Pathology of the Female genital tract -2

uterine pathology
Inflammation of the endometrium is seen as part of:

- The spectrum of pelvic inflammatory disease, a condition with consequences for the integrity of the fallopian tubes and subsequent fertility, as discussed below.
- May be associated with retained products of conception subsequent to miscarriage or delivery.
- Or due to a foreign body such as an intrauterine device, acting as a nidus for infection, frequently by flora ascending from the vaginal and intestinal tract, and removal of the offending tissue or foreign body typically results in resolution.

Endometritis is classified as acute or chronic based on whether there is a predominant neutrophilic or lymphoplasmacytic response; however, components of both may be present in a given uterus.

Generally, the diagnosis of chronic endometritis requires the presence of plasma cells.
Histologically, neutrophilic infiltrate in the superficial endometrium and glands coexists with a stromal lymphoplasmacytic infiltrate.

All forms of endometritis may present with fever, abdominal pain, menstrual abnormalities, infertility and ectopic pregnancy due to damage to the fallopian tubes.

Occasionally tuberculosis may present with a granulomatous endometritis, frequently with tuberculous salpingitis and peritonitis. It is common in countries where tuberculosis is endemic and should receive consideration in the differential diagnosis of pelvic inflammatory disease in women who have recently emigrated from endemic areas.
refers to the growth of the basal layer of the endometrium down into the myometrium. Nests of endometrial stroma, glands, or both, are found well down in the myometrium between the muscle bundles.

The uterine wall often becomes thickened and the uterus is enlarged and globular as a result of the presence of endometrial tissue and a reactive hypertrophy of the myometrium. Because these glands derive from the stratum basalis of the endometrium, they do not undergo cyclical bleeding.

marked adenomyosis may produce menorrhagia, dysmenorrhea, and pelvic pain before the onset of menstruation.
Endometriosis is characterized by endometrial glands and stroma in a location outside the endomyometrium.

It occurs in as many as 10% of women in their reproductive years and in nearly half of women who have infertility.

It is a common cause of dysmenorrhea, and pelvic pain, and may present as a pelvic mass filled with degenerating blood (chocolate cyst).

It is frequently multifocal and may involve multiple tissues in the pelvis (ovaries, pouch of Douglas, uterine ligaments, tubes, and rectovaginal septum).

Less frequent sites include the peritoneal cavity and about the umbilicus and uncommonly lymph nodes, lungs, and even heart, skeletal muscle, or bone.
“Chocolate” cyst in an ovary
Three possibilities (not mutually exclusive) have been invoked to explain the origin of endometriosis lesions:

- The *regurgitation theory*, currently the most accepted, proposes menstrual backflow through the fallopian tubes with subsequent implantation. Indeed, menstrual endometrium is viable and survives when injected into the anterior abdominal wall; however, this theory cannot explain lesions in the lymph nodes, skeletal muscle, or lungs.

- The *metaplastic theory* proposes endometrial differentiation of coelomic epithelium, which is the origin of the endometrium itself. This theory, too, cannot explain endometriotic lesions in the lungs or lymph nodes.

- The *vascular or lymphatic dissemination theory* has been invoked to explain extrapelvic or intranodal implants.

Conceivably, all pathways are valid in individual instances.
Metaplastic differentiation of coelomic epithelium

Lymphatic dissemination

Regurgitation through fallopian tube

Extrapelvic dissemination through pelvic veins
In contrast to adenomyosis, endometriosis almost always contains *functionalis endometrium*, which undergoes cyclic bleeding.

Because blood collects in these aberrant foci, they usually appear grossly as red-blue to yellow-brown nodules or implants. They vary in size from microscopic to 1 to 2 cm in diameter and lie on or just under the affected serosal surface. Often individual lesions coalesce to form larger masses.

When the ovaries are involved, the lesions may form large, blood-filled cysts that are transformed into the characteristic so-called *chocolate cysts* as the blood ages.

Consequences: widespread fibrosis, adherence of pelvic structures, sealing of the tubal fimbriated ends, and distortion of the oviducts and ovaries.

The histologic diagnosis at all sites depends on finding two of the following three features within the lesions: endometrial glands, endometrial stroma, or hemosiderin pigment.
The various causes of dysfunctional bleeding can be segregated into four groups:

1. **Failure of ovulation.** The most common cause of DUB.
   - Anovulatory cycles are common at both ends of reproductive life
   - Any dysfunction of the hypothalamic-pituitary axis, adrenal, or thyroid
   - A functioning ovarian lesion producing an excess of estrogen
   - Malnutrition, obesity, or debilitating disease; and with severe physical or emotional stress.

Mechanism of bleeding: Failure of ovulation leads to an excess of estrogen relative to progesterone, (stroma requires progesterone for its support). The poorly supported endometrium partially collapses, with rupture of spiral arteries, accounting for the bleeding.
Dysfunctional Uterine Bleeding

2- **Inadequate luteal phase.** The corpus luteum may fail to mature normally or may regress prematurely, leading to a relative lack of progesterone. The endometrium under these circumstances reveals delay in the development of the secretory changes expected at the date of biopsy.

3- **Contraceptive-induced bleeding.** Older oral contraceptives containing synthetic estrogens and progestin induced a variety of endometrial responses—for example, decidua-like stroma and inactive, nonsecretory glands. The pills in current use have corrected these abnormalities.

4- **Endomyometrial disorders:** including chronic endometritis, endometrial polyps, submucosal leiomyomas, endometrial hyperplasia and cancers.
<table>
<thead>
<tr>
<th>Age Group</th>
<th>Cause(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prepuberty</td>
<td>Precocious puberty (hypothalamic, pituitary, or ovarian origin)</td>
</tr>
<tr>
<td>Adolescence</td>
<td>Anovulatory cycle</td>
</tr>
<tr>
<td>Reproductive age</td>
<td>Complications of pregnancy (abortion, trophoblastic disease, ectopic pregnancy) Organic lesions (leiomyoma, adenomyosis, polyps, endometrial hyperplasia, carcinoma)</td>
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<tr>
<td>Perimenopause</td>
<td>Anovulatory cycle Ovulatory dysfunctional bleeding (e.g., inadequate luteal phase)</td>
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<td></td>
<td>Irregular shedding Organic lesions (carcinoma, hyperplasia, polyps)</td>
</tr>
<tr>
<td>Postmenopause</td>
<td>Organic lesions (carcinoma, hyperplasia, polyps)</td>
</tr>
<tr>
<td></td>
<td>Endometrial atrophy</td>
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</tbody>
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Endometrial Hyperplasia

- An excess of estrogen relative to progestin, if sufficiently prolonged or marked, will induce exaggerated endometrial proliferation (hyperplasia), which can be preneoplastic.

- The severity of hyperplasia is classified based on architectural crowding and cytologic atypia, ranging from:
  1- Simple hyperplasia to
  2- Complex hyperplasia, and finally
  3- Atypical hyperplasia.

- These three categories represent a continuum based on the level and duration of the estrogen excess.

- In time the hyperplasia may become autonomously proliferating, no longer needing estrogenic influence, eventually giving rise to carcinoma.
Simple hyperplasia

Complex Hyperplasia

Atypical Hyperplasia
The risk of developing carcinoma is dependent on the severity of the hyperplastic changes and associated cellular atypia. Simple hyperplasia carries a negligible risk, while a person with atypical hyperplasia with has a 20% risk of developing endometrial carcinoma.

Any estrogen excess may lead to hyperplasia. Potential contributors include failure of ovulation, such as is seen around the menopause; prolonged administration of estrogenic steroids without counterbalancing progestin; estrogen-producing ovarian lesions such as polycystic ovaries; cortical stromal hyperplasia; and granulosa-theca cell tumors of the ovary. A common risk factor is obesity, because adipose tissue processes steroid precursors into estrogens.

When atypical hyperplasia is discovered, it must be carefully evaluated for the presence of cancer and must be monitored by repeated endometrial biopsy.
Endometrial Polyps

These are sessile, usually hemispheric (rarely pedunculated) lesions that are 0.5 to 3 cm in diameter. Larger polyps may project from the endometrial mucosa into the uterine cavity.

Histologically they are composed of endometrium resembling the basalis, frequently with small muscular arteries, more often they have cystically dilated glands.

The stromal cells in most endometrial polyps are monoclonal and have a cytogenetic rearrangement at 6p21, making it clear that they are the neoplastic component of the polyp.

Benign tumors with no risk of endometrial cancer.
Endometrial carcinoma is the most frequent cancer occurring in the female genital tract.

Some years ago, it was much less common than cervical cancer. However, early detection of CIN by periodic pap smear cytologic examinations and its appropriate treatment have dramatically reduced the incidence of invasive cervical cancer.

Endometrial cancer appears most frequently in 50s and 60s and is distinctly uncommon in women younger than 40 years of age.

There are two clinical settings in which endometrial carcinomas arise:

1) in perimenopausal women with estrogen excess
2) in older women with endometrial atrophy.

These scenarios are correlated with differences in histology: endometrioid and serous carcinoma of the endometrium, respectively.
Endometrioid carcinoma

- These tumors are termed *endometrioid* because of their similarity to normal endometrial glands.
- There is a constellation of well-defined risk factors for endometrioid carcinoma:
  - **Obesity**: increased synthesis of estrogens in fat depots and from adrenal and ovarian precursors;
  - **Diabetes**
  - **Hypertension** (mostly an association and not a true risk factor)
  - **Infertility**: women tend to be nulliparous, often with nonovulatory cycles.
  - **Prolonged estrogen replacement therapy**
  - **Estrogen-secreting ovarian tumors**.
- Many of these risk factors are the same as those for endometrial hyperplasia
  - *endometrial carcinoma frequently arises on a background of endometrial hyperplasia.*
- Breast carcinoma occurs in women with endometrial cancer (and vice versa) more frequently than by chance alone.
Dissecting the pathogenesis of endometrioid carcinoma is aided by analysis of two familial cancer syndromes that have an increased risk of the endometrioid type of endometrial carcinoma:

1. **Hereditary Nonpolyposis Colon Cancer Syndrome (HNPCC).** Endometrial carcinoma is the second most common cancer associated with an inherited genetic defect in a DNA mismatch repair gene. Sporadic cases of endometrioid-type endometrial carcinoma also have a high frequency of inactivation of these genes by methylation of the promoter, and as a consequence have relatively unstable genomes (microsatellite instability).

2. **Cowden's syndrome,** a multiple hamartoma syndrome that carries an increased risk of carcinoma of the breast, thyroid, and endometrium, have mutations in **PTEN,** a tumor suppressor gene. Sporadic cases of endometrioid carcinoma also harbor mutations in **PTEN.**

In fact, both mismatch repair gene and **PTEN** mutations are early events in endometrioid endometrial carcinogenesis, occurring in the progression from abnormal proliferation to atypical hyperplasia.
Serous carcinoma

- Serous carcinoma of the endometrium is pathophysiologically distinct.
- It typically arises in a background of atrophy, sometimes in the setting of an endometrial polyp (no relation with endometrial hyperplasia).
- Mutations in DNA mismatch repair genes and PTEN are rare in serous carcinoma; however, nearly all cases have mutations in the p53 tumor suppressor gene.
Endometrioid carcinomas closely resemble normal endometrium and may be exophytic or infiltrative. They frequently show a range of patterns, including mucinous, tubal (ciliated), and squamous (occasionally adenosquamous) differentiation.

Tumors originate in the mucosa and may infiltrate the myometrium and enter vascular spaces, with metastases to regional lymph nodes.

For this group of tumors, grading (grades I-III) and staging closely parallel outcome: stage I, confined to the corpus; stage II, involvement of the cervix; stage III, beyond the uterus but within the true pelvis; stage IV, distant metastases or involvement of other viscera.

Serous carcinoma forms small tufts and papillae rather than the glands seen in endometrioid carcinoma, and has much greater cytologic atypia. They behave as poorly differentiated cancers and are not graded, and are particularly aggressive.
Prognosis

- **Endometrioid carcinoma:** With therapy, stage I endometrioid carcinoma is associated with a 5-year survival rate of 90%; this rate drops to 30% to 50% in stage II and to less than 20% in stages III and IV.

- **The prognosis for serous carcinomas** is strongly dependent on the extent of tumor, as determined by operative staging with peritoneal cytology. This is critical, since even very small or superficial serous tumors may nonetheless spread via the fallopian tube to the peritoneal cavity, leading to an advanced stage at time of diagnosis.
Tumors of the myometrium

- Lieomyomas
  Benign tumors that arise from the smooth muscle cells in the myometrium, however, because they are firm, they are more often referred to as fibroids.

- They are the most common benign tumor in females and are found in 30% to 50% of women during reproductive life. Some genetic influence may be involved; for example, these tumors are considerably more frequent in blacks than in whites.

- Estrogens and possibly oral contraceptives stimulate their growth; conversely, they shrink postmenopausally.
Macroscopically leiomyomas are typically sharply circumscribed, firm gray-white masses with a characteristic whorled cut surface. They may be single, but most often multiple tumors are within the uterus. They range in size from small to massive neoplasms. Most commonly they are embedded within the myometrium (intramural), whereas others may lie directly beneath the endometrium (submucosal) or directly beneath the serosa (subserosal). The latter may develop attenuated stalks and even become attached to surrounding organs, from which they develop a blood supply and then free themselves from the uterus to become "parasitic" leiomyomas.

Larger neoplasms may develop foci of ischemic necrosis with areas of hemorrhage and cystic softening, and after menopause they may become densely collagenous and even calcified.
Histologically, the tumors are characterized by whorling bundles of smooth muscle cells as those of the normal myometrium. Foci of fibrosis, calcification, cystic degeneration, and hemorrhage may be present.

Leiomyomas of the uterus may be entirely asymptomatic and be discovered only on routine pelvic or post mortem examination.

The most frequent manifestation, when present, is menorrhagia, with or without metrorrhagia. Large masses in the pelvic region may become palpable to the woman or may produce a dragging sensation.

Benign leiomyomas almost never transform into sarcomas, and the presence of multiple lesions does not increase the risk of harboring a malignancy.
Lieomyosarcoma

- Typically arise de novo from the smooth muscle cells of the myometrium, not from preexisting leiomyomas.
- They are almost always solitary tumors, in contrast to the frequently multiple leiomyomas.
- They are frequently soft, hemorrhagic, and necrotic.
- Histologically, they present a wide range of differentiation, from those that closely resemble leiomyoma to wildly anaplastic tumors. With this range in morphology, it is understandable that some well-differentiated tumors lie at the interface between benign and malignant, and sometimes these are designated as smooth muscle tumors of uncertain malignant potential (STUMP).
Grossly, leiomyosarcomas develop in several distinct patterns: as bulky masses infiltrating the uterine wall; as polypoid lesions projecting into the uterine cavity; or as deceptively discrete tumors that masquerade as large, benign leiomyomas.
Lieomyosarcoma

- The diagnostic features of leiomyosarcoma include tumor coagulative necrosis, which is distinct from the degenerative necrosis frequently seen in leiomyomas, cytologic atypia, and mitotic activity. Since increased mitotic activity alone is sometimes seen in benign smooth muscle tumors in young women, an assessment of all three features is necessary to make a diagnosis of malignancy.
- Recurrence after removal is common with these cancers, and many metastasize, typically to the lungs, yielding a 5-year survival rate of about 40%.
- Understandably, the more anaplastic tumors have a poorer outlook than the better differentiated lesions.