Female Genital System
Part 2: Uterine Corpus

These photos are from the Galapagos Islands

Rex Bentley, M.D.
Duke University Medical Center
Durham, North Carolina
684-6423
Rex.Bentley@duke.edu
Goals for Today
At the end of today’s lecture you will be able to:

• List the common pathologic causes of abnormal endometrial bleeding
• Explain the relationship of endometrial hyperplasia to endometrial cancer
• Explain the role of estrogens in the development of endometrial hyperplasia and cancer
• Recognize the typical appearance of a leiomyoma
• Recognize and describe the pathology of endometrial disorders
Normal Endometrium

The endometrium varies in its appearance over time in the menstrual cycle.
The endometrium proliferates during the proliferative stage. Upon ovulation it switches into the secretory phase. If implantation doesn't happen the endometrium breaks down (menstrual phase).
Uterine Fundus: The Main Players

• Endometrium
  – Developmental
  – Endometritis
  – Endometriosis
  – Polyps
  – Dysfunctional Uterine Bleeding (DUB)
  – Hyperplasia
  – Carcinoma

• Myometrium
  – Adenomyosis
  – Leiomyoma (fibroids)
  – Leiomyosarcoma

Summary of what we will cover: rare
Normal uterus

This uterus has been cut in half coronally to reveal the endometrial cavity and endocervical canal.

- **Fundus**
- **Body**
- **Isthmus**
- **Internal cervical os**
- **External cervical os**

**Annotations:**
- Myometrium
- Endometrium
- Fallopian tubes come out up here.
Developmental Abnormalities

Many variations of fusion defects can be seen. Complete failure of the Mullerian ducts to fuse gives rise to two separate uteri ("uterus didelphys"), each with a cervix and single fallopian tube, and sometimes connecting to two separate vaginas. Partial fusion gives rise to bifid (also known as bicornuate) uterus, as seen above, and in the most minimal forms of fusion defect to a barely perceptible ridge at the fundus of the uterus.

Bifid Uterus

Pt can have normal pregnancies in one of these uteri.

Two separate endometrial cavities.
Endometritis

• Acute
  – Unusual, usually retained products of conception
  – Typically cured by removal of dead tissue.

• Chronic endometritis
  – STD’s
    • Often associated with pelvic inflammatory disease
  – IUD’s
    • Actinomyces
  – Treat infection and/or remove IUD
Chronic Endometritis

Plasma cells are not usually seen in the endometrium. If you see them = Chronic Endometritis.

Gonorrhea, chlamydia, and mycoplasmia are common causes.
Endometriosis

• Ectopic endometrium outside the uterus
• Major cause of pelvic pain, dysmenorrhea, and infertility
  – 5.5 million women in U.S. affected
  – Half of infertility patients
• Common sites
  – Ovaries
  – Fallopian tubes
  – Pelvic peritoneum
• Less common sites: lung, lymph nodes, bowel, etc

Also seen in the Lung, lymph nodes, bowel, skin -> it is very diverse, it can be almost anywhere. Unlike cancer it stops growing eventually.

This means you menstruate out of your mouth?
Endometriosis

• Etiology
  – ?Regurgitation
  – ?Metaplasia
  – ?Vascular dissemination

• Mechanism of injury
  – Repeated bleeding with menstrual cycle

• Inflammation
• Fibrosis, adhesions, and scarring
• Formation of large “chocolate” cysts (esp. in ovary)
  – May require surgical management

These pieces of endometrium undergo cycles of proliferation and breakdown. This cycle results in all of these ->

Theories on how it occurs. Endometrium is broken down monthly, some of it gets into the pelvic cavity.

Under the influence of hormones a lot of structures in the endometrium are capable of undergoing de novo development.

Some of these lesions (like in the brain) may have gotten there via the vasculature (but we don't know how).

Disorts surrounding tissue

15-20 cm in size.
The ovary and fallopian tube on each side are so distorted and fibrosed that they are nearly impossible to recognize. Some of the serosal surfaces still have dark maroon “powder burns” typical of active endometriosis.
Ovary, Endometriosis
“Chocolate Cyst”
Chocolate cyst

Endometrium lining chocolate cyst

The pigment is hemosiderin from broken down RBS's.
This patient developed a painful mass in a C-section scar, and the pain was worse each month during her menses.

Looks like endometrium, except it is in a location it shouldn't be in.
Endometriosis--Treatment

- **Hormonal tx:**
  - Progestins, oral contraceptives, pregnancy
  - GnRH analogs, menopause

- **Surgical excision of lesions**

- **Laser tx**

- **Pain meds (NSAIDs)**

   If you can get pregnant, endometriosis regresses.

   Menopause helps.

   Destroy the lesions.

   symptoms management.
Endometrial Polyps

- Sessile or pedunculated mass
- Composed of normal endometrium and fibrous stroma
- Common cause of abnormal bleeding in menopause and older
- Account for 25% of pts with abnormal bleeding

Stroma is replaced by fibrous tissue. These polyps are benign, but they cause bleeding. Bleeding is otherwise a sign of endometrial cancer.
Endometrial Polyp
Endometrial Polyp

totally benign

“Whole Mount” H&E stained section of endometrial polyp
Abnormal Uterine Bleeding

• Abnormal amount or timing of bleeding
  – Menorrhagia: bleeding too much or too long at time of period
  – Metrorrhagia: bleeding between periods
  – Menometrorrhagia: both!

• One of most common reasons women seek medical attention

• Experienced by most women at some point
Abnormal Uterine Bleeding

Large number of causes

- Leiomyomas
- Polyps
- Endometritis
- Hyperplasia/carcinoma
- Hormonal disorders (pituitary/hypothalamic)
- Complications of pregnancy
- Atrophy
- Coagulation disorders

These are the most common causes of bleeding.
Biopsy the endometrium with this thing. Its simple. Family med doc's can use it.
One would slip it right in, pull on a piston that sucks in some tissue for sampling.
Dysfunctional Uterine Bleeding

• “DUB”: abnormal bleeding with no identifiable “organic” cause

• Most related to anovulatory cycles
  – Continuous estrogen stimulates endometrium to grow.
  – Outstrips ability of stroma to support and breaks down, with bleeding.

Most DUB Pt's are anovulatory. They have follicles, but no ovulation. Can persist for a while. Pt is exposed to continuous estrogen but little progesterone. Estrogen makes the endometrium grow. Eventually the endometrium starts falling apart because it gets to big.
Anovulation

- Persistent proliferation leads to disordered growth of glands
Anovulation

- Persistent proliferation leads to disordered growth of glands
- And large ectatic vessels that bleed (and bleed, and bleed...)

Abnormal vessels, no muscle in the wall. Without muscles the vessels can't constrict when bleeding starts.
Anovulation can be a result of:
- Normal due to menopause
- Hypothalamic/Pituitary dysfunction
- Low weight women
- No understandable reasons
Endometrial Hyperplasia:
Precursor to Adenocarcinoma
Endometrial Hyperplasia

- Estrogen stimulates endometrial proliferation
- Hyperplasia caused by continuous estrogen exposure without progestin ("unopposed" estrogen)

The glands are outgrowing the stroma.
Endometrial Hyperplasia

• Risk factors:
  – Anovulation
  – Obesity
  – Diabetes Mellitus
  – Hypertension
  – Exogenous unopposed estrogenic agents (including tamoxifen—a weak estrogen agonist in the endometrium)
  – Estrogen secreting tumors
# Endometrial Hyperplasia

**Protective Effect of Progestins in Hormone Replacement Therapy**

<table>
<thead>
<tr>
<th>Estrogen</th>
<th>Progestin</th>
<th>Hyperplasia</th>
</tr>
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<tbody>
<tr>
<td>+</td>
<td>-</td>
<td>56%</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>0%</td>
</tr>
</tbody>
</table>

*The original thought was: Estrogen helps with the symptoms, so let's give Pt's only estrogen. Result: 5 yrs later most Pt's had hyperplasia (Bad).*

*Risk of having hyperplasia after 5 years of hormonal therapy.*
Endometrial Hyperplasia Classification

- Simple → No atypia
  → With atypia

- Complex → No atypia
  → With atypia
Endometrial Hyperplasia

- Endometrial Intraepithelial Neoplasia (EIN) is alternate concept/terminology
- EIN encompasses all of the atypical hyperplasias
Normal Proliferative Endometrium

20% of the tissue is gland compared to stroma.
Simple Hyperplasia

Glands are now more crowded.

Mild gland crowding
Marked gland crowding

A lot of gland crowding. They are "back to back"
Atypical Complex Hyperplasia

Pink cytoplasm. The glands look different.
<table>
<thead>
<tr>
<th>No atypia</th>
<th>Yes atypia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Simple/Complex Hyperplasia</strong></td>
<td><strong>Atypical hyperplasia</strong></td>
</tr>
<tr>
<td><strong>Progress to carcinoma</strong></td>
<td><strong>23%</strong></td>
</tr>
<tr>
<td>Rate of progression to adenocarcinoma on long term follow-up (10-20 years).</td>
<td>2%</td>
</tr>
</tbody>
</table>
Summary:
Pathogenesis of Endometrial Carcinoma

*We start out with Proliferative endometrium. We then go on to disorder and hyperplasia. The cells then begin looking atypical. Finally we develop adenocarcinoma.
*Estrogens drive the entire process.
*We can reverse the lesions with progestins. There are even a few adenocarcinomas that can be cured with progesterins.
*The ability to cure lesions with progestins declines as the lesions progress towards cancer.
Endometrial Cancer
<table>
<thead>
<tr>
<th></th>
<th></th>
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<tbody>
<tr>
<td>Corpus</td>
<td>40,100</td>
<td>7,470</td>
</tr>
<tr>
<td>Ovary</td>
<td>21,650</td>
<td>15,520</td>
</tr>
<tr>
<td>Cervix</td>
<td>11,070</td>
<td>3,870</td>
</tr>
<tr>
<td>Vulva</td>
<td>3,460</td>
<td>870</td>
</tr>
<tr>
<td>Vagina/other</td>
<td>2,210</td>
<td>760</td>
</tr>
</tbody>
</table>

- **Corpus** is the most common site.
- **Ovary** is the most common cause of death.
Endometrial Carcinoma

- “Endometrioid” type most common
- Peak age 55-65; rare <40
- Most arise from hyperplasia
- Risk factors similar to hyperplasia
- 2nd most common cancer in HNPCC (mismatch repair defects, Lynch syndr.)

Generally in post menopausal women.

Hereditary nonpolyposis colorectal cancer syndrome: results from a mismatch repair defect. Pt with endometrial cancer or colon cancer should be screened for this defect.
Endometrial Carcinoma

- Important feature of endometrial carcinomas is tendency to bleed
- This results in the patients coming to clinical attention early
- Most endometrial cancers are found at an early stage!
Carcinoma

Hemorrhagic -> Pt comes to the clinic early.
Endometrioid Adenocarcinoma

In this example, the cancer has replaced the endometrium in the right side of the photograph, but there is no invasion into underlying myometrium.

Growing along the surface. The majority of endometrial cancers are caught in this early stage.
Endometrioid Adenocarcinoma

“Cribriform” architecture—multiple gland lumina being formed within one large nest of tumor.
Endometrial Cancer
Mode of Spread

Pelvic and para-aortic nodes are primary sites of nodal metastasis.
## Endometrial Cancer

### 5 year survival

<table>
<thead>
<tr>
<th>Stage</th>
<th>Grade -1-</th>
<th>Grade -2-</th>
<th>Grade -3-</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>97%</td>
<td>66%</td>
<td>57%</td>
</tr>
<tr>
<td>IB</td>
<td>82%</td>
<td>71%</td>
<td>44%</td>
</tr>
<tr>
<td>II</td>
<td>80%</td>
<td>42%</td>
<td>12%</td>
</tr>
<tr>
<td>III/IV</td>
<td>25%</td>
<td>33%</td>
<td>17%</td>
</tr>
</tbody>
</table>

Note that both stage and grade are strong predictors of survival for endometrial cancer.

Stage = How big is the tumor? Does it invade anything?

Grade = level of differentiation.
Type II Carcinomas

- Papillary Serous and Clear Cell
- Not associated with Estrogen use
- Older population
- High grade aggressive tumors with much worse prognosis even when low stage.
- 5-10% of endometrial cancers are in this category
Carcinosarcoma

• Also known as **Malignant Mixed Mullerian Tumor (MMMT)**

• Very poorly differentiated carcinoma that has undergone differentiation into a mesenchymal cell type (skeletal muscle, fat, cartilage, etc)

• **Mixture of carcinoma and sarcoma**

• Very aggressive tumor with poor prognosis.
Carcinosarcoma

Skeletal muscle (cross-striations)

MMMT
Myometrium
Adenomyosis

- Extension of endometrium into myometrium
- Myometrium thickened
- Common cause of dysmenorrhea
- 20% of women

Half of the uterine wall. The cysts within the wall are focus of endometrium.

Pain with a period
Adenomyosis
Whole Mount

All of these holes are endometrium. Some can pass through the entire myometrium.
Leiomyomas ("Fibroids")

- Benign neoplasms of smooth muscle
- 30’s and 40’s peak age
- Often multiple and very large
- Extremely common
  - Present in 80% of uteri in peak age ranges
  - 25% of women symptomatic
  - Major indication for hysterectomy
Leiomyomas can occur in many different locations within the uterus, and their location determines how they present clinically.
Leiomyomas

Leiomyoma: Large pelvic mass on CT; typical white, whorled gross appearance, with the tumor bulging over the cut surface; and microscopic appearance—closely resembles normal smooth muscle.

Looks like normal smooth muscle.
Multiple Leiomyomas
Large Leiomyoma!

"When I said leiomyomas can be very large, I wasn't kidding!"
Leiomyomas

Clinical presentation
- Abnormal bleeding
- Pelvic pain/pressure
- Infertility

Treatment
- Hormone suppression
- Embolization
- Myomectomy
- Hysterectomy
Leiomyosarcomas

- Rare (0.1% of leiomyomas)
- Distinguished from leiomyomas by high mitotic rate, necrosis, and marked nuclear atypia.
- Behave like other high grade sarcomas
  - Local invasion
  - Distant blood-borne metastases
  - Poor prognosis
Summary

• Reviewed common non-neoplastic causes of abnormal uterine bleeding
• Defined endometriosis and described some of the common complications
• Described the progression of endometrial hyperplasia to adenocarcinoma
• Discussed the basic epidemiology of endometrial adenocarcinoma
• Described common pathologic lesions in the myometrium
The End
Gyn Part 2