**Pathology of the Vulva, Vagina and Cervix**

**CERVIX**

**Review of Normal Anatomy/Histology**

*Cervix*; Consists of ectocervix and endocervix
- Ectocervix: covered by stratified nonkeratinizing squamous epithelium
  - (note “ectocervix” is sometimes referred to “exocervix”)
- Endocervix: covered by simple columnar, mucus secreting epithelium

**Squamocolumnar junction:**
- The point at which the above two types of epithelia meet
- The location of the squamocolumnar junction (SCJ) varies with age and hormonal status. Under the influence of estrogen, it everts outward into the ectocervix during adolescence, pregnancy and the use of oral contraceptive pills. It regresses into the endocervical canal with menopause and other low estrogen states.

*Why does squamous metaplasia develop in the cervix?*

At puberty, the rise in estrogen levels leads to increased glycogen stores in the nonkeratinized squamous epithelium of the lower genital tract. Glycogen provides a carbohydrate source for lactobacilli which become a dominant vaginal flora. The bacteria produce lactic acid which lowers the vaginal pH to <4.5. This low vaginal pH is the suspected stimulus for squamous metaplasia, the ongoing replacement of columnar epithelium by squamous epithelium on the cervix.

Relatively undifferentiated cells underlying the cervical epithelia are the precursors of the new metaplastic cells which differentiate further into squamous epithelium. Squamous metaplasia is most active during adolescence and pregnancy.

**Transformation zone:** band of squamous metaplasia lying between the original (prepubertal) squamocolumnar junction and the new (current) squamocolumnar junction.

*The transformation zone is vulnerable to HPV infection, cervical dysplasia and cervical cancer*
**Endocervical canal:** connects the internal and external cervical os, from the squamocolumnar junction to the upper end of endocervix

**Cervical squamous epithelium – background for students**

*Divided into four layers:*
- Superficial squamous cells: at the surface with small nuclei and large amount of cytoplasm
- Intermediate squamous Cells
- Parabasal cells
- Basal cells: at the base with larger nuclear and small amount cytoplasm (high N/C ratio), able to proliferate

Squamous cell maturation
Estrogen: stimulates squamous cells to mature by taking up glycogen
Squamous cell maturation:
- Cells moving from basal layer to upper layer, become superficial cells and eventually shed;
- Shedding cells release glycogen which is used by vaginal flora for growth and produce a drop in pH
- Cervix responds to chemical changes, under the effect of estrogen by squamous metaplasia (forming transformation zone)

**Pap smear - Papanicolaou test**
Screening test and the most successful test to eradicate cervical cancer. It mainly detects squamous cell lesions, including treatable precursor lesions (cervical intraepithelial neoplasia [CIN]; squamous intraepithelial lesions [SIL]) and carcinoma. It prevents cervical cancer by allowing identification and treatment of precancerous lesions, and making an early diagnosis of cervical cancer

**Human papillomavirus (HPV)**
HPV is a DNA virus
HPV virus typing is based on its DNA sequences and subgroups

- **Low risk types:** 6, 11, 42, 44, 53, 54, 62, 66, associated with Condylomas.
- Lesions associated with low risk HPV usually regress, and only rarely persist

- **High risk types:** 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, lesions associated with high risk HPV may regress, persist or progress to precancerous lesions

High risk HPV express E6 and E7 proteins which results in neutralization of the functions of the tumor suppressor genes p53 and Rb

**Summary of HPV infection**
*Early phases of infection with all HPV types likely involve episomal viral propagation throughout a polyclonal epithelial field, with an LSIL cytology. Oncogenic types of HPV are prone to subsequent genomic integration of virus and promote monoclonal outgrowth of cells driven by transforming viral proteins (E6/E7) with progression to HSIL.*
CIN and cervical carcinoma
Both lesions are associated with human papillomavirus (HPV) infection. Infection depends on both host and virus characteristics.

Risk factors
- Early age at first intercourse
- Multiple sexual partners
- Increased parity
- Male partner with multiple previous partners
- High-risk HPV types and persistent detection of high-risk HPV types
- Oral contraceptive and nicotine
- Genital infections (Chlamydia)

Both cervical intraepithelial neoplasia (CIN) and cervical cancer arise most frequently in the transformation zone.

Condyloma – “wart” strongly associated with HPV 6,11
In cervix may be flat or exophytic (condyloma acuminatum)
CIN is divided into:

**Low grade dysplasia:**
Mild dysplasia (CIN I) – low grade squamous intraepithelial lesion (LSIL)

**High grade dysplasia:**
Moderate dysplasia (CIN II) and severe dysplasia (CIN III) - high grade squamous intraepithelial lesion (HSIL)

**Koilocytes**
Squamous cells infected by human papillomavirus
Morphologic features:
- Nuclear enlargement (two to three times normal size)
- Irregularity of the nuclear membrane contour
- Hyperchromasia
- A clear area around the nucleus- perinuclear halo.

**Histology of cervical dysplasia**
Low grade dysplasia:
- CIN I/LSIL: Flat lesions with koilocytic atypia “flat condyloma”
- High grade dysplasia/HSIL: variable nuclear size, loss of cell polarity, hyperchromasia and **high N/C ratio**
- CIN II: Atypia in >1/3 epithelium
- CIN III: Atypia in >2/3 epithelium

**Types of cervical cancer**
Squamous cell carcinoma is most common, followed by adenocarcinoma (2nd most common)

**Epidemiology of cervical squamous cell cancer:**
Most common histologic type of cervical cancer
Caused most cancer deaths in US women in the 1950’s.
Mortality from cervical squamous cell carcinoma has MARKEDLY declined. The decline in death rate is due to Pap test screening and early detection of preinvasive lesions.
There are 13,000 invasive carcinomas and 1 million squamous intraepithelial lesions (SILs) diagnosed in US per year.
Most women who are diagnosed with advanced squamous cell carcinoma of the cervix have never had a PAP smear, or the past smear was many years ago

**Symptoms of cervical squamous cell carcinoma:** vaginal bleeding, leukorrhea, dyspareunia, dysuria
With advanced disease tumors invade through the wall of the uterus. Invade into the bladder, blocking ureters resulting in hydronephrosis and renal failure (post-renal, obstructive renal failure)

**Cervical adenocarcinoma**
2nd most common cervical cancer with recent increased in detection / incidence.
Approximately 60% of glandular lesions have an associated squamous lesion. The pathogenesis is similar to squamous lesions, (association with HPV infection) and it is highly associated with HPV 18.
Cervical cancer staging
Stage 0: carcinoma in situ
Stage I: confined to cervix
Stage II: extends beyond cervix but not to pelvic wall, involves vagina but not lower 1/3
Stage III: extends to pelvic wall, involves vagina lower 1/3.
Stage IV: extends beyond true pelvis or involves bladder or rectum.

HPV vaccine
Approved and licensed by FDA in 2006. It is a recombinant vaccine produced from non-infectious, DNA-free, virus-like particles to induce high levels of serum antibodies. Bivalent vaccine is specifically targeted to HPV 16 and 18, the type most associated with cervical high grade dysplasia and malignancies. Quadrivalent vaccine is targeted to HPV 16, 18 and 6, 11. (6 and 11 protect against the development of condyloma.) Ideally patients should be vaccinated before the onset of sexual activity, when they may be exposed to HPV.

Vulva
Vulvar intraepithelial neoplasia
Spectrum of dysplastic changes in vulvar skin, analogous to dysplasia of cervix. Classified as:
-Low grade: Mild dysplasia (VIN I), or condyloma
-High grade: Moderate dysplasia (VIN II) and severe dysplasia (VIN III)
-Carcinoma in situ/ (VIN III)
VIN with high-risk HPV infection in 90% of cases
Risk of malignancy is higher in older or immunosuppressed women

Squamous Cell Carcinoma of Vulva
Uncommon
VIN and HPV are risks
Another risk factor for carcinoma of the vulva is “ Lichen sclerosis”

Lichen Sclerosis (Chronic Atrophic Vulvitis)
Clinically occurs in any age; most common in postmenopausal
Presents as smooth white plaques (leukoplakia), and resembles parchment paper.
Histology: Thinning of epidermis, fibrotic dermis and dermal inflammation
Not pre-malignant but advanced disease is associated with increased risk of developing squamous cell carcinoma.

Lichen Simplex Chronicus of the Vulva
Clinically presents as leukoplakia, thick leathery skin.
Histology: Epithelial thickening (hyperplasia), expansion of stratum granulosum, dermal lymphocytic infiltrates and hyperkeratosis
Underlining cause is non-specific, may be caused by chronic scratching/ itching
Paget Disease of Vulva
“extramammary Paget disease”
Arises from intra-epidermal progenitor cells
Presents as erythematous, pruritic, ulcerated vulvar skin
Histology: intraepidermal proliferation of single malignant cells with clear cytoplasm, filled with glycosaminoglycans; “carcinoma in-situ”, no underlying/invasive tumor
Cells are PAS positive, keratin positive (marker for epithelial cells)

Important histologic differential diagnosis is Melanoma
Melanoma cells are S-100 positive (normally present in cells derived from the neural crest); keratin and PAS negative
**Summary: Vulvar Leukoplakia**

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<tr>
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<th>Lichen Sclerosis</th>
<th>Lichen Simplex Chronicus</th>
<th>Squamous Cell Carcinoma</th>
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<tbody>
<tr>
<td><strong>Histology</strong></td>
<td>Thinning of epidermis</td>
<td>Hyperplasia of epithelium</td>
<td>Infiltrating nests of malignant cells arising from squamous epithelium lining vulva</td>
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<td><strong>Etiology</strong></td>
<td>Likely autoimmune</td>
<td>Chronic irritation</td>
<td>HPV Non-HPV (Lichen Sclerosis)</td>
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<td><strong>Prognosis</strong></td>
<td>Small risk of progression to cancer, elderly women</td>
<td>Benign</td>
<td>Invades and spreads, regional LNs and beyond</td>
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<tr>
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<th><strong>VULVA</strong></th>
<th><strong>VAGINA</strong></th>
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<tbody>
<tr>
<td>Development of Squamous Cell Carcinoma?</td>
<td>yes</td>
<td>yes</td>
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<tr>
<td>How common?</td>
<td>3% of all female genital cancers</td>
<td>Extremely uncommon</td>
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<tr>
<td>Population</td>
<td>&gt;60 years old</td>
<td>&gt; 50 years old</td>
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<tr>
<td>Risk Factor(s)</td>
<td>a) High risk HPV 16-18</td>
<td>High risk HPV</td>
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<td>b) Non-HPV related: Lichen Sclerosis</td>
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<td>Precursor</td>
<td>Vulvar intraepithelial neoplasia (VIN)</td>
<td>Vaginal intraepithelial neoplasia (VIN)</td>
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<td>Presentation</td>
<td>Leukoplakia</td>
<td>Vaginal bleeding, discharge</td>
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<tr>
<td>Metastases</td>
<td>Regional Lymph Nodes</td>
<td>Regional Lymph Nodes lower 2/3 - Inguinal, upper 1/3 - Iliac</td>
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Vagina

**Squamous Cell Carcinoma (SCC)**
Primary SCC uncommon in the vagina, need to rule out metastatic carcinoma or cancer extending from adjacent tissue such as cervix  
Epidemiology: women usually >60 years old  
Risk factor: high risk HPV  
Gross: Plaque like mass

**Clear cell adenocarcinoma of vagina**
Rare malignancy  
Occurs in young women, associated with Diethylstilbestrol (DES) exposure in utero  
*DES = synthetic estrogen; multiple uses including to prevent adverse outcomes in women with prior miscarriages 1940s-1960s*  
Precursor lesion: Vaginal adenosis - Remnant of cervical type glandular epithelium in vaginal mucosa

**Embryonal Rhabdomyosarcoma (Sarcoma botryoides)**
Rare tumor, a subtype of embryonal rhabdomyosarcoma, occurs in the walls of hollow, mucosa lined structures, such as the nasopharynx, common bile duct, urinary bladder of infants and young children and in the vagina in females, typically younger than age 8. Name comes from the gross appearance of "grape bunches" (botryoid in Greek).  
*Clinical examination: Polypoid mass filling and protruding out of the vagina. Microscopically: Small tumor cells with oval nuclei, and occasional striations; tumor cells also form “cambium layer” beneath vaginal epithelium (tumor cells are crowded in a distinct layer beneath the vaginal epithelium). Immunohistochemistry: cells are Desmin, myogenin positive, reflecting skeletal muscle differentiation. Pathogenesis – most likely dysregulation of genes that control skeletal muscle differentiation*