Topics

- Normal cyclic endometrium
- DUB, Endometritis, Metaplasias, Polyps
- Exogenous hormones and their effects
- Endometrial hyperplasia and EIN
- Endometrial adenocarcinoma

Normal endometrium

- Basal layer (stratum basalis):
  - Adjacent to the myometrium
  - No secretory activity
  - No or minimal mitotic activity
- Functional zone (stratum functionalis)
  - Superficial compact layer, stroma prominent decidual reaction
  - Deeper spongy layer, maximal secretory activity but unresponsive stroma

Normal endometrium

- Junction with the fallopian tube epithelium is usually abrupt whereas gradual transition at the junction of the endometrial with endocervical epithelium (lower uterine segment)
- Isthmic endometrium, mixture of columnar cells admixed with ciliated cells, stroma with more fibrous

Morphologic features used in endometrial dating

Glandular changes
1. Tortuosity
2. Mitoses
3. Orientation of nuclei (pseudostratified or basal)
4. Subnuclear cytoplasmic vacuoles
5. Secretory exhaustion (luminal secretions)

Stromal changes
1. Edema
2. Mitoses
3. Prodecidua
4. Granular lymphocyte infiltrate
Proliferative phase changes
Early (4–7 days)
Thin regenerating epithelium
Short narrow glands with epithelial mitoses
Stroma compact with mitoses (cells stellate or spindle shaped)
Mid (8–10 days)
Long, curving glands
Columnar surface epithelium
Stroma variably edematous, mitoses frequent
Late (11–14 days)
Tortuous glands
Pseudotratified nuclei
Moderately dense, actively growing stroma

Artifact

Endometrial dating, Secretory phase
Internal phase, 5–15 days: No detectable changes for 36–46 hours after ovulation
Early secretory phase, 16–20 days: Glandular changes prominent
Endometrial dating, Secretory phase
16.4. Secretory vacuoles (Note: Scattered small round vacuoles can be caused by estrogen alone.)
16.4. Secretory vacuoles—milk laced up with cuboidal vacuoles
16.4. Vascular dilatation in utro
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Abnormal uterine bleeding
• Dysfunctional uterine bleeding
• Endometritis
• Endometrial polyp
• Endometrial hyperplasia
• Endometrial carcinoma

Causes of abnormal uterine bleeding in adolescence
Common
• Dysfunctional uterine bleeding
• Anovulatory cycles
• Complications of pregnancy
Uncommon
• Endometritis
• Clotting disorders
### Causes of abnormal uterine bleeding in the reproductive years

**Common**
- Complications of pregnancy
- Endometritis
- Dysfunctional uterine bleeding: anovulatory cycles, inadequate luteal phase
- Organic lesions: LM, polyps, adenomyosis
- Exogenous hormones: birth control, progestin therapy

**Uncommon**
- Hyperplasia
- Neoplasia: endometrial CA, cervical CA
- Clotting disorders

### Dysfunctional uterine bleeding

- Lack of ovulation following follicular development (estrogen-related bleeding)
- Luteal phase abnormalities (progesterone-related bleeding)
- Often manage by Hormonal Tx before biopsy taken

### Causes of abnormal uterine bleeding in perimenopausal years

**Common**
- Dysfunctional uterine bleeding: anovulatory cycles
- Organic lesions: hyperplasia, polyps
- Exogenous hormones: birth control, estrogen replacement, progestin therapy

**Uncommon**
- Complication of pregnancy
- Endometritis
- Adenomyosis
- Neoplasia: cervical CA, endometrial CA, sarcoma
- Clotting disorders

### Estrogen-related bleeding

- Proliferative with glandular and stromal breakdown:
  - Resulting from anovulatory cycles
  - Most common abnormality in abnormal bleeding esp in perimenopausal women
  - Proliferative pattern with glandular and stromal breakdown
  - Amount of tissue and architectural pattern of glands depend on duration of unopposed estrogenic stimulation

### Causes of abnormal uterine bleeding in postmenopausal years

**Common**
- Atrophy
- Organic lesions: hyperplasia, polyps
- Neoplasia: endometrial CA
- Exogenous hormones: estrogen replacement, progestin therapy

**Uncommon**
- Endometritis
- Sarcoma
- Clotting disorders

### Estrogen-related bleeding

- Proliferative with glandular and stromal breakdown, cont.
  - Tubal metaplasia, eosinophilic cell changes
  - Prolonged unopposed estrogen may lead to hyperplasia and well differentiated adenocarcinoma
  - Breakdown and bleeding pattern strongly suggests anovulatory cycles but exogenous estrogen can causes similar patterns, clinical correlation is required
  - Exclude organic lesion including inflammation, polyps, leiomyomas
Menstrual endometrium VS anovulatory endometrium with stromal breakdown
- Absence of fragments of endometrium showing changes of secretory exhaustion
- Presence of fibrin thrombi
- Focal rather than diffuse, not uniformly occur
- May occur with organic lesions such as inflammation, polyps, hyperplasia, or carcinoma
- Hemosiderin deposition, foam cells, eosinophilic changes seen in abnormal bleeding patterns

Estrogen-related bleeding
- Disordered Proliferative Endometrium/Persistent Proliferative phase
- Focal branching and some dilatation, disorganized glands
- Diagnosis should be reserved for intact, well orientated fragments of tissue otherwise, it is best to diagnosis only as proliferative endometrium
- Similar to simple hyperplasia but limited in extent and interspersed among glands with normal proliferative pattern

Menstrual Endometrium

Glandular and Stromal breakdown ass w/ DUB

Estrogen-related bleeding
- Atrophy:
  - Important cause of abnormal uterine bleeding in postmenopausal patients
  - Scant, often consisting only of a small amount of mucoid material, not consider as insufficient or inadequate
  - Tiny wisps of surface endometrium and detached fragmented endometrial glands
  - Epithelium showing dark nuclei, low columnar to cuboidal
  - Absent mitotic activity
Atrophic endometrium

Endometritis

- Lymphocytes are normal constituent in endometrium and their presence does not indicate endometritis, when arranged in follicles forming germinal center, endometritis is likely
- Plasma cells are seldom found in normal endometrium, their presence is indicative of chronic endometritis
- Neutrophils may also be found in normal endometrial cycle esp. around menstruation period

Progestosterone-related bleeding

- Luteal Phase Defects
  - Insufficient corpus luteum, premature regression or failing to produce adequate progesterone
  - Glands with secretory changes but lacking tortuosity of late secretory phase, focal breakdown
- Irregular Shedding
  - Persistent corpus luteum with prolonged progesterone production
  - Mixed pattern of secretory and proliferative at least 5 days after onset of bleeding or secretory development more than 4 days difference in the morphologic date

Report

- Presence or absence of morphologic changes of breakdown as well as specific lesions
- Proliferative endometrium with glandular and stromal breakdown
- Abnormal secretory phase pattern with breakdown
- Recognize features of atrophy: consistent with atrophy
- Withdrawal and Breakthrough terms should be avoided in pathologic diagnoses since they lack clear definitions

Endometritis

- Nonspecific endometritis (Acute/Chronic)
- Specific forms of endometritis
  - Chlamydia trachomatis and Neisseria gonorrhoeae: large number of plasma cells in stroma, neutrophils at endometrial surface epithelium (>5/ hpf)
  - Mycoplasma
  - CMV
  - HSV
- Tuberculous endometritis, almost always secondary to disease from lungs, GI tract
- Actinomyces Israelii: IUD usage, risk of infection related to duration than type of IUD (85% of cases with 3 or more years)
Actinomyces Israeli Endometrial polyp

- Monoclonal overgrowths of genetically altered endometrial stromal cells with secondary induction of polyclonal benign glands
- Response variably to circulating estrogen and progesterone, most polyps are non-functional
- Glands showing dilated, slightly branching or irregularly distributed

Endometrial polyp

Endometrial metaplasia

- Changes in cellular differentiation to type that is not present in the normal endometrium
- Altered differentiation may be seen in benign, premalignant, or malignant endometria and should be placed within the broad diagnosis context of reactive, hormonal, or neoplastic process
- Epithelial metaplasia (arias-stella, tubal, squamous, mucinous, eosinophilic, papillary syncytial)
- Mesenchymal metaplasia (osseous, extramedullary hematopoiesis)

Tubal metaplasia

- Most common form
- Occasional round secretory cells in ciliated cells, resemble FT
- Can be normally found in normal proliferative endometrium
- Related to estrogenic stimuli?
Squamous metaplasia

- Stratified epithelium typically result from chronic irritation or infection
- Morular type, most common in neoplastic setting
- Terminal differentiation state (loss of ER, PR)

Exogenous hormonal effect

- Estrogenic hormone
- Progesterin
- Combined estrogen and progesterin

Papillary syncytial metaplasia

- Not true metaplasia, degenerative process caused by endometrial breakdown
- Resemble squamous cells but lack true squamous differentiation
- No true papillae with fibrovascular core

Exogenous hormonal effect

- Estrogenic hormone
  - Associated with increased risk for development of endometrial CA
  - Effect depend on duration > dose
  - Disordered proliferative endometrium, endometrial hyperplasia, endometrial carcinoma (low grade)
  - May be identical to anovulatory cycles including superimposed breakdown and bleeding
  - Squamous differentiation and tubal metaplasia

Exogenous hormonal effect

- Progesterin
  - Various forms either alone or in combination with estrogen
  - Effects can be placed into 3 general morphologic patterns, decidual changes, secretory changes, and atrophic changes depend of the estrogen priming of the endometrium, dose and duration
Patterns of progestin effects

**Decidual (pregnancy-like) effects**
- Abundant tissue, often polypoid
- Glands show marked secretory activity
- Stroma appears decidualized with lymphoid infiltrate
- Vascular ectasia

**Secretory effects**
- Moderate to sparse amount of tissue
- Mildly tortuous secretory glands lined by columnar cells
- Stromal cells plump, oval (predecidual)
- Vascular ectasia

**Atrophic effects**
- Sparse tissue
- Glands small and atrophic, not coiled
- Variable amount of stroma with plump to spindle-shaped cells

4. Benign endometrial hyperplasia and EIN

- **Nonatypical hyperplasia**
  - Simple
  - Complex

- **Atypical hyperplasia**
  - Simple
  - Complex

- **Benign endometrial hyperplasia**
- **Endometrial intraepithelial neoplasia (EIN)**

Combined estrogen and progestin as replacement therapy for menopausal women

- Usually proliferative pattern with small, tubular glands in scant stroma
- Mild tortuosity, cytoplasmic vacuoles, scant secretion

Endometrial hyperplasia

- 1994, WHO and International Society of Gynecologic Pathologists adopted system for endometrial cancer precursor lesions based on the Kurman et al’ work in 1885 which showed significant stratification of prognosis using this system
- Based on:
  - Gland architecture – simple VS complex
  - Nuclear atypia – non-atypical VS atypical
- Poor reproducibility

Endometrial Hyperplasia

- Diffuse abnormality
- Increased in gland-to-stroma ratio
- Irregularities in gland and shape
- Variation of gland size
- Mitotic activity
- Significant amount of tissue
### Hyperplasia without atypia
- Cytologic features
- Nuclei
- Pseudostatified
- Cigar-shaped to oval with smooth contours
- Uniform chromatin distribution
- Small to indistinct nucleoli
- Mitotic activity, variable amount
- Cytoplasm
- Variable, often amphophilic
- Glands
- Irregular, variable size, some dilated
- Branching, infolding and outpouching
- Simple hyperplasia
- Haphazardly spaced in abundant stroma
- Complex hyperplasia
- Closely spaced with decreased stroma
- Highly irregular outlines
- Frequent associated features
- Polypoid growth
- Ullated cells
- Elastic remains
- Breakdown and bleeding

### Atypical hyperplasia
- Cytologic features
- Nuclei
- Stratification with loss of polarity
- Enlarged, rounded with irregular shapes
- Coarsening of chromatin creating a vesicular appearance
- Prominent nucleoli
- Mitotic activity, variable amount
- Cytoplasm
- Eosinophilia, diffuse or focal
- Glands
- Irregular, variable size, some dilated
- Simple atypical hyperplasia
- Haphazardly spaced in abundant stroma
- Complex atypical hyperplasia
- Closely spaced with decreased stroma
- Highly irregular outlines
- Frequent associated features
- Papillary infoldings into glands (no bridging)
- Decreased stroma
- Ciliated cells
- Squamous metaplasia

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**Complex hyperplasia**

**Simple hyperplasia**

**Complex atypical hyperplasia**
Endometrial intraepithelial neoplasia (EIN)

- Proposed by Mutter and associates
- Based purely on morphologic criteria
- Highly predictive values than WHO system
- Key potential advantage is to discriminate benign processes at low end of the spectrum (simple and non-atypical) from true neoplastic precursors

Endometrial intraepithelial neoplasia (EIN)

- Clonal proliferation of architecturally and cytological altered premalignant endometrial glands
- Prone to malignant transformation to endometrioid (type I) endometrial adenocarcinoma
- Management follows guidelines established for atypical endometrial hyperplasia
- 89-Fold increased cancer risk that those without EIN

Endometrial intraepithelial neoplasia (EIN)

- Diagnostic tissue should be obtained 2-4 wks after stopping exogenous hormones in patients on progestins
- Although computerized morphometry has been a useful tool in identifying features of EIN, interpretation using criteria at standard microscope is adequate
Endometrial carcinoma

- No effective methods of screening
- Pap test is ineffective due to lack of sensitivity
- Histopathologic evaluation of endometrial biopsy is very important

WHO classification

- Endometrioid CA
  - variant with squamous differentiation
  - villoglandular variant
  - secretory variant
  - ciliated cell variant
- Mucinous adenoCA
- Serous adenoCA
- Clear cell adenoCA
- Mixed cell adenoCA
- Squamous cell CA
- Transitional cell CA
- Small cell CA
- Undifferentiated CA
Endometrioid carcinoma

- Most common type (80%)
- Peri- or postmenopausal - mean age 60 years (only 5% occur <40 years)
- Associated with unopposed estrogen
- Gross:
  - Most arise in the corpus but some may originate in LUS
  - Single, 2 or more or diffuse thickening of the endometrium
  - Frequently on the posterior than the anterior wall

Risk factors

- Estrogens, both exogenous and endogenous, similar whether continuously or cyclically
- Tamoxifen: antiestrogenic effect in childbearing age and inducts endometrial inactivity or atrophy but in postmenopausal women may have weak estrogenic effect
- Endogenous risk factor: late menopause, low parity, obesity, HT, ovarian thecoma and granulosa cell tumor
- Polycystic ovary syndrome

<table>
<thead>
<tr>
<th>Histologic patterns</th>
<th>Endometrioid (type I)</th>
<th>Non-endometrioid (type II)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade</td>
<td>I-3</td>
<td>N/A</td>
</tr>
<tr>
<td>Behavior</td>
<td>Indolent</td>
<td>Aggressive</td>
</tr>
<tr>
<td>Average age (years)</td>
<td>59</td>
<td>66</td>
</tr>
<tr>
<td>Risk factors</td>
<td>Unopposed estrogen</td>
<td>Unknown</td>
</tr>
<tr>
<td>Precursor lesion</td>
<td>EIN</td>
<td>Serous EIC</td>
</tr>
<tr>
<td>P53 mutation</td>
<td>5-10%</td>
<td>80-90%</td>
</tr>
<tr>
<td>PTEN inactivation</td>
<td>55%</td>
<td>2%</td>
</tr>
<tr>
<td>Beta-catenin mutation</td>
<td>25-38%</td>
<td>Rare</td>
</tr>
<tr>
<td>Loss of ER and PR</td>
<td>27-30%</td>
<td>76-84%</td>
</tr>
</tbody>
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Lax SS. Vitale's Arch 1994
Glandular architectural patterns in endometrial compartment

Endometrioid carcinoma
- Other variants:
  - Villoglandular: cytologic features are same as typical endometrioid CA, usually grade I nuclei
  - Secretory
  - Sertoliform

Myometrial invasion
- Malignant glands have transgressed endometrial-myometrial junction into the underlying muscular uterine wall
- Endometrial-myometrial boundary is irregular
- Desmoplastic reaction is the primary diagnostic feature but often that myoinvasive elicits no desmoplastic response
- Do not include carcinoma involving adenomyosis in the depth calculation

Endometrioid carcinoma
- Other variants:
  - Squamous differentiation: at least 10% of tumor volume, prognosis can be predicted by the glandular grade alone since differentiation was shown to parallel that of the glandular component
  - Ciliated cells: rare, occasionally individual ciliated cells can be found. Only at least 75% of tumor cells are ciliated in order to call "ciliated cell carcinoma"

Myometrial invasion
- Endometrial carcinoma extending into foci of adenomyosis should not be considered invasive unless tumor cells extend outwards into the myometrium itself. In that case, depth of invasion is measured not from the point of adenomyotic transgression, but from the endometrial-myometrial junction underling the surface endometrium.
Myoinvasion in endometrial adenocarcinoma

Behavior and treatment
- Behavior of the variants is the same, grade for grade, as that of typical endometrioid adenocarcinoma
- Standard treatment is surgical
- Practices regarding in pelvic and paraaortic LN dissection, if F/S demonstrates:
  - Deep myometrial invasion
  - Cervical involvement
- Non-endometrioid type

Histologic grading - FIGO
- Grade I – 5% or less non-squamous solid growth pattern
- Grade II – 6% to 50% non-squamous solid growth pattern
- Grade III – more than 50% non-squamous solid growth pattern

Serous Adenocarcinoma
- Patients are 10 years older than in endometrioid CA
- Unassociated with estrogen stimulation
- Extrauterine spread as many as 75% at presentation
- Gross: generally the same as endometrioid CA, uterus is more frequently atrophic
- Histology:
  - Complex papillary, tufting, budding patterns
  - Fibrovascular cores covered by stratified epithelial cells
  - Psammoma bodies in 1/3
- Grade 3 nuclear features

Serous Adenocarcinoma
- Many involve endometrial polyps
- Myometrial, cervical invasion as well as LVI are common
- Background of atrophic endometrium
- May be associated with microscopic in situ lesion, EIC
- High frequency of p53 (80-90%) and p16 immunohistochemical study
- Mixed tumors, same prognosis as serous CA if at least 25% of the tumor has features of serous differentiation
Precursor lesions, serous endometrial intraepithelial carcinoma (serous EIC)

- Single and multiple layers of malignant cells that replace endometrial surface epithelium or glands
- Cytologic features resembling the cells of high-grade tumor yet lacking invasive component
- Commonly seen in endometrium adjacent to serous CA and also as carcinosarcoma, often occur within polyp
- Setting of atrophic endometrium

Precursor lesions, serous endometrial intraepithelial carcinoma (serous EIC)

- IHC: intense p53, high Ki-67 index, loss of ER/ and PR
- Frequently and specifically associated with concurrent serous adenoCA
- Capacity for peritoneal metastasis or metastasis to extraterine organs even without invasive component
- Even microscopic disease was associated with recurrence
- Diagnosis of EIC in endometrial biopsy is an indication for further evaluation
Clear cell Carcinoma
- Histology
  - Tubulocystic, glandular, papillary, solid patterns
  - Most have mixture of at least 2 patterns
  - Abundant clear or eosinophilic cytoplasm
  - Tubulocystic area frequently contain cells with “hobnail” appearance
  - Papillary cores have hyalinized stroma
  - High grade nuclei by definition

Mucinous adenocarcinoma
- >90% (at least 50%) of the cells must have intracytoplasmic mucin production
- Usually arise in conjunction with endometrioid component and thus considered within the endometrioid class of endometrial CA
- Usually well‐moderately differentiated
- Similar behavior to endometrioid

Mixed carcinoma
- It is common to find small areas of one histologic type in a tumor that is predominantly of another type
- If exceeds 10%, referred to “mixed carcinoma”

Carcinosarcoma (MMMT)
- Mixed tumor composed of epithelial elements and mesenchymal elements, both of them are histologically malignant
- History of prior pelvic irradiation (7–37%) with time interval between 10–20 years
Carcinosarcoma (MMMT)

- Gross, lack characteristic, more typically as a broad-based polyp often protruding through the cervix with smooth surface
- Microscopic:
  - Carcinomatous component corresponding to any Mullerian type, usually poorly differentiated serous CA
  - Stromal component, homologous or hertologous
  - Proportion of both components varies, any neoplasm composed of high grade sarcoma esp. heterologous should be extensively sampled to exclude

Carcinosarcoma (MMMT)

- Heterologous VS Homologous, variation in histologic grading and mitotic activity in the stroma have little bearing on the eventual outcome
- Epithelial elements may be prognostically significant with serous, clear cell or undifferentiated elements associated with worse prognosis

Carcinosarcoma (MMMT)

- Histogenesis:
  - Collision theory, independently arisen
  - Combination theory, arose from stem cells with ability to differentiate along both lines
  - Conversion theory, sarcomatous elements derived from carcinoma during tumor’s evolution
  - Similar to breast, urinary bladder = Metaplastic carcinoma or Carcinoma with sarcomatous metaplasia
  - Some authors now believed that it should be classified with endometrial adenocarcinoma
Synchronous endometrial and ovarian carcinoma

- Better prognosis of patients with synchronous primary tumors
- Presence of precancerous process is strong evidence of in situ genesis (EIN of Ut, Ov endometriosis or preexisting benign, borderline)
- Disparate histologic types (but not grade) are good evidence of independent primaries but similar histology cannot exclude independent primary
- Synchronous tumor that are regarded as metastasis are usually of high grade histologic grade

Endocervical VS Endometrial

- Endometrioid CA of endocervix is rare
- Association of AIS is helpful
- Endometrioid: vimentin/ER/PR +, CEA – or weak
- Endocervical: vimentin –, CEA +, ER – or weak
- P16 diffuse in endocervical and focal in endometrioid

Staging FIGO 2009

- Endocervical glandular involvement only should be considered as Stage I and no longer as Stage II.
- Positive cytology has to be reported separately without changing the stage.