-spectrum antibiotics: See table 16-1
Survey for sepsis syndrome: a. Vital signs, examination (including mental status) b. Blood cell counts and chemistries c. Coagulation studies d. Chest x-ray, EKG e. Urine output
Close monitoring: for pain, tenderness and sepsis syndrome
Guided drainage of TOA: within 24 to 48 hours should be strongly considered if there is no definite improvement or at the outset if abscess is large. a. Transvaginal approach using an endovaginal sonographic probe with needle guide should be considered first; if not possible proceed to CT or US guided transcutaneous approach, or laparoscopic approach. b. Colpotomy drainage may be used only if the abscess is fixed and distending the low rectovaginal septum in the midline c. Aspirate should be send for microbiologic evaluation (and cytologic analysis if fluid is serous or cloudy)
Correct any underlying medical derangements: (e.g., anemia, hyperglycemia, hypoproteinemia, hypoxia)

Table 16-2: Outline of management of TOM

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Chapter 17

Disorders of pubertal development

Gynecologists are more familiar when dealing with delayed menarche or primary amenorrhea rather than delayed growth or development, which are usually dealt with by pediatricians. However it should be remembered that the onset of menstruation while it is an important sign of puberty it should be considered in the overall context of sexual maturation.

If by the fifteen years of age a girl did not get her first period but has normal sexual development she is not necessarily abnormal. But if by that age she has no signs of secondary sexual development this is abnormal and requires further investigations.

By the end of this chapter you should be able to:

- **Define puberty**: The period of time that involves physiological, physical, psychological and behavioral changes.
- **Describe the sequences of normal pubertal development:**
- List the factors that influence age of puberty: racial, genetic and the role of body weight particularly the role of " leptin" hormone.
- **Describe the approach to the diagnosis of precocious and delayed puberty**.
- **Describe the endocrinological changes that forms the physiological bases of puberty**: (1) The hypothalamic pituitary axis (Gonadostat), (2) ovarian sex steroids production "Gonadarche", (3) The adrenal androgen activation (Adrenarche)
- **Describe the physical changes of puberty:** Growth spurt, breast development, pubic hair, and pelvic organ changes.
- **Definitions of Delayed Puberty vs. Primary Amenorrhea:**
- **List the causes of primary amenorrhea:**
- **Describe the DD and approach to patients with Primary amenorrhea:** History, Examination and investigations.
- **Outline the Management of patients with primary amenorrhea**: Place of surgery, hormonal replacement, and place of fertility restoration.

Normal Puberty

Definition: Puberty is the period of human life during which there are major physiological, physical, psychological and behavioral changes, which are responsible for transforming an individual from a child to a person capable of reproduction and function as an adult.

Age of puberty: The average age of puberty is based on studies, which have defined an age range with upper and lower boundaries limits based on 95 percentile values. The original studies by Tanner and colleagues in the 1960s sat the upper and lower boundary for puberty for girls at 8 years and 15 years respectively with a mean of 13 years.

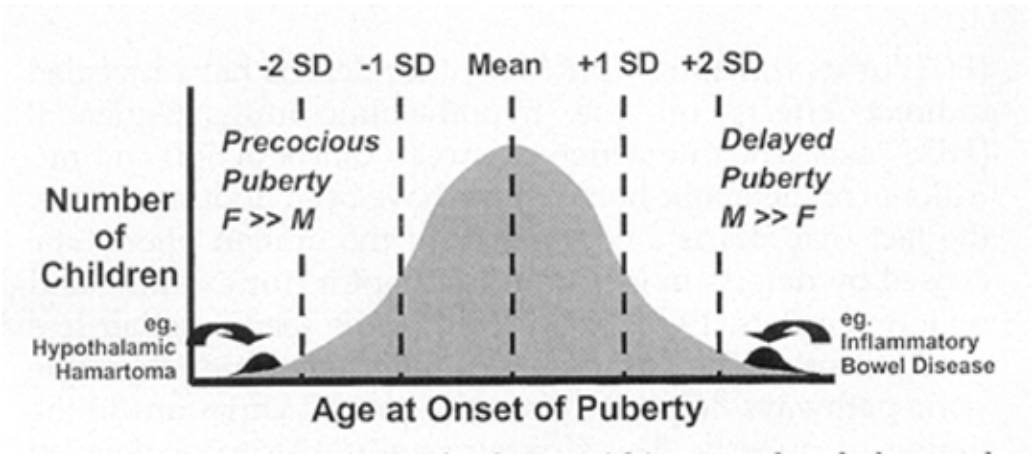

Figure 17-1: Palmer M. R, Boepple P. A, Variation in the Timing of Puberty: Clinical Spectrum and Genetic Investigation, Journal of Clinical Endocrinology and Metabolism Volume 86 - Number 6 - June 2001

Accordingly puberty is considered delayed if by the age of 13 there is no signs of pubertal growth and precocious if sings of maturity begins before the age of 8 (Figure 17-1).

Factors influences the age of puberty: The age of pubertal changes is influenced by many factors including: genetic, nutrition, racial, geographical location, and the general health.

- *Role of Nutrition and Leptin hormone*: Observational studies have shown that moderately obese girls (20-30% over normal weight) have earlier menarche than normal weight girls. Conversely underweight, girls suffering from anorexia or athletic girls on severe exercise have delayed menarche or secondary amenorrhea.

  The relationship between body fat and pubertal changes seems to be through the

hormone "Leptin" which is expressed and secreted by adipose tissues. The level of Leptin was found to increases throughout childhood until the onset of puberty, and before any raise in gonadotropin hormones, suggesting that a threshold level of Leptin (and therefore a critical amount of adipose tissue) is necessary for puberty to begin. Furthermore it was found that a higher the level of Leptin is associated with earlier age at onset of menarche.

It is thus concluded that Leptin plays an important role in initiating pubertal changes by giving signals to the central nervous system, that energy stores are ready for the pubertal progression to begin.

Endocrinology changes at puberty:

The endocrinal changes responsible for pubertal maturation involve three critical changes:

1. Activation of the hypothalamic GnRH hormone production "the Gonadostat": During childhood the release of GnRH by the hypothalamic is "restrained" by an intrinsic central inhibitory mechanism. As a girl approach puberty there is gradual increase in both the amplitude and the frequency of pulsatile GnRH production, which leads to secondary increase in pituitary FSH, and LH secretion. This is sometimes knows as "Gonadostat". However the mechanisms that trigger the "Gonadostat" are incompletely understood. But Leptin hormone might be the triggering factor for initiation of the hypothalamic activity.
2. Activation of ovarian sex steroids production "Gonadarche": In parallel with the Gonadostat the ovary gradually becomes more sensitive to the increasing level of gonadotropins (FSH, and LH). This result in follicular maturation and production of estrogens.
3. Activation of adrenal androgen production "Adrenarche": (namely dehydroepiandrosterone (DHA), dehydroepiandrosterone sulphate (DHAS), and androstenedione "pubarche"): The factors that control the "Adrenarche" remain obscure. It is not under control of gonadotropin or ACTH and precedes the change in GnRH secretion. It results in increase growth of axillary and pubic hair beginning from late childhood (about 7-6 years of age) to adolescence (13-15 years of age).

Patients with Turner's syndrome experience adrenarche, which indicates the onset of adrenal androgen secretion is independent of ovarian function.

Physical changes of puberty:

The major physical features of puberty are:

- Acceleration of growth rate.
- Development of secondary sexual characteristics: breast and sexual hair.

The appearance of the physical changes of puberty is described along stages known as Marshal and Tanner's stages of breast and pubic hair development (Marshal and Tanner's 1969). There is however wide variation at both the age of onset and the sequence of development of the various signs of puberty.

- *Breast development:* Is described over five stages. It begins with breast budding (thelarche), which indicates enlargement and elevation of the nipple and areola followed by the sequence of developments as shown in Figure 19-2.

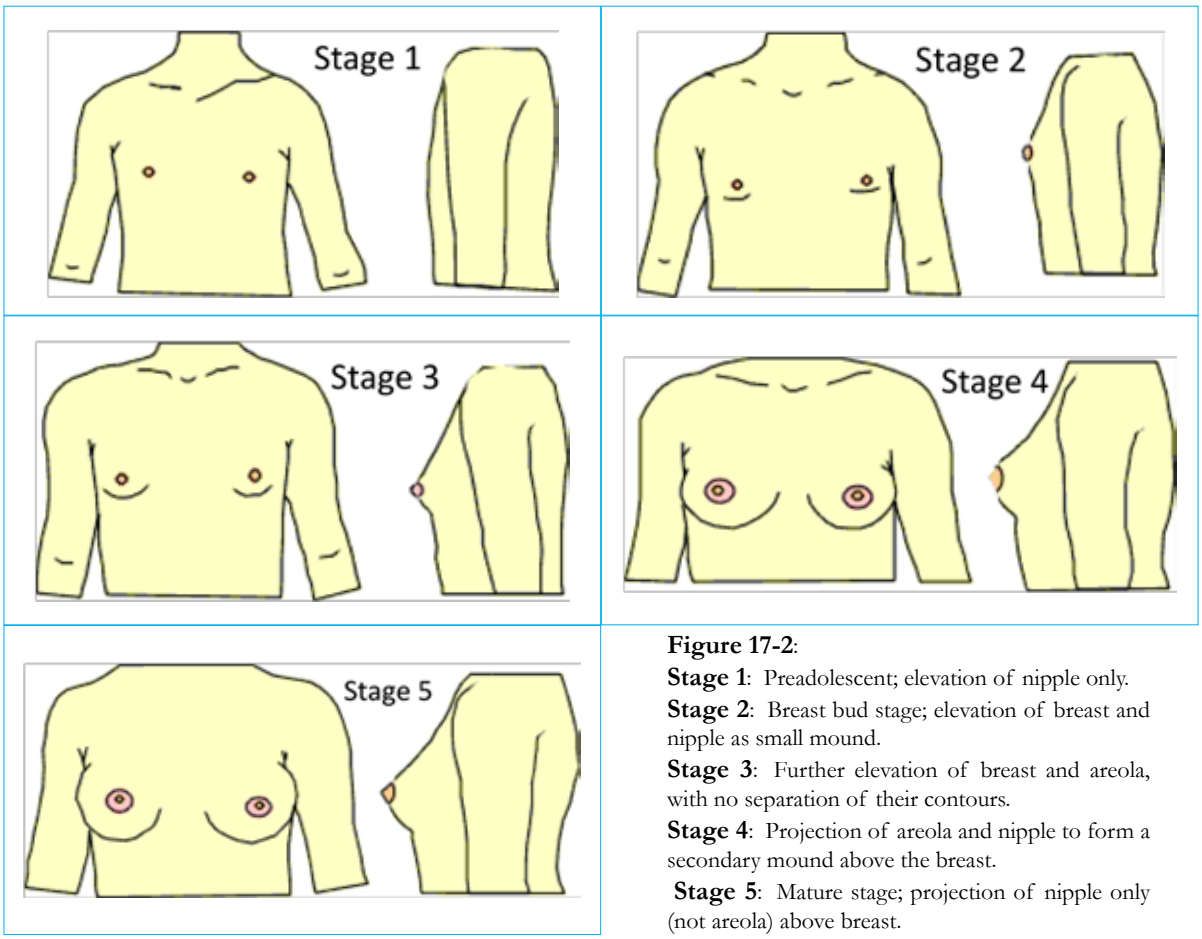

Figure 17-2:
Stage 1: Preadolescent; elevation of nipple only.
Stage 2: Breast bud stage; elevation of breast and nipple as small mound.
Stage 3: Further elevation of breast and areola, with no separation of their contours.
Stage 4: Projection of areola and nipple to form a secondary mound above the breast.
Stage 5: Mature stage; projection of nipple only (not areola) above breast.

- *Adrenarche (pubic hair)* usually appear about six months or so after the breast budding with the axillary hair growth two years later. In approximately 20% of children pubic hair growth is the first sign of puberty (figure 19-3).

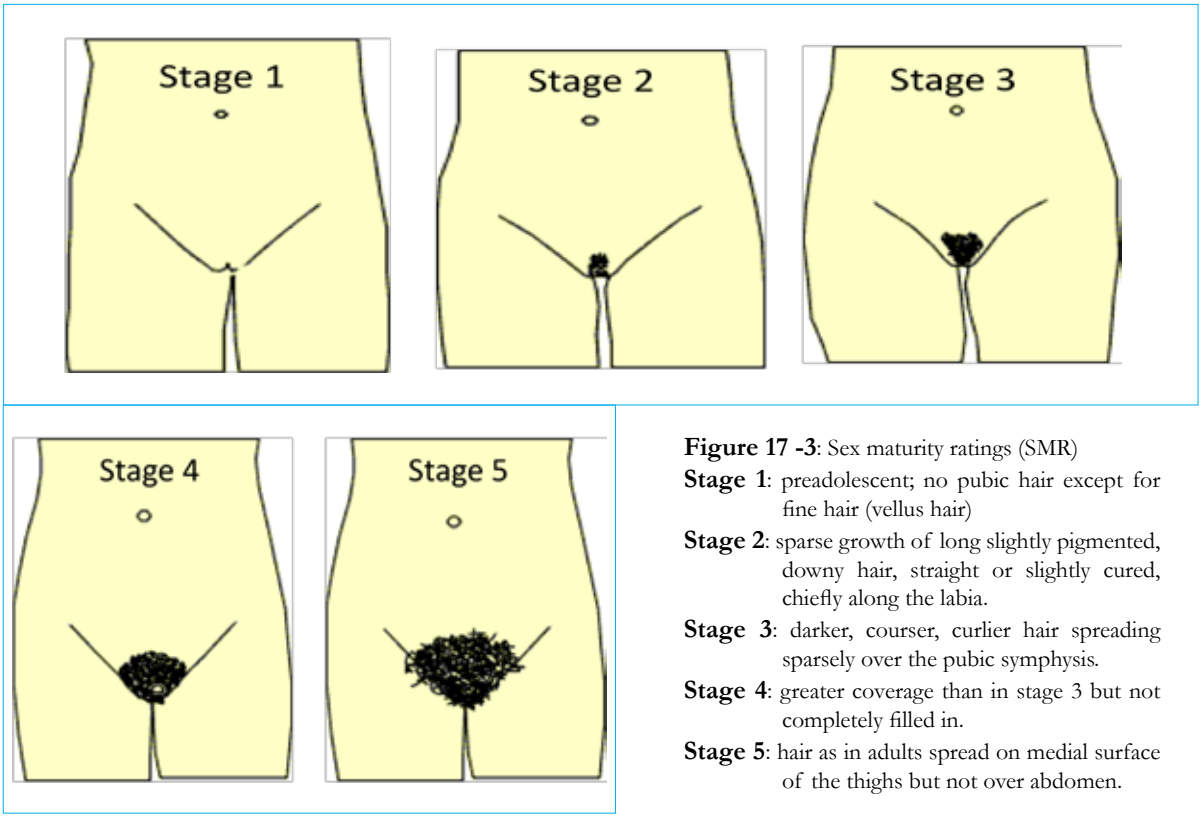

Figure 17 -3: Sex maturity ratings (SMR)
Stage 1: preadolescent; no pubic hair except for fine hair (vellus hair)
Stage 2: sparse growth of long slightly pigmented, downy hair, straight or slightly cured, chiefly along the labia.
Stage 3: darker, courser, curlier hair spreading sparsely over the pubic symphysis.
Stage 4: greater coverage than in stage 3 but not completely filled in.
Stage 5: hair as in adults spread on medial surface of the thighs but not over abdomen.

- *Growth spurt*: In girls adolescent growth spurt occurs about 2 years earlier (at about 11-12 years) than in boys. The average girl reaches her growth peak about 2 years after breast budding and 1 year prior to menarche. Normal growth at puberty require the combined action of three hormones; growth hormone, insulin like-growth factor-I, and sex steroids namely estrogen.
- *The menstrual cycles:* the first menstrual cycle, known as "The Menarche" usually follows

In both boys and girls estrogen is the principle sex steroid involved in pubertal growth. The source of estrogen in boys is aromatization of androgens. Estrogen stimulates growth hormone production, which in turn stimulates production of IGF-I. The sex steroid hormones also limit the ultimate height attained by stimulating epiphysial fusion.

spurt in skeletal growth, pubic hair development to Tanner stage 4 and breast development to Tanner stage 3-4.

The Post-menarche cycles are initially anovulatory and usually remain so for few years. Ovulatory cycles begin when the final maturation of the hypothalamic-pituitary-ovarian axis is achieved. This occurs when positive and negative feed back mechanisms develop. In the "positive feed back" rise of estrogen induce rise in LH secretion "LH peak" necessary for ovulation. At the same time the rise in estrogen, together with the hormone inhibin, inhibits FSH release "negative feedback".

Usually the cycles follow the menarche are anovulatory, irregular and occasionally heavy.

Ovulation increases in frequency as puberty progresses but it is common for 25-50 % of adolescents to remain anovulatory up to four years after menarche.

- *Pelvic organs changes*: At approximately Tanner stage 4 the uterus becomes about 5 times larger, the ovaries increases in size and develop a multicystic appearance the vagina increases in length and the mucosa change from the prepubertal reddish, less moist appearance to the pale or pinkish, moist appearance of pubertal vaginal mucosa.

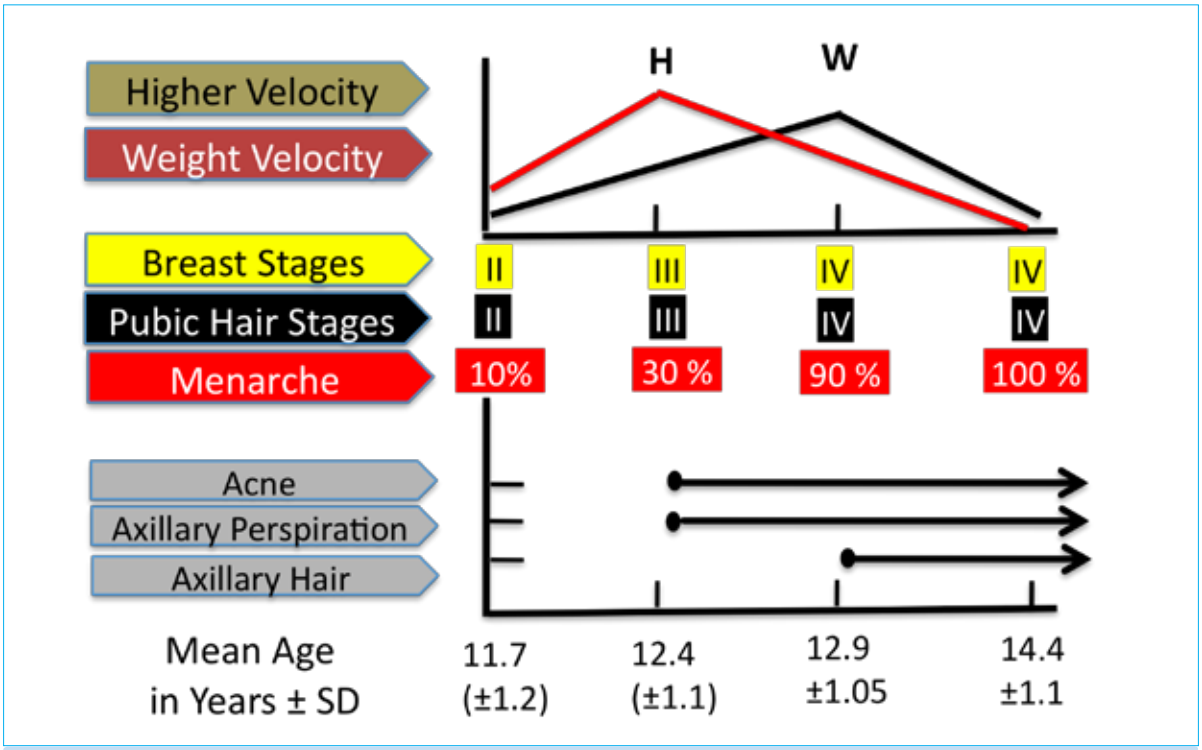

Figure 17-4: Average age of pubertal changes. Adapted from Lee PA, et al. Age of puberty: data from the United States of America. Acta Pathol Microbiol et Immunol Scand.

Delayed Puberty – Primary Amenorrhea

Definition: Delayed puberty is defined as lack of the initial signs of sexual maturation by an age that is more than 2–2.5 SD above the mean for the population (~13 years in girls and 14 years in boys).

Primary amenorrhea: Is the absence of menarche by age 16 years or within 5 years of pubertal onset.

As mentioned before the term primary amenorrhea focuses on merely one of the features of puberty, whereas delayed puberty implies interference with the general process of sexual maturation.

Incidence: Using these criteria, approximately o.4 % of healthy girls above the age of 13 will be identified as having pubertal delay. This figure however varies between populations with different racial background.

Physiology of the menarche:

The first menstrual cycle "Menarche" occurs as a result of activation of the hypothalamus that begins a cascade of events in the anterior pituitary and then the gonads. This establishes what to be known as the hypothalamic-hypophysial-ovarian axis, which goes on for the rest of the female reproductive life.

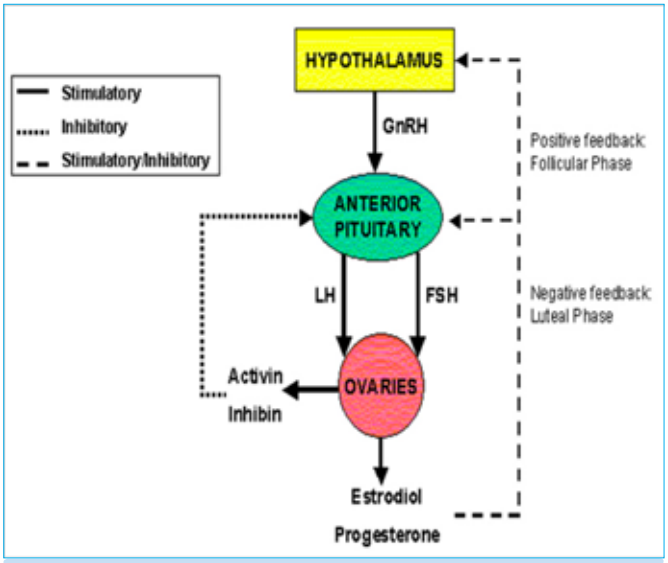

Figure 17-5: hypothalamic-hypophysial-ovarian axis

- The hypothalamus discharges gonadotropin-releasing hormone (GnRH), which is transported along a portal venous system to the anterior pituitary.
- In the anterior pituitary GnRh stimulates the gonadotrophs cells to secrete the gonadotropins: follicle-stimulating hormone (FSH), and luteinizing hormone (LH).
- The FSH and LH stimulate the gonads to synthesize and secrete sex steroids.

The sex steroid estrogen and progesterone regulate the release of the FSH and LH through

both negative and positive feed back mechanisms.

- A low level of estrogen at the first half of the cycle has a positive feedback on the hypothalmas, which stimulate release of GnRh.
- whereas a rise in steroid hormone has a negative feedback directly on anterior pituitary gonadotrophs and indirectly at the level of the hypothalamus.

Causes of Primary amenorrhea with delayed puberty:

The causes and differential diagnosis of primary amenorrhea with or without delayed puberty are listed in table 19-1.

In general the causes can be grouped under four main categories:

I. Constitutional (idiopathic) delay: It is considered a variant of normal growth rather than a disorder, even though it may result in psychological difficulties that warrant treatment. In this group the child bone age, estimated from radiographic studies of the left hand and wrist, is consistent with the child's height age rather than chronologic age.

II. Hypogonadotropic hypogonadism: May be due **reversible causes** (e.g. excessive loss of weight as in anorexia nervosa and the athletic female or lesions amenable to surgery e.g. tumors) or **irreversible causes** (e.g. genetic, inflammatory process, vascular lesion, radiation, and trauma).

III. **Hypergonadotropic hypogonadism:** This category includes patients with gonadal failure. The causes of ovarian failure include: chromosomal (e.g. Turner's syndrome), immunological (e.g. premature idiopathic ovarian failure or resistance ovary syndrome) and acquired causes such as infections (e.g. mumps), radiotherapy or chemotherapy.

IV. Anatomical causes: This includes obstructive lesions (e.g. imperforate hymen) and Müllerian tract agenesis. Agenesis of the Mullerian tract may occur as a developmental defect (agenesis or hypoplasia) in a normal 46XX female or as a part of syndrome as in 46 XY syndrome (testicular feminization syndrome)

Differential diagnosis of Primary Amenorrhea		
Constitutional (idiopathic) delay		
A variant of normal growth	Bone age consistent with the child's height age not the chronologic age	
Anatomical causes		
Congenital defect of the Urogenital sinus	Imperforate hymen Agenesis of lower vagina	
Müllerian tract agenesis	○ - In a normal 46XX female ○ - As a part of syndrome e.g. in 46 XY syndrome, 5-Alpha-reductase deficiency, defect in testis determining factor, Vanishing testes syndrome	
Hypogonadotropic hypogonadism		
Reversible causes	Weight loss, eating disorders, exercise, Stress, severe or prolonged illness, anorexia nervosa, bulimia	Hormonal prolife: Low or normal LH concentrations, absent LH surges, low serum estradiol. Serum FSH concentrations are usually in the normal range, with high FSH to LH ratio
Irreversible causes Genetic diseases associated with Congenital GnRH deficiency:	Syndromes	○ Kallmann syndrome ○ Without anosmia ○ Associated with adrenal hypoplasia congenita
	Syndromes associated with mental retardation	Prader-Willi Laurence-Moon-Biedl
	Isolated Gonadotropin Deficiency syndrome	May be sporadic or inherited as an autosomal dominant, autosomal recessive, or X-linked recessive trait
Tumors (could be reversible if amenable to surgical treatment)	○ Benign tumors (e.g. Prolactinoma): Prolactinoma is rare in preadolescent and adolescent girls.	
	○ Craniopharyngiomas ○ Germinomas, meningiomas, gliomas, astrocytomas ○ Metastatic tumors (breast, lung, prostate)	
Inflammatory or infiltrative diseases	○ Hemochromatosis ○ Granulomatous diseases ○ Histocytosis	
Trauma	Cranial irradiation Brain injury - trauma Hemorrhage Hydrocephalus	
Hypergonadotropic hypogonadism		
Congenital	Turner Syndrome: gonads are fibrous streak tissue	
	Gonadal Dysgenesis	
	Premature, autoimmune ovarian failure	
Acquired	Radiation or Surgical removal of the ovaries	

Table 17-1: Summary of causes of primary amenorrhea with or without pubertal delay.

Approach to the diagnosis and management of patients with primary amenorrhea

The approach to an adolescent girl, who probably never had a gynecologic examination need to be sensitive taking in consideration her psychosocial and emotional background. Adequate time and understanding is required in taking detailed history that span the period since the childbirth.

History: A full detailed history should be taken with emphasis on:

- Other signs of puberty namely secondary sexual characters including: growth spurt, breast development, and growth of axillary and pubic hair.

Absence of other pubertal sings suggest ovarian, pituitary or chromosomal anomaly

- History of recent stress including change in weight, diet, exercise habits; or illness.
- Congenital or neonatal events (e.g. surgery for hydrocephalus, neonatal crisis suggest adrenal hyperplasia). Also poor linear growth during the neonatal period and childhood may reflect long-standing abnormalities of development.
- Family history: consanguinity; history of delayed puberty or menarche in the parents or sibling may suggest constitutional puberty delay.
- History of anosmia, or hyposmia which suggest Kallaman syndrome.
- History of glactorraea or intake of drugs that is known to increase serum prolactin (e.g. antipsychotic drugs).
- History suggestive of hypothalamic pituitary disease such as headaches, visual filed defects, fatigue, plyuria or polydepsia.
- History of or relevant systemic and endocrinological disorders (e.g. diabetes, thyroid,).
- Symptoms of virilization e.g. excessive hair growth, acne..etc (in case of late onset congenital adrenal hyperplasia or rarely polycystic ovarian disease)

Kallmann syndrome

A rare genetic condition more common in boys than girls. It accounts for about 5% of all cases of delayed puberty in girls. It is due to deficient secretion of GnRH associated with hyposmia or anosmia in which the affected individuals are usually not aware of it. It presents as primary amenorrhea with infantile sexual development. It usually has an X linked inheritance (but autosomal dominant and recessive inheritance forms have also been described)

Examination:

- General examination:
  - Evaluation of pubertal development: height, weight and arm span (normal arm span of adults is within 5 cm of height).
  - Development of secondary sexual character including voice and breast development.
  - Examination for the features of Turner's syndrome. The main two features are short stature and infantilism.
  - Signs of androgen overproduction (heterosexual features such as deep voice, abnormal hair growth, enlarged clitoris…etc.) could suggest late onset congenital adrenal hyperplasia.
  - Attention should also be paid for features of other endocrine disorders e.g. cortisol overproduction, hypothyroidism, galactorrhea, acromegaly.

Other typical features of Turner's syndrome such as webbed neck and cubitus valgus, hair line, shield chest and widely spaced nipples may or may not be present (usually absent in cases of mosaicism).

- Genital examination:
  - The external genitalia are examined for normal development, clitoral size, shape of pubertal hair, the hymen shape and intactness and any palpable masses along the labia suggestive of testicular mass.
  - The internal genitalia (the vagina, cervix and uterus) are better evaluated by ultrasound examination.

Investigations:

At the end of the history and examination a presumptive diagnosis can usually be reached. The investigations requested needs to be selective and not exhaustive, based on the findings of the physical examination (Figure 19-6). Collaboration with pediatric endocrinologist and pediatric or adolescent psychologist may be required.

- Pelvic ultrasound: Is the primary test that should be performed to confirm the presence of vagina, uterus and cervix. Is considered the single most important examination.
- Other imaging studies CT or MRI should be requested only if there is suspicion of CNS lesions and also in cases with hyperprolactinemia.
- Bone age study (X ray of wrist and hand) is essential for the diagnosis of

constitutional growth delay.

- Hormonal tests: basic tests include measurement of serum levels of gonadotropins (FSH and LH), to differentiate between hypo and hypergonadotrophic amenorrhea, in addition to estradiol and prolactin.
- Other hormonal studies such thyroid or adrenal hormonal profile tests are ordered according to clinical findings from history and examination.
- A Progesterone withdrawal test can also be performed. It is a simple test that provides valuable information about the status of endogenous estrogen and exclude obstructive lesion of the genital tract.
- Karyotype should be requested if there are elevated serum gonadotropin levels (suggestive of Turner syndrome) or absence of Müllerian structures. If the results positive for a Y chromosome this indicates male pseudohermaphroditism, mixed gonadal dysgenesis, or true hermaphroditism. But a final diagnosis can be made only after gonadal biopsy.
- Laparoscopic examination and gonadal biopsy may have to be performed in some cases (e.g. mixed gonadal dysgenesis).
- In cases of primary amenorrhea with virilizing features consideration should be given for sources of androgen e.g. late onset congenital adrenal hyperplasia (high urinary 17-ketosteroids, pregnanetriol, plasma testosterone, and 17-hydroxyprogesterone establishes the diagnosis). In rare cases ovarian or adrenal tumors that develop before menarche can cause primary amenorrhea and clitoromegaly.

Progesterone withdrawal test

medroxyprogesterone acetate (Provera), 10 mg/day orally for 5 days.

Normally withdrawal bleeding should occur 3-5 days after stopping of the medication.

This indicates the presence of endogenous estrogens stimulation of the endometrium, an intact uterus and patent genital tract.

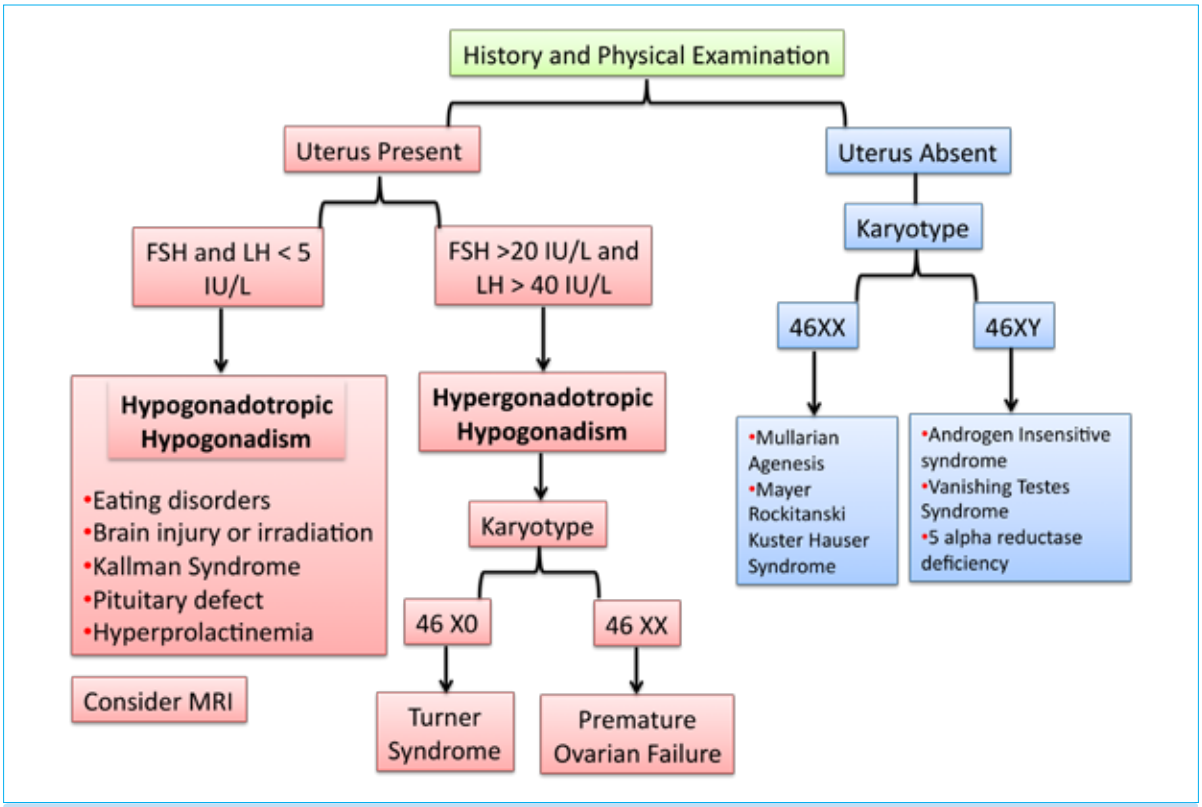

Figure 17-6: Algorithm for the diagnosis of primary amenorrhea

Treatment:

The treatment of patient with delayed puberty depends on the cause. In addition to careful counseling and sensitive approach, both medical and surgical intervention may be required. The goals of treatment are:

1. To help the patient attains normal feminine physical and psychological development.
2. To restore the patient's fertility potential whenever this is possible.

- ***Surgical treatment***: The type of surgery depends on the cause of the primary amenorrhea:
  - Obstructive mullerian abnormalities (imperforate hymen or vaginal septum).
  - Pituitary adenomas (prolactinoma) and craniopharyngiomas are treated by surgery or radiotherapy or both.
  - Creation of neovagina for patients with Mullerian failure: this is often delayed until the patient is emotionally mature and ready to participate in the

postoperative care required for maintaining vaginal patency.

- In patients with Y chromosome, gonadectomy should be performed to prevent gonadal neoplasia. Usually the operation is delayed until after puberty.

- ***Medical treatment***:
  - Specific disorders such as disorders of diet with or without psychological disorders should be treated according to the case.
  - Hormone (estrogen) replacement therapy is required in cases of gonadal failure (e.g. Turner syndrome) and patients with hypothalamic amenorrhea. It may also be required, for short period, in cases of significant constitutional delay with psychological disorder.

The goals of estrogen therapy are 1) induction of normal pubertal changes (breast development and other secondary sexual features) 2) establishment of menarche and regular menses 3) Prevention of osteoporosis.

Induction of puberty:

Estrogen replacement may be started with a transdermal estradiol patch or small daily doses of conjugated estrogens or ethinyl estradiol. The dose is gradually increased to adult replacement levels. Careful monitoring of secondary sexual characteristics and growth is required.

Cyclic hormonal replacement, typically with low-dose oral contraceptives, should be instituted after 1 to 2 years of estrogen replacement or once breakthrough bleeding has occurred

Hormonal Regiment for Induction of Puberty

Ethinylestradiol, 1 μg/day orally (or conjugated estrogens, 0.3 mg/day) starting at 12-13 years of age. The dose is increased to 2μg, 5μg, 10μg and eventually 20μg (or 0.6 to 1.25 mg of conjugated estrogen) with increments at six months intervals. The maintenance dose should be the minimal amount to maintain secondary sexual characteristics. After breakthrough bleeding occurs, or no later than 6 months after the start of cyclic therapy, a progestogen (e.g., medroxyprogesterone acetate, 5 mg/day) is added on days 12 through 21 of the month.

Fertility:

In some cases ovulation can be induced whenever pregnancy is desired. Example of such cases are patients with amenorrhea due to hypothalamic or pituitary disorders in whom ovulation can be induced by gonadotropin therapy or, in hyperprolactinemic states, by

administration of Bromocriptine.

For the woman with gonadal dysgenesis or müllerian agenesis advances in in-vitro fertilization and embryo transfer (IVF-ET) have expanded their reproductive alternatives. For example ovum donation has allowed patients with Turner's syndrome to undergo IVF-ET with partner's sperm and their own uterus. Also patients with müllerian agenesis may be candidates for a surrogate uterus. However the ethical issues surrounding those options do not make it feasible ones for all couples and in all societies particularly among Moslem societies. **According to the Islamic regulations any approach where a third party (either egg or sperm or uterus) is involved is prohibited.**

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Chapter 18

The menstrual Syndromes Dysmenorrhea, Pre-Menstrual Syndrome and Premenstrual dysphoric disorder

Ovarian steroid hormones receptors are widely distributed all over the body including in the central nervous system. Therefore it is no surprise that its dynamic cyclic fluctuation during women reproductive life can sometime be reflected in various forms of somatic and affective "emotional" symptoms.

The challenge to gynecologists is to decide at what point the physiological effects of this hormonal fluctuation on women health would be considered pathological and require therapeutic intervention. It should be appreciated that menstrual syndromes can have serious social and economic impact not only on the individual woman but also on her family and the society as whole.

This chapter deals with two of the most common "menstrual syndromes" that seems to be directly related to gonadal hormones namely Dysmenorrhea and Premenstrual syndrome.

By the end of this chapter you should be able to:

- **Define and differentiate:** Primary and Secondary Dysmenorrhea
- **Describe**: the pathogenesis of primary dysmenorrhea
- **Describe:** the approach to the diagnosis of primary and secondary dysmenorrhea
- **Describe:** the management of dysmenorrhea
- **Define and differentiate:** between Premenstrual syndrome and premenstrual Dysphoric disorder
- **Diagnose:** Premenstrual syndrome and premenstrual Dysphoric disorder
- **Appreciate**: the impact of menstrual syndrome on personal life and society as a whole
- **Describe:** the approach to the management of patient with Premenstrual syndrome and premenstrual Dysphoric disorder

Dysmenorrhea

Dysmenorrhea, or painful menstruation, is one of the most common problems experienced by reproductive age women.

Clinically dysmenorrhea is divided into two broad categories:

- **Primary dysmenorrhea (PD) (sometime called spasmodic):** is defined as menstrual pain not associated with macroscopic pelvic pathology (i.e. absence of pelvic disease). It typically occurs in the first few years after menarche and affects up to 50% of females.
- **Secondary dysmenorrhea: (sometimes called congestive)**: menstrual pain resulting from anatomic and/or macroscopic pelvic pathology e.g. endometriosis, adenomyosis, uterine leiomyomas, or chronic pelvic inflammatory disease. This condition is most often observed in women aged 30-45 years.

Mortality/Morbidity

Dysmenorrhea can disrupt personal life, and cause significant public health problem associated with substantial economic loss related to work absences. It is estimated that ten percent of women with the condition have severe pain that can be incapacitating.

Primary dysmenorrhea

Pathogenesis:

The exact pathogenesis of PD is not known, but the evidence point out to accumulation of prostaglandin F 2-alpha (PGF2), prostaglandin E2 (PGE2), and leukotrienes in the secretory endometrium as the underlying pathogenesis. This occurs in ovulatory cycles.

The prostaglandins induce abnormal myometrial contractions and vasoconstriction. The resultant myometrial ischemia "myometrial angina" leads to accumulation of anaerobic metabolites, which stimulates type C pain neu-

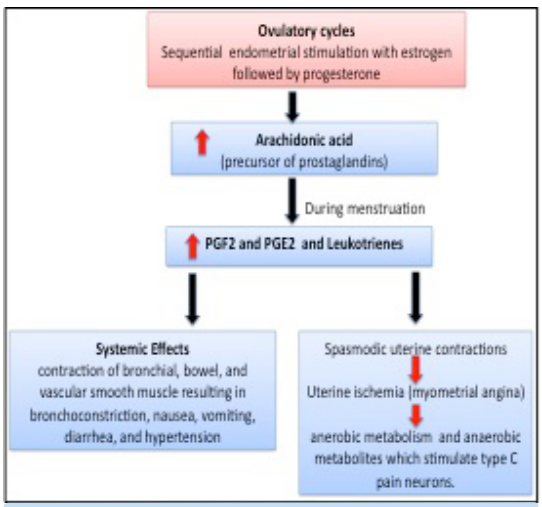

Figure 18-1: Pathogenesis of PD

rons. Leukotrienes seem to heighten the sensitivity of pain fibers in the uterus.

In severe cases the prostaglandin also induces variable degrees of systemic effects leading to nausea, vomiting, diarrhea…etc (see Figure 18-1).

Risk factors for primary Dysmenorrhea:

Epidemiological studies have identified the association of the following factors with severe form of dysmenorrhea:

- Earlier age at menarche
- Long menstrual periods
- Heavy menstrual flow
- Smoking
- Positive family history

Clinical manifestations and diagnosis of PD:

The diagnosis of PD is made clinically in women with characteristic symptoms who have no evidence of pelvic pathology.

Symptoms: Typically the patient complains of spasmodic pain begins just before or with the onset of menstrual bleeding and gradually diminishes over 12 to 72 hours. There is usually constant lower abdominal pain, which radiates to the back or anterior and/or medial thigh.

General symptoms e.g. nausea, diarrhea, fatigue, headache, and a general sense of malaise often accompany the pain.

Investigations: Laboratory tests,

Evaluation of patient with PD

➢ **History:**

- **Age at menarche and at onset of pain**: PD almost invariably occurs in ovulatory cycles. Therefore it usually appears within a year after menarche.
- Interval between the first day of each menses, number of days of menstrual bleeding, estimate of menstrual flow, presence of intermenstrual bleeding or premenstrual staining
- Relationship between onset of symptoms and onset of menstrual flow
- Associated general symptoms: e.g. nausea, vomiting, diarrhea, back pain, dizziness, or headache during menstruation
- Presence of dyspareunia or dyschezia
- Severity and impact of dysmenorrhea on daily activities, such as attendance at school, work or exercise
- Previous medication use, and its efficacy
- Progression of symptom severity

➢ **Examination**: examine for signs suggestive of pelvic pathologies, such as endometriosis, adenomyosis, uterine leiomyomata, or PID.

imaging studies, and laparoscopy are not mandatory to exclude these disorders, but should be performed, as indicated, if pelvic disease is suspected.

Treatment of PD:

Grading dysmenorrhea according to the severity of pain and limitation of daily activities may help guide treatment decisions (table 18-1). In most women with PD, therapy can be initiated empirically.

Grade	Grade Working ability	Systemic symptoms	Analgesics
Grade 0: Menstruation is not painful and daily activity is unaffected	Unaffected	None	None required
Grade 1: Menstruation is painful but seldom inhibits normal activity; analgesics are seldom required; mild pain	Rarely affected	None	Rarely required
Grade 2: Daily activity is affected; analgesics required and give sufficient relief so that absence from school is unusual; moderate pain	Moderately affected	Few	Required
Grade 3: Activity clearly inhibited; poor effect of analgesics; vegetative symptoms (headache, fatigue, vomiting, and diarrhea); severe pain	Clearly inhibited	Apparent	Poor effect

Table 18-1: scoring system for assessment of dysmenorrhea. Adapted from Andersch, B, Milsom, I, Am J Obstet Gynecol 1982; 144:655.

Multiple approaches are usually required in the management of patients with PD.

General approach: General measures for therapy include patient reassurance and education.

Non-pharmacological interventions:

- Heat: Application of heat to the lower abdomen appears to be as effective as oral analgesics for relief of dysmenorrhea.
- Dietary: vitamin, and herbal treatments: A variety of dietary and vitamin therapies may reduce the severity of menstrual pain. Both a low-fat vegetarian diet and fish-oil supplements have been reported to reduce menstrual pain in some women.

- Exercise: There are few evidences to support decrease in the prevalence of dysmenorrhea and/or improved of symptoms with exercise. But exercise is beneficial for general feeling of wellbeing.

Pharmacologic interventions:

Nonsteroidal anti-inflammatory agents (NSAIDs) and hormonal contraceptives represent the main of pharmacologic therapy

- NSAIDs: decrease menstrual pain by decreasing intrauterine pressure and lowering PGF2alpha levels in menstrual fluid:
  - Acetic acids (Type I): Indomethacin 25 25 tid
  - Propionic acids (Type I): Ibuprofen 400 400 every 6 h
  - Fenamates (Type I): Mefenamic acid 500 250 every 4 h
- Hormonal contraception: Patients who do not respond to NSAID and do not wish to conceive can be prescribed the combined oral contraceptive pills OCs. The combined OCs works by suppression of the hypothalamic-pituitary-ovarian axis and thereby inhibits ovulation and prevents prostaglandin production in the late luteal phase. This reduces the amount of menstrual flow and alleviates primary dysmenorrhea in most patients.
- Treatment with both oral contraceptives and NSAIDs may be effective in women who remain symptomatic on either drug alone.
- Patients with dysmenorrhea who do not respond to two to three cycles of NSAIDs and oral contraceptives may have a gynecologic disease, such as endometriosis, and would require further evaluation that may include diagnostic laparoscopy (see secondary amenorrhea).

  Alternatively, empirical treatment with a gonadotropin-releasing hormone (GnRH) agonist analogue, such as leuprolide acetate depot (3.75 mg intramuscularly every four weeks) based on a clinical diagnosis of endometriosis may be prescribed.

Secondary dysmenorrhea

A different pattern of pain is observed with secondary dysmenorrhea that is not limited to the onset of menses.

Typically, the pain progressively increases during the luteal phase until it peaks around the onset of .menstruation

The following may indicate secondary dysmenorrhea:

- Dysmenorrhea occurring during the first or second cycles after menarche, which may indicate congenital outflow obstruction (usually the first few cycles are anovulatory and should almost be painless)
- Dysmenorrhea beginning after the age of 25 years
- Pelvic abnormality on physical examination
- Little or no response to therapy with NSAIDs, OCs, or both

Causes of Secondary dysmenorrhea

Gynecologic causes:
Intrauterine contraceptive devices
Adenomyosis
Uterine myoma (fibroids)
Uterine polyps
PID or pelvic Adhesions
Congenital malformation of the müllerian system
Cervical strictures or stenosis
Pelvic congestion syndrome
Endometriosis

Non-Gynecological causes of pain:
Inflammatory bowel disease
Irritable bowel syndrome
Urinary tract infection

Psychogenic pain

Approach to patient with secondary amenorrhea:

- A pelvic examination: is indicated at the initial evaluation, which should be carefully performed in order to exclude uterine irregularities, cul-de-sac tenderness, or nodularity that may suggest endometriosis, pelvic inflammatory disease, or a pelvic mass.
- Investigations: One or more of the following investigations may be performed to exclude organic causes of dysmenorrhea:
  - Cervical culture to exclude sexually transmitted diseases
  - WBC count and Sedimentation rate to exclude infection
  - Abdominal and transvaginal ultrasound.
  - hysterosalpingography may be required to exclude endometrial polyps, leiomyomas, and congenital abnormalities of the uterus.
  - An endometrial biopsy may be indicated if endometritis is considered likely.
  - Laparoscopy especially if pelvic pathology is suspected.
  - Hysteroscopy, and dilatation and curettage, may be indicated to evaluate intrauterine pathology found on imaging.

Premenstrual Syndrome "PMS" and Premenstrual dysphoric disorder "PMDD"

Premenstrual Syndrome "PMS" and premenstrual dysphoric disorder "PMDD" are two extreme of the same condition. They refer to group of affective and physical symptoms that recur during the luteal phase and may continue to the early days of menstrual flow. The symptoms should be severe enough to interfere with some aspect of woman life.

Frequency:

- Mild form: About 80% of women experience some mild premenstrual symptoms. The most common symptoms being fatigue, bloating, breast tenderness, and may be some mood changes.
- Moderate to severe symptoms occurs in approximately 20% to 30% of women.
- About 2% to 6% of women suffer from the more severe variant known as PMDD.

Symptoms and diagnostic criteria:

The symptoms of PMS may be divided into physical and emotional symptoms.

- **Physical symptoms**: The most common are abdominal bloating and an extreme sense of fatigue, breast tenderness and headaches.
- **Behavioral symptom**: include labile mood, irritability, tension, depressed mood, increased appetite, and forgetfulness and difficulty concentrating.

Other common findings include acne, oversensitivity to environmental stimuli, anger, easy crying, and gastrointestinal upset. Hot flashes, heart palpitations, and dizziness occur in 15 to 20 percent of patients

The diagnosis of PMS/PMDD is established by history in which the following criteria can be established:

- The specific symptom (i.e. symptoms should be characteristic of PMS)
- The timing with which these symptoms occur (i.e. they should occur in the luteal phase)
- The severity of the symptoms (i.e. they should impair some facet of the woman's life)
- The absence of hormone or drug ingestion and the exclusion of other diagnoses

Currently, the most commonly used set of diagnostic criteria are the American Psychiatric

Association DSM-IV criteria for PMDD, and the University of California, San Diego (UCSD) criteria for PMS (Table 18-2)

PMDD should always be differentiated from premenstrual exacerbation of an underlying major psychiatric disorder, as well as medical conditions such as hyper- or hypothyroidism.

Pathogenesis of PMS and PMDD:

The exact pathogenesis of PMS is not known. But the available evidence suggests that PMS is a disorder triggered by changes in gonadal steroids during the luteal phase in susceptible women.

The cyclic changes in ovarian steroids interact with central neurotransmitters particularly serotonin. Other transmitters include beta-endorphin, gamma-aminobutyric acid (GABA), and the autonomic nervous system.

1. The presence by self report of at least one of the following somatic and affective symptoms during the five days prior to menses in each of the three menstrual cycles:	
Affective	
- Depression	- Angry outbursts
- Irritability	- Confusion
- Social withdrawal	- Fatigue
- Somatic	- Affective
- Depression	
Somatic	
- Breast tenderness	
- Abdominal bloating	
- Headache	
- Swollen extremities	
2. Relief of the above symptoms within four days of the onset of menses, without recurrence until at least cycle day 12.	
3. The symptoms are present in the absence of any pharmacologic therapy, hormone ingestion, drug or alcohol use.	
4. Identifiable dysfunction in social or economic performance by one of the following criteria:	
- Marital or relationship discord confirmed by partner	
- Difficulties in parenting	
- Poor work or school performance, attendance/tardiness	
- Increased social isolation	
- Legal difficulties	
- Suicidal ideation	
- Seeking medical attention for a somatic symptom(s)	

Table 18-2: University of California, San Diego (UCSD) criteria for PMS. Adapted from Mortola, JF, Girton, L, Yen SSC, Am J Obstet Gynecol 1989; 161:1682.

Risk factors for PMS:

- Genetic factors: PMS was found to be highly heritable. Preliminary evidence suggests that risk for premenstrual dysphoric disorder is associated with genetic variation in ESR1, the estrogen receptor alpha gene.
- However in susceptible women environmental factors plays important role in development of PMS.
- The condition is more common with lower education and cigarette smoking, and a history of traumatic events or anxiety disorder.
- In addition, because of some of the systemic manifestations, such as feeling of bloating, may be produced by peripheral mechanisms. There may also be a role for trace elements in the pathogenesis of PMS.

Treatment:

- There is no known cure for PMS. Therefore the goal of treatment is to alleviating the symptoms of PMS.
- The diagnosis should first be confirmed using subjective criteria (table 18-2) and other causes of psychosomatic disorders are excluded.
- For better diagnosis and evaluation of severity of the disorder patient may be asked to chart registering mood and physical symptoms daily over the course of at least one menstrual cycle.
- Women with severe PMS should ideally receive care from a multi-disciplinary team consisting of a gynecologist, psychiatrist or psychologist, dietician and counselor.

The options of treatment depends on the severity of symptoms:

➢ **In mild cases:**

General measures:

- In the absence of substantial distress or social dysfunction, the patient should be advised to consider exercise, moderate vitamin (B-6) supplementation dose should not exceeds 100 mgs per day.

➢ **Moderate to severe cases:**

Pharmacologic intervention:

Serotonin reuptake inhibitors (SRIs) are the first line therapy: Fluoxetine 20 mg/day or Sertraline 50 to 150 mgs daily. SRIs can be administered as a daily therapy or luteal phase-only treatment. Approximately 15 percent of patients will experience significant side effects from an SRI, including nausea, jitteriness, and headache. In such patients, a

trial of either a lower starting dose or a second .SRI is warranted

- Cycle depression: If the patient is not responsive to prior treatment, she is a candidate for ovulation suppression agents. A GnRH agonist with estrogen and progestin addback is preferable to danazol because of the more favorable side effect profile. Oral contraceptive pills as continues regimen may also be tried.

➢ **Severe non-responding cases:**

- Surgical therapy: In the rare event of severe, disabling symptoms of refractory PMDD in which medical therapy fails surgery may be considered (see blue box for guidelines on surgical therapy).

  Surgical therapy includes oophorectomy with or without hystrectomy.

Criteria must be fulfilled prior to surgical treatment

- The diagnosis of PMDD must be confirmed with prospective symptom recording
- GnRH agonist therapy must be the only medical approach that has been effective, and it must have been continuously effective for a minimum of six months
- Tolerance of estrogen (or estrogen-progestin) replacement therapy has been tested during the GnRH agonist therapy
- Childbearing is complete

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Chapter 19

Abnormal Uterine Bleeding

Genital bleeding other than the normal scheduled menstrual cycles is one of the common and very annoying complaints among women of the reproductive age. It is rarely a life threatening one but can have serious consequences on women general health, social, and family life. In addition for Muslim woman it can disrupt her religious obligations (prayer and fasting).

Genital bleeding is often attributed to a uterine source; other lower (vulva, vagina, and cervix) and upper genital tracts (fallopian tubes, and ovaries) lesions should be excluded. It could also have a non-gynecologic organ, such as the urethra, bladder, or bowel.

This chapter deals with causes and differential diagnosis of abnormal uterine bleeding; with particular emphasis on uterine bleeding in the absence of physical pathology or what is know as dysfunction uterine bleeding "DUB".

By the end of this chapter you should be able to:

- **Describe** the normal menstrual cycle
- **Describe** the function and the dysfunction of hypothalamic – pituitary-ovarian axis and its dysfunction
- **Define** abnormal uterine bleeding
- **List** the DD of abnormal uterine bleeding
- **Describe** the pathogenesis of DUB
- **Describe** the approach to the diagnosis and management of patient presents with abnormal genital bleeding:
- **Diagnose** DUB
- **Counsel** patient on the options of management of DUB

The Normal Menstrual Cycle

The normal menstrual cycle is divided into two phases: follicular and luteal phases.

- The follicular phase begins with the onset of menses (by convention is considered as day 1) and ends on the day of the luteinizing hormone (LH) surge.
- The luteal phase begins on the day of the LH surge and ends at the onset of the next menses.

The average adult menstrual cycle lasts 28 to 35 days, with approximately 14 to 12 days in the follicular phase and 14 days in the luteal phase. Changes in intermenstrual interval are primarily due to changes in the follicular phase; in comparison, the luteal phase remains relatively constant.

The follicular phase:

- Early in the follicular phase there is gradual increase in gonadotropin-releasing hormone (GnRH) pulse frequency. This result in increase in serum follicle-stimulating hormone (FSH) concentrations.
- The increase in FSH secretion result in recruitment of cohort of developing ovarian follicles, one of which will become the dominant and ultimately ovulatory follicle during that cycle. The rest of the growing cohort of follicles gradually undergoes atresia. Successful maturation of the dominant follicle depends on the presence of a dominant estrogenic intraovarian environment. This is provided by the interaction between the theca cells synthesizing androgen which then converted by the granulosa cells to estrogen (Figure 19-1)
- The growing follicles produce increasing amount of estradiol, and inhibin A from the granulosa cells.

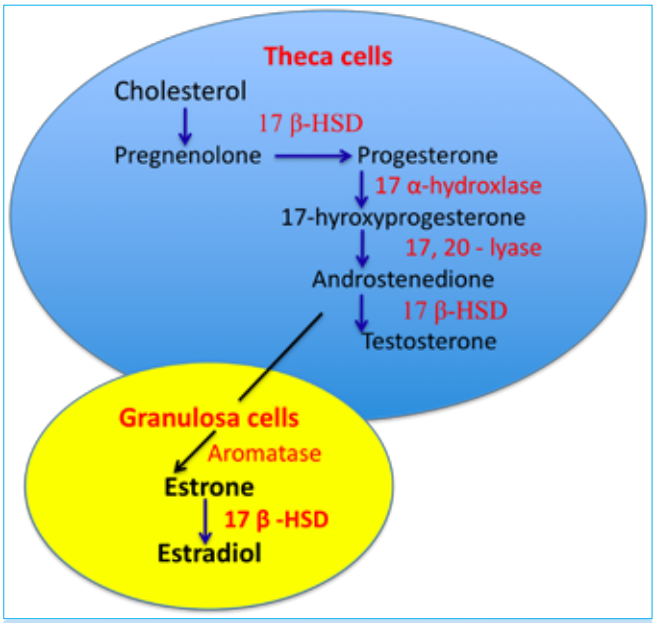

Figure 19-1: The theca cells produce androgen, which is converted by granulosa cells into estradiol. Extrinsic and/or intrinsic factors may disturb this balance leading to overproduction of androgen which change the intraovarian environment to androgenic one (see text)

The rising estradiol is responsible for the observed endometrial and cervical mucus changes (Figure 19-3, 4)

- The continuous rise in estradiol and inhibin A production induces negative feeds back on the hypothalamus and pituitary, resulting in suppression of mean serum FSH and LH concentrations as well as the LH pulse amplitude.

The Endometrium: undergoes proliferation, becomes thicker, with an increase in the number of glands. On US imaging it can be seen as a "triple stripe" pattern.

Cervical mucus: Rising serum estradiol result in gradual increase in the amount and "stringiness" (Spinnbarkeit) of the cervical mucus. Awareness of the change in mucus feature can be used as evidence of ovulation and/or use of contraception

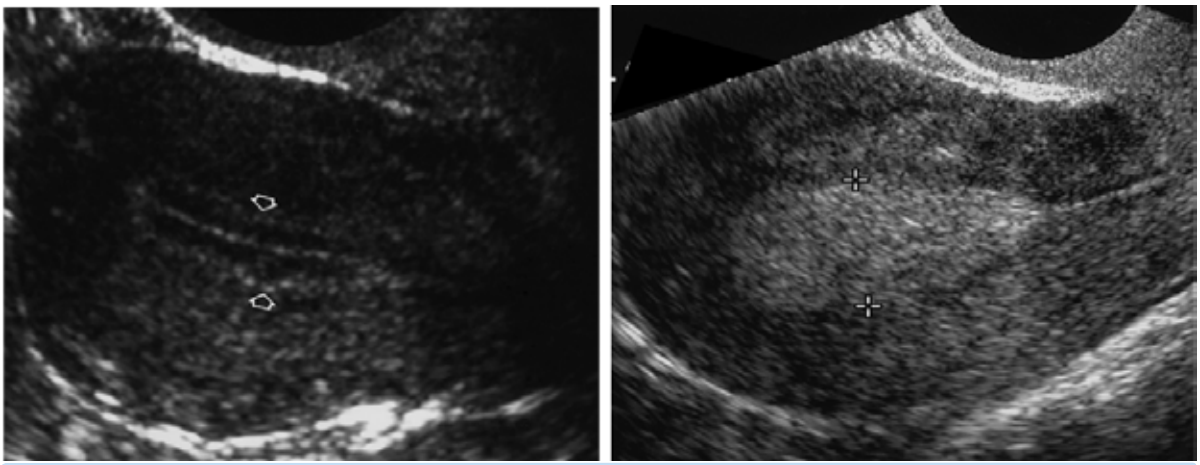

Figure 19-2: TV, US picture showing **Left**: the triple stripe appearance indicating well proliferated endometrium at the end of the follicular phase. **Righ**t: after ovulation under the effect of progesterone the proliferative changes ceases and secretory changes begins. The "triple stripe" image is lost and the endometrium becomes more uniformly bright

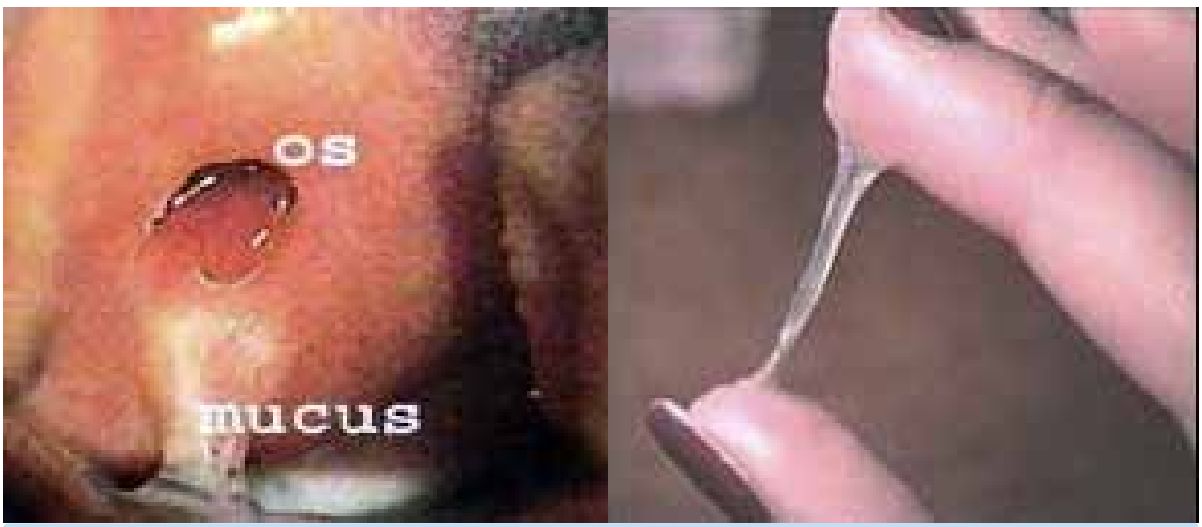

Figure 19-3: Picture showing the profuse cervical mucus under the effect of estrogen. The mucus becomes abundant, clear, and stretchable, like egg white (Spinnbarkeit). Some women can detect this change in mucus as a marker for the fertility days.

The Luteal phase:

- Midcycle LH surge and Ovulation:

  The rise in serum estradiol concentrations reaches a peak approximately one day before ovulation. This together with yet unknown factors trigger the unique phenomenon of the mid-cycle LH surge (The surge is a switch from negative feedback control of LH secretion to a sudden positive feedback effect) resulting in a 10-fold increase in serum LH concentrations and a smaller rise in serum FSH concentrations

  Endometrium

  The gradually increasing serum progesterone leads to cessation of proliferative changes (mitoses and "organization" of the glands) and initiate secretory changes. This changes can be detected on ultrasonography relatively soon after ovulation: the "triple stripe" image is lost and the endometrium becomes more uniformly bright (see picture)

  The LH surge initiates substantial changes in the ovary.

  - The oocyte in the dominant follicle completes its first meiotic division.
  - Release of oocytes from the follicle (ovulation) occurs approximately 36 hours after the LH surge.
  - Lutinsation of the granulosa cells and progesterone production begin to take place even before the oocyte is released.

- Middle to late luteal phase: Progesterone secretion from the corpus luteum continues to rise. This leads to progressive slowing of LH pulses. Inhibin A is also produced by the corpus luteum, and serum concentrations of inhibin A peak in the mid-luteal phase.

  If, fertilization occurs, the embryo implants and the trophoblast begins to make chorionic gonadotropin, which maintains the corpus luteum and progesterone production.

  In the absence of fertilization and gradual decrease in LH secretion the corpus luteum cannot be maintained which results in gradual fall in progesterone and estradiol production by the corpus luteum.

- Menstruation: The decline in estradiol and progesterone release from the resolving corpus luteum results in the loss of endometrial blood supply, endometrial sloughing, and the onset of menses approximately 14 days after the LH surge.

  In response to falling progesterone and estradiol production, the hypothalamic-pituitary axis is released from their negative feedback and FSH levels rise, thereby beginning the next cycle.

Functional Disorder of Menstrual Cycle:

The normal menstrual cycle pattern depends on a delicate balance between hypothalamic-pituitary hormones, ovarian hormones and normal uterine endometrial response. Disorder of menstrual cycle can result from dysfunction at any level. This is illustrated in Figure 19-2 and further discussed below in the section on dysfunction uterine bleeding.

- The hypothalamic pituitary axis: dysfunction can occur either primary or secondary to specific lesion (e.g. adenoma). Immature H-P axis (as in the post menarche period), if there is loss of normal feed back response (e.g. genetic lesions or in PCOS where there is tonic production of LH)
- Ovarian level: depletion of follicles (granulosa cells) as in premenopausal years, or cases of premature menopause. Abnormal intraovarian environment e.g. androgenic environment either due to primary or secondary steroidogenesis dysfunction result in suppression of normal follicular maturation e.g. in PCOS.

Ovarian level:

Depletion of follicles (granulosa cells) as in premenopausal years, or cases of premature menopause.

Abnormal intraovarian environment e.g. androgenic environment either due to primary or secondary steroidogenesis dysfunction result in suppression of normal follicular maturation e.g. in PCOS.

The hypothalamic pituitary axis: Immature H-P axis (e.g. post menarche period)

Loss of normal feed back response (e.g. genetic lesions or in PCOS where there is tonic production of LH)

Secondary dysfunction: to specific lesion (e.g. adenoma).

Endometrial disorder: Unstable endometrium could be secondary to defects in steroid hormones levels or due to local endometrial factors that interfere with normal hemostasis with the result of heavy menstrual flow.

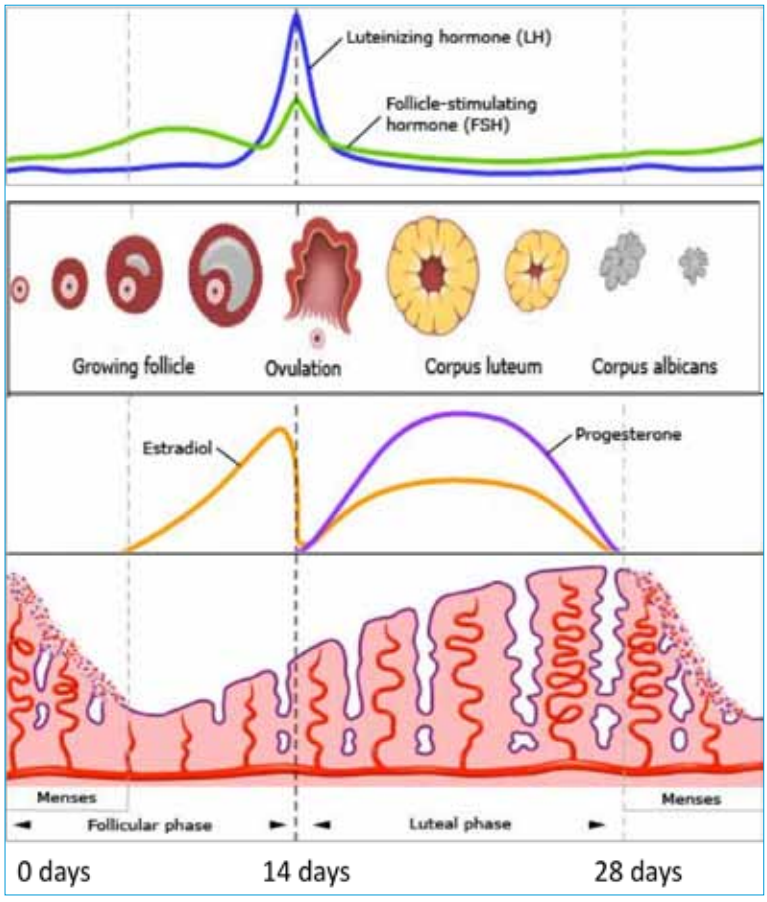

Figure 19-4: diagram showing the changes at the hypothalamic-pituitary-ovarian and endometrial levels in normal 28 days menstrual cycle. Dysfunction at any one or more level could lead to abnormal uterine bleeding. In the absence of physical causes the condition is known as dysfunctional uterine bleeding.

- Endometrial disorder: normal menstrual flow depends on local factors including prostaglandins and other factors. Unstable endometrium could be secondary to defects in steroid hormones levels or due to local endometrial factors that interfere with normal hemostasis with the result of heavy menstrual flow.

Abnormal uterine bleeding

➢ Definition:

The term of abnormal uterine bleeding refers to bleeding that is unpredictable in term of time, duration, volume, and/or frequency of menses for at least the previous 3 months.

➢ Causes of abnormal genital bleeding:

Throughout woman life abnormal genital bleeding could be due to many causes including local (inflammatory, neoplastic, traumatic) and systemic ones. Table 19-1 shows the likely causes of genital bleeding from time of birth to the postmenopausal years.

Neonates	**Reproductive years**
Estrogen withdrawal	Anovulation (DUB)
Premenarchal	Pregnancy
Foreign body	Cancer
Trauma, including sexual abuse	Polyps, fibroids, adenomyosis
Infection	Infection
Urethral prolapse	Endocrine dysfunction (PCOS, Thyroid, Pituitary adenoma)
Sarcoma botryoides	Bleeding diathesis
Ovarian tumor	Medication related (e.g. OCC)
Precocious puberty	**Perimenopausal**
Early Postmenarche	Anovulation (DUB)
Anovulation (DUB)	Polyps, fibroids, adenomyosis
Bleeding diathesis	Cancer
Stress (psychogenic, exercise)	**Menopause**
Pregnancy	Atrophy
Infection	Cancer
	HRT

Table 19-1: Causes of abnormal uterine bleeding throughout female phases of life. From APGO educational series on women's health issues, Clinical management of abnormal uterine bleeding. Association of Professors of Gynecology and Obstetrics, May 2002.

Most cases of genital bleeding among women in the reproductive age are due to uterine source.

In attempt to set an objective classification for the different causes of uterine bleeding the FIGO (International Federation of Gynecology and Obstetrics) have recently defined 9 categories (PALM-COEIN) (Table 19-2 that include most of the causes of abnormal uterine bleeding.

The "PALM" categories: (**Structural Causes**)
P: polyp
A: adenomyosis
L: leiomayoma
M: malignancy and hyperplasia.

The "COEIN" Categories: (Non structural Causes, entities that are not defined on imaging or histopathology testing)
C: coagulopathy
O: ovulatory dysfunction: **Dysfunctional uterine bleeding and PCO**
E: endometrial
I : Iatrogenic: use of exogenous gonadal steroids, intrauterine systems or devices, or other systemic or local agents
N: not yet classified (miscellaneous)

Table 19-2: Causes of abnormal uterine bleeding: Recent classification by the FIGO (Feral International of Gynecology and Obstetrics). Int J Gynecol Obstet. 2011;113:3-13.

The objective of this classification is to facilitate comparison of epidemiological studies, effectiveness of various treatment intervention and management.

After exclusion of pregnancy complication the most common entity of abnormal uterine bleeding in women of reproductive age is ovulatory dysfunction or dysfunctional uterine bleeding (DUB), which is discussed in the following section.

Dysfunctional uterine bleeding

Definition: Dysfunctional uterine bleeding (DUB) is abnormal uterine bleeding that occurs in the absence of recognizable pelvic pathology, general medical disease, or pregnancy.

It is considered a diagnosis of exclusion. This condition usually is associated with anovulatory menstrual cycles but also can occur in ovulation (or oligoovulation).

The bleeding pattern is unpredictable in many ways. It might be excessively heavy or light, prolonged, frequent, or random.

Pathophysiology:

The pathophysiology of dysfunctional uterine bleeding is largely unknown, but it seems to varies between anovulatory DUB (occur in 90% of cases) and ovulatory DUB (occur in 10% of cases)

- Anovulatory DUB: is more of a systemic disorder, occurring secondary to disorder in the hypothalamic-pituitary-ovarian axis.

  With anovulation the endometrium is exposed to constant, non-cycling estrogen stimulation that result in endometrium proliferation. Eventually the endometrium outgrows its blood supply and undergoes focal necrosis with partial shedding. Since shedding is not uniform, bleeding is usually irregular, prolonged, and heavy. It could take different forms such metrorrhagia, and menometrorhagia. In general, the more prolonged the anovulation with hyperplasic proliferative endometrium; the greater the risk of excessive bleeding "menorrhagia".

Anovulation

Can occur at anytime during the reproductive years and has many causes but is more common:

- In adolescents: because of immature hypothalamic-pituitary axis and in
- Menopausal transition: because of decline in ovarian function.

In women of reproductive age: Polycystic ovary syndrome (PCOS) is the most common endocrine disorder associated with anovulation,

- Ovulatory DUB: Ovulatory dysfunctional bleeding occurs secondary to defects in local endometrial hemostasis (elevated endomyometrial vasodilatory prostaglandins and decreased vasoconstrictive prostaglandins). Therefore, these women lose blood at rates about 3 times faster than women with normal menses. However a larger proportion of in this group has some pathology (e.g. polyp, fibroid, adenomyosis, neoplasm, foreign body, infection or hemostatic defect)

Epidemiology and Frequency:

Dysfunctional uterine bleeding particularly anovulatory DUB is most common at the extreme ages of women reproductive years, but it may occur at any time during her reproductive life.

- In adolescence age: DUB is not uncommon during the first 2 years after the onset of

menstruation, because of immature hypothalamic-pituitary axis that fail to respond to estrogen and progesterone, resulting in anovulation.

- In the perimenopausal period: As patient approach menopause (>40) the number and quality of ovarian follicles diminishes. Follicles continue to develop but do not produce enough estrogen in response to FSH to trigger ovulation. The cycles are anovulatory and the estrogen that is produced usually results in late-cycle estrogen breakthrough bleeding.

➢ Mortality/Morbidity:

In rare occasion the bleeding can be severe enough to cause hemorrhagic shock.

More often heavy bleeding "Menorrhagia" results in anemia, reduced quality of life, and increased healthcare costs. In Western countries it is estimated that Excessive menstrual bleeding accounts for two thirds of all hysterectomies and most endoscopic endometrial destructive surgery. Among Moslem women DUB adversely affects women religious obligation (Fasting and Praying).

➢ Clinical Presentation and diagnosis of DUB:

Patient usually present complaining of "abnormal genital bleeding", in all cases a full history, examination and targeted investigations should be taken the goals are:

- To determine the uterine source of bleeding and excludes other causes such as perineal, vaginal cervical and other non-genital sources.
- Determine the severity and pattern of abnormal bleeding (Menorrhagia, Menometrorrhagia, Metrorrhagia, Premenstrual spotting)
- The diagnosis of DUB is made after exclusion of systemic and physical causes abnormal uterine bleeding (see table 19-2).
- Once a diagnosis of DUB is made it is important to determine whether the woman is ovulating or not because the etiologies and management of anovulatory and ovulatory bleeding are generally different.

History:

- To valuate severity of bleeding: The amount (e.g. *clots, number of pads used at time of presentation in comparison to previous ones*), frequency of bleeding and the duration of symptoms, as well as the relationship to the menstrual cycle, should be established.
- Symptoms suggestive of Ovulatory DUB are regular cycles, and presence of molimina (e.g., breast tenderness, bloating or pelvic discomfort, mood changes, thin vaginal discharge)
- Menstrual history: Age of menarche, previous pattern of menstrual cycles and and presence of dysmenorrhea
- Postcoital bleeding
- Obstetric history: Gravida and para
- Contraceptive use: type and duration.
- Medical history with emphasis on:
  - History of endocrine diseases: e.g. Thyroid disease, diabetes …etc
  - Recent illness, psychological stress
  - Excessive exercise, or weight change
  - Liver disease
  - Bleeding disorder: known diseases or presence of family history, menorrhagia since menarche, bruises or bleeding from other sites
  - Medication usage: exogenous hormones, anticoagulants, aspirin, anticonvulsants, and antibiotics

Examination:

General: Standard general examination with emphasis on:

- Vital signs, including postural changes.
- Assessment of the patient's volume status and degree of anemia.
- Any evidence of bleeding diathesis (e.g. petechiae, purpura, and mucosal bleeding (eg, gums).
- Signs of liver disease e.g. spider angioma, palmar erythema.
- Sings of polycystic ovary disease: namely signs of hyperandorgenism (hirsutism, obesity, acne), and acanthosis nigricans (hyperpigmentation typically in the folds of the skin in the neck, groin, or axilla)
- Signs of thyroid disease: Goiter, eye findings, tremors, changes in skin texture, and weight change.

Gynecological pelvic examination: speculum, and bimanual examination:

- To exclude local vaginal or cervical causes or uterine or ovarian structural abnormalities e.g. fibroid uterus, or palapable ovarian masses.
- In young virgin adolescent especially with mild form of menorrhagia pelvic examination can be omitted.

Investigations: Full history, examination together with office ultrasound examination either transabdominal and/or transvaginal should enable establishment of the diagnosis in a large proportion of cases.
Further investigations are requested depending on the findings and patient age (see management of DUB) in order to establish the diagnosis of DUB:

Laboratory:

- BHCG to exclude pregnancy in women of reproductive age
- Hemoglobin and/or hematocrit.
- Cervical cytology
- Serum ferritin and serum iron binding capacity.
- Thyroid function tests
- Coagulation studies
- FSH, LH, Prolactin, serum progesterone (in suspected ovulatory DUB)
- Liver function tests

Imaging studies:

- Transvaginal US for endometrial thickness
- Pelvic MRI (in suspected adenomyosis)
- Hystrosonography

Invasive tests:

- Endometrial biopsy
- Hysteroscopy
- Dilatation and curettage
- Laparoscopy

Endometrial biopsy: indicated in the following situations:

- Women over age 35 to rule out endometrial cancer or a premalignant lesion (endometrial hyperplasia)
- Women between the ages of 18 and 35 who have risk factors for endometrial cancer namely: family or personal history of ovarian, breast, colon, or endometrial cancer; Tamoxifen use; chronic anovulation; obesity; estrogen therapy; prior endometrial hyperplasia; diabetes.

➢ Management of DUB:

Once the diagnosis of DUB is confirmed the treatment depends on the severity of bleeding, the patient age, fertility wishes, and any additional risk factors.

The options of treatment include one or more of the following modalities:

- Simple reassurance with conservative follows up. This option is often adopted in case of an adolescent with mild menorrhagia (have no evidence of anemia, HB > 11 gm/dl). The adolescent should be educated about the maturation of the menstrual control. Vitamin and iron supplementation may be prescribed.
- Medical treatment: hormonal and non-hormonal agents: are used in adolescent with moderate DUB (HB 9-11 gm/dl) and usually as first choice in women of reproductive age group < 35 years of age. In the latter group if hormonal treatment is not successful following 2-3 cycles endometrial biopsy should be performed.
- Surgical treatment: surgical treatment is usually reserved for women in the pre-menopausal age (> 40 years of age). It includes either conservative surgery using one of the measures of endometrial ablation or rarely hystrectomy. Medical treatment including hormonal and non-hormonal agents is prescribe for women >35 years of age after endometrial biopsy to exclude endometrial cancer.

Medical treatment:

- **Combined Estrogen-progestin contraceptives:** are the first choice of therapy for most women with heavy or prolonged uterine bleeding
- **Levonorgestrel-IUD "The LNG-IUD"** Mirena®**:** was found to reduces menstrual blood loss by 74 to 97 percent after one year of use and is appropriate for women with bleeding disorders.

  Mechanism of action: The LNG-IUD releases 20 mcg levonorgestrel per day. This high local progestin concentration results in a thinning of the endometrium.
- **Nonsteroidal anti-inflammatory drugs: (e.g.** Mefenamic acid 500 mg three times per day, Ibuprofen 600 mg once per day). Nonsteroidal anti-inflammatory drugs (NSAIDs) reduce the volume of menstrual blood loss by 20 to 50 percent in most women with heavy uterine bleeding.

  Mechanism of action: NSAID induce reduction in the rate of prostaglandin (PGE2 and PGF2 alpha) synthesis in the endometrium, leading to vasoconstriction and reduced bleeding. They need to be taken only during menses.
- **Anti-fibrinolytic agents**: such as tranexamic acid (1300 mg three times per day during menses for a maximum of five days) and aminocaproic acid, reduce menstrual flow 30 to 55 percent from baseline and are more effective than placebo.

Mechanism of action: It diminishes fibrinolytic activity within endometrial vessels to prevent bleeding.

They only need to be taken on the days of menses and do not interfere with fertility. They should not be used if there is high risk of thrombosis.

- **Oral or parenteral progestins:** Oral or parenteral progestin therapy can be used to prevent excessive bleeding related to endometrial hyperplasia in women with chronic anovulation.

  However it is not recommended as luteal phase support (administered from cycle days 15 to 26) in women with ovulatory DUB.

- **Gonadotropin-releasing hormone agonists:** GnRH analogs (eg, goserelin) induce a menopausal state in premenopausal women that leads to amenorrhea. The disadvantages of this treatment in addition to its high cost are menopausal symptoms and bone loss with long-term use. Therefore estrogen or progestin addback therapy are needed GnRH are used for more than three to six months. They often use as short term therapy to induce amenorrhea and allowing women to build their own store of hemoglobin and iron.

Surgical treatment:

- **Endometrial ablation:** Endometrial ablation is a minimally invasive option in which the endometrium must be destroyed or resected to the level of the basalis.

  Its effectiveness in prevention and or reduction menstrual blood flow is comparable to LNG-IUD in reducing menstrual blood flow.

  Indication: for treatment of heavy or prolonged uterine bleeding if medical therapy fails or for women who do not want to use chronic medical therapy.

  Endometrial ablation is considered a conservative surgical treatment because the uterus is preserved and it is usually a day case or sometime office procedure. **However pregnancy is contraindicated after endometrial ablation, but contraception is still required.**

  Methods: endometrial ablation can be achieved either through:

  - Non-resectoscopic technique: refers to endometrial destruction using disposable device which is inserted into the uterine cavity and delivers energy to uniformly destroy the uterine lining (bipolar radiofrequency (Novasure®); hot liquid filled balloon (ThermaChoice®); cryotherapy

(Her Option®); circulating hot water (Hydro ThermAblator®); and microwave (Microwave Endometrial Ablation)

- Resectoscopic technique: refers to endometrial resection performed under hysteroscopic visualization with resectoscopic electrosurgical instruments (eg, rollerball, wire loop, vaporizing electrode) or with laser.

- **Hysterectomy**: Is the final and definitive treatment for uterine bleeding. It has a high rate of patient satisfaction because it is curative, is not associated with drug-related side effects, and does not require repeated procedures or prolonged follow-up. However it is still major surgical procedure associated with perioperative complications.

Emergency Management

Patient who present with heavy bleeding and are Hemodynamically unstable should be immediately admitted to hospital for emergency treatment which involve:

- Resuscitative measure: ABCs measures for management of hemorrhagic shock (Initiate 2 large-bore intravenous lines (IVs), oxygen, and cardiac monitor)
- Administration of IV conjugated estrogen (Premarin) 25 mg IV every 4-6 hours until the bleeding stop.
- In women with severe, persistent uterine bleeding, an immediate dilation and curettage (D&C) procedure may be necessary.
- Once bleeding is under control initiate oral contraceptive with 35 mcg of ethinyl estradiol can be taken twice a day until the bleeding stops for up to 7 days, at which time the dose is decreased to once a day until the pack is completed.

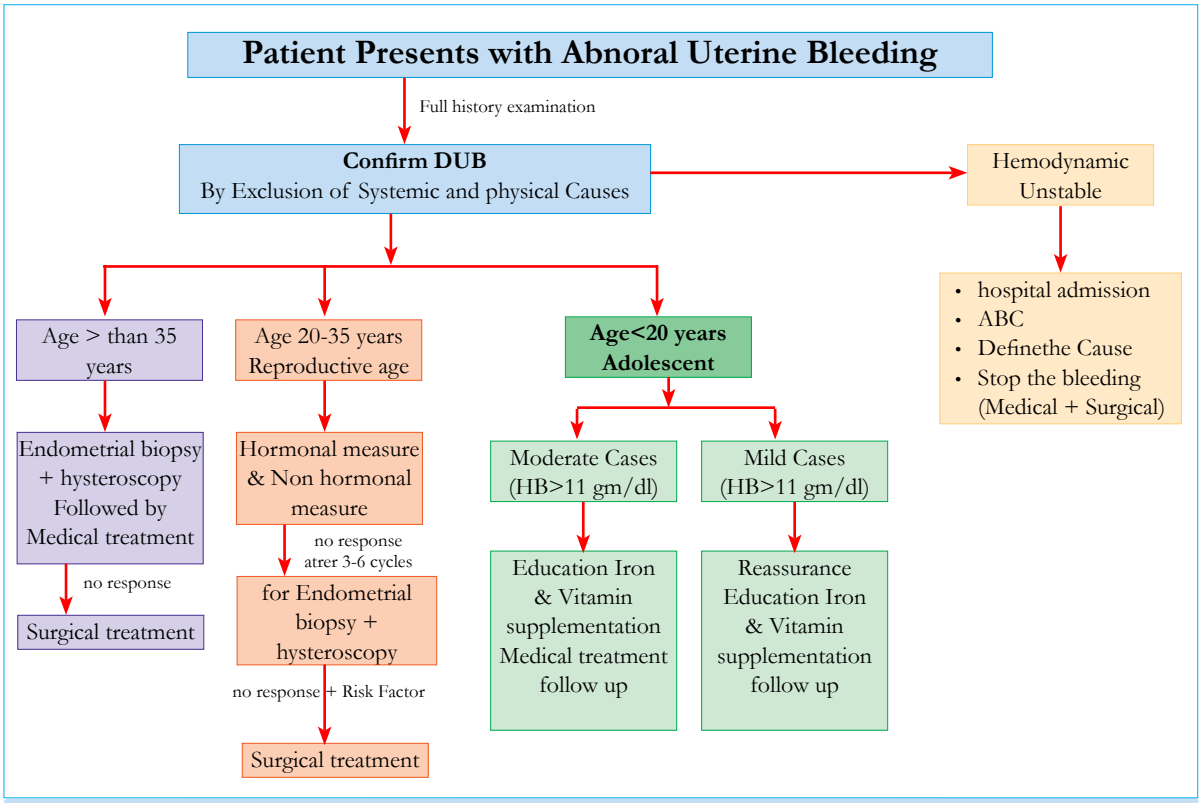

Figure 19-----: Algorithm of approach to management of patient with abnormal uterine bleeding

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Chapter 20

Secondary Amenorrhea

Secondary amenorrhea and Oligomenorrhea have the same pathogenesis. Both conditions require systematic approach for diagnosis and treatment. As in primary amenorrhea the pathogenesis of secondary amenorrhea could be due to dysfunction at any of the hypothalamus, pituitary, ovaries, and uterine levels.

Secondary amenorrhea can be a transient, intermittent, or permanent condition.

By the end of this chapter you should be able to:

- **Define** secondary amenorrhea
- **Describe** the causes of secondary amenorrhea
- **Describe** the clinical presentation of PCO Hyperprolactinemia:
- **List** the causes of hyperprolactinemia
- **Describe** the diagnosis and treatment of Prolactinoma
- **Describe** the approach to the diagnoses of secondary amenorrhea
- **Outline** the aim of management of woman with secondary amenorrhea

Definition:

Secondary amenorrhea is defined as absence of menses for more than three cycles or six months in women who previously had menses.

Causes of secondary amenorrhea:

- **Pregnancy**: Pregnancy is the most common cause of secondary amenorrhea. It should be excluded in all cases even in women using contraception by measurements of serum or urinary human chorionic gonadotropin (hCG). Once pregnancy is ruled out, the frequency of the remaining causes of secondary amenorrhea are distributed as follow:

- Ovary: 40 percent
- Hypothalamus: 35 percent
- Pituitary: 19 percent
- Uterus: 5 percent
- Other: 1 percent

- **Hypothalamic dysfunction:** Functional hypothalamic amenorrhea is characterized by a decrease in hypothalamic gonadotropin-releasing hormone (GnRH) secretion. This leads to decreased pulses of gonadotropins, absent midcycle surges of luteinizing hormone (LH) secretion, absence of normal follicular development, anovulation, and low serum estradiol concentration. The causes of hypothalamic dysfunction include:

1. **Congenital GnRH deficiency**: it usually presents as primary amenorrhea. However occasionally GnRH receptor mutations may not cause complete receptor dysfunction therefore there may be history of menstrual bleeding. It is called "idiopathic hypogonadotropic hypogonadism" or, if it is associated with anosmia, "Kallmann syndrome".

2. **Functional hypothalamic amenorrhea**: could be due to:
   - Eating disorders: such as anorexia nervosa, exercise, and stress. However it can be caused by nutritional deficiencies that are not associated with weigh loss or strenuous exercise. Such as severe restriction of fat consumption as in celiac disease.
   - In few women with functional hypothalamic amenorrhea no obvious precipitating factor is evident.
3. **Infiltrative lesions:** Infiltrative diseases of the hypothalamus (e.g. lymphoma, Langerhans cell histiocytosis, sarcoidosis) can result in decreased GnRH secretion, low or normal serum gonadotropin concentrations, and amenorrhea. However, these lesions are rare compared with functional hypothalamic amenorrhea.

Weight loss and amenorrhea

Weight loss below a certain target level (approximately 10 percent below ideal body weight) and exercise is associated with amenorrhea. The "female athlete triad" is defined as the presence of amenorrhea, disordered eating and osteoporosis or osteopenia. However there is marked interpatient variability in the degree of weight loss or exercise required to induce amenorrhea. This may in part be due to an underlying genetic predisposition in susceptible individuals.

- **Pituitary disease:**

1. **Hyperprolactinemia:**
   - Pathogenesis: Unlike the other pituitary hormones, prolactin release is under negative control, which means that its secretion from the anterior pituitary is controlled by inhibition by hypothalamic dopamine. Any disruption of the pituitary stalk that connects the hypothalamus with the pituitry, by trauma or a large tumor, leads to hyperprolactinemia which causes amenorrhea by suppressing hypothalamic GnRH secretion, leading to low gonadotropin and estradiol concentrations
   - Presentation: Hyperprolactinemia has a similar presentation to functional hypothalamic amenorrhea except for the occasional additional finding of galactorrhea in some –not all- women. Hyperprolactinemia it causes, diagnosis and management are discussed below.
2. **Other sellar masses:** Any other sellar mass, such as other kinds of pituitary adenomas, craniopharyngiomas, meningiomas, cysts, etc, can also interrupt normal gonadotropin secretion and cause amenorrhea, with or without hyperprolactinemia.
3. **Sheehan's syndrome**: Is infarction of the pituitary gland that may complicate severe postpartum hemorrhage. In developed countries, postpartum hemorrhage now less often results in Sheehan's syndrome than previously, largely due to improvements in obstetrical care

   Clinical features of Sheehan's syndrome:
   - A history of severe postpartum hemorrhages causing hypotension and require transfusion of multiple units of blood.
   - Development of lethargy, anorexia, weight loss, and inability to lactate during the first days or weeks after delivery.
   - Loss of all anterior pituitary hormones: including variable degree of deficiency of growth hormone, prolactin, and gonadotropin TSH and ACTH. Rarely patient develop overt diabetes insipidus, although subclinical vasopressin deficiency is common.

   In less severe hypopituitarism, failure of postpartum lactation and failure to resume menses may not occur till weeks and months after delivery, together with loss of sexual hair, as well as milder degrees of fatigue, anorexia, and weight loss.

   When the hypopituitarism is mild, possible delay in recognition for many years after the inciting event.
4. **Other rare causes of pituitary damage:** such as due to radiation, or infiltrative

lesions of the pituitary gland, such as hemochromatosis, and lymphocytic hypophysitis, are all uncommon causes of gonadotropin deficiency.

- **Ovarian disorders:**

1. **Polycystic ovary syndrome**: Polycystic ovary syndrome (PCOS) is a common disorder accounting for approximately 20 percent of cases of amenorrhea. PCOS is not a specific disease but rather a syndrome that present with spectrum of symptoms and sings that varies in severity. The minimal criteria for the diagnosis of PCOS are two out of three of the following: (1) hyperandrogenism, (2) oligomenorrhea or amenorrhea and (3) polycystic ovaries on ultrasound. The syndrome is discussed in details in chapter 21 (hyperandrogenism). PCOS is a diagnosis of exclusion. Important distinguishing features are its peripubertal onset and worsening with weight gain.

2. **Premature ovarian failure (Primary ovarian insufficiency):** Primary ovarian insufficiency (premature menopause or premature ovarian failure): refers to depletion of oocytes before age 40 years. This disorder is typically characterized by a waxing and waning clinical course. As a result, intermittent follicular development, estradiol production, menstrual bleeding, LH surges, and ovulation can occur between months of hypoestrogenemia. When primary ovarian insufficiency is complete, lack of ovarian function leads to estrogen deficiency, endometrial atrophy, and cessation of menstruation.

> Loss of the negative feedback effect of estradiol and inhibins A and B on the hypothalamus and pituitary results in high serum FSH concentrations, which clearly distinguishes ovarian insufficiency from hypothalamic amenorrhea in which serum FSH concentrations are low or normal

Causes of premature ovarian failure:

a) **Turner syndrome:** Most women with Turner syndrome have primary amenorrhea, but some, especially those with mosaicism, may have either primary or secondary amenorrhea.

b) A karyotype should be obtained to exclude Turner syndrome (and associated complications), mosaic Turner syndrome or the presence of Y chromatin material.

c) The presence of a Y chromosome is associated with a high risk of gonadal tumors, and makes gonadectomy mandatory.

d) **The fragile X permutation:** an X-linked form of mental retardation. Female

carriers of the fragile X premutation are at increased risk of developing primary ovarian insufficiency. In addition, their offspring are at risk of having the fragile X syndrome, an X-linked form of mental retardation.

e) **Autoimmune ovarian destruction or "idiopathic ovarian failure":** Characterized pathologically by a lymphocytic infiltrate in the theca cells of ovarian follicles. Other common autoimmunity associated with primary ovarian insufficiency is adrenal and thyroid autoimmune diseases.

f) **Radiation therapy or chemotherapy**: especially with alkylating agents such as cyclophosphamide may also result in premature ovarian failure.

- **Uterine disorders:**

Asherman's syndrome is the only uterine cause of secondary amenorrhea. This syndrome results from acquired scarring of the endometrial lining, usually secondary to postpartum hemorrhage or endometrial infection followed by instrumentation such as a dilatation and curettage.

This abnormality prevents the normal build-up and shedding of endometrial cells, leading to very light or absent menses.

The diagnosis is suggested by the absence of a normal uterine stripe on pelvic ultrasound and may be confirmed by the absence of withdrawal bleeding after administration of estrogen and then progestin for several weeks. The presence of Asherman syndrome can be confirmed by hysterosalpingogram and hysteroscopic evaluation of the endometrium.

Thyroid disease and secondary amenorrhea: Thyroid disorders are more likely to irregular menstrual bleeding such as menometrorrhagia. But primary hypothyroidism can be associated with amenorrhea through induced hyperprolactinemia. This is because hypothyroidism is a potential cause of an enlarged pituitary gland (due to thyrotroph hyperplasia, lactotroph hyperplasia, or both) and hyperprolactinemia.

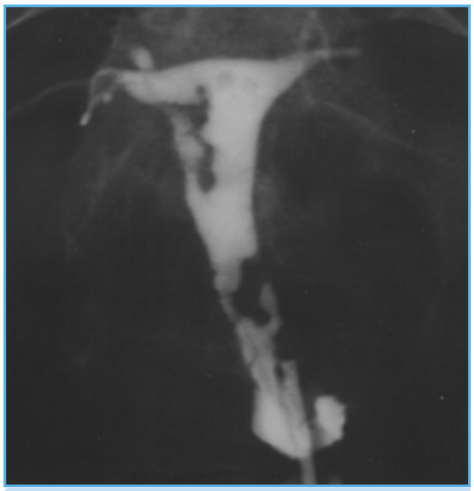

Figure 20-1: Picture of HSG for Asherman's syndrome

Hyperprolactinemia with or without Galactorrhea

Prolactin is a single-chain protein hormone closely related to growth hormone secreted by the lactotroph cells of the pituitary gland.

Physiologic function: During pregnancy, prolactin stimulates growth of the breast, but high estrogen and progesterone secretion prevent milk production. After delivery, estrogen and progesterone levels drop, and prolactin stimulates the secretion of milk by alveolar cells in the breast.

Control of prolactin secretion: in contrast to all other pituitary hormones, the control of prolactin secretion is maintained via tonic hypothalamic suppression by prolactin inhibitory factor "Dopamine".

Dopamine is secreted by hypothalamic neurons and reach the pituitary gland via portal blood where binds to receptors on lactotrophs and inhibits both the synthesis and secretion of prolactin.

Hyperprolactinemia: excessive prolactin secretion could be due to physiologic, pathologic or pharmacologic (drugs induced) causes. In some cases if no cause can be found the condition is described as "Idiopathic hyperprolactinemia"

- **Physiologic causes "physiological hyperprolactinemia":**
  - **Pregnancy:** hyperprolactinemia in pregnancy is the result of increasing serum estradiol concentrations. Prolactin level reaches its peak at the end of the pregnancy. By six weeks after delivery, estradiol secretion has decreased and the basal serum prolactin concentration is usually normal even when the mother is breastfeeding.
  - **Nipple stimulation and breast-feeding:** Nipple stimulation increases serum prolactin concentrations, presumably via a neural pathway. However the magnitude of the increase is directly proportional to the degree of preexisting estrogen induced lactotroph hyperplasia. Therefore after the few weeks or months of delivery suckling induces minimal increases prolactin level.

    In non-lactating women, nipple stimulation or breast examination usually does not increase prolactin secretion.
  - **Stress, intercourse and sleep**: are associated with increase in serum prolactin concentration.

- **Pathological causes:**
  - **Lactotroph adenomas (prolactinomas):** Prolactinomas are benign tumors of the lactotroph cells. It account for 25 to 30% of functioning pituitary tumors. It is the most frequent cause of chronic hyperprolactinemia
  - **Disorders that decrease dopaminergic inhibition of prolactin secretion**: This include any disease in or near the hypothalamus or pituitary that interferes with the secretion of dopamine and/or its delivery to the hypothalamus:
    a) Tumors of the hypothalamus, both benign (eg, craniopharyngiomas) and malignant (eg, metastatic breast carcinoma)
    b) Infiltrative diseases of the hypothalamus (e.g. sarcoidosis)
    c) Section of the hypothalamic-pituitary stalk (e.g. due to head trauma or surgery)
    d) Adenomas of the pituitary other than lactotroph adenomas
- **Pharmacologic causes:** Several groups of drugs can induce hyperprolactinemia through the hypothalamic dopamine system and/or pituitary dopamine receptors (table 20-1).
- **Other systemic diseases**:
  - Hypothyroidism: Hypothyroidism with secondary increase in TRH (thyrotropin-releasing hormone) is associated with hyperprolactinemia. Thus thyroid function should be checked in all cases of hyperprolactinemia. The exact mechanism of hyperprolactinemia in hypothyroidism is not known.
  - Chest wall injury: Chest wall injuries, such as severe burns, increase prolactin secretion, presumably due to a neural mechanism similar to that of suckling.
  - Chronic renal failure:
- **Idiopathic hyperprolactinemia:** In a substantial number of patients no cause can be found. However some patients in this group may have microadenomas that is not visible on imaging studies.

Clinical features:

The triad of clinical presentation of hyperprolactinemia includes symptoms and sings

related to hypogonadism, galactorrhea, and intracranial pressure (mass effects):

- Symptoms of hypogonadism: infertility, oligomenorrhea or amenorrhea, decreased libido, and hypoestrogenemia, which can eventually lead to osteoporosis
- Galactorrhea: may or may not be present. It should also be noted that not all cases of galactorrhea are due to hyperprolactinemia.
- Neurological symptoms caused by mass effects of the pituitary tumor such as headaches, visual filed defects…etc.

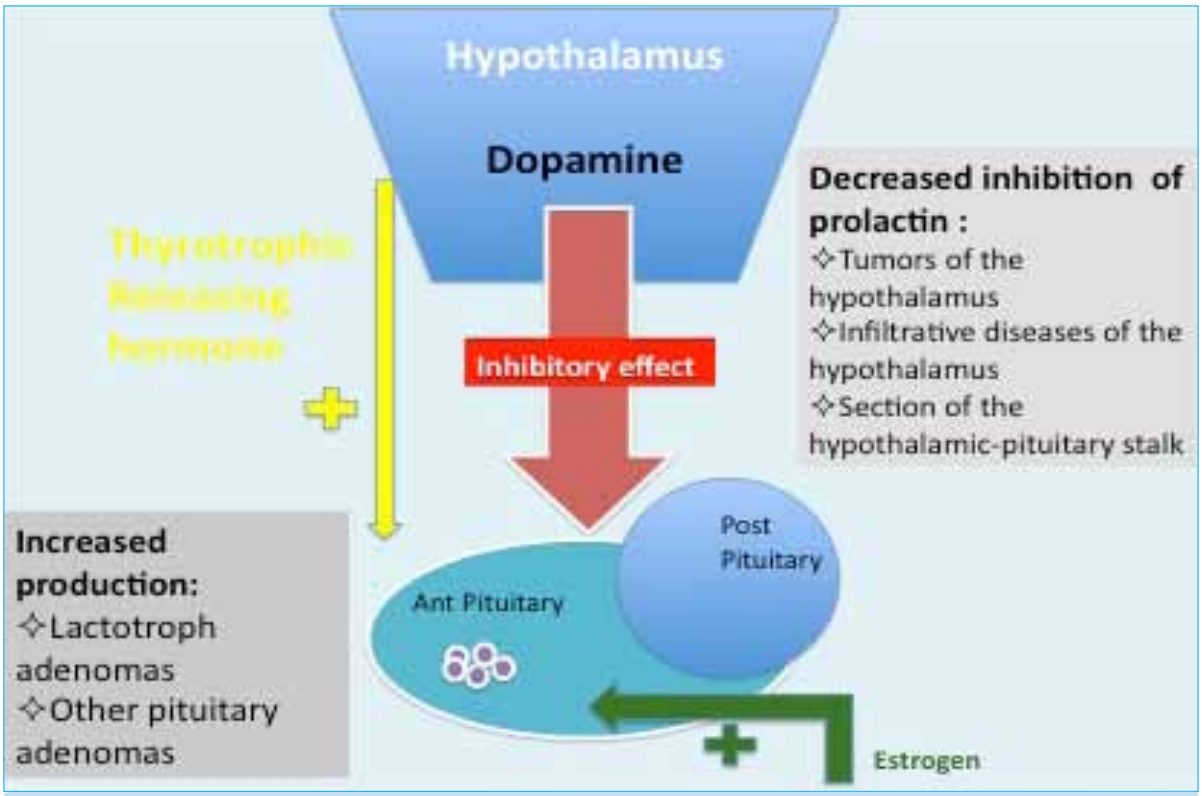

Figure 20-2: diagram showing the mechanism controlling prolactin secretion by lactotroph cells in the anterior pituitary gland. Dopamine is secreted by hypothalamic neurons and reach the pituitary gland via portal blood where binds to receptors on lactotrophs and inhibits both the synthesis and secretion of prolactin.
Hyperprolactinemia could be due to any factors that decrease dopamine secretion or increased production due to pituitary tumors

Diagnostic Evaluation

- Hyperproalctinemia with or without galactorrhea is relatively common findings among women who have menstrual disorders (oligomenorrhea or amenorrhea) and infertility.

- The diagnosis is made when serum prolactin levels are found on two separate occasions (to eliminate the possible effect of stress) to be above the norm established for the laboratory used (usually 20 to 25 ng/mL or 400 to 500 mU/L).
- Once the diagnosis is confirmed a systematic work up that aims to exclude all the known physiological causes (e.g. pregnancy, lactation, stress) and pathological causes (most common prolactinoma and hypothyroidism) begin. A detailed history of systemic disease or intake of medications known to increase prolactin level should be excluded.
- If no cause can be identified imaging of the hypothalamic-pituitary area should be undertaken to exclude adenoma or sellar masses. Magnetic resonance imaging "MRI" with gadolinium enhancement is the gold standard that provides the best visualization of the sellar area (Figure 20-3).
- In cases where other causes of hyperprolactinemia have been excluded and no adenoma can be visualized with MRI, the hyperprolactinemia is referred to as "idiopathic."

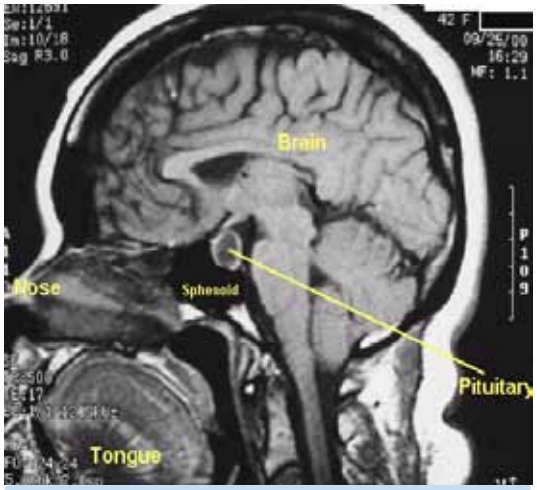

Figure 20-3: MRI showing Macro adenoma

Treatment:

The aim of treatment is to correct gonadal dysfunction and in case of macro-adenoma (prolactinoma > 10 mm in size) to prevent existing or impending neurologic symptoms due to the size of a lactotroph adenoma. The treatment depends on the cause.

Treatment with thyroxin supplements should be commenced if there is evidence of hypothyroidism, and serum prolactin repeated when normal thyroid function is achieved.

- Medical treatment "Dopamine agonists": medical treatment with one of the dopamine agonists (e.g. Cabergoline and Bromocriptine) is the first treatment for patients

Medical treatment for Hyperprolactinemia

Cabergoline: an ergot dopamine agonist administered 1-2 tablet/week.

Bromocriptine: an ergot derivative that has should be given at least twice a day

Adverse effects: nausea, postural hypotension, and mental fogginess.

The side effects can be avoided by starting with a small dose and by giving it with food or at bedtime. A small percentage of patients have side effects even at the lowest doses. In women, nausea can be avoided by intravaginal administration.

with hyperprolactinemia of any cause including lactotroph adenomas of all sizes, because these drugs decrease hyperprolactinemia due to any cause and decrease the size and secretion of most lactotroph adenomas

- Surgical treatment "Trans-sphenoidal resection" of the tumor: is reserved for patients whose adenomas are resistant to dopamine agonists or who cannot tolerate these drugs and for those who are taking a medication, such as an antipsychotic drug, that cannot be discontinued.
- Patient with giant macroadinoma (>3 cm), who wish to become pregnant, even if the adenoma responds to a dopamine agonist. The rationale for this approach is that if such a patient becomes pregnant and discontinues

Approach to the diagnosis of Secondary Amenorrhea:

The approach to diagnosis of secondary amenorrhea begin with exclusion of pregnancy and the uterine cause namely Asherman's syndrome.

All of the remaining causes of amenorrhea are associated with anovulation due to hypothalamic, pituitary, or ovarian disorders.

A focused history and examination should include the following items:

- **History**: The woman should be questioned about any past medical history, risk factors, or symptoms that might suggest any of the major causes of secondary amenorrhea or oligomenorrhea:
  - Recent stress; change in weight, diet or exercise habits; or illness.
  - Drugs that might cause or be associated with amenorrhea (e.g. recent initiation or discontinuation of an oral contraceptive, or antipsychotic drug increasing serum prolactin)
  - Systemic illness that itself can cause hypothalamic amenorrhea.
  - Development of new acne, hirsutism,
  - Symptoms of other hypothalamic-pituitary disease, including headaches, visual field defects, fatigue, or polyuria and polydipsia (suggestive of Sheehan's syndrome).
  - History of obstetrical catastrophe, severe bleeding
  - Symptoms of estrogen deficiency: hot flashes, vaginal dryness, and poor sleep, or decreased libido
  - Presence of galactorrhea

Dilatation and curettage, or endometritis suggestive endometrial adhesions (Asherman›s (syndrome

- **Physical examination**:
  - Measurements of height and weight and body mass index
  - Examination for signs of hyperandrogenism e.g. hirsutism, acne.
  - Striae, acanthosis nigricans , vitiligo, and easy bruisability (Cushing syndrome and Insulin resistance)
  - Breasts examination for galactorrhea
  - Vulvovaginal exam should look for signs of estrogen deficiency

- BMI > 30 kg/m2 in approximately 50 % of women with PCOS.

- Women with a BMI < 18.5 kg/m2 may have functional hypothalamic amenorrhea due to an eating disorder, strenuous exercise, or systemic illness.

Basic laboratory testing:

- Serum hCG to rule out pregnancy
- Measurements of serum prolactin, FSH, and TSH to test for hyperprolactinemia, ovarian failure, and thyroid disease respectively
- If there is clinical evidence of hyperandrogenism, serum total testosterone should be measured.

Further tests laboratory tests for evaluation depend upon the results of the initial evalua-.(tion (see blue box

- If intrauterine adhesion "Asherman's syndrome" is suspected as in patients with normal serum prolactin and FSH concentrations with history of uterine instrumentation preceding amenorrhea a progesterone withdrawal test can be performed. A positive test will also indicate adequate endogenous estrogen status
- Measurement of 17-hydroxyprogesterone to rule out nonclassic 21-hydroxylase deficiency, and dehydroepiandrosterone sulfate (DHEA-S) to look for an adrenal source of androgens.
- A karyotype should be considered in cases with high gonadotropin levels.
- MRI of the sella region is indicated in all women without a clear explanation for hypogonadotropic hypogonadism and in most women who have normal laboratory findings and symptoms such as visual field defects, headaches, or other signs of hypothalamic-pituitary dysfunction.

Treatment of secondary amenorrhea:

Treatment of women with secondary amenorrhea aims to:

- Correcting the underlying pathology: e.g. treatment of prolactinoma, ovarian or adrenal tumor. Also release of adhesions in cases with Asherman's syndrome. This is done by hysteroscopic approach.
- Helping the woman to achieve fertility if possible.
- Medical treatment to prevent complications of the disease process (eg, estrogen replacement to prevent osteoporosis).

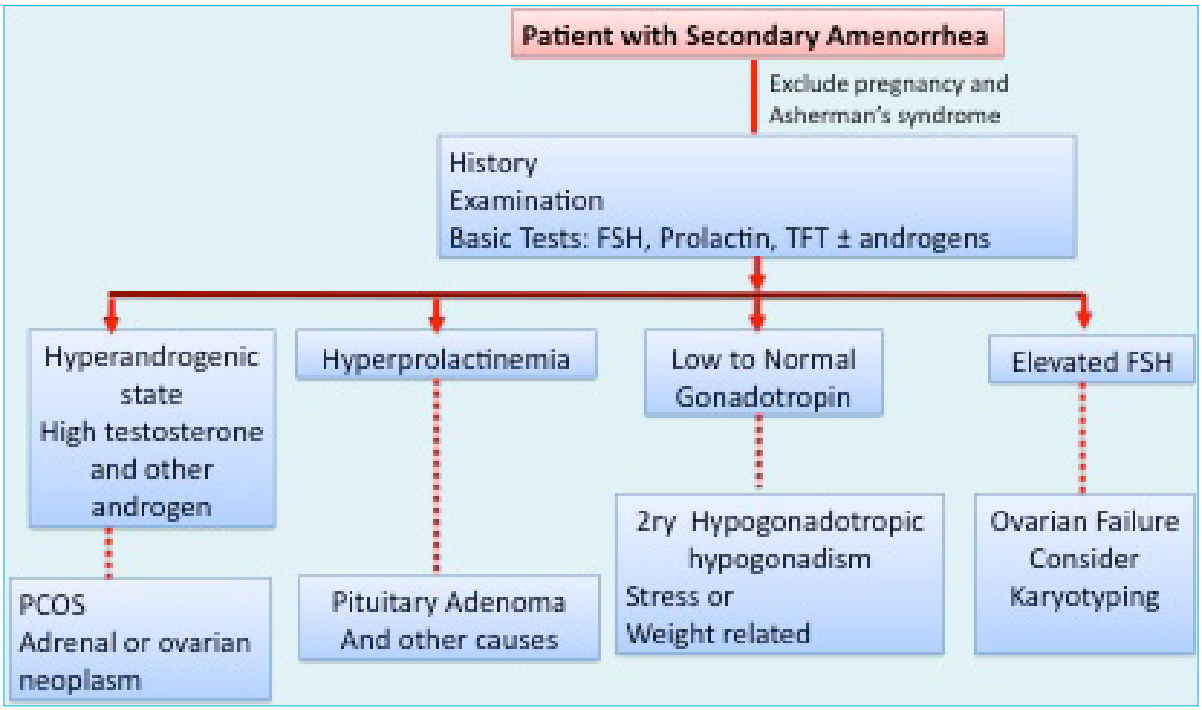

Figure 20-4: Diagram showing approach to the patient with secondary amenorrhea. See text for focused history, examination and basic tests. More specialized tests are indicated depending on the results of primary evaluation. Tumors are typically associated with the rapid onset of virilizing symptoms

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Chapter 21

Hyperandrogenism

Hirsutism is not uncommon complaint among women of the reproductive age. It usually begins around the pubertal age. The most common causes are idiopathic or PCOS. However, gynecologists should be aware of the other rare but serious causes of hyperandorgenism namely ovarian and adrenal neoplasms. This should be suspected in severe and progressive cases of hirsutism or in cases of delayed onset of hyperandrogenism.

By the end of this chapter you should be able to:

- **Define** hirsutism and virilism
- **Describe** the factors that affect its frequency among different population
- **Describe** the pathogenesis of hirsutism and realize its inconsistent relation to serum androgen level
- **List** the causes of hirsutism: PCOS, Idiopathic, PSOS, Androgen producing tumors in the ovary or adrenal glands and drugs.
- **Describe** the Ferriman-Gallwey score for evaluation of hirsutism.
- **Describe** the approach to evaluation and management of women presenting with hirsutism.
- **Describe** the pathogenesis of PCOS: Pituitary disorder, primary ovarian or adrenal steroidogenesis dysfunction, and the role of insulin resistance.
- **Describe** the spectrum of clinical manifestation of PCOS
- **Realize** the long term consequences of PCOS
- **Describe** the option of management of PCOS and the indication of each option

Definitions:

Hirsutism: Refers to excessive male-pattern hair growth or excessive quantity of androgen-dependent terminal hair growth (the lip, chin, chest, abdomen, and back, areas).

Hirsutism may be the initial sign of an underlying androgen disorder. Other cutaneous disorders that may be present include acne and male-pattern balding (androgenic alopecia).

Virilization: refers to more advanced state of higher androgen levels that causes not only hirsutism, but also additional signs and symptoms such as deepening of the voice, breast atrophy, increased muscle bulk, and clitoromegaly.

Hirsutism should be differentiated from other conditions of excessive hair growth that is not related to androgen excess which include:

– Androgen-independent hair: which is the soft vellus unpigmented hair that covers the entire body. In infants, this hair is called lanugo.

Hypertrichosis: refers to diffusely increased total body hair growth. This is a rare condition that is usually caused by a drug, and with some systemic illnesses.

Hypertrichosis

Drugs: e.g. phenytoin, penicillamine, diazoxide, minoxidil, and cyclosporine.
Systemic illnesses: e.g. hypothyroidism, anorexia nervosa, malnutrition, porphyria.

Pathophysiology of androgen dependant hair growth:

The role of androgen in hair growth: Androgens are necessary for terminal hair and sebaceous gland development and mediate differentiation of pilosebaceous units (PSU's) (The pilosebaceous unit consists of the hair shaft, the hair follicle, the sebaceous gland which makes sebum, and the erector pili muscle which causes the hair to stand up when it contracts) into either a terminal hair follicle (the long, coarse pigmented hair) or a sebaceous gland with a vellus hair (fine, soft, and not pigmented) (Figure 21-1).

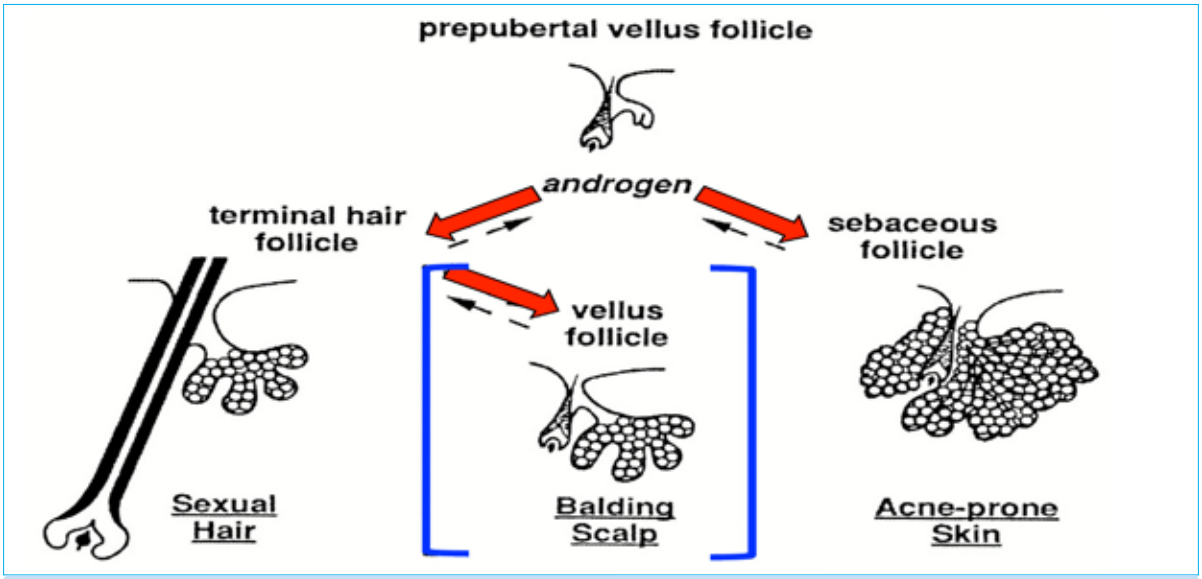

Figure 21-1: Role of androgen in the development of the pilosebaceous unit.
Red Arrows: indicate effects of androgens;
Dotted lines: indicate effects of antiandrogens.
In balding scalp (Blue bracketed area), terminal hairs not previously dependent on androgen regress to vellus hairs under the influence of androgen
from R. L. Rosenfield and D. Deplewski: Am J Med 98:80S–88S, 1995 (1A)

However it should be noted that:

- The hormonal regulation of hair growth cycle depends on the body site. E.g. androgen excess in women leads to increased hair growth in androgen sensitive sites, and hair loss in the scalp region.

There is limited correlation between the quantity of hair growth and androgen level because hirsutism is a result of the interaction between circulating serum androgens and the sensitivity of the hair follicle to androgens.

- **In hirsutism several different androgens may be secreted in excess.**
    - Excess testosterone is usually of ovarian origin (although in normal women both the adrenal and ovaries contribute equally to testosterone production).
    - Dehydroepiandrosterone sulfate (DHEA-S) excess is of adrenal origin
    - Androstenedione excess can be of either adrenal or ovarian origin

Although DHEA and DHEA-S are general markers of adrenal androgen production, they have little intrinsic androgenic activity. Small amounts are converted to androstenedione and then to testosterone and to estrogen in both the adrenal glands and peripheral tissues, including hair follicles and external genitalia.

Causes of hirsutism:

Hirsutism affects between 5 and 10 per cent of women of reproductive age. However the incidence of hirsutism varies depending on racial, and genetic factors.

Most of cases or hirsutism are due to either polycystic ovary syndrome or idiopathic causes. However other rare causes should be considered severe hyperandrogenism and or progressive cases of hirsutism (Table 21-1).

- **Polycystic ovary syndrome**: The polycystic ovary syndrome (PCOS) is the most common cause of androgen excess in women. The syndrome is characterized by menstrual irregularity, evidence of hyperandrogenism whether clinical (hirsutism, acne, or male pattern balding) or biochemical (elevated serum androgen concentrations). In PCOS the androgen excess usually becomes evident about the time of puberty or soon thereafter, because androgen production is increased by both puberty (increased ovarian steroid production) and adrenarche (increased adrenal androgen production). The diagnostic criteria, clinical manifestations, and treatment of PCOS are discussed below.
- **Idiopathic hirsutism**: The diagnosis of idiopathic hirsutism is made in women with hirsutism who have normal serum androgen concentrations, no menstrual irregularity, and no identifiable cause of their hirsutism. The condition may be a mild degree of PCOS.

- **Congenital adrenal hyperplasia "CAH"**: late-onset (also called nonclassic) forms CAH. Affected women present peripubertally with hirsutism and sometimes menstrual irregularity or primary amenorrhea; they have no manifestations of cortisol deficiency. It is nearly always due to 21-hydroxylase (P450c21) deficiency. This leads to increased serum level of both 17-hydroxyprogesterone (the substrate for 21-hydroxylase and an androgen precursor) and androstenedione.
- **Ovarian tumors:** Hirsutism caused by an androgen-secreting tumor is most likely to occur later in life and progress more rapidly than when the cause is the polycystic ovary syndrome. Histologically they are Sertoli-Leydig cell tumors (androblastoma, arrhenoblastoma), granulosa-theca cell (stromal cell) tumors, and hilus-cell tumors. Many but not all of these tumors can be identified by transvaginal ultrasonography.

> Most of the women have serum testosterone concentrations greater than 150 to 200 ng/dL (5.2 to 6.9 nmol/L). (The upper limit of normal for serum testosterone in women varies from 60 to 80 ng/dL [2.1 to 2.8 nmol/L] in most laboratories.)

- **Adrenal tumors:** Adrenal tumors are a rare cause of androgen excess. A few are adrenal adenomas that secrete mostly testosterone, but most are carcinomas that secrete androgen and cortisol. This manifest clinically with androgen excess and Cushings syndrome.
- **Hyperthecosis**: Hyperthecosis is a nonmalignant ovarian disorder characterized by increased production of testosterone by luteinized thecal cells in the stroma, leading to increased serum testosterone concentrations. It is still unclear if hyperthecosis is a distinct disorder or is part of the spectrum of the polycystic ovary syndrome.
- **Severe insulin resistance syndromes**: Women who have one of the syndromes of severe insulin resistance and marked hyperinsulinemia. The marked hyperinsulinemia act via the theca-cell receptors for insulin and insulin-like growth factor-1 leading to excessive ovarian androgen. Insulin also decreases serum sex hormone-binding globulin concentrations, thereby increasing the fraction of free serum testosterone.

> **Insulin Resistance Syndrome**
>
> Include genetic defects in the insulin receptor, the production of antibodies to the insulin receptor, and syndromes of lipoatrophy and lipodystrophy.

Drugs: e.g. Androgen therapy (testosterone or DHEA), Danazol, a drug commonly used in the past for the treatment of endometriosis is associated with hirsutism.

- **Hyperprolactinemia:** Some women with hirsutism have mild hyperprolactinemia.

Most probably those women have some degree of PCOS the hirsutism in such cases is probably due more to the ovarian hyperandrogenism characteristic of the polycystic ovarian syndrome.

Common
Polycystic ovary syndrome
Idiopathic hirsutism
Uncommon
Drugs
Congenital adrenal hyperplasia (most often 21-hydroxylase deficiency)
Hyperthecosis
Ovarian tumors - Sertoli-Leydig cell tumors - Granulosa-theca cell tumors - Hilus-cell tumors
Adrenal tumors
Severe insulin resistance syndromes
Hyperprolactinemia

Table 21-1: causes of hirsutism

Evaluation of patient with hirsutism:

The aims of clinical evaluation (history, examination and investigations) are to:

- Evaluate severity of androgen excess.
- Define the specific cause. In particular to rule out rare and more serious causes of hirsutism (ovarian or adrenal tumors). This should be suspected in the following cases:
  - Abrupt onset, short duration (typically less than 1 year), or progressive worsening of hirsutism
  - Onset in the third decade of life or later, rather than near puberty
  - Symptoms or signs of virilization, including frontal balding, acne, clitoromegaly, increased muscle mass, or deepening of voice.

History: The history should include the following information:

- Menstrual history: age at menarche, regularity of menstrual cycles, and presence of symptoms of ovulation or of premenstrual symptoms (ovulatory pain, premenstrual

discomfort, breast tenderness).

- Obstetric history: number of pregnancies if any.
- History of oral contraceptive use: why, when, for how long, which pills, and response,
- Time of onset and course of symptoms of hirsutism: The age at onset, the rate of progression (e.g. change in frequency of shaving or hair removal), and any change with any treatment or with fluctuations in weight should be determined.

It should be noted that an individual woman's perception of hirsutism may vary not only depending upon her ethnic background but also upon her interpretation of normal, which may be influenced by popular images of hairless female beauty.

- Weight history: Obese women have increased androgen production and menstrual irregularity, especially those with PCOS.
- Medication history: Drugs that cause hirsutism or have other androgenic effects include Danazol.
- Family history: Hirsutism, acne, menstrual irregularity, infertility, and obesity are potential indicators of a familial tendency towards PCOS.

Physical examination: Physical examination aims specifically for the following signs:

- To differentiate between hirsutism and hypertrichosis:
- Evaluation of the severity of hyperandrogenism "the Ferriman-Gallwey score": This score was developed to objectively grade hair growth. Using this method, nine androgen-sensitive sites are graded from 0 to 4 (Figure 21-2). Approximately 95 percent of women will have a score below 8.

Hair growth varies between racial/ethnic groups. E.g. Asian women are less likely to manifest hirsutism resulting from androgen excess than are Caucasian or African-American women. A Ferriman-Gallwey score >2 is considered to be abnormal in Asian women.

Scores above 8 is abnormal and suggest an excess of androgen-mediated hair growth that should be confirmed by hormonal evaluation. A score between 3-8 include variable proportion of normal individuals and patients with excessive androgen production.

Draw back of this scoring system in addition to racial and ethnic variation (the score was developed on Caucasian women) are the poor interobserver reproducibility and that most women are currently using cosmetic measures by the time they see their physician.

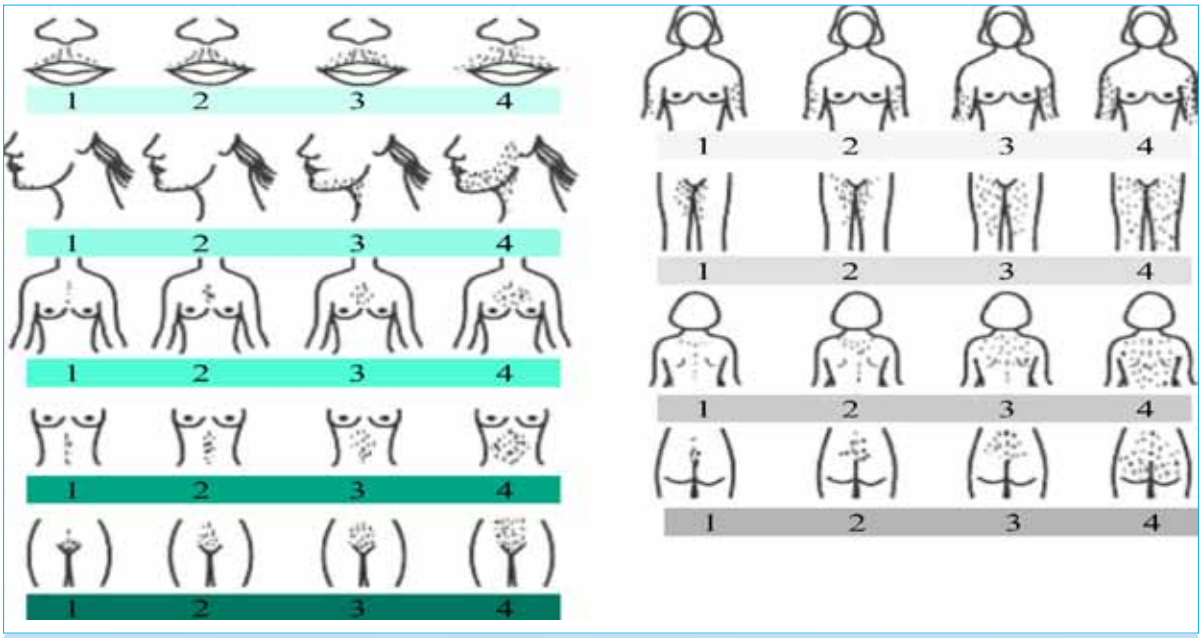

Figure 21-2: Modified Ferriman–Gallwey (F–G) hirsutism scoring system. Each of the nine body areas is rated from zero (absence of terminal hairs) to four (extensive terminal hair growth), and the numbers in each area are added for a total score
Reference:(Yildiz BO. Diagnosis of hyperandrogenism: clinical criteria. Best Pract Res Clin Endocrinol Metab 2006; 20: 167-76.

- Body habitus: Height, weight, and a calculation of body mass index (BMI) should be obtained. Features suggestive of Cushing syndrome (truncal obesity, a buffalo hump, and supraclavicular fat) should be noted.
- Skin: Acne, seborrhea, temporal balding (which are additional signs of androgen excess), acanthosis nigricans, striae, thin skin, or bruising should be sought. The last three findings suggest the possible presence of Cushing's syndrome, whereas acanthosis nigricans may suggest insulin resistance.
- Signs of virilisation: In addition to acne, deepening of the voice, frontal (or crown) balding, increased muscle mass, and clitoromegaly indicate the presence of moderate androgen excess.
- Galactorrhea: The presence of any breast discharge, spontaneous or expressible, is suggestive of hyperprolactinemia and warrants measurement of serum prolactin even if the woman's menstrual cycles are regular.
- Abdominal and pelvic examination: These examinations may reveal mass lesions that could indicate the presence of an androgen-secreting tumor.

Investigations and laboratory testing:

Several laboratory tests including invasive tests can be performed in patients with features

of hyperandrogenism. However not all tests are for patients with hirsutism. In mild cases the most likely cause of hirsutism is either idiopathic or mild degree of PCOS and no further tests are necessary. However laboratory testing are indicated for:

- Women with moderate or severe hirsutism
- Hirsutism of any degree if it is sudden in onset and rapidly progressive, or associated with irregular menses, obesity, or evidence of virilisation (clitoromegaly)

The principal circulating steroids involved in the etiology of hirsutism are androstenedione (AD), dehydroepiandrosterone (DHEA), and its sulfated form (DHEAS), and testosterone (T).

- Normally the ovaries and adrenal glands contribute approximately equally to testosterone production.
- Approximately half of the total testosterone originates from direct glandular secretion, while the remaining half is derived from the peripheral conversion of androstenedione and dehydroepiandrosterone. Conversion occurs in the liver, adipose tissue, and skin.

▸ **Serum androgens**:

- Testosterone: The serum testosterone concentration provides the best overall estimate of androgen production in hirsute women. Serum total testosterone values below 150 ng/dL (5.2 nmol/L) exclude ovarian or adrenal tumors.

  However if hirsutism is progressive in spite of therapy this is an indication for measurement of total and free testosterone.

- DHEA-S: should be measured if there is suspicion that an adrenal androgen-secreting tumor might be present; concentrations >700 mcg/dL (13.6 μmol/L) raise suspicion for an adrenal androgen-secreting tumor.

▸ Serum prolactin: Serum prolactin should be measured in women with hirsutism and irregular menstrual cycles to rule out hyperprolactinemia.

▸ Serum luteinizing hormone (LH): Women with PCOS tend to have elevated serum LH concentrations and normal or low serum FSH concentrations.

▸ Pelvic ultrasonography: to look for polycystic ovary morphology and to screen for ovarian androgen-secreting tumors. Suspicious findings include large cysts, solid masses, and complex cysts should be followed up and/or treated accordingly.

  However, ultrasonogrpraphy has limited sensitivity and specificity for the diagnosis of ovarian tumors in hyperandrogenic women. This because small hilus-cell tumors of the ovary that produce large amounts of testosterone may not be seen by ultrasonography or even at the time of surgery. In addition, other tumors, including androgen-secreting sex cord stromal tumors, are often not visualized. Therefore

failure to identify a tumor does not rule out its presence, as these tumors may be very small.

- 17-OH progesterone: is indicated if (late-onset) congenital adrenal hyperplasia is suspected. This is usually in cases of development of symptoms and signs of androgen excess in girls at the time of puberty or soon thereafter, in women with a family history, and in women from high-risk ethnic groups.
- Testing for Cushing's syndrome: Screening for this disorder is indicated in hirsute women who have symptoms and signs of cortisol excess, such as obesity, hypertension, striae, that suggest the presence of Cushing's syndrome. This can be done by measuring 24-hour urinary excretion of cortisol (and creatinine) or by performing an overnight dexamethasone suppression test.
- Abdominal CT or MRI: Adrenal imaging is indicated to look for an adrenal mass if the woman has a markedly elevated serum DHEA-S concentration or other evidence of excess adrenal steroid production.
- Surgical exploration: One of these procedures should be considered in a hirsute woman who has menstrual abnormalities, a serum testosterone concentration above 200 ng/dL (6.9 nmol/L), no evidence of an adrenal tumor, and a negative pelvic ultrasound. Such a patient may have a small ovarian tumor (especially a hilus-cell tumor) that is too small to be detected by pelvic ultrasonography.
- Ovarian and adrenal vein sampling: Organ-specific venous sampling may be used to localize the site of excessive testosterone production in a woman in whom vaginal ultrasonography and abdominal imaging are normal, in anticipation of surgical exploration. However, the need for this procedure is very limited, and its value is highly dependent upon the skill of the radiologist.

Treatment of Hirsutism:

In the absence of neoplasms whether adrenal or ovarian, the treatment of hirsutism depends on:

- The patient wishes and the degree of her concern with hirsutism.
- The severity of hirsutism: In some cases, hirsutism is mild and requires only reassurance and cosmetic therapy, while in others, it causes significant psychological distress and requires more extensive intervention.

The options of treatment include:

- **Combined estrogen-progestin contraceptive "OC":** is the treatment of choice in

majority of cases. An OC that contains a progestin with low androgenicity or an antiandrogen effect is chosen e.g. cyproterone acetate or drospirenone).

The mechanisms by which OCs reduces serum androgens and therefore hirsutism include the following:

- Inhibition of luteinizing hormone (LH) secretion and therefore LH-dependent ovarian androgen production
- Increased hepatic synthesis of sex hormone-binding globulin (SHBG) by estrogen, resulting in decreased concentrations of serum free testosterone and other SHBG-bound androgens
- Inhibition of adrenal androgen secretion.

Principles of drug therapy

- Duration of therapy: because the approximate half life of a hair follicle is six months, therefore to consider a change in dose or drug, should not be considered before such period.
- Pharmacological therapy: is usually continued indefinitely, as the underlying condition is typically lifelong and hirsutism recurs when treatment is discontinued.
- When pregnancy is desired, all pharmacological treatments for hirsutism must be discontinued particularly antiandrogens in particular because of potential adverse effects on male sexual development.

» **Antiandrogen therapy**:

Available antiandrogens include the following:

- Spironolactone: an aldosterone and androgen receptor antagonist that is structurally similar to progestins. It competes with dihydrotestosterone (DHT) for binding to the androgen receptor, and inhibits enzymes involved in androgen biosynthesis.
- Cyproterone acetate (CPA): a 17-hydroxyprogesterone derivative competes with DHT for binding to the androgen receptor and reduces serum LH and ovarian androgen concentrations.
- Flutamide: is a nonsteroidal androgen receptor antagonist. It is used primarily in the management of prostate cancer, but has been used off-label for managing hirsutism.

» **Glucocorticoids:** Exogenous glucocorticoids, which suppress hypothalamic corticotropin-releasing hormone (CRH) production and, therefore, pituitary corticotropin (ACTH) and adrenal androgen production, are used long-term to manage hirsutism and maintain ovulatory cycles in women with classic 21-hydroxylase (CYP21A2) deficiency.

- **Topical therapy**: Vaniqa (eflornithine hydrochloride cream 13.9%) is a topical drug that is available for the treatment of unwanted facial hair in women. It is an inhibitor of hair growth.
- **Cosmetic and mechanical treatments:**
  - Cosmetic methods: Physical methods of removing hair or making it less visible (shaving, plucking, waxing, bleaching) can be effective, and their use is reasonable either alone or as a supplement to drug therapy.
  - Permanent hair reduction: Direct or mechanical methods of hair removal, including electrolysis and photoepilation (laser and intense pulsed light), are also referred to as "permanent" hair reduction techniques. However, women with underlying hyperandrogenemia are likely to experience hair regrowth.

Polycystic Ovarian Syndrome

Definition:

Polycystic ovary syndrome was originally described in 1935 by Stein and Leventhal as a syndrome consisting of amenorrhea, hirsutism, and obesity in association with enlarged polycystic ovaries.

Since then and for many years the classic definition of PCOS includes women who are anovulatory, have irregular periods and hyperandrogenism (as determined by signs such as hirsutism or elevated blood levels of androgens: testosterone or DHEA-S). The definition did not require the findings on ultrasound (US) of characteristic polycystic ovaries.

More recently however the diagnostic criteria have been modified. The current criteria include ultrasound characteristic imaging of the polycystic ovarian changes (Table 21-2).

National Institute of Health criteria (1990)
Evidence of anovulation or oligo-ovulation
Evidence of clinical or biochemical hyperandrogenism (either)
o Clinical: hirsutism, acne, or male pattern balding
o Biochemical: high serum androgen concentration
Rotterdam criteria by the European Society of Human Reproduction and Embryology/ American Society of Reproductive Medicine (2003)
Two out of three following findings are required for diagnosis:
Evidence of anovulation or oligo-ovulation
Evidence of clinical or biochemical hyperandrogenism (either)
o Clinical: hirsutism, acne, or male pattern balding
o Biochemical: high serum androgen concentration
A polycystic ovary (by ultrasound)
Androgen Excess and PCOS Society criteria (2006)
Evidence of ovarian dysfunction (either)
o Evidence of anovulation or oligo-ovulation
o A polycystic ovary (by ultrasound)
Evidence of clinical or biochemical hyperandrogenism (either)
o Clinical: hirsutism, acne, or male pattern balding
o Biochemical: high serum androgen concentration

Table 21-2: Diagnostic criteria for polycystic ovary syndrome. All criteria involve exclusion of other causes of hyperandrogenism and menstrual irregularity.

Pathogenesis:

The cause of PCO remains area for research and theories. There is however genetic predisposition for development of PCOD as evident from high concordance rate in twins and from studies that shows either epigenetic or dominant inheritance patterns. Nonetheless, a consistent hereditary pattern has not been identified.

The disease tend to evolve in adolescent age however some cases may develop later in life even after the woman already had given birth to one or two children. In both cases environmental factors such as obesity and stress seems to play important role in the evolution of the disease.

The polycystic changes in the ovaries are due to changes in the intraovarian milieu characterized by excess intraovarian androgen, which is responsible for both anovulation and the formation of multiple ovarian "cysts" through stimulated excessive growth of small follicles and hindrance of the maturation of the dominant follicle (see normal menstrual cycle above).

Excess androgen also causes thecal and ovarian stromal hyperplasia that result in the larger ovarian volume.

The cause(s) of the excess intraovarian androgen is not exactly known. However endocrinologic dysfunction in PCOS suggest Characteristic endocrinologic features including abnormal gonadotropin secretion, adrenal dysfunction and insulin resistance and other systemic metabolic disorders.

- **Disorder of pituitary gonadotropin secretion**: In PSOCS there is either increased gonadotropin-releasing hormone (GnRH) pulse amplitude or increased pituitary sensitivity to GnRH. Furthermore the pituitary gonadotropin is less sensitive to suppression by sex steroids as compared with controls.

  These abnormalities result in tonically elevated levels of luteinizing hormone (LH). The high level of LH enhances androgen production and secretion by ovarian theca cells.

  It should be noted that because FSH levels in women with PCOS are normal or low, an elevated LH–FSH ratio has been used to diagnose PCOS. Now the LH or the LH–FSH ratio should not be part of the diagnostic evaluation of PCOS.

- **A disorder of ovarian and/or adrenal steroidogenesis:** In PCOS there is dysregulation in the rate limiting enzymes (17-hydroxylase and 17,20 lyase activity) in androgen production either in the ovary (Functional ovarian hyperandrogenism (FOH) or in the adrenal Functional adrenal hyperandrogenism (FAH) or in both.

This dysregulation typically leads to patterns of overactive steroidogenesis with increased circulating levels of androgens production (Table 21-3)

Androgen	Ovary	Adrenal	Peripheral conversion
DHEA-S	<5	>95	0
Androstenedione (A)	60	35	5 (From DHES-S)
Testosterone (T)	60	5	35 (From A)
Dihydrotestosterone (DHT)	0	0	100 (From A and T)
3-Androstendiol Glucuronide	0	0	100 (From DHT)

Table 21-3: Sources of serum androgens in women with PCOS. Values are percent of total production at the different sites.
DHEA-S (Dihydroepiandrostenedione sulphate) is produced primarily from the adrenal while testosterone and androstenedione are primarily ovarian products.
The remaining androgens are peripheral tissue conversion

However despite high level of androgen it seems that the clinical presentation with hirsutism depends on whether those androgens are converted peripherally by 5αreductase to the more potent androgen DHT, as reflected by increased circulating levels of 3αdiol-G.

- **Insulin resistance**: insulin resistance occurs in most women with PCOS even those of normal weight. Insulin and insulin-like growth factor-I (IGF-I) enhance ovarian androgen production by potentiating the stimulatory action of LH on ovarian androstenedione and testosterone secretion.

  It is not clear why women with PCOS have insulin resistance. The insulin resistance in PCOS is greater than in age-matched and weight-matched controls and enhanced in obese women. Insulin resistance in PCOS is disproportionate to that expected from the body mass index.

- **Increased levels of biologically active estradiol (non-SHBG-bound fraction)**, although total-circulating levels of estradiol is not increased. This increase in amount of non-SHBG-bound estradiol is caused by:

  - A decrease in SHBG levels, which is brought about by the increased levels

of androgens and obesity with high insulin levels present in many of these women.

- Increased peripheral (adipose) conversion of androgen to estrogen (which is more enhanced in obese women).

The tonically increased levels of biologically active estradiol stimulate increased GnRH pulsatility and produce tonically elevated LH levels and anovulation.

While the lowered SHBG level increases the biologically active fractions of the elevated androgens in the circulation.

This relative hyperestrogenism (elevated estrone and non-SHBG-bound estradiol), which is unopposed by progesterone because of anovulation, increases the risk of endometrial hypoplasia.

- **Other organs contributing to dysregulated steroidogenesis:** There is evidence that hepatic, skin, and adipose metabolism of steroid precursors contribute to the androgen excess of PCOS.

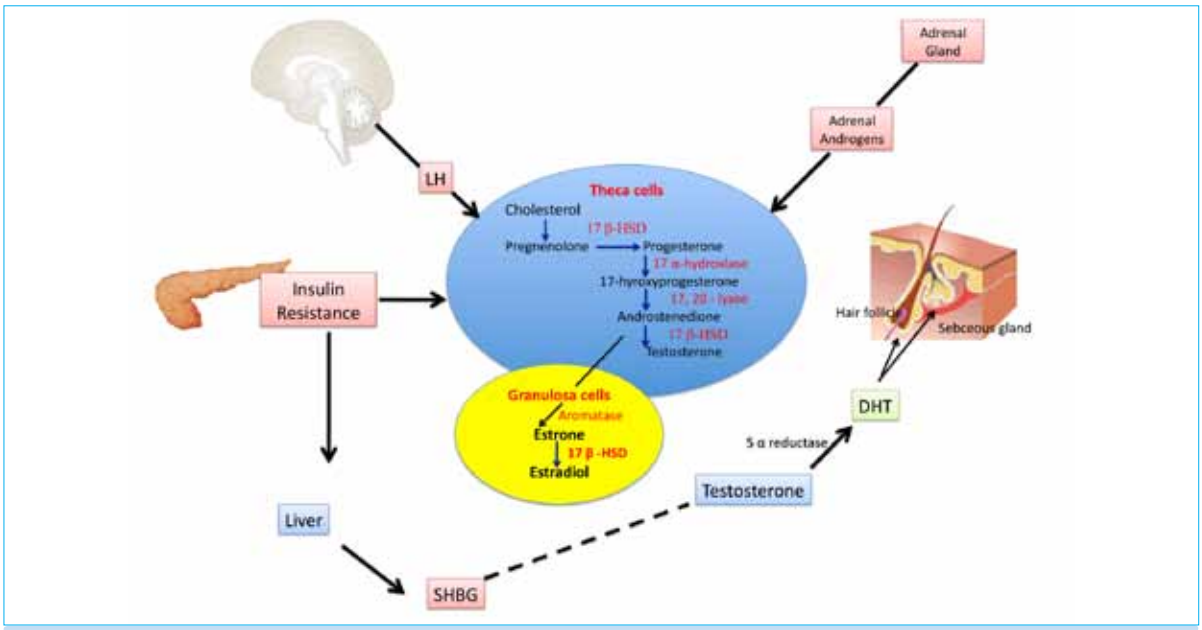

Figure 21-3: diagram shows the major hormonal and metabolic disorders in the pathogenesis of PCOS.
Disorder of Gonadotropins production result in tonic increase in LH secretion, which stimulate the Theca cells, and subsequent increase in ovarian androgen production.
Primary Functional ovarian hyperandrogenism (FOH): due to dysregulation of the rate limiting enzymes (17-hydroxylase and 17,20 lyase activity) with the result of excess androgen production.
Primary Functional Adrenal hyperandrogenism (FOH): due to dysregulation of the rate limiting enzymes (17-hydroxylase and 17,20 lyase activity) with the result of excess adrenal androgen production. This contribute to the general androgenic status and increase ovarian androgen environment
Insulin resistance "hyperinsulinemia": excess insulin and insulin growth factors enhance ovarian androgen production by potentiating the stimulatory action of LH on ovarian androstenedione and testosterone secretion. It also inhibit liver production of SHBG. This result in excess free estradiol which perpetuate pituitary LH secretion and induce endometrial hyperplasia. High serum level of estrogen also comes from conversion of androgen to estrone in the peripheral adipose tissue.
SHBG: sex hormone binding globulin, 17-β HSD=17-hydroxylase, DHT =Dihydrotestosterone.

Clinical Presentation and diagnosis of PCOS:

PCOS is an extremely common disorder, affects approximately 3% to 7% of the reproductive-age population.

The diagnosis of PCOS is confirmed from the combination of menstrual irregularity (oligo-ovulation or anovulation), androgen excess (clinically or with biochemical confirmation), and typical ovarian cysts on ultrasound. Being a syndrome rather than a specific disease its clinical manifestation can be very heterogeneous in term of the presenting symptom and its severity.

- Menstrual irregularity: The menstrual irregularity typically begins in the peripubertal period, and menarche may be delayed. It usually takes the form of oligomenorrhea (fewer than nine menstrual periods in a year) or amenorrhea (no menstrual periods for three or more consecutive months). In addition to menstrual irregularity, cycles are usually anovulatory (infertility), resulting in heavy bleeding at times, and an increased risk of endometrial hyperplasia.
- Hyperandrogenism: Most women with PCOS have both clinical and biochemical evidence of hyperandrogenism, but only one or the other is required to make the diagnosis. Clinically it presents as hirsutism, acne, and male-pattern hair loss.
- Pelvic ultrasound: The more recent diagnostic criteria (the Rotterdam criteria) include polycystic ovaries on ultrasound (enlarged ovaries (>10 cm3) and/ or the presence of 10 or more peripherally oriented cystic structures (2 to 8 mm) surrounding a dense stroma) as one of the diagnostic criteria (Figure 21-4). It should be noted that sonographic appearance of polycystic appearance alone is non-specific, since it can also be seen in women with idiopathic hirsutism, other androgen excess disorders, and even normal women.

Mood disorders: PCOS can be associated with mood disorders (depression and anxiety), impaired quality of life, and eating disorders (binge eating), even when compared to women with the same BMI.

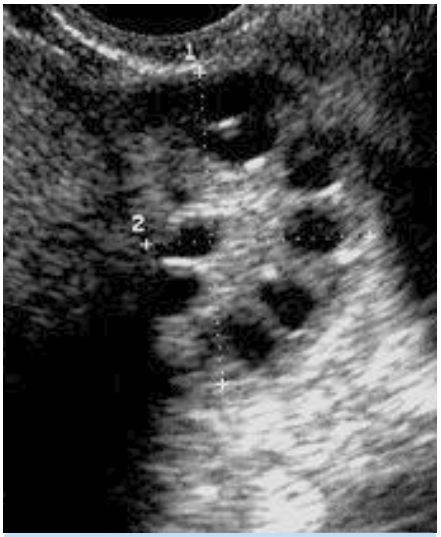

Figure 21-4: Ultrasound picture of PCO showing multiple ovarian cysts (ring of black circles on right) that are suggestive, although not diagnostic, of polycystic ovary syndrome.

Signs:

There are no specific diagnostic signs for PCOS. However in typical cases patient is usually overweight or obese, showing mild to moderate signs of hyperandrogenism (acne, hirsutism).

Acanthosis nigricans: Acanthosis nigricans is a skin lesion characterized by brown, velvety, hyperkeratotic plaques. The lesions are usually found on the back of the neck, the axilla, the groin, and over the elbows. Acanthosis nigricans is usually associated with insulin resistance.

Figure 21-5: Acanthosis nigricans in the axillary area

Investigations:

Minimal laboratory testing should include measurements of serum prolactin, thyrotropin, and FSH to rule out hyperprolactinemia, thyroid disease, and ovarian failure respectively.

Tests for Metabolic abnormalities: in PCOS the metabolic abnormalities namely Dyslipaedemia and impaired glucose tolerance varies in severity. Screening for metabolic abnormalities particularly for glucose tolerance is recommended Professional organization including the American College of Obstetricians and Gynecologists (ACOG).

- Screening for glucose intolerance: by two hours glucose tolerance test. Patients with normal glucose tolerance should be rescreened at least once every two years, or more frequently if additional risk factors are identified
- Dyslipidemia: Lipid abnormalities, in particular low serum HDL, high serum triglycerides, and high serum LDL concentrations. Screening for Dyslipidemia is not routinely recommended except in high risk patients.

Other biochemical findings that are often, but not universally present, may include elevation of serum luteinizing hormone (LH) concentrations, normal serum estradiol, and increased serum estrone concentrations. None of these hormones are part of the diagnostic criteria for PCOS and therefore, do not need to be measured.

Measurements of Serum androgens: routine measurement of serum androgen concentrations in women with mild hirsutism is not indicated. However, in women with moderate-to-severe hirsutism, measurement of total testosterone concentration, and if there are concerns about a possible androgen-secreting tumor causing the hyperandrogenism, dehydroepiandrosterone sulfate (DHEA-S) should be measured.

Differential diagnosis of PCOS:

The DD of PCOS includes other causes of hyperandrogenism and anovulation.

Other causes of hyperandrogenism:

Adult-onset 21-hydroxylase deficiency: can be excluded by measurement of serum 17-hydroxyprogesterone when there is clear androgen excess.

Cushing syndrome: evaluation for Cushing syndrome should be undertaken when findings, including hypertension and/or characteristic body habitus features are present.

Androgen-secreting adrenal or ovarian tumor: should be excluded if there are features of rapid and/or excessive severe masculinizing. It warrants measurement of androgens (total testosterone, dehydroepiandrosterone [DHEAS]) to exclude evidence of an androgen-secreting adrenal or ovarian tumor.

Causes of anovulation should be excluded including hyperprolactinemia, premature ovarian failure, and thyroid disease.

Complications and Long-Term Outlook

The diagnosis of PCOS is important because of its short and long-term consequences.

On the short term the common concert is infertility. However long term risk include development of endometrial cancer and risk of metabolic disorders which include complications of dyslipidemia, type 2 diabetes and the metabolic syndrome.

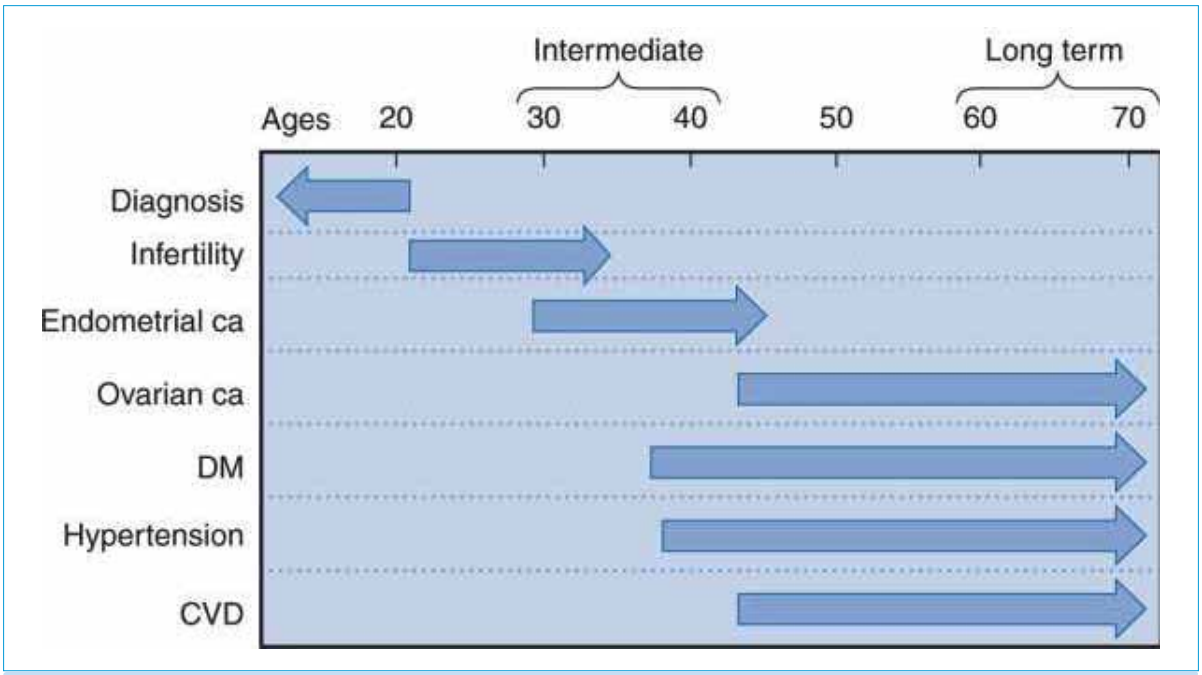

Figure 21-6: schematic presentation of the short, intermediate and long term consequences of PCOS

Management of PCOS:

The approach to the management of PCOS depends on the primary presentation of the syndrome (hirsutism, oligomenorrhea, infertility, obesity, and glucose intolerance), and the patient's goals.

Hirsutism

Oral contraceptive: combined preparation containing 30 to 35 mcg of ethinyl estradiol combined with a progestin with minimal androgenicity (such as norethindrone, norgestimate, desogestrel, and drospirenone).

After six months of therapy, if there is no satisfactory growth an antiandrogen can be added e.g. spironolactone 100-200 mg daily, and cyproterone acetate.

Benefits of combined OCP

- OCP Suppress gonadotropic (particularly luteinizing hormone) stimulation of ovarian androgen production.
- The estrogenic component elevates circulating sex-hormone binding globulin (SHBG), which reduces free and bioavailable testosterone levels.
- Progestational components with less-androgenic (drospirenone, desogestrel) provide relief from androgenic symptoms.

Endometrium:

Protection of the endometrium against consequences of unopposed oestrogen which preventing dysfunctional uterine bleeding and possibly endometrial cancer. The options are:

- Oral combined contraceptive pills.
- Intermittent progestin: 12 days courses of medroxyprogesterone acetate 10 mg daily or norethindrone acetate 5 mg daily are effective and safe for this purpose when taken every 1-2 months for women with PCOS who choose not to or cannot take oral contraceptives.

Ovulation induction:

Is the recommended option for women who desire pregnancy. The approach for ovulation induction usually takes stepwise fashion beginning with weight loss, followed by clomiphene citrate. If this is unsuccessful, other ovulation induction strategies including use of gonadotropins (see chapter on infertility).

Obesity: The approach to obesity management is the same as that for patients without PCOS, starting with lifestyle changes (diet and exercise). Modest weight loss in women with PCOS may result in restoration of normal ovulatory cycles.

Glucose intolerance: For women with PCOS who are found to have type 2 diabetes mellitus or impaired glucose tolerance, the management is the same as other non-PCOS patients with these disorders.

Metformin: (a biguanide product 1500 to 2000 mg/day) reduces hepatic production of glucose and limiting intestinal absorption of glucose. Metformin reduces insulin resistance and the levels of androgens. As a result in subset of women with PCOS resume regular ovulation and menses when treated with metformin, obviating the need for progestational therapy or ovulation-induction medications to protect endometrial health.

Surgical Treatment for induction of ovulation in PCOS: in the past surgical treatment for PCOS entails bilateral wedge resection. The procedure was followed by restoration of menses and ovulatory cycles. Apparently wedge resection act mainly through destruction of stromal (androgen-producing) ovarian elements. Nevertheless the procedure is not any more performed because it results in high rate of postoperative adhesion formation.

Currently the surgical treatment depends on creating focal areas of damage in the ovarian cortex and stroma via laparoscopic approach using one of several methods including electrocautery (also known as diathermy), laser "drilling," and multiple biopsy.

The procedure is followed by transient normalization of some of the endocrine abnormalities associated with the polycystic ovary syndrome (serum androstenedione concentrations fall transiently and serum luteinizing hormone (LH), testosterone, and inhibin concentrations fall more permanently. Conversely, serum follicle-stimulating hormone (FSH) concentrations rise). It is also associated with conception rate similar to treatment with gonadotropin.

Mechanism of action: The mechanism(s) by which controlled partial destruction of the ovary results in follicle development and ovulation is unknown. It may be due to a sudden drop in intraovarian androgens (and perhaps estrogens) that results in increased FSH secretion and an intrafollicular environment more conducive to normal follicular maturation and ovulation.

Place of laparoscopic surgical treatment for inductono of ovulaton in PCOS: Surgical treatment may be resorted to in women who are anovulatory despite an adequate trial of clomiphene citrate and metformin thus and would otherwise be treated with gonadotropin.

Advantages and disadvantages: The advantages of laparoscopic surgery in PCOS is that it avoid the risks associated with gonadotropin namely risk of multiple gestation and hyperstimulation syndrome thus the need for careful monitoring and possibly higher cost. However, there are potential risks and morbidity of laparoscopic surgery with general anesthesia, postoperative adhesion formation, and the theoretical risk of premature ovarian failure.

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Chapter 22

Infertility and Assisted Reproduction

Inability to conceive or infertility goes far beyond being just a medial problem in fact it has significant adverse psychosocial and economical consequences. In some cases infertility can be attributed to a defined pathological condition such as azoospermia, longstanding amenorrhea, or bilateral tubal obstruction. However even after thorough evaluation there remain cases in which no cause can be identified and would be labeled as "unexplained infertility". The approaches to the diagnosis and management of infertility have been revolutionized since the introduction of in-vitro fertilization and micromanipulation technology. These and other related technologies are expensive involve invasive measures and need to be carried out in specialized centers with respect of evidence based principles.

By the end of this chapter you should be able to:

- **Define**: infertility (primary and secondary), and Fecundity and its prevalence.
- **List** the causes of infertility and the relevant importance of each cause
- **In Female:** anovulation and its causes, tubal factor, others (endometriosis, cervical and uterine factors)
- **In Male:** the normal semen count
- **Describe methods of evaluation of infertility in male and female:**
    - Semen analysis.
    - Assessment of ovulation:
    - Assessment of tubal patency:
    - Assessment of peritoneal factor (endometriosis)
    - Other hormonal factors: Prolactin
- **List** the available treatment modalities for infertility:
    - Ovulation induction: common mediations, and its indications
- **Describe** the complications of induction of ovulation: hyperstimulation syndrome and multiple pregnancy
- **Describe** the meaning of Assisted Reproduction Technology "ART"
- **List** the main steps in IVF and Intracytoplasmic injection

Definitions:

Infertility is defined as inability to conceive after 12 or more months of regular intercourse without contraception.

This definition was based on historical study of 5574 women engaging in unprotected intercourse. By the end of 12 months 85% of women had conceived.

Infertility can be considered as:

Primary infertility: This diagnosis is made in couples with no previous history of conception.

Secondary infertility: this diagnosis is made if there is a prior documentation of conception by a minimum of a positive human chorionic gonadotropin (hCG), histology, or ultrasound.

Fecundability: Is the probability of achieving a pregnancy in one menstrual cycle. Fecundability decreases with women aging due to a decline in both the quantity and quality of the oocytes (Figure 22-1).

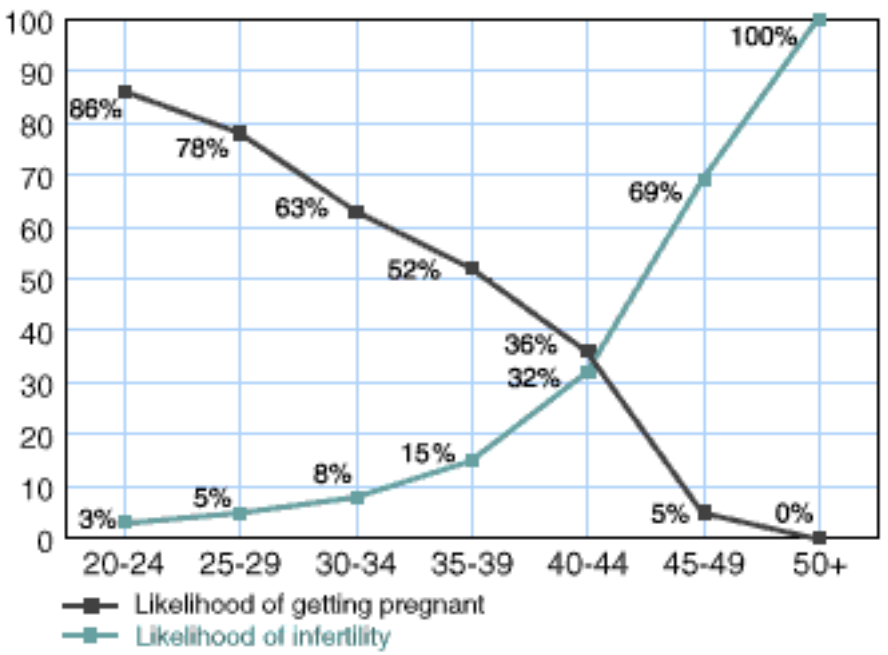

Figure 22-1: The relation between age and fertility in women. From 35 years there is sharp decrease in fecundity (see text)

Prevalence: infertility affects about 10 -15 % of couples. However the prevalence of infertility increases with increasing age particularly the age of the wife

Prevalence of infertility in relation to women age
25 -29 years 9%
30 – 34 years 15%
35 – 39 years 22%

⇒ **Causes of infertility:**

The causes of infertility are almost equally distributed between males and females. It is not uncommon that both couples may have one or more contributing factor for infertility. Therefore both the wife and husband should be evaluated when there is problem of infertility.

The major causes of infertility may be one of the or more of following factors:

1. **Male factor:** occur in approximately 20% as the main responsible factor and as a contributory one in another 30% to 40%. Male infertility is usually defined by abnormal results of semen analysis. However even if results of semen analysis are normal other male factors may be present e.g. inadequate ejaculation
2. **Ovulatory factor (ovulatory dysfunction):** Infrequent (oligoovulation) or absent (anovulation) are obvious causes of infertility. The causes of anovulation are classified into three main groups; Hypogonadotrophic hypogonadism, Normogonadotropic hypogonadism, or Hypergonadotropin hypogonadism in addition to hyperprolactinemia (Table 23-1).
3. **Tubal factor**: This include diseases that causes occlusion of the tube or prevent normal function of the tube i.e. transport of sperm and ovum such as PID caused by chlamydia or gonorrhea or peri-tubal adhesions from previous surgery (e.g. appendicitis, inflammatory bowel disease), endometriosis and pelvic tuberculosis.
4. **Peritoneal disease (namely endometriosis):** The association of endometriosis with infertility could be due to several mechanisms including anatomic tubal distortion from pelvic adhesions, damage to ovarian tissue by endometrioma formation, and/or the production of substances such as cytokines and growth factors that may impair the normal processes of ovulation, fertilization, and implantation.

The World Health Organization classified of major categories of anovulation		
Class	**Hormonal profile**	**Common causes**
WHO class 1: Hypogonadotropic hypogonadal anovulation (hypothalamic amenorrhea)	Low level of (GnRH) secretion or pituitary unresponsiveness to GnRH. Low serum estradiol concentrations	- Stress- or exercise-related amenorrhea. - Anorexia nervosa. - Kallmann's syndrome (isolated gonadotropin deficiency).
WHO class 2: Normogonadotropic normoestrogenic anovulation	Gonadotropins and estrogens are within normal range.	This group constitutes the largest proportion of patient (70 to 85 percent of cases). Include patient with polycystic ovary syndrome (PCOS).
WHO class 3: Hypergonadotropic hypoestrogenic anovulation	High Gonadotropins level Low ovarian steroid level	Accounts for 10 to 30 % of cases of anovulation e.g. Premature ovarian failure or ovarian resistance syndrome
Hyperprolactinemic anovulation	Those women are anovulatory because hyperprolactinemia inhibits gonadotropin They may have regular anovulatory cycles, but most have oligomenorrhea or amenorrhea. Gonadotropin level is normal	Hyperprolactinemia accounts for 5 to 10 percent of women with anovulation. - Prolactinoma. - Drug induced. - Hypothyroidism. - Idiopathic.

Table 22-1: Classification of cases of infertility according to the WHO classification

5. **Other contributing factors:** in some cases uterine or cervical pathology may contribute to impaired patient fecundability and hence contribute to infertility.

   - **Uterine factors:** in general uterine lesions such as fibroids particularly submucus, anomalies such as septated uterus or uterine adhesions are more likely to cause miscarriages through interfering with implantation rather than infertility.

   - **Cervical factors:** Normally prior to the midcycle the cervical mucus become profuse, watery in order to facilitates the transport of sperm. This change in mucus property is known as spinnbarkeit property and can be tested by stretching the mucus (like an egg white) between two slides to at least 6 cm.

     Trauma to the cervix (including surgery) and some congenital malformations

and may affect the ability of the cervix to produce normal mucus, thereby impairing fertility. Also cervical infection and antibodies in cervical mucus may impede normal sperm migration or sperm viability.

Unexplained infertility: This diagnosis should only be made after exclusion of all known causes of infertility. Many cases of unexplained infertility may be due to small contributions from multiple factors (borderline semen analysis, the presence of antisperm antibodies, minimal endometriosis, etc).

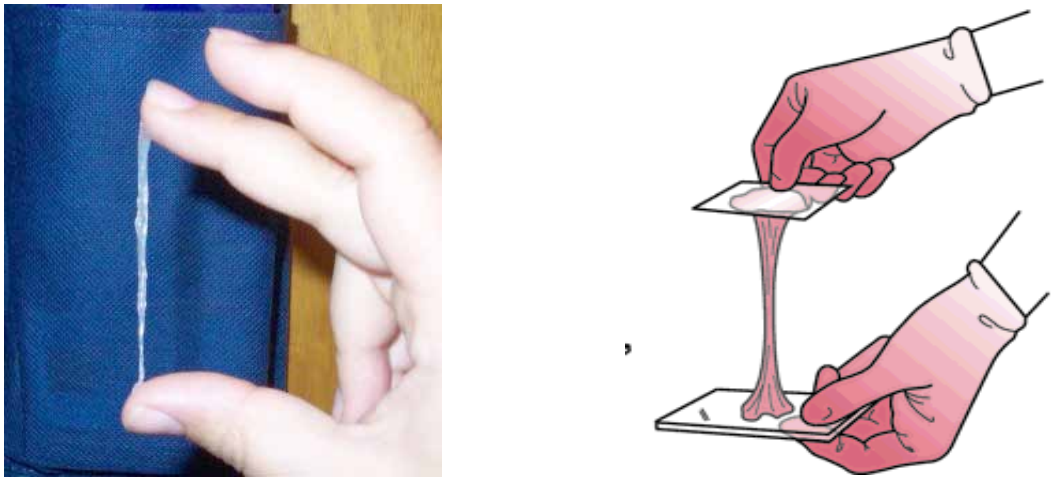

Figure 22-1: Under the influence of estrogen cervical mucus becomes abundant, clear, and stretchable this is responsible for the spinnbarkeit property shown in the picture. After ovulation, the character of cervical mucus changes, and under the influence of progesterone it becomes thick, scant, and sticky (non stretchable).

⇒ Evaluation of infertile couple:

A health care provider who deals with infertile couple must be aware of the psychosocial impact of infertility on them, hence he/she must be sensitive and understanding to the patient's needs.

Based on the definition of infertility evaluation for infertility may not be initiated unless after 12 months of normal regular marital life without using contraception. This however may not be appropriate in all cases e.g. women above 35 years of age or in cases with medical history and/or physical findings that are known to impair fertility (e.g. history of pelvic surgery or inflammatory disease or low sperm count).

History: history should be taken from both the wife and the husband with emphasis on:

- The age particularly the age of the wife: as pointed before fecundability decreases with aging due to a decline in both the quantity and quality of the oocytes despite apparently normal menstrual cycles.
- The type of infertility whether primary or secondary, duration and any previous investigations or treatment.
- The menstrual history: In young woman regular menstrual cycles almost ensures ovulation.
- Any history suggestive of pelvic pathology: history of PID, dysmenorrhea or dyspareunia suggestive of endometriosis

Table 22-2 highlights the important pints in the history for both the male and female partners.

Examination:

➢ General examination:

- Patient height, weight and body mass index (BMI).
- Assessment for signs of potential causes of infertility:
  - Abnormalities of the thyroid gland
  - Galactorrhea
  - Signs of androgen excess (hirsutism, acne, baldness)

➢ Pelvic examination:

- Inspection for vaginal and or cervical abnormalities.
- Assessment of uterine size, irregularity, or lack of mobility.
- Tenderness or masses in the adnexae or posterior cul-de-sac (suggestive of PID or endometriosis)

Investigations:

Include tests for male and female factors that may contribute to delayed conception or infertility. The basic investigations are:

1. Semen analysis
2. Tests for assessment of ovulation
3. Determination of tubal patency and presence or absence of abnormalities of the uterine cavity

In addition other tests include measurement of serum prolactin, thyroid function. In some cases laparoscopy may be performed to role out endometriosis.

Male	Female
Duration of infertility	Duration of infertility
Fertility in other relationships (previous or current marriage)	Prior pregnancies (including ectopic and miscarriages), fertility in other relationship
	Menstrual history: (age at menarche, cycle length, and regularity), presence of molimina or vasomotor symptoms (hot flashes)
Medical and surgical history, including testicular surgery and history of mumps	Gynecologic history: - History of pelvic inflammatory disease, fibroids, endometriosis (dyspareunia or dysmenorrhea). - Previous surgery of the cervix, ovary, uterus, fallopian tube or pelvic and abdomen. - Previous contraception: IUD
	Other symptoms: Breast discharge or galactorrhea. Changes in hair growth. Change in body weight: Relevant medical disorders: e.g. thyroid
Sexual history: dysfunction or impotence, frequency of intercourse, use of lubricants	
History of chemotherapy or radiation	
Cigarette smoking, alcohol, and other environmental and occupational exposures	
Medications of relevance e.g. steroid, antiepileptic, antidepressants...etc	
Previous infertility testing and therapies	
Family history of birth defects, mental retardation, or reproductive failure	

Table 22-2: the important pints in the history for both the male and female partners.

In some cases the cause(s) of infertility are easily identifiable, such as azoospermia, long-standing amenorrhea, or bilateral tubal obstruction. However in other situations there may be difficulty in assigning a certain causal relationship even if abnormality is found .e.g. low sperm count or fine tubal adhesions

The following section discusses the tests that are commonly used in evaluation of infertility. The order and kind of investigations to be requested is usually individualized and largely guided by the finding from the history and examination

Evaluation of Male factor (Semen analysis):

Semen sample should be obtained after abstinence from sexual activity for 2-3 days but not more than 7 days. The specimen may be collected at home by masturbation or by intercourse using special semen collection condoms. It should be kept in room or body temperature and examined within 1 hour of collection.

A result of semen analysis that falls below the standard range (Table 22-3) should be repeated over a 3-month period prior to making any final conclusion regarding sperm quality or quantity.

Parameter	5th %tile	10th%tile
Semen Volume (ml)	1.5 ml	2 ml
Concentration (Mill/cc)	15 Mill/cc	22 Mill/cc
Total Number (Mill/Ejac)	39 Mill	69 Mill/Ejac
Motility (%)	40 %	45 %
Progressive Motility (%)	32 %	39 %
Normal Forms (%)	4 %	5.5 %
Vitality (%)	58 %	64

Table 22-3 (WHO) Reference Values for Fertile men the 5%tile being the lower limit. Motility is measured within 60 minutes. Some times it is considered into 4 grades

If initial semen analysis demonstrates an abnormal male reproductive history a full evaluation by urologist or specialized andrologist should be undertaken.

Evaluation of Female factors:

- **Assessment of ovulatory factor:** The method for ovulation assessment include:
  - **Clinical assessment:** clinical assessment of ovulation can be made from the menstrual history e.g. regular predictable cyclic menses almost always reflect regular ovulation, while amenorrhea or oligomenorrhea implies absence or erratic ovulation.
  - **Serum progesterone measurement in the mid-luteal phase:** This is the most commonly used method to confirm ovulation. The test should be performed in the mid-luteal phase about 18 to 24 days after the onset of menses. The normal progesterone level in ovulatory cycle ranges from 6 to 25 ng/mL (19 to 80 nmol/L).
  - **Basal - body - temperature chart**

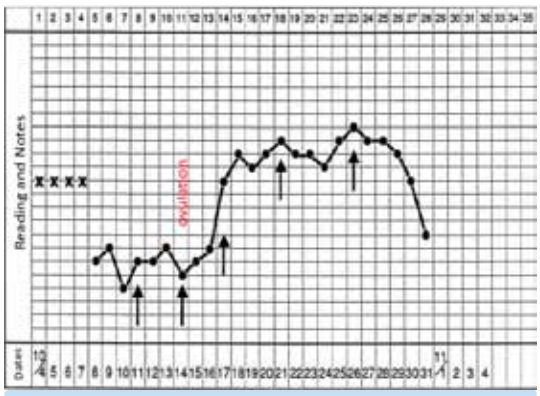

Figure 22-2: BBT chart. Provide simple retrospective diagnosis of ovulation

"BBT": The use of BBT chart (Figure 22-2) is a simple, self- applied method to confirm clinical impression of ovulation. In this method the patient is instructed to take her temperature every morning beginning from the first day of the period while she is still in the basal state (i.e. before she gets out of bed, uses the bathroom, or has anything to eat or drink). In a normal cycle, the temperature rise begins one or two days after the LH surge and persists for at least 10 days. The rise in temperature is due to the thermogenic effect of progesterone. However the BBT is not commonly used being difficult to do and also because temperature may be rise due to other factors.

- **Detection of the LH surge**: The LH surge precedes ovulation by approximately 38 hours. This surge can be detected using special test kit that provide colorimetric assays in which a blue or pink color appears when the urinary LH concentration exceeds a certain threshold; usually 40 IU/L. The test should be performed several days before anticipated ovulation to establish a few negative results before the positive one. The test has the advantages that the patient can do it herself however its sensitivity is approximately 85%.
- **Endometrial biopsy**: Documentation of a secretory endometrium is a reliable indication of ovulation. However it is invasive, expensive, and uncomfortable. Therefore today it is seldom performed for detection of ovulation.

  Another possible indication of endometrial biopsy is histological dating of the endometrium for the diagnosis of "luteal phase defect LPD". The diagnosis of LPD is made if two consecutive endometrial biopsy specimens show histology more than two days behind the actual biopsy date calculated from the previous LH surge. This could indicate inadequate production of progesterone by the corpus luteum, which is necessary for preparing the endometrium for implantation. Patient with LPD can have impairment of normal implantation and therefore infertil-.ity and/or recurrent early miscarriage

  The endometrial biopsy is not used in the routine evaluation of infertility since several studies have shown that histologic dating did not discriminate between fertile and infertile women (up to 50 % of normal fertile women may have a two-day lag in endometrial maturation on a single biopsy).

➢ **Tubal factor/ uterine factors:** Tubal patency can be tested by one of the following tests:

- **Hysterosalpingography (HSG):** HSG is performed to evaluate the uterine and fallopian tubes radiographically after injection of a radio-opaque medium through the cervical canal.

Advantages: Does not require special preparation. It evaluates both the uterine cavity (detection of uterine synechiae "adhesions", myomas, or septa) and the tubes for patency and normal shape (Figure 22-3). In addition to its diagnostic value, HSG may also have therapeutic effects since it is associated with increased fecundability after the procedure. This may be due to some factors such as mechanical dislodging of substances (mucus, cellular debris), which may obstruct the fallopian tubes.

Timing: should be done during the follicular phase (usually before the 10th menstrual day) of the cycle to minimize the chance of interfering with a possible early pregnancy.

Disadvantages:

- Compared to laparoscopy HSG provides little or no information about the outer contour of the uterus, ovaries, or pelvis (e.g. peritubal or ovarian adhesions).
- In some cases HSG gives false negative (e.g. appearance of patent tubes due to extravasations of dye) or false positive (e.g. appearance of tubal obstruction may be due to tubal spasm) results. In such cases laparoscopy should be performed.
- Rarely HSG is associated with some complications such as infection, allergic reactions, and syncope.

Contraindications:

- Suspected active infection in the pelvis or in the cervix/vagina.
- Active bleeding.
- Pregnancy is an absolute contraindication.

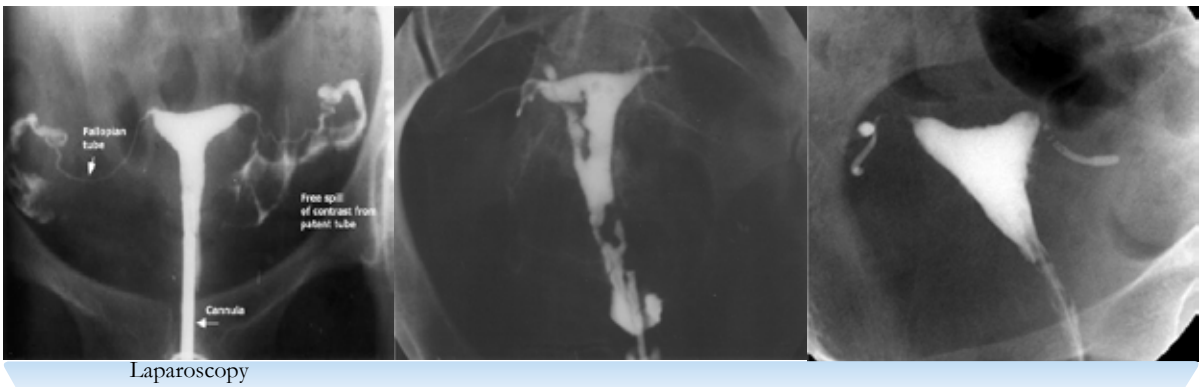

Figure 22-3: Left: normal HSG showing patent tubes and normal uterine shape. Middle: HSG showing intrauterine adhesions "synechiae". Right: tubal blockage at the isthmus.

- **Laparoscopy:**

  The advantages of using laparoscopy over HSG that in addition to testing tubal patency it also allow visualization of the abdominal and pelvic organs for lesions such as peritubal adhesions or endometriosis (Figure 22-4).

  In addition therapeutic procedures e.g. lyses of adhesions, ablation of endometriosis may be undertaken.

  Disadvantages:

  Laparoscopy is invasive and expensive procedure. It is associated with all the potential risks of surgical procedures (risk of anesthesia, trauma to vessels or visceral organs) although such complications are very rare.

  However the place of laparoscopy has diminished since the introduction of assisted reproductive technology (ART) because most patient who fails to conceive would opt for IVF rather than going for laparoscopic procedure. Example of indications are:

  1. Patients with unexplained infertility.
  2. Suspected endometriosis or pelvic adhesions (e.g. history of pelvic pain, complicated appendicitis, pelvic infection, pelvic surgery, or ectopic pregnancy)
  3. Inconclusive HSG.

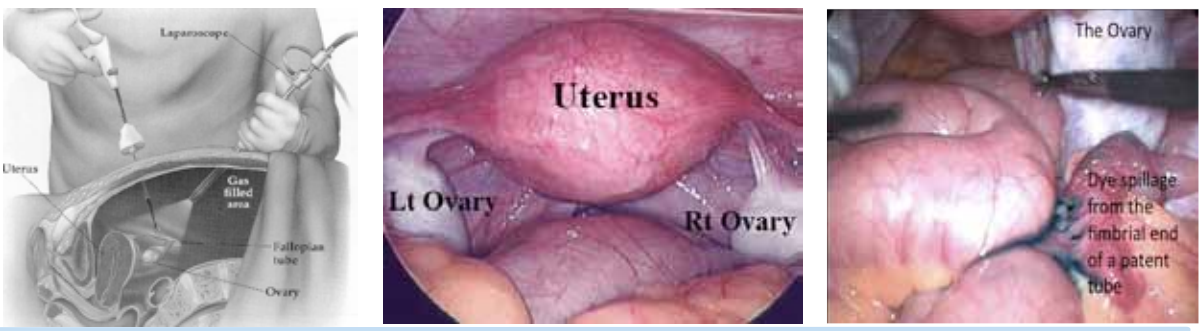

Figure 22-4: Left upper: Laparoscope being inserted after insufflations of the abdomen with CO2 gas.
Right upper: typical view of healthy pelvics.
Right lower: Testing for tubal patency - the blue dye is injected from the vagina and if it comes thru the tubes smoothly it shows that the tubes are patent.

:Treatment of infertility

- Teaching and education: An important element in the management is to ensure that the woman and her husband understand the basic physiological principles of ovulation and conception including the most fertile days of the cycle and the importance of timed intercourse.
- Changes in lifestyle factors, which may contribute to subfertility, should be emphasized including achieving an ideal body mass index, cessation of smoking, and limiting exposure to caffeine and alcohol.

There are several therapeutic modalities for treating infertile couples including medical and surgical measures. The choice of a specific one does not only depends on the cause but also other factors most important one is the age of the wife e.g. infertility due to anovulation at age of 25 may treated by trial of induction of ovulation and timed intercourse whereas if the patient is 35 years of age she may chose to go for in-vitro fertilization as first option.

The following section is a discussion of the management options for infertility, its indications and potential complications.

Induction of ovulation:

The choice of the method and the approach for ovulation induction depends on:

1. The cause of anovulation: There are different drugs that can be prescribed for induction of ovulation. Table 22-4 describe the common drugs available, its indications and major side effects.
2. The plane of management monofollicular vs. controlled hyperstimulation: in standard ovulation induction the aim is the development of one or two follicles (monofollicular development). In contract in cases planned for assisted reproductive technique the aim is to induce multiple follicular development (controlled hyperstimulation).

Clomiphene citrate "CC": Is usually the first line of treatment for induction of ovulation. It belongs to the selective estrogen receptor modulator group .(of drugs (SERM) (see the blue box

Selective estrogen receptor modulators (SERM)
Are drugs that have both estrogenic and anti-estrogenic effects depending upon the target tissue.
SERM drugs includes:
Clomiphene citrate: *for induction of ovulation*
Tamoxifen: *used in breast cancer.*
Raloxifene: *used in osteoprosis*

➢ **Gonadotropin therapy**:

Gonadotropins are administered in a way that simulate the normal cycle. Therefore FSH is administered in the first half of the cycle to

induce follicular maturation. When the follicle is mature LH is administered to trigger ovulation.

The FSH substance is prepared from urine of menopausal women, which contain both FSH and LH (Human Menopausal gonadotropin "HMG"). Recently purified forms of FSH and also recombinant FSH using genetic engineering technology have been prepared.

- **Dopamine agonists**: "Bromocriptine" and "Cabergoline" are used in cases of hyperprolactinemic anovulation.
- **Other drugs**:
  - Metformin: is an insulin-sensitizing drug. It is used to treat the hyperinsulinemia in patients with PCOS. In these women the elevated insulin secretion may directly stimulate ovarian androgen secretion and result in anovulation. Metformin is usually combined with clomiphene citrate but may be used alone.
  - Aromatase inhibitors "AI" (Femara or Letrozole**):** As in clomiphene citrate, aromatase inhibitors induce hypoestrogenemia, which reduces the negative estrogenic feedback at the pituitary, and result in increases in pituitary gonadotrophin stimulation. However unlike CC which blocks estrogen action aromatase inhibitors block estrogen synthesis.
  - Dexamethozone: May be administered in combination with clomiphene treatment in some cases of PCO with elevated dehydroepiandrosterone sulfate (DHEA-S)

Complications of Induction of ovulation:

The two main complications of ovulation induction are (1) excessive ovarian stimulation or hyperstimulation syndrome (see later) and (2) increased rate of multiple gestations. The frequency and severity of these complications varies depending on the drug used (CC or HMG) and the objective of management (monofollicular vs. controlled hyperstimulation).

Clomiphene citrate:

- Mild form of cystic ovarian enlargement is not uncommon with CC therapy. It can be avoided by ultrasound examination prior to initiation of a clomiphene cycle of therapy.
- Multiple pregnancies: occur in approximately 8% of cases, usually as twin pregnancy (1% of cases exceeds twin)

Gonadotropin therapy:

The sensitivity of the ovaries to FSH stimulation varies among individual women and

from cycle to cycle in the same woman. Therefore treatment with gonadotropins carries much higher risk of ovarian hyperstimulation and multiple pregnancy (twin occur in up to 20 % of cases with 5% of higher order pregnancies). Therefore specific treatment and monitoring protocols are required to achieve the desired objective and avoid complications.

Monitoring: The ovarian response to gonadotropin therapy is should be monitored using (a) transvaginal ultrasonography to measure follicular diameter and (b) measurement of serum estradiol level especially in patients going for controlled hyperstimulation.

Indications	Mechanism of action	Dose
Clomiphene Citrate (CC)		
o Anovulatory infertility with Normogonadotropic function" WHO class 2 (e.g. PCO)	Compete with endogenous estrogen for the estrogen receptors at the hypothalamus and pituitary thus induces state of pseudohypoesrog-enism. This results in secondary rise in pituitary FSH and LH secretion.	Dose: 50 mg daily beginning 2nd or 5th of the menstrual flow can be repeated for 6 cycles with increasing dose up to 250 mg day. Monitoring: of ovulation can be performed by BBT, or Fertil test or by midluteal phase serum progesterone or ultrasound
Gonadotropin therapy		
o Failed respond to CC (WHO class 2) o Anovulatory women withhypopituitarism. "Hypogonadotropic amenorrhea (WHO class 1)	Aim is to simulate normal cycles by inducing follicular maturation using FSH like substance and when the follicle reach maturity ovulation is induced using HCS (LH)	Dose: as IM or sometimes SC injection of 75 or 150 unit. The dose and protocol depends on the objectives of management: Either monofollicular development or controlled hyperstimulation for patient going for assisted reproduction (either IUI or IVF)
Dopamine agonist		
Anovulation due to hyperprolactinemia	Anovulation due to hyperprolactinemia	Bromocriptine: major side effects are nausea and vomiting. Should be given low dose with gradual increase. Cabergoline : side effects are less
Pulsatile GnRH		
hypogonadotropic amenorrhea (WHO class 1)	Administered via small portable pump either SC or IV in small pulses every 90 to 120 minutes. This will stimulate pituitary gonadotropins. However if this treatment is not available then gonadotropin are used.	
Other drugs:		
Metoformin	Is insulin senstiser, usually combined with clomiphene in PCO	
Aromatase inhibitors	Block estrogen synthesis rather than action thus induces hypoestrogenemai which causes secondary rise in FSH	
Dexamethazone	In some cases of PCO with elevated DHEA-S together with CC	

Table 22-3: Common drugs used for induction of ovulation, its indications, mechanism of action.

Ovarian hyperstimulation syndrome (OHSS): The term OHSS refers to excessive stimulation of the ovary with multiple cysts and fluid shift into the extravascular space. Its Complications include ascites, hemoconcentration, hypovolemia, and electrolyte im-.balances

It is a gynecological emergency the severe form of OHSS is a critical illness with life .threatening complications

Classifications: according to its severity, OHSS is classified into three grades:

- Grade I (mild hyperstimulation): characterized by bilateral ovarian enlargement with multiple follicular and corpus luteum cysts measuring up to 5 by 5 cm.
- Grade II (moderate hyperstimulation): the ovaries are enlarged up to 12 by 12 cm, accompanied by abdominal discomfort and gastrointestinal symptoms (e.g., nausea, vomiting, and diarrhea).
- Grade III (severe hyperstimulation): enlarged ovarian cysts (more than 12 by 12 cm) with development of ascites, and, in some patients, pleural and/or pericardial effusion. In addition there is electrolyte imbalance (hyponatremia, hyperkalemia), hypovolemia, and hypovolemic shock. Marked hmoconcentration, increased blood viscosity, and thromboembolic phenomena including disseminated intravascular coagulation occur in the most severe cases.

Treatment:

- Prevention: OHSS is an iatrogenic illness which can be avoided by careful monitoring of ovarian stimulation by ultrasound and measurement of serum estoriol level. If there are multiple follicles and the level of serum estriol reaches > 3000 pgm/l the HCG should not be administered in order to prevent ovulation.
- Treatment of established cases:
  - Mild cases can be followed up on outpatient bases with bed rest, provision of adequate fluids, and sonographic monitoring of cyst

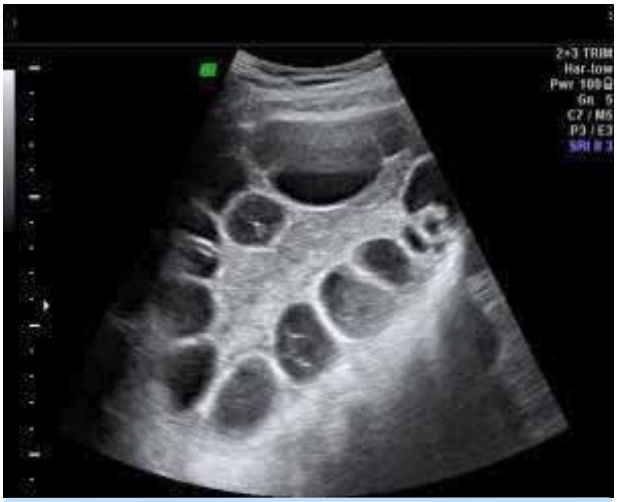

Figure 22-5: Transvaginal US picture for a hyperstimulated ovary with multiple follicles during a course of FSH administration. In this case LH should not be administered in order to prevent the development of HSS

size. Intercourse and strenuous exercise should be avoided for fear of cyst rupture.

- In more advanced cases patients should be admitted to the hospital often in critical care unit under multidisciplinary care. The treatment is directed toward:
  - Maintaining blood volume.
  - Correcting the disturbed fluid and electrolyte balance.
  - Relieving ascites and hydrothorax.
  - Preventing thromboembolic phenomena.

In most cases the OHSS is self-limiting complication within 10 to 14 days. Rarely sugary is required if there is hemorrhage from ruptured cyst or acute pain from ovarian torsion.

Surgical treatment for induction of ovulation:

Ovarian drilling: Laparoscopic ovarian drilling is a form of controlled partial destruction of the ovary. It may be considered in women with PCOS who fail to ovulate despite an adequate trial of medial induction of ovulation. Following this procedure return of menstruation and ovulation is often noted.

The exact mechanism of action of such procedure is not known. It may be due to the hormonal changes that take place after this procedure which include transient fall in serum androstenedione concentrations and serum luteinizing hormone (LH), testosterone, and inhibin concentrations. The net effect is normalization of some of the endocrine abnormalities associated with the polycystic ovary syndrome.

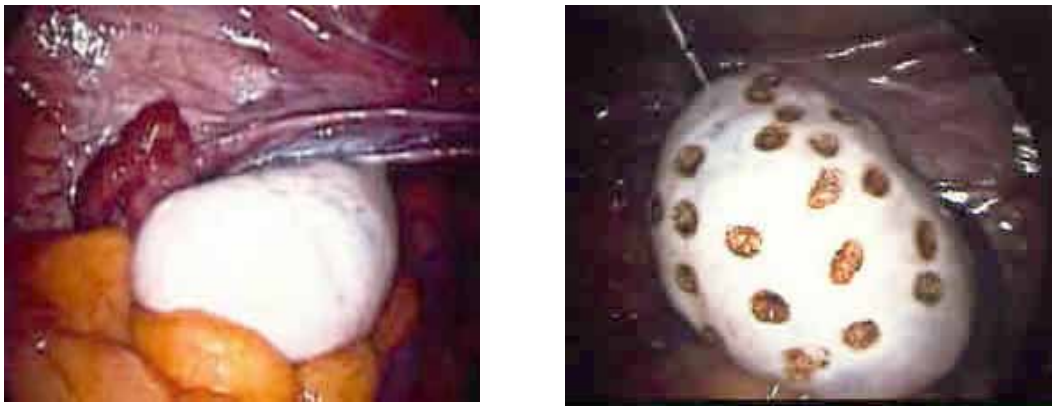

Figure 22-6: Left: enlarged polycystic ovary at laparoscopy, the outer surface appears thickened and "pearly white". Right: The ovary after "drilling" using electrocutery.

Assisted reproductive technology (ART)

Definition:

The term ART refers to the procedures in which artificial means that bypass intercourse are used to achieve pregnancy.

Generally ART include intrauterine insemination and in vitro fertilization (IVF) a process in which oocytes are fertilized in the laboratory.

Development and indications: ART has become an important method for treatment of infertility. When it was first developed the indication for IVF was for infertility due to tubal damage. Now the indications has widened to include many other conditions e.g. unexplained infertility, endometriosis, infertility due to male factor and other causes.

- **Intrauterine insemination "IUI":** is a procedure in which processed and concentrated sperm are placed directly into the uterine cavity around the ovulation time. In this way the chance of fertilization increases over natural intercourse (Figure 22-7).

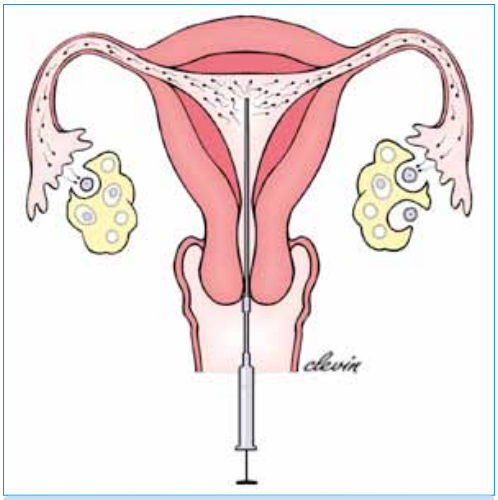

Figure 22-7: Illustration of the procedure of IUI in which prepared semen are placed directly in the vicinity of the uterine fundus in close proximity to the ovaries

Indications: IUI is used to treat infertility related to a variety of causes. Some of the common indications include:

- Ejaculatory dysfunction (including sexual dysfunction and impotence)
- Severe vaginismus
- Cervical factor infertility
- Male factor infertility
- Unexplained infertility
- Stage I or II endometriosis

Contraindications: IUI is contraindicated in women with an active cervical, intrauterine, or pelvic infection.

The technique: IUI is performed on outpatient bases. Can be performed on natural cycles or following ovarian stimulation to produce more ova but no more than three eggs. On the day of the procedure the semen specimen is collected into a sterile cup; then undergoes

special preparation before intrauterine insemination.

- **In vitro fertilization**: Is the most common procedure in assisted reproductive technology. The technique of IVF can be described under four steps (Figure 22-8):
  - Controlled ovarian hyperstimulation: using FSH (usually hMG, purified or recombinant FSH). Once the follicles reaches reasonable size (16-18 mm) and estradiol level is within the safe range hCG is administered.
  - Collection of oocytes: is performed under transvaginal ultrasound guidance. This usually takes place after approximately 36 hours of hCG injection when ovum maturation would be completed.
  - Fertilization in vitro: by incubation of the aspirated ovum with the sperm in special incubator.
  - Transfer of the embryo(s) into the uterus. Usually after 48 or 72 hours the fertilized embryo is transferred to the uterus.

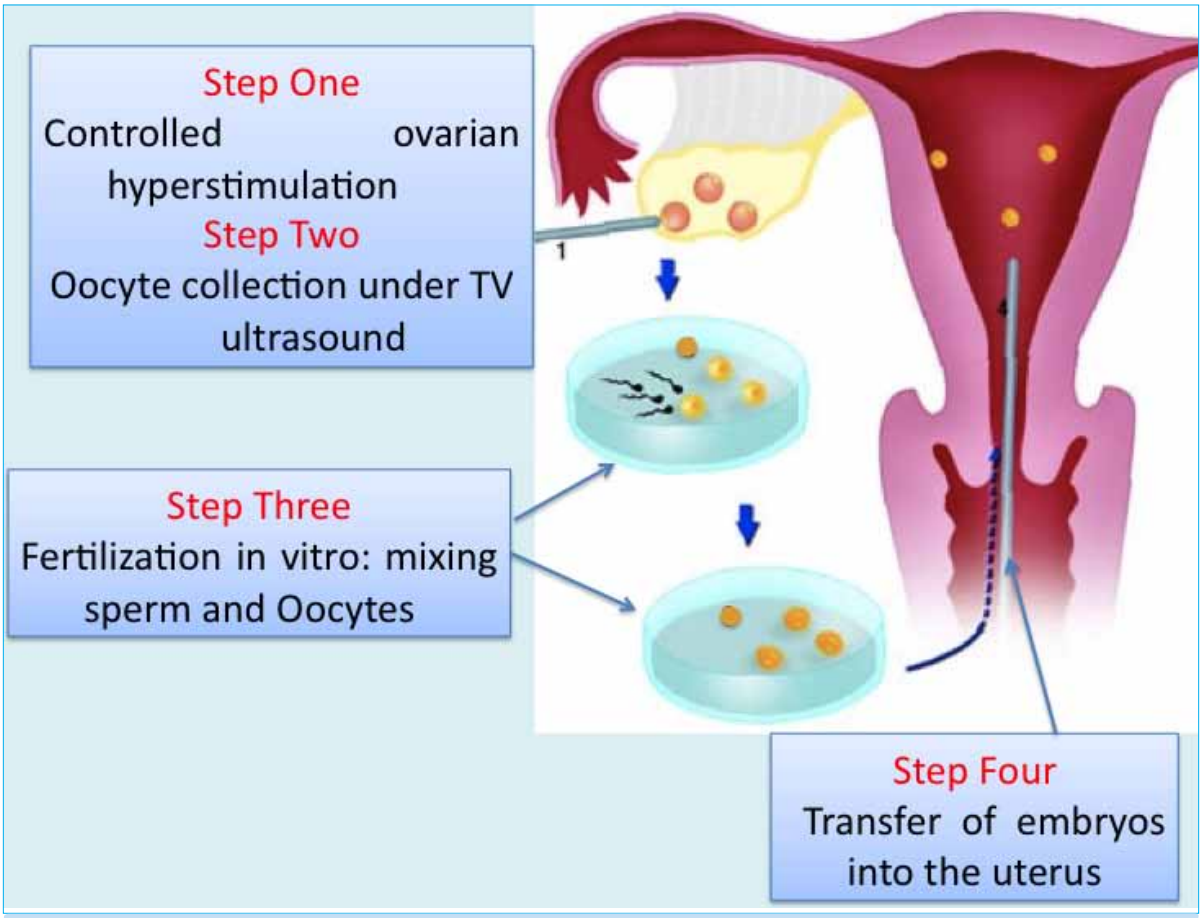

Figure 22-8: Illustration showing the four basic steps in standard IVF procedure

Intracytoplasmic sperm injection (ICSI): refers to a specialized technique used in couples with severe sperm abnormalities. It is performed in conjunction with IVF whereby fertilization is accomplished by injecting a single sperm directly into the egg (Fig-.(ure 22-9

The procedure involve high skill and advanced technology that is available in .few centers. It is also more expensive

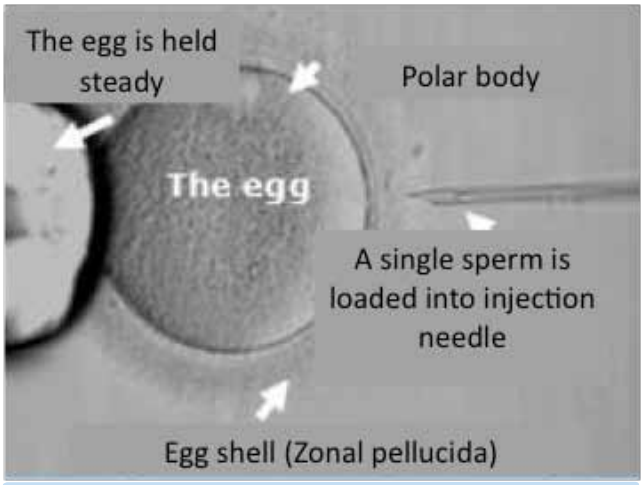

Figure 22-9: A diagram showing the process of ICSI. The procedure require high skill and advanced technology

Draw back of IVF:

There is no doubt that the introduction of IVF is a landmark in the treatment of infertility. It also paved the way to more therapeutic option such as intracytoplasmic injection, which enabled many husbands with very low sperm counts, or sometimes ejaculatory azoospermia (in such cases sperms can be retrieved from testicular biopsy) to father children. The parallel development in genetics combined with IVF lead to pre-implantation genetic diagnosis and opened the way for stem cell research and soon therpay.

However IVF still a costly procedure with relatively low success rate. In addition it is associated with some risks to the women (from ovulation induction and invasive procedures), and increased rate of multiple gestations, which accounts for much of the direct cost of pregnancies conceived via IVF. Furthermore the ethical aspects and potential abuse of this technology is an area of continues debate. In this respect according to the Islamic regulations the primary ethical issue is that no third party should be involved between the husband and the wife (e.g. donated sperm, ova or surrogate uterus) any other ethical issue is subject to discussion.

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Chapter 23

The Menopause

Menarche and Menopause are the two biological landmarks in women reproductive life. In both, the physiological and biological changes are respectively related to the rise and fall in ovarian reproductive and endocrine functions. For a variable number of years prior to menopause, the ovarian reproductive function will decline fist followed by gradual decline in its hormonal function. Because the age of the menopause has not changed while human life span has greatly increased, women now spend more than one third of their lives in an estrogen deficient environment. Estrogen deprivation is associated with both short and long term adverse consequences. Gynecologists and health care providers have an important duty to provide women with the proper health advice, and appropriate medical intervention to ensure that women spend their postmenopausal years in the optimum possible physical and mental health.

By the end of this chapter you will be able to:

- **Define:** premenopause, menopause, peri-menopaue, post-menopause (early and late), and climacteric.
- **Describe:** the hormonal changes in the menopausal transition and postmenopausal years.
- **List the potential impact of cessation of ovarian function (estrogen deficiency) on women health:** on the short term (hot flushes, genitourinary atrophy, psychological and mood changes) and the long term (osteoporosis, cardiovascular diseases).
- **Discuss:** the approach to the diagnosis and management of menopausal disorders and the role of health care provider

⇒ Definitions and terminology:

Menopause: is defined as "Permanent cessation of menstruation resulting from the loss of ovarian follicles" (WHO). It is a retrospective diagnosis begins 12 months after the final menses and indicates permanent cessation of menstrual periods. Menopause is not a disease but is a natural transition from the reproductive to the non-reproductive phase of a woman's life.

It should be realized that it is not the stopping of menstrual periods that matters but what happens to the ovaries is the key to the menopause. For example the period may stop (i.e. amenorrhea) following hystrectomy or endometrial ablation but that does not indicate menopause if the ovaries are still functioning.

Perimenopause: Perimenopause means "around the menopause". It include the period of menopausal transition which may start 5-10 years or more before menopause often with vasomotor symptoms and irregular menses and the 12 months after the last menstrual period.

Postmenopause: the postmenopausal period is classified into:

- Early postmenopause: defined as the first five years after the final menstrual period.
- Late post menopause: begins five years after the final menstrual period and ends with death

Climacteric: is the general term that describes the time from the period of this transition to the early postmenopausal phase of a woman's reproductive life cycle.

Stages	-5	- 4	-3	-2	-1		+1	+2
Terminology	Reproductive			Menopausal Transition			Postmenopause	
	Early	Peak	Late	Early	Late		Early	Late
				Peri-menopaue				
Duration of stage:	Variable			Variable		(a) 1 yr	(b) 4 yrs	Until demise
Menstrual cycles:	Variable to regular		Regular	Variable cycle length (>7 days different from normal)	≥ 2 skipped cycles and an interval of amenorrhea (≥ 60 days)	Amn For 12 Months	None	
Endocrine	Normal FSH			Rise of pituitary FSH		FSH Initially rise- Plateaued - Decline		

Table 23-1: the phases of women reproductive life – Menopause after 12 months of amenorrhea

⇒ Physiology of the menopausal transition and the menopause:

- Menopausal transition: begins several years (5-10 years) before menopause. The physiological changes during this period affect both the reproductive and hormonal functions of the ovaries.

In the early menopausal transition:

- Ovarian reproductive function: There is rapid decline in the number of ovarian follicles and the fertility rates are reduced. However conception can still occur, but there is high rate of miscarriages, and genetic abnormalities (Trisomies)
- Hormonal function:
    - Inhibin hormone: inhibin level is dependent on follicular number, therefore the decline in follicular number results in decline in the serum level of inhibin.
    - FSH hormone: Since inhibin has a negative feedback on pituitary FSH secretion, reduction in inhibin level causes secondary rise of pituitary FSH production.
    - Estradiol level remain relatively preserved (normal to high levels), but with low luteal phase progesterone concentrations. As a result the patient may begin to experience some menstrual irregularity (e.g. short cycles).

In the late menopausal transition: cycle variability and fluctuations in serum concentrations of FSH and estradiol between high and low values increases. Therefore, a single serum FSH value in the postmenopausal range, even with undetectable estradiol levels is not diagnostic for establishment of menopause. The increase in FSH is due to:

- Decline in follicular number.
- Decrease in hypothalamic-pituitary sensitivity to estrogen.
- Decrease in the biological activities of the FSH and LH produced in the postmenopausal years (the FSH and LH contain more carbohydrate and the serums half-lives of the hormones are prolonged as compared with young women).

➢ Postmenopause:

- FSH: Its level is elevated 10 to 20 times above premenopausal levels, reaches plateau 1 to 3 years after the menopause, before starting to gradually decline.
- LH: its level rise to two to threefold after menopause, reach plateau 1 to 3 years after the menopause, after which there is a gradual decline.
- Estrogen level: Ovarian estradiol and estrone (a weaker estrogen) secretion is negligible secondary to depletion of ovarian follicles.

  However menopausal women have variable amount of estrogen as a result of peripheral conversion of androgen precursors in adipose tissues to

estrone. Therefore estrogen levels vary with the degree of adiposity, obesity can lead to a state of relative estrogen excess. Therefore obese women are more likely to have hyperestrogenemia and risk of endometrial hyperplasia.

- Androgen secretion: Ovarian androgen [androstenedione (AD), testosterone, dehydroepiandrosterone (DHA)] secretion continues for several years after menopause under the continued stimulation of ovarian stromal and hilar cells by pituitary LH although at a decreased rate compared to the premenopause (*AD and DHA production falls by almost 50% while Testosterone production remains relatively constant*).

  The final results are that in the postmenopause the overall rate of ovarian androgen production decreases but the women is more sensitive to the androgenic effects because of lost estrogen opposition. This may cause some untoward symptoms of skin changes, or may be related to decreased libido.

⇒ Age of menopause:

The age of menopause unlike the average age of menarche, which is affected by trends in nutritional status and general health, has not changed much over time. Although for individual woman some factors may affect the age of menopause including genetic factors, and smoking which is associated with earlier menopause.

The average age at menopause is approximately 51 years, for 5 percent of women, it occurs after age 55 (late menopause), and for another 5 percent, between ages 40 to 45 years (early menopause).

Premature menopause (premature ovarian failure): menopause is considered premature if it occurs prior to the age of 40 years. It occurs in approximately 0.3% of cases.

Etiologies of premature ovarian failure: Premature menopause may be idiopathic. Some of the causes of premature ovarian failure include karyotype abnormality affecting the X chromosome, autoimmune disorders and enzymatic abnormalities such as galactosemia.

⇒ Clinical Manifestations of the Perimenopause and Menopause:

The hormonal changes mainly estrogen withdrawal is often associated with clinical consequences both on the short and long terms.

Short-term manifestations:

- Menstrual disorders.

- Vasomotor symptoms.
- Genitourinary chagnes.
- Psychological and mood changes.

Long-term consequences:

- Osteoporosis.
- Cardiovascular complications.
- Dementia and neurological complications.

The severity and extend of the clinical manifestations varies between women. Furthermore not all manifestations are necessary due to estrogen withdrawal. Other factors such as concomitant diseases, social circumstances and the natural process of aging play important role.

- *Menstrual Disorders*: can take different forms:
  - Dysfunctional uterine bleeding (DUB) in the forms of polymenorrhea (frequent cycles) with or without menorrhagia (excessive flow): is not uncommon during the early perimenopause. This is explained by anovulatory cycles with progesterone deficiency. In some cases prolonged periods of unopposed estrogen exposure can lead to endometrial hyperplasia. This is more common in obese women with higher level of estrogen production from peripheral conversion of pro-androgens.
  - Midcycle spotting: this may be due to estrogen withdrawal secondary to drop in estradiol levels just before ovulation.
  - Oligomenorrhea (infrequent cycles): As the menopause approaches, missed periods are common and cycles length increases until permanent cessation of menses occurs.
- *Vasomotor Symptoms" hot flushes"*: Hot flushes (or flashes) are the typical symptoms of the peri-menopause. It is most common in the late menopausal transition and early postmenopausal periods. It takes the form of hot flushes, with or without bought of cold night sweats, palpitations and headaches. Its prevalence is quite variable and in some culture it can affects up to 75 percent

Hot flashes (or hot flushes)

Are sensations of heat that may be accompanied by a red, flushed face and sweating, when the blood vessels near the skin's surface dilate to cool. The patient may also perspire to cool down the body. Hot flashes accompanied with sweating can also occur at night and called "night sweats". An episode of hot flash usually lasts for few minutes. Recurrent and severe ones can be very disturbing during the day, and interferes with sleep at night. The cause is not known.

of women. Usually only about 20 percent may seek medical advice.

Vasomotor symptoms are usually self-limited, and resolve without treatment within one to five years, although some women may continue to have hot flashes until after age 70. The only hormonal changes associated with hot flushes is increased FSH level.

- *Genitourinary symptoms:* because the epithelial lining of the vagina, bladder and urethra are very sensitive to estrogen, genitourinary symptoms due to estrogen deficiency are not uncommon in the menopausal years, it include:
  - Symptoms of atrophic vaginitis: the dryness, thinning of the vaginal epithelium and rise of the vaginal pH up to 7 (*normal vaginal pH is <4.5 in the reproductive years*) can lead to dyspareunia, itching and impaired protection against vaginal infection.
  - Sexual dysfunction: Several causes can explain sexual dysfunction in menopausal women these include:
    - Decreased vaginal lubrication secondary to decreased blood flow causing dryness and dyspareunia.
    - Decreased sensation in the clitoral and vulvar area that may result from neuropathy changes in the perineal nerve
    - The elasticity of the vaginal wall may decrease and the entire vagina can become shorter and/or narrower.
    - Finally in late post menopause decrease in ovarian androgen production can be responsible for decreased libido.

Sexual dysfunction in the menopause

- Atrophic vaginal changes are reversible with estrogen therapy
- Continuing sexual activity may prevent changes in size and shape of the vagina, even in the absence of estrogen therapy

  - Urinary Symptoms: include:
  - Increased risk of stress and urge urinary incontinence secondary to atrophic urethritis, diminished urethral mucosal seal, and loss of urethral compliance.
  - Recurrent urinary tract infections.
- Psychological symptoms and mood changes: include symptoms such as irritability, nervousness, loss of concentration, lethargy; frequent mood change and depression are not uncommon. A prior history of depression or (premenstrual symptoms) is a strong predictor of depressive recurrence during the menopausal transition.

However depression and other psychological symptoms may be related to non-hormonal events such as mid-life adjustment, aging parents, children leaving home, career disappointments, chronic illness, and physical limitations

⇒ Long Term consequences of estrogen deficiency:

Although the long-term consequences associated with estrogen deficiency are not symptomatic they are the more serious, carries risk of morbidity and mortality. It includes osteoporosis, cardiovascular disease, and dementia.

➢ Osteoporosis:

Osteoporosis is a skeletal condition characterized by low bone mass, microarchitectural disruption, increased skeletal fragility and an increased risk of fractures. Osteoporosis affects women three times more than men.

Osteoporosis often leads to vertebral compression and excessive curvature of the spine as well as loss of height, especially during the post-menopausal years and increased rate of fracture. Moreover, 15 to 25% of patients die secondary to osteoporotic hip fractures or its complications.

Bone loss in the perimenopausal years: Bone loss is part of the normal aging process. It begins prior to menopause, and in women it accelerates during the late perimenopause and the postmenopausal years as a consequence of estrogen deficiency. It is estimated that after menopause bone loss occurs at an annual loss rate of approximately 2-4%.

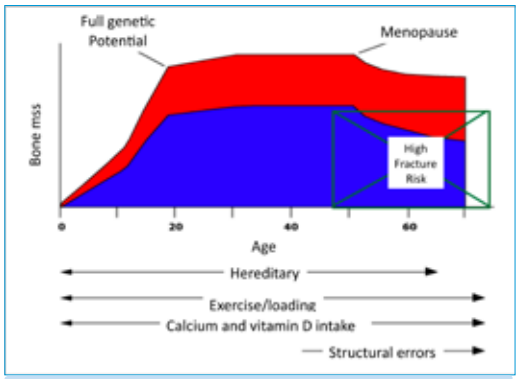

Figure 23-1: Peak bone mass is influenced by genetic and environmental factors (adequate dietary calcium and increased weight-bearing activity) during adolescence and are thought to account for 20 percent of the variance in peak bone mass.

However not all women develop osteoporosis. For a given women the development of osteoporosis depends on the several factors including the peak bone mass, which is normally attained by approximately 30 years of age (figure 24-1).

In addition to some diseases that is associated with secondary osteoporosis epidemiological studies have identified some factors that increases women risk of developing osteoporosis (table 24-2).

Advancing age
Previous fracture
Glucocorticoid therapy
Parental history of hip fracture
Low body weight
Current cigarette smoking
Excessive alcohol consumption
Rheumatoid arthritis
Secondary osteoporosis (e.g., hypogonadism or premature menopause, malabsorption, chronic liver disease, inflammatory bowel disease)

Table 23-2: Risk factors for osteoporosis

Diagnosis of osteoporosis:

The problem of osteoporosis is that it is a silent disease that has no clinical manifestations until there is a fracture.

Therefore the diagnosis of osteoporosis or osteopenia depends on measurement bone mineral density (BMD). Currently the gold standard for diagnosis of osteoporosis is BMD measurement using dual-energy x-ray absorptiometry (DXA) and correlating the results in number of deviation from the mean value from young adults (number of T score).

According to the World Health Organization (WHO) osteoporosis in postmenopausal women is diagnosed if the bone mineral density (BMD) value at the spine, hip, or forearm is 2.5 or more SD (standard deviations) below the young adult mean (T-score ≤ -2.5) (figure 24-2).

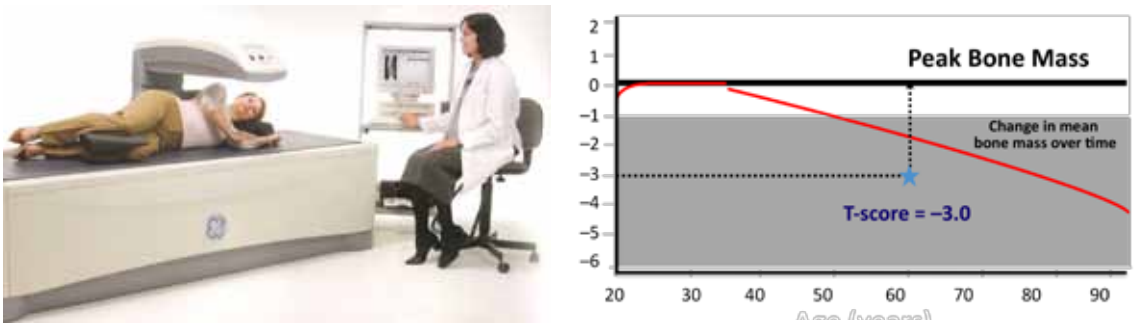

Figure 23-2: Left: dual-energy x-ray absorptiometry (DXA). Right: T-score = Number of standard deviations (SDs) by which the patient's bone mass falls above or below the mean peak bone mass for normal young adult women. ★ = T-score for patient, a 60-year-old woman; here, T = –3.0

➢ **Cardiovascular diseases:**

- Epidemiological studies show that cardiovascular diseases (CVDs) including atherosclerosis, angina, and stroke are the leading causes of death in women. Responsible for more deaths each year than all other causes combined (figure 24-3).

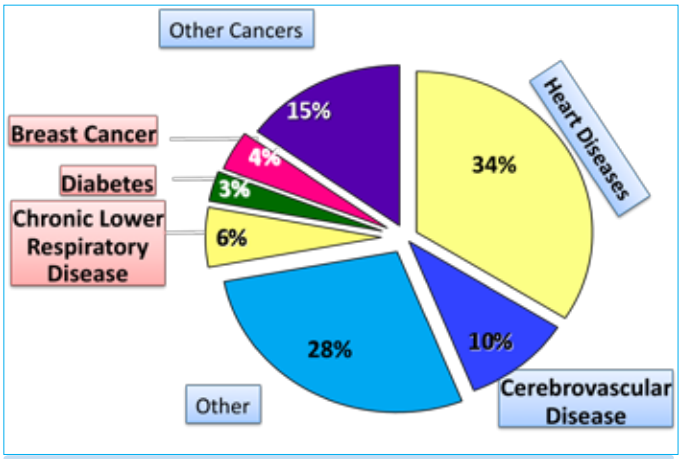

Figure 23-3: Percentage of total deaths in 1999 among women aged 65 years and older.

- Furthermore during the childbearing years women seems to be largely protected against CVDs even though they may have the same risk factors as men such as smoking, high blood cholesterol levels, and a family history of heart disease.
- After menopause, the incidence of CVD increases, with each passing year posing a greater risk.

⇒ Diagnosis and investigations of menopause:

The diagnosis of menopause is usually made in retrospect, once it has been 12 months since the last menstruation. No specific tests are required for the diagnosis of menopause.

⇒ Treatment of the menopause:

Since menopause is not a disease, it does not require specific treatment. However, the perimenopausal and menopausal periods provide excellent opportunity for health care provider to set management strategy that help women achieve their optimum health potential during their aging period. The aims of this strategy include: counseling and educations, screening for potential complications of estrogen deficiency, and treatment of specific complications.

Positive lifestyle changes

- Adequate calcium and vitamin D intake (1000 to 1200 mg elemental calcium and 400 to 800 IU vitamin D3 daily)
- Regular weight-bearing exercise.
- Cessation of smoking.
- Achievement of normal body weight, and avoidance of excessive dieting.

I. Counseling and educations strategy: Women and their husbands need to understand in simple terms the

physiological changes related to the menopause, that explain some of the possible symptoms such as menstrual disorders or hot flushes. They need to be educated regarding the importance of "positive life style" changes on the long term.

II. Screening strategy: aims at detection of risk factors or early diseases in asymptomatic patients.

- Health risk assessment and physical examination: identification of risk factors for CVD and, cancer in medical and family history.
- Annual physical examination including breast and pelvic examination.
- Screening for Hyperlipidemia (serum cholesterol and lipid profile), diabetes (measurement of fasting blood glucose) and hypothyroidism (measurement of serum TSH).
- Mammography (once year from 40-50 and once year after 50)
- Pap smear every 1 to 3 years depending on previous results.
- Test for occult blood in stool and/or sigmoidoscopy according to age and risk factors.
    - Strategy against CVD: The menopausal physician has an important role to play in prevention and treatment of CVD. Identification and treatment of modifiable risk factors for CVDs such high blood pressure, hyperlipidemia, and cessation of smoking can significantly reduce the risk of having cardiovascular event (e.g. stroke, or coronary attack).

      For that purpose several screening models have been developed in order to help gynecologists and menopausal physicians to provide approximate risk of cardiovascular event for an individual patient.

    - Strategy against osteoporosis:

      The primary role of menopausal health care provider is prevention of development of osteoporosis through clinical screening and emphasizing positive life style for all perimenopausal and menopausal women. Routine screening for osteoporosis is not cost effective before approximately the age of 60 years. Figure 24-4 provides an algorithm for the management plan for menopausal and postmenopausal women with concern about osteoporosis. Women diagnosed to have osteoporosis are best referred for treatment by specialist rheumatologists or endocrinologists.

Pharmacologic therapies for osteoporosis: in premenopausal women pharmacologic therapy is reserved for those with fracture or accelerated bone loss based on BMD results:

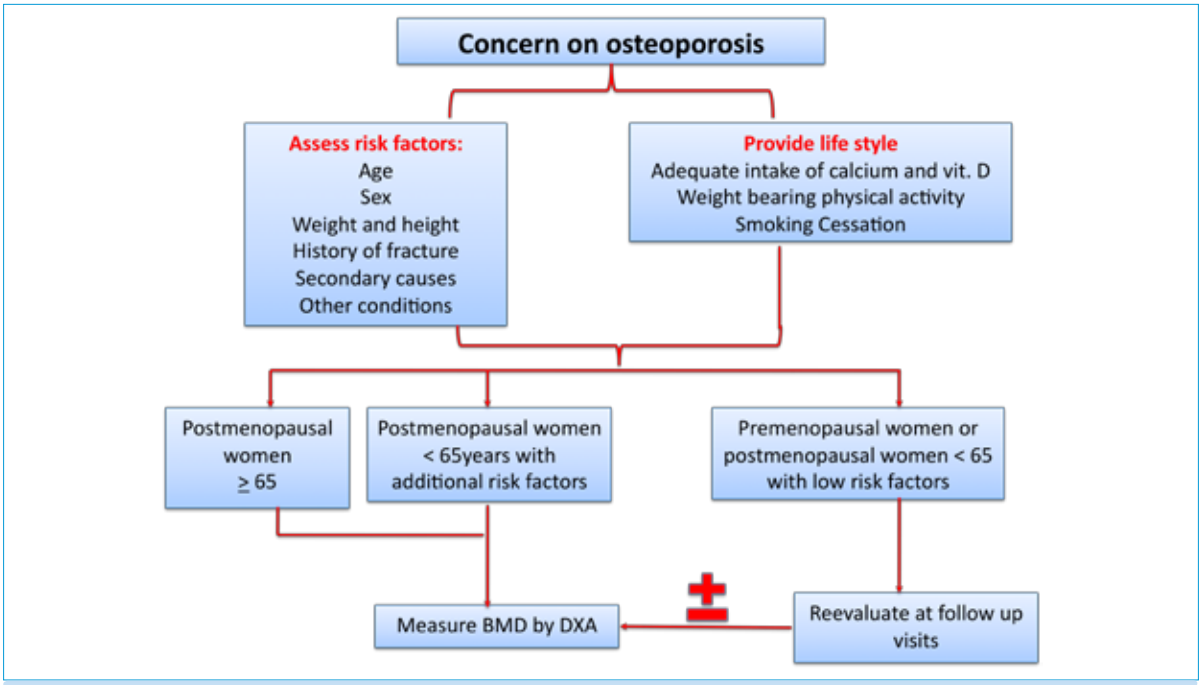

Figure 23-4: Algorithm for screening for osteoporosis using DEXA. Pharmacotherapy is usually considered based on BMD results.

- Estrogen replacement therapy: estrogen is effective in preserving bone loss, however it is usually not prescribed for the sole treatment or prevention of osteoporosis (see later guidelines for HRT).
- Treatment and follow for established cases of osteoporosis is best provided in combination with specialist endocrinologist. The treatment is usually by agents that reduce bone resorption. The commonly used agents for treatment of osteoporosis include e.g. bisphosphonates, selective estrogen receptor modulator "SERMs", and calcitonin.

III. Specific treatment:

- Vasomotor symptoms "Hot flushes": are best treated with hormonal replacement therapy either estrogen

Raloxifene

Is a drug that belongs to the selective estrogen receptor modulators (SERM) group. It selectively acts on estrogen receptors in the bone to decrease bone resorption. It does not stimulate estrogen receptors in the breast or the uterus.

Calcitonin

Is a peptide hormone that acts by inhibiting osteoclasts, which are involved in bone resorption activity. Serum calcium levels must be monitored in patients taking this drug.

Bisphosphonates

Are the most useful pharmacological intervention and work as antiresorptives.

or combined estrogen and progesterone. If hormone replacement therapy is indicated a careful history should be taken and the woman should be counseled regarding its the pros and cons based on the current evidence. If estrogen is contraindicated or the patient does not want to take estrogen alternative therapy may be prescribed (see later).

- Treatment of menstrual disorders: DUB and inter-menstrual bleeding are treated according to its severity and type (see chapter on abnormal uterine bleeding).
- Genital atrophy: symptoms related to genital atrophy (e.g. atrophic vaginitis or dyspareunia) are best treated with topical estrogen that can be administered intravaginally.
- Treatment of disorders such as hypothyroidism, high blood pressure, high blood glucose, osteopenia or osteoporosis etc. may be provided by the gynecologist or in combination with specialized clinic depending on the extend and severity of the disorder.

⇒ Hormonal Replacement Therapy and Menopause:

Hormonal replacement therapy (estrogen and combined estrogen and progesterone) used to be widely prescribed for treatment of menopausal symptoms and prevention of complications associated with estrogen withdrawal namely CVD, osteoporosis and dementia. This approach was based on results from observational studies. However more recently results from large randomized studies, mainly the WHI (women health initiative study) have provided new evidences that balance the risks and benefits of HRT.

According to these studies current guidelines for the use of HRT in pregnancy are as follow:

- Hormonal replacement therapy (estrogen or combined estrogen and progesterone) is only indicted for relief of vasomotor symptoms; genitourinary discomfort and other quality of life issues. Although estrogen is effective in prevention and treatment of osteoporosis, it should not be prescribed for those purposes.
- There are evidences that estrogen in HRT has a beneficial effect on the risk of CVD if administered in the perimenopausal or early menopausal years. The benefit of estrogen on cardiovascular mortality rates appears to be related to its effect on lipid metabolism, which includes reducing low-density lipoprotein (LDL) and increasing high-density lipoprotein (HDL).
- Women with intact uterus should receive combined estrogen and progesterone either as concurrent medication or for 10 days per cycle (e.g. conjugated estrogens 0.625 mg and Medroxyprogesterone acetate 2.5 mg/daily). Progestogen is important for

protection against endometrial hyperplasia that may develop secondary to unopposed estrogens administration. This is not necessary in women who had hystrectomy.

- The dose and length of treatment should be minimized depending on individual patient complains and clinical course.

Prior to initiation HRT carful history should be taken. Some patients might have relative or absolute contraindications for hormonal replacement therapy such as: smoking, undiagnosed vaginal bleeding, severe liver disease, pregnancy, venous thrombosis, and personal history of breast cancer.

Each patient should be able to make her own choice after careful counseling and explanation of the different options available.

Hormone therapy can be administered systemically through the oral, transdermal. Topical preparations are used solely to treat vaginal symptoms.

Adverse effects of HRT: may include bloating, mastodynia, vaginal bleeding, and headaches. Unexplained adverse effects are often the reason for discontinuation of therapy, and reassuring counseling as well as options and dose combinations should be tried before therapy is stopped.

Alternative products: for patients who does not wants to take estrogen or in whom HRT is contraindicated some alternative medications may be prescribed e.g.:

- Some herbal preparations and dietary supplements that contain various phytoestrogens, are reputed to ease the transition from perimenopause to postmenopause. However, these agents have not undergone the same scrutiny in randomized controlled trials as the pharmaceutical products.
- The selective serotonin reuptake inhibitors (SSRIs) and SNRIs (in particular, venlafaxine) have been shown to alleviate vasomotor symptoms.

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Chapter 24

Chemotherapy and radiotherapy in Gynecological Oncology

The aim of using Chemotherapy and radiotherapy in treating malignant diseases are to selectively destroy malignant cells while sparing normal healthy tissue. Unfortunately despite major development in both fields this objective has not been completely achieved. Hence patients scheduled for any or both modalities are at risk of significant and sometime potentially lethal toxic effects.

Future research aims to aim to develop targeted therapy based on tumor cells DNA hence sparing damage of normal cells.

Women with suspected cancer should be cared for in specialized "gynecological oncology centers" with full team of highly trained oncology surgeons, pathologist, radiotherapists as well as social works and psychiatrists.

However for a generalist gynecologist he/she should be familiar with development in modalities of treatment of gynecology oncology and its potential risks.

By the end of this chapter you should be able to:

- **Describe** the place of radiotherapy and chemotherapy.
- **Describe** the major types of Radiotherapy
- **List** the potential complications of radiotherapy and chemotherapy

Radiation therapy in Gynecology
Principle and application

Radiation therapy (RT) represents an important therapeutic component in the management of many gynecologic malignancies.

The indications and place varies depending on the type and stage of malignancies (Table 24-1)

Type of Cancer	*% of Radiation*
Cervical cancer	60
Endometrial cancer	45
Vulvar cancer	35
Vaginal cancer	100
Ovarian cancer	5

Table 24-1: variation in the rate of utilization of radiotherapy according to the type of cancer.

Effect of Radiotherapy: Radiation therapy exert its damaging effect by direct and indirect :mechanisms

- Direct mechanism: damage result by breaks in DNA chains or base deletions
- Indirect mechanism: damage by toxic free radicals released by interaction of radiation with intracellular water.

In radiotherapy the dose is fractionated over several sessions. This is because:

- The damaging effect work of both normal and neoplastic cells. In radiotherapy the aim is to maximize damage of neoplastic cells. Therefore fractionation of the dose increases the lethal damage to tumour cells while allowing repair or normal tissues.
- Cells vary in their response to the effect of radiotherapy throughout the cell cycle. Cells in the G1, early S and G2/M phases are highly sensitive, whereas cells in the late S phase are relatively resistant. Fractionation of the dos of radiotherapy exploits the redistribution of cells throughout the stages of the cell cycle.

Methods of Radiotherapy:

Radiotherapy for patient with gynecological cancer is usually given either:

- **Teletherapy**: use of radiation whose source is distant from the patient. Often referred to as External beam therapy.

  With the development of computed tomography (CT) planning of radiotherapy involve three dimensions localization of the treatment volume and assessment of the surrounding normal tissue. This process of "CT simulation "allows for delineation of the tumor and normal structure in three-dimensions. In addition, radidotherapy is delivered through a variable number of beams, each of which can be shaped in

order to best conform to the shape of the tumor while shielding of shielding of normal tissue by leads blocks.

Brachytherapy: use of radiotherapy source placed in close proximity to the treated tissue e.g. intracavitary therapy. It can be used as monotherapy or in conjunction with EBRT E.g. to address peripheral areas such as pelvic lymph nodes. Brachytherapy allows for the precise delivery of high-dose radiation to the target tissue and sparing of the surrounding normal tissue, notably, the small bowel, rectum, and bladder.

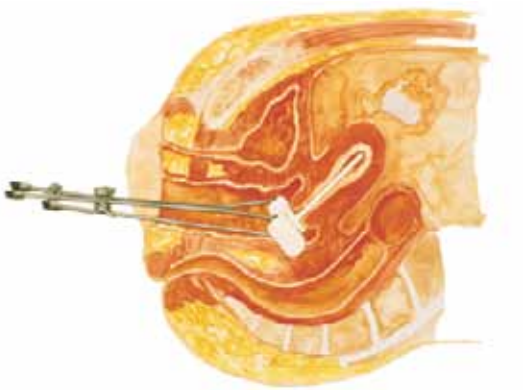


Figure 24-1: Demonstrate delivery of brachytherapy using applicators placed in the cervix

Brachytherapy is performed by placing a radioactive source in close proximity to the tumor or tissues at risk for harboring occult disease. It requires insertion of the source or instruments through which the brachytherapy source is applied. Placement of the applicators and delivery of brachytherapy may be performed under sedation or anesthesia to minimize patient discomfort.

Modern brachytherapy utilizes afterloading, in which inert needles, catheters, or custom applicators are inserted before the radioactive source is advanced.

Bothe intracavitary brachytherapy and interstitial brachytherapy are used. With intracavitary brachytherapy, applicators that will be loaded with the radioactive source are placed inside a pre-existing body cavity, such as the vagina or uterus. With interstitial brachytherapy, needles are placed into the tissues at risk, such as the parametria or paravaginal tissues. The radiation source(s) are then inserted into the needles.

Adverse effects of radiotherapy:

The incidence and severity of radiation therapy side effects depend upon the site and volume of tissue exposed; the dose, type of radiation, and schedule; and modifying factors such as previous surgery, concomitant chemotherapy, and condition of the patient.

zTable 24-2 lists the acute or short term and the late potential complications of radiotherapy on different organs.

Organ/System	Complications
Acute	
Skin reaction	Erythema and moist desquamation of the skin
Enteritis and colitis	Diarrhea
Bladder irritability	Frequency and dysuria
Bone Marrow Suppression	Anemia, thrombocytopenia, neutropenia
Late	
Small bowel	Subacute or acute bowel obstruction, bleeding, perforation, fistula and malabsorption
Large bowel	Proctosigmoiditis, rectovaginal fistula and recotsigmoid obstruction, stricture, perforation or fistulous communication with other intraabdominal organs
Bladder	Contracture with reduced capacity, hemorrhagic cystitis, vesicovaginal fistula, ureteric obstruction and hydronephrosis
Ovarian failure	Menopausal
Vagina atrophy and stenosis	Sexual problem

Table 24-2: short term and the late potential complications of radiotherapy on different organs.

Chemotherapy Principle and Application

Chemotherapy is used in a variety of situation in gynecological oncology as:

- Adjuvant and neoadjuvant (i.e. prior to surgery) treatment in ovarian cancer
- Primary treatment of gestational trophoblastic disease
- Relapsed ovarian cancer
- Advanced or replaces ovarian cancer
- Chemoradiation in cervical and vulvar cancer
- Advanced and relapsed endometrial cancer
- Sarcoma and non-epithelial ovarian tumors

The most common utilization is in the course of treatment for epithelial ovarian cancer treatment. However the best-known example of cure with chemotherapy, sometimes with single agents, is chemotherapy of gestational trophoblastic diseases.

Treatment intent:

In some situation the treatment intent may be curative the best example being trophoblastic

tumour, while in others the intent is palliative as in recurrent epithelial ovarian tumour. The intent of treatment should be clearly made to the patient with clear explanation of the balance of risk and benefit.

Drug resistance:

The mechanism of action of various drugs differs. Failure of response to a drug is most often due to the development of drug resistance. Several strategies are used to reduce or prevent drug resistance include the use of non-cross reacting agents in multi drug regimens, drugs with different toxicities, dose, route of administration and dose scheduling.

Risk and Toxicity of Chemotherapy:

Conventional chemotherapy used to kill tumour cells will also kill normal healthy cells. Table 24-3 summaries the most common drug complications.

Organ / System	Complications of chemotherapy
Hematological	Myelosuppression causing: Granulocytopenia Thromobcytopenia Anemia
Gastrointestinal	Nausea and vomiting Mucsitis: mouth and pharyngeal ulceration Oesophagitis: Dyspepsia Bowel ulceration: diarrhea, necrotizing enterocolitis *IV hydration, antimotility drugs e.g. codeine phosphate and vancomycin in NEC*
Genitourinary	Acute renal failure (cisplatin) *Pre-Post treatment intravenous hydration* Hemorrhagic cystitis *Hydration, diuretics*
Hepatotoxicity	Elevation of liver enzymes
Neurotoxicity	Cisplatim: causes ototoxicity, peripheral neuropathy
Immunosuppression	Suppression of cellular and humoral immunity predispose to opportunistic infection
Hypersensitivity reactions	Anaphylaxis with cisplatin
Alopecia	Usually reversible
Gonadal dysfunction	Infertility: many cytotoxics causes infertility
Teratogenicity	All cytotxic drugs carry risk of teratogenicity
Second malignancies	Cisplatin is associated with the development of acute leukemia

Table 24-3: The most common chemotherapeutic drug complications.

References and Further Readings:

- Yashar, CM. Basic principle in gynecologic radiotherapy. In: Clinical Gynecologic Oncology, 7th ed, DiSaia, P, Creasman, W (Ed), Elsevier, Amsterdam, 2007. p. 775.
- Halperin, EC, Perez, CA, Brady, LW. Perez and Brady's principles and practice of radiation oncology, 5th ed, Lippincott Williams & Wilkins, Philadelphia 2004.
- National Comprehensive Cancer Network (NCCN) guidelines www.nccn.org
- www.sgo.org/policy/IPChemotherapy.pdf.

Chapter 25

Cervical Cancer and Precancerous lesions

There are two main types of cervical cancer: squamous cell carcinoma and adenocarcinoma. Squamous cell carcinoma of the cervix is more prevalent than adenocarcinoma.

Cervical cancer especially squamous cell carcinoma is a potentially preventable disease. In most developed countries the incidence and mortality of cervical cancer has decreased by 75 percent over the past 50 years largely due to the wide speared implementation of screening programs. This however is not the case in developing countries.

More recently the development of vaccination against HPV, the primary cause of cervical cancer is expected to further contribute to the decrease in the incidence of cervical cancer.

While the management of cervical cancer should be handled by specialized oncology team, general gynecologists should be aware of risk factors of cervical cancer, able to counsel patients regarding the preventive measures, vaccination, importance of screening for precancerous lesions, and interpretation screening test results.

By the end of this chapter you should be able to:

- **Understand** the impact of cervical cancer on personal and society level
- **Describe** the pathogenesis, epidemiology of cervical cancer: role and risk factors for HPV infection.
- **Describe** the screening methods for cervical cancer. The prose and cones of each one.
- **Describe** the interpretation of Pap smear result and correlation between cytological smear according to the Bethesda system and the histological finding of precancerous lesion CIN 1,2 and 3.
- **Describe** the management of patient with abnormal Pap smear.
- **Counsel** patient with precancerous lesions, significance and treatment options
- **List** the symptoms and sings of cervical cancer
- **Approach** to management of cervical cancer: Diagnosis (tissue biopsy) and Staging.
- **Outline** the options of management of patient with invasive cervical cancer and factors that affect treatment choice and prognosis.
- **Describe** HPV vaccination and its role

Frequency: Cervical cancer is the second most common cancer among women worldwide, with 83 percent of cases occurring in developing countries. In the US in 2010, there are estimated to be 12,200 new cases of invasive cervical cancer per year.

Cervical cancer has serious implicatoins on patient and family life. However its impact extends beyond the burden of the disease itself, to include the resources devoted to cervical cancer screening including material, experience and expertise.

➢ **Risk Factors and Pathogenesis of cervical cancer:**

- Cervical cancer occurs in sexually active women. **The main risk factor is infection with high-risk strains of human papillomavirus (HPV**). Most other variables such as behavioral, sexual, and socioeconomic variables are dependent upon HPV infection and do not hold up as independent risk factors.
- Infection with HPV virus is directly correlated with duration of sexual activities and number of partners. Even in those with one partner HPV infection risk is relatively high (4 to 20 percent). Data from Western countries indicate that approximately 40% acquire genital HPV infection by age 50. There is no data as to the prevalence of HPV infection among local population in Saudi Arabia.

▸ HPV infection and cervical cancer:

There are approximately 30 to 40 HPV genotypes that infect the mucosa of the genital tract.

Only 8, considered high-risk types, are responsible for 95 percent of cervical cancers, and two types (16 and 18) are responsible for about 70 percent of the cervical cancer (Table 25-1).

Of the low risk types, two (6 and 11) cause about 90 percent of benign anogenital warts.

High risk (oncogenic or cancer associated) types
Common types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 69, 82
Low-risk (non-oncogenic) types
Common types: 6, 11, 40, 42, 43, 44, 54, 61, 72, 81

Table 25-1: Risk of cervical cancer with HPV. National Cancer Institute Factsheet. Human papillomavirus and cancer: Available at: www.cancer.gov/cancertopics/factsheet/Risk/HPV.

Acute infection with HPV may follow one of the following courses:

1. Latent infection that is spontaneously cleared without physical, cytological, or histological manifestations. This is occurring in 90% cases.

2. HPV replication, but without integration into the genome. This usually occurs with low-risk subtypes, such as HPV 6 and 11. It causes low-grade lesions (e.g., LSIL and CIN 1) that resolve spontaneously /or manifest as benign condylomatous genital warts.
3. Persistent infection with integration in the cellular genome with the risk of inducing high-grade precancerous lesion (e.g. HSIL and CIN 2 and 3). This occurs with high-risk subtypes of HPV (16 and 18)

Since in the majority of cases HPV infection does not cause high-grade lesions or cancer, it was found that the two factors associated with development of high-grade lesions and cervical cancer is:

- The HPV subtype
- And persistence of infection.

However some other factors was found to alter the individual's susceptibility to oncogenic HPV types and may have a role as cofactor in the pathogenesis of cervical cancer:

The likelihood of persistence of HPV infection is related to several factors:

- Older age:
- Duration of infection: *The longer an HPV infection has been recognized, the longer it will take to clear.*
- High oncogenic HPV DNA type
- Viral load:

- **Individual immunity and / or Immunosuppression:** Women with chronic conditions requiring long-term immunosuppressive therapy e.g. transplant recipients and women with systemic lupus erythematosus
- **HIV infection:** The incidence of CIN is increased in HIV-infected women due to the greater prevalence of HPV infection in these women and increasing degrees of Immunosuppression.
- **Cigarette smoking:** Cigarette smoking and HPV infection have synergistic effects on the development of CIN and cervical cancer
- **Other sexually transmitted diseases:** e.g. Herpes simplex virus and chlamydia may modulate host immunity, thereby facilitating persistence of oncogenic HPV virus.
- **Oral contraceptives:** Long-term use of oral contraceptives has been implicated as a cofactor that increases the risk of cervical carcinoma in women who are HPV positive. However, oral contraceptive use may be a surrogate

Breakdown products of cigarette smoke, such as nicotine, cotinine, or NNK (ie, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone) are concentrated in cervical mucous, where they may induce cellular abnormalities in cervical epithelium and decrease local immunity which may then allow persistence of oncogenic virus.

marker of exposure to HPV, rather than a causal factor.

Natural history of development of cervical cancer: the development of cervical cancer occurs over four major steps:

1. Infection with oncogenic HPV of the metaplastic epithelium at the transformation zone, the dynamic area between the original and present squamocolumnar junction.
2. Persistence of the HPV infection
3. Progression of a clone of epithelial cells from persistent viral infection to precancers "Cervical intraepithelial neoplasia-CIN" lesions
4. Development of carcinoma and invasion through the basement membrane

The time from initial infection, development of CIN lesion and finally invasive cancer takes an average of 15 years, although more rapid courses have been reported.

A zoologist named George N. Papanicolaou was the first to indicate that CIN lesions can be predicted by microscopic examination of cellular changes in cervical scarping "smear". The correlation between cervical cytological changes and CIN lesions was used to develop the Pap test.

The ability to predict the cervical cellular lesions (CIN lesions) by cytological examination of cervical scrapings "Pap smear" and the slow malignant transformation of these lesions form the bases of screening for cervical cancer.

Screening for cervical cancer-The Papanicolaou Smear "Pap Test"

The purpose of screening for cervical cancer is to detect pre-invasive neoplasia (CIN lesions), thereby making treatment possible before the disease becomes invasive. The Pap smear is administered to asymptomatic patients, rather than a diagnostic test to confirm or refute the suspicion of disease (*suspicious lesions should be biopsied*).

Methods of screening for cervical cancer:

1. Cervical cytology (Pap test)
2. Human papillomavirus (HPV) test: testing for HPV infection, an automated test may be adopted especially when there are not enough resources. A positive result indicates infection by a high-risk type of HPV and hence the needs for further follow up. A negative result indicates the absence of infection by one of the high-risk types of HPV.

Cervical cytology (Pap test): is the most common screening method. Currently there are two methods for cervical cytology (Pap test)

- The conventional Pap smear: consists of cells, sampled from the cervix and vagina using a brush or spatula, which are placed directly on a slide and fixed with a chemical fixative in the office or clinic. The false negative rate with this method for high-grade intraepithelial lesions is generally about 20%, even higher for glandular lesions and invasive cancer.

- Liquid-based cytology: In this method the sampling of cells is performed as in the conventional method, but then the cells are suspended in a liquid transport medium, to subsequently be filtered in the laboratory and examined. The liquid-based cytology method eliminate potential errors and reduce false positive rate of the conventional Pap smear that may be due to:
  - Failure of properly plating the abnormal cells on the slide
  - Less fixation and drying artifact.
  - Eliminating cellular obscuration on the slide by blood, mucus and inflammatory cells.

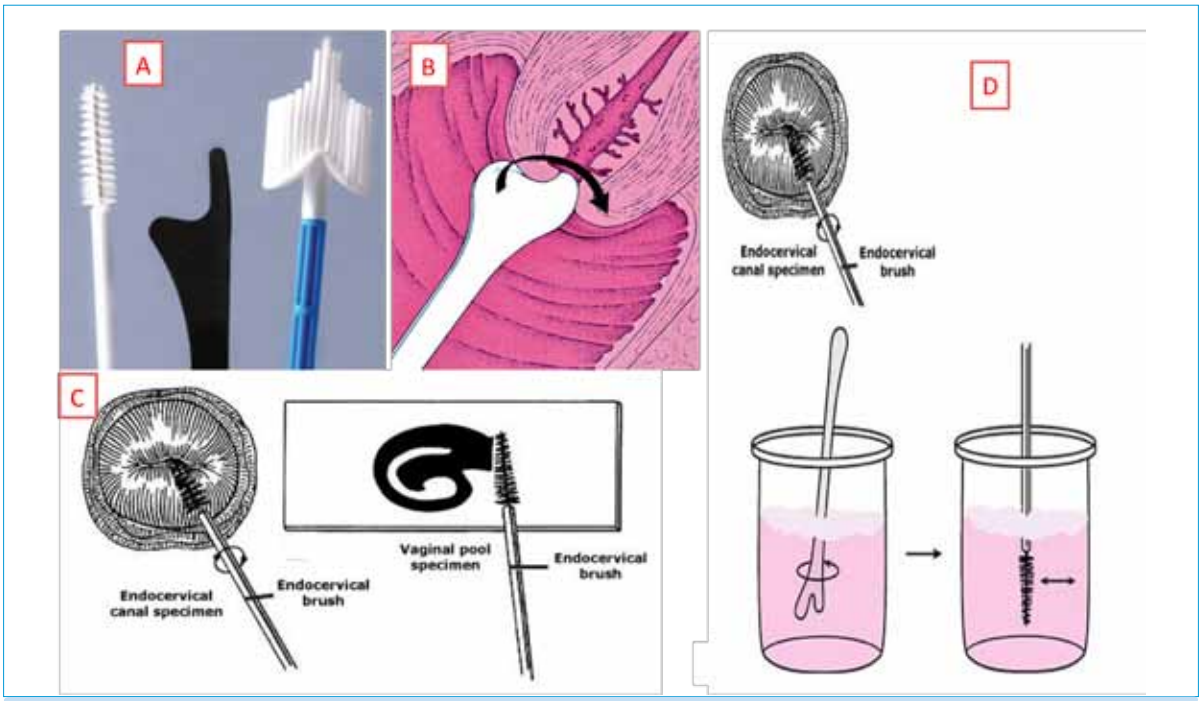


Figure 25-1: **A**: Different devices used for pap smear (spatula or brush). **B**: Close up diagram of sampling shows importance of include the squamo-columnar junction of the cervical epithelium. **C:** the smear is spread and fixed on slide (conventional test) or **D:** dipped in liquid base medium

Interpretation of the Pap test result "Bethesda system":

Pap smear results are now widely classified according to the **Bethesda system**, first introduced in 1988, and revised in 2001 (Figure 25-2).

According to the Bethesda system the Pap test results are interpreted as:

- **Negative for intraepithelial lesions or malignancy**
- **Epithelial cell abnormality is specified.**

- Squamous (cervical squamous intraepithelial lesions (CSIL):
  - Low grade squamous intraepithelial lesion (LSIL): LSIL, especially in young women, is generally a transient HPV infection
  - High grade squamous intraepithelial lesion (HSIL): HSIL is more likely to be associated with persistent HPV infection and a higher risk of progression to cervical cancer
- Glandular:
  - **Atypical epithelial cells (for cases where a squamous versus glandular origin cannot be determined)**

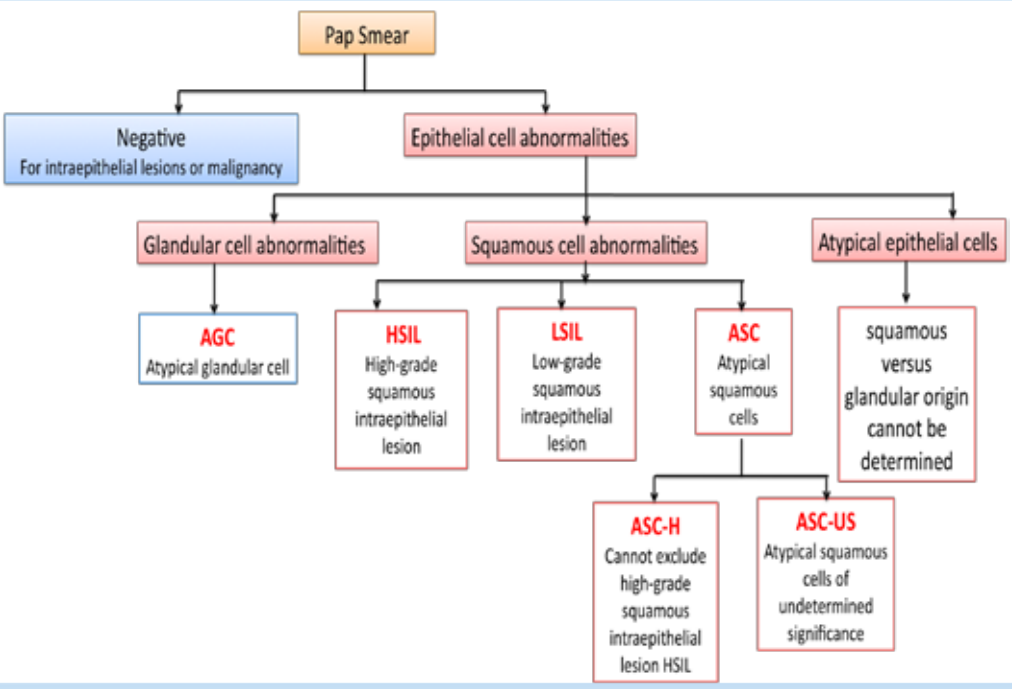


Figure 25-2: the Bethesda system for classification for interpretation of Pap smear test results

As pointed before there is correlation between cytological "Pap smear results and histological "CIN" lesions (Figure 25-3). However this correlation is not absolute and either of the cytologic findings (LSIL or HSIL) may be associated with a subsequent histologic finding that is more or less severe. It is estimated that direct correspondence occurs only in about half of patients. Hence in most cases following abnormal smears a tissue biopsy is required.

Implications and Risks of Screening: in national mass screening program abnormal cervical cytology results are relatively common (4-5%). Therefore gynecologist should be able to counsel women not only on the benefit of Pap screening but also on its potential risks and the significance of normal and abnormal result**.** The risks of Pap test include:

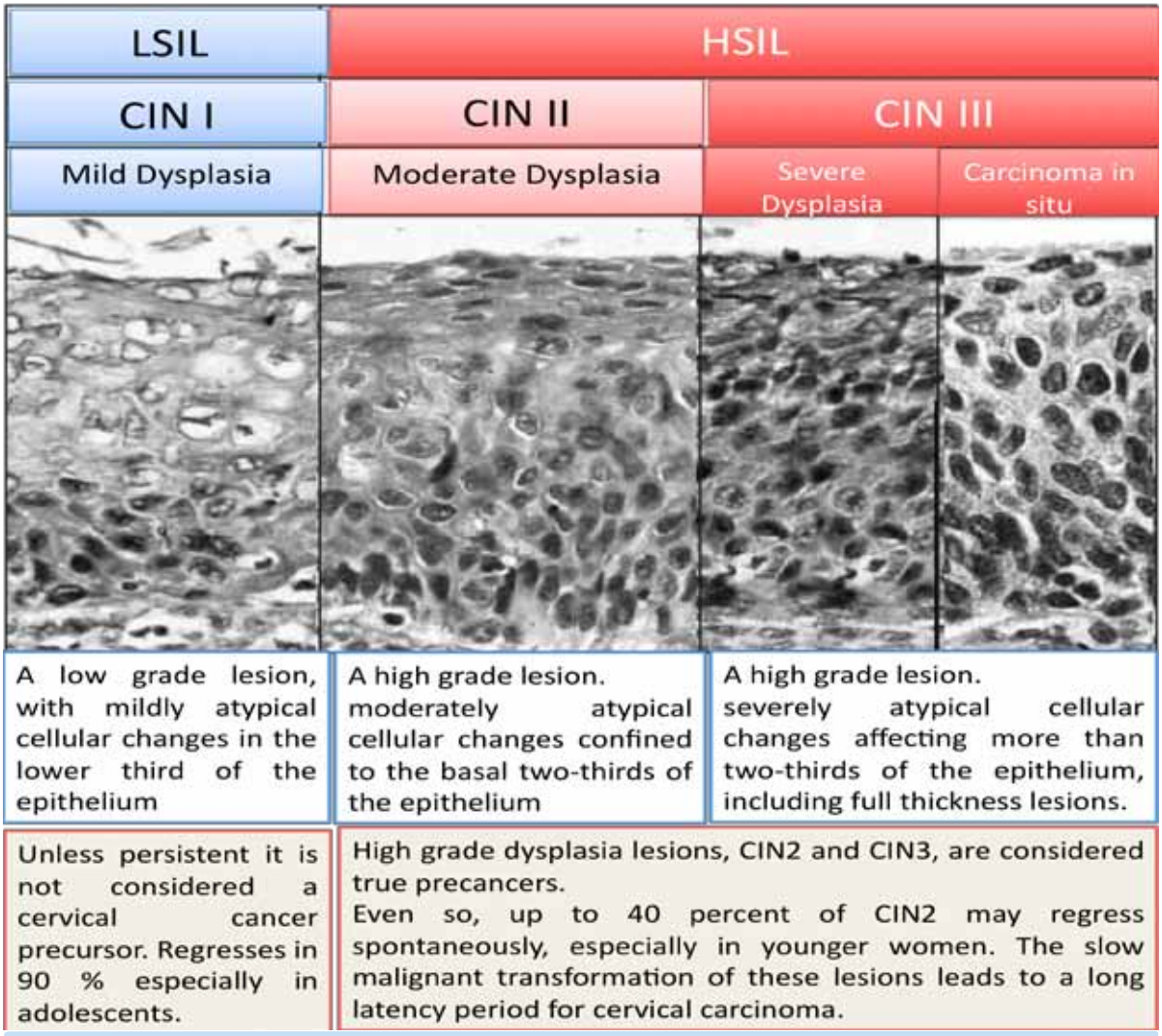


Figure 25-3: Correlation between Cytologic and histologic findings

- Discomfort and inconvenience:
- Psychosocial consequences: These are common consequences that need to be carefully addressed.
- Adverse health outcomes: may results from over treatment or follow up.
- And costs.

Recommendations for screening for cervical cancer:

Based on follow-up and observational studies most of professional organizations recommend the following guidelines regarding screening for cervical cancer:

- **Starting age:** Normally cervical screening should be initiating at age 21 (*older guidelines used to recommend initiating screening at age 21 or three years after the onset of sexual activity, whichever comes first*).
- **Stopping age:** Cervical screening can be stopped at 65 to 70 years of age who have had three or more consecutive normal smears, and no abnormal results in the previous ten years.
- **Frequency:** biennial for women under age 30 and reducing the frequency to every two to three years for women aged 30 and older who have had three consecutive normal Pap tests, or no more than every three years if they also are tested for HPV DNA.

Risk groups that may require more frequent screening:

- HIV infection.
- Immunosuppression
- In utero DES exposure
- Women who have been treated in the past for CIN2, CIN3, or cervical cancer

Management of Patient with Abnormal Pap smear

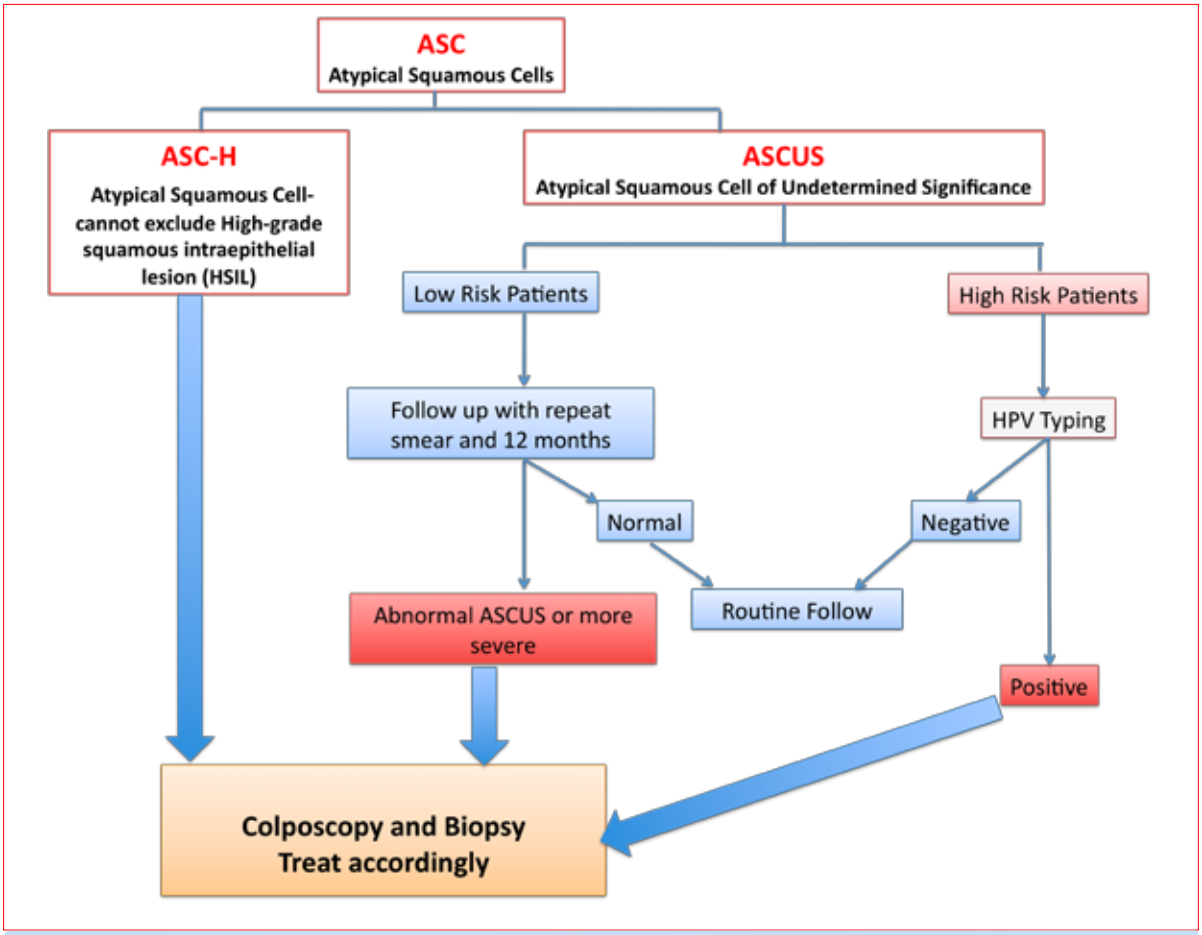
Abnormal Pap smear is not uncommon, it is estimated that about 4 % of smears will be abnormal. The most frequent cytological finding is the atypical squamous cells of undetermined significance (ASC-US), occurs in 5% of Pap smears.

Appropriate management requires referral to gynecological oncologist. Nevertheless a gynecologist should be able to counsel patient as regard the need for further evaluation, follow up, significance and prognosis of abnormal lesions.

The results of cytological examination (Pap test) reflect the degree of pathological lesion. However as pointed earlier the correlation between abnormal cytology and tissue histology is not absolute. Therefore management is never based on cytological results alone. Therefore as a general principle: **An abnormal Pap smear result should be evaluated by tissue biopsy** usually a colposcopically directed biopsies.

Further treatment decisions are then made based upon diagnostic results from histologic examination (see next section on CIN lesion).

The following section describes algorithms for management of the different grades of abnormal cervical smears further detailed algorithms can be found online at www.ASCCP.org



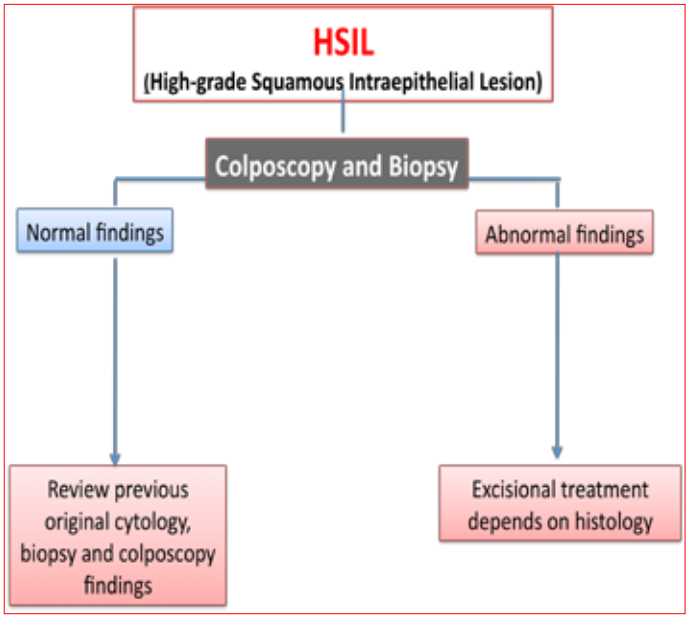
Algorithm-1: In (ASC-US) the potential risks are low include:
Associated CIN 2 or 3: 5-17%

- Association cervical carcinoma: 0.1 - 0.2 %
- Therefore follow up is acceptable before resorting to colposcopy and biopsy especially in low risk patients. This is not the case in ASC-H in which biopsy is first option (exceptions may be in adolescents see text.

Management of LSIL (Low-grade Squamous Intraepithelial Lesion)

15%- 20% will have CIN 2-3 identified on subsequent cervical biopsy
Colposcopy with directed biopsies is the initial best option.

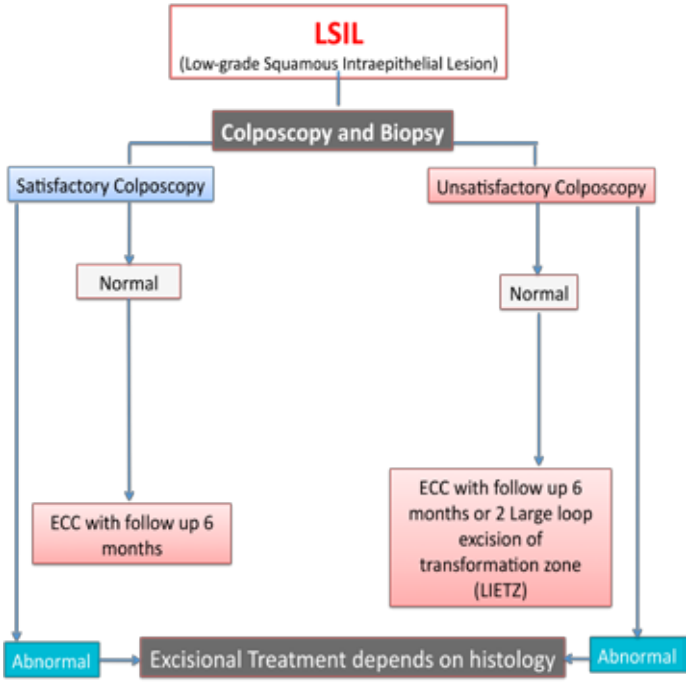
- Satisfactory colposcopy:
- Unsatisfactory colposcopy:
  Endocervical curetting (ECC) in non-pregnant with follow up in 6 months if normal or directly LLETZ.
- Pregnancy: Colposcopy with biopsy in suspected lesions.
- Adolescents: Acceptable option is, follow up in 6 months without colposcopy.



Management of HSIL (High-grade Squamous Intraepithelial Lesion)

- Associated CIN2 or CIN3: 70-75%
- Associated with cervical carcinoma: 1-2%

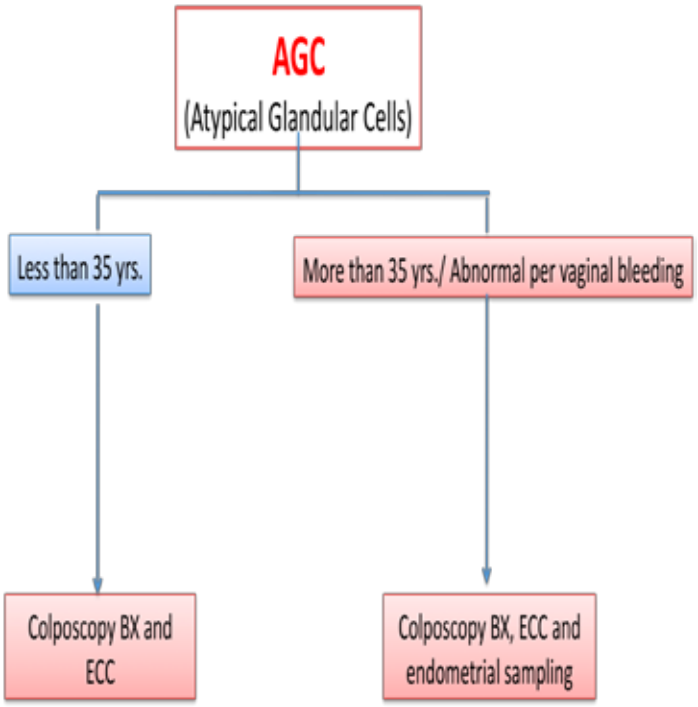
Recommended options:
Refer directly to colposcopy.
If colposcopy and biopsies fail to identify CIN, review of the original colposcopy cytology.
Biopsy and treatment is recommended, if the review confirms HSIL.
Diagnostic Excisional procedure, such as electro-loop excision of the transformation zone in non-pregnant patients.



Algorithm 2: management of LSIL and HSIL. In both cases biopsy is primary option (exceptions in adolescents and pregnancy with LSIL)

Management of AGC (Atypical glandular cells)

- AGC is associated with a premalignant or malignant lesion of the endocervix or endometrium in 10 to 40 percent of cases
- Women over age 50 at higher risk of having uterine cancer than younger women (8 and 1 percent, respectively).
- Premenopausal women with AGC are more likely to have CIN 2,3 or AIS than postmenopausal women.
- Endometrial biopsy: for women > age 35 and in younger women with risk factors for endometrial neoplasia, such as unexplained or anovulatory bleeding.



Algorithm 3: for management of Pap smear wit atypical glandular cells. (ECC= endocervical curettage)

Cervical intraepithelial neoplasia (CIN)

Cervical intraepithelial neoplasia (CIN) refers to the pre-invasive pathologic lesions "dysplasia" induced in the cervical epithelial cells, by the HPV infection. **CIN changes are histologic diagnosis based on tissue specimen obtained by tissue biopsy**.

Cervical intraepithelial neoplasia (CIN) encompasses a range of histological diagnoses with minimal potential for developing malignancy to high-grade lesion with high risk of progression to malignancy. It is categorized according to the depth of involvement and the atypicality of the cellular changes as follows:

- **CIN 1 is considered a low-grade lesion**: It refers to mildly atypical cellular changes in the lower third of the epithelium (formerly called mild dysplasia). CIN1 is not considered a cervical cancer precursor and is usually caused by low risk HPV types
- **CIN 2 is considered a high-grade lesion**: It refers to moderately atypical cellular changes confined to the basal two-thirds of the epithelium (formerly called

moderate dysplasia) with preservation of epithelial maturation.

- **CIN 3 a high-grade lesion**: It refers to severely atypical cellular changes encompassing greater than two-thirds of the epithelial thickness, and includes full-thickness lesions (formerly called severe dysplasia or carcinoma in situ).

Treatment of patients with CIN:

The goal in managing women with CIN is to prevent possible progression to invasive cancer. At the same time avoid overtreatment of lesions that are likely to regress (CIN 1).

There are two general management approaches to CIN:

- **Expectant treatment**: This entails follow-up with HPV testing at 12 months or repeat cytology at 6 and 12 months. After two negative smears or a negative HPV DNA test, routine screening may be resumed.

  Expected management is offered for:

  - Patients with CIN 1, in whom the entire lesion and limits of the transformation zone are completely visualized (i.e., satisfactory colposcopic examination). Provided patient is complaint with follow up plan.
  - Adolescent patients because undetected high grade disease is uncommon in this setting, invasive cancer is rare, and regression to normal is common.
  - Pregnant women: Follow-up of pregnant women with CIN 1 is deferred until at least six weeks postpartum, to allow time for the cervix to return to the pregravid state.

- **Immediate treatment**: entails Ablation or Excision.
  - **Ablative therapy**: aims to ablate the abnormal tissue; therefore there is no

Exceptions for expectant management for patient with CIN 1

- Persistence of CIN > 24 months
- High-risk patients
- Risk of loss of follow up
- Preceded by HSIL cytology
- Unsatisfactory colposcopy
- ECC is positive
- Women > childbearing age

Indications for excisional therapy are

- Suspected microinvasion
- Unsatisfactory colposcopy
- Lesion extending into the endocervical canal
- Endocervical curettage showing CIN or a glandular abnormality
- Lack of correlation between the cytology and colposcopy/biopsies
- Suspected adenocarcinoma in situ
- Recurrence after an ablative or previous excision.

specimen for additional histologic evaluation. It can be offered if there is no suspected glandular or invasive squamous disease and patient is compliant with follow-up.

- **Excisional therapy**: the area of abnormality is excised which provide tissue for histological examination.

Excisional treatment can be performed by cold knife conization (cone biopsy), laser conization, or the loop electrosurgical excision procedure (LEEP), also called large loop excision of the transformation zone (LLETZ). The depth of conization should be limited to the minimum necessary in reproductive age women (Figure 25-4).

Hysterectomy:

In some case hystrectomy may be indicated such as:

- Conization specimen margins that is positive for CIN 2,3, especially in the women who have completed childbearing and/or expected poor compliance with follow-up.
- Presence of coexistent gynecologic conditions requiring hysterectomy: e.g. fibroid or prolapse.
- Patient request and persistent or recurrent CIN 2,3

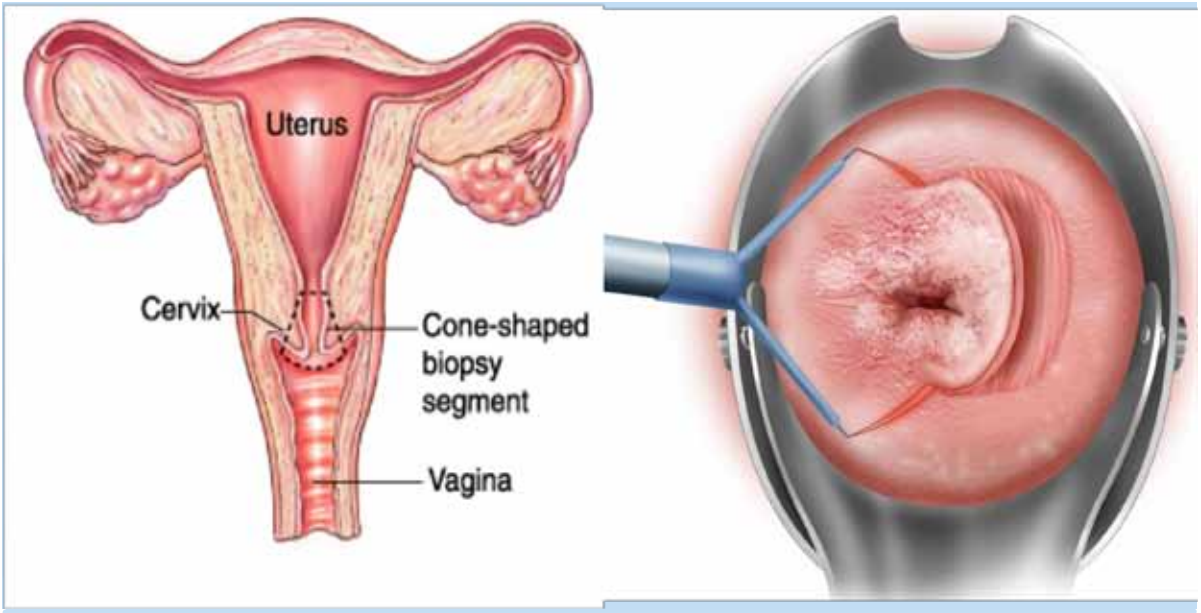


Figure 25- 4: Picture of cone biopsy (cold knife biopsy) including the whole area of the squamo-columnar junction. LEEP procedure: only the area of the lesion is removed

Invasive Cervical Cancer

Incidence: The development of invasive cervical cancer is related to age, with a mean age at diagnosis of 47 years (Table 25-2).

Squamous cell carcinoma (SCC) accounts for approximately 80 percent of cervical cancers, adenocarcinoma for 15 percent, and adenosquamous carcinoma for 3 to 5 percent

Risk Factors: Same as those for HPV infection:

- Early onset of sexual activity, multiple sexual partners, a high-risk sexual partner (e.g. promiscuous sexual activity, sexual exposure to a partner with human papillomavirus infection)
- History of sexually transmitted diseases (e.g. Chlamydia trachomatis, herpes simplex virus).
- Smoking
- High parity
- Immunosuppression
- Low socioeconomic status
- Prolonged use of oral contraceptives
- Previous history of vulvar or vaginal squamous dysplasia.

Incidence of cervical cancer by age per 100000/year	
Under age 20	0
20 to 24 years	1.7
45 to 49 years.	16.5

Table 25-2: Data from the USA (seer.cancer.gov/csr/1973_1999/cervix.pdf.). Only 10 percent of cases occur in women age 75 or older

Clinical Manifestations:

- **Symptoms**: Early cervical cancer is often asymptomatic. Presentation in symptomatic cases varies with the stage of the disease it could include one or more of the following symptoms:
  - Postcoital bleeding
  - Abnormal vaginal bleeding
  - Vaginal discharge that may be watery, mucoid, or purulent and malodorous. The vaginal discharge may be mistaken for severe cervicitis, especially if the woman is young and the cervical cytology smear shows severe inflammation, which is a common finding in overt malignancy.
  - Pelvic or lower back pain, which may radiate along the posterior side of the lower extremities, can occur with advanced disease.

- Bowel or urinary symptoms, such as pressure-related complaints, hematuria, hematochezia, or vaginal passage of urine or stool, are uncommon and suggest advanced disease.

➢ **Cervical examination:**

The clinical presentation varies from:

- A normal appearing cervix. The presentation in such cases is abnormal cervical cytology (Papanicolaou) smear
- To a grossly abnormal cervix. The lesion may manifest as superficial ulceration, exophytic tumor in the exocervix, or infiltration of the endocervix. Endophytic tumors can result in an enlarged, indurated cervix whose surface is smooth (barrel shaped cervix).

Routes of spread:

- Direct extension: into the uterine corpus, vagina, parametria, peritoneal cavity, bladder, or rectum.
- Lymphatic: The risk of lymph node metastasis increases with increasing depth of invasion. Affected lymph nodes include the obturator lymph nodes, the lymph nodes on the pelvic sidewall to the common iliac, and the paraaortic group.
- Hematogenous dissemination: The most common sites for hematogenous spread are the lungs, liver, and bone. Other sites as the bowel, adrenal glands, spleen, and brain are less frequent sites.

Management of invasive cervical cancer: The management begins with confirmation of the diagnosis then staging.

- **Confirmation of the Diagnosis**: The diagnosis of any suspicious lesion should first be confirmed by tissue biopsy, which is obtained either by: A punch biopsy from any visible lesion (from the edge of the tumor) or if the lesion is not visible and the only finding is abnormal cytology smear a directed biopsy under colposcopic examination is obtained.

  If the entire lesion cannot be visualized on colposcopy cervical conization is necessary for diagnosis of microinvasive lesions (stage IA). In this stage cervical conization can be an adequate therapy.

- **Staging**: the "stage" of the disease needs to be determined after histologic confirmation of invasive cervical cancer. Staging is based on the classification sat by professional bodies (*the International Federation of Gynecology and Obstetrics (FIGO) in collaboration with the World Health Organization (WHO) and the International Union Against Cancer (IUCC)* (Table 25-3).

Stage 0	Carcinoma-in-situ (pre-invasive carcinoma)		
Stage I	**The tumor is confined to the cervix**		
	IA	Microinvasive disease, with the lesion not grossly visible: no deeper than 5 mm and no wider than 7 mm	
		IA1	Invasion <3 mm and no wider than 7 mm
		IA2	Invasion >3 mm but <5 mm and no wider than 7 mm
	IB	Larger tumor than in IA or grossly visible, confined to cervix	
		IB1	Clinical lesion no greater than 4 cm
		IIB	Clinical lesion greater than 4 cm
Stage II	**Extends beyond the cervix, but does not involve the pelvic side wall or lowest third of the vagina**		
	IIA	Involvement of the upper 2/3 of vagina, without lateral extension into the parametrium	
	IIB	Lateral extension into parametrial tissue	
Stage III	**Involves the lowest third of the vagina or pelvic side wall, or causes hydronephrosis**		
	IIIA	Involvement of the lowest third of the vagina	
	IIIB	Involvement of pelvic side wall or hydronephrosis	
Stage IV	**Extensive local infiltration or has spread to a distant site**		
	IVA	Involvement of bladder or rectal mucosa	
	IVB	Distant metastases	

Table 25-3: Simplified summary of the most commonly used staging system for cervical cancer sat by International Federation of Gynecology and Obstetrics (FIGO) in collaboration with the World Health Organization (WHO) and the International Union Against Cancer (IUCC) (FIGO Committee on Gynecologic Oncology. Int J Gynaecol Obstet 2000; 70:209.) American Joint Committee on Cancer. Cervix Uteri. In: AJCC Cancer Staging Manual, 2010.)

In contrary to other types of cancer staging of cervical cancer is based on clinical criteria following thorough physical examination, sometime the examination has to be performed under general anesthesia. Accurate staging is critical, and should be done by experience oncologist sine the staging determines the therapeutic approach. Staging include:

- Careful inspection and palpation of the cervix and entire vagina to identify overt tumor or subepithelial vaginal extension.
- Rectovaginal examination for assessment of parametrial involvement and tumor size.
- Palpation of the liver and inguinal and supraclavicular lymph nodes is important to screen for metastatic disease.
- Investigations necessary for complete staging include: chest radiograph, assessment of the urinary tract (*magnetic resonance imaging and computed tomography urography have replaced IVP*), complete blood count, renal and liver function tests, and, in suspected advanced disease, cystoscopy and/or proctosigmoidoscopy.

Therapeutic options for Invasive Cervical Cancer:

The therapeutic options include:

- Primary surgery or chemoradiation usually reserved for early stage disease (stage I-IIA). Surgery entails radical hysterectomy [*excision of the uterus en bloc with the parametrium (ie, round, broad, cardinal, and uterosacral ligaments) and the upper one-third to one-half of the vagina, with the ovaries left intact*].

  In selected cases of stage IA1 Conization may be accepted as therapeutic option (e.g. in young patients with no lymphovascular space invasion)
- Primary chemo-radiation for locally advanced disease with or without surgery.
- Systemic chemotherapy for disease with distant metastases

The optimal choice depends upon:

- Disease factors: tumor stage, and features of increased risk of recurrence that may be revealed after histopathological review of surgical specimens.
- Patient's factors: age and childbearing plans, presence of comorbidities (e.g. fitness for particular therapeutic intervention) and preference.

The details of management, prose and cones of each option, follow up, and management of recurrence and complications of invasive cervical cancer are beyond the scope of this text. This issue are normally dealt with by specialized oncology team.

FIGO stage	5 years survival (%)
IA1	97.5
IA2	94.8
IB1	89.1
IB2	75.7
IIA	73.4
IIB	65.8
IIIA	39.7
IIIB	41.5
IVA	22.0
IVB	9.3

Table 25-4: 5 years survival rate of cervical cancer in relation to FIGO staging. Quinn, MA, Benedet, JL, Odicino, F, et al. Int J Gynaecol Obstet 2006; 95:S43.

Prognosis of cervical cancer:

Several factors influence the prognosis of patients with invasive cervical cancer. However the most important two factors are:

- Disease stage
- Followed by lymph node status

The 5 years survival according to the FIGO tumor stage is demonstrate in table 25-4.

However lymph nodes involvement can significantly modify the prognosis e.g. women with stage IB or IIA disease who have negative pelvic lymph nodes have a five-year survival of 88 to 96 percent, compared to 64 to 74 percent for those with similar stage disease and pelvic nodal metastasis

HPV Vaccination in women with CIN:

Over the last few years' researchers have managed to develop vaccines against HPV viral infection. Currently there are two types of HPV vaccines:

- **Quadrivalent HPV vaccine** (Gardasil™): targets HPV types 16 and 18, and HPV types 6 and 11, which cause 90 percent of genital warts. Gardasil is administered in three doses at time 0, and at 2 and 6 months of follow-up
- **Bivalent HPV vaccine** (Cervarix™): targets HPV types 16 and 18, is administered in three doses at time 0, and at 1 and 6 months of follow-up.

Both vaccines use virus-like particles (VLPs), which mimic the viral capsid. VLPs do not contain genetic material and are produced in biologic systems, which have well-established safety records.

Vaccination is not recommended in pregnancy although neither HPV vaccine contains

live virus; but it is categorized as category B drug because of limited data on safety in this setting.

Effectiveness of HPV vaccine:

Randomized clinical trials have confirmed the effectiveness of HPV vaccines as prophylactic and not therapeutic, they do not prevent disease due to vaccine HPV types from occurring in individuals already infected with those types. The incidence of CIN lesions was significantly less likely to develop in females who have received vaccination compared to those who have not.

Guidelines for HPV vaccination: Guideline from different professional committees recommend administration of HPV vaccination to girls before onset of sexual activities (between 11 and 13 years of age). Delayed administration to older women is not cost effective; in addition women may already have acquired the HPV infection.

A woman with a history suggestive of HPV infection may still benefit from vaccination, because immunization may provide protection against infection with HPV types that have not yet been acquired.

The development of HPV vaccination is a major step forward toward prevention of cancer cervix. However there are still many questions that need to be answered such as the duration of protection from vaccination and some issues related to long-term safety and value of vaccination of male partners.

It should also be appreciated that adoption of mass vaccination in any society should be based on benefit vs. harm and cost ratio. This require accurate data on prevalence of HPV infection and incidence of abnormal Pap smears.

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Chapter 26

Ovarian Cancer

Ovarian cancer is the second most common gynecologic malignancy and the most common cause of death among women with gynecologic cancer. Despite the major development that has been made in treatment modalities, this has not been paralleled by similar improvement in the survival rate of ovarian cancer patients. This is because in contrast to cervical cancer there is no effective screening method for early detection of ovarian cancer hence the presentation is often delayed.

The majority (90 percent) of primary ovarian tumors are derived from epithelial cells; the remainders arise from other ovarian cell types (germ cell tumors, sex cord-stromal tumors, and mixed cell tumors).

By the end of this chapter you should be able to:

- **Describe** the cellular origin of primary ovarian cancer
- **Describe** the theory of pathogenesis and risk factors for ovarian cancer
- **Describe** the options for management of patient with genetic risk for ovarian cancer
- **List** the histological types of EOC
- **Describe** the clinical presentation of ovarian cancer: late and early cases
- **List** the staging of ovarian cancer and its relevance to survival
- **Describe** the approach to management: Preoperative workup, Diagnosis (surgical), Staging,
- **Appreciate** the importance o of the surgical cytoreduction
- **List** the different the types of "sex cord-stroma ovarian tumors", and describe the clinical presentation and approach to management
- **List** the different types of "Ovarian gem cell tumors", and describe clinical presentation and approach to management.

Incidence and Epidemiology:

Worldwide, approximately 200,000 women are diagnosed with ovarian cancer and 125,000 die from this disease each year. The estimated lifetime risk of ovarian cancer in the general population of women is 1.4 percent. The median age of diagnosis of ovarian cancer is > 63 years. However among women with a hereditary ovarian cancer syndrome the mean age at diagnosis of ovarian cancer is about 10 years earlier.

There is also some geographical variation in the incidence of epithelial ovarian cancer "EOC". Western countries, including the United States, have rates approximately three to seven-folds greater than Japan, although the rate is higher in Japanese immigrants to the United States. This suggests possible environmental factors.

Histological classification of ovarian tumors:

- Primary ovarian tumors falls into three main categories (Figure 26-1) with the fourth one being non specific:
  - Epithelial tumors (90%): largely originate from the epithelial cells on the surface of the ovary and forms the majority of primary ovarian neoplasm.
  - Germ cell tumors:
  - Sex cord-stromal tumors:
  - Non specific and mixed cell type:

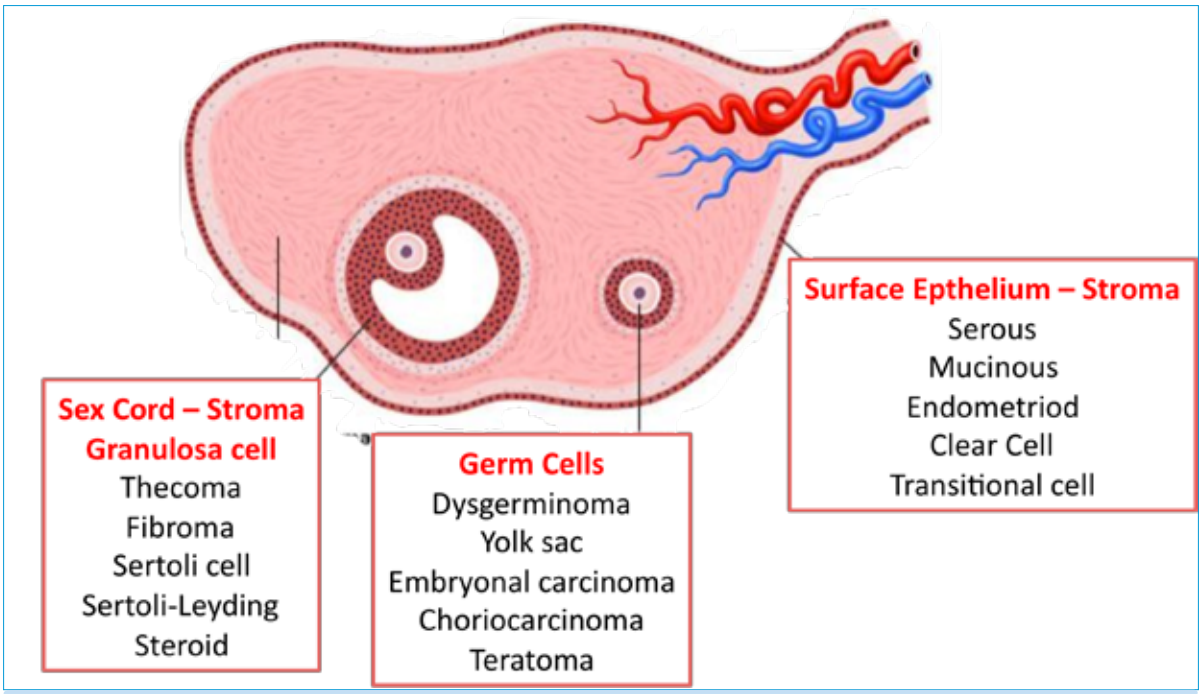

Figure 26-1: diagram presents the categories and origin of ovarian neoplasms

- Secondary metastatic ovarian tumors: especially from breast cancer or Krukenberg tumors (mucin producing neoplastic signet-ring cells involving the ovarian stroma) from the gastrointestinal tract.

Epithelial ovarian neoplasms

Approximately 90% of primary ovarian tumors are derived from epithelial cells on the surface of the ovary.

Pathogenesis and risk factors of EOC "Epithelial ovarian cancer":

It is not exactly known what trigger molecular transformation of the ovarian surface epithelium into cancerous cells. Two general hypotheses have been proposed to explain the pathogenesis of EOC.

- Repeated trauma and repair to the ovarian epithelium induced by incessant ovulation. Hence the protective effect of multiparity and oral contraceptives on the incidence of EOC.
- Excess gonadotropin secretion, promoting high estrogen concentrations, which lead to epithelial proliferation, and, possibly, malignant transformation.

Risk Factors for EOC: Epidemiological studies show association between the following factors and increased risk of EOC:

- Reproductive and hormonal factors:
  - Infertility (but not infertility treatment)
  - Nulligravidity (multiparty seem to be protective)
  - Early menarche (<12) or late menopause (>50)
  - Endometriosis:
- Genetic factors: implicated in 10% of EOC. Either in patients with family history of ovarian cancer or as a component of a syndrome e.g. site-specific ovarian cancer, breast-ovarian cancer syndrome, and the Lynch

Family history of ovarian cancer: Occur in women with history of single or two-affected family member. Such women have respectively ≅5 % risk, and ≅ 7% risk of developing ovarian cancer.

Hereditary ovarian cancer syndromes: having at least two first-degree relatives with EOC. Such woman has a risk of ≅ 25 to 50 percent for developing EOC.

- Breast-ovarian cancer syndrome (BRCA 1 and2 mutations) account of 90% of hereditary ovarian cancer
- Lynch syndrome ("hereditary nonpolyposis colorectal cancer; HNPCC") is associated with other cancers, in particular, endometrial, ovarian, urogenital, and other gastrointestinal primaries.

syndrome.

- Environmental factors:

  EOC can be triggered by an environmental carcinogen entering the lower genital tract and migrate upward through the uterus and fallopian tubes to enter the peritoneal cavity. As an example, the association between use of talc containing asbestos and increased risk of EOC. This hypothesis could also explain the lower rate of ovarian cancer in women who had tubal ligation or hystrectomy.

- Cigarette smoking: Current smoking or past smoking appears to increase the risk of mucinous ovarian cancer, but not other types of EOC
- Obesity: High body mass index (BMI) appears to increase ovarian cancer risk.

Histological classification of EOT:

Table 26-1 shows common pathological and main clinical features for epithelial ovarian tumour according to the histological classification of the FIGO and WHO.

Spread of ovarian cancer:

- Direct spear: The earliest mode of spread is intraperitoneally by exfoliation of cells that implant along the surfaces of the peritoneal cavity giving rise to metastatic foci in the posterior cul-de-sac, the paracolic gutters, on the diaphragmatic surface, the liver capsule, the surface of the intestines, and the omentum. The disease seldom invades the intestinal lumen, but progressively agglutinates loops of bowel leading to functional intestinal obstruction, or carcinomatous ileus. Eventually patients usually dies from complications of progressive bowel obstruction.
- Lymphatic channels: to pelvic, and para-aortic nodes is common in advanced disease.
- Hematogenous dissemination to the liver and lungs is common.

Epithelial Tumour	Benign – Borderline - Malignant
Serous 40% of ovarian tumors	Cell lining simulates the epithelium of the fallopian tube. **Cystadenoma (benign):** usually unilateral thin walled, multilocular cysts with septations. May have papilla. Most common benign tumour of Middle aged females **Cystadenocarcinoma:** comprise 60% - 80% of all ovarian carcinomas. Thick walled and multilocular with multiple papilla. Calcifications "psammoma bodies"may be present. More than half of these tumors are bilateral (50% to 70%).
Mucinous 10% of ovarian tumors	Cell lining simulates the endocervical epithelium. **Mucinous Cystadenoma:** Middle aged females Usually found in middle aged women Unusually large (15-30 cm), Usually unilateral. Cyst filled with sticky, gelatin-like material. Multilocular cystic spaces. Benign type more common than malignant **Mucinous Cystadenocarcinoma**: found in 10% of menopausal women. May be unilateral or bilateral (20% of patients). Mucinous cystadenocarcinomas tend to have very thick, irregular walls and septations. can also become very large and are more likely than the benign form to rupture causing pseudomyxoma peritonei.
Endometrioid 10% of ovarian tumors	Cell lining simulates endometrial cancer
Clear cell mesonephroid tumour	Cell lining Simulates "clear cells", seen in renal cell carcinomas. Can also arise from endometriosis
Brenner tumor 2-3%	Small, solid masses composed of nests of transitional epithelium within the fibrous stroma. Only 2% are malignant.
Undifferentiated carcinoma	No discernible histologic differentiation
Mixed carcinomas	Containing two or more distinct histologic types

Table 26-1: Some of the pathologic and clinical features of epithelial ovarian tumors. Classification based on the based on the FIGO and WHO classification.

Management of women at high risk:

The management of a woman with a strong family history of EOC depends upon her age, reproductive plans, and the extent of risk.

Women at risk of hereditary cancer syndromes (e.g., BRCA mutation carriers, HNPCC)

should have appropriate specialized counseling and informed consent for genetic testing. The options of management of women with BRCA1 and BRCA2 gene mutations include:

- Intensive screening by transvaginal sonography and serum CA 125 every six to 12 months beginning between age 25 and 35 years.
- The use of oral contraceptive pills to reduce the risk of ovarian cancer although its value is not very unclear.
- Prophylactic salpingo-oophorectomy after childbearing (ideally by age 35) is also another option although it does not completely eliminate the possibility of primary peritoneal serous cancer.

Clinical Presentation of Epithelial Ovarian Cancer "EOC":

Most women with EOCs are diagnosed between the ages of 40 and 65. Nonepithelial histologies (germ cell tumors, sex cord-stromal tumors, and mixed cell tumors) are more common in girls and younger women (see later).

Symptoms:

- Symptoms of early stage disease:

Unfortunate at early stages the symptoms are vague and ill defined and often ignored by patients. Not uncommonly an adnexal mass is accidentally discovered. Early symptoms, if present, may include recent onset of abdominal or pelvic symptoms (i.e., bloating, increased abdominal size, urinary urgency or frequency, difficulty eating or feeling full, and abdominal or pelvic pain).

- Acute symptoms due to ovarian rupture or torsion of an EOC are unusual.
- Symptoms of advanced stage disease:

The majority of cases of EOC are advanced (stage III or IV) at the time of diagnosis. The symptoms include: abdominal distention, nausea, anorexia, or early satiety due to the presence of ascites and omental or bowel metastases; dyspnea is occasionally present due to a pleural effusion.

Signs:

- Early stages ovarian malignancy: No specific features since it is difficult to feel the ovaries on routine pelvic examination. However if a pelvic mass is palpable in postmenopausal women malignancy should be suspected.
- Advanced stage disease A pelvic or pelvi-abdominal mass is felt by abdominal and pelvic examination. features strongly suggestive of ovarian malignancy are: the

presence of a solid, irregular, fixed pelvic mass. The diagnosis is almost certain if associated with an upper abdominal mass or ascites. Examination should also include:

- Rectovaginal exam and fecal occult blood testing are performed to exclude a rectal mass or bleeding.
- Breast examination: to detect breast masses.

Once a diagnosis is suspected, surgery will be necessary for confirmation, staging, and treatment of EOC.

Preoperative evaluation workup:

The goal of preoperative workup is to evaluate the extent of the disease and the patient general health and fitness.

▸ Imaging studies:

Ultrasound: Ultrasound plays an important role as a non-invasive test in predicting the nature of ovarian tumors. Some sonographic features were found to be highly suggestive of malignancy, whereas its absence is reassuring and may allow conservative follow up particularly in young women (Table 26-2 and Figure 26-1).

Presence of solid, nodular or papillary components
Septations, especially if thick (> 2 to 3 mm)
Color or power Doppler demonstration of flow in the solid component. Especially with low resistance
Presence of ascites (any peritoneal fluid in postpostmenopausal women and more than a small amount of peritoneal fluid in premenopausal women is abnormal)

Table 26-2: Some sonographic features of malignancy

Additional imaging studies: Abdominopelvic computerized tomography (CT) or magnetic resonance imaging (MRI) may demonstrate sites of metastatic spread, which can be helpful to the surgeon in planning the optimal surgical procedure.

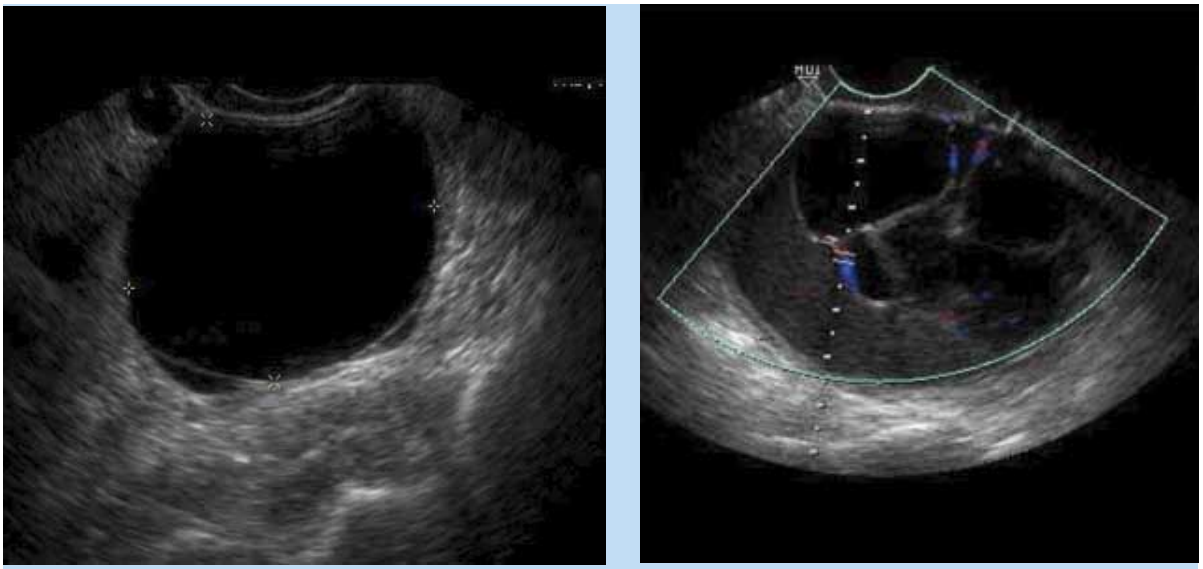

Table 26-2: Ultrasound picture showing features of ovarian cyst. Left: benign, cyst with clear contents. Right: Complex cyst with features suggestive of malignancy (septa, with increased vascularity). Additional features on ultrasound include bilateralism of cysts, and presene of ascieties. .

▸ Laboratory evaluation:

Tumor markers: the currently approved markers for EOC are:

CA 125-tumor marker: Is a glycoprotein (normal <35 units/mL) that is found to be elevated (>65 units/mL) in over 80 percent of women with advanced EOC.

The sensitivity of CA 125 depends
- The stage of the disease: 50% for stage I vs. 90% for stage II or higher.
- The histology: elevated serum CA 125 is highest in women with serous histology (the most common type of EOC) and lowest in those with mucinous tumors.

Although CA 125 is not diagnostic but the finding of raised CA 125 in postmenopausal woman with a pelvic or abdominal mass is highly suspicious of EOC. In premenopausal women, elevated CA 125 could be due to other benign conditions (see DD).

Important value of CA 125 base line measurement is in evaluating the success of subsequent treatment if the patient is found to have a malignancy.

DD diagnosis of elevated CA 125: CA 125 is not specific for EOC. It is also increased in patients with other malignancies, including endometrial cancer and certain pancreatic cancers; in a variety of benign conditions, such as endometriosis, uterine leiomyoma, and pelvic inflammatory disease; and in approximately 1 percent of healthy women (table 7).

Human epididymis protein 4 (HE4): is a recently approved tumor marker for monitoring patients with ovarian cancer for disease progression or recurrence.

- Specific investigations to exclude extra ovarian primary: In some cases the possibility of cancers commonly metastatic to the ovary (fallopian, primary peritoneal, gastric, colorectal, appendiceal, breast, endometrial) should be excluded.
    - Gastrointestinal evaluation: To exclude primary gastrointestinal tumors (e.g., gastric cancer) with metastases to the peritoneum or ovaries (Krukenberg tumors). Gastroscopy, colonoscopy or barium enema may be required for suspected case.
    - Mammography: Bilateral mammography should be performed in the presence of a breast mass.
    - Image-guided biopsy: of the peritoneum or omental cake may help exclude a nonovarian malignancy.
    - Paracentesis or thoracentesis: In patients with ascites, paracentesis or thoracentesis may be considered in some caes.
    - Endocervical curettage and/or biopsy: Should be considered in women with abnormal uterine bleeding to exclude the presence of endocervical or endometrial cancer.
- Investigation for evaluation of patient general health and fitness:
    - Complete blood count, liver and renal function tests, electrolytes, glucose, coagulation tests, and baseline CA 125.
    - Nutritional assessment**:** and assessment of intercurrent medical diseases, which should be under optimum control (eg, good glycemic control in women with diabetes).
    - Chest radiograph, electrocardiogram, and computed tomography (CT) of the abdomen.
    - Liver imaging helps to determine whether metastatic disease, if present, is confined to surface implants or whether a partial hepatic resection of parenchymal disease may be required.

Surgical management ovarian cancer:

Surgery is almost always performed in women with suspected ovarian cancer even when advanced. The aims of surgery are:

- To confirm the diagnosis: in early stages with tumour confined to the ovary it is

common practice to send a frozen section to confirm the diagnosis. Subsequent surgical procedure depends on the results of the pathology. This is not usually required in advanced stages of the disease.

- Staging of the disease: Proper staging is crucial since prognosis and subsequent treatment are strongly depended on the stage of the disease. Staging of ovarian cancer is based on FIGO classification (Table 26-5 for details). The procedure for staging follows a systematic approach and should be performed by specialist in gynecological oncology (Table 26-4 for basic staging procedure).

Stage I disease is confined to the ovaries;

Stage II includes extension into other pelvic tissues

Stage III refers to disease that has spread beyond the pelvis or to retroperitoneal lymph nodes but remains in the abdomen;

Stage IV: presence of distant metastasis or involvement of liver parenchyma.

- Attempt optimal cytoreduction: defined as surgical removal of the primary tumour with all the metastases. Cytoreduction is crucial for successful treatment since there is inverse correlation between the remaining residual disease and survival rate. Cytoreduction surgery is considered optimal when there is no visible disease or residual disease < 1 cm in maximum.

Outline of treatment plan of EOC: Details of treatment of ovarian cancer is beyond the scope of this text. For optimum results a specialized gynecology oncology team should be the ones to take care of oncology patients. However the plan of management is strongly influenced by the stage of the disease, in addition to other patient's general health factors.

- In approximately 25 percent of patients present with tumor confined to the ovary (stage I) or tumor beyond the ovary but confined to the pelvis (stage II). These patients are managed initially with a maximal cytoreductive procedure. Systemic chemotherapy may or may not be recommended.

  Fertility preservation can be considered in early Stage Ia disease in young patients who wish to complete their families.

- Unfortunately 75 percent of women with EOC present with advanced disease (stage III) or (stage IV). The standard of care for these patients is surgery followed by systemic chemotherapy. Exceptions this role are:

  - Patients who are poor candidates for surgery because of significant comorbidities (eg, preexisting medical conditions, severe malnutrition, massive ascites). In some cases chemotherapy may be initiated first with latter evaluation of response and consideration of cytoreduction surgery.

- Patients in whom initial cytoreduction is not be feasible because of disease bulk.

Post-treatment surveillance:

Post treatment surveillance to detect recurrent or persistent disease is performed at regular intervals. The frequency of visits may vary but it generally entails:

- Visits every two to four months for two years, then every six months for three years, then annually.
- CA-125 level at every visit
- Pelvic examination, chest radiographs, and chest/abdomen/pelvic CT scan as clinically indicated

FIGO stage	Overall Survival percent		
	1 year	2 years	5 years
IA	98.4	96.2	89.6
IB	100	93.9	86.1
IC	96.3	91.4	83. 4
IIA	93.0	87.2	70.7
IIB	93.4	84.5	65.5
IIC	93.6	85.6	71.4
IIIA	88.1	72.6	46.7
IIIB	85.7	70.6	41.5
IIIC	84.8	64.5	32.5
IV	72.4	48.4	18.6

Table 26-3: Carcinoma of the ovary: FIGO stage and overall survival for patients. from: Heintz, AP, et al. Carcinoma of the ovary. Int J Gynaecol Obstet 2006; 95:S161.

Prognosis and prognostic factors:

Disease stage strongly influences the prognosis. The 5 years survival range from 90% for stage Ia diseases to less than 20% for stage IV disease. The survival rate by stage is shown in table 26-3 in one of the recent studies published studies.

Other factors prognostic factors associated with improved outcome include:

- Patient age: younger age, more likely to have tumors of less aggressive histology and lower grade, and better baseline performance status
- Low volume of residual disease.

1. **Collection of fluid for cytology**: Obtain any free fluid for cytologic evaluation
2. If no free fluid is present, obtain washings by instilling and recovering 50 to 100 mL of saline. The fluid should irrigate the cul de sac, paracolic gutters, and area beneath each diaphragm.
3. **Exploratory laparotomy**: entails systematic exploration of all intraabdominal organs and surfaces: bowel, liver, gallbladder, diaphragms, mesentery, omentum, and the entire peritoneum should be visualized and palpated, as indicated. It includes also palpation of retroperitoneal structures and lymph nodes. Suspicious nodes should be removed and sent for frozen section examination.
4. Suspicious areas or adhesions should be biopsied. If there are no suspicious areas, multiple biopsies should be obtained from the peritoneum of the cul-de-sac, paracolic gutters, bladder, and intestinal mesentery
5. The diaphragm should be biopsied or scraped for cytology. A laparoscope and biopsy instrument may be used.
6. The omentum should be resected from the transverse colon.
7. The paraaortic nodes should be exposed and enlarged nodes removed. Nodes superior to the inferior mesenteric artery should also be resected. (Routine lymphadenectomy is not required for sex cord-stromal tumors).
8. In the absence of suspicious nodes, pelvic and paraaortic nodes should still be sampled to exclude the possibility of microscopic stage III disease. (Routine lymph node sampling is not required for sex cord-stromal tumors).
9. **Hysterectomy and salpingo-oophorectomy**: Hysterectomy and bilateral salpingo-oophorectomy are performed in virtually all women with ovarian cancer. The aim is to remove any occult metastases in the contralateral ovary, adnexa, or uterus, or a synchronous primary endometrial cancer. However, if the contralateral ovary appears normal, a unilateral salpingo-oophorectomy may be considered for apparent Stage IA EOC in women who strongly desire to preserve fertility. Fertility-conserving surgery may be an option for some women in young women with ovarian tumors of low malignant potential or nonepithelial ovarian cancers. Fertility preservation is also an option for women with stage IA EOC.

Table 26-4: principle steps in staging surgery of EOC

Stage I	Growth limited to the ovary	
	Stage Ia	Growth limited to one ovary, no ascites. No tumor on the surface; capsule intact
	Stage Ib	Growth limited to both ovaries, no ascites. No tumor on the surface
	Stage Ic	Either stage Ia or Ib but with tumour on surface of one or both ovaries or with capsule ruptured or with ascites present containing malignant cells or with positive peritoneal washings
Stage II	Grwoth involving one or both ovaries with pelvic extension	
	Stage IIa	Extension or metastasis or both to the uterus or tubes or both
	Stage IIb	Extension to other pelvic tissues
	Stage IIc	Tumor either stage IIa or IIb but with tumour 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 III	Tumor involving one or both ovaries with peritoneal implants outside the pelvis or positive retroperitoneal or inguinal nodes or both. Superficial liver metastasis equals stage III. Tumor is limited to the true pelvis but with histologically proven malignant extension to small bowel or omentum	
	Stage IIIa	Tumor grossly limited to the true pelvis with negative nodes but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces
	Stage IIIb	Tumor of one or both ovaries with histologically confirmed implants of the abdominal peritoneal surfaces, none exceeding 2 cm in diameter. Nodes negative for disease
	Stage IIIc	Abdominal implants >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 to stage IV. Parenchymal live metastais equals stage IV.	

Table 26-5: International Federation of Gynecology and Obstetrics (FIGO) staging for primary carcinoma of the ovary

Ovarian sex cord - stromal tumors

Ovarian sex cord-stromal tumors are a heterogeneous group of tumors that develop from the cells surrounding the oocytes, which contains granulosa cells, theca cells, Sertoli cells, Leydig cells, and fibroblasts of gonadal stromal origin (Figure 26-1).

It constitutes around 5-8% of all primary ovarian neoplasms. The tumors are generally considered to be low-grade malignancies.

Clinical presentation: sex cord-stromal tumors are diagnosed at earlier stages than epithelial tumor because it often produces steroid hormones (Table 26-6). Therefore

the diagnosis should be suspected in patients who present with signs of estrogen excess or androgen excess (virilization) as in Leyding cell tumour.

The diagnosis is confirmed by histology at time of surgical excision "oophorectomy".

Management: Preoperative preparation, intraopertive staging and management are the same as for patient with epithelidal tumour.

Sings of estrogen excess

- **In childhood:** precocious puberty
- **In Adults:** abnormal uterine bleeding, breast tenderness endometrial hyperplasia or carcinoma
- **In menopausal patients:** postmenopausal bleeding

A total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH-BSO) and complete surgical staging are recommended for women who have completed their family.

▸ Granulosa cell tumor:

Granulosa cell tumor is the most common type of sex cord cell tumors. It has malignant potential (i.e., the ability to recur and metastasize). Two types are recognized:

- The adult type is the most common one, median age of presentation 50-54 years.
- The rare juvenile typed (5%) presents before puberty and in young women.

Clinical features: typically presents as a large asymptomatic mass noted on abdominal or pelvic examination.

In 50% of cases complications of estrogen excess "hyperestrogenism" occur in tumor that produces estrogen

Treatment: total abdominal hysterectomy and bilateral salpingo-oophorectomy for women with granulosa cell tumors who have completed childbearing

Women with stage I disease who wish to preserve childbearing capacity : unilateral oophorectomy alone may be offered.

Fibroma:

Fibromas are the most common of the sex-cord **stromal** tumors. Pure fibromas are benign solid tumors, usually unilateral, that primarily occur in postmenopausal women. Ascites is present in 10 to 15 percent of cases and hydrothorax in 1 percent, especially with larger lesions.

Pseudo-Meigs' syndrome has been reported from a number of sources, such as leiomyomas, struma ovarii, mucinous cystadenoma, teratoma, and tumors that are metastatic to the ovary (particularly colorectal cancer).

The association of ovarian fibroma with ascites and/

or pleural effusion is termed Meigs' syndrome. The disease in benign even in the presence of elevated serum CA 125 levels does not indicate malignancy.

Thecoma: Thecomas are solid, fibromatous tumors and are generally benign, composed of theca cells and arise from the ovarian stroma.

The most common symptom of thecomas is abnormal uterine bleeding as a result of endometrial stimulation from estrogen produced by theca cells. Endometrial hyperplasia and carcinoma are present in approximately 15 and 25 percent of cases, respectively.

	AFP	hCG	LDH	E2	Inhibin	Testost	Andro	DHEA
Germ cell tumors								
Dysgerminoma			+	±	–	–	–	–
Embryonal	±	+	±	±	–	–	–	–
Immature teratoma	±	–	±	±	–	–	–	±
Choriocarcinoma	–	+	±	–	–	–	–	–
Endodermal sinus	+	–	+	–	–	–	–	–
GonadoblastomaΔ	–	–	–	±	±	±	±	±
Polyembryona	±	+	–	–	–	–	–	–
Mixed germ cell	±	±	±	–	–	–	–	–
Sex cord-stromal tumors								
Thecoma-fibroma	–	–	–	–	–	–	–	–
Granulosa cell	–	–	–	±	+	±	–	–
Sertoli-Leydig	±	–	–	±	±	±	±	±

Table 26-6: Markers secreted by germ cell and sex cord-stromal tumors of the ovary.
AFP: alpha-fetoprotein; hCG: human chorionic gonadotrophin; LDH: lactate dehydrogenase; E2: estradiol; testost: testosterone; andro: androstenedione; DHEA: dihydroepiandrostenedione.
Δ Type of germ cell-sex cord stromal tumor consisting of neoplastic germ cells and sex cord-stromal derivatives.

Ovarian germ cell tumors

Ovarian germ cell tumors are derived from primordial germ cells of the ovary. They may be benign or malignant.

The histological types of ovarian germ cell tumors (OGCTs) that arise from the ovary are similar to those developing in the testes of men

Epidemiology: OGCTs arise primarily in young women between 10 and 30 years of age; they represent 70 percent of ovarian tumors in this age group.

It comprises approximately 20 to 25 percent of overall ovarian neoplasms, but account for only about 5 percent of all malignant ovarian neoplasms.

Clinical manifestations: In general OGCTs tends to present early with one or more of the following signs and symptoms:

- Abdominal enlargement and pain: occur in majority of cases. Often from the mass itself, ascites, or both
- Acute abdominal pain: from rupture or torsion (occur in 10% of cases)
- Effects of hormones production such as: Precocious puberty, abnormal vaginal bleeding: occur in 10% of cases. Presumably from hCG production, or Symptoms of pregnancy: from hCG production

Diagnosis: The diagnosis is made by histology at time of surgical excision.

But in some cases it can usually strongly suggested preoperatively by imaging (e.g. in Dermoid cyst) and an elevated level of an associated tumor marker (e.g., hCG, alpha fetoprotein [AFP])

Staging and surgical treatment: follows the general line of the International Federation of Gynecology and Obstetrics (FIGO) staging system for epithelial ovarian cancer.

Table 26-7 summaries the common germ cell tumour, the cell of origin, epidemiology and potential for malignancy. Teratoma (the immature variety) and Dysgerminoma are the most common ones.

	Epidemiology	Benign vs. Malignancy	Histology
Dysgerminoma (female version of the male seminoma)	Children, adolescents and young adults	All dysgerminomas are malignant but only about one-third behave aggressively	Undifferentiated germ cells
Endodermal sinus tumor (Yolk sac tumor)	Premenarcha girls and women; median age at presentation is 23 y	14 to 20 percent of all malignant OGCTs	Derived from the primitive yolk sac
Embryonal carcinoma	The average age at diagnosis is 15 years	Aggressive ovarian malignancies Accounts for 4 percent of malignant OGCTs	Resembles the more common embryonal carcinoma of the testis
Polyembryoma	Young girls and may present with signs of pseudopuberty	Very aggressive tumor with extensive local infiltration and distant metastasis	Composed of embryoid bodies that morphologically resemble normal embryos
Choriocarcinoma "Non-gestational choriocarcinoma"	Very rare type of tumor	Highly malignant, tend to develop early hematogenous metastasis In contrast to gestational choriocarcinomas, ovarian tumors are relatively chemoresistant	Histologically identical to primary gestational choriocarcinoma
Teratoma	The most common type of germ cell tumor Most, but not all, teratomas are benign Formed of "Germ cell" that differentiate toward somatic-type of tissues it include:		
▶ **Immature** (malignant teratoma): < 1% of teratoma ▶ **Mature** ○ Cystic (Dermoid Cyst) ○ Solid (rare) ▶ **Monodermal or highly specialized**			

Table 26-7: most common types of germ cell tumors OGCT, its epidemiological features, malignant tendency and cell origin

Teratoma: Teratomas are the most common type of germ cell tumor. Most, but not all, teratomas are benign.

Teratoma comprise of varied group of tumors that show differentiation toward somatic-

type tissues, which can be typical of either adult or embryonic development.

Teratoma are divided into three categories:

- Mature (cystic or solid, benign),
- Immature (malignant).
- Monodermal or highly specialized.

➢ **Mature cystic teratomas**

Accounts for more than 95 percent of all ovarian teratomas known as "Dermoid cysts" is almost invariably benign. It is the most common ovarian tumor in women in the second and third decade of life

Mature cystic teratomas contain mature tissue of ectodermal (e.g. skin, hair follicles, sebaceous glands), mesodermal, and endodermal origin.

The characteristic macroscopic appearance of benign cystic teratomas is a multicystic mass that contains hair, teeth, and/or skin that is mixed into sebaceous, thick, sticky, and often foul-smelling material (Figure26-3).

Clinical manifestations: Not uncommonly dermoid cysts are discovered accidentally during routine examination. Symptoms if present, depend upon the size of the mass and or complications e.g. Torsion or rupture, which are rare events.

Diagnosis: These tumors have a characteristic ultrasound appearance, which allows reasonably accurate noninvasive diagnosis in many cases. Definitive confirmation of diagnosis is made at the time of surgical excision.

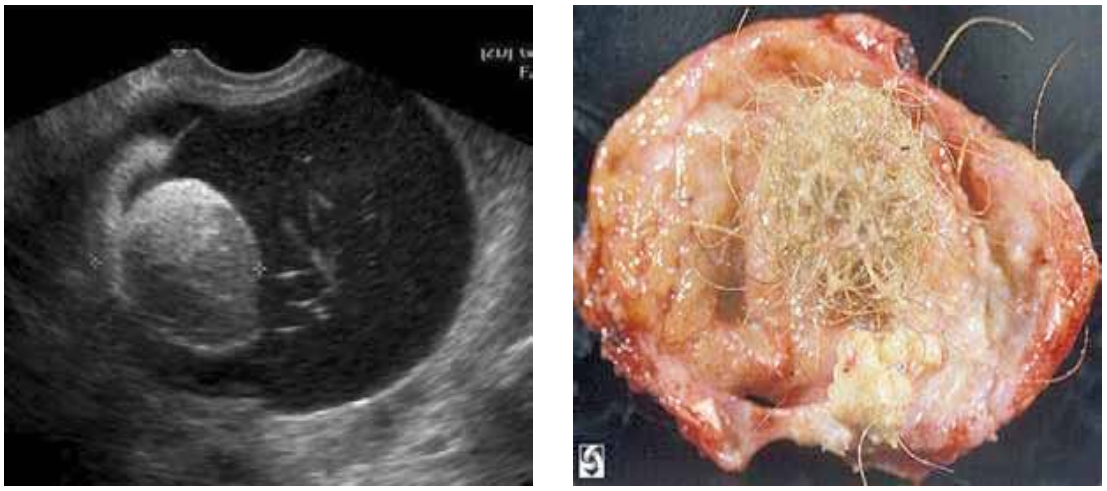

Figure 26-3: Gross and US appearance of Dermoid cyst (Right and Left respectively)

Treatment: by ovarian cystectomy for young women. For women who have completed childbearing, salpingo-oophorectomy is an acceptable treatment. Care should be taken to avoid rupture and spillage of the sebaceous cyst fluid with the consequence of a marked granulomatous reaction (chemical peritonitis) that leads to formation of dense adhesions.

Risk of malignant transformation: Malignant transformation occurs in 0.2 to 2 percent of mature cystic teratomas. Although any of the components of a mature cystic teratoma may undergo malignant degeneration, squamous cell carcinoma arising from the ectoderm is the most common secondary tumor.

Mature solid Teratoma: In rare instances, a teratoma is solid but is composed entirely of benign-appearing heterogeneous collections of tissue and organized structures derived from all three-cell layers. It may be difficult to differentiate these tumors from malignant immature teratomas, which are almost always solid

➢ **Monodermal highly specialized teratomas**:

The specialized or monodermal teratomas are a rare category of teratomas that consist of a predominant specific cell type, the most common of which are struma ovarii and carcinoid.

- Struma ovarii: is a benign teratoma predominantly composed of mature thyroid tissue. The secretion of thyroid hormones results in clinical hyperthyroidism in 25 to 35 percent of patients.
- Carcinoid tumors: composed of gastrointestinal or respiratory epithelium within a mature cystic teratoma. Carcinoid syndrome develops in about one-third of cases.

➢ **Immature Teratoma**:

Immature teratomas are also called malignant teratoma, teratoblastoma, or embryonal teratoma . They comprise less than 1 percent of ovarian teratomas and are most common in the first two decades of life.

Histopathology: These tumors are composed of tissue from the three germ cell layers: ectoderm, mesoderm, and endoderm, which are often arranged in a haphazard manner. Histologically, there are varying amounts of immature tissue differentiating toward cartilage, glands, bone, muscle, nerve, and others.

The tumor is usually graded according to degree of differentiation (ranging from I [well differentiated] to III [poorly differentiated]).

Dysgerminoma:

Account for 32.8 percent of malignant OGCTs.

The majority of cases (75 percent) arise in adolescents and young adults, in whom they account for about one-third of all ovarian malignancies. Because of their predilection for young women, they are one of the more common ovarian malignancies detected during pregnancy. Nevertheless, dysgerminoma can occur at any age; case reports have described patients with dysgerminoma between 7 months and 70 years of age.

Histopathology: All dysgerminomas are malignant but the degree of histologic atypia is variable, and only about one-third behave aggressively.

Dysgerminomas may develop within a gonadoblastoma (a benign or in situ germ cell ovarian tumor composed of germ cells and sex cord stroma) in phenotypic females who have a Y chromosome (e.g. patients with pure gonadal dysgenesis 46XY, mixed gonadal dysgenesis 45X/46XY, or complete androgen insensitivity 46XY).

These tumors may produce either testosterone or estrogens. Clinical presentation may include developmental abnormalities of the genitalia, primary amenorrhea, or virilization.

Clinical manifestations: The growth of dysgerminomas is usually rapid; as a result, patients often present with abdominal enlargement and pain due to rupture with hemoperitoneum or torsion. Menstrual abnormalities may occur if the tumor is hormonally active.

Treatment: Surgery is performed for definitive diagnosis, staging, and initial treatment. For a unilateral tumor confined to the ovary without capsular involvement or rupture (stage IC), simple salpingo-oophorectomy is curative in over 95 percent.

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Chapter 27

Vulvar and Vaginal Cancer

Vulvar and vaginal cancer are relatively rare diseases. ItIt is associated with not only significant physical but also and psychosexual morbidity. Failure to recognize early lesions from either the patient or the physician side is responsible for delayed diagnosis in significant proportion of cases. The common embryological origin of the lower genital tract (cervix, vagina, vulva) render it susceptible to neoplasia from exposure to similar carcinogenic stimuli most known one is exposure to HPV.

While the incidence of cancer has generally remained stable, the rates of precancerous lesions seem to be increasing apparently because of increased rate of some risk factors particularly HPV infection.

By the end of this chapter you should be able to:

- **Describe** the different histological types of vulvar cancer: It is essentially a skin-related cancer. 90% are squamous cell cancer.
- List epidemiology and risk factors for vaginal and vulvar cancer
- **Describe** the clinical manifestations (signs & symptoms) of vaginal and vulvar cancer: Note that in large proportion the lesions are asymptomatic. Diagnosis depends on biopsy.
- Describe FIGO staging system: in Vulvar cancer it is surgical while in Vaginal cancer is clinical
- **Describe** diagnosis and significance of precancerous lesions – role of colposcopy.
- **Describe** the principle of treatment and factors determine the choice of therapy

Premalignant vulvar cancer

The premalignant phase of vulvar squamous cell cancer has several different names: carcinoma-in-situ, vulvar intraepithelial neoplasia grade III, (VIN III), severe dysplasia and Bowen›s disease. The is condition is diagnosed by tissue biopsy and is characterized by a full thickness disorder of maturation of the squamous epithelium.

Classification and types: vulvar intraepithelial neoplasia VIN was categorized as VIN 1, 2 and 3, according to the degree of abnormality whether it involve one, two or two thirds (full thickness) of the squamous epithelium. However since there is no evidence that VIN 1 is a precursor of cancer that require treatment, the term vulvar intraepithelial neoplasia (VIN) is now used exclusively for high grade lesions that include the former VIN 2 and 3 while the term VIN 1 was dropped, as it is not a premalignant lesion.

Therefore Ppremalignant vulvar cancer or VIN "vulvar intraepithelial neoplasia" is currently classified into two main groups:

(1) **VIN, usual type**: which encompasses the VIN, warty type; VIN, basaloid type; and VIN, mixed (warty, basaloid) type which encompasses two subtypes (1) The basaloid type; (2) warty typeand (3) mixed (warty, basaloid) type.

(2) **VIN, differentiated type:type**:

Rare cases that do not fit into these categories are termed «unclassified type.» (table 271-)

Types of VIN	
VIN, usual type Occurs in younger premenopausal women. Risk factors are similar to those for vulvar cancer "ie. HPV"	**The basaloid subtype**: has a thickened epithelium with a relatively flat, smooth surface.
	The warty (condylomatous) subtype: is characterized by a surface that is undulating or spiking, giving it a condylomatous appearance.
VIN, differentiated type Comprises < 5 % of VIN and typically occurs in postmenopausal women.	The epithelium is thickened and parakeratotic with elongated and anastomosing rete ridges. Differentiated VIN are is probably a precursor of HPV-negative vulvar cancer It is usually unifocal and unicentric and often associated with lichen sclerosus, but not with HPV infection.
Classification of of vulvar disease International Society for the Study of Vulvar Diseases (ISSVD) (2004)	

Table 27-3: Types of VIN

Incidence: The incidence of VIN is increasing worldwide, primarily due to its increasing occurrence in young women, who account for 75 percent of cases

Risk factors for VIN: As pointed out the "usual VIN type" typically occurs in younger, premenopausal women. The risk factors are similar to those for vulvar cancer, and include human papillomavirus (HPV) infection, cigarette smoking, and immunodeficiency or immunosuppression.

Clinical presentation:

Symptoms: The most common presenting symptom is pruritus. Other presentations include perineal pain or burning, or dysuria. Patients may also present complaining of a visible lesion or, a palpable abnormality,perineal pain or burning, or dysuria.

However 50 percent of women are asymptomatic and are diagnosed either when a lesion is observed during a routine gynecological examination or at colposcopy for abnormal cervical cytology.

Sings: Grossly, the lesions can be flat, raised (maculopapular), or verrucous. In color, they may be brown (hyperpigmented), red (erythroplastic), white, or discolored (Figure 271-).

The lesions may not be appreciated without thorough colposcopic examination of the skin of the vulva, perineum, and perianal area.

Confirmation of diagnosis:

Colposcopy and biopsy of any suspicious lesion should be performed and is considered the gold standard for diagnosis.

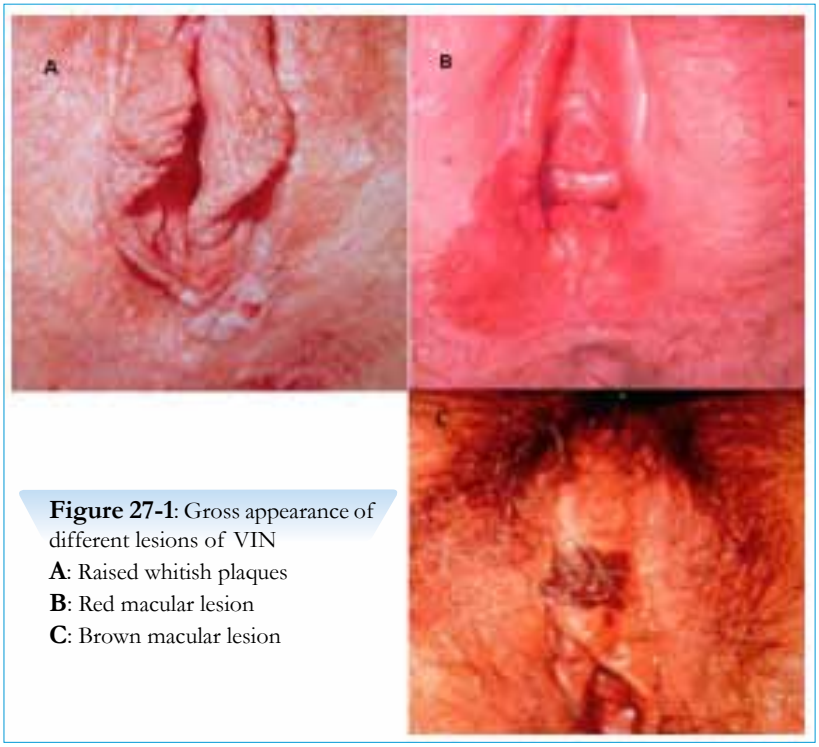

Figure 27-1: Gross appearance of different lesions of VIN
A: Raised whitish plaques
B: Red macular lesion
C: Brown macular lesion

Differential diagnosis of VIN:

DD include: benign lesions such as ulcers of a sexually transmitted disease (syphilis, herpes, or granuloma inguinale) pyogenic infections, or benign tumors, such as a granular cell myoblastoma.

Risk of VIN: The long-term risk of malignant transformation of treated VIN III has been estimated at 3.4-7% while the risk for progression of untreated VIN is thought to be higher.

Treatment:

The goals of treatment of VIN are to prevent development of invasive vulvar cancer and relieve symptoms, at the same time preserve normal vulvar anatomy and function.

The choice of treatment depends on biopsy results, location and extent of disease, and the woman's symptoms.

The options include:

- Wide local excision: Local excision of an individual lesion with a one centimeter margin followed by reapproximation of the defect
- Skinning vulvectomy: for extensive lesion in this procedure the vulvar skin is removed and replaced by a split thickness skin graft.
- Laser ablation: effective for multiple lesions. Disadvantages of the laser include painful recovery and lack of pathology specimens.
- Topical treatment: e.g.
    - Imiquimod (e.g. Aldara®) a topical immune response modifier.
    - Topical 5-fluorouracil cream: causes a chemical desquamation of the VIN lesion. However it is poorly tolerated because of significant burning, pain, inflammation, edema, or painful ulcerations. Has a limited role in the primary therapy of VIN because.

Follow-Up

Intraepithelial carcinoma of the vulva is often one manifestation of multifocal disease. For this reason, follow up is required for number of years. Recommended follow-up includes thorough pelvic examinations with colposcopy every 3-4 months until the patient is disease-free for 2 years. If the patient is disease-free for a 2-year period, examinations can be done every 6 months.

Vulvar Cancer

Incidence: constitute about 4% of gynecological cancer

Pathology and types of vulvar cancer:

The vulva is essentially epithelial skin, and so the main tumor types that affect this area are skin-related cancers. Most vulvar cancers are squamous cell carcinomas; other histologies include melanoma, Bartholin gland adenocarcinoma, sarcoma, Paget disease, or basal cell carcinoma (see Table 27-1)

Both vaginal squamous cell carcinomas, vulvar squamous cell cancers are slow-growing and usually develop from "precancerous", pre-invasive areas called vulvar intraepithelial neoplasia (VIN II and III). See table 27-1 for types of vulvar cancer.

Figure 27-1: Sites of development of cancer in the vulvar area.

Pathogenesis of vulvar cancer: it is possible to define two independent pathogenic types of carcinogenesis:

- The first related to mucosal HPV infection, responsible for 60% of vulvar cancers. Tends to occur in younger women.
- The second related to chronic inflammatory (vulvar dystrophy) Autoimmune processes.

Epidemiology and risk factors:

- Human papillomavirus (HPV) infection and its risk factors (see blue box)
- Cigarette smoking
- Vulvar dystrophy (e.g. lichen sclerosus),
- Vulvar or cervical intraepithelial neoplasia: Although most cases of VIN never progress to cancer. However, since it is not possible to tell which cases will become cancers, treatment or close medical follow-up is needed for all cases (see VIN).

Risk factors associated with HPV infection

Early age at first intercourse
Multiple sexual partners
Human immunodeficiency virus (HIV) infection,
Cigarette smoking.

- Other genital cancers: Women with cervical cancer have a higher risk of vulvar cancer. This is probably because both types of cancer share the same risk factor of HPV infection.
- Melanoma or atypical moles
- Immunodeficiency syndromes

Squamous cell carcinoma 90 %	Two subtypes: - Keratinizing: more common, occurs in older women - Bowenoid type: warty shape, more in younger women, predominantly associated with HPV infection
Verrucous carcinoma	Is a Subtype of squamous cell carcinoma. Cauliflower-like in appearance, Grows slowly and rarely, but it may be locally destructive
Melanoma 5 to 10 %	Melanoma is the second most common vulvar cancer Common sites the labia minora and clitoris.
Paget disease < 1 %	Appears as well demarcaed, eczematoid, multifocal lesion with slightly raised edges. Pruritus is the most common symptom,
Sarcoma 1-2%	Including leiomyosarcomas, rhabdomyosarcomas, liposarcomas, angiosarcomas, neurofibrosarcomas, fibrous histiocytomas, and epithelioid sarcomas
Basal cell carcinoma 2%	The typical appearance is that of a "rodent" ulcer with rolled edges and central ulceration;
Adenocarcinoma Bartholin gland carcinoma	Most adenocarcinoma arise from Bartholin gland. But can also arise form in the sweat glands of the vulvar skin. the vulva occur in the Bartholin gland Enlargement of the Bartholin gland in a postmenopausal woman is worrisome for The gland should be biopsied in older (over 40 years of age) women with a mass in this location

Table 27-1: main histological types of vulvar cancer

Clinical Manifestations:

The signs and symptoms of all histological types of vulvar malignancy are similar.

- **Symptoms**:

  Many patients are asymptomatic at the time of diagnosis. But symptoms may include in descending order:

- Pruritus: is probably most common complaint especially in association with vulvar dystrophy (e.g. lichen sclerosus or squamous cell hyperplasia).
- Vulvar bleeding or discharge
- Dysuria
- Enlarged groin lymph node in the groin suggestive of advanced disease.

- **Sings:**

A patient usually presents with a unifocal vulvar plaque, ulcer, or mass (fleshy, nodular, or warty) on the labia majora (most common site); the labia minora, perineum, clitoris, and mons (Figure 27-2).

In 10 percent of cases, the lesion is too extensive to determine the actual site of origin. In about 5% of cases the disease is multifocal.

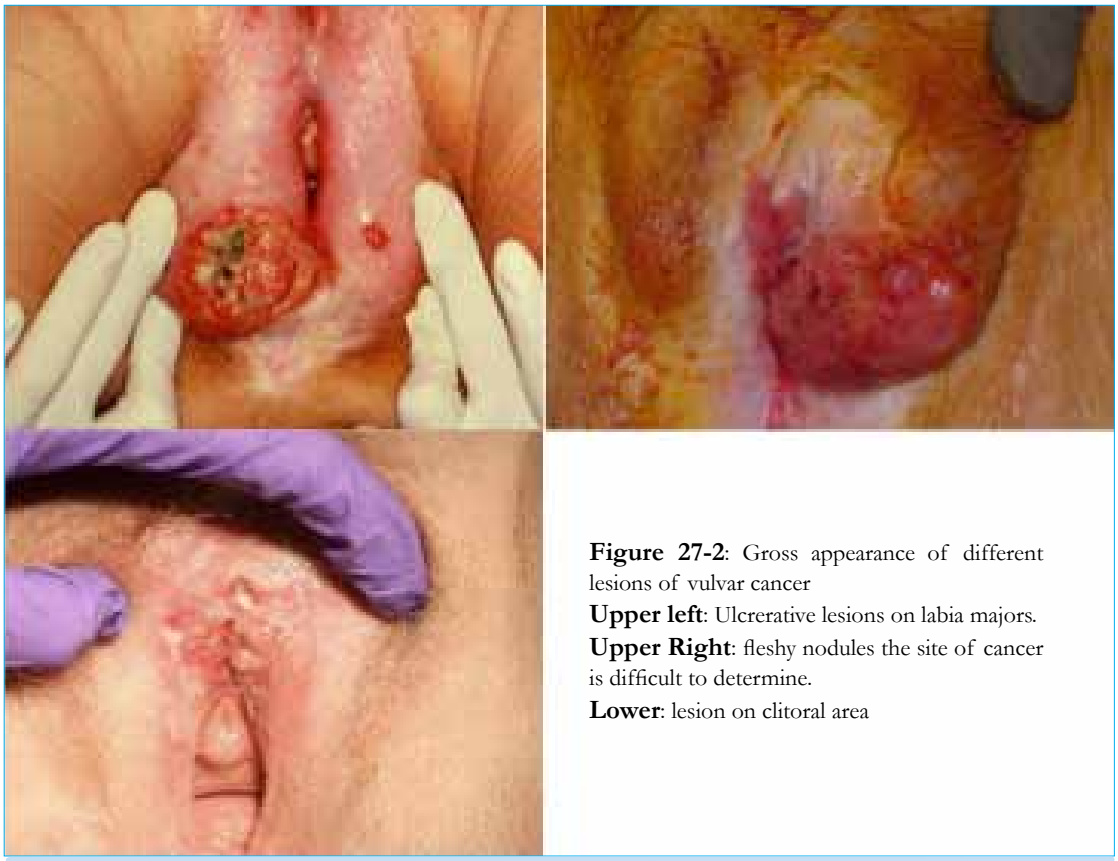

Figure 27-2: Gross appearance of different lesions of vulvar cancer
Upper left: Ulcrerative lesions on labia majors.
Upper Right: fleshy nodules the site of cancer is difficult to determine.
Lower: lesion on clitoral area

Figure 27-2: different gross appearances of vulvar cancer

A synchronous second malignancy, most commonly cervical neoplasia, is found in up to 22 percent of patients with a vulvar malignancy.

Diagnosis:

Vulvar biopsy should be performed in patients with suspicious lesions, including those with persistent pruritic eczematous lesions that fail to resolve within six weeks of appropriate antieczema therapy.

If multiple abnormal areas are present, then multiple biopsies should be taken to "map" all potential sites of vulvar pathology.

Biopsy under directed colposcopy examination: this is undertaken if a lesion is not grossly evident, but clinical suspicion is high, colposcopic vulvar examination should be undertaken using 5 percent acetic acid solution. The acetic acid dehydrate the cells and allow well definition of the lesion as white area "acetowhite lesions" with their underlying vascular changes. The ccetowhite areas with abnormal vascular patterns should be biopsied.

Mode of spread:

Vulvar carcinoma metastasizes by a variety of mechanisms.

- Direct extension to adjacent structures (e.g. vagina, urethra, clitoris, anus).
- Lymphatic embolization to regional lymph nodes can occur early in the course of disease, even in patients with small lesions. The pathway for lymphatic drainage of the vulva, in most women, begins at the superficial inguinal nodes, followed by drainage to the deep inguinal and femoral lymph nodes below the cribriform fascia, and then to the pelvic lymphatics.

  Lateral lesions spread to the ipsilateral nodal group; central lesions may metastasize to ipsilateral, contralateral, or both groups of nodes.
- Hematogenous dissemination: occurs late in the course of the disease, and is rare in patients without inguinofemoral lymph node involvement.

Staging:

Staging and primary surgical treatment are a single procedure. The International Federation of Gynecology and Obstetrics (FIGO) use staging system based on primary surgical treatment and pathologic examination. Staging takes into account the most important factors related to prognosis, which are: tumor size, depth of invasion, lymph node involvement, and presence of distant metastases.

Stage 0	Carcinoma in situ, intraepithelial carcinoma
Stage I	Tumor confined to the vulva or perineum or both and 2 cm or less in greatest dimension; no nodal metastasis Stage Ia: As above with stroma invasion ≤ 1 mm Stage Ib: As above with stromal invasion > 1 mm
Stage II	Tumor confined to the vulva or perineum or both and more than 2 cm in greatest dimension; no nodal metastasis
Stage III	Tumor of any size with: 1. Adjacent spread to urethra and/or vagina, and/or the anus 2. Unilateral regional lymph node metastasis or a combination
Stage IV	Stage Iva: Tumor invades any of the following upper urethra, bladder mucosa, rectal mucosa, pelvic bone or bilateral regional node metastasis or a combination Stage IVb: Any distant metastasis including pelvic lymph nodes

Figure 27-2: Classification of Vulvar cancer according to FIGO system

Treatment:

- **Surgical:** Vulvar cancers are usually treated by surgery. Historically the standard surgical approach used to be removal of the entire vulva down to the level of the deep fascia of the thigh, the periosteum of the pubis, and the inferior fascia of the urogenital diaphragm is performed through a single incision that circumscribes the labia majora and extends to the groins bilaterally to include en bloc inguinofemoral LND (lymph nodes).

  Currently the area of excision is individualized depending on the size and site of the lesion with excision of the cancer with approximately 2 cm margin of uninvolved tissue around and removal of the regional lymph nodes.

  The current conservative approach optimizes survival while minimizing perioperative morbidity and maximizing long-term psychosexual and physical well-being.

- **Radiation**: If the cancer is very large and a radical resection would require removal of the anus, rectum or urethra then primary treatment using chemotherapeutic agents such as cisplatin and 5-FU have been combined with radiation therapy.

Morbidity:

Complications of surgery are wound breakdown with prolonged healing and sometimes a collection of fluid in the groin and lymphedema.

The prognosis: If the lymph nodes are negative then the chance for a cure is excellent. Even with positive lymph nodes a significant number are cured.

Vaginal intraepithelial neoplasia

Definition: Vaginal intraepithelial neoplasia "VAIN": is defined as the presence of squamous cell atypia without invasion.

Classification: VAIN is classified according to the depth of epithelial involvement:

- VAIN 1: involve the lower one-third.
- VAIN 2: involve two-thirds of the epithelium.
- VAIN 3: involve more than two-thirds of the epithelium. Carcinoma in situ, which encompasses the full thickness of the epithelium, is included under VAIN 3.

"DES (Diethylstilbestrol) exposure in Utero"

DES is a synthetic nonsteroidal estrogen used to be administered to pregnant women to prevent pregnancy loss. It was latter found that females who had been exposed to DES in utero "DES daughters" are at risk of neoplastic and non neoplastic complications which include:

Neoplastic complications:

- Vaginal adenosis: (30%) in this abnormality the vaginal epithelium behave as cervical columnar epithelium. It undergoes metaplastic changes, with the risk of development of adenocarcinoma "Clear cell adenocarcinoma".

Non-neoplastic anomalies:

- Structural anomalies of the cervix and vagina (25%): include transverse vaginal septum, cervical collar, and cervical hypoplasia with risk of incompetence.
- T-shaped uterus and small uterine cavity (25%)

Atypical vaginal adenosis: is a separate entity of VAIN. This lesion has a well-established association with in utero diethylstilbestrol (DES) exposure. It may be a precursor to DES-associated clear-cell adenocarcinoma (see blue box).

Incidence and risk factors:

The true incidence of VAIN is unknown, but is estimated at 0.2 to 0.3 cases per 100,000 women in the United States.

The average patient age is between 43 and 60 years.

Risk factors:

- Human papillomavirus (HPV) infection
- Smoker
- Immunosuppression both genetic and acquired including human immunodeficiency virus (HIV) infection.
- Prior or concurrent neoplasia elsewhere in the lower genital tract

Diagnosis:

- Vaginal intraepithelial neoplasia is usually asymptomatic, although patients can present with postcoital spotting or vaginal discharge.
- VAIN should be excluded in all women with an abnormal Pap smear who are posthysterectomy or who do not have identifiable cervical lesions that could account for the abnormality.

The examination should include digital palpation to assess for thickening or irregularity of the vaginal wall and a thorough colposcopic assessment of the entire vagina.

The majority of lesions are located in the upper one-third of the vagina.

For postmenopausal patient, a few weeks of topical estrogen treatment will often accentuate visualization and improve detection of VAIN.

Treatment:

- Exclude invasive disease by colposcopy and biopsy, especially before undertaking nonexcisional therapy that does not permit histologic confirmation of disease.
- A broad range of treatment options are available for therapy of VAIN that include: surveillance (in VAIN 1), excision, ablation, topical chemotherapy, and radiation of lesions. Consultation with gynecologist oncologist should be undertaken.
- The factors that determine choice of treatment are: Previous treatment failures, the presence of multifocal disease, the patient's general health, her medical risks from surgery, her desire to preserve sexual function, and the certainty with which invasive disease has been excluded.
- Following therapy, gynecologic examination and vaginal cytology should be performed at three-month intervals to evaluate for persistent or progressive disease. Thereafter, patients can be followed at six-month intervals.

Management of women exposed to DES: women exposed to DES in utero should have careful gynecological surveillance as early as possible. The plan for follow up include:

- Careful assessment of the cervix and vagina.
- Colposcopic inspection of the cervix and vagina, yearly cytologic examination of the cervix and vagina, and careful palpation of the cervix and entire vaginal wall.

Vaginal Cancer

Incidence and risk factors: The incidence of in situ or invasive squamous cell cancer of the vagina is 1 per 100,000 women.

Pathology:

Vagina cancer may be primary (rare) or metastatic, which is more common:

- Primary vaginal cancer: comprise heterogeneous group of malignancies (see below). The most common affected site is the upper one-third of the vagina. However the diseases tend to be multicentric, thus, the entire vaginal mucosa is at risk.
- Metastatic vaginal cancer: Either by direct extension from primary cancer of cervix, vulva, or endometrium or by lymphatic or hematogenous spread from distant cancer e.g., breast, ovary, kidney.

Types of primary vaginal cancer:

- **Squamous cell carcinoma**: The mean age at diagnosis of squamous cell carcinomas is approximately 60 years. Grossly, these tumors may be nodular, ulcerative, indurated, endophytic, or exophytic.

Verrucous carcinoma: is an uncommon variant of vaginal squamous cell carcinoma. It is well differentiated and has low malignant potential. It usually presents as a large, warty, . fungating mass that is locally aggressive but rarely metastasizes

- **Adenocarcinoma**: common in younger age. May arise in areas of vaginal adenosis in women been exposed to DES in utero, Wolffian rest elements, periurethral glands, and foci of endometriosis.
- **Sarcoma**: major types of primary vaginal sarcomas include Leiomyosarcomas, endometrial stromal sarcomas, malignant mixed müllerian tumors, and rhabdomyosarcomas or botryoides sarcoma. ("botrys" in Greek means "grapes") (Figure 27-3).

Clear-cell Adenocarcinomas

Is the most common type of adenocarcinoma. Occurs in young women who have been exposed in utero to diethylstilbestrol (DES). usually present as polypoid masses, most often on the anterior wall of the vagina.

- **Melanoma**: of the vaginal mucosa are rare. It originates from mucosal melanocytes. They appear as a blue-black or black-brown mass, plaque, or ulceration, most frequently on the distal one-third of the anterior vaginal wall.

Botryoides sarcoma

Embryonal rhabdomyosarcoma is the most common type: is a highly malignant tumor that occurs in the vagina during infancy and early childhood (mean age three years). It presents as soft nodules that fill and sometimes protrude from the vagina, resembling a bunch of grapes.

Spread of vaginal cancer:

Vaginal tumors may invade locally and disseminate by several routes:

Direct extension: to pelvic soft tissue structures: parametria, bladder, urethra, rectum and . eventually, the bony pelvis

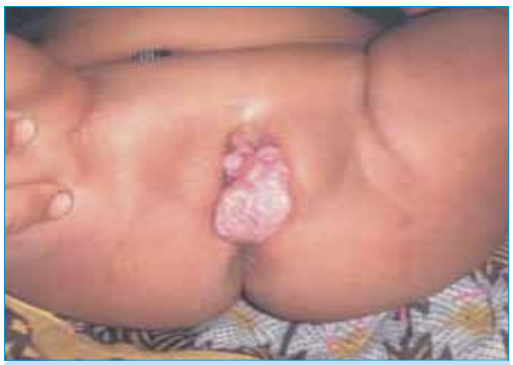

Figure 27-3: botryoides sarcoma

- **Lymphatic spread: The** lymphatic drainage of the upper vagina communicates with that of the cervix, draining initially into the pelvic nodes and then the paraaortic nodes. The lymphatics of the distal one third of the vagina drain first into the inguinal and femoral nodes, and secondarily into the pelvic nodes.
- **Hematogenous:** spread to other organs, including the lungs, liver, and bone, usually is a late manifestation.

Risk factors:

- HPV: Most cases of primary vaginal cancer are likely mediated by human papillomavirus (HPV) infection. Therefore its risk factors as in vulvar and cervical neoplasia are those of HPV infection namely: multiple sexual partners, early age at first intercourse, and current smoker.
- Prior history of gynecologic malignancy e.g. cervix or vulvar cancer.

Clinical manifestations:

- **Symptoms**:
  - Vaginal bleeding: either postmenopausal or postcoital
  - Other symptoms: include a watery, blood-tinged, or malodorous vaginal discharge,

vaginal mass, urinary symptoms (e.g., frequency, dysuria, hematuria), or gastrointestinal complaints (e.g., tenesmus, constipation, melena)

- Pelvic pain: which indicate extension of disease beyond the vagina occur in 5 percent of patients.
- However, as many as 20 percent of women are asymptomatic at time of diagnosis and are detected as a result of cytological screening for cervical cancer.

- **Signs**:

  The lesion may appear as a mass, a plaque, or an ulcer. Small lesions can easily be missed during initial speculum examination because the anterior and posterior blades of the speculum obscure the lower vaginal wall.

- **Diagnosis:** Definitive diagnosis requires biopsy of the suspected lesion. If a lesion is not visualized in the presence of abnormal cytologic results, colposcopy of the cervix and vagina must be performed with acetic acid followed by Lugol's iodine stain.

Staging of vaginal cancer:

According to the International Federation of Gynecology and Obstetrics the staging system of vaginal cancer is clinical one based upon findings from physical and pelvic examination, cystoscopy, proctoscopy, and chest and skeletal radiography.

Stage I	Carcinoma limited to the vaginal wall
Stage II	Carcinoma has involved the subvaginal tissue but has not extended onto the pelvic side wall
Stage III	Carcinoma has extended to the pelvic side wall
Stage IV	Carcinoma has extended beyond the true pelvis or has involved the mucosa of the bladder or rectum
Stage Iva	Spread to bladder or rectum
Stage IVb	Spread to distant organs

Table 27- : FIGO classification of vaginal cancer

Treatment:

Detailed discussion of treatment is beyond the scope of this text but treatment plans of vaginal carcinoma should be individualized depending upon the location, size, and clinical stage of the tumor.

- Modalities of treatment include surgery, radiation and chemotherapy.
- Factors that must be considered when treating vaginal cancer include the proximity of the tumor to adjacent structures that preclude the administration of high dose rate radiation; local anatomic constraints, which may not permit wide negative surgical margins without an exenterative procedure; and psychosexual issues.

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Chapter 28

Endometrial hyperplasia and Uterine Corpus Cancer

Endometrial hyperplasia is a histologic diagnosis. There are two main verities of hyperplasia either with or without cellular atypia. While the first one is benign the second one is a recognized precancerous lesion. In both the pathogenesis is endometrial exposure to un-opposed estrogen,

Uterine cancer is the most common gynecologic malignancy. Fortunately, most cases presents with abnormal uterine bleeding that enable diagnosis at an early stage when surgery alone may be adequate for cure.

By the end of this chapter you should be able to:

- **List** the types, and risk factors of endometrial hyperplasia
- **Describe** the pathogenesis and clinical manifestations of endometrial hyperplasia
- **List** the diagnostic approach to suspected endometrial hyperplasia
- **Describe** the outline of treatment for patient with endometrial hyperplasia and the effect of age, and histology on treatment choice.
- **Describe** the epidemiology of endometrial cancer.
- **Identify** risk factors for endometrial cancer
- **List** the histological classification of endometrial cancer: the common, hormonally dependant type 1 and the less common type II.
- **Describe** the approach to the diagnosis, staging and principle of treatment of endometrial carcinoma
- **Describe** the classification of uterine sarcoma with emphasis on the common variety leiomyosarcomas

Endometrial hyperplasia

Endometrial hyperplasia is a histological diagnosis characterized by excessive proliferation of endometrial glands resulting in a greater gland-to-stroma ratio than observed in normal endometrium.

Classification:

The classification of endometrial hyperplasia is the one adopted by the WHO is based upon two factors:

- The pattern of glandular/stromal architectural, which is either simple or complex
- The presence or absence of nuclear atypia

From clinical point of view the presence of nuclear atypia is the most worrying diagnosis because:

- Simple hyperplasia without glandular atypia is unlikely to progress to cancer (the risk is <1-3%)
- While approximately 25 to 40 percent of complex hyperplasia with atypia may progress to cancer if not treated. In fact complex endometrial hyperplasia with atypia can be difficult to distinguish from endometrial cancer.

Causes and risk factors of hyperplasia:

The risk factors for endometrial hyperplasia are the same as those for endometrial cancer mainly exposure to unopposed estrogen from either endogenous or exogenous sources.

- Endogenous estrogen: this occur in different situation such as:
  - Chronic anovulation: is the most common cause. Occurs typically in polycystic ovary syndrome (PCOS) and in premenopausal women "the menopausal transition age". In both cases the sources of estrogen are (1) anovulation and continued ovarian secretion of estrogen and (2) the conversion of the androgens androstenedione and testosterone to estrone and estradiol, respectively, by aromatase in adipocytes.
  - Obesity: Obese women even with out PCO have high level of endogenous estrogen because of the same mechanism mention before.
  - Estrogen secreting ovarian tumors: e.g. granulosa cell tumor. These are rare causes of endogenous estrogen but should be considered in non-obese women who are not taking estrogen replacement but have hyperestrogenism.
- Exogenous estrogen:
  - Postmenopausal women on un-opposed estrogen hormonal replacement:

Clinical manifestations of endometrial hyperplasia:

The most common manifestation is abnormal uterine bleeding, which could presents as:

- Heavy, prolonged menorrhagia following a period of amenorrhea or as frequent bleeding (i.e., less than 21 days).
- Irregular uterine bleeding in women in the menopausal transition
- Any bleeding in postmenopausal women.

Other less common manifestation which raise suspicion of endometrial hyperplasia include:

- Atypical glandular cells accidentally detected by cervical cytology: This should be investigated with an endometrial biopsy to determine whether endometrial hyperplasia or carcinoma is the cause. (See "Cervical cytology: Evaluation of atypical and malignant glandular cells".)
- The presence of endometrial cells on Pap smear cytology may be of significance in older ≥40 years of age women.

Management cases suspected hyperplasia:

Patients who presents with any of the above features should have full evaluation that often includes endometrial biopsy for histological confirmation. The initial test is transvaginal ultrasound. An endometrial biopsy is then decided based on the ultrasound appearance and thickness of the endometrium. In few cases a formal surgical dilatation and curettage may be indicated.

Over age 40 years with abnormal uterine bleeding
Under age 40 years with abnormal uterine bleeding and risk factors (e.g., chronic anovulation, obesity, Tamoxifen, diabetes, family history of endometrial/ovarian/breast/colon cancer)
Failure to respond to medical treatment of abnormal uterine bleeding
Women with uterus in situ receiving unopposed estrogen replacement therapy
Presence of atypical glandular cells on cervical cytology
Presence of endometrial cells on cervical cytology in a woman ≥40 years of age

Table 28-1: indications for endometrial biopsy

- Transvaginal ultrasound "TV": On TV ultrasound examination if the endometrial thickness is > 4 or 5 mm it is an indication for endometrial biopsy if the woman is not on hormonal replacement in order to exclude endometrial hyperplasia or malignancy (Figure 28-1). However the role of transvaginal ultrasound is less useful for evaluating the endometrium of premenopausal women.
- Endometrial biopsy: Is necessary to confirm the diagnosis. The indications are shown in table 28-1. (See chapter 3)

- Surgical dilatation and curettage: Currently its indications are limited to the following situations:
  - Endometrial hyperplasia: discovered on office biopsy sample. To exclude the presence of atypia or a coexistent endometrial adenocarcinoma.
  - Failure to obtain endometrial cells "Non-diagnostic office biopsy"
  - Persistent bleeding: after a benign endometrial biopsy or treatment of endometrial pathology.

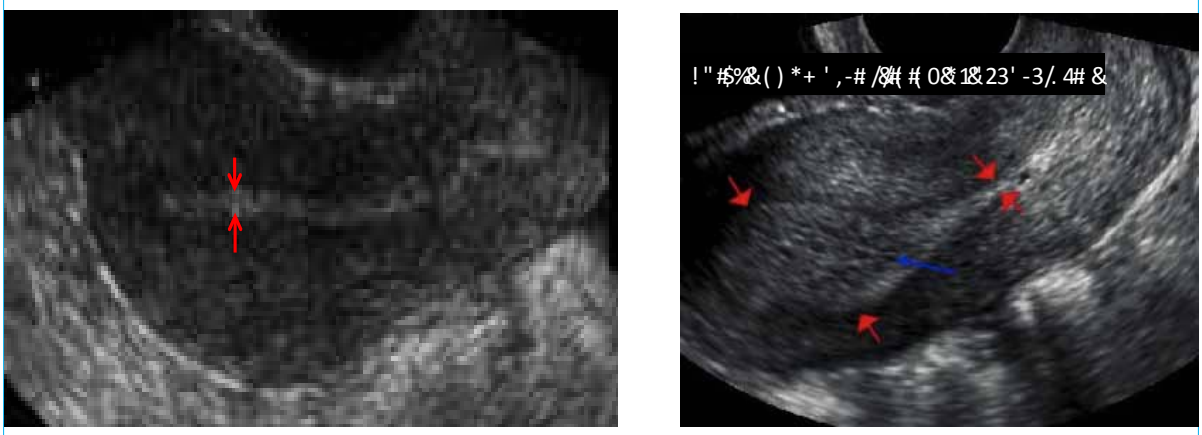

Figure 28-1: Left: Atrophic endometrium in postmenopause. Right: Thick endometrium in postmenopausal woman. Endometrial biopsy is needed to exclude malignancy.

Treatment: depends primarily on the type of hyperplasia as well as patient age and fertility desire.

- Endometrial hyperplasia without atypia: In such cases the objective of treatment is primarily to control abnormal uterine bleeding, and secondly to prevent the remote risk of progression to cancer (<1 to 3 percent). Therefore the treatment is medical usually by progestin agent.
- Endometrial hyperplasia with atypia: In this case the primary objective is to prevent the significant risk of endometrial cancer (17 to 53 percent), hence the treatment recommendations typically include surgery.

Role of Progestins in Treatment of Endometrial Hyperplasia

- Reverse endometrial hyperplasia by activation of progesterone receptors, which results in stromal decidualization and subsequent thinning of the endometrium (atrophic changes).
- Decreases estrogen and progesterone receptors and activates hydroxylase enzymes to convert estradiol to its less active metabolite estrone.

Premenopausal women: Progestogen can be administered in various forms such as:

- Medroxyprogesterone acetate (MPA) 10 mg daily for 12 to 14 days each month for three to six months with follow-up sampling to document regression.
- Insertion of a levonorgestrel containing intrauterine contraception (IUC): is also effective, especially in women who desire this type of contraceptive
- Ovulation induction: for younger who desire pregnancy, this result in formation of a corpus luteum and exposure to progestins.

However if atypia is present and the patient desire to maintain fertility treatment with continuous oral megestrol acetate 80 mg twice per day every day or levonorgestrel-releasing intrauterine system is recommended. A repeat endometrial biopsy should be performed in three months. Hystrectomy should be recommended if retreatment fails and/or patient complete her family.

Postmenopausal women

- No atypia: treatment with continuous medroxyprogesterone acetate (MPA) 10 mg daily for three months. A follow-up endometrial biopsy should be performed after cessation of drug therapy.
- With atypia: Endometrial hyperplasia with atypia is considered a premalignant condition, the preferred treatment is hysterectomy. At the time of surgery, the hysterectomy specimen should be assessed by the pathologist for endometrial cancer and staging should be performed if endometrial cancer is identified.

Prevention of endometrial hyperplasia:

The physician and the patient should be aware of the increased risk of hyperplasia in-patient with chronic anovulation such as PCOS. In such cases prevention of hyperplasia can be accomplished by combined estrogen-progestin therapy, such as oral contraceptive pills (OCs). An alternative treatments is intermittent progestogen e.g. Medroxyprogesterone acetate (5 to 10 mg) daily for 12 to 14 days per month or use of Levonorgestrel intrauterine contraception (Mirena®).

Endometrial Cancer

Epidemiology:

Endometrial cancer accounts for 6 percent of all cancers in women with a lifetime risk of women having endometrial cancer of approximately 2.5 percent. However endometrial carcinoma usually occurs in postmenopausal women (mean age early 60s).

Risk Factors:

- **Excess estrogen in the absence of progestins:** As in endometrial hyperplasia the sources of unopposed estrogen could be endogenous or exogenous sources (see risk factors of hyperplasia).
- Women on Tamoxifen therapy: Tamoxifen is a drug used in treatment and prophylaxis for breast cancer. Tamoxifen has both agonist and antagonist estrogen activity depending on the specific site e.g. it suppresses growth of breast tissue but stimulate the endometrial lining. Women on Tamoxifen run risk of developing endometrial pathology, both benign and malignant.
- **Nulliparity:** Epidemiological studies show that the risk of endometrial cancer is inversely related to parity. This is probably due the high frequency of anovulatory cycles in infertile women.
- **Diabetes and hypertension**: Women with diabetes mellitus and hypertension are at increased risk for endometrial cancer. It is not clear whether this risk occur because of the diseases or because of common associated obesity with these disorder.
- **Early menarche and late menopause:** In both situations the increased risk may be attributed to increased duration of exposure of the endometrium to estrogen.
- **Familial predisposition and genetics**: A familial tendency toward isolated endometrial cancer has been suggested for first-degree relatives, although no candidate genes have been identified consistently.

  Other familial risks associations with endometrial cancer include:

  - Lynch syndrome (hereditary nonpolyposis colorectal cancer): Women with Lynch syndrome are also at an elevated risk of colon and ovarian cancer, along with other malignancies. In women with Lynch syndrome, the lifetime risk of endometrial cancer is 27 to 71 percent compared with 3 percent in the general population.
  - Breast cancer: A history of breast cancer is a risk factor for development of endometrial cancer, in part because both diseases share some common risk factors (e.g., obesity, nulliparity).

Pathology:

Endometrial cancers are classified into two major divisions (types I and II), based upon light microscopic appearance, clinical behavior, and epidemiology:

- Type I endometrioid adenocarcinomas: comprise 70 to 80 percent of cases. It has endometrioid histology, they are associated with chronic exposure to estrogen unopposed by a progestin, and are often preceded by premalignant disease (endometrial

hyperplasia). Most endometrioid adenocarcinomas are well-differentiated.

- Type II nonendometrioid endometrial cancers: these have nonendometrioid histology (usually papillary serous or clear cell cancer). These subtypes account for 1 to 5 and 5 to 10 percent of endometrial cancer cases, respectively. Both are considered to be high grade are highly aggressive tumors and confer a poorer prognosis commonly present at a more advanced stage. No association to exposure to estrogen hormone.
- Mixed pattern cancers: Mixed carcinomas in which serous and endometrioid histology abut each other may occur.
- Rare subtypes: Mucinous, squamous cell, transitional cell, and small cell cancers comprise less than 2 percent of endometrial cancers.

Grading of adenocarcinoma:

Adenocarcinomas are graded according to the degree of abnormality of the glandular structure and cellular atypia into three grades (Table 28-2). The grading affects the prognosis and choice of adjuvant therapy but does not change the stage (see below)

Grade 1 **Well-differentiated**	Glandular almost similar to normal endometrium with ≤ 5 % solid (nonglandular) growth.
Grade 2 **Moderate to poorly**	Differentiated tumors have 6 to 50 percent of the tumor composed of solid growth
Grade 3 **Poorly differentiated**	Tumors contain more than 50 percent solid growth
Bizarre nuclear atypia of glandular cells raises the grade by one (from 1 to 2 or 2 to 3).	

Table 28-2 Grading system of endometrial cancer

Spread of endometrial cancer:

- Direct spread: Is the most common method of spread, by invading the myometrium into the serosa and/or down growth to involve the cervix. Uncommonly it may involve the vagina, parametrium, rectum or bladder.
- By exfoliation of cells through the fallopian tubes: This leads to implantation on the ovaries, visceral or parietal peritoneum or the omentum.
- Lymphatic spread: To the pelvic lymph nodes, then the paraaortic nodes.
- Hematogenous spread: is a rare mode of spread. Common sites the lungs, liver or both.

Screening for endometrial cancer:

There is no effective method for population screening for endometrial cancer. But the lesion usually presents at early stages as "abnormal uterine bleeding". However screening should be considered for patients at high risk for endometrial cancer this include:

- Women with a family history of Lynch syndrome.
- Patients with PCO
- Women with intact uterus taking estrogen replacement
- Women on Tamoxifen

In such cases screening can be performed by follow up for any symptoms of abnormal bleeding and transvaginal ultrasound for endometrial thickness.

Clinical presentation:

- Abnormal uterine bleeding: is the most common clinical presentation. Occur in 90% of cases, and is responsible for presentation of endometrial cancer at early stage.

  It is estimated that 5 to 20 percent of women with postmenopausal bleeding "PBM" will have endometrial cancer. Other causes of PMB should be excluded (see blue box for DD of PMB). It should be noted that the amount of bleeding does not correlate with the risk of cancer. Therefore any postmenopausal woman who has uterine bleeding should be carefully evaluated by transvaginal ultrasound and/or endometrial sampling (see below)

Causes of postmenopausal bleeding
- Hormonal replacement
- Atrophic changes (uterine or vaginal)
- Endometrial cancer
- Endometrial or cervical polyps
- Endometrial hyperplasia
- Miscellaneous (e.g. cervical cancer trauma urethral caruncle)

- Endometrial cells on cervical cancer screening: In asymptomatic women endometrial carcinoma may accidentally be discovered following the finding of endometrial cells in a Pap smear test. This finding could reflect physiologic shedding (especially in menstruating women in the first half of the menstrual cycle) but also could reflect shedding in response to a pathological process. The risk of cancer is high when atypical endometrial cells are noted.

Diagnosis:

The diagnosis of endometrial cancer is a histological one; therefore tissue sample should be obtained. This is usually accomplished through one or more of the following measures:

- Endometrial sampling biopsy: this can be performed as an office procedure using a

Pipelle sampling device (see chapter 3).

- Hysteroscopy with dilation and curettage (D&C): The disadvantages of this procedure that it often requires anesthesia and is associated with a number of potential complications.

  Therefore it is often be reserved for cases with suspicious biopsy (e.g. hyperplasia with atypia, necrosis, pyometra) or persistent symptoms i.e. bleeding despite negative initial endometrial biopsy.

In premenopausal women**:** While tissue sampling is almost necessary in menopausal women in premenopausal women endometrial sampling is indicated certain situations including: high-risk women, failure of response to medical treatment or suspicious transvaginal ultrasound.

Pretreatment evaluation: Prior to definitive surgical treatment complete evaluation should be undertaken for the tumor and the and the patient general condition this include:

- Evaluation of the size and mobility of the uterus and the presence of extrauterine masses or ascites; potential sites of nodal metastases should also be examined (e.g. supraclavicular nodes).
- Cervical cancer screening should be performed as appropriate.
- Patient evaluation: complete blood count, renal and liver function tests, blood glucose test for diabetes and chest x -ray. Further laboratory or imaging studies are performed as indicated for the planned treatment (e.g. major surgery, chemotherapy, radiation), patient comorbidities, and suspicion of metastases.

Staging:

The prognosis and therapeutic plan depends on the stage of the disease. The staging of endometrial cancer, according to FIGO classification system is surgical one (Table 28-3). It depends on the extend of spread of the disease. It is performed after pathological examination of tissues specimens obtained following total hysterectomy with bilateral salpingo-oophorectomy with pelvic and paraaortic lymph node dissection. Completion of staging should also include biopsy of any areas where metastases are suspected.

Stage I	
Ia	Tumor limited to the endometrium or invades less than one-half of the myometrium
Ib	Tumor invades one-half or more of the myometrium
Stage II	
	Tumor invades stromal connective tissue of the cervix but does not extend beyond uterus
Stage III	
IIIa	Tumor invades serosa or adnexa, or both
IIIb	Vaginal involvement (direct extension or metastasis) or parametrial involvement
IIIC1	Regional lymph node metastasis to pelvic or para-aortic lymph nodes or both
Stage IV	
IVa	Tumor invasion of bladder or bowel mucosa or both
IVb	Distant metastases including intraabdominal or inguinal lymph nodes or both

Table 28-3: FIGO classification of Endometrial cancer

Treatment:

The plan of treatment and prognosis of endometrial cancer depends on:

- The stage of the cancer
- The histological grade of cancer cells
- The general fitness of the patient

Briefly, surgery is the corner stone of management of patient with endometrial cancer unless it is contraindicated because of advanced tumor stage or patient medical condition.

- Stage I: with grade 1 or 2 endometrial carcinoma confined to the inner half of the myometrium may be treated only with surgery (total hysterectomy with bilateral salpingo-oophorectomy) without adjuvant therap.
- All other stages will require adjuvant radiotherapy. Either as vault brachytherapy to reduce risk of vault recurrence with or without external pelvic beam irradiation (if there is positive pelvic nodes)
- For advanced stages treatment is individualized with surgery followed or preceded by radiotherapy depending on the case. Patients may also receive hormonal therapy with or without chemotherapy.

Adjuvant hormone therapy of endometrial cancer:

Endometrial cancer is a hormone responsive cancer. The goal of hormone therapy in treating endometrial cancer is to reduce the body's level of estrogen and reduce the chances of recurrence and slow spread of existing cancer cells. The use of Progestogens is recognized as an adjuvant treatment for some cases of endometrial cancer.

The two progestins used most commonly are medroxyprogesterone acetate (Provera 50 mg three times a day), Dep-provera (400 mg intramuscularly weekly) and megestrol acetate (80 mg twice daily)

Post treatment surveillance:

- Physical examination every three to six months for two years, then every six months or annually for 3 years.
- Vaginal cytology every six months for two years, then annually. This is to detect vault recurrence.

Prognosis: The prognosis of endometrial cancer is determined primarily by disease stage and histology (grade of differentiation and histologic subtype). Other factors that influence prognosis are patient age and general health status.

Table 28-4 shows the 5 years survival rate in stratified by disease stage .

Stage	5 years survival %
Stage IA	89.6
Stage IB	77.6
Stage II	73.5
Stage IIIA	56.3
Stage IIIB	36.2
Stage IIIC1	57
Stage IIIC2	49.4
Stage IVA	22
Stage IVB	21.1

Table 28-4: 5 years survival rate of endometrial cancer by stage. Lewin SN et al Obstet Gynecol 2010; 116:1141.

Uterine Sarcoma

Uterine sarcomas arise from the myometrium or from connective tissue elements within the endometrium. Uterine sarcoma accounts for about 3% of uterine cancers. Compared to adenocarcinoma, uterine sarcomas behave more aggressively and are associated with a poorer prognosis. The mean age at presentation is 60 years of age.

Clinical Presentation:

Uterine sarcomas typically present with vaginal bleeding, pelvic pressure symptoms (e.g. urinary frequency, constipation), or abdominal distension.

On pelvic examination, the uterus is often enlarged.

The diagnosis of uterine sarcoma is based upon histological examination. Endometrial biopsy may yield an accurate diagnosis in some patients, but a negative biopsy does not rule out the disease.

Classification: The histologic classification of these tumors is based upon the type of cancerous cell and its presumed tissue of origin. Therefore uterine sarcomas are referred to as homologous (i.e., arise from native uterine tissue) or heterologous (i.e. contain tissue elements that is not normally present in the uterus)

Homologous: arise from native uterine tissue

- Endometrium (ESS): The cells resemble proliferative endometrial stroma.
- Muscle (leiomyosarcoma),
- Sarcomas of nonspecific supporting tissue (e.g., connective tissue, blood vessels, lymphatics).

Heterologous tumors: contain tissue elements that are not normally present in the uterus (e.g. skeletal muscle, cartilage, bone).

The most common two verities are: Leiomyosarcomas and endometrial stromal sarcoma.

Leiomyosarcoma:

Leiomyosarcomas and leiomyomas are independent entities. Leiomyosarcomas are rare and may coexist in the same uterus with benign leiomyomas (fibroids). Leiomyosarcomas

exhibit differing cytogenetic abnormalities. The histologic criteria for diagnosis of Leiomyosarcomas are known as Satnford criteria, which include the triad: (1) prominent cellular atypia, (2) abundant mitoses (≥10 per 10 high power fields), and (3) areas of coagulative tumor cell necrosis.

- Clinically: the mean age at presentation is 55 years. The presenting features include: pelvic pain, uterine bleeding or pelvic mass.

  Cases may be suspected preoperatively because of rapidly enlarging size of a known fibroid. But more commonly the condition is discovered at the time of exploratory surgery.

Endometrial stromal sarcomas "ESS":

Endometrial stromal tumors can be either benign (endometrial stromal nodules) or malignant (ESS) of varies potential (low to high grade sarcoma).

- Pathology: ESSs are low-grade, well differentiated tumors that lack significant cellular atypia. The cells resemble proliferative endometrial stroma. The tumor arises within the endometrium, is generally surrounded by a network of arterioles, and often infiltrates the myometrium; lymphatic extension is common.
- Gross picture: ESS is usually disseminated throughout the myometrium (appearance is similar to adenomyosis) and may invade the serosa; less commonly, it occurs as a solitary intramural nodule.

Treatment and prognosis:

Treatment modalities include surgery with total hystrectomy and bilateral salpingo-oophorectomy. Adjuvant pelvic radiation is often used. But response to chemotherapy is very low.

Generally the prognosis for uterine sarcoma is poor due to early hematogenous spread of the disease, the overall 5 years survival rate about 30-40%.

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Chapter 29

Trophoblastic Disease And Trophoblastic Neoplasia

Gestational Trophoblastic disease "GTD" is a term that encompasses both benign and malignant lesions of trophoblastic tissue. Its pathogenesis is unique in that its origin is not a maternal but fetal tissue lesion.

The most common type is hydatidiform mole. It is considered an aberration of fertilization that result in trophoblastic proliferation rather than a neoplasm. However it has the potential of developing into invasive malignant neoplasm, hence the importance of treatment and close follow up. Particularly because, malignant GTD or trophoblastic neoplasia "GTN" is one of the most chemotherapy-responsive and highly curable cancers, even in the presence of widespread metastatic disease

By the end of this chapter you should be able to:

- **List** the pathology and the types of GTD and differentiate between benign and malignant types.
- **List** the clinical manifestations and diagnostic work up for molar pregnancy. Role of US and B-hCG.
- **Describe** the pathology and genetics of complete and partial mole
- **Describe** the management plan for molar pregnancy: Evacuation and follow up
- **Describe** the risk factors for development of GTN
- **List** the types of malignant GTD "GTN"
- **Describe**: The clinical presentation and diagnosis of GTN following molar and non molar pregnancy
- **Define:** The role of staging and risk factors in the management of GTN
- **Outlined** the management of GTN: preoperative workup, single vs. multiple chemotherapeutic agents, follow up plan and place of hystrectomy.

Pathology:

Gestational trophoblastic disease "GTD" comprises a heterogeneous group of lesions that arise from abnormal proliferation of trophoblast of the placenta.

According to the histological features the following types of GTD are recognized:

- **Benign**: develop as a result of an faulty fertilization event that leads to a proliferative process
    1. Hydatidiform mole (complete or partial): comprise 90% of cases of GTD.
- **Malignant**: Malignant GTD has potential for local invasion and metastases hence it is called Gestational Trophoblastic Neoplasia "GTN". Malignant GTD can develop after molar (i.e. a Hydatidiform mole pregnancy) or non-molar pregnancies such as spontaneous or induced abortion, ectopic pregnancy, or preterm and term pregnancy. GTN include:
    2. Persistent/invasive gestational trophoblastic neoplasia (GTN): Complicate about 20 of complete mole but only 2 percent of partial moles.
    3. Choriocarcinoma: most often a sequela of a molar pregnancy, but it may develop after any gestational event (normal pregnancy, miscarriage or ectopic pregnancy).
    4. Placental site trophoblastic tumors: is very rare type of malignant neoplasms that originate from intermediate cytotrophoblast cells.

Epidemiology:

The incidence of GTD varies widely in different regions of the world in general it is more common among Asian than Western population. In North American and European countries the incidence of hydatidiform mole is low compared to Asian countries (1 per 1000 to 1500 pregnancies compared to 1 per 125-200 pregnancies respectively).

Risk factors:

The two main risk factors for GTD are extremes of maternal age (over age 35 years) and a history of previous GTD.

- Maternal age: the risk is significantly increased in women > 35 years of age and slightly increased in those under age 20.
- History of previous GTD: women with a history of one molar pregnancy (partial, complete, or persistent GTN) have an approximately 1 percent chance of recurrence in subsequent pregnancies. The recurrence rate is much higher after two molar pregnancies (16 to 28 percent).

- Other associated risk factors include: current smoking (>15 cigarettes per day), maternal blood type AB, A, or B, history of infertility, nulliparity, and use of oral contraceptives.

Hydatidiform mole

The hydatidiform mole is the most common form of GTD, representing 80 percent of cases. It may be complete or partial. They vary in the karyotype, gross morphology, histologic appearance, and clinical features (Table 29-1). Both types result from non-invasive proliferation of trophoblastic tissue that follows aberrant fertilization.

- In case of complete mole Fertilization of an empty ovum by two sperms or a single sperm that duplicates
- In incomplete mole fertilization of a haploid ovum by two sperm or duplication of one sperm

Feature	Complete mole	Partial mole
Incidence	1/1500 pregnancies	1/750 pregnancies
Fertilization	Fertilization of an empty ovum by two sperms or a single sperm that duplicates	fertilization of a haploid ovum by two sperm or duplication of one sperm
Karyotype	Diploid: 46, XX (< 15% 46, XY)	Triploid: 69 XXY, 69 XXX, 69 XYY
Embryonic / Fetal tissues	Typically absent	Present
Villi	Diffusely hydropic	Hydropic villi with marked scalloping mixed with normal appearing chorionic villi and fetal tissue; hydropic changes are focal and less prominent than in complete mole
Trophoblastic proliferation	Hyperplastic	Less trophoblastic hyperplasia than in complete mole; trophoblastic stromal inclusions can be seen
Trophoblastic atypia	Often present	Infrequent
Uterine size	Often large for dates	Often small for dates
Theca lutein cysts	Present in ≤ 25%	Rare
Persistent mole	15 to 20%	3 to 5 %
Choriocarcinoma	3 %	0 %

Table 29-1: Characteristics of complete versus partial hydatidiform
* Human chorionic gonadotropin. • Placental alkaline phosphatase.
Adapted from Blaustein's Pathology of the Female Genital Tract (see references)

Clinical presentation:

- **Symptoms:**

In both complete and partial molar pregnancy patient usually present with one or more of the following symptoms:

- Vaginal bleeding: this is more common to occur in complete rather than incomplete mole. It results from separation of the tumor from the underlying decidua. Characteristically the bleeding is painless and often initially attributed to threatened abortion. In complete mole the patient may report passage of "vesicles" or grape like tissue from the vagina.
- Excessive nausea and vomiting: which is one of the complications of high level of BhCG.
- Rarely there may be associated symptoms of hypertension due to early onset severe pre-eclampsia (headache, epigastric pain, visual symptoms) and or hyperthyroidism (tachycardia and tachypnea). These complications are associated with high level of hCG, hence they more likely with complete rather than partial mole.

- **Signs:**

The general physical sings varies according to the amount of bleeding, week of gestation and type of molar pregnancy.

- In complete molar pregnancy: the uterus is usually larger than the date of gestation, and on auscultation the fetal heart sound are absent. Vaginal examination reveals some blood clots and grapelike vesicles may be detected.
- In Incomplete mole: the physical signs are less prominent since the uterus may be smaller for date, and the fetal heart sounds are usually present.
- Ovarian enlargement by theca-lutein cysts occurs in one third of women and is not usually detected by abdominal examination.

Diagnosis:

The differentiation diagnosis of bleeding with or without pain in early pregnancy should always include the possibility of GTD (other DD include miscarriage, multiple gestation, ectopic pregnancy). A definite diagnosis can be made after ultrasound and measurement of Human chorionic gonadotropin "BHCG".

- Serum Human chorionic gonadotropin "hCG": The serum hCG concentration is always much higher in women with complete mole than that observed with intrauterine or ectopic pregnancies of the same gestational age.

In partial hydatidiform mole hCG levels are generally lower than those observed with a complete mole.

- Ultrasound examination:

  The sensitivity of ultrasound in the diagnoses of molar pregnancy depends on the week of gestation, whether the molar pregnancy is complete or partial and experience of the operator.

Complete mole: the characteristic features of ultrasound include:

- The absence of an embryo or fetus
- No amniotic fluid
- The uterine cavity is distended with a heterogeneous mass formed of numerous discrete anechoic spaces, which correspond to the hydropic chorionic villi giving the typical picture described as a "snowstorm pattern" on older ultrasounds (Figure 29-1)
- Theca lutein cysts (complications Infection, hemorrhage, or rupture occur in 3% of cases)

Partial mole: The characteristic features of ultrasound include:

- A fetus is present, may be viable, and is often growth restricted or displaying some structural anomalies.
- Amniotic fluid is present, but may be reduced
- Focal anechoic spaces and/or increased echogenicity of chorionic villi (Swiss cheese pattern)
- Increased transverse diameter of the gestational sac
- Theca lutein cysts are usually absent

The diagnosis of partial mole by ultrasound is more difficult because of the presence of fetus. Thus, a partial mole is often misdiagnosed as an incomplete or missed abortion (if the fetus is dead) and the correct diagnosis of GTD is made only after histologic review of the surgical specimen.

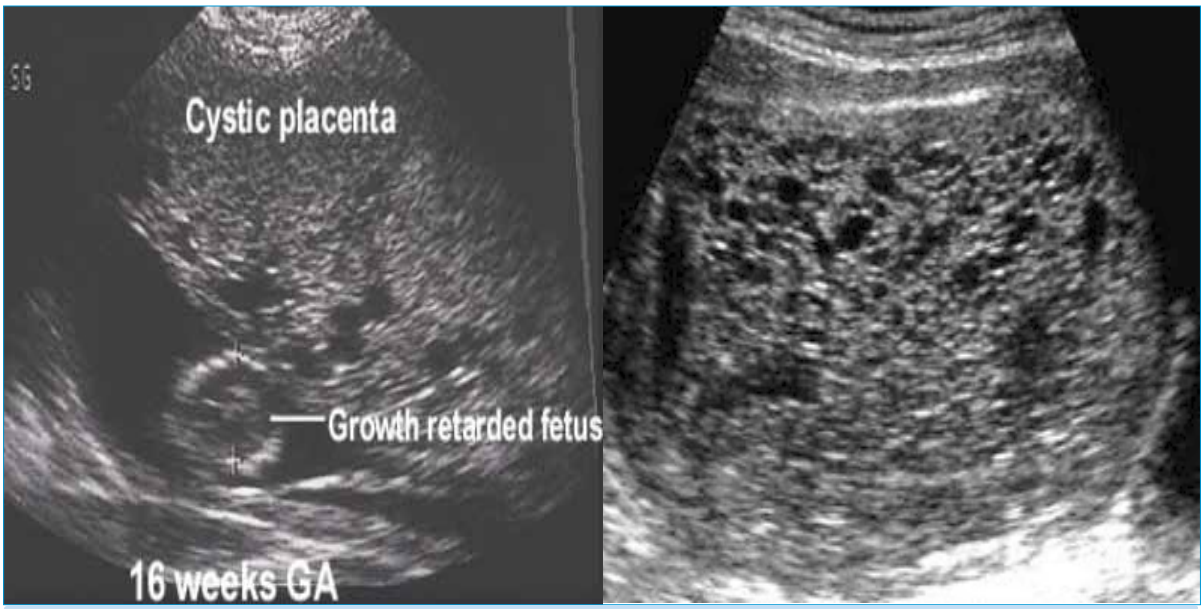

Figure 29-1: Transabdominal Ultrasound image of Molar pregnancy Left: partial showing a growth restricted fetus (BPD measure 12 weeks but the pregnancy is 16 weeks) and molar placenta. and Right: complete mole showing the typical appearance of bulky uterus filled with a mixed echogenic mass. Multiple tiny anechoic cystic spaces are seen in the uterine cavity giving the picture of "snow storm" appearance.

Management of Molar pregnancy:

Management of molar pregnancy "Hydatidiform mole":

The principles of management are uterine evacuation and follow up.

- **Uterine evacuation**: evacuation for both complete and partial mole is undertaken by suction curettage.

Because of its relative safety suction curettage has replaced the sharp curettage and medical evacuation using oxytocin as the preferred evacuation method. The procedure is performed under general anesthesia by experienced surgeon.

The risk associated with the procedure include excessive hemorrhage and/ uterine trauma. Therefore oxytocin is simultaneously administered during the evacuation to reduce blood loss, and blood should be ready for transfusion is needed.

Preoperative workup:
- Baseline hCG level
- Complete blood counts, and renal, liver, and thyroid function tests.
- Blood type and antibody screen should also be obtained, to prepare for heavy bleeding necessitating transfusion.

Rh-negative patient:
Although there is no fetus in a complete mole, anti-Rh(D) immune globulin is administered to Rh(D) negative women with both complete and partial moles, as trophoblastic tissue expresses the Rh(D) antigen.

Hystrectomy may be considered for a woman who has no desire of future fertility. This

will eliminates the risk of local invasion, but does not prevent metastasis and need for follow up.

- **Post-molar follow-up:**

Follow up is essential because of the risk of development of GTN. Currently the standard plan for follow up is: Weekly hCG levels until three consecutive normal values are obtained. The assay of B-hCG should be specific one because the titers drop to a low level, hence a non-specific test will cross react with LH hormone.

Figure 29-2 demonstrate comparison between the expected duration of decline in hCG after term delivery, abortion, and evacuation of GTD.

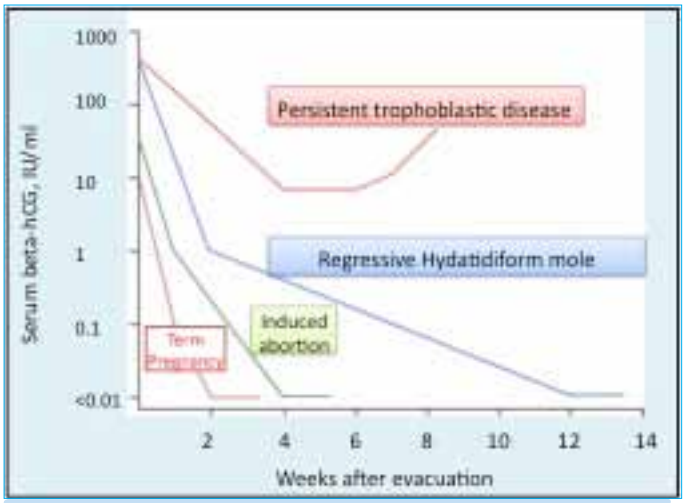

Figure 29-2: approximate duration of decline in hCG after term delivery, abortion, and evacuation of GTD. Pastorfide, et al, Am J Obstet Gynecol 1974; 118: 293, and Pastorfide, et al, Am J Obstet Gynecol 1974; 120:1025

Contraception: pregnancy should be avoided during the follow up period. The recommended method is combined OCs is the recommended

Diagnosis of GTN following molar pregnancy:

The diagnosis of development of GTN is a clinical rather than a histological diagnosis. It should be made if on one of the following criteria are present:

- Plateauing of beta-hCG levels over at least three weeks
- A 10 percent or greater rise in beta-hCG for three or more values over at least two weeks
- Persistence of beta-hCG six months after molar evacuation

Treatment:

The treatment for either persistent/invasive GTN or choriocarcinoma is generally the same. Both are usually treated with chemotherapy. Therefore, an exact histologic diagnosis is not usually required (see section on treatment of GTN)

Invasive or Persistent mole

Persistent or invasive mole is a complication in 15 to 20 percent of complete mole, and 3 to 5 percent of partial mole. Some risk factors are associated with increased likelihood of development of GTN after molar evacuation (see table 9-2).

As mentioned before a patient who exhibits one or more of those factors may receive prophylactic chemotherapy at the time of molar evacuation.

Risk factors of development of GTN after molar evacuation:
Large theca lutein cysts (≥ 6 cm)
Excessively enlarged uterus for dates
Age over 40
Previous GTD
Initial hCG > 100,000 mIU/mL
The presence of hyperplasia or atypia on histology
Heterozygosity (dispermic moles)

Table 29-2: factors associated with increased rate of development of GTN after molar evacuation

Clinical manifestation:

- Usually there are no specific symptoms and the diagnosis is made in during routine hCG monitoring after evacuation of a molar pregnancy.
- The most common symptom if one is present is vaginal bleeding. Rarely uterine rupture may occur due to local invasion and penetration of the uterine wall resulting in hemoperitoneum.
- Distant metastases are not common with invasive mole and if present it virtually always due to choriocarcinoma and rarely placental site trophoblastic tumors are rare.

Choriocarcinoma

Choriocarcinoma is the most aggressive GTN, and is characterized by early vascular invasion and widespread metastases.

- In 50% of cases choriocarcinoma arise from complete hydatidiform mole.
- In 25 percent arise after normal pregnancies
- And 25 percent follow spontaneous abortion or ectopic pregnancy

Clinical manifestation:

- The typical clinical presentation is late postpartum bleeding or irregular vaginal bleeding. Hemorrhage can be severe if the tumor erodes through the myometrium

or uterine vessels. The bleeding might develop a year or more after an antecedent pregnancy.

- At the time of diagnosis, the majority of patients have metastatic disease, most commonly to the lung. It could present as respiratory symptoms (eg, cough, chest pain, hemoptysis) or signs of gastrointestinal, urologic, and intracerebral bleeding. Hepatic involvement from advanced disease may cause epigastric or right upper quadrant pain.
- Physical examination often reveals an enlarged uterus and bilateral ovarian cysts. Vaginal metastases are present in about 30 percent of cases; these lesions are very vascular and prone to bleeding; they may also become infected.

Placental site trophoblastic tumors

Placental site trophoblastic tumors (PSTT) are rare (<0.2 percent of all cases of GTD), slowly growing malignant tumors that are derived from intermediate cytotrophoblast cells that are present in the placenta (unlike choriocarcinoma, which arises from villous trophoblast). This explains the rather low level of hCG in PSTT compared to the other GTDs.

Clinical manifestation: PSTT generally present months to years after a term gestation. More than 30 percent of patients already have metastases at presentation. Common presentation:

- Irregular vaginal bleeding and an enlarged uterus are common, amenorrhea or virilization may occur, and nephrotic syndrome has been reported.
- The serum hCG concentration in PSTT is relatively low relative to the tumor volume.

Treatment of Gestational Trophoblastic Neoplasia:

Once a diagnosis of GTN (invasive mole, choriocarcinoma, or PSTT) is clinically made following a molar (see table 29….) or non molar pregnancy event (i.e. term, preterm, miscarriage or ectopic gestation) then chemotherapy should be started.

The treatment for either persistent/invasive GTN or choriocarcinoma is generally the same. Both are usually treated with chemotherapy. Therefore, an exact histologic diagnosis is not usually required

The choice of single agent versus combination chemotherapy depends on prognostic factors including disease stage, and previous drug treatment …etc (Table 29----).

Pretreatment evaluation: Patients who have or who are suspected of having persistent GTN, choriocarcinoma, or PSTT must undergo a thorough evaluation prior to institution of therapy. In preparation for treatment,

Blood tests:

- Complete blood count
- Renal and hepatic function
- Baseline serum hCG levels.

Radiographic evaluation:

- Pelvic ultrasound, both to look for evidence of retained trophoblastic tissue, and to evaluate the pelvis for local spread.
- Chest X ray or CT: as the lungs are the most common site of metastatic disease.
- CT scan or magnetic resonance imaging (MRI) of the brain: is usually not required in asymptomatic patients with normal chest and pelvic imaging. Alternatively is recommended in women with persistent disease who have vaginal or lung metastases and in all patients with choriocarcinoma.
- Lumber puncture for assay of b-hCG in the CSF and comparing it to serum level. Because b-hCG dose not cross the blood brain barrier a high ratio of serum to CSF b-hCG indicate CNS involvement. However, the sensitivity is not sufficient to replace brain imaging

Staging and Prognostic Factors for GTN:

Four anatomic stages are identified based on The International Federation of Gynecology and Obstetrics (FIGO) system:

- **Stage I:** tumor confined to the uterus.
- **Stage II:** The presence of tumor outside of the uterus, but limited to the vagina and/or pelvis.
- **Stage III:** Pulmonary metastases with or without uterine, vaginal, or pelvic involvement.
- **Stage IV:** All other metastatic sites (e.g. brain, liver, kidneys, gastrointestinal tract).

However some factors other than the anatomic site of the disease were found to influence the cure rate in GTN. These prognostic factors are used to distinguish between clinically high-risk and low-risk disease especially for patient in FIGO stage II and III disease.

The utilization of staging together with prognostic factors can predict patients who are

likely to respond poorly to single-agent chemotherapy (see table 29---- for prognostic factors).

Prognostic factor	Risk score*			
	0	1	2	4
Age	<40	≥		
Antecedent pregnancy	Hydatidiform mole	Abortion	Term pregnancy	
Interval months from index pregnancy	<4	4-6	7-12	>12
Pretreatment serum hCG (IU/mL)	< 1000	1000 to < 10,000	10,000 to <100,000	≥100,000
Largest tumor size, including uterus (cm)	>3	3-5	>5	
Site of metastases	Lungs	Spleen, kidney	GIT tract	Brain, liver
Number of metastases		1-4	5-8	>8
Previous failed chemotherapy			Single drug	Two or more drugs
Total Score				

Table 29-2: Prognostic factors for GTN. For example A prognostic score of 7 or higher is considered a high-risk score; all of these patients are more likely to be resistant to single agent therapy and require combination chemotherapy. Patients with scores under 7 are considered low-risk and can usually be managed using single-agent chemotherapy.

Single and multiple chemotherapeutic regiments:

Single agent chemotherapy alone can achieve remission in over 90 percent of patients with stage I disease, and over 80 percent of women with low-risk stage II and III disease. The definition of remission is three consecutive normal hCG levels over a 14 to 21 day period.

The most often used agents are methotrexate (MTX) or Actinomycin. Folinic acid (Leucovorin) is usually combined with MTX to reduce risks of bone loss, GIT and liver toxicity.

Multiagent chemotherapy: Combination chemotherapy is used for disease that is refractory to single-agent therapy, for newly diagnosed high-risk malignant GTD (defined as stage IV disease or stage II/III disease with a high prognostic risk score), and for PSTT.

Surgical treatment "Hystrectomy""

The indication for hystrectomy include:

- Women with choriocarcinoma who do not desire future fertility. Hystrectomy is usually performed before chemotherapy. Its advantages are that it prevents the persistence of drug-resistant local disease, and can shorten the duration and amount of chemotherapy required to produce remission.
- Cases of PSTT: In contrast to choriocarcinoma, hysterectomy is the primary therapy for stage I or II PSTT because the tumor is usually limited to the uterus, and the response to chemotherapy is more variable than with other malignant forms of GTD
- Chemotherapy-resistant disease: Hysterectomy should also be considered in the subset of women who have chemotherapy-resistant disease, particularly if the histology is PS
- Hysterectomy may also be necessary to control uterine bleeding or ongoing sepsis due to infection of necrotic tumor.

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