Female Genital System
Part I: Vulva, Vagina, and Cervix

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Goals for today
By the end of today’s lecture you should be able to:

1. Identify common non-neoplastic diseases of the vulva and vagina based on clinical presentation and pathology
2. Recognize and describe the commonly occurring cancers of the vulva, vagina and cervix
3. Explain the role of human papilloma virus in cancers of the cervix
4. Explain the relationship of cervical dysplasia to cervical cancer
5. Describe the role of screening prevention of cervical cancer
Outline of lecture

1. Diseases of the Vulva
   - Developmental
   - Inflammatory
   - Infectious
   - Neoplastic

2. Diseases of the Vagina
   - Developmental
   - Infectious
   - Neoplastic

3. Diseases of the Cervix
   - Infectious
   - Non-neoplastic lesions
   - Neoplasms
     - Carcinoma
     - Dysplasia

4. Screening/Pap smears
Diseases of the Vulva

- Developmental
- Inflammatory Diseases
- Infectious
  - STD’s, see Dr. Hick’s lecture 6/9/11
  - HPV
- Neoplastic diseases
Developmental

• Abnormalities of sexual differentiation
  – Beyond scope of lecture, see specialized textbooks for details

• Middlesex: A Novel by Jeffrey Eugenides
Developmental

Imperforate Hymen

Bartholin’s cyst

Bartholin's glands: normal secretory glands located posteriolaterally on the vulva. Quite large cysts and abscesses can form due to inflammatory plugging of the glands.

Imperforate hymen


Secretory products are not released. Treated by perforation.

RX: open or remove gland entirely
Diseases of the Vulva

• Developmental
• Inflammatory Diseases
• Infectious
  – STD’s, covered elsewhere
  – HPV
• Neoplastic diseases
Inflammatory Diseases

• **Lichen Sclerosus**
  – Clinical
    • Postmenopausal
    • Itching, pain
    • White “parchment paper” like appearance
  – **Elevated risk of squamous cell carcinoma**
    • 10-15% develop carcinoma on follow-up
  – **Treated with topical steroids**

Pathophysiology -- unknown
Lichen Sclerosus

What 2 symptoms might have this patient complained of?

Features demonstrated
- White parchment like appearance
- Erythema
Lichen Sclerosus

- No rete pegs
- Homogenous, hyalinized layer of collagen
- Scant inflammation

Rete pegs: normal extensions of epithelium into dermis
Diseases of the Vulva

- Non-neoplastic
- Inflammatory Diseases
- Infectious
  - STD’s, covered elsewhere
  - HPV
- Neoplastic diseases
Vulva-HPV

• **Condyloma acuminata**
  = Anogenital warts
  = *Condyloma lata* is unrelated (syphilis)

• Usually **transmitted sexually**
  – Local control problem in immunosuppressed patients (HIV)
  – Can develop dysplasia as in cervix
  – See also lecture from Dr. Cardones 6/22 for additional information on HPV

Don't confuse condyloma acuminata (HPV induced vulvar skin lesions) with condyloma lata (syphilis induced vulvar skin lesions)

Can overgrow anogenital region in patients with depressed cell mediated immunity.

HIGH RISK HPV TYPES ONLY (16,18)
Condyloma Acuminata

Features demonstrated:
- Verrucous (warty) appearance
- Multifocality
Diseases of the Vulva

- Non-neoplastic
- Inflammatory Diseases
- Infectious
  - STD’s, covered elsewhere
  - HPV
- Neoplastic diseases
Neoplasms of the Vulva

• Vulvar Intraepithelial Neoplasia (VIN)
  – Aka “Dysplasia”
• Squamous cell carcinoma
• Paget’s Disease of the vulva
VIN

- **Dysplasia**, aka Bowen’s disease
- Graded as VIN-1, 2, or 3 (mild, moderate, severe dysplasia /carcinoma in situ)
  - Oncogenic HPV 16, 18 in high grade VIN
  - Do not usually cause condyloma acuminata!
- Presents with itching or pain
  - 50% asymptomatic
- White patch (leukoplakia), sometimes red or even hyperpigmented
- May remain non-invasive for many years.
- **Treatment**: Destroy lesion (surgery, laser, chemicals)

Based on lecture contents thus far, what is your differential diagnosis for an itchy or painful white area on the vulva?
**VIN-3**

Features demonstrated
- Full thickness dysplasia
- Koilocytic atypia (indicates HPV infection)
- Lack of basement membrane invasion

Normal

Both images are same magnification
Squamous Cell Carcinoma

• 90% of vulvar cancers
  – 3% genital tract cancers
  – 4000 cases/year, 800 deaths in US

• Risk factors
  – VIN
  – Lichen sclerosus
  – Smoking
  – History of cervical cancer

Cervical cancer development is promoted by the same high risk HPV strains (16,18) that cause vulvar neoplasia.

Take home
1. SCC accounts for the majority of vulvar cancer.
2. Vulvar cancer is a relatively uncommon cause of female genitourinary cancer.

Nobody should die of this disease -- it should in theory be caught early in everyone considering the accessibility of the vulva for examination and excision.
Squamous Cell Carcinoma

- Spreads first to local superficial groin nodes
- Risk of spread related to size and depth of invasion (i.e. stage)
- Low stage disease cured by local resection only.
Squamous Cell Carcinoma

Features of vulvar SCC demonstrated by this radical vulvectomy specimen:
- Erythematous, raised process
- Large, deeply invasive process

Why is asking your patient about his or her sexual history pertinent to this lesion?
Squamous Cell Carcinoma

Features demonstrated:
- Nests and tongues of malignant squamous epithelium
- Central keratin pearls
- Dermal invasion

Name two precursor lesions to SCC of the vulva.
Paget’s Disease

• Aka “Extramammary” Paget’s disease
• Unique form of intraepithelial adenocarcinoma
• Red, itchy lesions often mistaken for inflammation clinically

Differential diagnosis (4)
- Lichen sclerosis (has red parts)
- Contact dermatitis
- Vulvar intraepithelial neoplasia (can be red or white)
- Vulvar squamous cell carcinoma
Paget’s Disease

• Most (>95%) patients have no invasive component (all tumor cells limited to epidermis)
• Prognosis excellent unless invasive cancer found
• Treatment mostly symptomatic
• Note that although histologically indistinguishable from Paget’s disease of the nipple, this has a very different biology
Paget’s Disease of the Vulva

Large cells with pale cytoplasm (mucin containing), located within the epidermis

Features
- Mucinous halos surround nuclei
- Small clusters of neoplastic cells confined to epidermis
Diseases of the Vagina

• Relatively rare site of significant disease
  – Congenital anomalies
  – Infections
  – Cancers
Congenital Anomalies

• Septate or double vagina
• Gartner’s duct cyst (mesonephric duct remnants)
  – Located laterally (sidewalls)

**Septate or double vagina:**
Fusion of the paramesonephric (mullerian) ducts is required to form the normal uterus and upper vagina (recall that the lower vagina is derived from the urogenital sinus). Failure of these paired ducts to fuse can lead to a septate or double vagina. This abnormality is almost always accompanied by a double uterus. Risk factors include DES exposure, genetic syndromes, teratogens.

**Gartner’s duct cyst:**
Common lesions found on the lateral walls of the vagina. Typically fluid filled cysts that are 1-2 cm in size and localized submucosally. Important to keep these in mind because they are benign but on a differential that includes neoplastic and infectious processes.
Vaginal Infections

• Bacterial vaginosis
  – Most common cause of vaginal discharge,
    • 15-20% prevalence
  – Complex change in vaginal flora with loss of lactobacilli, overgrowth of anaerobes, and increase in pH
  – “Fishy” odor
  – Tx clindamycin or metronidazole

Treatment is indicated by the patient being bothered by odor/discharge.
Bacterial vaginosis-diagnosis

1. Homogeneous, thin, grayish-white discharge that smoothly coats the vaginal walls,
2. Vaginal pH greater than 4.5,
3. Positive whiff-amine test, defined as the presence of a fishy odor when 10 percent potassium hydroxide (KOH) is added to a sample of vaginal discharge,
4. “Clue cells” on saline wet mount.

“Clue cell”
Vaginal epithelial cell coated with adherent bacteria
Vaginal Infections

• Candidiasis
  – Also common, 75% lifetime incidence
  – Itching, “cottage cheese” discharge
  – Associated with recent antibiotic use
  – Treated with oral or intravaginal antifungal agents, many available over the counter. Fluconazole
Vaginal Infections

• Candidiasis
  – Dx: KOH prep, wet mount

Features
- Pseudohyphae
- Budding yeast forms
Vaginal Infections

- **Bacterial vaginosis**
- **Candidiasis**
- **Trichomonas vaginalis**
  - Sexually transmitted *protozoan*
  - 3-5 million cases/year in U.S.
  - Itching, pain, discharge
  - Motile-identified on wet prep!
  - Tx, *Metronidazole* or tinidazole—partner also should be treated
- **Other STD’s covered by Dr. Hicks**
Vaginal Infections

Trichomonas--diagnosis

Motile protozoa

What drug would you administer to treat this patient’s vaginitis?

http://www.youtube.com/watch?v=XVNJQZLJRJw

Check this video out and you will never forget Trichomonas is motile.
Vaginal Cancer

• Very uncommon \text{0.6 per 100,000 women yearly}
  – Most common primary tumor squamous cell carcinoma \text{associated with HPV 16,18}
  – Secondary spread from adjacent sites more common (gyn tract, colon, bladder)
Vaginal Cancer

- Sarcoma botryoides (embryonal rhabdomyosarcoma)
- Occurs in young children (<5 years)
- Rare but important to recognize—can be cured!

Locally invasive, can cause death by penetrating into the peritoneal cavity or obstructing the ureters leading to ARF.

Features demonstrated
- Frequently project out of vagina
- Polypoid, rounded, bulky
- Grapelike clusters (botryoides = grapelike)
Vaginal Cancer

• Clear cell carcinoma of vagina
  – Rare tumor almost exclusively seen in young women whose mothers took DES (diethylstilbestrol, a synthetic estrogen)
  – Important because it established principle of **trans-generational teratogenicity** for drugs

This cancer is not high yield for the wards, but the fact that it demonstrates the principal of trans-generational teratogenicity makes it board worthy. I suggest you check out some histologic images of the neoplasm online or on page 1016 in Robbins.
http://www.webpathology.com/image.asp?n=17&Case=543
Pathology of the Uterus

- Cervix (today)
- Endometrium (gyn part 2)
- Myometrium (gyn part 2)
Cervix

- **Infectious**
  - STDs
  - Any vaginitis will also involve cervix

- **Non-neoplastic lesions**

- **Neoplasms**
  - Dysplasia
  - Cancer
Cervix

• Infectious

• Non-neoplastic lesions
  – Ectropion
  – Squamous metaplasia
  – Nabothian Cysts
  – Endocervical polyp

• Neoplasms
  – Dysplasia
  – Cancer
**Squamocolumnar junction moves with age**

- **AT BIRTH**
  - Uterus
  - Endocervix
  - Columnar epithelium
  - Squamocolumnar junction at exocervix
  - Squamous cells

- **IN THE YOUNG ADULT**
  - Endocervix
  - Exocervix
  - Squamocolumnar junction
  - Ectropion with exposed columnar epithelium

- **IN THE ADULT**
  - Exocervix with restored squamo-columnar junction at original site
  - "Transformation zone" with regrowth of squamous epithelium

**Ectropion:**
- Glandular epithelium on ectocervix
- Often mistaken for cervical neoplasia.

**Post-menopausal**

- Probably a younger woman, hopefully they did not think this was cancer.

- The harsh exposures of the exocervix cause squamous metaplasia of any exposed columnar epithelium as women age. Thus, ectropion is not normally found in older post-menopausal women.

**Ectropion is a completely normal finding in younger women.**
Squamous Metaplasia

• Process by which endocervical mucinous columnar epithelium changes to squamous epithelium
• Completely normal, no neoplastic potential by itself, but…
• “Transformation Zone” (entire region that has undergone squamous metaplasia) is site of cervical dysplasias and cancers.

Pap smears MUST SAMPLE THE TRANSFORMATION ZONE!!
Early Squamous Metaplasia

- Stratified squamous, non-kertanizing epithelium
- Mucinous columnar epithelium
- Endocervical gland
Mature Squamous Metaplasia

Squamous epithelium has grown over endocervical glands
Nabothian cysts

- Squamous metaplasia grows over endocervical glands
- Mucin gets trapped in glands, leading to cystic dilation—“Nabothian cyst”
  - Can be very large
- Extremely common, of no clinical significance
Nabothian cysts

Endometrial gland duct blocked off by metaplastic squamous epithelium. Secretions back up in the papillary dermis resulting in the formation of a large cyst.
Endocervical Polyp

- Present as mass lesions or with bleeding, completely benign

Part of your differential for abnormal bleeding. (vaginal "spotting")

Normal looking cervical epithelium and glandular stroma that has formed a polyp. No cytologic features of malignancy.
Endocervical Polyp

Occur in 2-5% of adult women.
Rx if symptomatic: surgical removal.

Two masses protruding through cervical os.
Cervix

- Infectious
- Non-neoplastic lesions
- Neoplasms
  - Dysplasia
  - Cancer
Cervical Cancer

- 11,070 new U.S. cases in 2008 (estimated)
- 3,870 deaths
- Mean age 47
- Risk factors
  - Number of sexual partners
  - Male partners who have multiple previous partners
  - Early onset of sexual activity
  - History STD’s
  - Genital HPV lesions
  - Smoking
  - Immunosuppression
  - No Pap smear screening
Cervical Cancer

Features demonstrated:
- Highly infiltrative (note erosion of the cervical os)
- Hemorrhagic
Cervical Cancer

Uterine fundus

Tumor

- Arose in squamocolumnar junction
- Invaded the vagina
Most patients with high stage cervical carcinoma die due to local extension into the urinary tract. Obstruction of the ureters can cause post-renal azotemia and predispose patients to pyelonephritis/uresepsis.
Cervical Carcinoma

• 80-95% squamous cell carcinoma
• Remainder adenocarcinoma
• All contain HPV DNA
Squamous Cell Carcinoma
Cervical Cancer Staging

Stage 1: Limited to cervix
• 90% 5 yr survival

Stage 2: Beyond cx but not to pelvic wall or lower 1/3rd vagina
• 82% 5 yr survival

Stage 3: To pelvic wall or lower 1/3rd vagina
• 35% 5 yr survival

Stage 4: To mucosa of bladder or rectum, or beyond pelvis
• 10% 5 yr survival

*Staging (and survival) is based on the degree of invasion.*
Cervical Cancer--Treatment

--Surgery for stage 1

--Chemoradiation for stage 2-4
Cervical Dysplasia

Four Key Concepts!

1. Caused by HPV infection
2. Precursor to most if not all cervical cancers
3. Long interval to progression (up to 20 years or more)
4. Most will spontaneously regress
Cervical Dysplasia

Translating classification systems

Mild dysplasia → CIN-1 → Low grade SIL
Moderate dysplasia → CIN-2 → High grade SIL
Severe dysplasia → CIN-3
Carcinoma in-situ

CIN= “Cervical Intraepithelial Neoplasia”

Bethesda System, SIL= “Squamous Intraepithelial Lesion”
Dysplasia
Cervical Dysplasia

Features of dysplasia
- Nuclear enlargement
- Hyperchromasia
- Variation in nuclear size and shape
- Koilocytic atypia (if HPV-induced)

Translating this to the Bethesda system:
CIN I/II = Low grade squamous intraepithelial lesion (LSIL)
CIN III/CIS = High grade squamous intraepithelial lesion (HSIL)

This progression takes years (10-20+). This, in part, is the reason why the Pap smear has been so effective at reducing the tole of cervical cancer on American women.
The characteristic nuclear change with a perinuclear halo, indicative of HPV infection, is referred to as *koilocytic atypia.*

80% of LSIL and 100% of HSIL is associated with infection by high risk (16, 18, 31, 33, 45) strains of HPV.
## HPV & Neoplasia

>100 Known HPV types:

**Key concept:** “High Risk Serotype”

<table>
<thead>
<tr>
<th>Serotype</th>
<th>Disease association</th>
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<tbody>
<tr>
<td>6, 11 (“low risk”)</td>
<td>Genital warts (condyloma acuminata)</td>
</tr>
<tr>
<td>16, 18 (“high risk”)</td>
<td>Dysplasias, 65% cancers</td>
</tr>
<tr>
<td>31, 33, 45, others (&quot;high risk&quot;)</td>
<td>Dysplasias, 35% cancers</td>
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</table>

What causes condyloma lata?
Pathway to Cervical Cancer

Sexual Activity

HPV

HPV exposure (millions/yr)

Immune status
Genetic vulnerability
Other factors

Low-risk HPV (6,11) episomal infection

High-risk HPV (16, 18, others) viral integration

Condyloma acuminata (hundreds of thousands/yr)

CIN (million/yr)

Persistent infection

Higher grade CIN

Invasive cancer (10,500/yr)

Metastasis (5000/yr)

Eye sore, but you won't get cancer because of it.

© Elsevier. Kumar et al; Robbins Basic Pathology 8e - www.studentconsult.com
Cervical Cancer Screening: Success of the Pap Smear

- 1940: Cervical cancer most common cancer in women in U.S.
- Use of Papanicolaou (cytologic) screening lowered cancer rate by 75%
- 60% of patients with cervical cancer have not been screened in past 5 years or have never been screened

Pap smear is by far the most effective cancer screening and prevention technique in use
Death rates in women for common cancers in the U.S.
Pap Smear

- Surface of cervix lightly scraped or brushed
  - Smear on slide and fixed with alcohol, or
  - Transferred to liquid fixative and slide prepared in lab
  - Stained with Papanicolaou stain.
  - Can also be tested for high risk HPV

Robbins says:
- First smear should be at 21 years of age or within 3 years of onset of sexual activity followed by annual smears
- Women with three consecutive normal results may be screened every 2-3 years
- Women with high risk HPV serovars should have cervical cytology repeated every 6-12 months
- HPV testing is not indicated in women under 30 due to low specificity of results
Pap Smear

Normal
Pap Smear

High grade SIL
(severe dysplasia)
Cervical Dysplasia

1) Screening → Pap Smear
2) Confirmation → Colposcopy, Biopsy
3) Treatment → Destroy Lesion: freeze, burn, or excise

Colposcopy: Special examination of cervix with magnification and acetic acid or iodine to highlight abnormal areas for biopsy.

Images courtesy of Dr. Peter Cartwright, DUMC
Implementation of Pap screening markedly reduces rate of cervical cancer
Cervical Cancer

HPV vaccines

- Effective in preventing high grade CIN
- Approved by FDA for women age 9-26
- Less effective in older women already exposed to HPV
- Do not cover all oncogenic HPV types.
- Current recommendations are for vaccinated women to continue standard screening
Review
After today’s lecture, you should be able to:

1. Identify common non-neoplastic diseases of the vulva and vagina based on clinical presentation and pathology
2. Recognize and describe the commonly occurring cancers of the vulva, vagina and cervix
3. Explain the role of human papilloma virus in cancers of the cervix
4. Explain the relationship of cervical dysplasia to cervical cancer
5. Describe the role of screening prevention of cervical cancer
Take home message:

Please make sure female patients age 21 and older get cervical cancer screening!
End Gyn Part 1
Gardnerella vaginalis

A pleomorphic, gram-variable rod that causes vaginosis presenting as a gray vaginal discharge with a fishy smell; nonpainful. Mobiluncus, an anaerobe, is also involved. Associated with sexual activity, but not an STD. Bacterial vaginosis is characterized by overgrowth of certain bacteria in vagina. Treatment: metronidazole. Clue cells, or vaginal epithelial cells covered with bacteria, are visible under the microscope (see Image 13). I don’t have a clue why I smell fish in the vagina garden!
| Trichomonas vaginalis (see Image 10) | Vaginitis: foul-smelling, greenish discharge, itching and burning, do not confuse with Gardnerella vaginalis, a gram-negative bacterium that causes vaginosis | Sexual (cannot exist outside human because it cannot form cysts) | Trophozoites (motile) on wet mount | Metronidazole |
Vaginal carcinoma

1. Squamous cell carcinoma (SCC) — 2° to cervical SCC.
2. Clear cell adenocarcinoma — affects women who had exposure to DES in utero.
3. Sarcoma botryoides (rhabdomyosarcoma variant) — affects girls < 4 years of age; spindle-shaped tumor cells that are desmin positive.
4. Bartholin’s gland cyst — rare; pain in labia majora; can result from previous infection.
<table>
<thead>
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<th>Cervical pathology</th>
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<td>Dysplasia and carcinoma in situ</td>
<td>Disordered epithelial growth; begins at basal layer of squamo-columnar junction and extends outward. Classified as CIN 1, CIN 2, or CIN 3 (carcinoma in situ), depending on extent of dysplasia. Associated with HPV 16, 18. Vaccine available. May progress slowly to invasive carcinoma if left untreated. Risk factors: multiple sexual partners, smoking, early sexual intercourse, HIV infection.</td>
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<tr>
<td>Invasive carcinoma</td>
<td>Often squamous cell carcinoma. Pap smear can catch cervical dysplasia (koilocytes) before it progresses to invasive carcinoma. Lateral invasion can block ureters, causing renal failure.</td>
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(Reproduced, with permission, from Kantarjian HM et al. MD Anderson Manual of Medical Oncology. New York: McGraw-Hill, 2006, Fig. 24-4B.)
Gynecologic tumor epidemiology

Incidence—endometrial > ovarian > cervical (data pertain to the United States; cervical cancer is most common worldwide).

Worst prognosis—ovarian > cervical > endometrial.