Pathology of the Ovary and Fallopian Tube

Non-neoplastic

**Follicular cysts** – result from unruptured Graafian follicles or ruptured follicle that immediately seals. Common; usually no symptoms

**Corpus luteum cysts** – result from delayed resolution of a corpus luteum’s central cavity. Hemorrhage into a corpus luteum may result in hemorrhagic corpus luteum cyst

**Polycystic Ovarian Disease (PCOD)**
Common disorder affecting women of reproductive age. Prevalence between 5% and 15%. Pathophysiologically, results from complex, and not yet fully understood, interactions between the ovaries, androgens, gonadotropins, and insulin. Characterized by increased LH relative to FSH, which induces excess androgen production from theca cells. Androgen is converted to estrone in adipose tissue.


*Increased ovarian androgen biosynthesis results from abnormalities at all levels of the hypothalamic–pituitary–ovarian axis. The increased frequency of luteinizing hormone (LH) pulses in the polycystic ovary syndrome appears to result from an increased frequency of hypothalamic gonadotropin-releasing hormone (GnRH) pulses. The latter can result from an intrinsic abnormality in the hypothalamic GnRH pulse generator, favoring the production of luteinizing hormone over follicle-stimulating hormone (FSH) in patients with the polycystic ovary syndrome (in whom the administration of progesterone can restrain the rapid pulse frequency). The relative increase in pituitary secretion of LH leads to an increase in androgen production by ovarian theca cells. Increased efficiency in the conversion of androgenic precursors in theca cells leads to enhanced production of androstenedione, which is then converted by 17β-hydroxysteroid dehydrogenase (17β) to form testosterone or aromatized by the aromatase enzyme to form estrone.*

Within the granulosa cell, estrone is then converted into estradiol.

Numerous autocrine, paracrine, and endocrine factors modulate the effects of both luteinizing hormone and insulin on the androgen production of theca cells; insulin acts synergistically with LH to enhance androgen production. Insulin also inhibits hepatic synthesis of sex hormone-binding globulin, the key circulating protein that binds to testosterone and thus increases the proportion of testosterone that circulates in the unbound, biologically available, or “free,” state. Testosterone inhibits and estrogen stimulates hepatic synthesis of sex hormone-binding globulin.

Often in PCOD, follicles fail to grow to a size that triggers ovulation and multiple small cysts develop and accumulate in the ovary.

The effects of PCOS range from mild to severe and include infertility, hirsutism, acne, alopecia, and insulin resistance. The disorder also seems to increase the long-term risk for various diseases, including type 2-diabetes mellitus and dyslipidemia

High levels of estrone increase risk for endometrial hyperplasia and endometrial endometrioid carcinoma.
Neoplastic

**Surface epithelial tumors:** Most common neoplasms of the ovary

The most common: serous tumors, mucinous
Less common endometrioid, Brenner tumor, clear cell

**Serous Tumors:** consists of 30% of all ovarian tumors: 60% benign, 10% borderline, 30% malignant

*Benign serous tumors - Serous cystadenoma*
Thin smooth glistening cyst wall with watery fluid, cyst lining composed of single layer of epithelium resembling that of fallopian tube mucosa or surface epithelium of the ovary - Absent or minimal cellular stratification or atypia - No invasion of stroma

*Malignant - Serous carcinoma: Serous papillary cystadenocarcinoma*
Papillary structures with destructive stromal invasion - May have presence of psamomma bodies (concretions)

**Mucinous Tumors:** 15% of all ovarian tumors

*Benign mucinous tumors - Mucinous cystadenoma*
Comprise 80% of all mucinous tumors - Multiple cystic mass filled by sticky, gelatinous fluid - Lining epithelium single row of uniform mucin-filled columnar cells with basal nuclei - Absent or minimal cellular stratification, no or minimal cellular atypia

*Mucinous carcinoma: Mucinous cystadenocarcinoma*
Destructive stromal invasion, cytologic atypia
Mechanisms of Human Disease II

Pathology of the Female Genital Tract – III

Wednesday, March 14, 2018

Kamran M. Mirza, MD PhD

**Surface Epithelial Tumors**

<table>
<thead>
<tr>
<th></th>
<th>Serous</th>
<th>Mucinous</th>
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</thead>
<tbody>
<tr>
<td>Benign Cystadenomas %</td>
<td>60%</td>
<td>82%</td>
</tr>
<tr>
<td>Age</td>
<td>30-40 years</td>
<td>30-40 years</td>
</tr>
<tr>
<td>Gross</td>
<td>Single cystic</td>
<td>Usually multicystic</td>
</tr>
<tr>
<td>Histology</td>
<td>Single layer II columnar cells</td>
<td>Mucin producing epithelial cells</td>
</tr>
<tr>
<td>Malignant Cystadenocarcinomas %</td>
<td>30%</td>
<td>10%</td>
</tr>
<tr>
<td>Age</td>
<td>45-60 years</td>
<td>45-60 years</td>
</tr>
<tr>
<td>Gross</td>
<td>Bulky tumors</td>
<td>Bulky tumors</td>
</tr>
<tr>
<td>Histology</td>
<td>Complex papillary formations, invasion of stroma</td>
<td>Complex architecture, cytologic atypia, stroma invasion</td>
</tr>
</tbody>
</table>

**General comments:** Risk factors for ovarian carcinoma: Nulliparity & family history of ovarian cancer, gonadal dysgenesis, genetic mutations in BRCA-1 and BRCA-2. **There are NO effective screening modalities.** Generally poor prognosis – stage at diagnosis is primary predictor of outcome.

CA-125 tumor marker for monitoring response to tx and for disease recurrence

**“Borderline” tumors**

Morphology and behavior “in between” benign and malignant

Limited invasive potential

Better prognosis than overtly malignant carcinomas

May seed the peritoneum

**Serous borderline tumors**

- Gross: Cystic mass with watery fluid
- Surface lining cells with nuclear stratification, epithelial tufting, mild to - moderate nuclear atypia,
- No destructive stromal invasion

![Image of ovarian tumors](https://example.com/image.png)

(Odby of Dr. Christopher Crum, Brigham and Women’s Hospital, Boston, Massachusetts.)
Mucinous borderline tumors
-Gross: Cystic mass (usually multiloculated) with solid and/or papillary areas
-Lining cells in cystic wall: Epithelial stratification (< 4 cells in height), tufting and mild to moderate atypia
-No destructive stromal invasion

Germ Cell Tumors
General features
Often occur in children and young adults
Most common ovarian cancer in children and adolescent female

Histogenesis of Tumors of Germ Cell Origin

Mature cystic teratoma (Dermoid Cyst)
Most common germ cell tumor in women
80% occur in women of reproductive age
Gross- cystic mass containing hair, teeth, skin, fat and yellow-brown sebaceous material
Microscopic - adult type tissue derived from all three germ cell layers (endoderm, mesoderm, ectoderm)
In 1%, may have malignant transformation of tissue – usually to squamous cell carcinoma, thyroid carcinoma

Immature teratoma
Uncommon tumor, composed of mature and immature (primitive cells) embryonal type tissues (resembles fetal tissue)
Most commonly diagnosed in prepubertal girls, adolescents and young woman, mean age 18
Rapidly growing tumor with frequent capsular rupture
Grossly: Bulky solid mass with smooth capsular surface, and foci of necrosis and hemorrhage
Histology: Mixed mature and immature tissue.
Immature tissue: predominantly neuroepithelial elements
Dysgerminoma
Ovarian counterpart of the testicular seminoma

*Most common malignant germ cell tumor of ovary*

Occurs in childhood, second and third decades of life
- Gonadal dysgenesis is a predisposing factor
- Grossly: solid, unilateral tumors with soft and fleshy cut surface
- Microscopically: a monotonous proliferation of primitive germ cells forming sheets or cords separated by connective tissue septa containing varying amount of lymphocytes and macrophages
- Radiosensitive, as is seminoma

**Endodermal Sinus Tumor (yolk sac tumor)**
- Second most common malignant tumor of germ cell origin
- Most common in children/young females
- Clinically patients present with abdominal pain, pelvic mass and elevated serum AFP
- Grossly - unilateral, solid and cystic, large necrotic tumor
- Microscopically - Characterized reticular or microcystic pattern and glomerulus-like structures, Schiller-Duval body: a structure seen in endodermal sinus tumor consisting of a central vessel surrounded by tumor cells
- High grade tumor but chemotherapy has improved prognosis

Choriocarcinoma
- Neoplasm attempts to recapitulate placental tissue; trophoblasts and syncytiotrophoblasts minus chorionic villi
- hCG tumor marker
- Most are mixed component of other germ cell tumors

Embryonal carcinoma
- Very rare ovarian tumor
- Most have mixed components with other germ cell tumors
- Occur in 4-28 year old women
- Most patients present with adnexal mass
- Gross: solid and cystic unilateral adnexal mass, with soft yellow tan cut surface
- Micro: Tumor cells are large and pleomorphic, they form nests, gland or slit like structures

<table>
<thead>
<tr>
<th>Behavior</th>
<th>Dysgerminoma</th>
<th>Endodermal Sinus Tumor (Yolk Sac Tumor)</th>
<th>Choriocarcinoma</th>
<th>Embryonal Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gross</td>
<td>Malignant</td>
<td>Malignant</td>
<td>Malignant</td>
<td>Malignant, aggressive</td>
</tr>
<tr>
<td></td>
<td>Radio sensitive</td>
<td></td>
<td>Early metastatic, often fatal</td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td>Solid mass</td>
<td>Friable mass</td>
<td>Small, hemorrhagic</td>
<td>Unilateral mass</td>
</tr>
<tr>
<td></td>
<td>Large cells, clear cytoplasm, stroma with lymphocytes</td>
<td>Schiller-Duval bodies (glomerulus-like structure)</td>
<td>Like placental tissue with trophoblasts and syncytiotrophoblast (NO villi)</td>
<td>Large primitive cells</td>
</tr>
<tr>
<td>Tumor marker</td>
<td>LDH</td>
<td>AFP</td>
<td>hCG</td>
<td></td>
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<tr>
<td>other</td>
<td>Male counterpart = testis seminoma, associated with gonadal dysgenesis</td>
<td>Pure choriocarcinoma rare, usually component of other germ cell tumor</td>
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</table>
Sex cord-Stromal Tumors (derived from ovarian stroma)

Granulosa cell tumor (may have theca component – Granulosa-theca cell tumor)
Occurs in all ages but peak in postmenopausal female (adult type)
Most common ovarian tumor with estrogen production, 5% of tumors are associated with endometrial cancer due to estrogen production
Grossly: large, hemorrhagic mass, solid and cystic, may be ruptured
Microscopically: Tumor cells: uniform, coffee-bean shaped nuclei with grooves, small distinctive gland like structures filled with eosinophilic material (call-Exner bodies)
Behavior: Cannot predict clinical behavior from histologic evaluation of the tumor, all have potential for aggressive behavior, may recur after many years

Leydig cell tumor
Rare tumor of the pre- and perimenopausal women (<0.5% of ovarian tumors)
Tend to be virilizing
Grossly: unilateral, solid, lobulated mass with grey to golden yellow cut surface
Microscopically: diversity of patterns, may be tubular, cystic, solid, containing pure sertoli cells or mixture of both
May locally recur - rarely metastasize

Thecoma-Fibromas
Occur in all ages but most patients are postmenopausal
Clinical behavior – benign
Rarely, they are associated with Meig’s Syndrome: right sided pleural effusion, ascites, ovarian mass
Grossly - solid, spherical or slightly lobulated and encapsulated, with firm cut surface
Rarely hormonally active; if so produce estrogen
Micro: Composed of fibroblasts (fibroma) and plumped spindle cells with lipid droplets (thecoma), can be mixed

<table>
<thead>
<tr>
<th></th>
<th>Granulosa cell tumor</th>
<th>Sertoli-Leydig cell tumor</th>
<th>Thecoma-Fibroma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Histology</strong></td>
<td>Neoplastic granulosa cells; “Call-exner bodies”</td>
<td>“testicular” Sertoli cells (tubules)</td>
<td>-Fibroblasts (fibroma)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-Leydig cells</td>
<td>-Lipid-laden theca cells (thecoma)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-Reinke crystals</td>
<td>Mixed proportions</td>
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<tr>
<td><strong>Endocrine</strong></td>
<td><strong>Estrogen Production</strong></td>
<td><strong>Androgen Production</strong></td>
<td>May produce estrogen</td>
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<tr>
<td><strong>Clinical</strong></td>
<td>Prepuberty – precocious puberty</td>
<td>Block female sexual development in children</td>
<td><strong>Meigs Syndrome</strong></td>
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<td>Reproductive Age-bleeding</td>
<td>Hirsutism Virilization</td>
<td>-right sided pleural effusions</td>
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<td></td>
<td>Postmenopause-endometrial hyperplasia</td>
<td></td>
<td>-ascites</td>
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<td></td>
<td></td>
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<td>-ovarian mass</td>
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</tbody>
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Tumors metastatic to ovary
Krukenberg tumor – metastatic mucinous tumor to both ovaries
Most commonly gastric carcinoma origin
*Pseudomyxoma peritonii*
Extensive intraperitoneal mucous
Ddx: appendiceal primary vs ovarian mucinous primary

Pathology of fallopian tube:

Acute salpingitis:
Ascending sexually transmitted; most common organisms: Gonococcus and Chlamydia

Paratubal cysts
Very common

Carcinomas of fallopian tube
- Account for <1% of all gynecological cancers
- Women with fallopian tube cancer have increased risk for cancers of ovary, breast and endometrium
- Most BRCA-related tumors: arising in fimbria, some tumors involving ipsilateral ovary
- Most common type: serous carcinoma
- Pathology: Grossly distended fallopian tube, sausage like appearance; micro: Tumor located inside the lumen of fallopian tube, involving tubal mucosa with carcinoma in situ component