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بسم الله الرحمن الرحيم

Ovarian & Fallopian Pathology

FINAL | Lecture 3

﴿ قُلْ بِفَضْلِ ٱللَّهِ وَبِرَحْمَتِهِۦ فَبِذَٰلِكَ فَلْيَفْرَحُوا۟ هُوَ خَيْرٌ مِّمَّا يَجْمَعُونَ ﴾

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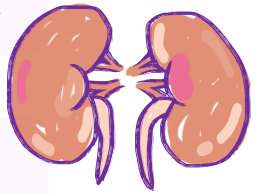

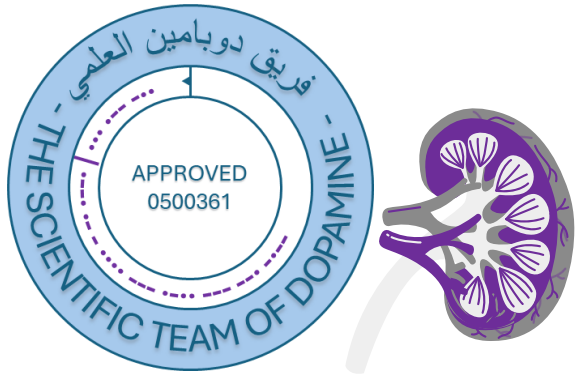

Ovarian and Fallopian Tube Pathology

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University of Jordan, School of Medicine

Topics covered in this lecture:

- **Ovarian neoplasms:**
  - Classification
  - Serous tumors
  - Mucinous tumors
  - Teratomas
  - Clinical aspects
- **Fallopian tube diseases:**
  - Ectopic pregnancy
  - Tubal malignancies

Ovarian Neoplasms

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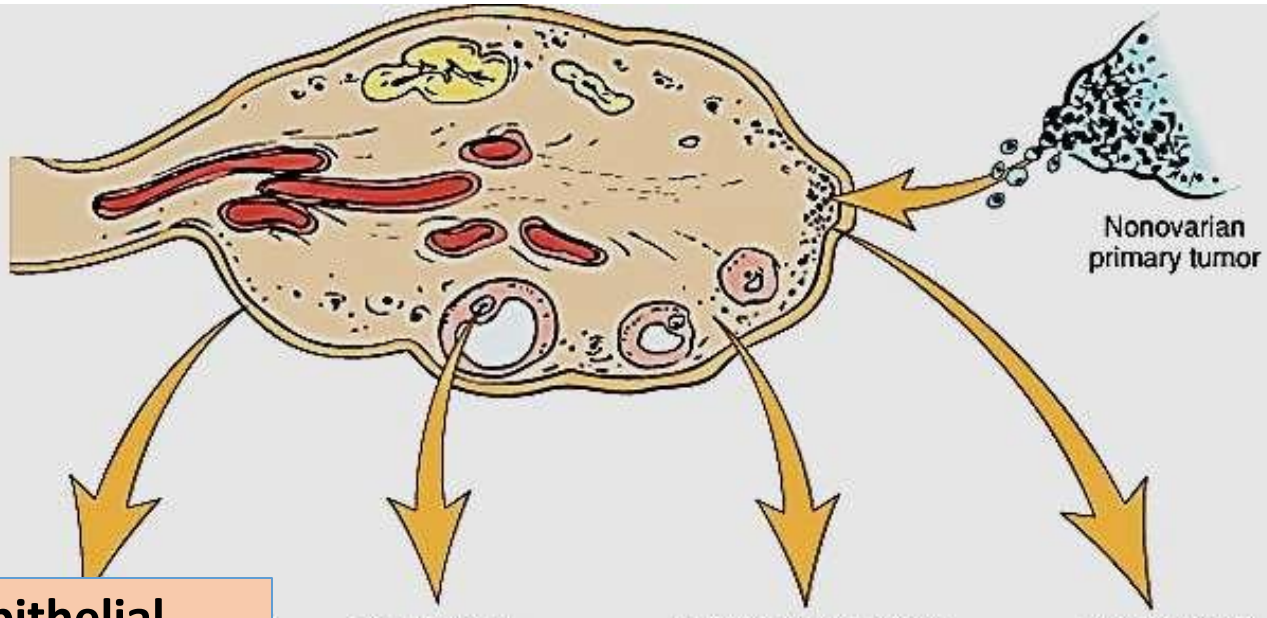


ORIGIN	Epithelial tumors	GERM CELL	SEX CORD–STROMA	METASTASIS TO OVARIES
Overall frequency	65%–70%	15%–20%	5%–10%	5%
Proportion of malignant ovarian tumors	90%	3%–5%	2%–3%	5%
Age group affected	20+ years	0–25+ years	All ages	Variable
Types	• Serous tumor • Mucinous tumor • Endometrioid tumor • Clear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

Ovarian neoplasms

Definition:

Ovarian neoplasms include all benign and malignant tumors arising in the ovary.

They are classified into:

1. Primary ovarian tumors

Originate from the ovary itself.

Classified according to the **cell of origin** into:

- **Epithelial tumors**
- **Germ cell tumors**
- **Sex cord-stromal tumors**

2. Secondary ovarian tumors

Spread to the ovary from another primary site (metastasis).

Are considered **always malignant**.

Overview of Ovarian Tumor Types

1- Epithelial Tumors:

➢ Represent the **most common ovarian tumors overall**.

➢ Also account for the **majority of malignant ovarian tumors**, making them the most clinically important group.

➢ **Important examples:**

- **Serous tumors** → the **most common epithelial ovarian tumor**
- **Mucinous tumors**

2- Germ Cell Tumors:

➢ Occur mainly in the **younger age group**.

➢ Most commonly seen in:

- **Children**
- **Young adults**

Important example:

Teratoma → the **most common germ cell tumor**

3- Sex Cord-Stromal Tumors:

Can occur at **any age**.

Ovarian Neoplastic Diseases

- 5th most common cancer in women.
- 5th leading cause of cancer death in women.
- 3 Origins of primary ovarian tumors:
  1. **epithelium**
  2. **germ cells**
  3. **sex cord/stromal cells.**

 - Each of these cell types gives rise to a variety of tumors

- Secondary tumors of the ovary are metastatic malignancies that spread to the ovaries.

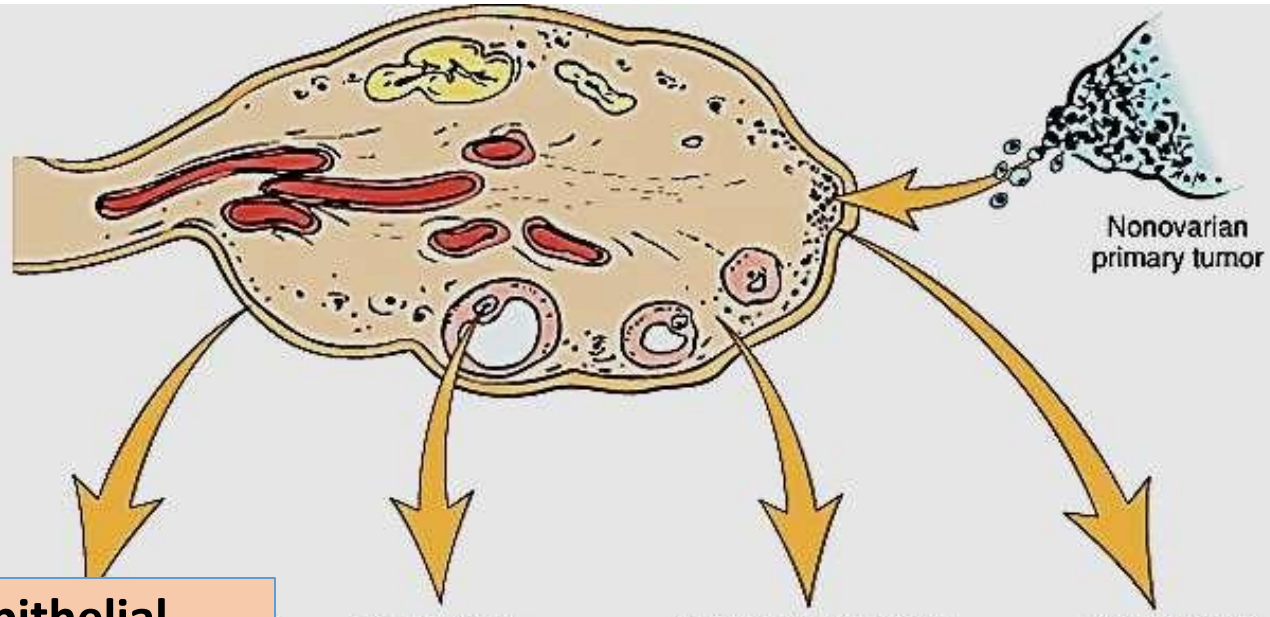
Epithelial Ovarian Neoplasms

- Account for the majority of ovarian tumors
- in their malignant forms, account for 90% of ovarian cancers
- Previously were thought to arise from coelomic epithelium that covers the ovarian surface
- Recent studies have shown that they actually arise from the fimbriated end of fallopian tube or epithelial cysts in the cortex of ovary.

Germ cell and sex cord–stromal cell tumors

- less frequent
- constitute 20% to 30% of ovarian tumors
- collectively responsible for less than 10% of malignant tumors of the ovary (so many of them are benign)

Ovarian Neoplasms



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Ovarian neoplasms - Pathogenesis:

- Risk factors:
- **nulliparity** (A woman who has **never had a viable delivery**)
- **family history** (Only 10%)

- Note: OCPs may **reduce** risk.

Ovarian Epithelial Neoplasms-Pathogenesis:

- Sporadic cases
- ***BRCA*** 1 and 2 mutations: 10% of sporadic cases
- ***p53*** (serous)
- **HER2/NEU** over-expression (35%)
- **K-RAS** protein over-expression (30%) (mucinous)

- Familial cases
- **BRCA1** and **2**

EPITHELIAL TUMORS - types:

- **1- Serous**
- **2- Mucinous**
- **3- Endometrioid**
- **4- Clear cell**
- **5- Brenner**

- **All types include benign, borderline, and malignant tumors**

EPITHELIAL TUMORS

Forms of Epithelial Ovarian Tumors:

- Each histological type can occur in **three different forms:**
  - ✓ **Benign**
  - ✓ **Borderline**
  - ✓ **Malignant**

- **Borderline Tumors**

Borderline tumors represent an **intermediate category** between benign and malignant tumors.

They are considered a **separate distinct group** because they do not fit completely into either category.

- **Behavior of Borderline Tumors**
  - ✓ Less aggressive than malignant tumors
  - ✓ More proliferative and atypical than benign tumors
  - ✓ Show intermediate biological behavior

Borderline tumors are seen **ONLY in Epithelial Tumors**

1- Serous Tumors

- The term **“serous”** refers to the type of secretion produced by the tumor cells.
- This secretion is:
- ✓**Thin**
- ✓**Watery**
- ✓**Colorless**

- Because these tumor cells produce fluid, they commonly cause **fluid accumulation within the ovary**, leading to the formation of **cystic structures**.
- Therefore, **serous ovarian tumors are usually cystic in nature**.

1- Serous Tumors

- the most frequent ovarian tumors.
- Include: 60% benign, 15% borderline, and 25% malignant.
- the most common malignant ovarian tumors (60%)
- Genetics:
- *BRAF* and *K-RAS* mutations→ borderline & low grade serous carcinomas
- *p53* and *BRCA1* mutations → High-grade serous carcinomas

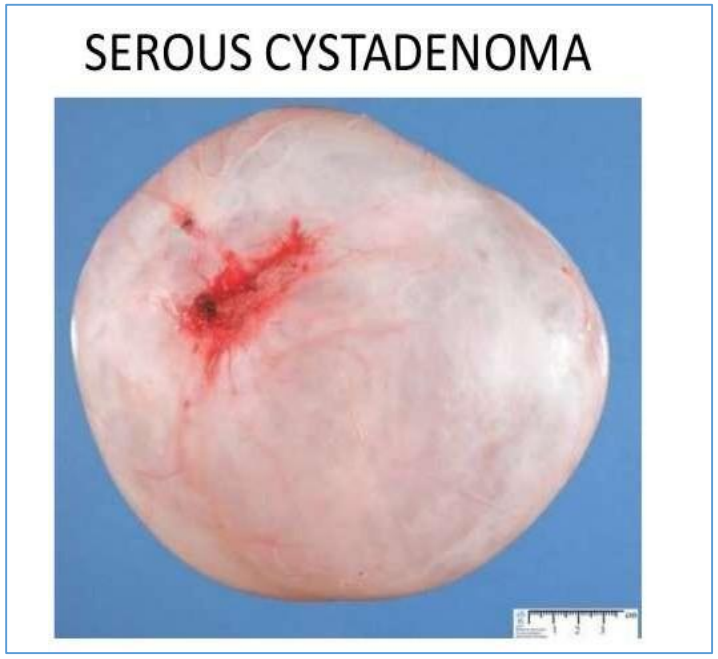
Benign serous tumors: Morphology

Serous Cystadenoma

- Serous cystadenoma is a **benign serous ovarian tumor**.
- The name explains the nature of the tumor:
- ✓ **Serous** → refers to the type of fluid produced, which is **thin, watery, and colorless**
- ✓ **Cyst** → indicates that the tumor forms a **fluid-filled cystic structure**
- ✓ **Adenoma** → means it is a **benign epithelial tumor**
- These tumors arise from **epithelial cells that produce serous fluid**, leading to the formation of cysts.
- Serous cystadenomas can become very large, sometimes reaching up to **30 cm in diameter**, producing a large pelvic mass.
- On gross examination or during surgery, the cyst contains:
- ✓ **Thin**
- ✓ **Clear**
- ✓ **Watery serous fluid**.

Benign serous tumors: Morphology

- **Benign serous tumors**:
- cystic ; large; (30 cm).
- May be bilateral. Both are primary
- filled with a clear serous fluid
- **single layer** of columnar epithelium. Some cells are ciliated.
- **Psammoma bodies** (laminated calcified concretions) are common in tips of papillae of **all** serous tumors



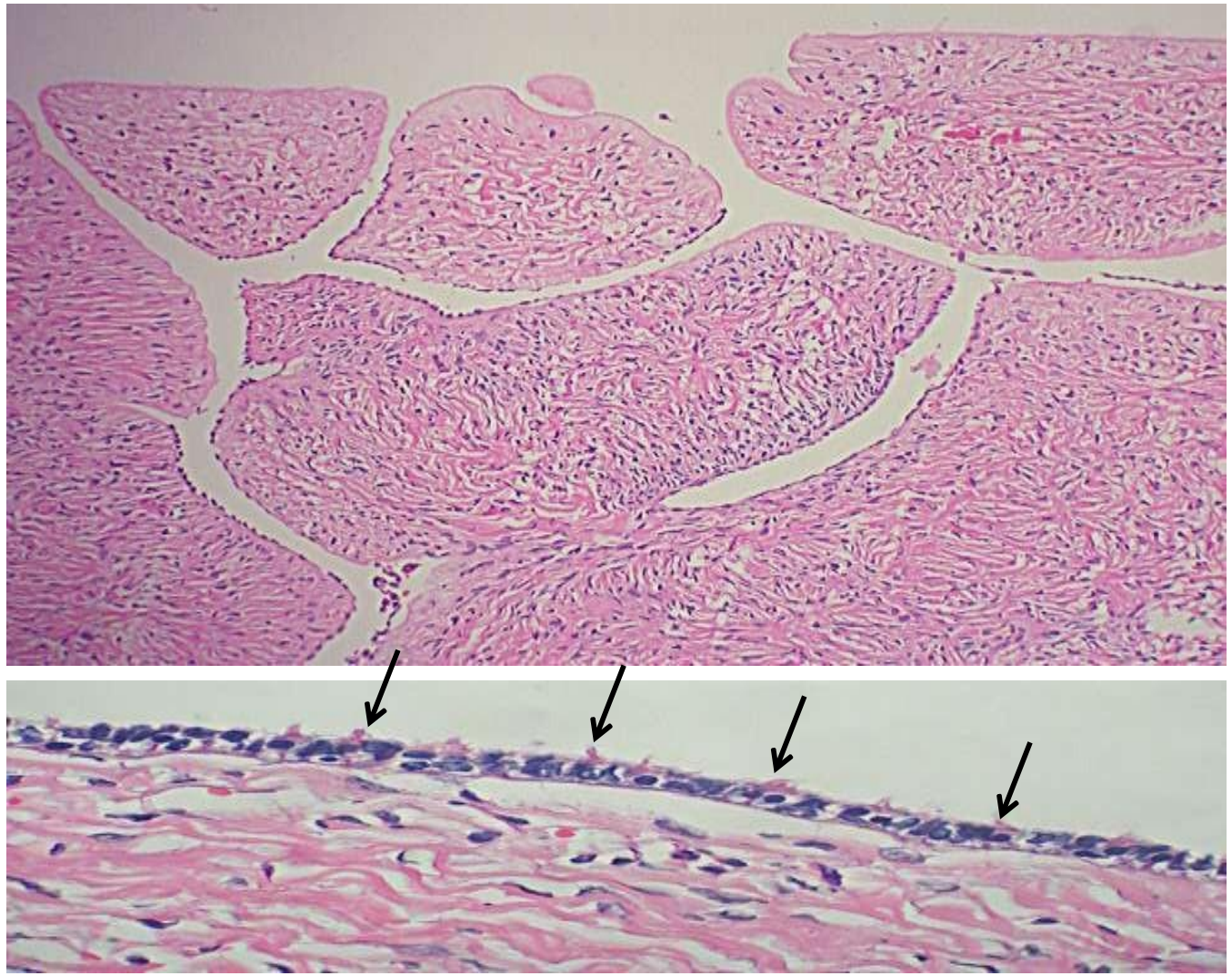
Behavior of the Tumor

- The tumor shows an **excellent prognosis** because it:
- ✓ Does **not invade** surrounding tissues
- ✓ Does **not produce metastases**
- ✓ Remains **localized** within the ovary
- ✓ Usually grows as a **cystic mass**
- Therefore, the clinical outcome is very favorable, with a **5-year survival rate of nearly 100%**.
- Overall, the tumor follows a **benign clinical course without malignant spread**.

Gross Appearance

- The cyst typically has: A **smooth and thin inner lining**
- This feature is important in helping identify the tumor type.

Benign serous tumors



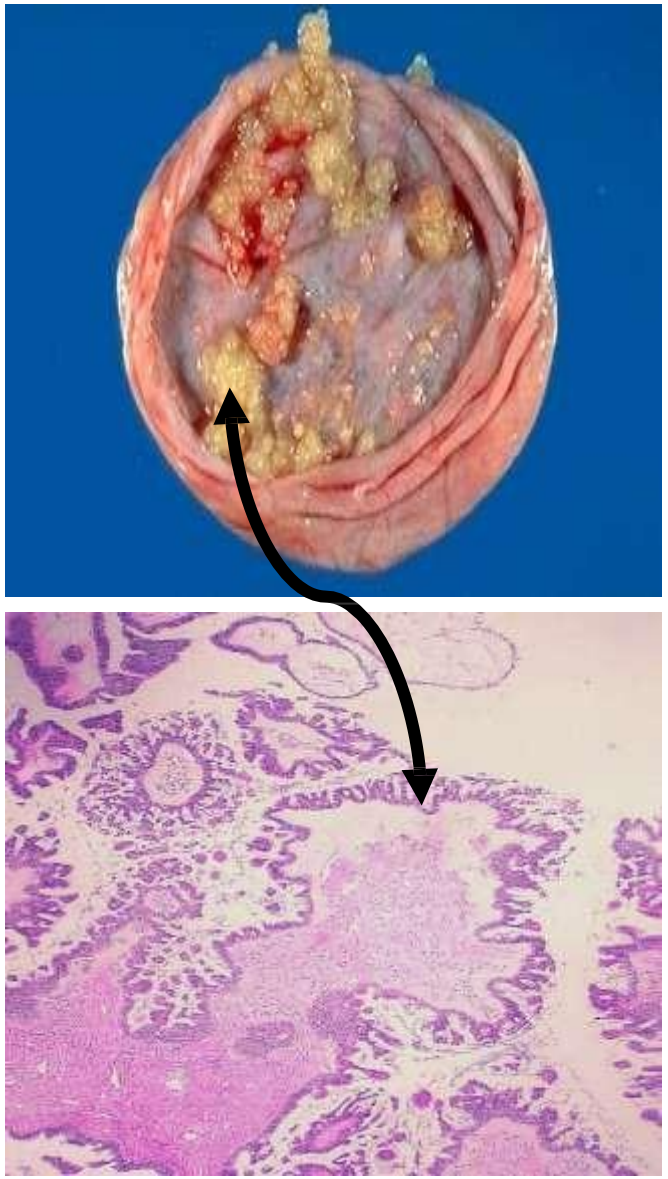
Microscopic Appearance of Serous Cystadenoma

- Microscopically, the inner wall of the cyst is lined by a thin layer of neoplastic epithelial cells that are mainly: **Columnar epithelial cells**, with some cells being **ciliated**
- Histologically, this lining closely resembles the **epithelium of the fallopian tube (tubal epithelium)** because serous tumors mainly arise from the **fimbriated epithelium of the fallopian tube**.

Borderline Serous Tumors

A mixture between benign and malignant tumors' characteristics

- **Complex architecture**
- Mild cytologic atypia
- **No** stromal invasion
- May have peritoneal implants
- can recur and some can progress to carcinoma
- Prognosis: intermediate between benign and malignant types
- (survival with peritoneal metastases 75%)



- Borderline serous tumors show a more **complex architecture** than benign serous tumors.
- Their gross and microscopic appearance may include: **Papillary growths, Nodules** and **Plaques**
- Microscopically, the tumor cells show: **Mild cytologic atypia**
- An important feature is that there is: **No stromal invasion**
- However, these tumors may spread to the peritoneum and form **peritoneal implants**, which behave similarly to metastases.
- Their prognosis is intermediate between benign and malignant tumors.

Malignant Serous Tumors-There are two types of ovarian serous carcinomas:

acording their pathogenetic mechanism of formation and their behavior

- **low-grade serous carcinoma:**

- arise from borderline lesions
- progress slowly to become invasive carcinoma
- Differentiated morphology
- mutations in KRAS

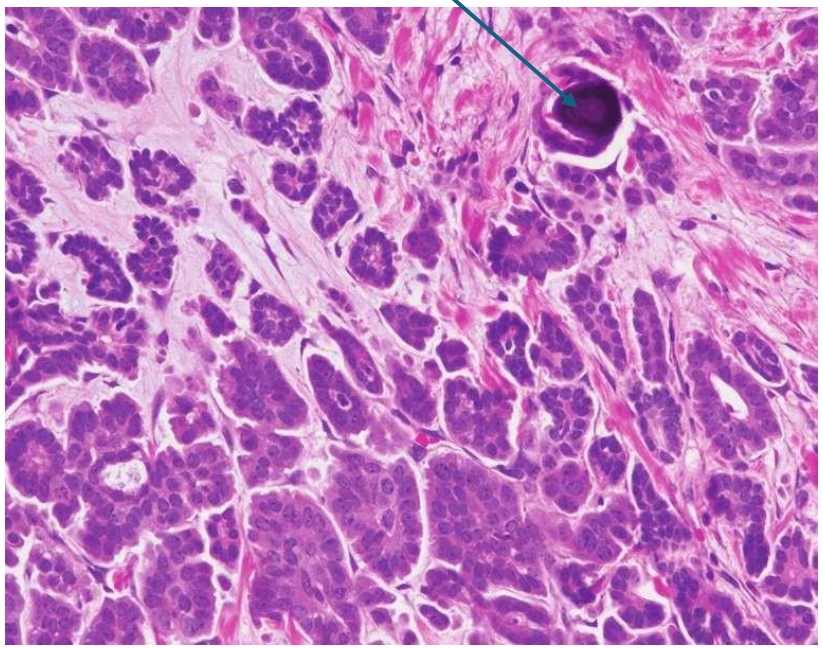
- **high-grade serous carcinoma:**

- develop rapidly and they are very aggressive tumors and may have many different sites of origin, some being outside the ovaries
- many arise form fallopian tube via serous tubal intraepithelial carcinoma, rather than ovarian coelomic epithelium.
- mutations in TP53

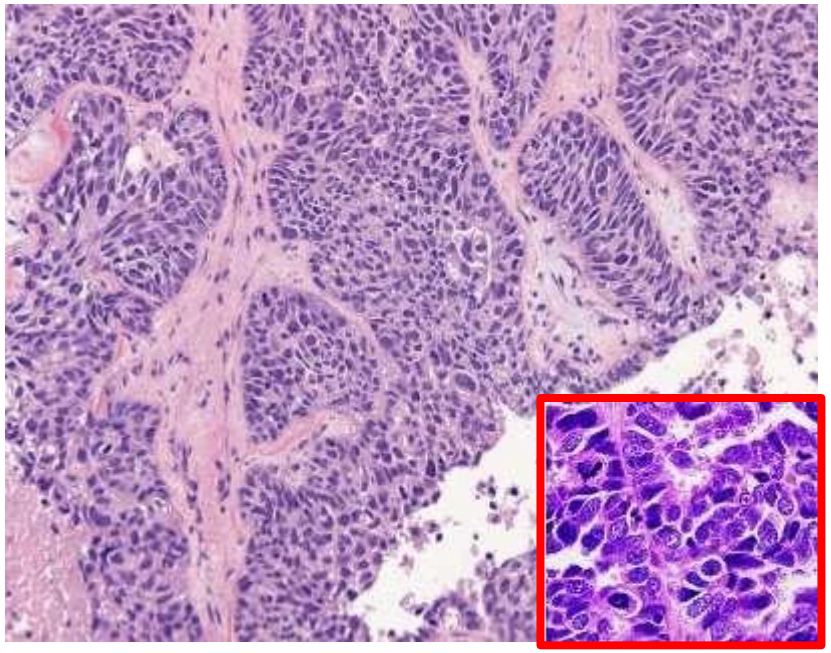
- Anaplasia of cells and invasion of the stroma.
- prognosis poor, depends on stage at the time of diagnosis.

Low grade serous carcinoma

Psammoma body



High grade serous carcinoma

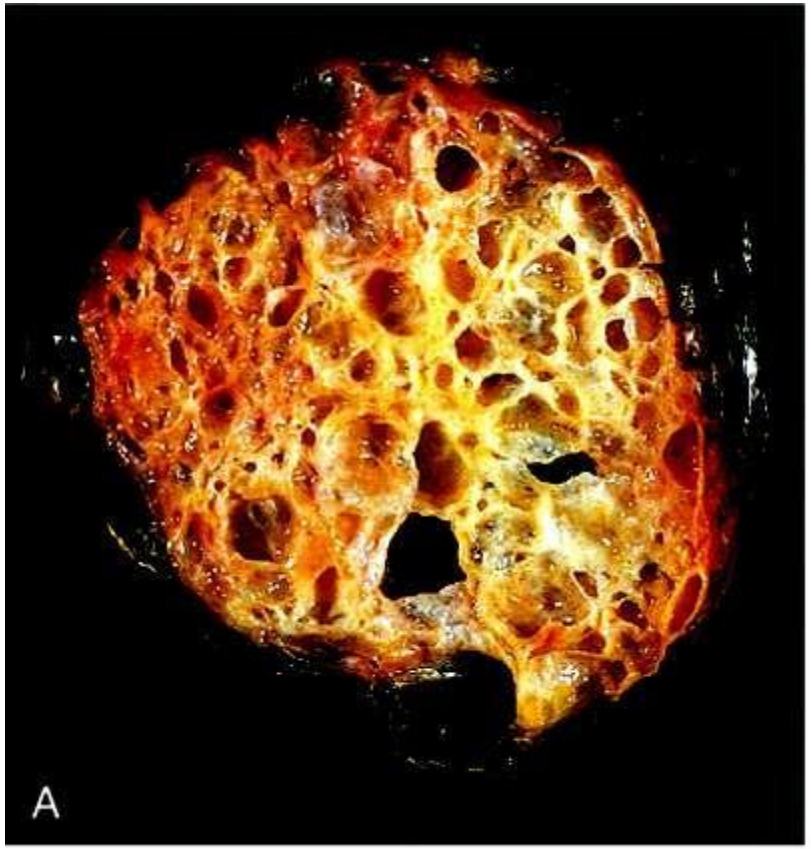


2- Mucinous ovarian tumors

- **mucin-secreting** epithelial cells.
  - These cells proliferate and continuously produce **mucin**, which gradually accumulates inside the ovary, leading to the formation of a cystic tumor over time.
  - The cyst can become very large, sometimes reaching up to **30 cm in diameter**, forming a large ovarian or pelvic mass.
  - Unlike serous tumors, the cyst contents are:
  - ✓ **Thick**
  - ✓ **Gelatinous**
  - ✓ **Mucoid (gel-like)**
- 80% benign; 10% borderline; **10% malignant** *(cystadenocarcinoma)*
  Depending on the proliferation and mutations in the epithelial tumor cells, the tumor behavior may be benign with limited growth, malignant with stromal invasion and aggressive behavior, or borderline with intermediate features between benign and malignant tumors.
- **Usually large** and **multilocular** (having multiple smaller cysts inside the original cyst) cystic tumors
- psammoma bodies **not** found
- stage is major determinant of prognosis

Mucinous ovarian tumors

Picture A represents the internal appearance of the tumor, which is multilocular. When the cyst is opened, thick, mucoid, gelatinous fluid comes out



Picture B represents the microscopic appearance of the epithelial tumor cells

Germ Cell Tumors

- Types according to differentiation:
- dysgerminoma (differentiation to oogonia)
- Embryonal carcinoma (differentiation to primitive embryonal tissue)
- yolk sac tumor(differentiation to endodermal sinus)
- choriocarcinoma (differentiation to placental tissue)
- Teratoma (differentiation to multiple tissue types).

- Teratomas are tumors that originates from germ cells, which are **totipotential or pluripotential** (can differentiate into different types of somatic tissues)

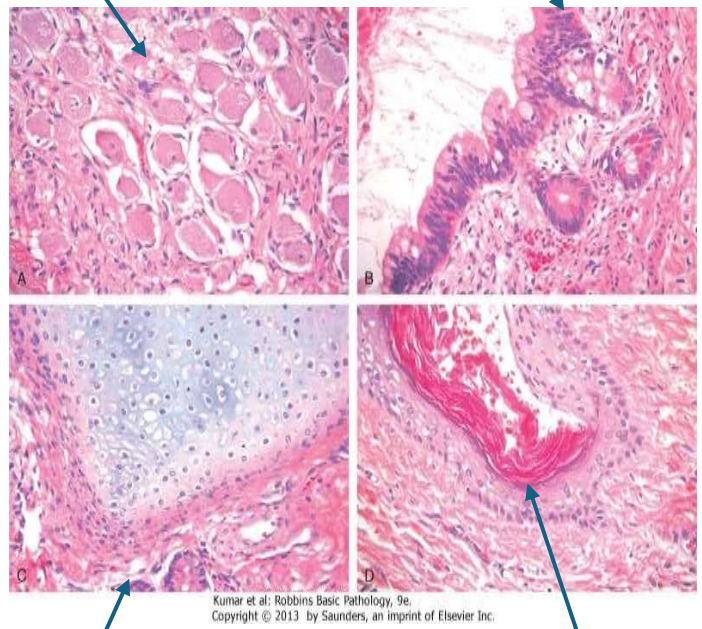
Benign (Mature) Cystic Teratoma

- totipotential germ cells form mature tissues of all three germ cell layers (endoderm ,mesoderm ectoderm)
- 15% -20% of ovarian tumors
- Many discovered incidentally, meaning that multiple cases are usually asymptomatic.
- 90% unilateral
- cyst filled with sebaceous secretion and hair; bone and cartilage; epithelium, or teeth.
- This is because teratoma originates from totipotent germ cells that can differentiate into any of these somatic tissues
- > 90% are benign mature cystic teratomas
- immature (malignant variant) is rare.
- torsion (10% to 15% of cases)
- Its benign behavior causes it to present usually with symptoms related to local mass effect or mechanical complications rather than constitutional or aggressive malignant symptoms, in some patients may present with dull pelvic or abdominal pain, while acute abdominal pain may result from ovarian torsion, which twisting along the vascular axsis, leading to ischemia, necrosis, and ovarian infarction. But mostly its benign

Benign (Mature) Cystic Teratoma

This the classic picture of teratoma which is cyst and when examine the inside aspects of the cyst we can find different types of tissues such as hair and may be tooth

Under the microscope, various types of of mature somatic tissues may be seen, either as a single tissue type or as a combination of different tissues.



Clinical Correlations for All Ovarian Tumors

- Clinical presentation of all is similar:

- Abd. pain, gastrointestinal complaints, urinary frequency; rarely torsion producing severe abdominal pain mimicking an "acute abdomen."

- Ascites (in Fibromas and malignant serous tumors).

- Functioning ovarian tumors : Estrogens or androgens

- Treatment: surgery + chemotherapy +

- Outcome of ovarian **cancers** remains unsatisfactory

- **Malignant** tumors are usually discovered in advanced stages
- survival minimally improved since 1970s.
- No early Screening methods are yet available

See next slide for further explaination

Clinical Presentation of Ovarian Tumors

- The clinical presentation of ovarian tumors is generally similar among different tumor types.
- Common symptoms include:
  - ✓ Abdominal or pelvic pain
  - ✓ Gastrointestinal complaints
  - ✓ Urinary frequency due to pressure effects
  - ✓ Increased abdominal girth from the enlarging mass
  - ✓ Rarely, ovarian torsion may occur, causing severe abdominal pain that mimics an **acute abdomen**.
  - ✓ Ascites may be seen especially in: Fibromas (sex cord–stromal tumors) and Malignant serous tumors

Functioning Ovarian Tumors

- ✓ Some ovarian tumors are functional and produce hormones, mainly: Estrogens and androgens
- ✓ Patients may present because of the hormonal effects caused by these tumors.

Treatment and Prognosis

- Benign ovarian tumors usually have an excellent prognosis and are treated by surgical excision.
- Malignant ovarian tumors are treated with: Surgery, Chemotherapy and Radiotherapy
- The prognosis of ovarian cancer remains relatively poor because:
  - ✓ Most malignant tumors are detected at advanced stages
  - ✓ Survival has improved only slightly since the 1970s
  - ✓ No highly effective early screening method is currently available

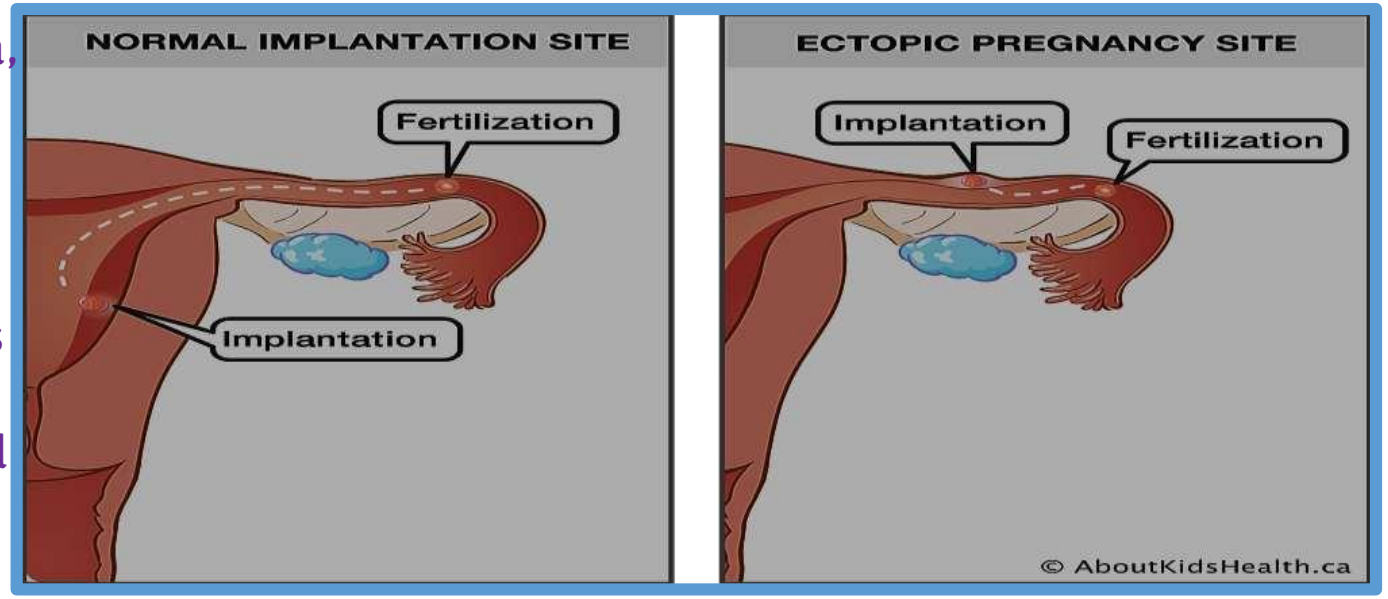
Pathology of the Fallopian tubes

ECTOPIC PREGNANCY

- implantation of the fertilized ovum outside uterus
- Incidence: 1%
- 90% of cases occur in fallopian tubes
- other sites: ovaries, abdominal cavity
- Mechanical Predisposing factors: tubal obstruction (50%); PID; tumors; endometriosis; **IUCD**…
- In 50% : no anatomic cause can be demonstrated.

Normal versus ectopic pregnancy

In normal implantation, the fertilized ovum travels toward the uterine cavity and implants in the endometrium, which is the site that receives the fertilized ovum and provides nutrition for the growing fetus



In ectopic pregnancy, after fertilization, the journey of the fertilized ovum is interrupted within the fallopian tube, so implantation occurs there. The fallopian tube cannot support the growing gestational sac mechanically or provide an adequate blood supply for the fetus

Early: development of embryo and placental tissue
Later: placenta burrows there and it will burrow through tubal wall causing intratubal hematoma (hematosalpinx and intraperitoneal hemorrhage.
Rupture: intense abdominal pain (acute abdomen), often
followed by Prompt surgical intervention is necessary

See Next slide

Progression and Rupture of Tubal Ectopic Pregnancy

➢ **Early Stage**

Initially, the embryo and placental tissue begin developing inside the fallopian tube.

➢ **Later Stage**

As the placenta grows, it invades and erodes nearby tubal wall and blood vessels, leading to:

✓ **Intratubal hemorrhage (hematosalpinx)** → bleeding into the fallopian tube

✓ **Intraperitoneal hemorrhage** → bleeding into the peritoneal cavity

✓ **Intratubal Hematoma that is susceptible for rupture**

➢ Rupture of the **Intratubal Hematoma** causes:

✓ Severe internal hemorrhage

✓ Intense abdominal pain resembling an **acute abdomen**

✓ Possible **hypovolemic shock** if not treated promptly

This is a medical emergency and requires urgent surgical intervention.

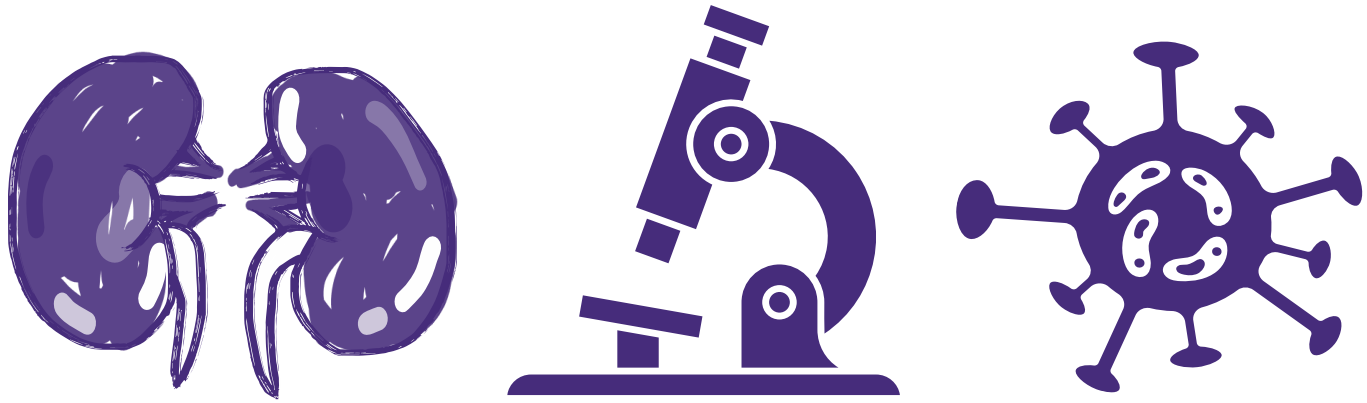
Ectopic pregnancy- Management

This picture is ectopic gestational sac in the fallopian tube

This is after removing the gestational sac

Tubal malignancies

- **most common histologic type is serous carcinoma.**
- may be the **origin** for many ovarian high-grade serous carcinomas
- **serous tubal intraepithelial carcinoma (STIC**) **(carcinoma in situ)** in fimbriated ends of fallopian tubes.
- STICs have mutations in TP53 in 90% of cases
- These carcinoma in situ lesions harbor **p53 mutations** and can develop into invasive tumors in the fallopian tube. They can also **spread malignant cells to the ovary, leading to high-grade serous ovarian tumors.**
- increased in women with ***BRCA (BRCA1 and BRCA2)*** **mutations**
- Because of critical location of the fallopian tubes (in proximity with the abdominal cavity), tubal tumors usually have easy **access to peritoneal cavity** , fallopian tube carcinomas frequently spread to omentum and peritoneal cavity at time of presentation (advanced).
- Therefore, cancer arising in the fimbriated ends of the fallopian tubes can spread and metastasize early on, causing these tumors to be usually discovered at advanced stages.



PATHOLOGY QUIZ LECTURE 3

External Resources

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References as cited:

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