



Pathology of cervix

Lecture 8

430 Pathology Team

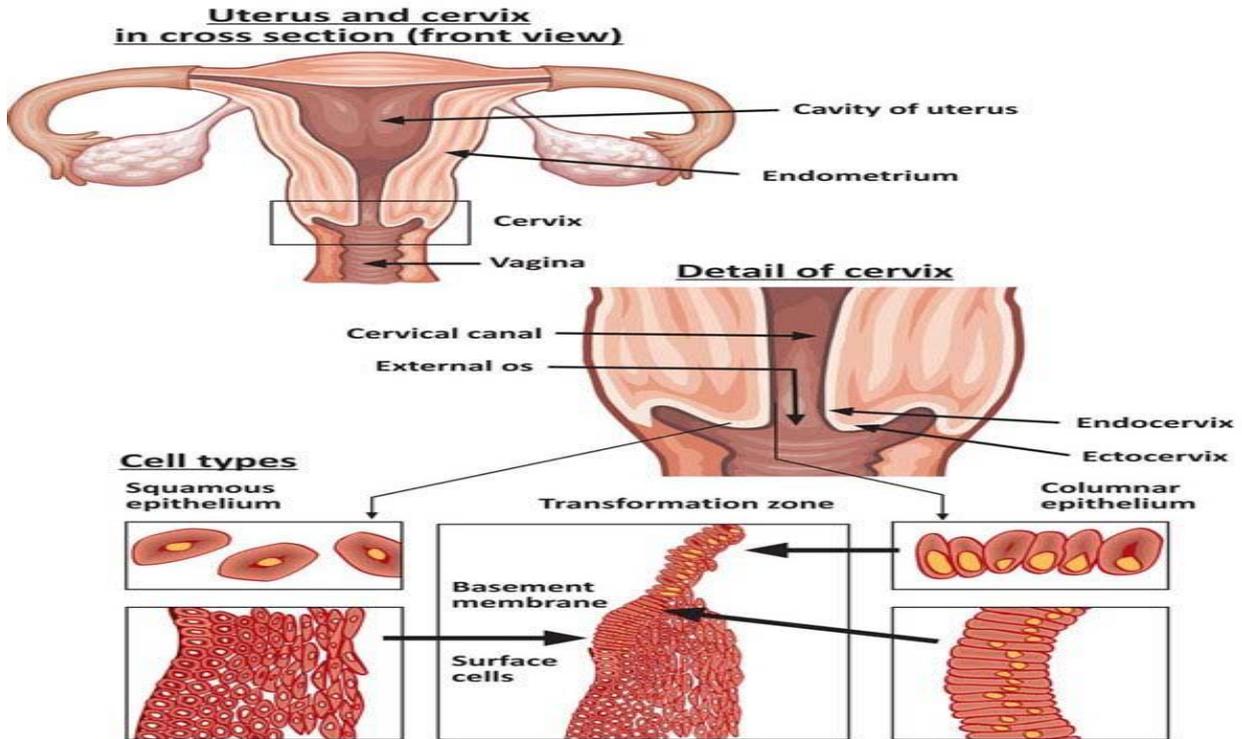
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Red: Doctors' and important notes.

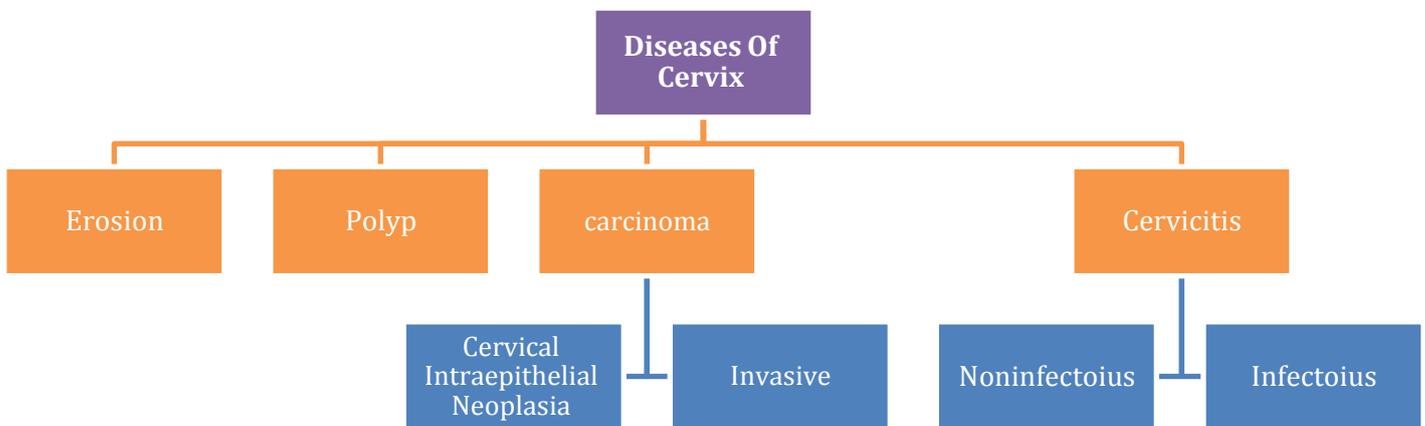
Green: Team notes.

Anatomy:



The cervix is divided into ectocervix and endocervix. The endocervix is lined by columnar epithelium while the ectocervix is lined by Squamous epithelium.

Pathology:



Erosion/Ectropion:

- Ectropion is characterized by columnar epithelium replacing squamous epithelium, grossly resulting in an erythematous area while metaplasia is characterized by squamous epithelium replacing the columnar epithelium and it is very common.
- It is a typical response to a variety of stimuli including hormones, chronic irritation and inflammation (chronic cervicitis).
- It is benign and has no malignant potential.

Cervical polyp:

- This is a small, pedunculated, often sessile mass.
- Most **originate from the endocervix** (endocervical polyps) (**lined by columnar epithelium**) with a few from the ectocervix (ectocervical polyps) (**lined by squamous epithelium**).
- They are **inflammatory proliferations** of cervical mucosa and are **not true neoplasms (benign no malignant potential)**.
- The lesion is characterized by overgrowth of benign stroma covered by epithelium.
- Endocervical polyps are **covered by** endocervical, **squamo-columnar or metaplastic squamous epithelium** while ectocervical ones are covered by stratified squamous epithelium.
- The stroma contains thick-walled blood vessels and fibrous and some inflammatory cells.
- **Most will cause bleeding especially if there is erosions.**

Cervicitis:

- Inflammation of cervix.
- Can be non-infectious or infectious.

1. Noninfectious (Nonspecific) Cervicitis:

Definition: this is inflammation of the cervix caused by chemical (e.g. douche, deodorant) or mechanical (e.g. tampon, diaphragm) irritation. It is often acute but may be chronic.

Clinical appearances:

- Noninfectious cervicitis is often asymptomatic.
- The cervix appears red and swollen

Histology:

- The histological features are **nonspecific**. The **inflammatory infiltrate** may comprise neutrophils or plasma cells and lymphocytes or a combination of these cells.
- **Squamous metaplasia** of the endocervical glandular epithelium is **common in chronic cervicitis**. Often some of the mucous glands are obstructed and dilate to form mucus-filled cysts called **nabothian cysts**.

2. Infectious cervicitis:

- Can be caused by various organisms e.g. staphylococci, enterococci, Gardnerella vaginalis, Trichomonas vaginalis, Candida albicans and Chlamydia trachomatis.
- Most often involves the endocervix.
- Is often asymptomatic, may manifest as **vaginal discharge**

A. Candidiasis (moniliasis):

- Common form of vaginitis /cervicitis.
- Caused by Candida albicans, a normal component of the vaginal flora.
- Associated with diabetes mellitus, pregnancy, broad spectrum antibiotic therapy, oral contraceptive use and immunosuppression.
- Characterized by **white patchy mucosal lesions** with thick white discharge and vulvovaginal pruritis.
- **Pregnant woman should be treated and the baby should be delivered by cesarean section along with HSV type 2 or the baby will get it.**

Histology:

Colonies of the fungus are present on the surface and extend into the epithelium but not into the underlying tissues. Mild edema and chronic inflammatory cells are present. Ulcers may develop. Cytological smears show (**spores**) yeast forms and branching **pseudohyphae**

B. Trichomoniasis:

- Caused by a unicellular flagellated protozoan **that is pear shaped**, Trichomonas vaginalis. It is sexually transmitted disease
- Involves the **vagina and cervix** also.

Clinical presentation:

Most infections are **asymptomatic** and pass unnoticed. Occasionally, a copious, thin, frothy, yellow green to gray offensive discharge is produced. There may be vulvas itching or burning or dyspareunia (**painful sexual intercourse**)

Histology:

Presence of an inflammatory infiltrate of lymphocytes and plasma cells. The organisms are not seen in biopsies because they do not invade the vaginal wall. Diagnosis is made by examination of a saline wet preparation in which the motile trophozoites are seen. The organism can also be found in Pap-stained vaginal smears.

C. Chlamydia trachomatis Cervicitis:

- Chlamydial cervicitis is the most common sexually transmitted disease in the developed countries. It may coexist with Neisseria gonorrhoea infection.
- Chlamydia trachomatis is an obligate, **gram-negative intracellular pathogen**.
- It is a **frequent cause of pelvic inflammatory disease**.
- Is most often asymptomatic.
- Chlamydial infection may also cause a condition known as lymphogranuloma venereum (**infectious disease caused by a species of chlamydia bacterium; transmitted by sexual contact characterized by genital lesions and swelling of lymph nodes in the groin**)

Clinical appearances:

The disease may be symptomatic or asymptomatic. In symptomatic cases there is a mucopurulent cervical **discharge with a reddened, congested and edematous cervix**. It may be associated with urethritis.

D. Herpes simplex virus (HSV) Cervicitis:

- HSV **Type 2** infection accounts for majority of genital herpes cases and is spread by sexual contact.
- It **always produces vesicles** and **ulcers** that can involve the cervix, vagina, vulva, urethra and perianal skin.

E. Human papilloma virus (HPV) Infection:

- HPV infection of the cervix is common.
- Over 20 serotypes infect the female genital areas. They cause a variety of different lesions with the different serotypes.

Clinical behavior:

HPV infection is **associated with increased risk of subsequent cervical cancer** and so long-term follow-up with attention to the cervix, vagina and vulva is necessary.

HPV infection may cause any of the following depending on the serotype

1. **Condyloma**. This develops in the squamous epithelium of the ectocervix and in foci of squamous metaplasia in the endocervix. The lesions may be flat or exophytic (**growing outward**) condylomma acuminatum. Can be caused by any HPV serotype but more commonly by types **6 and 11**.
2. **Mild dysplasia** is usually caused by "**low risk**" HPV serotypes, **6 and 11**.
3. **High- grade dysplasia** is caused by "**high risk**" HPV (**types 16 and 18**) and moderate risk HPV (types **31, 33, 35**).

Cervix Carcinoma:

- One of the major causes of cancer-related death in women, especially in developing world.
- Most common cervical cancer is squamous cell carcinoma. Other types are adenocarcinoma, neuroendocrine carcinoma etc.
- Nowadays there is dramatic improvement because of early diagnosis and treatment.
- The wide use of PAP screening lowered the incidence of invasive cancer.

Precancerous lesion:

- All invasive squamous cell carcinomas arise from pre-cancer epithelial changes referred as Cervical Intraepithelial Neoplasia (CIN) (**histological term and has three grades**) or squamous intraepithelial lesions (SIL) (**cytological term and has two grades**).
- Squamous Intraepithelial Lesion (SIL) is the pre-cancerous (non invasive) lesion and detection of these lesions made curative treatment possible.
- **Not all cases of CIN progress to invasive cancer.**
- they do not invariably progress to cancer and may spontaneously regress,
- the risk of persistence or progression to cancer increases in the high grade precancerous lesions;
- they are associated with **papillomaviruses**, and high-risk HPV types are found in increasing frequency in the higher-grade precursors

1. CIN:

- Cytological examination can detect CIN (SIL) long before any abnormality can be seen grossly.
- Pre-cancer changes can precede the development of an overt cancer by many years.
- CIN lesions may begin as Low Grade CIN and progress to High Grade CIN, or they might start as high grade lesion.

Histology:

On the basis of histology, pre-cancer lesions are graded as follows depending on the thickness of the atypical cells:

- CIN I : Mild Dysplasia (**atypical epithelium involve the lower third**)
- CIN II : Moderate Dysplasia (**atypical epithelium involve the two thirds**)
- CIN III : Severe Dysplasia and Carcinoma in situ (**atypical epithelium involve the whole thickness**).

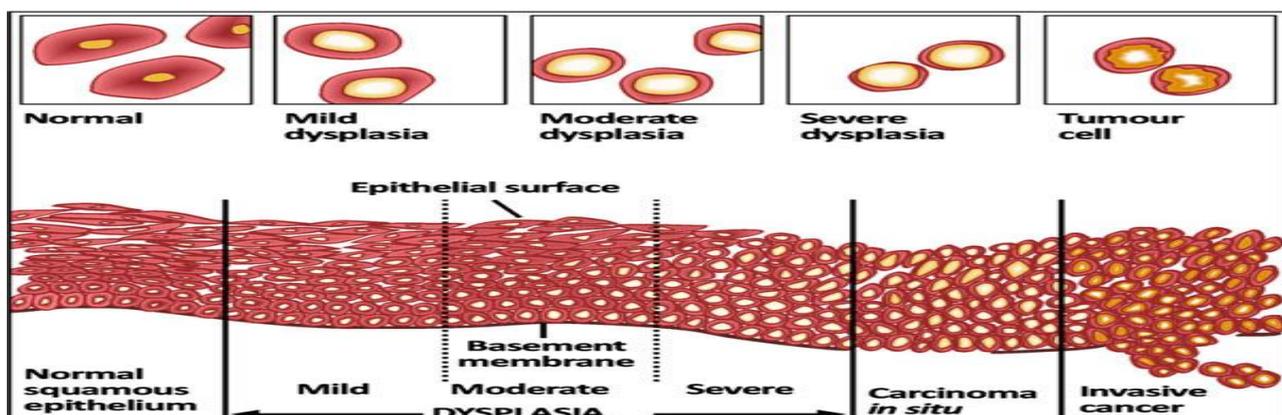
Cytology screening for precancerous lesions:

The cervix is examined and the cells lining the cervical wall at the transformation zone are scrapped/sampled with a spatula and then spread on a slide. They are then fixed, stained (Papanicolaou stain) and examined under a light microscope.

Cytology Pap Screening:

In cytology smears we separate pre-cancer lesions into two groups:

1. Low Grade SIL 1-5 % become invasive
2. High grade SIL incidence is 6-74%



Risk Factors:

- Early age at first intercourse
- Multiple sexual partners
- A male partner with multiple previous sexual partners
- Persistent infection by high risk papillomaviruses
- Some other risk factors; **low socioeconomic groups**
- Rare among virgins, multiple pregnancies.

Causes:

- HPV can be detected in 85 -90 % of pre-cancer lesions
- High risk types HPV: **16, 18, 31, 33, 35**, 39, 45, 52, 56, 58, and 59.
- Low risk types HPV: **6, 11**, 42, 44. These types result in condylomas.
- The cause is determined to be HPV virus .The HPV is the number one reason for abnormal cells of the cervix.
- **HPV** is a skin virus, which **results in warts**, common warts, flat warts, genital warts (condylomas), planter warts, and precancerous lesions.

Signs:

- There **are no visible symptoms** that you have dysplasia of the cervix till late stages, without a Pap smear or Pap exam.
- This is why we should have regular pap exams, as to detect any abnormal cells.

Screening:

- The Pap smear detects early HPV infection.
- The common testing procedure for HPV infection is an annual pap exam.
- There is the HPV **DNA ISH (in situ hybridization)** test, the Diegene Hyprid Capture test. **This test will determine whether you carry high or low risk strains of the virus.**

2. Cervical Carcinoma ,Invasive:

- 75 -90% of invasive cancers are **Squamous cell carcinomas**, which generally evolve from pre-cancer CIN. The remainders are Adenocarcinoma **both are caused by HPV virus especially the high risk group 16, 18.**
- Squamous cell cancers are appearing in increasingly younger women, now with a peak incidence at about 45 years, about 10-15 years after detection of their precursors.

Morphology:

- Mainly in the region of the **transformation (junctional) zone**, and range from microscopic foci of early stromal invasion to grossly frank tumors encircling the Os .
- The tumors may be invisible or exophytic.
- Cervical carcinomas are graded from 1 to 3 based on cellular differentiation and staged from 1 to 4 depending on clinical spread.

Staging:

- Carcinoma in Situ = **stage 0 (without infiltration)**
- Confined to the cervix = **stage 1 (with infiltration but still in the cervix)**
- Extension beyond the cervix without extension to the lower third of Vagina or Pelvic Wall = **stage 2**
- Extension to the pelvic wall and / or lower third of the vagina = **stage 3**
- Extends to adjacent organs = **stage 4**

Clinical Course:

- Many of cervical cancers are diagnosed in early stages, and the vast majority is diagnosed in the pre-invasive phase.
- More advanced cases are seen in women who either have never had a Pap smear or have waited many years since the prior smear.

Survival:

Laser (radiotherapy) or cone biopsy is the most effective method of managing patients with High grade SIL (low stage) in cancer prevention. A cone biopsy is a surgical procedure in which a cone-shaped tissue sample from the cervix is removed for examination. Also called cervical conization, a cone biopsy is done to diagnose cervical cancer or to remove cancerous or precancerous tissue.

Summary

- **Erosion/Ectropion:** is characterized by columnar epithelium replacing squamous epithelium, grossly resulting in an erythematous area while metaplasia is characterized by squamous epithelium replacing the columnar epithelium and it is very common. It is benign and has no malignant potential.
- **Cervical polyp:** most originate from the endocervix (endocervical polyps) (lined by columnar epithelium) with a few from the ectocervix (ectocervical polyps) (lined by squamous epithelium). They are not true neoplasms. The lesion is characterized by overgrowth of benign stroma covered by epithelium.
- **Cervicitis:** can be non-infectious or infectious.
- **Noninfectious (Nonspecific) Cervicitis: Clinical appearances:** noninfectious cervicitis is often asymptomatic. **Histology:** the inflammatory infiltrate may comprise neutrophils or plasma cells and lymphocytes or a combination of these cells. Squamous metaplasia of the endocervical glandular epithelium is common in chronic cervicitis. Often some of the mucous glands are obstructed and dilate to form mucus-filled cysts called nabothian cysts.
- **Infectious cervicitis:** can be caused by various organisms. Most often involves the endocervix. It is often asymptomatic, may manifest as vaginal discharge
- **Candidiasis (moniliasis):** associated with diabetes mellitus, pregnancy, broad spectrum antibiotic therapy, oral contraceptive use and immunosuppression. It is characterized by white patchy mucosal lesions with thick white discharge and vulvovaginal pruritis. **Histology:** cytological smears show (spores) yeast forms and branching pseudohyphae
- **Trichomoniasis:** protozoan is pear shaped, Involves the vagina and cervix. **Clinical presentation:**
- Most infections are asymptomatic and pass unnoticed. Occasionally, a copious, thin, frothy, yellow green to gray offensive discharge is produced.
- **Chlamydia trachomatis Cervicitis:** it is the most common sexually transmitted disease in the developed countries Trachomatis is an obligate, gram-negative intracellular pathogen. It is a frequent cause of pelvic inflammatory disease. It may cause a condition known as lymphogranuloma venereum
- **Herpes simplex virus (HSV) Cervicitis:** HSV Type 2 infection accounts for majority of genital herpes cases and is spread by sexual contact. It always produces vesicles and ulcers
- **Human papilloma virus (HPV) Infection:** it is associated with increased risk of subsequent cervical cancer. **it may cause Condyloma** more commonly by types 6 and 11. **Mild dysplasia** is usually caused by "low risk" HPV serotypes, 6 and 11. **High- grade dysplasia** is caused by "high risk" HPV (types 16 and 18) and moderate risk HPV (types 31, 33, 35).
- **Cervix Carcinoma:** most common cervical cancer is squamous cell carcinoma. Other types are adenocarcinoma, neuroendocrine carcinoma etc. All invasive squamous cell carcinomas arise from pre-cancer epithelial changes referred as Cervical Intraepithelial Neoplasia (CIN) or squamous intraepithelial lesions (SIL). Not all cases of CIN progress to invasive cancer. They are associated with papillomaviruses, and high-risk HPV types are found in increasing frequency in the higher-grade precursors.
- **CIN:** CIN lesions may begin as Low Grade CIN and progress to High Grade CIN, or they might start as HG lesion. On the basis of histology, pre-cancer lesions are graded as follows depending on the thickness of the atypical cells: CIN I : Mild Dysplasia (atypical epithelium involve the lower third), CIN II : Moderate Dysplasia (atypical epithelium involve the two thirds), CIN III : Severe Dysplasia and Carcinoma in situ (atypical epithelium involve the whole thickness).
- **Cervical Carcinoma ,Invasive:** 75 -90% of invasive cancers are Squamous cell carcinomas, the remainders are Adenocarcinoma Mainly in the region of the transformation (junctional) zone.

Questions

1. **A 38-year-old healthy woman has had a white, curd-like vaginal discharge for the past week. There is no bleeding. A Pap smear demonstrates normal appearing squamous epithelial cells along with scattered neutrophils and budding cells with pseudohyphae. Which of the following infectious agents is most likely to be present in this woman?**
- A. *Treponema pallidum*
 - B. *Chlamydia trachomatis*
 - C. Herpes simplex virus
 - D. *Trichomonas vaginalis*
 - E. *Candida albicans*

Answer: (E). Vaginal yeast infections are quite common. Fungal vulvovaginitis is the second most common cause of vaginal infections in the U.S. (Bacterial vaginosis is the most frequent cause). The *Candida* organisms have the morphologic appearance with budding cells, often with pseudohyphae.

2. **A 28-year-old woman goes to her physician for a routine examination. She is sexually active. Pelvic examination reveals no abnormalities. A Pap smear is obtained. The cytopathology report indicates the presence of severely dysplastic cells (high grade squamous intraepithelial lesion, or HSIL). A biopsy of the cervix is performed, and on microscopic examination shows cervical intraepithelial neoplasia III (CIN III). Infection with which of the following organisms is most likely to cause her disease?**
- A. Herpes simplex virus infection
 - B. *Candida albicans*
 - C. Human papillomavirus
 - D. *Trichomonas vaginalis*
 - E. *Gardnerella vaginalis*

Answer: (C). HPV infections can lead to squamous epithelial dysplasia and carcinoma, particularly high grade subtypes such as HPV 16 and 18. The HPV vaccine immunizes against these subtypes, as well as the most common subtypes 6 and 11 associated with condyloma.

Q- What are cervical polyps?

A- Inflammatory proliferations of the cervical mucosa not associated with malignancy.

Q- Define cervicitis?

A- An inflammation of the cervix caused by a number of different organisms including staphylococci, enterococci, *Gardnerella vaginalis*, *Candida albicans*, *Trichomonas vaginalis*, *Chlamydia trachomatis* and *Neisseria gonorrhoeae*.

Q- What are the symptoms of cervicitis?

A- Vaginal discharge, bleeding, itching/ irritation of the external genitalia, pain during intercourse and lower back pain.

Q- What conditions are frequently associated with candidiasis?

A- Diabetes mellitus, pregnancy, broad-spectrum antibiotic therapy, oral contraceptive use and immunosuppression.

Q- How does candidiasis typically present?

A- With a thick, white discharge and vulvovaginal pruritus.

Q- What is the most common sexually transmitted disease?

A- Chlamydia trachomatis.

Q- What is a serious sequel of untreated chlamydial infection?

A- Pelvic inflammatory disease with the potential for infertility,

Q- Which of the herpes simplex viruses is associated with genital herpes and spreads via sexual contact?

A- Herpes simplex virus (HSV) type 2.

Q- What are the most common types of cervical cancer?

A- squamous cell cancer (arising from the ectocervix) and adenocarcinoma (arising from the endocervix).

Q- What are the epidemiologic risk factors for cervical cancer?

A- Early sexual activity, multiple sexual partners, lower socioeconomic status, cigarette smoking.