PATHOLOGY OF THE FEMALE GENITAL SYSTEM

VULVA
VULVITIS
The most important infectious agents are
1. Human papillomavirus (HPV), producing condylomata acuminata and vulvar intraepithelial neoplasia
2. Herpes simplex genitalis (HSV 1 or 2), causing a vesicular eruption
3. Gonococci producing suppurative infection of the vulvovaginal glands

Contact Dermatitis is one of the most common causes of vulvar pruritus. It presents as erythematous weeping and crusting papules and plaques. Causes include urine, soaps, detergents, deodorants, etc.

TUMORS
1. Condylomas and Low-Grade Vulvar Intraepithelial Neoplasia (VIN)
There are two biologic forms of anogenital warts (condylomas)
  a. Condylomata lata: are manifestations of secondary syphilis & are flat, and slightly elevated. (Fig. 10-1)
  b. Condylomata acuminate: are viral (HPV) warts and appear as elevated warty or flat & wrinkled localized lesions, red-pink lesions that measure up to several centimeters in diameter. (Fig. 10-2)
  
  Microscopically, there is acanthosis and hyper/parakeratosis, and koilocytosis. The latter are squamous cells with perinuclear cytoplasmic vacuoles and nuclear angulation. The koilocytes are characteristic of HPV infection.

2. High-Grade VIN and Carcinoma of the Vulva
Carcinoma of the vulva is used to be seen mostly in elderly women. The vast majority of vulvar carcinomas are of squamous type.

VAGINA
Vaginitis is a relatively common problem that produces a vaginal discharge (leukorrhea). Many of the offenders are normal commensals that become pathogenic in conditions such as diabetes, systemic antibiotic therapy, after abortion or pregnancy, or in AIDS. Gonorrheal vaginitis may occur and be transmitted to the newborn of the infected mother.

Nonspecific atrophic vaginitis is a common cause of postmenopausal bleeding. It is due to lack of estrogenic support of the vaginal epithelium.

Malignant Tumors
1. Squamous cell carcinoma is very rare & usually occurs in elderly women, with risk factors similar to those for cervical carcinoma

2. Sarcoma botryoides (embryonal rhabdomyosarcoma), produces soft polypoid masses and is usually seen in infants and children younger 5 years of age. (Fig. 10-5)
THE CERVIX UTERI

Cervicitis is a very common condition that is associated with a mucopurulent discharge. Cytologic examination of the discharge reveals inflammatory cells admixed with cervical epithelial cells, and possible microorganisms. It is often due to vaginal flora, streptococci, staphylococci, a E. coli, a Candida spp., Neisseria gonorrhoeae, herpes simplex II (genitalis), and HPV. Many of these microorganisms are transmitted sexually, and so the cervicitis may represent a sexually transmitted disease. The chronic form is very common consists of inflammation and epithelial regeneration. These changes may occur in both squamous and columnar mucosa.

Cervical Tumors
Despite dramatic improvements in early diagnosis and treatment, cervical carcinoma continues to be one of the major causes of cancer-related deaths in women in the developing world.

Cervical Intraepithelial Neoplasia (CIN)
The Pap smear, introduced 50 years ago by Papanicolaou, remains the most successful cancer screening test ever developed. In populations that are screened regularly, cervical cancer mortality is reduced by up to 99%. Nearly all invasive cervical squamous cell carcinomas arise from precursor epithelial changes referred to as cervical intraepithelial neoplasia (CIN). Detection of CIN by the Pap smear at an early stage permits curative treatment. Cytological examination can detect CIN long before any abnormality can be seen grossly. CIN begins as low-grade lesion that may progress to higher grade CIN, or it is a high-grade lesions from the outset; this depends on the location of the HPV infection in the transformation zone, the type of HPV infection.

On the basis of histology, precancerous changes are graded as:

CIN I: Mild dysplasia
CIN II: Moderate dysplasia
CIN III: Severe dysplasia/carcinoma in situ

The current Bethesda system divides the precancerous lesions into only two groups:
1. Low-grade SIL (SIL for squamous intraepithelial lesions), equivalent to CIN I
2. High-grade SIL. Equivalent to CIN II & III

Progression from low to high grade SIL may or may not occur. The higher the grade of CIN the greater the likelihood of progression to invasive carcinoma, this reaches to 70% with CIN III.

Epidemiology and Pathogenesis
- The peak age of CIN incidence is about 30 years, whereas that of invasive carcinoma is about 45 years i.e. precancerous changes usually take many years to evolve into overt carcinomas.
- Important risk factors for the development of CIN and invasive carcinoma are:
  1. Early age at first intercourse
  2. Multiple sexual partners
  3. Persistent infection by "high-risk" papilloma viruses
  4. Low socio-economic status
  5- cigarette smoking and immunodeficiency states such as AIDS.
• All of the above favor a sexually transmitted causative agent (HPV), which can be detected by molecular techniques in nearly all precancerous and cancerous lesions.

• By contrast, HPV types 16 & 18, most common, usually integrate into the host genome with subsequent inactivation of the tumor suppressor genes p53 and RB. The result is a transformed cell, capable of autonomous growth and (cancer progression).

Microscopic features
CIN & Carcinoma in situ

• CIN begins with CIN I. This lesion is characterized by koilocytic changes mostly in the superficial layers of the epithelium. Koilocytosis: is composed of nuclear hyperchromasia and angulation with perinuclear vacuolization produced by cytopathic effect of HPV. The dysplastic epithelium is limited to the lower third of the mucosa.

• In CIN II the dysplasia is more severe, involving the lower two-thirds of the mucosa. The superficial layer in some cases shows the koilocytic changes.

• CIN III shows dysplastic changes that affect virtually all layers of the epithelium. Surface cells and their koilocytic changes are usually absent. (Figs. 10-6).

• In time, dysplastic changes become more atypical and may extend into the endocervical glands, but the alterations are confined to the epithelial layer and its glands. These changes constitute carcinoma in situ.

• The next stage is invasive carcinoma.

The above progression sequences do not occur in all the cases.

Cervical cytology and cervical colposcopy remain the basis of cervical cancer prevention.

Invasive Carcinoma of the Cervix

The most common cervical carcinomas are (in descending order)
1. Squamous cell carcinomas (75%)
2. Adenocarcinomas and adenosquamous carcinomas (20%)
3. Small-cell neuroendocrine carcinomas (<5%).

The squamous cell carcinomas are increasingly appearing in younger women, (peak incidence at about 45 years); 10 to 15 years after detection of their precursors (CIN).

• Invasive carcinomas of the cervix develop in the region of the transformation zone (the squamo-columnar junction) and range from invisible microscopic foci of early stromal invasion to grossly visible exophytic ulcerating masses or deeply infiltrative cancer that encircle the os (Fig. 10-7 A).

• Three microscopic variants of cervical SCC squamous cell carcinoma exist, although admixtures and intermediate forms occur: (Fig. 10-7 B)
  1. Large cell nonkeratinizing
  2. Keratinizing
  3. Small cell; this should be distinguished from small cell neuroendocrine carcinoma

• Distant metastases, including para-aortic nodal involvement, remote organ involvement, or invasion of adjacent structures such as bladder or rectum, occur late in the course of disease.

Ideally cervical carcinomas should be diagnosed in the preinvasive phase; these appear as white areas on colposcopic examination after application of dilute acetic acid (Schiller test). Clinical features: vaginal bleeding, leukorrhea, painful coitus (dyspareunia), and dysuria. Mortality is most strongly related to the tumor stage. The 5-year survival in stage 1 is 90% but this figure drops to 10% in stage 4.
BODY OF UTERUS

Endometritis
This may be associated with retained products of conception subsequent to miscarriage or delivery, or a foreign body such as an intrauterine device, frequently by flora ascending from the vaginal or anal region.

Endometritis is either acute or chronic depending on whether there is a predominant neutrophilic or lymphoplasmacytic response.

Generally the diagnosis of chronic endometritis requires the presence of plasma cells (Fig 10-8).

Complications:
- menstrual abnormalities, infertility and ectopic pregnancy due to extension of the damaging inflammation to the fallopian tubes.

Adenomyosis
This refers to the “invagination of the stratum basalis of endometrium down into the myometrium.” Nests of endometrial stroma, glands, or both, are found well down in the myometrium between the muscle bundles.

Grossly:, the uterine wall often becomes thickened and the uterus is enlarged and globular. (Fig. 10-10) Because these glands derive from the stratum basalis, they do not undergo cyclical bleeding. Nevertheless, marked adenomyosis may produce menorrhagia, dysmenorrhea, and pelvic pain before the onset of menstruation.

Endometriosis
This is characterized by “the presence of endometrial glands and stroma in a location outside the endomyometrium.” It occurs in as many as 10% of women in their reproductive years and in nearly half of women with infertility.

It is frequently multifocal and may involve any tissue in the pelvis (ovaries, pouch of Douglas, uterine ligaments, tubes, and rectovaginal septum), less frequently in more remote sites of the peritoneal cavity and about the umbilicus.

Three possibilities have been suggested to explain the origin of these lesions:
1. The regurgitation theory, currently the most accepted, proposes menstrual backflow through the fallopian tubes with subsequent implantation.
2. The metaplastic theory proposes endometrial differentiation of coelomic epithelium.
3. The vascular or lymphatic dissemination theory has been raised to explain extrapelvic endometriosis.

Gross features
- Endometriosis almost always contains functioning endometrium, which undergoes cyclic bleeding. Because blood collects in these ectopic foci, they usually appear grossly as red-blue to yellow-brown nodules, of variable size.
- When the ovaries are involved, the lesions may form large, blood-filled cysts that are transformed into so-called chocolate cysts as the blood ages (Fig. 10-11).
- Fibrosis, adherence of pelvic structures, sealing of the tubal fimbriated ends, and distortion of the oviducts and ovaries.

Microscopic features
1. Endometrial glands
2. Endometrial stroma, or
3. Hemosiderin pigment.

Complications:
Extensive scarring of the oviducts and ovaries often causes sterility and pain.
Dysfunctional Uterine Bleeding (DUB): is an abnormal bleeding in the absence of a well-defined organic lesion in the uterus. Examples of the causes of DUB include

1. Anovulatory cycles are very common at both ends or reproductive life, and have several cause including
   1. Endocrine dysfunctions
   2. Ovarian lesions producing an excess of estrogen
   3. Malnutrition, obesity, or debilitating disease
   4. Severe physical or emotional stress.
   An anovulatory cycle leads to an excess of estrogen relative to progesterone; the endometrial glands may appear crowded with mild cystic changes with a relative scant stroma. (Fig. 10-12) The poorly supported endometrium partially collapses, with rupture of spiral arteries, accounting for the bleeding.

2. Inadequate luteal phase. The corpus luteum may fail to mature normally or may regress prematurely, leading to a relative lack of progesterone. The endometrium under these circumstances shows delay in the development of the secretory changes expected at the date of biopsy.

Endometrial Hyperplasia
This is an exaggerated endometrial proliferation induced by sufficiently prolonged excess of estrogen relative to progestin. The severity of hyperplasia is classified according to two parameters
a. architectural crowding of the glands & b. cytologic atypia.
Accordingly there are three categories
1. Simple hyperplasia
2. Complex hyperplasia
3. Atypical hyperplasia

Simple hyperplasia carries a negligible risk, while a woman with atypical hyperplasia has a 20% risk of developing endometrial carcinoma. Thus When atypical hyperplasia is discovered, it must be carefully evaluated for the presence of cancer and must be monitored by repeated endometrial biopsy.

Potential contributors include
1. Failure of ovulation, e.g. around the menopause
2. Prolonged administration of estrogenic steroids
3. Estrogen-producing ovarian lesions such as polycystic ovaries (Stein-Leventhal syndrome)
4. Obesity, because adipose tissue processes steroid precursors into estrogens.

Gross features
- In simple hyperplasia the endometrium is diffusely thickened (Fig. 10-13)
- In complex & atypical hyperplasia there is usually focal thickening of the endometrium.

Microscopic features
- Simple hyperplasia involves both the glands & stroma; The glands are proliferative and some are cystically dilated.
- Complex hyperplasia: there is focal glandular crowding with little stroma separating the proliferative glands. (Fig. 10-14).
- Simple and complex hyperplasias are further divided into atypical and non-atypical
- Atypical hyperplasia: characterized by atypical nuclei of the proliferative glands as evidenced by nuclear stratification, nuclear rounding and the presence of nucleoli. (Fig. 10-15)
Tumors of the Endometrium and Myometrium
The most common neoplasms of the body of the uterus are
1. Endometrial polyps,
2. Smooth muscle tumors. Leiomyomas
3. Endometrial carcinomas.
All tend to produce bleeding from the uterus as the earliest manifestation.

1-Endometrial Polyps are usually sessile, or pedunculated & may project from the endometrial mucosa into the uterine cavity & sometimes through the cervix into the vagina. Microscopically they are composed of cystically dilated glands with fibroblastic stroma.

2-Leiomyomas are benign tumors that arise from the smooth muscle cells in the myometrium. Because of their firmness they are also called fibroids. They are the most common benign tumor in females and are found in 30% to 50% of women during reproductive life

**Gross features:**
- They are sharply circumscribed, firm gray-white masses with a characteristic whorled cut surface.
- They may occur singly, but are often multiple tumors scattered within the uterus, ranging in size from small seedlings to massive neoplasms that dwarf the size of the uterus.
- Some are embedded within the myometrium (intramural), whereas others may lie directly beneath the endometrium (submucosal) or directly beneath the serosa (subserosal). (Fig. 10-17 A)
- Larger neoplasms may show foci of ischemic necrosis with cystic areas and hemorrhage.

**Microscopic features**
- There are whorling bundles of smooth muscle cells.
- Foci of fibrosis, calcification, ischemic necrosis, cystic degeneration, and hemorrhage may be present. (Fig. 10-17 B)

Leiomyomas sometimes are asymptomatic, and rarely transform into sarcomas.

Leiomyosarcomas typically arise de novo from the mesenchymal cells of the myometrium. They are almost always solitary tumors, in contradistinction to the frequently multiple leiomyomas.

**Gross features (Fig. 10-18)**
1. The tumor is typically bulky, soft, hemorrhagic, and necrotic
2. It infiltrates the uterine wall.
3. Sometimes it projects into the endometrial cavity.

**Microscopic features**
1. They show a wide range of differentiation, from those that closely resemble leiomyoma to wildly anaplastic tumors.
2. The diagnostic features of leiomyosarcoma include tumor necrosis, cytologic atypia, and mitotic activity.

Endometrial Carcinoma (EMC)
After the dramatic drop in the incidence of cervical carcinoma, **EMC is currently the most frequent cancer occurring in the female genital tract.**

**Epidemiology and Pathogenesis**
EMC appears most frequently around the age of 60 years. There are two clinico-pathological settings in which endometrial carcinomas arise:
1. In perimenopausal women with estrogen excess; these are of endometrioid type
2. In older women with endometrial atrophy; these are of serous type.
Well-defined risk factors for endometrioid carcinoma include:
a. Obesity  
b. Diabetes  
c. Hypertension  
d. Infertility.  
e- estrogen replacement therapy and estrogen-secreting ovarian tumors increase the risk of this form of cancer.  
f- Nearly all cases have mutations in the p53 tumor suppressor gene.  

**Gross features**  
- EMC may be exophytic (fungating, polypoid) or infiltrative. (Fig. 10-19 A)  

**Microscopic features**  
- The endometrioid carcinoma consists of malignant endometrial-like tubular glands of varying grades. Squamous metaplasia is frequent. Sometimes, the tumor is adeno-squamous carcinoma. (Fig. 10-19 B)  
- may infiltrate the myometrium and enter vascular spaces, with metastases to regional lymph nodes.  
- Serous carcinoma forms small tufts and papillary arrangements, and has much greater cytologic atypia. (Fig. 10-19 C).  

**Symptoms**  
1- Patients with EMC presents with leukorrhea and irregular bleeding.  
2- uterus may become palpable, and in time it becomes fixed to surrounding structures.

**Fallopian tubes**  
*Salpingitis* is inflammations of the tube and is almost always microbial in origin. streptococci and staphylococci, are now the major offenders..  
All forms of salpingitis may produce pelvic masses when the tubes become distended with either exudate or, later, burned-out inflammatory debris and secretions.  

**Complications**  
Adhesions that increases the risk of tubal ectopic pregnancy or infertility.

**Ovaries**  
*Follicle cyst and Luteal Cyst* are common and usually harmless lesions originate in unruptured graafian follicles or in follicles that have ruptured and immediately sealed. they achieve diameters of 4 to 5 cm and may thus become palpable and produce pelvic pain. They may also rupture, producing intraperitoneal bleeding and acute abdominal symptoms. (Fig. 10-22)

**Polycystic Ovaries (Stein-Leventhal syndrome)**  
**Symptoms**  
Oligomenorrhea, hirsutism, infertility, and sometimes obesity may appear in young women secondary to excessive production of androgens by multiple cystic follicles in the ovaries.  
**Gross:** The ovaries are usually twice the normal size, gray-white with a smooth outer surface, & studded with subcortical cysts 0.5 to 1.5 cm in diameter.  
**Microscopically,** there is a thickened, fibrotic tunica with underlying follicular cysts.  
Stigmata of previous ovulation are usually absent (corpora lutea or albicans). (Fig. 10-23)  

**Clinical findings :**  
1- In most patients there are excessive production of androgens,  
2- high concentrations of luteinizing hormone,  
3- low concentrations of follicle-stimulating hormone. These changes inhibit ovulation. The diagnosis of this syndrome made on; both clinical & endocrine data are also required.
TUMORS OF THE OVARY

Ovarian cancer is the fifth leading cause of cancer death in women. Tumors of the ovary are diverse and this diversity is attributable to the three cell types that make up the normal ovary:

1. The surface (coelomic) covering epithelium
2. The germ cells
3. The sex cord/stromal cells.

Each of these cell types gives rise to a variety of tumors (Fig. 10-24).

1- Neoplasms of surface epithelial constitute the great majority of primary ovarian tumors (70%), and their malignant forms account for 90% of ovarian cancers.
2- Germ-cell and sex cord/stromal cell tumors constitute 20% to 30% of ovarian tumors, but are collectively responsible for fewer than 10% of malignant tumors.

Pathogenesis

1- Nulliparity and family history are the two most important risk factors of epithelial ovarian cancers.
2- Higher incidence of carcinoma in unmarried women and married women with low parity.
3- the majority of the hereditary cancers seem to be caused by mutations in BRCA1 and BRCA2 genes.
4- Other molecular changes of ovarian neoplasms include HER2/NEU & K-RAS proteins over-expression and p53 mutation. The latter is present in about 50% of all ovarian cancers.

1-Surface Epithelial Tumors

These neoplasms are derived from the surface coelomic mesothelial covering of the ovary. With repeated ovulation and scarring the surface epithelium is pulled into the subjacent cortex, forming small epithelial cysts. These can undergo metaplasia with subsequent neoplastic transformation into the various histological types of the epithelial tumors.

Benign lesions are usually cystic (cystadenoma) or can have an accompanying stromal component (cystadenofibroma).

Malignant tumors may also be cystic (cystadenocarcinoma) or solid (carcinoma).

The surface epithelial tumors also have an intermediate, borderline category referred to as tumors of low malignant potential. They have a better prognosis.

Surface epithelial tumors are divided into serous, mucinous, endometrioid & Brenner tumors.

A. Serous Tumors are the most frequent of the ovarian tumors.

Gross features

- Most serous tumors are large, spherical, and cystic.
- About 25% of the benign forms are bilateral. These benign tumors display a smooth and glistening serosal covering.
- They are generally unilocular, but may be multilocular.
- The cystic spaces are usually filled with a clear serous fluid.
- Papillary projections that become more marked in malignant tumors. (Fig. 10-25)
- The surface of cystadenocarcinoma shows nodular or warty irregularities that represent cancerous penetration of the serosa. (Fig. 10-26)

Microscopic features

- The benign tumors show a single layer of tall columnar epithelium that lines the cyst(s)
- Psammoma bodies (rounded laminated calcified structures) are common.
- In carcinoma, the lining cells display malignant features with invasion of the stroma. Papillary formations are complex and multilayered.
- Borderline tumors show milder cytologic atypia and typically, no stromal invasion.
B. Mucinous Tumors differ from serous tumors essentially in the epithelium, which is of mucin-secreting cells similar to those of the endocervical or intestinal mucosa. These tumors occur in women in the same age range as those with serous tumors, but the majority are benign (80%), only 10% are malignant (cystadenocarcinomas), and 10% are of low malignant potential.

Gross features (Fig. 10-27)
- The incidence of bilateral ovarian involvement is much lower than for their serous type.
- Compared to their serous tumors, they show mucinous cystic contents and tend to be larger and multilocular but papillary formations are less common.

Microscopic features (Fig. 10-27).
- Mucinous tumors are classified according to the type of the mucin-producing epithelial cells
- Serosal penetration and solid areas point to malignancy.
Metastasis of mucinous tumor of the gastrointestinal tract to the ovaries (Krukenberg tumor) may also mimic an ovarian primary tumor.

C. Endometrioid Tumors may be solid or cystic, but sometimes they develop as a mass projecting from the wall of an endometriotic cyst. They are distinguished by the formation of tubular glands (similar to those of the endometrium) within the linings of cystic spaces. Endometrioid tumors are usually malignant. They are bilateral in about 30% of cases, and up to 30% of women with these ovarian tumors have a concomitant endometrial carcinoma.

D. Brenner Tumor is an uncommon, solid, usually unilateral ovarian tumor consisting of an abundant stroma containing nests of transitional epithelium resembling that of the urinary tract

2-Germ Cell Tumors
1. Dysgerminoma: these usually presents within 10 to 30 years of age. Their microscopic picture is analogous to testicular seminoma. All are malignant but only 30% are aggressive and disseminate.
2. Yolk sac tumor & embryonal carcinoma are similar to their testicular counterparts.
3. Choriocarcinoma presents within the first three decades of life. They are pathologically identical to placental choriocarcinoma.
4. Teratomas constitute up to 20% of ovarian tumors and arise in the first two decades of life; the younger the person, the greater is the likelihood of malignancy. However, more than 90% of these germ-cell neoplasms are benign mature cystic teratomas.

Benign (Mature) Cystic Teratomas (Fig. 10-28) are characterized by differentiation of totipotent germ cells into mature tissues representing all three germ cell layers: ectoderm, endoderm, and mesoderm. Usually there is the formation of a cyst lined by recognizable epidermis stuffed with adnexal appendages-hence the common designation dermoid cysts. They rarely exceed 10 cm in diameter. On opening, they are often filled with sebaceous secretion and matted hair. Sometimes there is a nodular projection from which teeth protrude. Occasionally, foci of bone and cartilage, nests of bronchial or gastrointestinal epithelium, . These tumors are prone to undergo torsion (10% of cases), producing an acute surgical emergency.

Im mature Malignant Teratomas differ from mature cystic teratoma by being often bulky, predominantly solid or near-solid, and areas of necrosis.
Microscopically, the distinguishing feature is a variety of immature tissues such as cartilage, bone, muscle, nerve, and other structures. (Fig. 10-29)

3-Sex cord tumors these include

1. Granulosa-thechal cell tumors: mostly seen in postmenopausal but can occur at any age. Microscopically; They are composed of mixture of granulosa cells (in cords, sheets, or strands) and spindled, plump lipid-laden thecal cells. Granulosal elements may recapitulate ovarian follicle as Call-Exner bodies (small round cavity containing eosinophilic material and often shrunken nuclei). Nuclear folds or grooves (coffee-bean” appearance) is an important diagnostic feature (Fig. 10-30)

Hyperestrinism occurs in 75% of cases; the effects depend on age: in children there is isosexual precocity; in adults & elderly there is abnormal uterine bleeding due to estrogen-induced endometrial hyperplasia.

2. Thecoma-fibroma group of tumors occur at any age. Ovarian fibroma is solid gray and consists of spindle fibroblastic cells. Ovarian thecoma is yellow in color because they are composed of lipid-laden, plump thecal cells.

3. Sertoli-Leydig cell tumors occur at any age. They are usually small and recapitulate the development of testis with tubules, or cords (Sertoli cells) and plump pink Leydig cells. Many of these tumors are functional (masculinizing or defeminizing). They are rarely malignant.

Clinical Correlations of ovarian cancers:
1-all ovarian neoplasms produce no symptoms or signs until they are well advanced
2- functioning neoplasms that may have hormonal effects.
3-producing severe abdominal pain mimicking an "acute abdomen
4- ascites, the latter resulting from metastatic seeding of the peritoneal cavity, so that tumor cells can be identified in the ascitic fluid.

Among the many markers that have been explored, elevations of the protein CA-125 have been reported in 75% to 90% of women with epithelial ovarian cancer. However, as with carcinoembryonic antigen (CEA) in colon cancer, CA-125 measurements are of greatest value in monitoring response to therapy.

DISEASES OF PREGNANCY
1- Placental Inflammations and Infections

2-Ectopic Pregnancy (Fig. 10-21) refers to implantation of the fertilized ovum in any site other than the normal uterine location. It occurs in 1% of pregnancies. In more than 90% it is a tubal pregnancy; other sites include the ovaries & abdominal cavity. Any factor that retards passage of the ovum along its course through the tube to the uterus predisposes to an ectopic pregnancy.

The tube is usually locally distended (up to 4 cm in diameter) by a contained mass of freshly clotted blood in which may be seen bits of gray placental tissue and fetal parts.

The histologic diagnosis depends on the visualization of placental villi or, rarely, of the embryo.
Gestational Trophoblastic Tumors
These are divided into four morphologic categories:
1. Hydatidiform mole
   a. Complete
   b. Incomplete
2. Invasive mole
3. Choriocarcinoma.
All the three produce human chorionic gonadotropin (hCG), which can be detected in the circulating blood and urine, at much higher titers than those found during normal pregnancy. The titers are progressively rising from hydatidiform mole to invasive mole to choriocarcinoma. In addition to aiding diagnosis, the fall or rise in the level of the hormone in the blood or urine can be used to monitor the effectiveness of treatment.

1. Hydatidiform Mole: Complete and Partial
The typical hydatidiform mole is a large mass of swollen chorionic villi, grossly as grapelike structures. The swollen villi are covered by varying amounts of sometimes highly atypical chorionic epithelium. Two distinctive subtypes of moles have been characterized: complete and partial moles.

A. The complete hydatidiform mole does not permit embryogenesis and thus does not contain fetal parts. All of the chorionic villi are abnormal, and the chorionic epithelial cells are diploid (46, XX or, uncommonly, 46, XY).

B. The partial hydatidiform mole permits early embryogenesis and therefore contains fetal parts, has some normal chorionic villi, and is almost always triploid (e.g., 69, XXY).

The two patterns result from abnormal fertilization; in both two spermatozoa fertilize an ovum; in a complete mole an empty egg is fertilized, which yields a diploid karyotype composed of entirely paternal genes, while in a partial mole a normal egg is fertilized, resulting in a triploid karyotype with a preponderance of paternal genes.

Early monitoring of pregnancies by ultrasound has lowered the gestational age of detection, leading to the more frequent diagnosis of "early complete hydatidiform mole.”
In either instance, elevations of hCG in the maternal blood and absence of fetal parts or fetal heart sounds are typical.

Gross features
- Uterine cavity is filled with a delicate, friable mass of thin-walled, translucent cystic structures (Fig. 10-32).
- Fetal parts are rarely seen in complete moles but are common in partial moles.. (Fig. 10-33)

Microscopic features
The complete mole
- There is hydropic swelling of all the chorionic villi, which are avascular.
- The chorionic epithelium almost always shows some degree of proliferation of both cytotrophoblast and syncytiotrophoblast (Fig. 10-32).

Partial moles
- The villous edematous swelling involves only some of the villi and the trophoblastic proliferation is focal and slight.
- The villi of partial moles have a characteristic irregular scalloped margin.
- In most cases of partial mole there is evidence of an embryo or fetus. This may be in the form of fetal red blood cells in placental villi or, in some cases. (Fig. 10-33)
10% of complete moles are invasive, but not more than 2% give rise to choriocarcinoma. Partial moles rarely give rise to choriocarcinomas. With complete moles, monitoring the post-curettage blood and urinary hCG concentrations

2. **Invasive Mole (Fig. 10-34)** is a complete mole that is more invasive locally but do not have the metastatic potential of a choriocarcinoma. An invasive mole **retains hydropic villi, which penetrate the uterine wall deeply**, possibly causing rupture and sometimes life-threatening hemorrhage. Local spread to the broad ligament and vagina may also occur.

Microscopically, the epithelium of the villi is hyperplastic and atypical.

3. **Choriocarcinoma** is a very aggressive malignant tumor arises either from gestational chorial epithelium or, less frequently, from totipotential cells within the gonads or elsewhere. They are much more common in Asian and African countries, reaching a frequency of 1 in 2000 pregnancies. The risk is somewhat greater before age 20 and is significantly elevated after age 40. Approximately 50% of choriocarcinomas complicate complete hydatidiform moles; about 25% arise after an abortion, and most of the remainder occur during what had been a normal pregnancy.

**Clinical features**
Most cases are discovered by the appearance of a bloody or brownish discharge accompanied by a rising titer of hCG, particularly the β-subunit, in blood and urine, and the absence of marked uterine enlargement.

**Gross features (Fig. 10-35)**
- The tumor appears as very hemorrhagic, soft, nodular, necrotic masses within the uterus.
- Sometimes the primary lesion may self-destruct, and only the metastases tell the story.

**Microscopic features**
- Cytotrophoblastic cells tend to grow in clusters and sheets, separated by streaming masses of syncytiotrophoblast, forming the characteristic dimorphic growth pattern of mononucleate cytotrophoblast and syncytiotrophoblast.
- Hemorrhage and necrosis are usually present.
- Chorionic villi are not formed.

Present-day chemotherapy has achieved nearly 100% cure.