



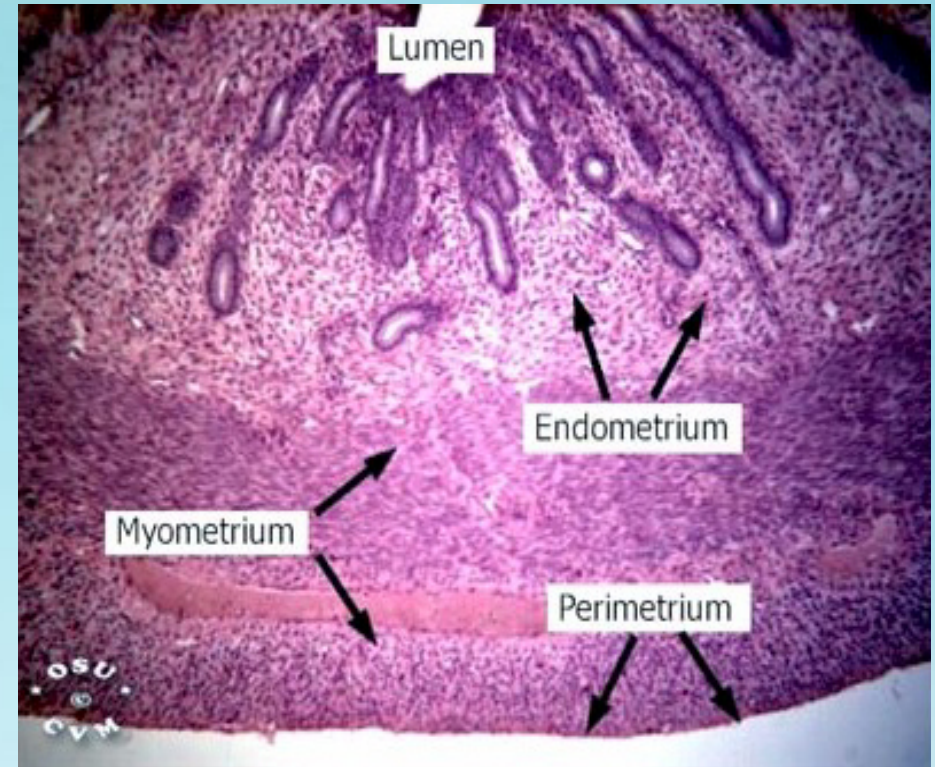
Female Genital Tract Pathology

LEC 2

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Uterus

- The body (corpus) of the uterus is composed of the **endometrium**, consisting of glands and stroma, and the **myometrium**, made up of smooth muscle.
- The more frequent and significant disorders of the uterus are:
- **Inflammation (endometritis)**
- **Adenomyosis/ Endometriosis**
- **Endometrial hyperplasia**
- **Tumors of the Endometrium and Myometrium**

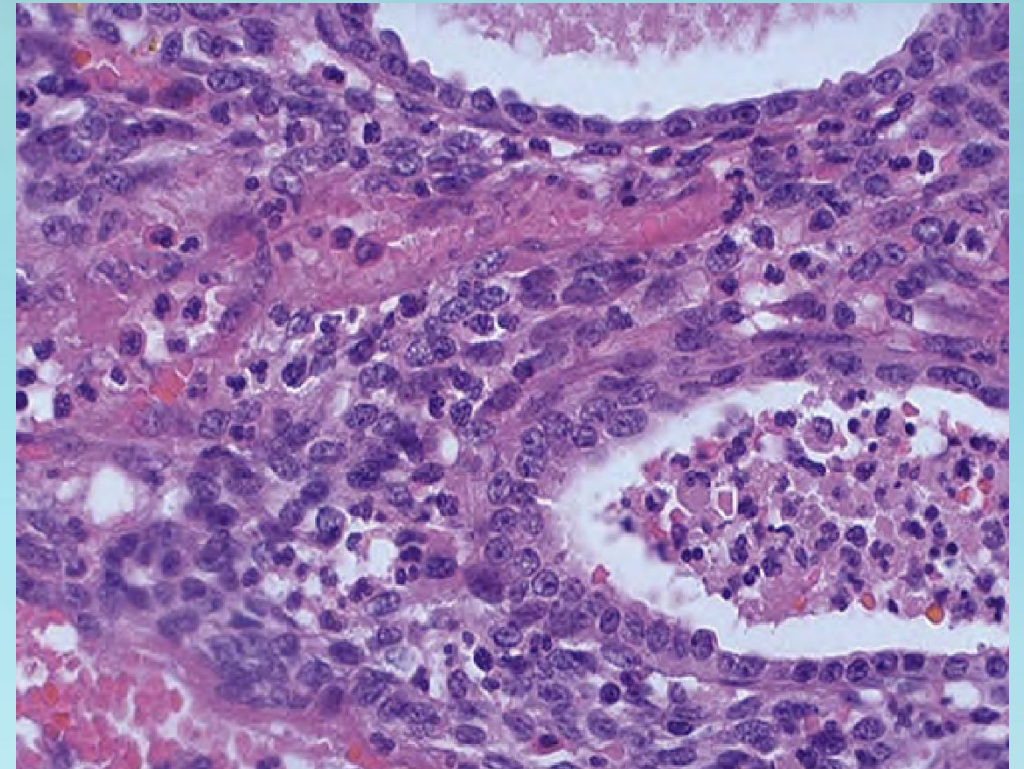


◆ Endometritis

- Inflammation of endometrium, classified as acute or chronic

□ Acute Endometritis:

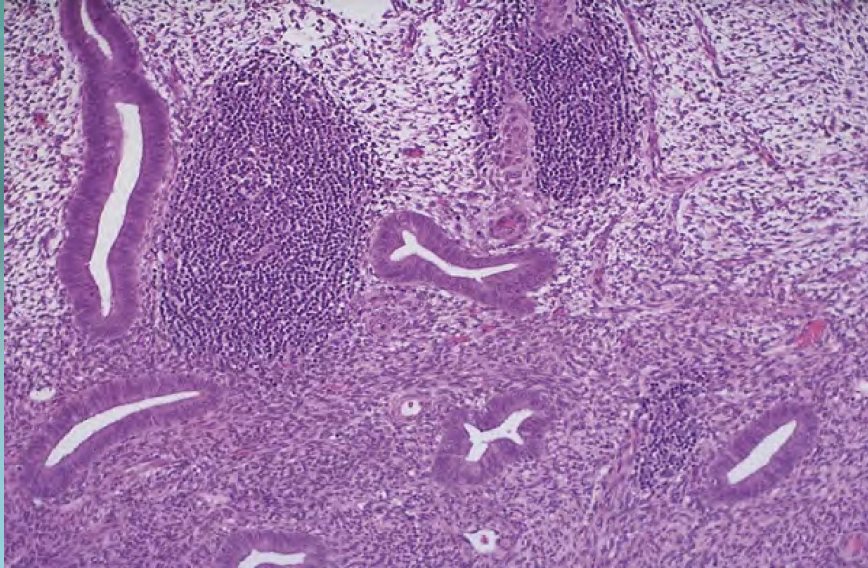
- Is uncommon, usually due to bacterial infections that arise **after delivery or abortion**.
- **Predisposing factors:** **Retained products of conception** because this retained tissues or foreign bodies act as a nidus for infection.
- **Histologic examination shows neutrophilic** infiltrate in the stroma and sometimes inside gland lumen.
- **Treatment:** Removal of the retained gestational products by **curettage** and **antibiotic** therapy to clear these infections.



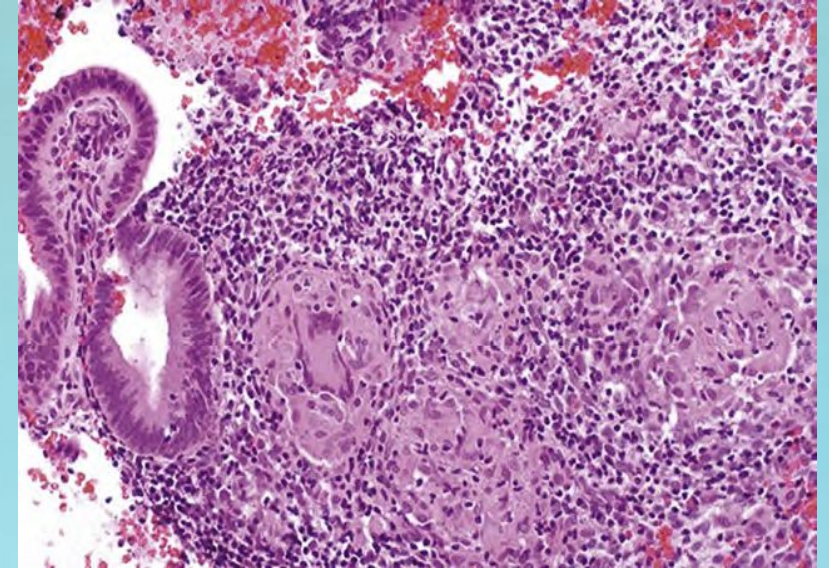
❑ **Chronic Endometritis:**

- Occurs in association with the following disorders:
 - ❑ Chronic pelvic inflammatory disease (**PID**).
 - ❑ Retained gestational tissue, postpartum or post abortion
 - ❑ Intrauterine contraceptive devices (**IUCD**)
 - ❑ Disseminated tuberculosis
- **Histologic examination shows plasma cells in the stroma** which are not seen in normal endometrium, also other chronic inflammatory cell are present like lymphocytes and macrophages in endometrial stroma.
- **Clinically, all forms of endometritis manifest with fever, abdominal pain, and menstrual abnormalities.** In addition, there is an **increased risk of infertility and ectopic pregnancy** due to extension of the damaging inflammation and scarring of the fallopian tubes.

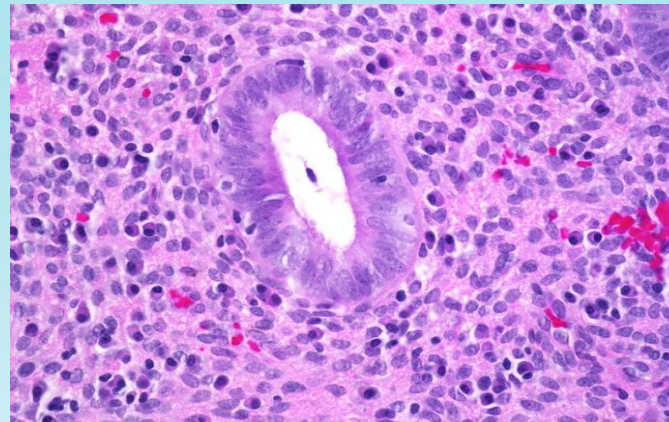
Microscopical features of Chronic Endometritis:



Collections of **lymphocytes** within the endometrial stroma are shown. Prominent **lymphoid follicles** may be seen, particularly **in chlamydial infection**.



TB endometritis: granuloma with giant cell



Numerous **plasma cells** within the endometrium.

◆ Adenomyosis:

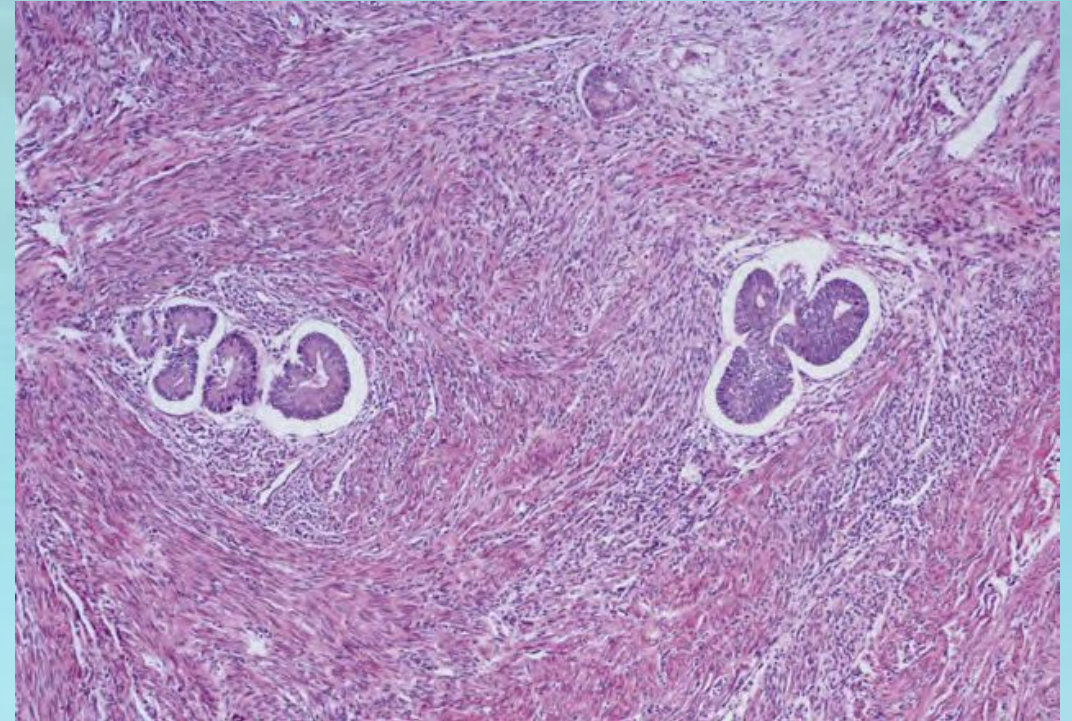
- Adenomyosis refers to the **presence of endometrial tissue in the myometrium.**
- **Pathogenesis:** invagination of the stratum basalis of endometrium down into the myometrium.
- **Mic.:** Nests of endometrial stroma, glands, or both, are found deep in the myometrium between the muscle bundles which induces reactive hypertrophy of the myometrium, resulting in an enlarged, globular uterus, often with a thickened uterine wall.
- **Clinical features:** usually **asymptomatic**, but Extensive adenomyosis may produce **menorrhagia, dysmenorrhea, and pelvic pain** before the onset of menstruation and can coexist with endometriosis.

Adenomyosis



Gross;

The thickened and spongy-appearing myometrial wall



Microscopically;

A cluster of endometrial tissue (glands and surrounding stroma), are found deep in the myometrium between the muscle bundles

❖ Endometriosis:

- Endometriosis is defined by the presence of endometrial glands and stroma in a location outside the uterus .
- **Age:** It occurs in as many as 10% of women in their reproductive years, and in nearly half of women with infertility.
- **Pathogenesis:** the exact etiology is unknown, but there are Four hypotheses have been suggested to explain the origin of these lesions:-
 1. The *regurgitation theory*, which is currently favored, proposes that **menstrual backflow** through the fallopian tubes leads to implantation.
 2. The *benign metastases theory*, holds that **endometrial tissue spread** from the uterus to distant sites via blood vessels and lymphatics and this explain extrapelvic endometriosis like in lung, bone and brain.
 3. The *metaplastic theory*, suggests endometrial differentiation of coelomic epithelium (mesothelium of pelvis and abdomen from which endometrium originates) as the source.
 4. The *extrauterine stem/progenitor cell theory*, proposes that circulating stem/progenitor cells from the bone marrow differentiate into endometrial tissue.

- **Site:**

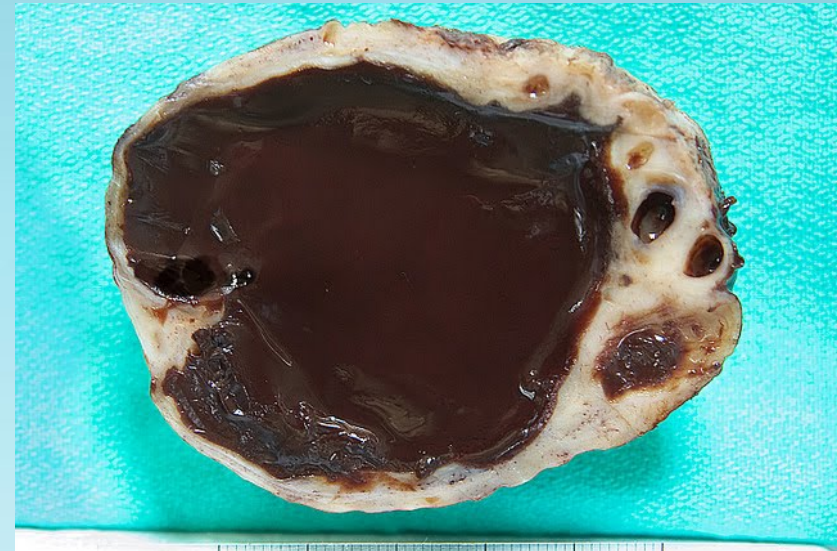
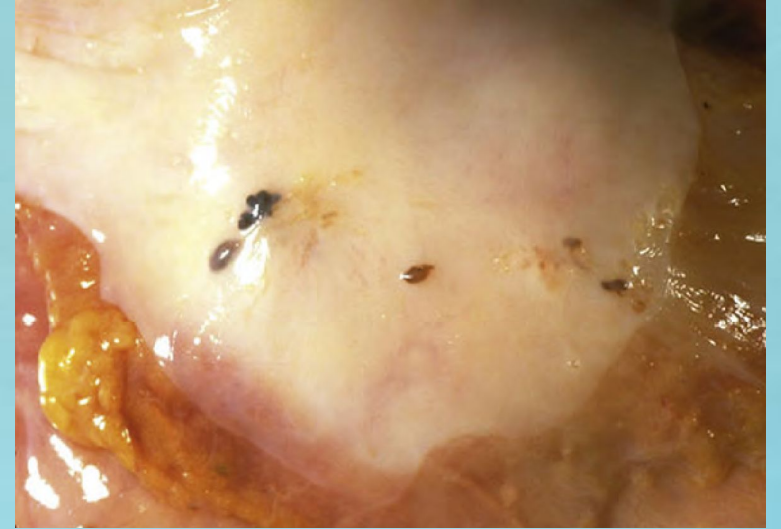
- It is **frequently** multifocal and often involves **pelvic structures** (ovaries, pouch of Douglas, uterine ligaments, tubes, and rectovaginal septum). **Less frequently**, distant areas of the peritoneal cavity or periumbilical tissues are involved.
- **Uncommonly**, distant sites such as lymph nodes, lungs, and even heart, skeletal muscle, or bone are affected.

- **Note:**

- **Studies suggest that endometriotic tissue is not just misplaced but is also abnormal.** As compared to normal endometrium, endometriotic tissue exhibits **increased levels of inflammatory mediators, particularly prostaglandin E2**. It is proposed that the inflammation results from the recruitment and activation of macrophages by factors made by endometrial stromal cells. Stromal cells also make **aromatase**, leading to local production of estrogen.
- These factors enhance the **survival and persistence** of the endometriotic tissue within a foreign location and help to explain the **beneficial effects of COX-2 inhibitors and aromatase inhibitors in the treatment of endometriosis**.

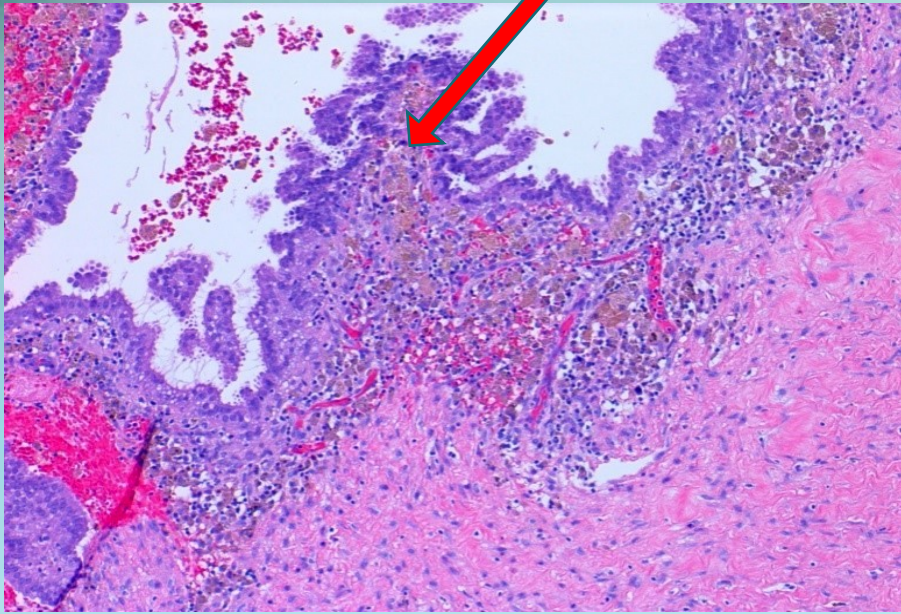
- **Gross:**

- **Endometriosis** typically consists of **functioning endometrium**, which undergoes cyclic bleeding.
- Because blood collects in these aberrant foci, they appear grossly as red-brown nodules or implants, vary in size from microscopic up to 2 cm in diameter just beneath the serosa of the posterior uterus **in the pouch of Douglas**. Often individual lesions coalesce to form larger masses.
- When the **ovaries** are involved, the lesions may form **large, blood-filled cysts that turn brown (Chocolate cysts)** as the blood ages.
- **Chocolate cyst** so named because the **old blood in the cystic space** formed by the hemorrhage is broken down to produce much **hemosiderin** and impart **a brown to black color** to the cyst contents.
- **Complications:** With leakage and organization of the blood, widespread fibrosis occurs, leading to **adhesions among pelvic structures, sealing of the tubal fimbriated ends, and distortion of the fallopian tubes and ovaries.**

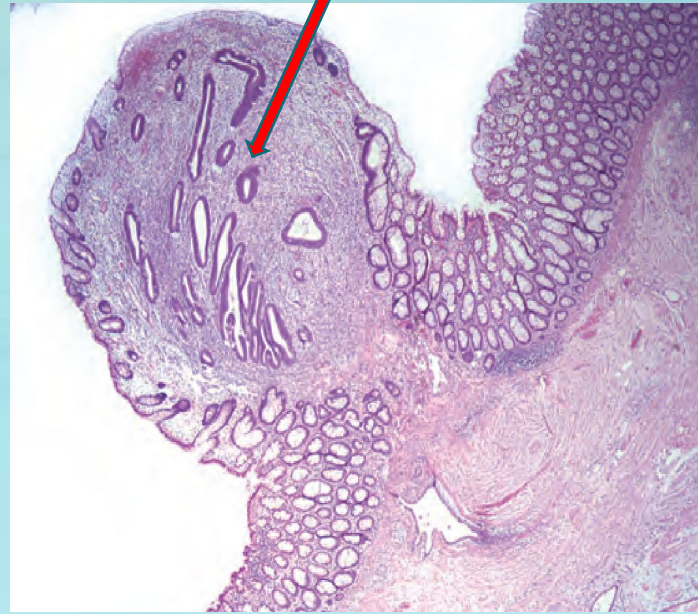


- **Microscopic features:**

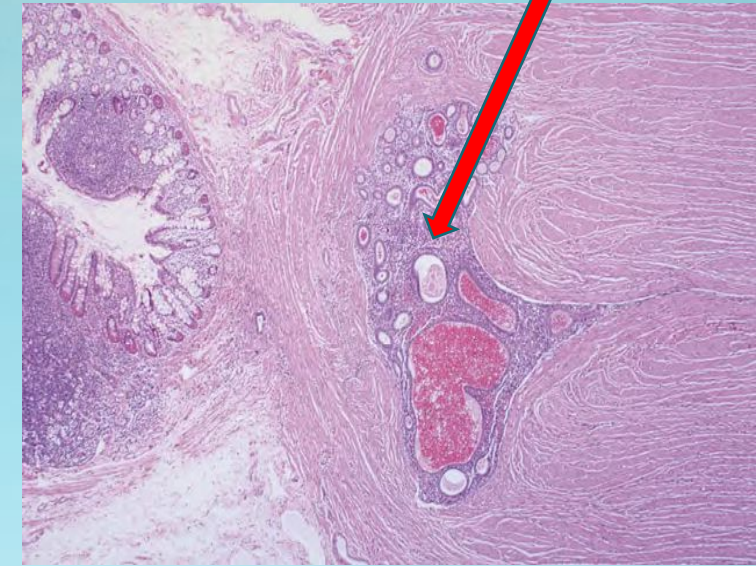
The diagnosis depends on finding both **endometrial glands and stroma** at sites external to the endometrium.



Ovarian endometriotic cyst demonstrates periglandular endometrial stroma with abundant hemosiderin laden macrophages and rich dilated capillary network.



Endometrial glands and stroma adjacent to normal **colonic mucosa**.



Endometrial glands and stroma with hemorrhage appears in the center, adjacent to **appendix** at the left.

- **Clinical signs and symptoms:**

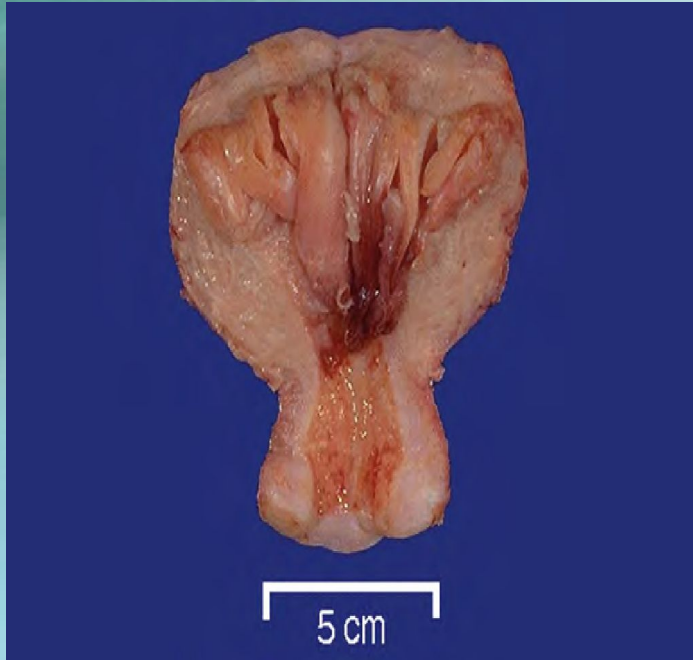
- The clinical manifestations of endometriosis **depend on the distribution** of the lesions.
- **Most of the cases:** **severe dysmenorrhea** (painful menstrual period), **dyspareunia** (painful intercourse) due to involvement of uterine serosa, and **pelvic pain** due to the intrapelvic bleeding and intraabdominal adhesions.
- **Menstrual irregularities** are common.
- **Infertility** is the presenting complaint in **30% to 40%** of women due to extensive scarring of the fallopian tubes and ovaries.
- **Pain on defecation** reflects rectal wall involvement, and **dysuria** reflect involvement of the bladder serosa.

◆ Endometrial Hyperplasia

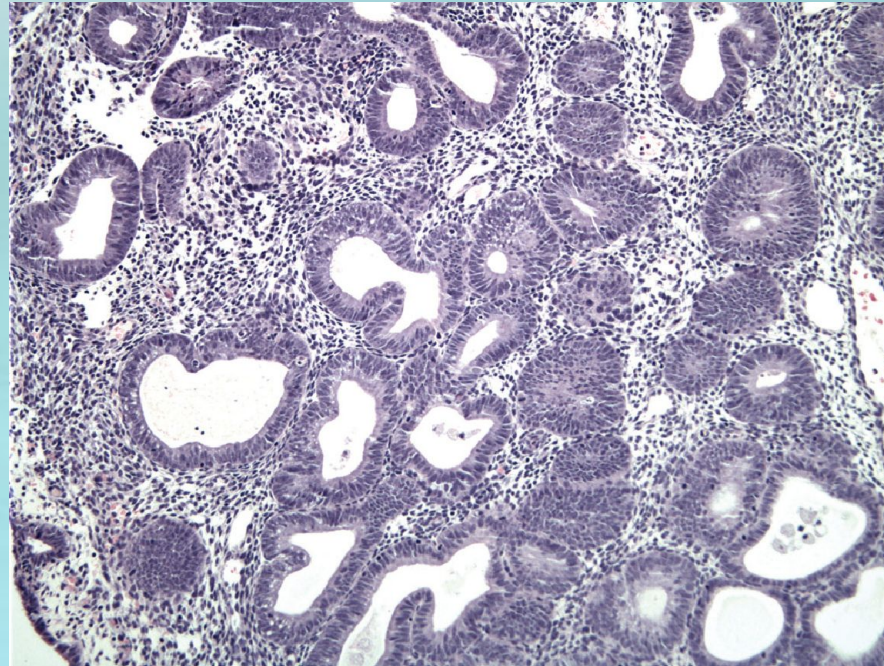
- Increased proliferation of endometrial glands relative to stroma resulting in increased gland: stroma ratio.
- It is important cause of abnormal uterine bleeding; and frequent precursor to endometrial carcinoma.
- Pathogenesis:
- Prolonged estrogenic stimulation of the endometrium, which can be due to anovulation (e.g. in polycystic ovarian syndrome, perimenopause), increased endogenous estrogen production (e.g. obesity where there is peripheral conversion of androgens to estrogens, functioning ovarian granulosa cell tumors or ovarian cortical stromal hyperplasia), or exogenous estrogen (e.g. estrogen replacement therapy).
- Inactivation of the *PTEN* tumor suppressor gene has been identified at a substantial frequency in hyperplasia with atypia (approximately 50%) and endometrioid carcinoma (>70%).

- **Endometrial hyperplasia is classified to two categories** based on the presence of cytologic atypia: hyperplasia without atypia and hyperplasia with atypia
- **The importance** of this classification is that the presence of cytologic atypia correlates with the development or concurrent finding of endometrial carcinoma.
- **Hyperplasia without cellular atypia** carries a **low risk** (between 1% and 3%) for progression to endometrial carcinoma.
- **Hyperplasia with atypia**, also called *endometrial intraepithelial neoplasia (EIN)*, is associated with a much **higher risk** (20%–50%).
- When hyperplasia with atypia is discovered, it must be carefully evaluated for the presence of cancer and usually warrants **a hysterectomy** in patients no longer desiring fertility.
- In younger patients, treatment with **high-dose progestin** may be used in an attempt to preserve the uterus.

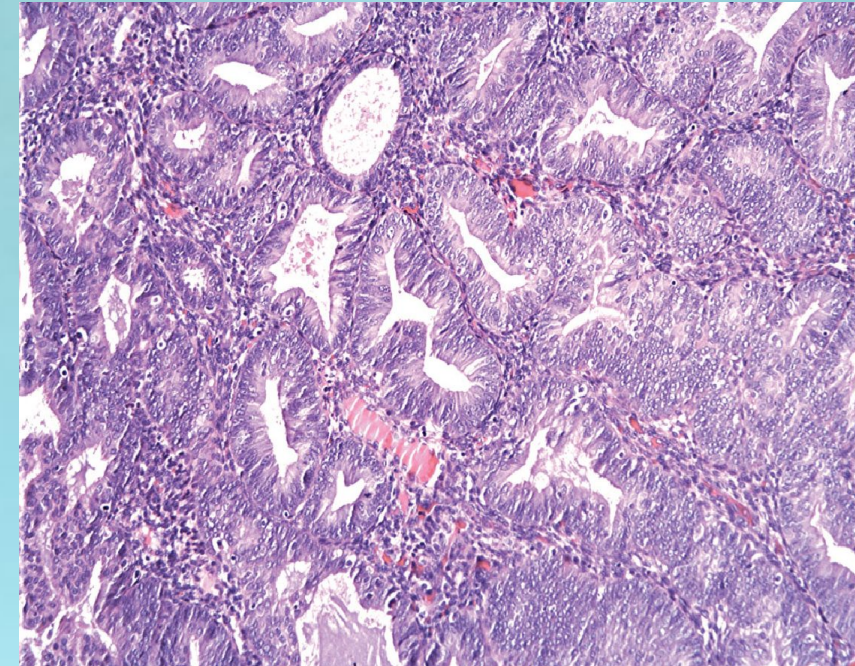
Endometrial hyperplasia



Gross: Endometrial cavity filled with fronds of hyperplastic endometrium



Mic.: Hyperplasia without atypia; Closely packed glands with variation in size and shape and may be cystically dilated. Some intervening stroma is usually retained.



Mic.: Hyperplasia with atypia; Glandular crowding and cellular atypia. The glands are back to back with complex outlines and branching structures, lined by columnar cells with rounded, vesicular nuclei with prominent nucleoli.

Tumors of the Endometrium and Myometrium

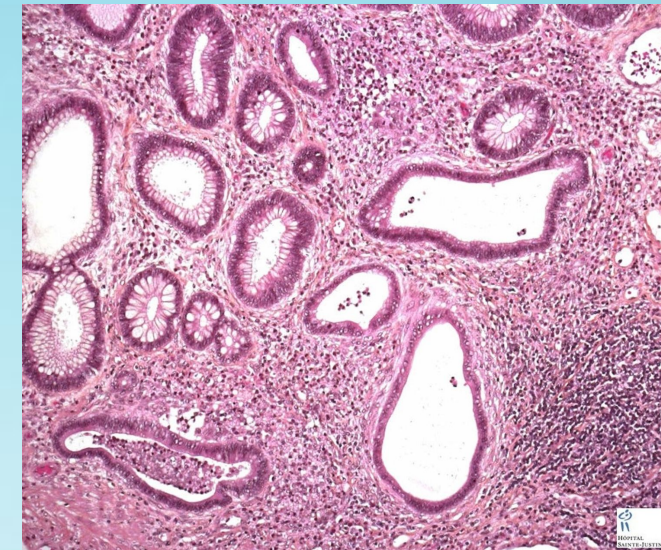
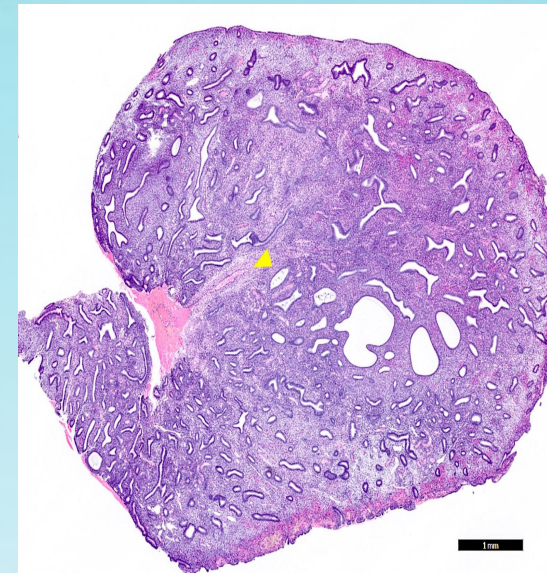
The most common neoplasms of the body of the uterus are:-

1. Endometrial polyps.
2. Endometrial carcinomas.
3. Smooth muscle tumors

All tend to produce **bleeding** from the uterus as the earliest manifestation.

❖ Endometrial Polyps

- Are **benign** exophytic masses of variable size that project into the endometrial cavity.
- **Gross:** They are usually **sessile, hemispheric lesions relatively small, measuring 0.5 to 3 cm in diameter. Larger polyps tend to be pedunculated** & may project from the endometrial mucosa into the uterine cavity & sometimes through the cervix into the vagina.
- **Microscopically:** They are composed of **cystically dilated glands with fibroblastic stroma** and **small muscular arteries** are often prominent.
- **The clinical significance:** abnormal uterine bleeding and more important, the risk (however rare), of giving rise to a cancer.



❖ Endometrial carcinoma

- Endometrial carcinoma is the most frequent cancer occurring in the female genital tract.
- It generally appears between the ages of 55 and 65 years and is uncommon before age 40.
- Endometrial carcinoma can be broadly divided into two histologically and pathogenically distinct
- Categories: endometrioid and serous carcinoma.

Characteristic	Endometrioid carcinoma	Serous carcinoma
	Most common (80%)	Less common (15%)
Age	55–65 years (perimenopausal Women)	65–75 years (older postmenopausal women)
Clinical setting	Risk factors for this type of carcinoma include (1) obesity, (2) diabetes, (3) hypertension, (4) infertility, and (5) exposure to unopposed estrogen (these increased estrogenic stimulation of the endometrium and are associated with endometrial hyperplasia).	Not associated with unopposed estrogen or endometrial hyperplasia.
Precursor	Endometrial hyperplasia	Serous endometrial intraepithelial carcinoma
Morphology	Malignant endometrial-like glands	Papillary pattern of growth with marked cytologic atypia
Mutated genes	Mutations in mismatch repair genes and the tumor suppressor gene <i>PTEN</i> .	Mutations in the <i>TP53</i> tumor suppressor gene,
Clinical Behavior	Low grade, Indolent Spreads via lymphatics Good prognosis	High grade, Aggressive Intraperitoneal and lymphatic spread Poor prognosis

□ Endometrioid carcinoma:

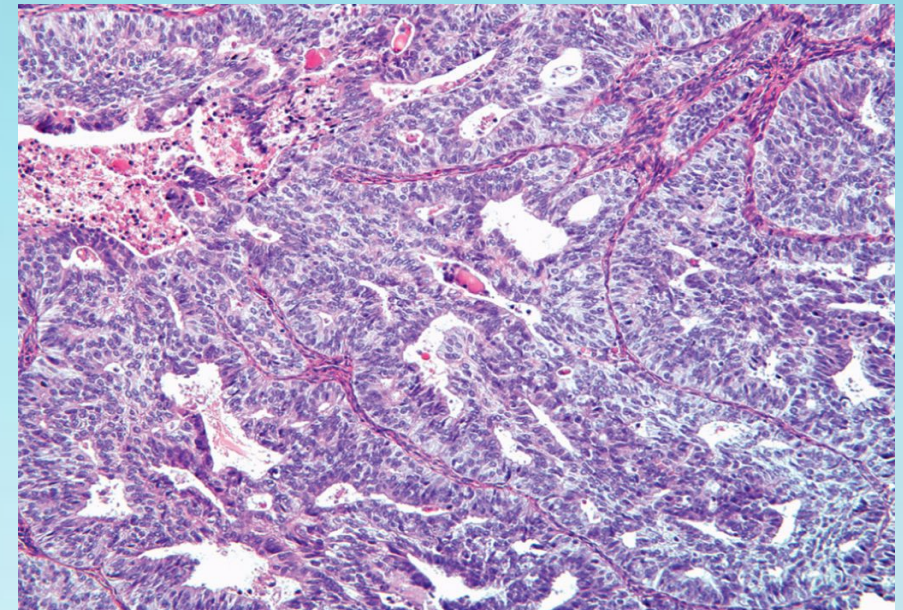
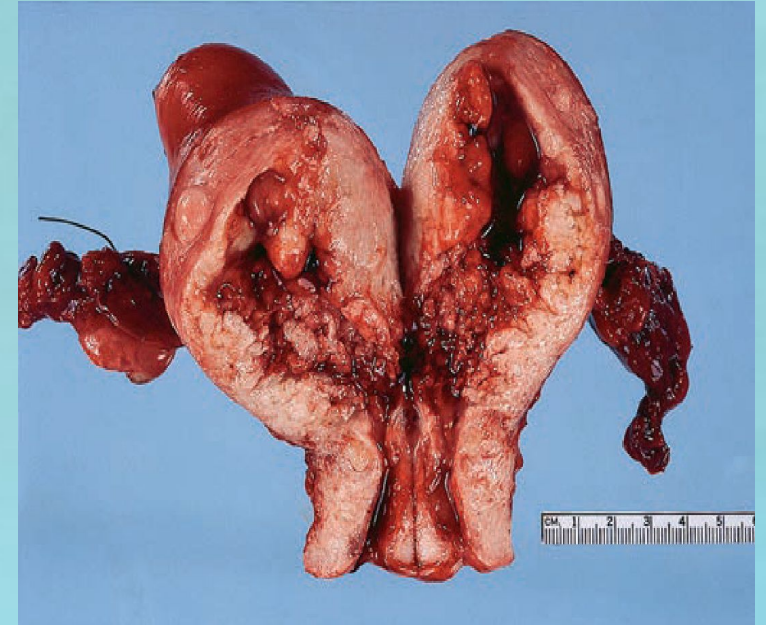
- This is **the most common type** of endometrial carcinoma, accounting for approximately **80% to 85%** of cases.
- **Age:** 55–65 years (perimenopausal women)
- Most are **well differentiated** and mimic proliferative endometrial glands, features that are the basis for their name.
- **Risk factors for endometrioid carcinoma:**
 - 1- Obesity:** associated with increased synthesis of estrogens in fatty tissue.
 - 2- Diabetes. 3- Hypertension.**
 - 4- Infertility:** women tend to be nulliparous; often with anovulatory cycles (hence have higher estrogenic states).
 - 5- prolonged estrogen replacement therapy**
 - 6- Estrogen-secreting ovarian tumors** increase the risk of this form of cancer.
- Many of these risk factors are **the same as those for endometrial hyperplasia**, and endometrial carcinoma frequently arises on a background of endometrial hyperplasia.
- **Mutations in mismatch repair genes and the tumor suppressor gene *PTEN*** are early events in the stepwise development of endometrioid carcinoma. Women with germline mutations in *PTEN* (Cowden Syndrome) and germline alterations in DNA mismatch repair genes (Lynch Syndrome) are at high risk for this cancer.

- **Gross:**

Exophytic (fungating, polypoid) mass or infiltrative leading to wall thickening.

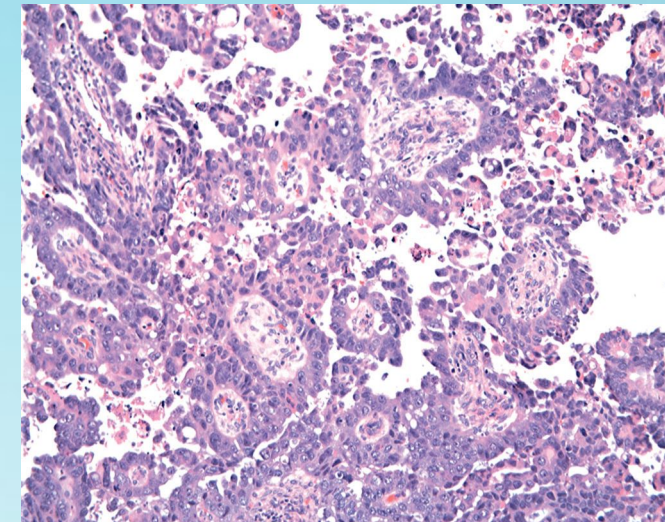
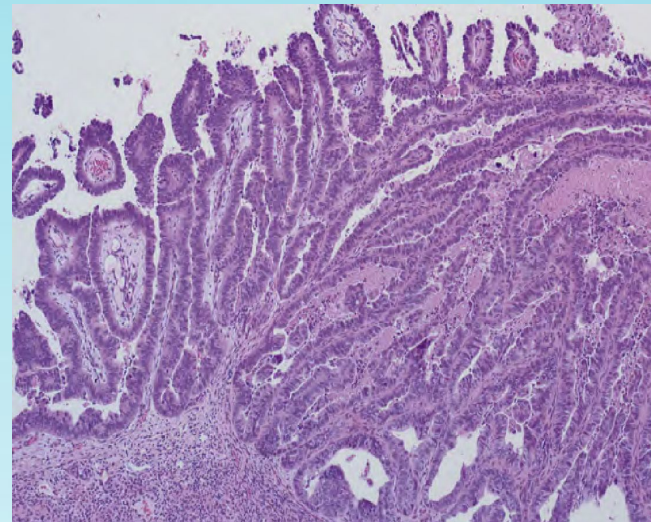
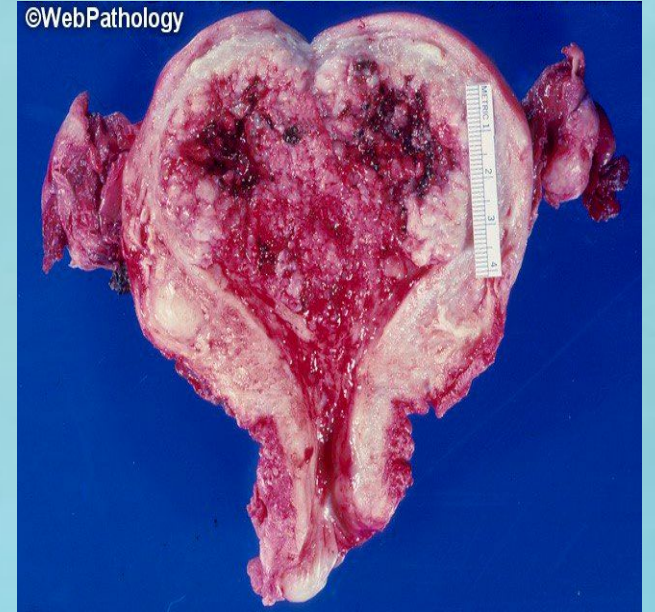
- **Microscopically:**

- The endometrioid carcinoma is adenocarcinoma consists of **malignant endometrial-like glands** (that is why called endometrioid).
- It is **graded from 1 to 3** based on the degree of differentiation and **grade 3** represent the high grade tumors with **poor differentiation**.
- Tumors originate in the mucosa and may infiltrate the **myometrium** and enter vascular spaces, with metastases to **regional lymph nodes**.



□ Serous carcinoma:

- Is less common (accounts for **15%** of tumors) but **more aggressive**.
- **Age:** 65–75 years (older postmenopausal women)
- Not associated with unopposed estrogen or endometrial hyperplasia.
- Nearly all cases of serous carcinoma have **mutations in the *TP53* tumor suppressor gene**.
- **Gross:** typically grow in small tufts and papillae with hemorrhagic and necrotic areas.
- **Mic.:** Papillary pattern of growth with marked cytologic atypia (pleomorphism, hyperchromasia, high nuclear-to-cytoplasmic ratio, giant nucleoli and atypical mitotic figures).



- **Clinical Features**

- Irregular or postmenopausal **bleeding**.
- With progression, the **uterus enlarges** and may become affixed to surrounding structures as the cancer infiltrates surrounding tissues.

- **Prognosis:**

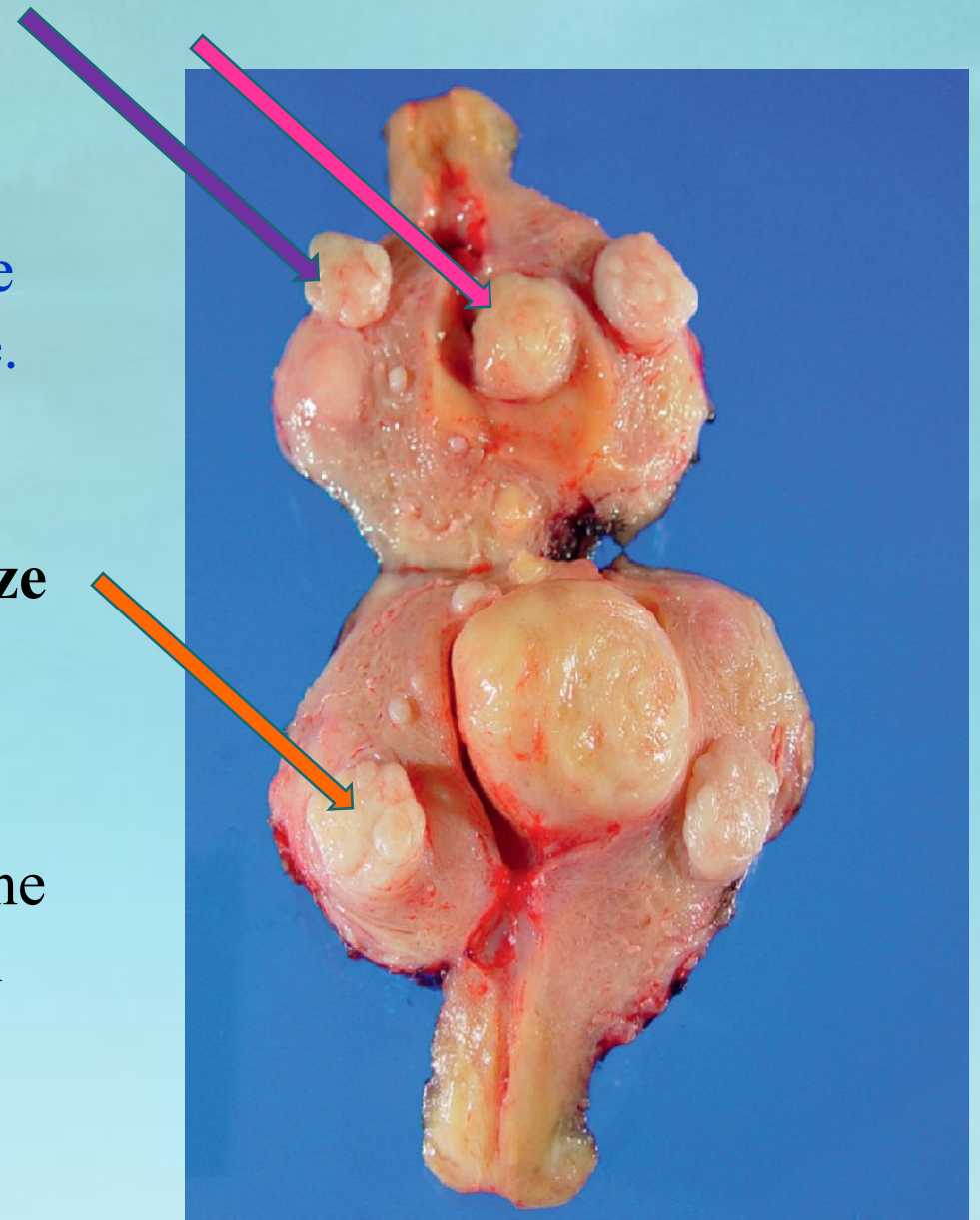
- **Endometrioid carcinoma** is usually is **slow to metastasize**, but if left untreated, eventually disseminates to regional nodes and more distant sites. **The prognosis depends mainly on the stage** of the disease. With therapy, the 5-year survival rate for early-stage endometrioid carcinoma is 90%, but survival drops quickly in higher-stage tumors.
- The prognosis with **Serous carcinoma** is strongly dependent on operative staging but because of its **aggressive behavior (regarded as grade 3)** it often presents as high-stage disease with **a poor prognosis** (because of their ability to **exfoliate, travel** through the fallopian tubes, and implant on peritoneal surfaces like their ovarian counterparts).
- As a result, they have often **spread outside of the uterus at the time of diagnosis**.

❖ Myometrial tumors

□ Leiomyoma

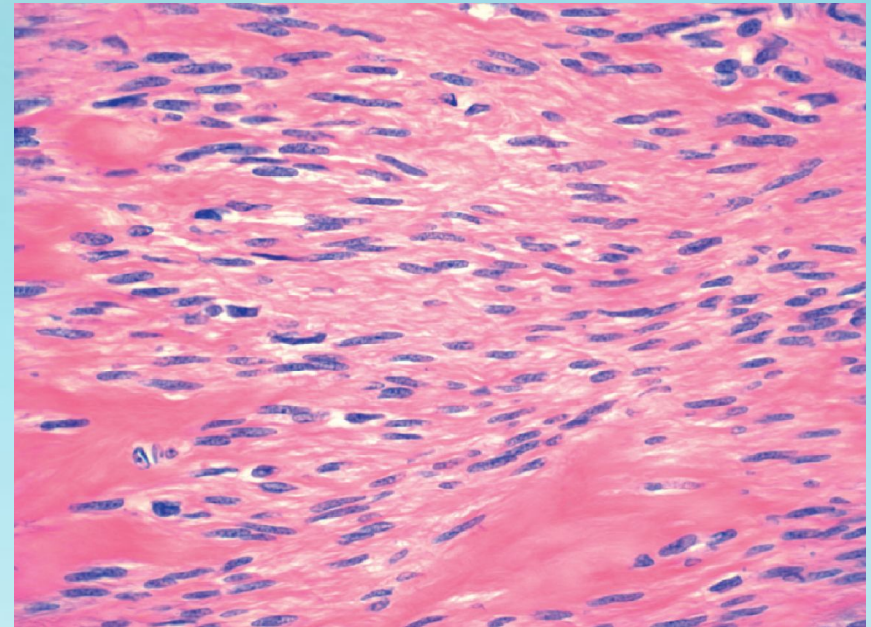
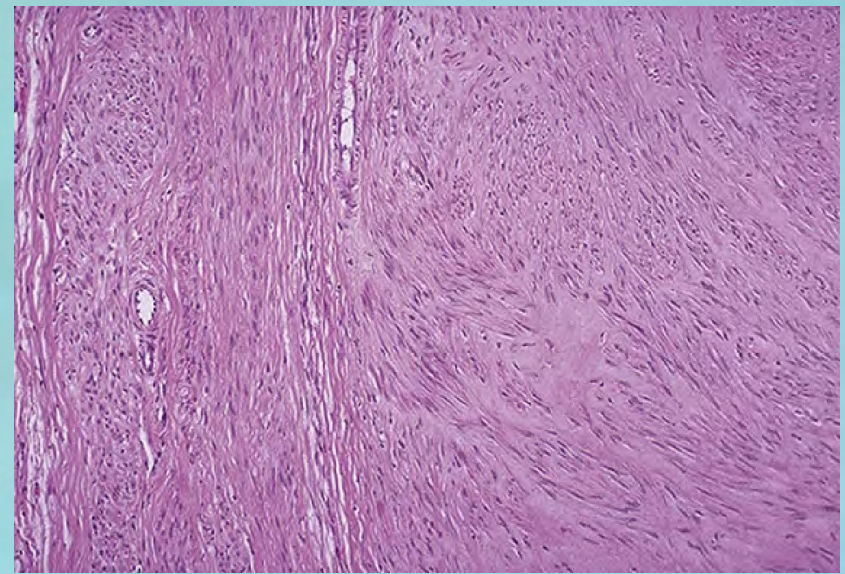
- Are **benign tumors** that arise from the smooth muscle cells in the myometrium.
- Because of their **firmness** they are also called **fibroids**.
- They are the **most common benign tumor in females** and are found in 30% to 50% of women **during reproductive life** and are considerably more frequent in black women.
- **Estrogens and possibly oral contraceptives stimulate their growth**; conversely, they shrink postmenopausally.
- Mutations in the ***MED12* gene**, have been identified in up to **70%** of leiomyomas.

- **Gross:**
- They are sharply **circumscribed**, firm gray-white masses with a characteristic whorled cut surface.
- They may occur singly, but are **often multiple** tumors scattered within the uterus, ranging in **size** from small small nodules to large tumor.
- Some are embedded within the myometrium (**intramural**), others may lie directly beneath the endometrium (**submucosal**) or directly beneath the serosa (**subserosal**).



- **Microscopic features:**

- There are **interlacing bundles of smooth muscle cells** mimicking the appearance of normal myometrium.
- Foci of fibrosis, calcification, and degenerative softening may be present.



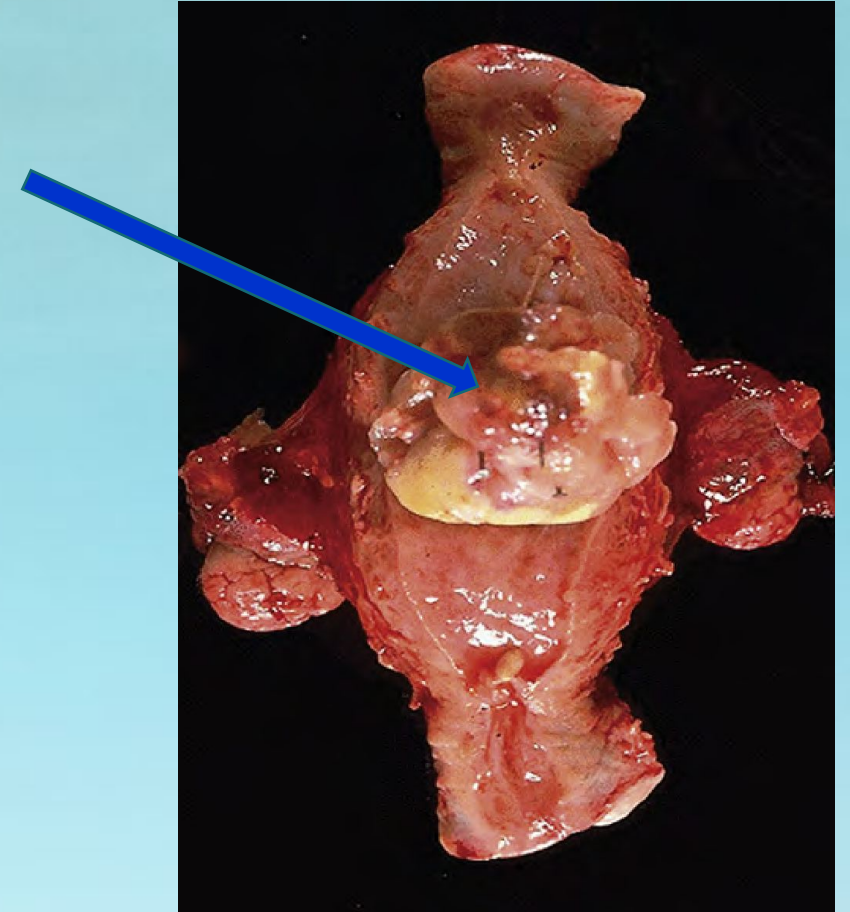
Elongated spindle cells with fibrillary acidophilic cytoplasm.

- **Clinical features:**

- **Asymptomatic** and be discovered only on routine pelvic examination or imaging studies.
- **The most frequent manifestation, when present;**
 - 1. Abnormal uterine bleeding** (menorrhagia with or without metrorrhagia)
 - 2. Urinary frequency** due to compression of the bladder.
 - 3. Sudden pain from infarction** of a large or pedunculated tumor.
 - 4. Impaired fertility.**
 - 5. In pregnant women,** leiomyomas may increase the frequency of spontaneous abortion.
- **Benign leiomyomas rarely transform into sarcomas.**

□ Leiomyosarcomas

- Typically **arise de novo** from the mesenchymal cells of the myometrium.
- They are almost always **solitary** and most often occur in **postmenopausal women**, in contrast to leiomyomas, which frequently are multiple and usually arise premenopausally.
- Recurrence after surgery is common with these cancers, and many metastasize, typically to the **lungs**.
- **Gross:**
Soft, hemorrhagic, necrotic mass.

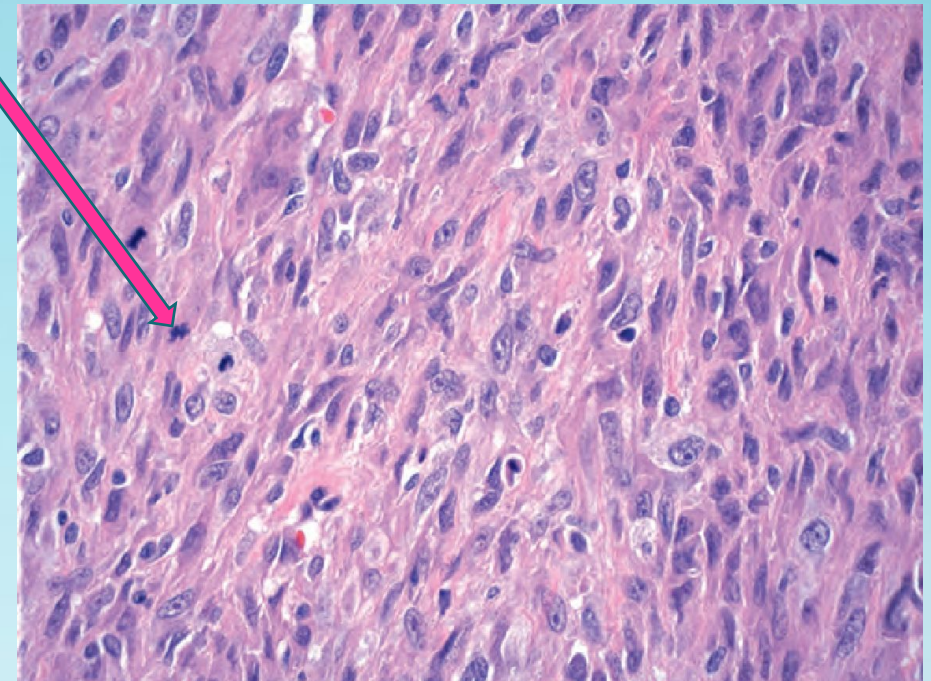
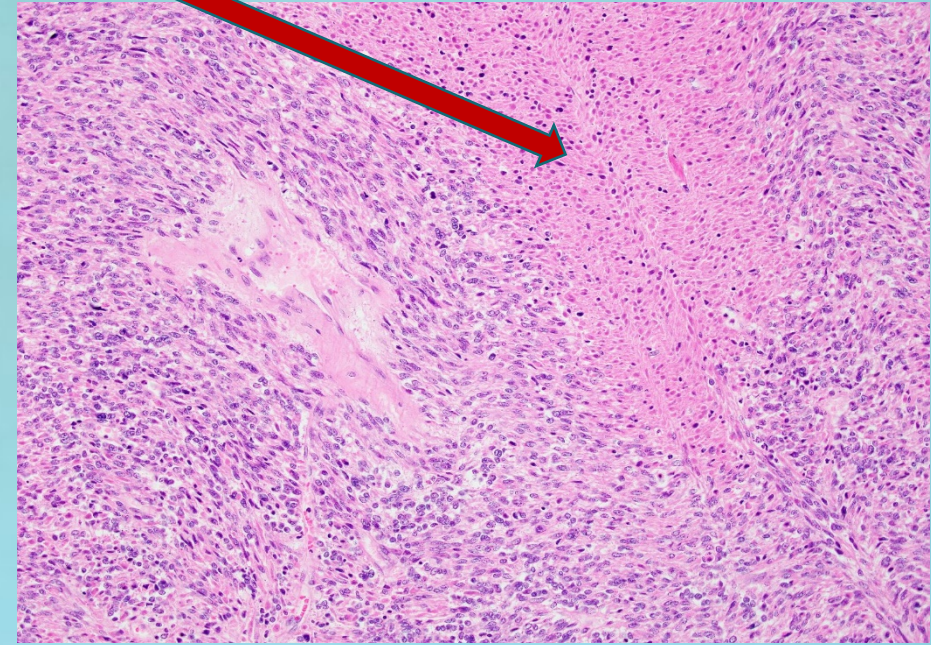


- **Microscopic features:**

- They show a wide range of differentiation, from those that closely resemble leiomyoma to wildly anaplastic tumors.
- The diagnostic features of leiomyosarcoma include:

Tumor necrosis, cytologic atypia, and mitotic activity.

- Because increased mitotic activity is sometimes seen in benign smooth muscle tumors particularly in young women, an assessment of all three features is necessary to make a diagnosis of malignancy.



Fallopian Tubes

Most commonly affected by **infections / inflammatory conditions** (e.g. **suppurative salpingitis** caused by pyogenic organisms, most commonly *Gonococcus* and *Chlamydiae*; **tuberculous salpingitis**).

Other conditions include **ectopic (tubal) pregnancy**, **endometriosis**, **paratubal cysts**

- **Tumors** of the fallopian tube are uncommon. Benign tumors include **adenomatoid tumors** (mesothelial origin). Malignant tumors include **adenocarcinoma**, can be associated with germline BRCA1 mutations.

Thanks

