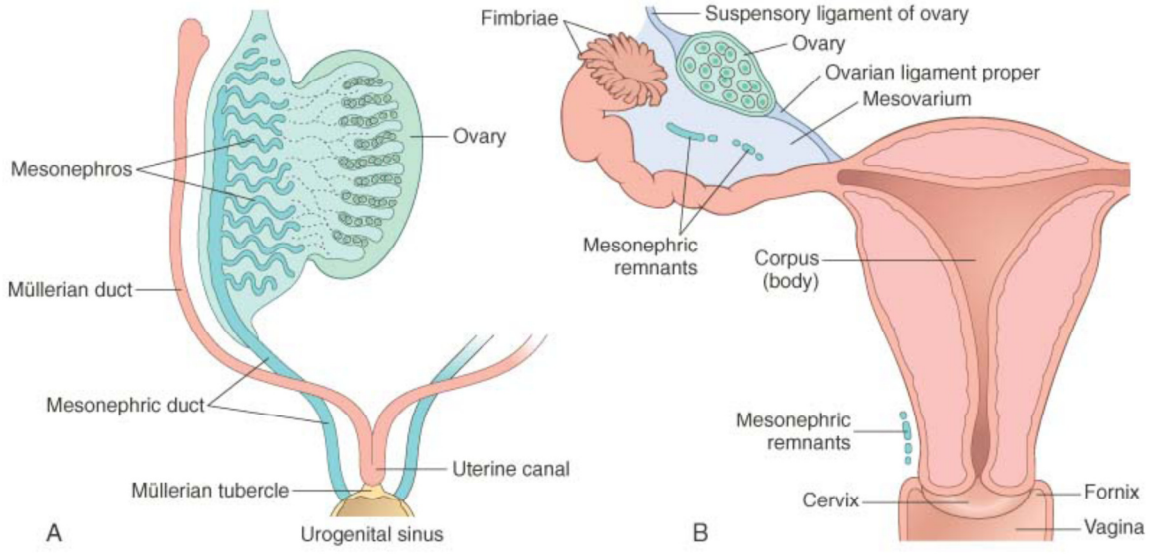
The Female Genital System and Breast

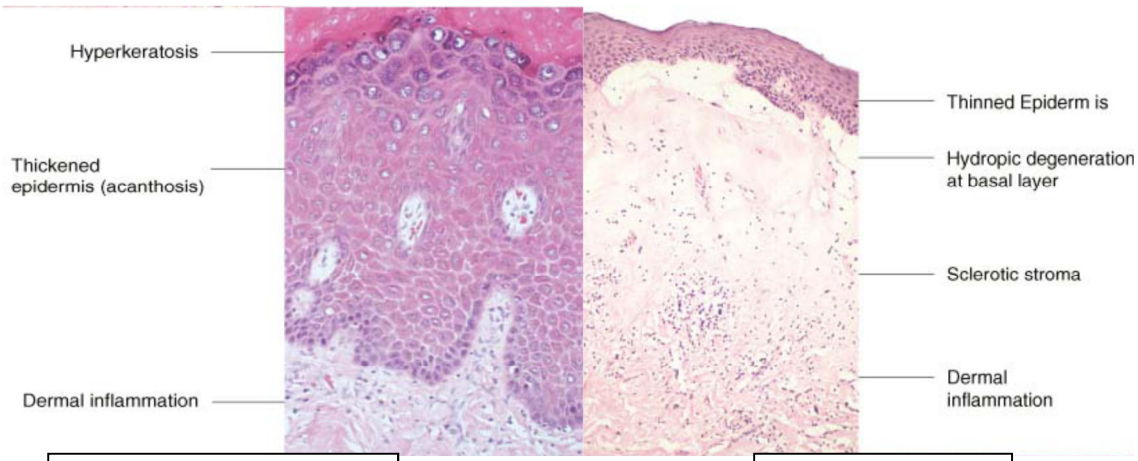


Vulva

Non- neoplastic epithelial disorders: include lichen sclerosis and lichen simplex chronicus. both may coexist in the same patient and both appear macroscopically as white paches known as ***leukoplakia.*** They should be **differentiated from** vitiligo, psoriasis and lichen planus, carcinoma in situ and invasive carcinoma.

Lichen sclerosis (LS): mainly seen in post menapausal women, clinically appears as smooth, white plaques or papules that coalesce together. The vulva becomes atrophic and stiffened; when the entire vulva is affected the vaginal orifices become constricted. Histologically LS characterized by thinning of the epidermis and disappearance of rete pegs, superficial hyperkeratosis and dermal fibrosis. Perivascular mononuclear inflammatory cell infiltrate. 1%-5% develop cancerous changes.

Lichen Simplex Chronicus: Histologically there is epithelial thickening with significant surface hyperkeratosis with no atypia. Intense Polymorphs cell infiltrate of the dermis. No increased predisposition to cancer is generally associated.



Lichen simplex chronicus

Lichen sclerosus

Tumors of the vulva:

***Condylomas*:** Condylomas are generally anogenital warts, usually warts are large in the vulva, it is either: **Condyomata lata** that occur in secondary syphilis, and rarely seen today.

Condylomata acuminata, may be papillary and distinctly elevated or flat and rugose. Usually multiple, from few mms – many cms in diameter, and are red – pink to pink – brown in color. Histologically: Hyperkeratosis, acanthosis, koilocytosis (perinclear vaculolization with nuclear angular pleomorphism). They have strong association with HPV 6 and 11 and can be transmitted venereally. It is not precancerous.

Carcinoma of the vulva: occurs most commonly in women older than 60 years, 90% are squamous cell carcinoma; the remainders are adenocarcinoma, melanoma and basal cell carcinoma. Melanoma is highly aggressive neoplasm account for 3-5% of vulval cancers.

Extramammary Paget Disease like that of the breast is an intraepithelial ca. histologically formed from scattered single cells and small clusters of malignant cells characterized by clear halos of mucopolysaccharide secreted by malignant cells. Clinically appear as well-demarkated geographic foci of red crusted areas easily mistaken as dermatitis.

Vagina

Vaginitis is relatively common clinical problem. It produces vaginal discharge called leukorrhea. The most common micro-organisms are:

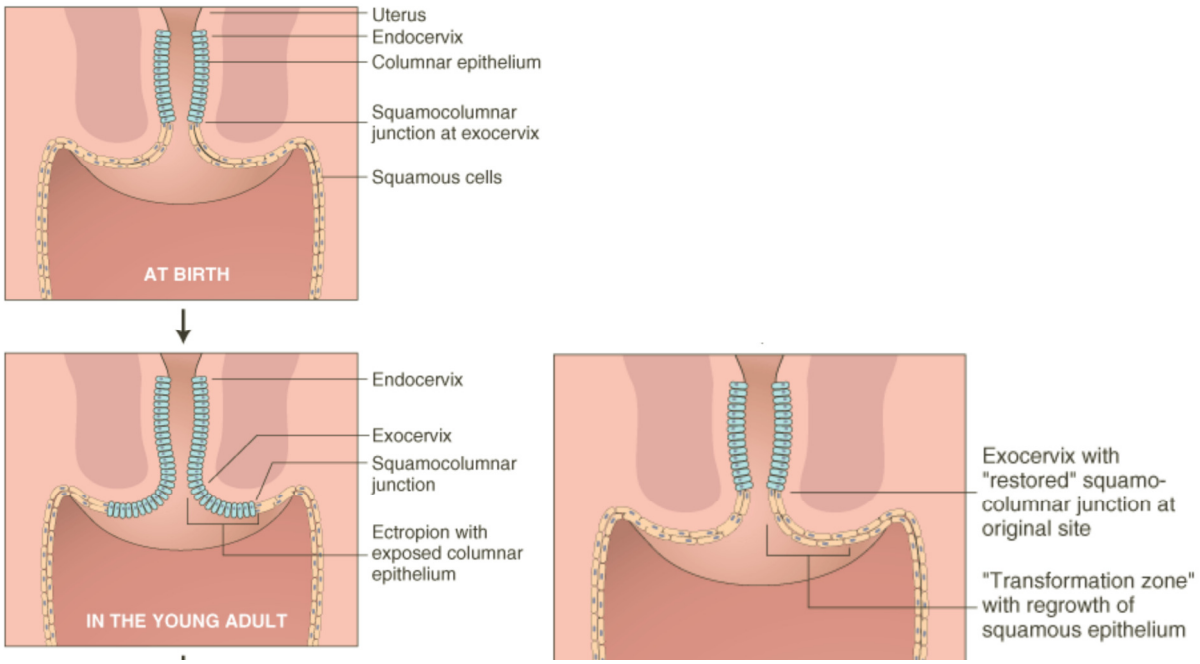
1. Mycotic and yeast infections; Candida albicans (monilia) are common; about 10% of women are thought to be carriers of vulvovaginal fungi. Monilia produces a thick whitish discharge causing pruritus. Diabetes mellitus, oral contraceptives, systemic antibiotic therapy and pregnancy are predisposing factors. The diagnosis is made by finding the organism in wet mounts of the lesions.
2. Trichmonas vaginilis a large, flagellated ovoid protozoan that can be readily identified in wet mounts of vaginal discharge. In infected patients produces a watery copious grey-green discharge. The underlying vaginal and cervical mucosa typically has a characteristic fiery red appearance, called strawberry cervix.
3. Gonorrheal vaginitis is uncommon and may occur in newborn to an infected mother.

Carcinoma of the vagina: Squamous cell carcinoma is extremely uncommon and usually occurs in women older 60 years. Vaginal clear cell adenocarcinoma usually encountered in girls in late teens whose mothers took diethylstilbestrol during pregnancy. Clear cell adenocarcinoma of the vagina shows vacuolated tumor cells in clusters and gland-like structures.

Sarcoma botryoides also called **embryonal rhabdomyosarcoma**. It is usually encountered in infants and children younger than 5 years. *Grossly* appear as soft gelatinous grapelike mass. *Microscopically* it is composed of primitive cells some of which contain eccentric strap-like processess. The malignant cells cluster beneath the mucosal surface known as cambium layer.

Cervix

At birth and during development, the columnar epithelium of the endocervix meets the squamous epithelia of the exocervix at the transformation zone. In reproductive woman there is down growth of columnar epithelium known as ectropion, thus the squamocolumnar junction (transformation zone) lies below the exocervix and can be seen by colposcopy. After menopause and as a result of the decrease in hormonal stimulation there is regression of the columnar epithelium in the endocevix and the squamocolumnar junction is restored in its original prepubertal phase.



Cervicitis is caused by Chlamydia trachomatis, Trichomonus vaginalis, Candida, Neisseria gonorrhea, Herpes simplex type II and HPV that causes viral warts, CIN and in situ carcinoma . But the most common cause is normal mixed vaginal flora e.g. strep.and enterococci as E. coli.

Endocervical Polyp. Protrude as polypoid mass through the exocervix , may be few centimeters in diameter they are soft and have smooth surface with underlying cystically dilated spaces, the stroma is edematous and dense fibrous covered with endocervical columnar epithelium.

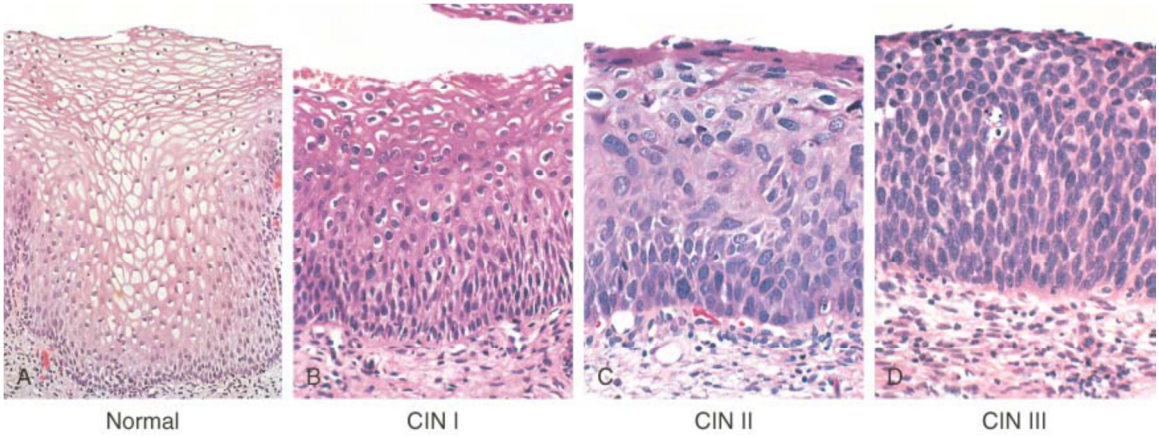
Cervical intraepithelial neoplasia: Epidemiology and pathogenesis. The peak age incidence of CIN is ~30 years whereas of invasive carcinoma is 45 years. Risk factors for development of CIN and invasive carcinoma are:

1. Early age at first intercourse.
2. Multiple sexual partners.
3. Infection with high risk HPV including 16, 18, 31, 35, 39, 45, 56, 59.
4. Low socioeconomic groups.

Cervical intraepithelial neoplasias are precancerous changes and graded as:

- CIN I: Mild dysplasia
- CIN II: Moderate dysplasia
- CIN III: Severe dysplasia and carcinoma in situ.

Morphology: CIN I or flat condyloma characterized by koilocytotic change (nuclear angulation, perinuclear vacuolization) in the superficial 1/3 of the epithelium. In CIN II the dysplasia is more severe affecting 2/3 of epithelium. In CIN III shows even more severe dysplasia affecting all layers or full thickness with disorientation of the cells, increase number of mitosis with abnormal mitosis but the basement membrane is intact.



- Regression of CIN I is 50 – 60 % .
- Regression of CIN III is only 33 % .

Invasive carcinoma of the cervix. 75% are squamous cell carcinoma which evolve from CIN, 20% adenocarcinoma 5% neuroendocrine carcinoma.
With Pap smear the majority of cervical carcinoma are diagnosed in preinvasive phase or in stage I.
More advanced cases are seen in women who have never had Pap smear such women have symptoms of unscheduled vaginal bleeding, painful coitus and dysuria.

- **Spread takes place in several ways :**
  a. Downward extension: This lead to uretric involvement and then to renal infection and renal failure.
  b. Lateral extension (around the external os, obstruction of cervical canal leading to pyometra).
  c. Anterior and posterior extensions: (bladder, rectum leading to fistula), also spread along uterosacral ligament involving sacral nerves …….severe pain .
  d. Lymphatic spread to pelvic lymph nodes (paracervical , obturator, sacral internal and external iliac group and paraaortic) .
- Patients commonly die before distant metastases appear.

Body of Uterus

Endometritis. The endometrium is relatively resistant to infections acute endometritis is limited to bacterial infection after labour or abortion. Chronic endometritis occurs in:

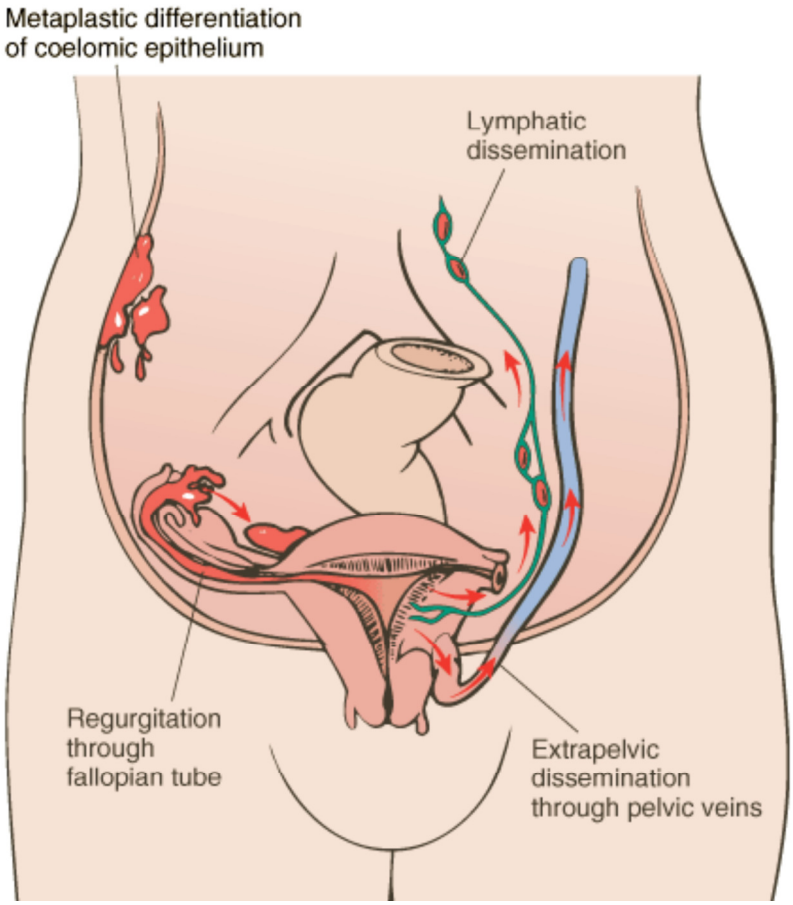
1. Chronic gonohrrea.
2. Tuberculosis.
3. Postabortion.
4. In patient with contraceptive device.
5. Spontaneously in 15% of cases.

Adenomyosis. Growth of the basal layer of the endometrium down into the myometrium. Cyclic bleeding into these nests is extremely unusual because stratum basalis of the endometrium is nonfunctional.

Endometriosis. Appearance of endometrial tissue in the pelvis (ovaries, pouch of Douglas, uterine ligaments, tubes), peritoneal cavity and about the umbilicus. Uncommonly the lymph nodes, lung and heart are involved.

Three theories to explain the origin of these lesions:

1. Regurgitation theory: backflow of menstrual blood through the fallopian tubes and subsequent implantation.
2. Metaplastic theory means differentiation of endometrial epithelium from coelomic epithelia but cannot explain the presence of endometrium in the lung and lymph nodes.
3. Vascular or lymphatic theory to explain extrapelvic and intranodal implant.



Morphology: endometriosis always contain functioning endometrium, which undergoes cyclic bleeding, grossly the blood collected in foci that appear as red to brown nodules sometimes these foci coalesce to form larger masses. When the ovaries are involved the lesions form large blood filled cysts called the **chocolate cysts**. Organization of the blood leads to fibrosis sealing of the tubal fimbriated ends.

Clinical manifestation: depend on the site of the lesion. Scarring of the ovary and oviducts cause discomfort in lower abdominal quadrant and sterility, rectal wall involvement causes pain on defecation. Dysuria reflects involvement of the urinary bladder.

Endometrial hyperplasia caused by excess estrogen relative to progestin:

1. Failure of ovulation like in premenopausal period.
2. Prolonged administration of estrogen.
3. Polycystic ovary.
4. Granulose and theca cell tumors.

There are 3 categories of endometrial hyperplasia: simple, complex and atypical. The atypical form has 20-25% risk of progression to adenocarcinoma.

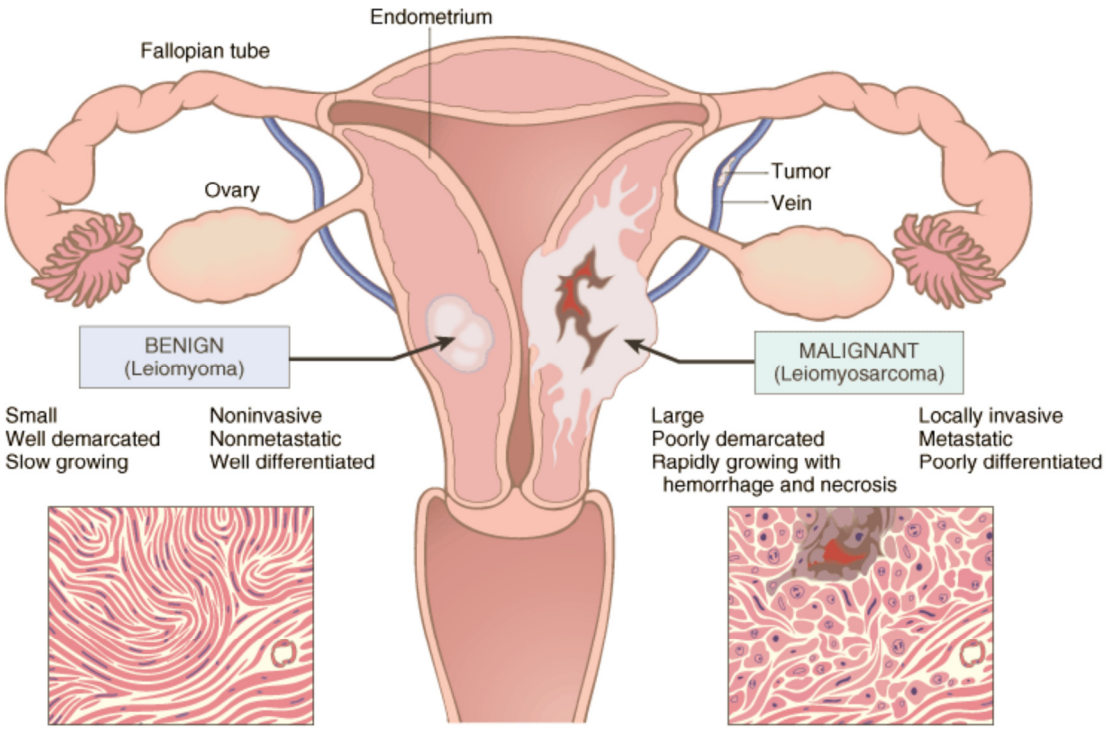
Tumors of the endometrium and myometrium

Endometrial polyps: these are sessile, 0.5-3 cm in diameter. On histological examination they are covered with columnar epithelia and have cystically dilated glands.

Leiomyoma and leiomyosarcoma

Leiomyomas are benign tumors of the smooth muscle cells of the myometrium known as fibroid. They are the most common benign tumor in females and are found in 30-50% of women during their reproductive life. Macroscopically are sharply circumscribed, firm grey white with whorled cut surface. Their location could be within the myometrium (intramural), directly beneath the endometrium (submucosal), or beneath the serosa (subserosal). The subserosal type may develop a stalk and become attached to surrounding organs from which develop blood supply and then free themselves from the uterus to become **parasitic leiomyoma**.

Histologically, they have whorling bundles of smooth muscle. Foci of fibrosis, calcification, necrosis, cystic degeneration, and hemorrhage may be present.
Leiomyosarcomas arise directly from myometrium not from preexisting leiomyoma, almost always solitary. Microscopically: there is wide range of differentiation. The diagnosis depends on both atypia and the number of mitosis.



Endometrial Carcinoma. In western countries endometrial carcinoma is the most frequent cancer of the female genital tract. It occurs between 55-65 years and uncommon below 40. The risk factors are:

1. Obesity causing increase estrogen synthesis.
2. Diabetes
3. Hypertension
4. Infertility, single women and nilliparous.

Many of these factors are the same of endometrial hyperplasia and endometrial carcinomas frequently arise from pre-existing atypical endometrial hyperplasia. About 20% of cancers are not associated with hyperestrinism, they are more poorly differentiated and associated with poor prognosis.

Clinically: there is marked leukorrhea and irregular bleeding in post-menopausal women. The uterus may be palpable and fixed to the surrounding structures. Stage I carcinoma is associated with 90% 5 years survival rate.

The Ovaries

The ovaries are infrequent sites for diseases; primary inflammation of the ovaries is rarities, but inflammation of the tubes (salpingitis) frequently causes salpingo-oophoritis.

Polycystic ovaries (Stein Leventhal syndrome)

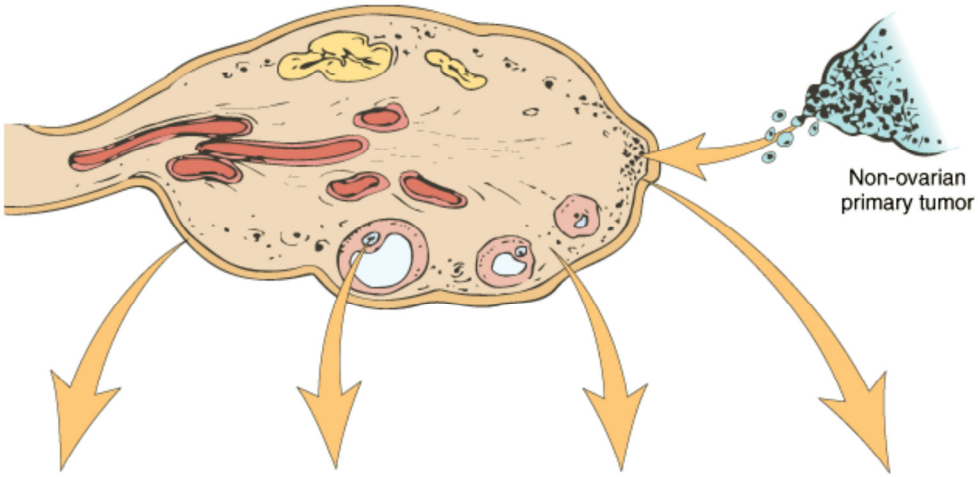
Symptoms: Oligomenorrhea, hirsutism, infertility and sometimes obesity appear in young women usually after menarche.

There is excessive production of estrogen and androgens. The ovaries are twice the normal size with smooth outer surface with subcortical cysts 0.5-1.5 cm in diameter. Histologically there are innumerable cysts lined by granulosa cells, atretic follicles with absence of corpora lutea and corpora albicans. Pathogenesis: the ovaries in this condition elaborate excess androgens which are converted in the peripheral fatty tissue into estrone. The estrone through the hypothalamus inhibits the secretion of FSH by the pituitary.

Tumors of the ovary. Pathogenesis: Two important risk factors are nulliparity and family history, i.e. there is higher incidence in unmarried and women with low parity. About 5-10% of ovarian ca. are familial. A majority are caused by mutation in *BRCA1 and BRCA 2* which are also associated with familial breast carcinoma. Prolonged use of oral contraceptive reduces the risk.

Three cell types make up the normal ovary, each of these gives rise to variety of tumors:

1. Multipotential surface epithelial covering.
2. Germ cells.
3. Sex cord/stromal cells.



ORIGIN	SURFACE EPITHELIAL CELLS (Surface epithelial–stromal cell tumors)	GERM CELL	SEX CORD–STROMA	METASTASIS TO OVARIES
Overall frequency	65%-70%	15%-20%	5%-10%	5%
Proportion of malignant ovarian tumors	90%	3%-5%	2%-3%	5%
Age group affected	20+ years	0-25+ years	All ages	Variable
Types	• Serous tumor • Mucinous tumor • Endometrioid tumor • Clear cell tumor • Brenner tumor • Cystadenofibroma	• Teratoma • Dysgerminoma • Endodermal sinus tumor • Choriocarcinoma	• Fibroma • Granulosa–theca cell tumor • Sertoli–Leydig cell tumor	

1) Surface Epithelia tumors could be benign, border line (intermediate) and malignant categories.

a) Serous tumors: they are the most frequent ovarian neoplasm; occur between 30-40 years. Grossly they are usually cystic so called **cystadenomas**, may be small 5-10 cm in diameter up to 40 cm., about 25% of the benign tumors are bilateral. The outer surface in benign tumor is smooth while cystadenocarcinoma shows nodular irregularities. On transaction may have single cavity but larger ones may be multiloculated filled with clear serous fluid. Polypoid projections into the lumen may indicate malignancy.

Histologically the benign tumors are characterized by single layer of tall columnar epithelium(which may be ciliated) lines the cysts, with focal papillary formation and psammoma bodies (concentrically laminated concretions) are common in the tip of the papillae, in malignant tumors anaplasia of the cells with invasion of the stroma, papillary formation are more complex with more psammoma bodies.

b) Mucinous Tumors differ from the serous tumors in that the epithelial lining is mucin secreting cells similar to endocervical mucosa and no psammoma bodies. They occur in the same age group as serous tumors but are less likely to be bilateral and less likely to be malignant. **Grossly** may be indistinguishable from serous tumors except by the mucinous content of the cyst. They are likely to be larger and multilocular. Rupture of the mucinous cyst may mucin deposition in the peritoneum (known as **pseudomyxoma peritonie**). The prognosis of mucinous cystadenocarcinomas is better than the serous counterpart.

c) Brenner Tumor is uncommon solid, usually unilateral ovarian tumor, microscopically consisting of nests of transitional like epithelium. Most of these tumors are benign but also border line and malignant are recorded.

2) Sex cord-stromal tumors:

a) Granulosa-theca cell tumor: Usually in postmenopausal women. Histologically consist of granulosa cells that arranged in similar way to normal follicles called Call-Exner bodies. The tumor cell elaborate large amount of estrogen, so produce menstrual disturbances and may induce endometrial and breast ca.

b) Fibroma: Occur at any age, the majority are hormonally inactive. About 40% for obscure reason produce ascites and hydrothorax (Meigs syndrome).

3) Germ cell tumors:

a) Teratomas these neoplasms of germ cell origin usually arise in the first 2 decades of life, the younger the patient the greater likelihood of malignancy.

b) Benign mature cystic teratomas constitute about 90% of teratomas, they are of ectodermal totipotential germ cells origin, so called **dermoid cyst**. Clinically they are discovered as abdominal mass, or discovered on abdominal radiograph because they contain foci of calcification produced by teeth. On transaction they are filled with sebaceous secretion and hair. Sometimes there is nodular projection from which teeth protrude. Sometimes bone or cartilage foci of gastric or bronchial epithelium are present.

Occasionally the tumor consists completely of thyroid tissue that may hyper function and produce hyperthyroidism, this is called **struma ovarii**, similarly ovarian **carcinoids** may develop and presented as carcinoid syndrome. Sometimes both condition appear together (struma ovarii + carcinoid) in the same ovary.

In about 10-15% of cases these tumors undergo torsion and produce abdominal emergency.

c) Immature malignant teratomas: The mean age is 18 years. They differ from benign teratomas in being solid on transaction with areas of necrosis; uncommonly one of the cysts may contain hair sebaceous secretion, microscopically areas of immature or undifferentiated cartilage, bone, neuroepithelial elements and other structures are present.

Metastases to the ovary: in older ages, mostly bilateral. Primaries are breast, lung, and GIT like ca. stomach and this is called (Krukenberg tumor), having signet ring mucin secreting cells.

Diseases of pregnancy

They are important causes of intrauterine or perinatal death, premature birth, congenital malformations, intrauterine growth retardation and maternal death.

Infections reach the placenta by 2 pathways:

1. Ascending infections, are the most common, they are usually bacterial from vaginal flora and are associated with premature birth and premature rupture of membranes. Histologically the chorioamnion shows leukocytic polymorphonuclear inflammation associated with edema and congestion. Ascending infection are also caused by mycoplasma, candida.
2. Hematogenous spread is uncommon, syphilis, tuberculosis, and toxoplasmosis. Transplacetal infection can give aise to TORCH complex which consists of the followings: **T** Toxoplasmosis, **R** Rubella, **C** Cytomegalovirus, **H** herpesvirus and **O** for other microbes such as T. pallidum.

Ectopic pregnancy is implantation of the fertilized ovum in any site other than the normal uterine location. It occurs as 1% of pregnancies. In > 90% of cases the implantation is in the oviduct, other sites include the ovaries, abdominal cavity and the intrauterine portion of the oviducts (interstitial pregnancy). Ovarian pregnancies results from fertilization of the ovum within the follicle just at the time of rupture.

Causes of ectopic pregnancy:

1. About 50% of cases the cause is unknown.
2. Chronic inflammation of the oviduct.
3. Intrauterine tumors.
4. Endometriosis**.**

Morphology: characterized by normal development of the embryo and placental tissue, however with tubal pregnancy the placenta invades through the wall of the oviduct causing intratubal hematoma (hematosalpinx) and intraperitoneal hemorrhage. The tube is distended up to 3-4 cm with a mass of fresh blood in which fetal parts may be seen.

Clinically: early ectopic pregnancy may be indistinguishable from normal one; with cessation of menstruation and elevation in blood and urine placental hormones. But rupture of ectopic pregnancy result in sudden onset of intense abdominal pain and signs of acute abdomen followed by shock.

Gestational trophoblastic diseases have been divided into 3 categories:

Hydatidiform mole, *Invasive* mole and *Choriocarcinoma*. All elaborate human chorionic gonadotrophin (HCG) they can be detected in blood and urine with titer higher than that found in normal pregnancy.

1) Hydatidiform mole (HM): Is voluminous mass of swollen cystically dilated chorionic villi appearing as grapelike structures. Two types of mole are present: *Complete and Partial mole*. The complete mole does not permit emberyogenesis so it never contains fetal parts. It results from fertilization of an empty egg by 2 spermatozoa. They are diploid (46XX), the partial mole there is early embryo formation and therefore contain fetal parts and always triploid (69XXY) result from fertilization of normal egg by 2 spermatozoa.

The incidence of complete HM is about 1 to 2000 pregnancies in western countries. For unknown reasons the incidence is much higher in Asian countries.

Clinically

1. Moles are most common before age 20 and after 40.
2. Usually discovered at 12 to 14 weeks of gestation as large for date.
3. By ultrasound there is absence of fetal parts and fetal heart sound.
4. Elevated hCG level.

Microscopically the complete mole shows hydropic swelling of chorionic villi. The central core of the villi is loose and edematous. The chorionic epithelium shows circumferential proliferation of both cytotrophoblast and syncytotrophoblast. In partial mole the villous edema involve some of villi, and the trophoblastic proliferation is focal and slight.

Prognosis: About 90% of moles remain normal after curettage, 10% of moles become invasive and ~3% change into choriocarcinoma.

2) **Invasive mole** they are complete moles that are invasive locally but do not have the metastatic potential of choriocarcinoma. Invasive mole may penetrate the uterine wall and cause life-threatening hemorrhage. Invasive mole cannot be completely removed by curettage thus hCG level remain high. In most cases cure is possible by chemotherapy.

3) Choriocarcinoma this is very aggressive malignant tumor arises either from chorionic epithelium or totipotential cells in the gonads. This tumor is more common in Eastern than in Western countries. The risk is higher before 20 and after 40 years. 50% of cases follow complete H. mole, 25% of cases follow abortion. Most of the remainders follow normal pregnancy.

Clinically patient has bloody brownish discharge, raising titer of hCG especially the B-subunit with absence of uterine enlargement.

Morphology grossly choriocarcinoma appears as very hemorrhagic necrotic masses in the uterus. Histologically the tumor does not contain villi. It consists purely of anaplastic cytotrophoblast and syncytotrophoblast.

Prognosis by the time the tumor is discovered it is usually wide spread via the blood most often to the lung vagina, brain, liver and kidneys.

Response to chemotherapy is good, nearly cure rate is100% even with metastasis. There are reports of infants born to the survivors women.