12. Pathology of the female genit tract II.

UTERUS CORPUS

ENDOMETRITIS

The endometrium is relatively resistant to infections.

Acute endometritis
- Occurs after parturition or miscarriage.
- Retained products of conception are the usual predisposing influence.
- Removal of the retained gestational fragments by curettage is followed by prompt remission.

Chronic endometritis
- Association with chronic gonorrheal pelvic disease
- Tuberculosis, granulomatous inflammation – from drainage of tuberculous salpingitis
- Intrauterine contraceptive devices (IUDs)
- Spontaneously without apparent cause (15% of the cases)

Histology: irregular proliferation of endometrial glands and mononuclear cell infiltrate with plasma cells

Clinically:
- Manifests with fever, abdominal pain, and menstrual abnormalities.
- There is an increased risk of infertility and ectopic pregnancy as a consequence of damage and scarring of the fallopian tubes.

ADENOMYOSIS

- Growth of the basal layer of the endometrium down into the myometrium
- There are nests of endometrial stroma (CD10+) or glands or both between the muscle bundles
- Cyclic bleeding into the glandular nests is very rare as the stratum basalis of the endometrium is nonfunctional

Clinically:
- Marked involvement may produce menorrhagia and pelvic pain before the onset of the menstruation

ENDOMETRIOSIS

- Endometriosis is far more important clinical condition than adenomyosis as it often causes infertility, pelvic pain and other problems.

Pathogenesis:
- Frequently multifocal.
- Foci of functioning endometrial tissue in the ovaries, pelvis, less frequently at other sites of abdomen, rarely lymph nodes, lung

Theories of origin (not mutually exclusive):
- Regurgitation theory: menstrual backflow through the Fallopian tubes and subsequent implantation.
- Vascular or lymphatic dissemination theory: explaining extrapelvic and intranodal implants.
- Endometriotic tissue is not just misplaced but is also abnormal, exhibits increased levels of inflammatory mediators—increased estrogen production → enhance the survival and persistence of the endometriotic tissue within a foreign location

Macro:
- Almost always contains functioning endometrium, which undergoes cyclic bleeding.
- As a result of the accumulating blood the foci are red-blue to yellow-brown.
- In the ovaries the lesions may form large blood filled cysts: chocolate cysts. Seepage of blood may lead to widespread pelvic fibrosis.

Micro:
- Endometrial glands, stroma and hemosiderin in disordered localisation i.e. ovaries.

Clinical features:
- Manifestations depend on the distribution of the lesions.
- Pelvic scarring often causes pain and sterility
- Intrapelvic bleeding results in severe dysmenorrhea
12. Pathology of the female genital tract II.

ENDOMETRIAL HYPERPLASIA
Defined as an increased proliferation of endometrial glands relative to the stroma.

_Causative factors:_
- Excess of estrogen relative to progesterin, sufficiently marked or prolonged
  - Failure of ovulation, e.g. around the menopause
  - Prolonged administration of estrogens
  - Estrogen producing ovarian lesions

_Types:_
- Simple hyperplasia
- Complex hyperplasia with architectural gland crowding without atypia
- Complex hyperplasia with cellular atypia
- EIN: endometrial intraepithelial neoplasia

This is a continuum based on the level and duration of the estrogen excess

_Clinically:_
- Abnormal uterine bleeding
- In time carcinoma may develop, the risk is proportional to the degree of cytological atypia noted
- Controll, follow up, in case necessary curettage, biopsy to determine progression!

_Risk for the development of adenocarcinoma:_
- Atypical hyperplasia: 20-50%
  Acquisition of _PTEN_ mutations is believed to be one of several key steps in the transformation of hyperplasias to endometrial carcinomas

TUMORS OF THE ENDOMETRIUM AND MYOMETRIUM

ENDOMETRIAL POLYPS

_Macro:_ sessile or pedunculated lesions

_Clinical features:_
Most common at the time of menopause, cause abnormal uterine bleeding, and very rarely give rise to cancer

ENDOMETRIAL CARCINOMA

_Epidemiology and Pathogenesis:_
On the basis of clinical and molecular data, two major types are recognized:
- Endometrioid carcinoma
- Serous carcinoma

_Endometrioid carcinoma_

_Frequently arises on a background of endometrial hyperplasia._
Breast carcinoma occurs in women with endometrial cancer (and vice versa) more frequently.
Mutations in mismatch repair genes and the tumor suppressor gene PTEN.

_Risk factors:_
- Obesity: increased synthesis of estrogen in fat depots from adrenal and ovarian precursors
- Diabetes
- Hypertension
- Infertility: nulliparous women, often have nonovulatory cycles
- Prolonged estrogen replacement therapy
- Estrogen secreting ovarian tumors

_Macro:_
- Infiltrative
- Exophytic

_Micro:_
Resemble the endometrial glands
12. Pathology of the female genital tract II.

**Serous carcinoma**
- Arises in older women
- Usually is associated with endometrial atrophy
- Mutations in the TP53 gene.
- They behave aggressively

*Grossly:* Tumors are usually large and bulky and deeply invasive.

*Microscopically:* papillary or glandular growth pattern with marked cellular atypia

**Clinical features for both:**
- Local spread: tumor extends through the uterine wall and infiltrates the periuterine structures
- Metastases to pelvic lymph nodes and to distant organs, lung, liver

Patients typically present with uterine bleeding. Stage is the major determinant of survival in both types. Serous tumors tend to manifest more frequently with extraterine extension and therefore have a worse prognosis than endometrioid carcinomas.

**TUMORS OF MYOMETRIUM**

**LEIOMYOMA**
- Benign tumor of smooth muscle cells
- They are the most common benign tumor in females
- Found in nearly half of women during reproductive life
- Estrogens stimulate their growth, they shrink postmenopausally

*Macro:* Sharply circumscribed, firm, gray-white masses with a whorled cut surface. Frequently multiple. After menopause they may become densely collagenous or even calcified.

*Micro:* Whorling bundles of smooth muscle cells, degenerative changes are often present

**Clinical features:**
- May be entirely asymptomatic
- They may manifest with menorrhagia or as a pelvic mass or may be detected as a cause of infertility
- No malignant transformation

**LEIOMYOSARCOMA**
- Malignant tumour of smooth muscle cells.
- Often occur in postmenopausal women.

*Macro:* soft, hemorrhagic, necrotic masses

*Micro:* criteria of malignancy include necrosis, cytologic atypia, and mitotic activity.

**Clinical features:**
- Arise directly from the mesenchymal cells of myometrium, not from preexisting leiomyomas
- Almost always solitary tumors
- Recurrence after removal and metastases are common (lung)
- The more anaplastic the tumor, the poorer the outlook is

**OVARIIES**

**NON-TUMOROUS DISEASES OF OVARIIES**

**Follicle and luteal cyst**
- Common
- Originate in unruptured graafian follicles
- Usually multiple, subcortical, filled with serous fluid
- Lining: granulosa or luteal cells
- Rarely may rupture: intraperitoneal bleeding and acute abdomen
Polycystic ovaries: Stein-Leventhal syndrome

Pathogenesis, principal biochemical abnormalities:

- Excessive production of androgens which are converted to estrogens in peripheral fatty depots, → inhibit the secretion FSH
- High levels of luteinizing hormone (LH)
- Low levels of follicle stimulating hormone (FSH)

The basis of excess ovarian androgen secretion is mysterious.

Macro: ovaries are enlarged, many subcortical small cyst
Micro: cortical stromal fibrosis + many follicular cysts, absence of corpora lutea

Clinically:
- Generally in young females following menarchae with symptoms of oligomenorrhea, hirsutism, infertility, sometimes obesity.

TUMORS OF THE OVARY

Tumors may arise from 1) coelomic surface epithelium 2) totipotent germ cells 3) multipotential sex cord-stromal cells

SURFACE EPITHELIAL TUMORS

Types according to biological behavior

- Benign: cystadenoma
- Borderline tumor of low malignant potential
- Malignant: cystadenocarcinoma or carcinoma

Types according to histology: serous, mucinosus and endometrioid tumors

Malignant forms of surface epithelial origin account for almost 90% of all ovarian cancers

Important risk factors for ovarian cancer include

- Nulliparity
- Family history, and germline mutations: familial, mutations of BRCA1 and BRCA2 tumor suppressor genes, that are also associated with hereditary breast cancer.

SEROUS TUMORS

Serous cystadenoma:

- 25% are bilateral
- Inner surface is smooth
- Serosal covering is smooth and glistening
- Lined by single layer of tall columnar ciliated or secretory cells
- Papillary formations, psammoma bodies are common in the tips of papillae

Borderline tumor of low malignant potential

- No significant stromal invasion

Serous cystadenocarcinoma

- 66% of aggressive forms are bilateral
- The inner surfaces show irregular papillary projections, solid areas may also be seen
- Serosal covering with nodular irregularities indicates penetration of capsule
- Complex, multilayered papillary formations
- Cytological atypia of the lining cells
- Invasion of the stroma

Types: Low-grade serous carcinomas

High-grade serous carcinomas

Low-grade serous carcinomas that arise from benign or borderline lesions progress slowly are associated with KRAS, BRAF, or ERBB2 mutations.

High-grade serous carcinomas develop rapidly, and most of them have mutations in TP53.

Spread:

- Commonly contiguous spread within the pelvis and peritoneal dissemination, peritoneal carcinosis
- Spread to regional lymph nodes is frequent
Pathology of the female genital tract II.

- Distant metastases are infrequent: lung, liver
  Prognosis is poor and depends on the stage at the time of the diagnosis.

**MUCINOUS TUMORS**

**Differences compared to serous tumors:**
- Most are benign mucinous cystadenomas
- The epithelium consists of mucin-secreting cells
- Cyst content is mucinous
- 20% of malignant tumors are bilateral

*Pseudomyxoma peritonei* results from rupture of mucinous cystadenocarcinoma or that of carcinoma with low malignant potential. The peritoneal cavity is filled with mucinous material multiple tumor implants are found on all serosal surfaces.

**ENDOMETRIOID TUMORS**

- Linings of the cysts are similar to those of the endometrium
- Endometrioid tumors are *usually* malignant, although benign and borderline forms exist
- They are bilateral in 30% of the cases
- In 15-30% of these patients there is a concomitant endometrial carcinoma

Similar to endometrioid-type carcinoma of the endometrium, endometrioid carcinomas of the ovary have mutations in the *PTEN* tumor suppressor gene.

**GERM CELL TUMORS, TERATOMAS**

- **Most common:** benign mature teratoma
  - Dermoid cyst

- **Rarely, similarly to testicular germ cell tumors**
  - Dysgerminoma (counterpart of testicular seminoma)
  - Embryonal carcinoma
  - Choriocarcinoma
  - Yolk sac carcinoma

**DERMOID CYST**

- Ectodermal differentiation of the totipotent germ cells
- The cyst is lined by epidermis with large number of adnexal appendages,
- Most are in young women
- The cyst is often filled with sebaceous material and matted hair
- Nodular thickening in the wall from which teeth protrude, bone, cartilage, nests of bronchial or gastrointestinal epithelium may also occur
- Rarely there is malignant transformation, squamous cell carcinoma

**SEX CORD-STROMAL TUMORS**

Sex cord–stromal tumors may display differentiation toward granulosa, Sertoli, Leydig, or ovarian stromal cell type. Depending on differentiation, they may produce estrogens or androgens.

**Granulosa cell tumors**

- Two thirds occur in postmenopausal women
- Are potentially malignant

**Clinical features:**
- Have the potential of producing large amounts of estrogen!
- Consequence: precocious sexual development, endometrial hyperplasia and predispose to endometrial carcinoma.

**METASTATIC TUMORS**

- Metastases of abdominal and breast tumors to the ovary are common.

- *Krukenberg tumor:* metastatic bilateral ovarian cancer
  - **Primary tumor:** signet ring cell carcinoma of stomach
12. Pathology of the female genital tract II.

DISEASES OF PREGNANCY

PLACENTAL INFLAMMATIONS AND INFECTIONS

Two pathways:

1. Ascending infection through the birth canal
   - Most common
   - Caused by bacteria, Mycoplasma and Candida
   - Associated with premature birth and premature rupture of the membranes

   Chorioamnionitis: chorioamnion shows leukocytic infiltrate with edema and congestion, infection may involve the cord and placental villi

2. Hematogeneous spread, rare

   Histologically the villi are most often affected (villitis).
   - Underlying conditions:
     - syphilis
     - tuberculosis
     - listeriosis
     - toxoplasmosis
     - various viral infections (rubella, cytomegalovirus, HSV)

ECTOPIC PREGNANCY

Implantation of the fertilized ovum in any site other than the normal uterine location, occurrence: in 1% of pregnancies.

Types:
   - Tubal pregnancy (90% of the cases)
   - Ovary
   - Abdominal cavity
   - Intratuterine portion of the tube (interstitial pregnancy)

General:
   - In ectopic pregnancy the early development of the embryo is fairly normal, including the formation of placental tissue, amniotic sac and decidual changes.
   - Abdominal pregnancy can occasionally carried to term.

Tubal pregnancy

Predisposing factors: any factors retarding the passage of the ovum

   - Chronic salpingitis (half of the cases)
   - Intrauterine tumors
   - Endometriosis
   - In almost half of the tubal cases no anatomic cause can be demonstrated

DG:
   - Elevated level of hCG similar to that seen in normal pregnancy, however lack of elevation does not exclude the diagnosis.
   - Curettage: decidual change, Areas Stella reaction in endometrial glands, but no chorionic villi or other fetal parts.

Tubal pregnancy, morphology: The tube is locally distended up to 3-4 cm containing of freshly clotted blood in which placental tissue and fetal parts may be seen. The histological diagnosis depends on the visualization of placental villi.

Clinically:
   - The invading placenta causes intratubal hemorrhage (hematosalpinx) → may rupture → hemoperitoneum.
   - Rupture of an ectopic pregnancy may be catastrophic, needing prompt surgical intervention.

GESTATIONAL TROPHOBLASTIC DISEASE

Gestational trophoblastic disease is a spectrum of tumor-like conditions, and tumors characterized by proliferation of trophoblastic tissue.
HYDATIFORM MOLE
There are two types, they result from abnormal fertilization.

<table>
<thead>
<tr>
<th>Complete moles</th>
<th>Partial moles</th>
</tr>
</thead>
<tbody>
<tr>
<td>No fetal parts</td>
<td>Contains fetal parts</td>
</tr>
<tr>
<td>All chorionic villi are abnormal</td>
<td>Has some normal chorionic villi</td>
</tr>
<tr>
<td>Diploid (46,XX &gt;46,XY)</td>
<td>Always triploid</td>
</tr>
</tbody>
</table>

Macro: the uterine cavity is filled with thin walled translucent cystic grapelike structures, cystic chorionic villi.

Micro:
- **Complete mole**: hydropic swelling of chorionic villi and virtual absence of vascularization + cytotrophoblast and syncytial trophoblast proliferation.
- **Partial mole**: affects only some of the villi and the trophoblastic proliferation is focal.

Clinically:
They are much more common before age 20 and after age 40. The usual presentation is painless vaginal bleeding, 12-14 weeks after conception. The uterus may be too large for dates and no fetal parts or heart sounds are present, hCG levels are elevated

**Clinical course:***
- Complete mole becomes invasive: 10%,
- Give rise to carcinoma: 2-3%
- HCG monitoring in the blood and urine permits detection of incomplete removal or complications
- Chemotherapy is almost always curative

INVASIVE MOLE
- Hydropic villi deeply penetrate the uterine wall
- Hydropic villi may embolize to distant organs, such as lungs or brain, but these are not true metastases and may regress spontaneously

**Clinically:** invasive moles are associated with persistently elevated hCG. The tumor responds well to chemotherapy but can result in uterine rupture and life-threatening hemorrhage

CHORIOCARCINOMA
Malignant tumor arising from gestational chorionic epithelium

- 50% follow a complete hydatiform mole, about 25% arise after abortion
- Most of the remainder occur in a previously normal pregnancy

**Macro and micro:**
- Very hemorrhagic and necrotic masses within the uterus, vascular invasion is a characteristic feature
- **Chorionic villi are not present**, the tumor is purely epithelial, the chorioepithelium is atypical

**Clinical features:**
- Bloody, brownish discharge
- Rising titer of hCG, the titers are much higher than in the case of a mole
- At the time of initial discovery, there is usually widespread dissemination via the blood

**Prognosis:**
- Chemotherapy: nearly 100% of cases localized to uterus have been cured,
- Maternal immune response against the foreign (paternal) antigens helps.
- **Important:** By contrast there is poor response to chemotherapy in choriocarcinomas that arise in the gonads (ovary or testis) from totipotential cells.