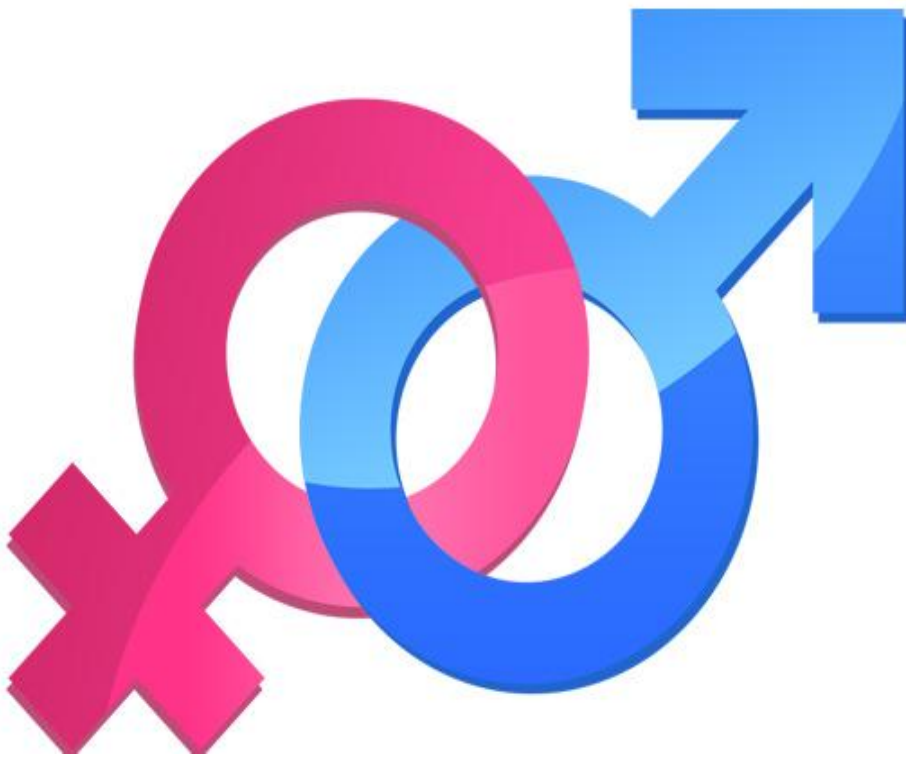


## PATHOLOGY TEAM 429



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### \*\*\* FEMALE REPRODUCTIVE SYSTEM PATHOLOGY \*\*\*

#### OVARIES & ENDOMETRIUM

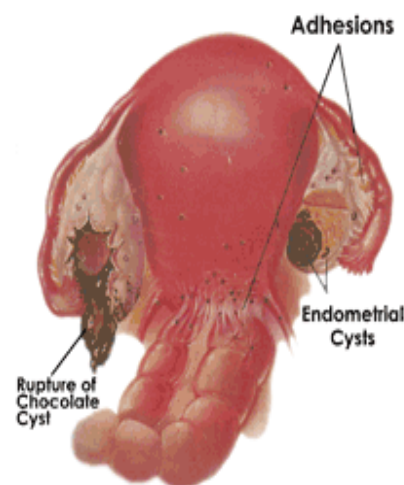
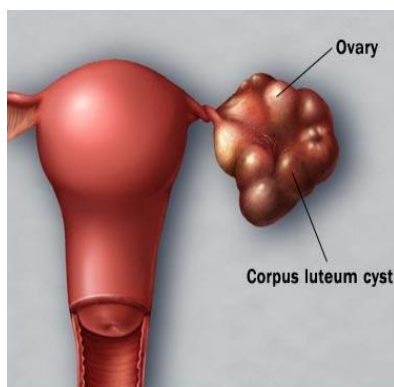
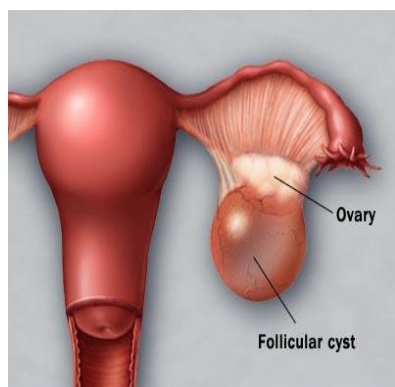
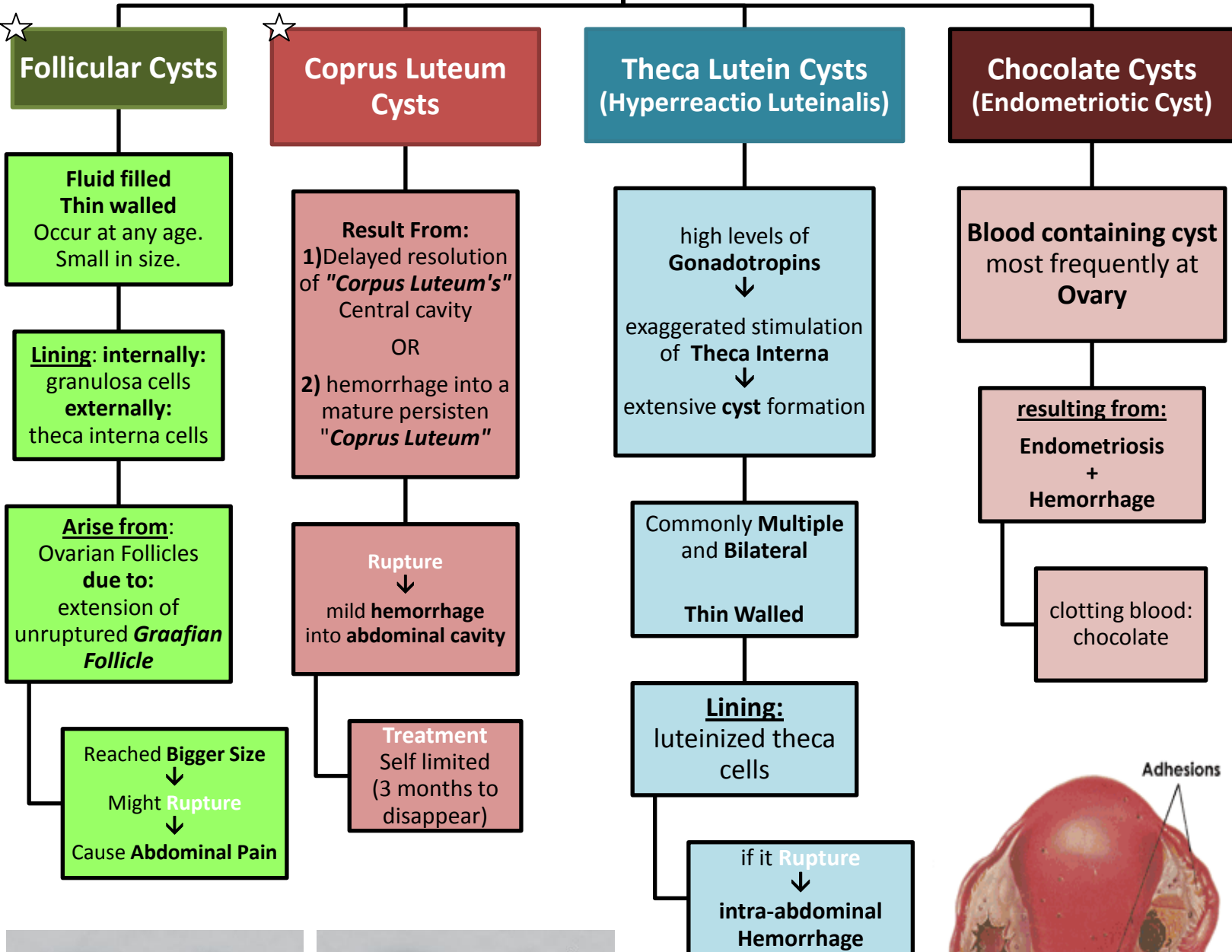
**Highlighted**; EXTREMELY IMPORTANT NOTE  
**Highlighted**; MCQ

# Ovarian Tumors

☆ : **Physiological (functional) cases;**  
self limited

## Non-Neplastic (Functiona Cysts)

## Neoplastic



# Ovarian Tumors

**Non-Neplastic  
(Functiona Cysts)**

**Neoplastic**

**Malignant Tumors:**

Metastasize & Kill

**Borderline Tumors:**

Metastasize but don't kill.

**Benign Tumors:**

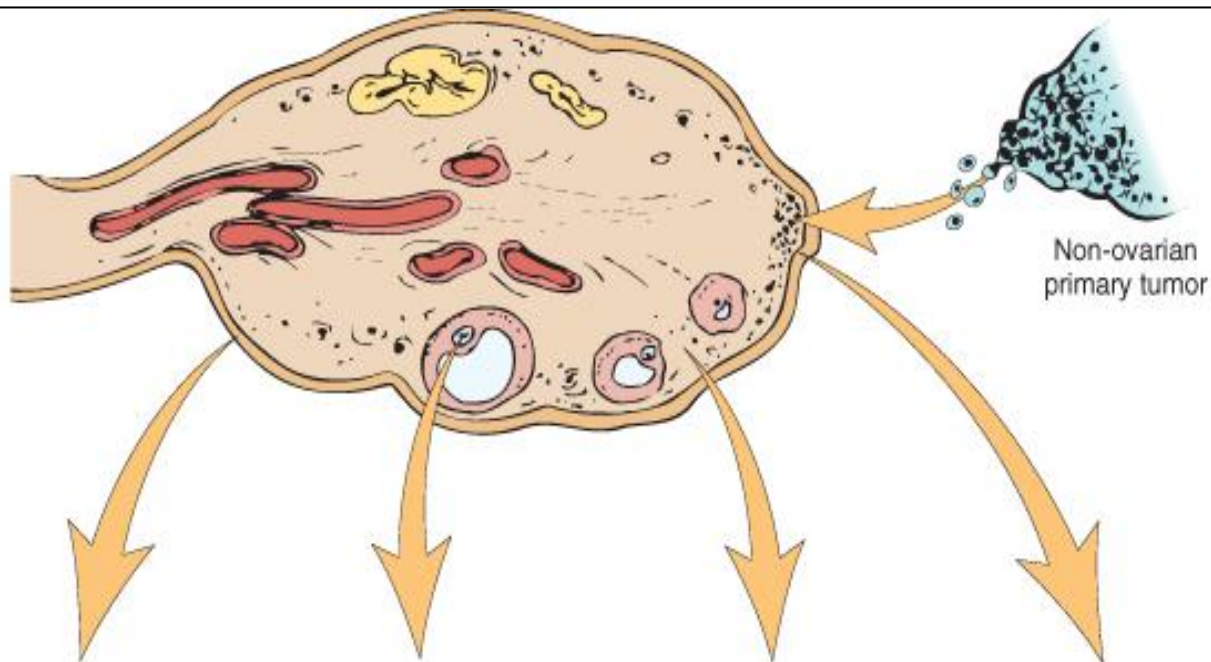
do not metastasize nor kill

**Epithelial  
Surface Tumors**

**Sex-Cord  
(Stromal cell)  
Tumors**

**Germ-cell  
Tumors**

**Metastatic  
Tumors**



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	<ul style="list-style-type: none"> <li>• Serosus tumor</li> <li>• Mucinous tumor</li> <li>• Endometrioid tumor</li> <li>• Clear cell tumor</li> <li>• Brenner tumor</li> <li>• Cvstadenofibroma</li> </ul>	<ul style="list-style-type: none"> <li>• Teratoma</li> <li>• Dysgerminoma</li> <li>• Endodermal sinus tumor</li> <li>• Choriocarcinoma</li> </ul>	<ul style="list-style-type: none"> <li>• Fibroma</li> <li>• Granulosa-theca cell tumor</li> <li>• Sertoli-Leydig cell tumor</li> </ul>	

Undifferentiated Carcinoma

## Epithelial Surface Tumors

Derived from the cells on the surface of the ovary.

**This is the most common form (80%)** and occurs primarily in adults.

type	Occurrence	Grade	Description
Serous tumors	<b>Most Common group</b>  Age is 30 -40  old patient, psammoma bodies, papillary and a lot of atypia → serous tumor  Often Bilateral  May be <u>solid</u> , and sometimes may be <u>mucoid</u>  Usually <u>cystic</u> and <u>filled with</u> : a clear serous fluid	-Benign (60%)	<b>SEROUS CYSTADENOMAS:</b> Large, entirely <b>cystic &amp; thin-walled</b> . Commonly unilocular lined by smooth epithelial surface Contain thin, clear yellow fluid.
		-Borderline(15%)	<b>Benign Feature:</b> May be <b>cystic</b> with <b>thin wall</b> and <b>smooth surface</b> . <b>Malignant Feature:</b> Often have <b>Multiple Papillary Excrescences</b> (grape-like clusters), protruding into the lumen in places.
		-Malignant (25%)	<b>SEROUS CYSTADENOCARCINOMA</b> <b>the commonest malignant ovarian tumor</b> - Partly <b>cystic</b> and partly <b>solid</b> with <b>exuberant excrescences</b> , often with <b>necrosis</b> and <b>hemorrhage</b> . - <b>Ovarian surface involvement</b> may be present. - Present with <b>Ascites</b> (when <b>abdominal metastases</b> )
Mucinous tumors	<b>25% of all ovarian neoplasms.</b> -Less likely to be <b>malignant</b> -Can be <b>very large</b> .  -Typically <b>cystic &amp; Multilocular</b>  - <u>Filled with</u> : <b>thick</b> sticky, viscous, less often, <b>thin</b> and watery fluid.	-Benign (80%)	Bilateral (5%)
	- <b>Epithelium consists of</b> Mucin-producing cells	-Borderline(10%)	Bilateral (10%)
		-Malignant (10%)	Bilateral (20%)
Endometrioid tumors	5% of all ovarian tumors.  "endometrium-like"  -Mostly <b>Malignant</b> .	-Benign -Borderline -malignant	-
Clear cell tumors	-	-Benign -Borderline -malignant	-
Transitional (Brenner) cell Tumors	-	-Benign -Borderline -Malignant -Transitional cell carcinoma	-

+ Undifferentiated Carcinoma

**Sex-Cord  
(Stromal cell)  
Tumors**

Rare in comparison to epithelial tumors (only 2% of ovarian tumors).  
This class of tumors often **produces steroid hormones**

type	General	Specific
<b>Granulosa Cell tumor</b>	<ul style="list-style-type: none"> <li>- 1-2% of ovarian tumors</li> <li>- <b>Character:</b> Unilateral, solid &amp; cystic (size vary)</li> <li>- <b>Clinical Picture:</b> Produce estrogen → Can present with <b>abnormal vaginal bleeding</b> Can be associated with <b>47 yr old female, ovarian mass &amp; high estrogen?? → granulosa cell tumor</b> Endometrial Hyperplasia and Carcinoma.</li> <li>- <b>Has 2 forms:</b> Adult and Juvenile.</li> <li>- Has a <b>malignant potential</b> (in 5-25%)</li> </ul>	<p><b>ADULT FORM</b> Typically occurs at any age after puberty but is more common in postmenopausal women.</p> <p><b>JUVENILE FORM</b> Occurs in the first three decades, can present with <b>isosexual precocity</b> (premature sex development – WHY??)</p>
<b>Thecoma-Fibroma</b>	<ul style="list-style-type: none"> <li>- Has two types, Thecomas or Fibromas</li> <li>- <b>Rarely malignant</b></li> <li>- Occur at <b>Any age</b></li> <li>- <b>Character:</b> Unilateral, Solid gray to yellow</li> </ul> <p>Usually occur in <b>middle-aged, perimenopausal women as unilateral, fibrous solid growths, with a hard, gray to white, whorled cut surface. They are frequently extensively calcified.</b></p>	<p><b>THECOMAS:</b> <b>Pure theca cell tumors</b> (functional tumors producing estrogen) also occur in <b>Postmenopausal Women</b>. <b>Character:</b> Vary in <b>size</b> from small to large, <b>solid tumors</b>, and vary in <b>color</b> from gray to yellow to orange depending on the amount of lipid content.</p> <p><b>FIBROMAS:</b> Are the <b>commonest</b> ovarian stromal tumors <b>Pure fibromas</b> (nonfunctioning) usually occur in <b>Middle-Aged, Perimenopausal Women</b> <b>Character:</b> As <b>unilateral, fibrous solid growths</b>, with a hard, <b>gray to white</b>, whorled cut surface. They are frequently extensively <b>calcified</b>.</p> <p><b>FIBROTHECOMAS</b> Are a mixture of fibromas and thecomas. May be estrogenic.</p>
<b>Sertoli-Leydig Cell Tumor</b>	<ul style="list-style-type: none"> <li>- <b>Less than 0.5% of ovarian tumors</b></li> <li>- <b>All ages but most often in young women</b></li> <li>- <b>Characteristics:</b> <b>Unilateral</b> Gray to yellow <b>solid</b> and <b>cystic</b>, or even <b>papillary</b></li> <li>- <b>Clinical Picture:</b> Produce <b>androgens</b> (male cells !!) → present with <b>virilization</b> (steroli) 1/3 of cases</li> </ul>	<p><i>Normally found in small numbers in female ovaries</i></p> <p><b>Uncommonly malignant:</b> Behavior correlates with degree of differentiation and stage <b>Virilization:</b> Oligomenorrhea, Amenorrhea, Loss of female secondary sex characteristics with hirsutism, clitoromegaly, deepening of voice</p>

+ Gynandroblastoma  
+ Unclassified

**Generally; To know about ovarian pathology:**

**Salpingitis:** inflammation of the fallopian tubes.

**Oophoritis:** inflammation of the ovaries.

Oophoritis is very rare and mostly happens when the fallopian tubes are inflamed (salpingitis).

## Germ-cell Tumors

**Derived from** the egg producing cells within the body of the ovary.

Occurs **primarily in children and teens**.

Rare by comparison to epithelial ovarian tumors but more common than sex-cord tumors

Type	Epidemiology	Morphology
Dysgerminoma	<ul style="list-style-type: none"> <li>- <b>3-5% of ovarian malignant tumors</b></li> <li>- 1<sup>st</sup> Most Common of Malignant Germ-cell Tumors</li> <li>- Occur in <b>2<sup>nd</sup> and 3<sup>rd</sup> decades</b></li> <li>- Counterpart to <b>Seminoma (testis – same form in males)</b> and <b>Germinoma (brain)</b> ((All malignant))</li> </ul>	<ul style="list-style-type: none"> <li>- <b>PLAP positive</b></li> <li>- <b>Characteristics:</b> Typically a <b>unilateral, solid, firm to fleshy</b></li> <li>- <b>Composed of</b> <ol style="list-style-type: none"> <li>1) <b>Malignant germ cells</b>, similar to primordial germ cells,</li> <li>2) Admixed with <b>Non-Neoplastic Chronic Inflammatory Cells</b></li> <li>3) And occasionally <b>Granulomatous Inflammation</b></li> </ol> </li> <li>- <b>Highly sensitive to radiation and/or chemo therapy</b></li> </ul>
Yolk Sac Tumor	<ul style="list-style-type: none"> <li>- 2<sup>nd</sup> most common malignant ovarian germ cell tumor</li> <li>- <b>Common in childhood, adolescence, and adult life (most &lt;30 years)</b></li> <li>- <b>Clinical Picture:</b> Most patients are children or young women presenting with <b>abdominal pain</b> and a <b>rapidly developing pelvic mass</b></li> <li>- <b>The tumors usually appear to involve a single ovary but grow rapidly and aggressively.</b></li> <li>- Highly malignant neoplasm that is radio resistant but responds to combination chemotherapy</li> </ul>	<ul style="list-style-type: none"> <li>- <b>Elevated serum AFP levels</b> (tumor is rich in <math>\alpha</math>-fetoprotein and <math>\alpha</math>1-antitrypsin)</li> <li>- Can be pure or a component of a mixed germ cell tumor</li> <li>- <b>Characteristics:</b> almost always a <b>unilateral solid or solid cystic</b> <ol style="list-style-type: none"> <li>1) <b>Glomerulus-like structure</b> composed of a central blood vessel</li> <li>2) Enveloped by <b>germ cells</b> within a space</li> <li>3) lined by germ cells (histologic feature; <b>Schiller-Duval body</b>)</li> </ol> </li> <li>→ <b>Classic Pattern:</b> Shows <b>perivascular formations (Schiller-Duval bodies)</b> and <b>Eosinophilic globules that contain AFP</b></li> </ul>
Embryonal Carcinoma	<ul style="list-style-type: none"> <li>- Uncommon ovarian germ cell neoplasm</li> <li>- <b>2<sup>nd</sup> and 3<sup>rd</sup> decade occurs in children and young adults</b></li> <li>- Aggressive, highly malignant neoplasm that is radioresistant but responds to combination chemotherapy</li> </ul>	<ul style="list-style-type: none"> <li>- <b>CD 30 positive</b></li> <li>- <b>Usually occurs in combination with yolk sac tumor</b></li> <li>- <b>Characteristics:</b> Typically <b>unilateral, solid</b> tumor with hemorrhage and necrosis</li> </ul>
Choriocarcinoma	<ul style="list-style-type: none"> <li>- <b>Rare</b></li> <li>- <b>occurs in children and young adults</b></li> <li>- <b>Clinical Picture:</b> generally have metastasized widely through the bloodstream to the lungs, liver, bone, and other viscera by the time of diagnosis.</li> <li>- Highly malignant neoplasm that responds to combination chemotherapy</li> </ul>	<ul style="list-style-type: none"> <li>- Associated with <b>elevated serum HCG levels</b> (Human Chorionic Gonadotropins- for <b>Diagnosis &amp; Recurrences</b>)</li> <li>- Occurs as: a <b>Pure Ovarian Neoplasm</b> or as a <b>Component of Mixed Germ Cell Tumor</b></li> <li>- <b>Characteristics:</b> typically a <b>unilateral, solid, hemorrhagic tumor</b> Composed of <b>malignant cytotrophoblast</b> and <b>syncytiotrophoblast</b></li> </ul>

# Teratoma : Mature, Immature

- 15-20 % of Ovarian tumors.
- Majority in the first 2 decades  
(The younger the patient, the greater the likelihood of malignancy).
- The tumors are subdivided into:
  - Mature
  - Immature
  - Monodermal
- Unlike those in the testis, the vast majority of ovarian germ cell tumors are **benign mature cystic teratomas**.  
While **Immature** teratomas are malignant and rare.

## MATURE CYSTIC TERATOMA

- Most common ovarian teratoma and most common ovarian germ cell tumor
- Benign** neoplasm that typically occurs during reproductive years
- Characteristic:** (Tumor with bone and hair?? )  
Cystic tumor with **firm capsule**, filled with **sebaceous material and hair (occasionally teeth can be found)**, thickened area from which hair and teeth arise is called "**Rokitansky's Protuberance**"
- Composed of **mature elements** derived from **all three germ layers (ectodermal elements** such as skin, hair, sebaceous glands, and mature neural tissue predominate; **cartilage, bone, respiratory and intestinal epithelium** are common)
- Complications include** torsion, rupture, infection etc.

## MONODERMAL TERATOMA

- A teratoma composed predominantly of ONE tissue element
- Most common type is:**  
"**struma ovarii**", which is mature thyroid tissue

## IMMATURE TERATOMA

- Malignant.** Occurs in children and young adults
- Characteristics:**  
Usually a **unilateral, solid tumor** similar to **mature teratoma** but contains **immature or embryonal tissues**.
- immature elements:**  
Almost always **immature neuroepithelium** ((Graded on the basis of the quantity of immature tissue)).

+ Polyembryoma

## Metastatic Tumors

Accounts for approximately 5% of ovarian tumors  
Older ages, Mostly Bilateral

**Primaries** are **Breast in Female, lung in male**, G.I.T. and hematopoietic system.

Features suggesting the metastatic nature of an ovarian neoplasm include:

- 1) bilaterality, presence of multiple nodules of tumor
- 2) Involvement of the surface and superficial cortex of the ovary
- 3) Smaller tumor size.

## Krukenberg tumor

One of the most classic forms of metastatic carcinoma involving the ovaries.

Composed of

**signet ring cells** embedded within a hypercellular ovarian stroma that *Mimics Sarcoma*.

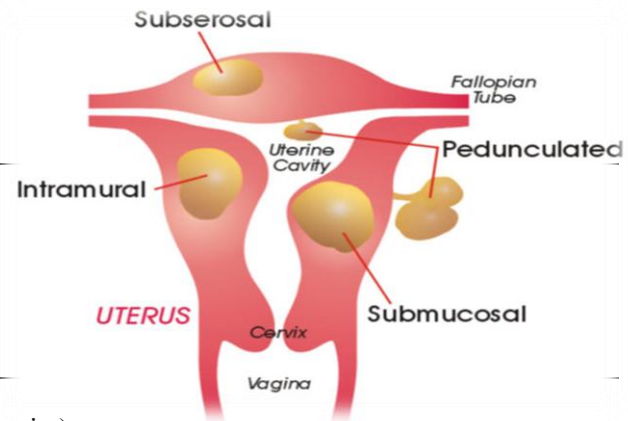
The most common sites of origin: stomach, colon and appendix.

This cancer is **highly malignant** → It metastasizes

# Pathology of the Endometrium:

Acute Endometritis	Chronic Endometritis	Endometrial polyp
<b>Mostly Related to:</b> <ol style="list-style-type: none"> <li>1) Intra-uterine trauma (e.g. <b>after abortion – spontaneous or even induced</b>)</li> <li>2) Pregnancy Complications</li> <li>3) Medical instrumentation</li> <li>4) Intra-uterine contraceptive device</li> </ol>	<b>Mostly Related to:</b> <ol style="list-style-type: none"> <li>1) Intra-uterine contraceptive device use</li> <li>2) Pelvic inflammatory disease</li> <li>3) Retained products of conception following an abortion or delivery (part of the placenta remains in the uterus after delivery or abortion).</li> </ol> <p>mostly the etiologic agent is not apparent and the patient is said to have non-specific chronic endometritis</p>	<p>Localized benign overgrowth of endometrial tissue covered by epithelium.</p> <ul style="list-style-type: none"> <li>- Most common in women between 40 and 50 years.</li> <li>- May cause irregular bleeding</li> </ul> <p><b>Clinical Behavior:</b> Endometrial polyps are <b>benign</b> with no malignant potential but sometimes malignant tumors may be found inside them.</p>
<b>Pathogenesis:</b> <b>A) MOST COMMONLY:</b> <b>Staphylococci or Streptococci</b> <b>B) Other organisms like:</b> N.gonorrhea, gram –ve bacilli, viruses or fungus.	<p>Patient may present with <b>irregular bleeding</b>. <b>Granulomatous Endometritis</b> is associated with</p> <p><b>Diagnosis:</b> by the presence of <b>plasma cells</b> in the endometrium</p>	<p><b>Histology:</b> Composed of:</p> <ul style="list-style-type: none"> <li>-Glands variable in size and shape</li> <li>-Fibric Stroma</li> <li>-Thick-walled blood vessels</li> </ul>

Leiomyoma	
Definition	<p>A benign tumor of smooth muscle origin.</p> <p><b>Most common</b> neoplasm of female genital tract (Especially African)</p> <p>Can be single or multiple, mostly multiple.</p> <p><b>Located</b> anywhere and most commonly within the <b>Myometrium</b> (Intramural)</p>
Morphology	<p><b>GROSS:</b> Appear as <b>Well-circumscribed, Spherical, dense and firm-to-hard</b> masses. With <b>Whorled, tan-white</b> cut surfaces</p> <p><b>HISTOLOGY:</b> Interlacing bundles of smooth muscles cells with collagenous stroma in between the bundles</p>
Clinical Behavior	<p>A benign tumor. Cause: 1) Anemia from <b>heavy/irregular bleeding</b></p> <p>2) Bowel or Urinary obstruction (depending on site)</p> <p>3) <b>Pelvic pain</b> 4) <b>Pelvic mass</b> 5) <b>Infertility</b>.</p> <p><b>An estrogen-responsive tumor → increase in size during pregnancy and decrease during menopause.</b></p> <p>In <b>pregnancy women</b>, may cause 1)Spontaneous abortion, 2)precipitate labor, 3)obstructed labor, 4)post-partum hemorrhage (due to interference with normal uterine contraction)</p> <p>5)<b>red degradation:</b></p> <p>Venous thrombosis and congestion with <b>interstitial hemorrhage</b> accompanied by pain (clinical picture of acute abdomen)</p>
Degenerative Changes	<p>-<b>Atrophy</b> → tumor reduces in size according to <b>estrogen</b> level (especially after pregnancy or at menopause)</p> <p>-<b>Hyaline Changes (Hyalinization)</b> → occurs as the tumor ages</p> <p>-<b>Calcification</b> → common in menopausal women</p> <p>-<b>Septic with necrosis</b> at the center → due to circulatory inadequacy</p> <p>-<b>Red Degradation.</b></p> <p><b>-Myxoid and Cystic change</b></p>



## Endometrial Hyperplasia

A process in which there is a **proliferation of endometrial glands** of irregular size and shape with an increase in gland/stroma ratio (compared to proliferative endometrium).

**Induced by** persistent, prolonged estrogenic stimulation of the endometrium. (increase estrogen >> hyperplasia)

**May progress to** Endometrial Adenocarcinoma.

The development of cancer is **based on**:

- 1) The level and duration of the estrogen excess.
- 2) The severity of the hyperplastic changes and association with cellular Atypia (The term is medical for an atypical, abnormal, cell).

### Classification:

- Simple Hyperplasia - Complex Hyperplasia (both are classified as with/without atypia)

- 1) **Common cause:** succession of anovulatory cycles (failure of ovulation)
- 2) **Excessive endogenously produced estrogen**, especially in:
  - Polycystic ovary syndrome (e.g. Stein-Leventhal)
  - Granulosa cell tumors of the ovary
  - Excessive ovarian cortical function (cortical stromal hyperplasia)
- 3) **Prolonged exogenous administration of estrogenic steroids** without counterbalancing **progestins**.

**Risk Factors:** Obesity – Western diet  
Nulliparity (never given birth) – DM  
Hypertension – Hyperestrinism (↑estrin)

- Milder forms occur in younger patients.
- Most of milder ones regress spontaneously or after treatment.
- More severe forms occur in peri & post-menopausal women. It had a high premalignant potential.
- Usually present with **Abnormal Uterine Bleeding**.

### Characterized by:

- 1) Proliferation of both glands and stroma
- 2) Glandular overcrowding occurs

### Classified according to:

- 1) **Architecture as:** simple or complex depending on the degree of **glandular complexity** and **crowding**
- 2) **Cytologic Features as:** with/without atypia

**MICROSCOPY:** both with/without atypia:

**Simple Hyperplasia (cystic hyperplasia)**  
glands are typically dilated and dispersed within abundant cellular stroma (SWISS CHEESE appearance)  
**Complex Hyperplasia**  
complex, crowded glands with papillary infoldings and irregular shapes.

## Endometrial Adenocarcinoma

**Common** neoplasm as 5<sup>th</sup> commonest cancer in women worldwide especially in the U.S

### Risk Factors: (important for scenario cases in the exam)

- 1) Obesity (especially women with upper body fat)
- 2) Estrogen therapy
- 3) Hyperestrinism (high estrin; estrogen)
- 4) Nulliparity (as a result of infertility due to chronic anovulation)
- 5) Chronic Anovulation
- 6) Late menopause
- 7) Hypertension
- 8) Diabetes
- 9) **Tamoxifen therapy** (estrogen receptor antagonist for **treating breast cancer**)
- 10) High socioeconomic status
- 11) Follows **Atypical hyperplasia** (younger patients) or occur independently (older patients).

- Most patients are between **50-59 years**
- Manifest as **Abnormal vaginal bleeding**
- Grow or diffuse in a **Polypoid Pattern**.
- Often involves multiple areas of the endometrium.

### GROSS:

May closely resemble normal endometrium or may be or exophytic (growing outward)  
May be infiltrative  
May be polypoid

### HISTOLOGY :

Composed of: **Glandular Cells**

(Commonest type: Endometrioid adenocarcinoma or: Clear cell, Adenosquamous & papillary serous adenocarcinoma)  
IF >>>

-Endometrioid carcinoma showed: areas of **benign-looking** squamous epithelium → referred as **adenocanthoma**  
-OR it showed: both glandular and squamous contents appearing malignant → referred as **adenosquamous**.

-**SOME** revert to normal spontaneously or with medical treatment  
 -**OTHERS** persist as hyperplasia  
 -**FEW** progress to endometrial adenocarcinoma (especially ones with atypia and in postmenopausal women)  
**Risk for developing carcinoma:**  
 Complex atypical (30%) > Simple atypical (10%)  
 Complex (3%) > Simple (1%).

**Hyperplasia with atypia is more dangerous**

-Depending on the histological type, grade (degree of differentiation) and the stage (extent of spread) as:

**Endometrioid carcinoma** has the best prognosis than other histologic types which occur at higher stages

**-Staging depends on:**

- 1) degree of myometrial invasion if either:  
cervical, adnexal and adjacent pelvic organ invasion
  - 2) Result of peritoneal fluid cytology
  - 3) Distant organ metastasis (especially **Lymph node** status)
- **The lesser the stage, the higher is the survival rate**

Tumor + unopposed estrogen (usually in younger) → have:  
 a- low histologic grade & clinical stage    b-better prognosis

20% of endometrial carcinoma has no association with **Hyperestrinism** or **pre-existing hyperplasia** and they tend to have poor prognosis

**Grading** is from 1 to 3 (done under microscope)

**Staging** is from 1 to 4 (the journey of the tumor)

**Stage 1** : confined to uterine corpus

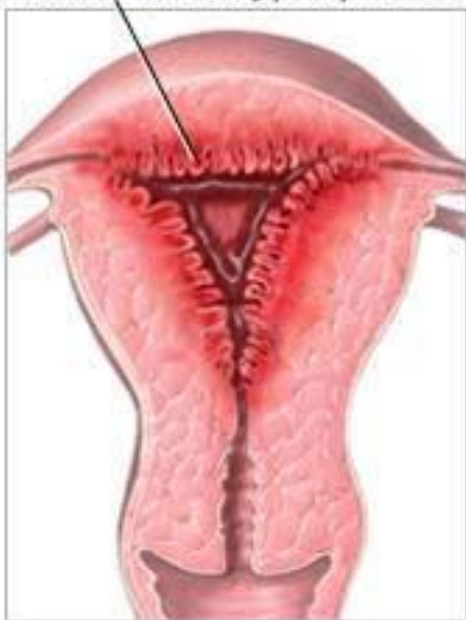
**Stage 2** : Cervix involvement

**Stage 3** : beyond the uterus but within true pelvis

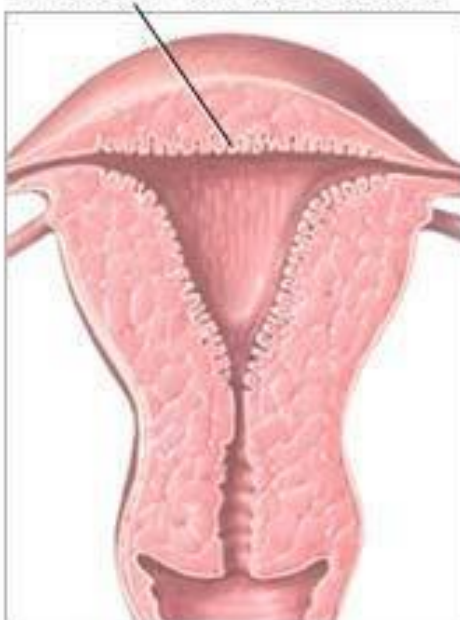
**Stage 4** : Distant metastasis (extrapelvic extension)

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Endometrial hyperplasia



Normal endometrium



Endometrial Cancer

