Uterus

Anatomy & Histology:

- Uterus is a pear-shaped hollow organ (cervix and uterus body)
- Uterine wall lined by a thin layer of endometrium and a thick layer of myometrium
- Endometrium is composed of endometrial glands and surrounding stroma - It is responsive to hormone stimulation, and undergoes monthly shedding (menstrual cycle)
- Myometrium: Consists of bundles of smooth muscle
- The monthly cycle of endometrium is divided into 3 phases:
  - proliferative, ovulatory, and secretory

Endometritis:
Acute endometritis: Uncommon, usually caused by bacterial infection associated with delivery or miscarriage. Microscopically: Moderate to large number of PMNs in non-bleeding endometrium; microabscess formation

Chronic endometritis: More common (Plasma cell endometritis) Causes: Pelvic inflammatory disease, retained gestational tissue, intrauterine devices, tuberculous salpingitis, or non-specific (no obvious primary cause), Chlamydia

Main clinical complaints: abnormal bleeding, pain, vaginal discharge and infertility

Main pathologic finding: Plasma cells within the endometrial stroma; as well as increased numbers of lymphocytes and lymphoid follicles (note that some lymphocytes are normally present in endometrial stroma)

Pelvic Inflammatory disease:
- Ascending genital tract infection: Cervicitis -- Endometritis -- Salpingitis -- Tuboovarian abscess
- Sexually transmitted, etiologies: Chlamydia trachomatis, Neisseria gonorrhoea; may be polymicrobial
- Clinical Presentation: Purulent cervical discharge, cervical motion tenderness

Endometriosis:
Endometrium glands or stroma presents in abnormal locations outside the uterus
Common sites: ovaries, uterine ligaments, retrovaginal septum, laparotomy scars
Affecting approximately 10% of women
Main clinical complaints:
Severe dysmenorrhea, dyspareunia, pelvic pain, menstrual irregularities, infertility (30 - 40%) and malignancies

The potential origin of the endometriosis:
*Regurgitation theory or retrograde menstruation through fallopian tube: Refluxed endometrial fragments adhere to and invade the peritoneal mesothelium, develop a blood supply which leads to implant survival and growth

*Metaplastic theory: Endometrium arising from coelomic epithelium. Metaplastic change of peritoneal mesothelial cells into endometrial glandular cells.

*Vascular/lymphatic dissemination theory: lung, lymph nodes. Aberrant lymphatic or vascular spread of endometrial tissue

Pathogenesis – Endometriotic tissue is more than just “displaced”. Exhibits increased level of inflammatory mediators, especially prostaglandin E2, increased estrogen production due to high aromatase activity of stromal cells. Role of activated macrophages being elucidated. Decreased immune clearance has been demonstrated. These changes enhance survival within foreign tissue.

Adenomyosis: The presence of endometrial glands and surrounding stroma deep within the myometrium. Grossly uterus may enlarge due to myometrial hypertrophy

Endometrial polyp:
- Usually within fundus
  - Sessile masses of variable sizes composed of monoclonal endometrial stromal cells and associated glands
  - Most women perimenopausal. May be asymptomatic or cause abnormal bleeding
  - Tamoxifen treatment association polyps, unusually large polyps
  - Rarely associated with malignancy, especially in older women

Endometrial hyperplasia
Related to high, prolonged estrogenic exposure
Clinical presentation: abnormal uterine bleeding, or postmenopausal bleeding
Subclassified into: Non-atypical hyperplasia and Atypical hyperplasia (or Endometrial Intraepithelial Neoplasia)
Significance of endometrial hyperplasia: Atypical Endometrial hyperplasia is associated with high risk of progression endometrial adenocarcinoma. Atypia reflects cytologic atypia of glandular cells
PTEN gene

A tumor suppressor gene; its gene product is a phosphate protein, which is involved in the regulation of the cell proliferation, growth, and apoptosis

PTEN can be lost by inactivation or mutation which occur in many cancers including endometrial carcinoma.
It is the most frequently altered gene in endometrioid carcinoma

**Endometrial carcinoma**

The most common invasive cancer of the female genital tract, typically develops in postmenopausal women.

**Endometrioid type**
Estrogen related, mimicking the appearance of endometrial glands
Accounts for 85% of endometrial carcinoma, usually diagnosed in an early stage
Associated with unopposed estrogen including:
- Polycystic ovary syndrome, Obesity, diabetes, HTN, infertility
- Estrogen secreting ovarian tumor
- Exogenous estrogen

Usually associated with atypical endometrial hyperplasia in background

**Gross:** polypoid mass or tumor diffusely involving the endometrial surface with myoinvasion

**Micro:** Mixture of the malignant glands and solid components

**Non-Endometrioid type, high grade, mainly including serous papillary type**

Comprises 5-10% of endometrial carcinomas, occurs in older women
No association with estrogen or background endometrial hyperplasia; (usually endometrium is atrophic)
Highly aggressive tumor, most patients have stage II-III disease at presentation
Early lymphovascular invasion and peritoneal spread

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### Endometrial Carcinoma

**Endometrioid**
- Arises from endometrial hyperplasia
- Risk factors – unopposed estrogen: Obesity, exogenous estrogen, early menarche, late menopause, DM, HTN, infertility with anovulatory cycles
- Presentation ~60 years
- Histology - appears reminiscent of “normal” endometrium
- PTEN mutations, early inactivation of DNA mismatch repair genes

**Serous**
- “Sporadic”
- No defined precursor lesion
- Arises from atrophic endometrium
- Presentation ~70 years
- Histology: Papillary structures
- p53 mutations
- Aggressive behavior
Staging of endometrial carcinoma

Stage I: confined to uterine corpus
Stage II: uterus and cervix
Stage III: extends outside uterus but not the true pelvis
Stage IV: extends outside true pelvis or involves bladder mucosa and rectum

Tumors of myometrium

Benign: Leiomyoma, a smooth muscle tumor (Fibroids)
Malignant: Leiomyosarcoma

Leiomyoma: The most common tumor in women, in up to 75% of women of reproductive age, more common in African Americans, estrogen responsive. Gross: Sharply circumscribed, round, firm nodules or mass, bulging, tan-white, whorled appearance, variable in sizes. Histology: well-delineated, whorled bundles of smooth muscle cells, resembling the surrounding normal myometrium. Linked with chromosomal abnormality.

Clinical presentation: depends on the location, size and number of tumors asymptomatic, abnormal uterine/excessive bleeding (submucosal leiomyoma), or increased abdominal girth

May cause bladder compression (urinary frequency), sudden pain (disruption of blood supply), impaired fertility, in pregnancy (spontaneous abortion, fetal malpresentation, postpartum hemorrhage
Leiomyosarcoma: Uncommon tumors, arise de novo from either myometrial layer or endometrial stroma. Peak incidence: 40s – 60s years of age. Unfavorable prognosis, overall 5 years survival rate: 40% (10 - 15% for high grade tumors). Gross morphology: One tumor or one large tumor among many small ones, bulky, fleshy, hemorrhagic and necrotic masses. Histology: nuclear atypia, mitoses, zonal necrosis or tumor cell necrosis

Abnormal Uterine Bleeding

Causes differ by age groups. Caused by distinct uterine organic lesions, systemic abnormalities or “dysfunctional uterine bleeding” absence/exclusion of distinct uterine lesions.

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Cause(s)</th>
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<tbody>
<tr>
<td>Prepuberty</td>
<td>Precocious puberty (hypothalamic, pituitary, or ovarian origin)</td>
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<tr>
<td>Adolescence</td>
<td>Anovulatory cycle</td>
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<tr>
<td>Reproductive age</td>
<td>Complications of pregnancy (abortion, trophoblastic disease, ectopic pregnancy)</td>
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<tr>
<td></td>
<td>Proliferations (leiomyoma, adenomyosis, polyps, endometrial hyperplasia, carcinoma)</td>
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<tr>
<td></td>
<td>Anovulatory cycle</td>
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<td></td>
<td>Ovulatory dysfunctional bleeding (e.g., inadequate luteal phase)</td>
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<tr>
<td>Perimenopause</td>
<td>Anovulatory cycle</td>
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<td>Irregular shedding</td>
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<tr>
<td></td>
<td>Proliferations (carcinoma, hyperplasia, polyps)</td>
</tr>
<tr>
<td>Postmenopause</td>
<td>Proliferations (carcinoma, hyperplasia, polyps)</td>
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<tr>
<td></td>
<td>Endometrial atrophy</td>
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Dysfunctional uterine bleeding also may result from an inadequate luteal phase, which is thought to stem from insufficient production of progesterone by the corpus luteum.

Dysfunctional uterine bleeding

Include a spectrum of changes that can occur during active reproductive life. The underlining causes varies by different age groups. It is usually functional disturbance in young women due to alterations in the pituitary-ovarian-endometrial hormonal axis

The most common clinical presentation: excessive and abnormal uterine bleeding during or between menstrual cycles. Anovulatory cycle is a common cause of “dysfunctional uterine bleeding”. It is associated with excessive and prolonged estrogenic stimulation without ovulation, no progestational (secretory) phase.

Why? If ovulation does not occur, no progesterone is produced, and a proliferative endometrium persists. At the tissue level, a chronic proliferative endometrium is typically associated with stromal breakdown, decreased spiral arteriole density and dilated and unstable venous capillaries. Because endometrial vessels become markedly dilated, bleeding can be severe. Also, there is increased endometrial responsiveness to vasodilating prostaglandins.