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Pathology of cervix

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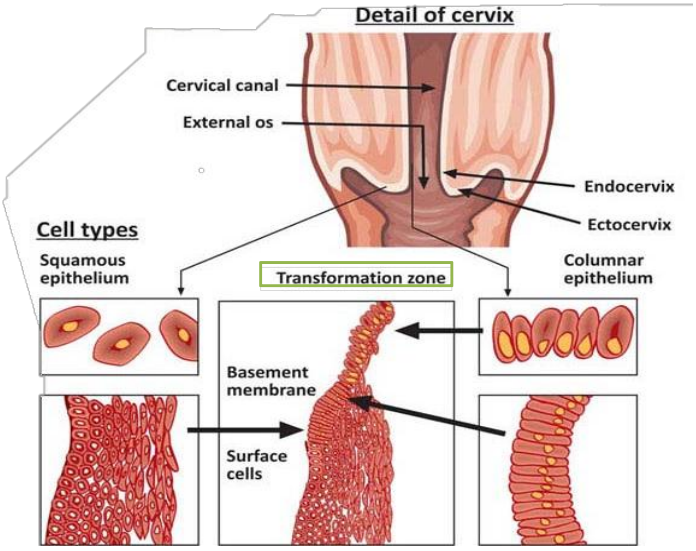
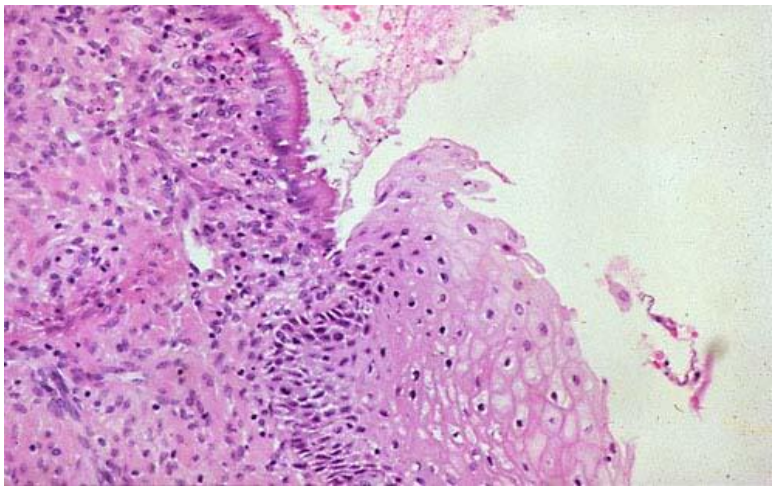
6th Lecture

PATHOLOGY OF THE CERVIX





The Transformation Zone (aka: the Squamo-Columnar Junction)

It is of great importance because it is the most common site for dysplasia and cancer.

Erosion/Ectropion: IMP

- Characterized by **columnar epithelium replacing squamous epithelium**, grossly resulting in an erythematous area.
- 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.

It happens in women with multiple deliveries caused by the excessive pushing leading to prolapse.
It is usually operated on and a hysterectomy may be indicated because most of the time it causes bladder prolapse with urgency and involuntary micturition.

Cervical Polyp:

Benign, very common and easily diagnosed

- This is a small, **pedunculated**, often **sessile** mass.
- They are inflammatory proliferations of cervical mucosa and are not true neoplasms.
- The lesion is characterized by overgrowth of **benign stroma covered by epithelium.**
- The stroma contains **thick-walled blood vessels** and **fibrous** and some **inflammatory cells.**

Endocervical polyps	Ectocervical polyps
Originate from the endocervix	Originate from the ectocervix
Majority are this kind	Not as common
Covered by endocervical, squamo-columnar or metaplastic squamous epithelium	Covered by stratified squamous epithelium.

Pap Smears:

- Important for early detection.
- Once a year after age of 35

Method: Cervical scrapings of **mucus and lining cells** → dyed with PAP stain

Mucus:
For detection of abnormalities including organisms inflammation and infection

Lining Cells:
Most importantly used for detection of dysplasia and carcinoma.

Cervicitis:

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

Noninfectious (Nonspecific) Cervicitis:

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

Clinical Presentation:

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

Histology:

- The histologic 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.
  Columnar endocervical epithelium becomes squamous epithelium. In ectropion it's the opposite.

Infectious Cervicitis:

- Can be caused by various organisims; 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

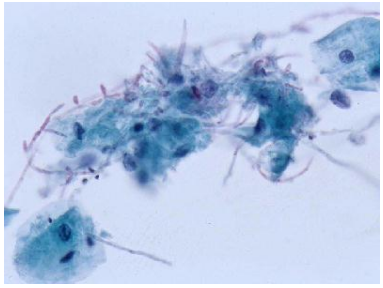
1. Candidiasis (moniliasis):

- 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 immunosupression.

Clinical Presentation:white patchy mucosal lesions with thick white discharge and vulvovaginal pruritis.

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 yeast forms (may have spores only)and branching pseudohyphae.



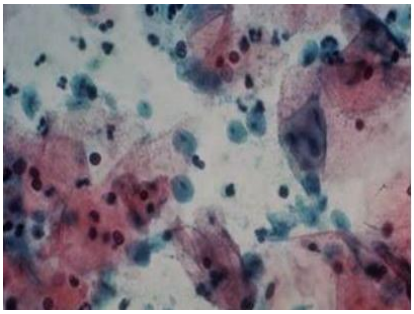
2. Trichomoniasis

- Caused by a **unicellular flagellated protozoan**: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

dyspareunia:(from Greek meaning "badly mated") is painful sexual intercourse.



Trichomoniasis continued…

Histology

- The organisms are not seen in biopsies because they do not invade the vaginal wall.
- An inflammatory infiltrate of lymphocytes and plasma cells.

Diagnosis

- Examination of a saline wet preparation in which the motile trophozoites are seen.
- The organism can also be found in Pap-stained vaginal smears."Dirty pap smear"

3. Chlamydia trachomatis Cervicitis

- Chlamydia trachomatis is an obligate, gram-negative intracellular pathogen.
- Chlamydial cervicitis is the most common sexually transmitted disease in the developed countries.
- It may coexist with **Neisseria Gonorrhoeae** infection.
- It is a frequent cause of pelvic inflammatory disease.
- Chlamydial infection may also cause a condition known as lymphogranuloma venereum(a sexually transmitted bacterial infection causing redness and inflammation of the cervix.)

Clinical appearance:

- Is most often asymptomatic.
- In symptomatic cases there is:
  - Mucopurulent cervical discharge.
  - **Reddened**, congested and edematous cervix.
- It may be associated with urethritis.

Herpes simplex virus (HSV) Cervicitis

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

Human papilloma virus (HPV) Infection: IMPORTANT

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

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.Proliferation of squamous cells due to HPV, with box shaped nuclei. May produce a protruding mass grossly.

The lesions may be flat or exophytic condylomma acuminatum.

Can be caused by any HPV serotype but more commonly by types 6 and 11.

2) Mild dysplasia:

Usually caused by "low risk" HPV serotypes, types 6 and 11.

3) High- grade dysplasia:

Caused by "high risk" HPV (types16 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.Due to lack of awareness of the importance of pap smears leading to less early detection.
- 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) or Squamous intraepithelial lesions.
- 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

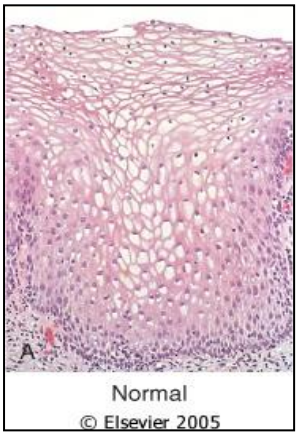
Cervical Intraepithelial Neoplasia(CIN)

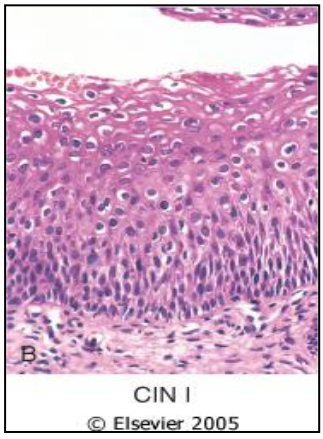
- Cytologic examination can detect CIN (SIL) long before any abnormality can be seen grossly.
- Pre-cancer changes can precede the development of an overt cancer by many years.Thus the importance of pap smears.
- CIN lesions may begin as Low Grade CIN and progress to High Grade CIN, or they might start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

Histology

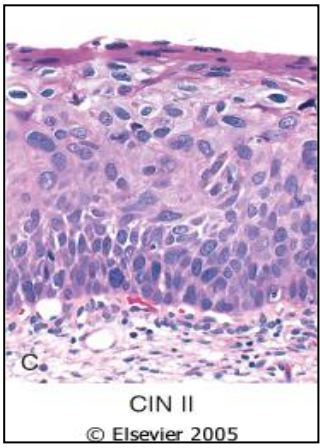
On the basis of histology, pre-cancer lesions are graded as follows:

- -CIN I: Mild Dysplasia
- -CIN II: Moderate Dysplasia
- -CIN III: Severe Dysplasia and Carcinoma in situ.

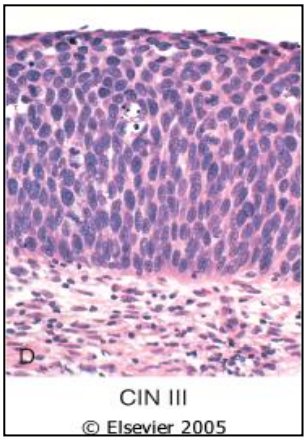




Lower 1/3rd of the epithelium is replaced by pleomorphic cells.



Lower 2/3rd of the epithelium is replaced by pleomorphic cells



All levels of the epithelium are replaced by pleomorphic cells, (full thickness)

Cytology screening for precancerous lesions

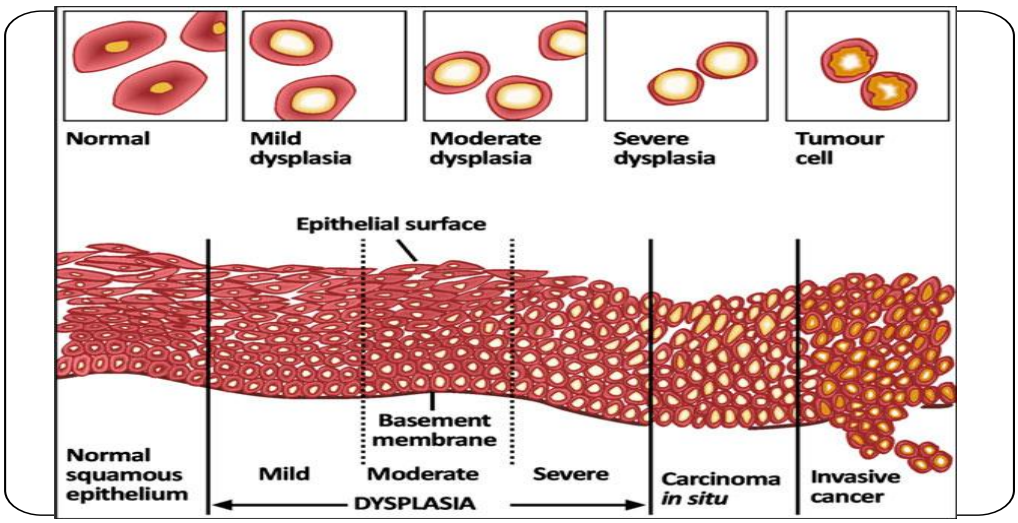
The cervix is examined and the cells lining the cervical wall at the transformation zone are scrapped/ sampled with a spatula and then spread on a slide. They are then fixed, stained (Papanicolaou stain) and examined under a light microscope.

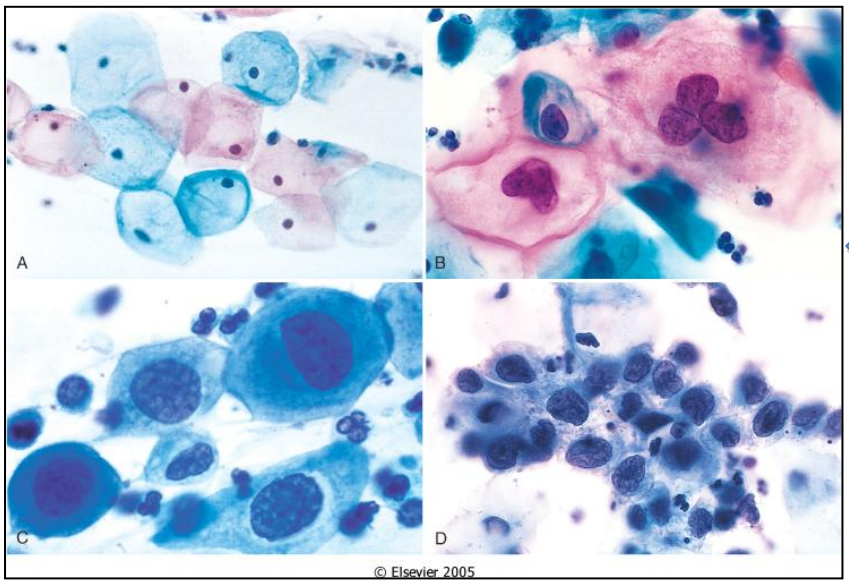
Cytology Pap Screening

- In cytology smears we separate pre-cancer lesions into two groups:
  - Low Grade SIL
  - High Grade SIL

→of Low Grade SIL 1-5 % become invasive

→of High Grade SIL incidence is 6-74%





Cytology of cervical intraepithelial neoplasia as seen on the Papanicolaou smear. Cytoplasmic staining in superficial cells (A&B) may be either red or blue. A, Normal exfoliated superficial squamous epithelial cells. B, CIN I. C, CIN II. D, CIN III. Note the reduction in cytoplasm and the increase in the nucleus to cytoplasm ratio, which occurs as the grade of the lesion increases. This reflects the progressive loss of cellular differentiation on the surface of the lesions from which these cells are exfoliated.

CIN Risk Factors

- **Early age at first intercourse**
- **Multiple sexual partners**
- A male partner with **multiple previous sexual partners**→vaccines are given to males in the West as well
- Persistent infection by high risk papillomaviruses
- Some other risk factors; low socioeconomic groups
- Rare among virgins, multiple pregnancies.

CIN 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.

Cervix Carcinoma:

Causes:

- 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,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 test ,the Diegene Hyprid Capture test . This test will determine whether you carry high or low risk strains of the virus.

Invasive Cervical Carcinoma:

- 75 -90% of invasive cancers are Squamous cell carcinomas,which generally evolves from pre-cancer CIN
- The remainders are Adenocarcinomas. → due to increased promiscuity in this age group
- 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.

Cervical Carcinoma, Morphology

- Mainly in the region of the transformation 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.

Cervical Carcinoma,Staging:

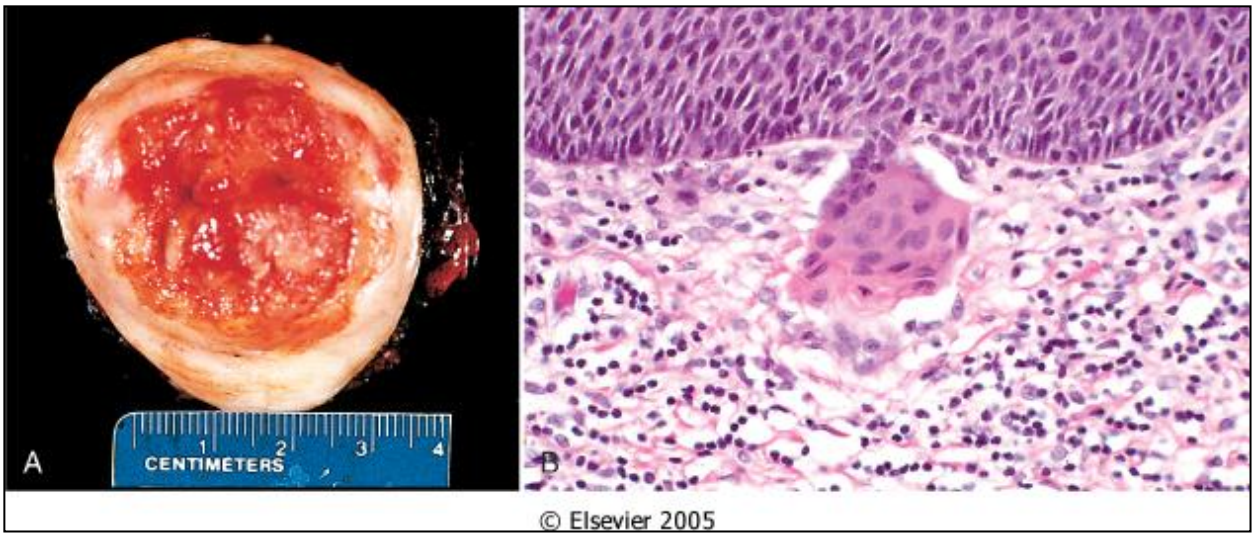
- 0- Carcinoma in Situ
- 1- Confined to the cervix
- 2- Extension beyond the cervix without extension to the lower third of Vagina or Pelvic Wall
- 3- Extension to the pelvic wall and / or lower third of the vagina
- 4- Extends to adjacent organs

Cervical Carcinoma, Clinical Course:

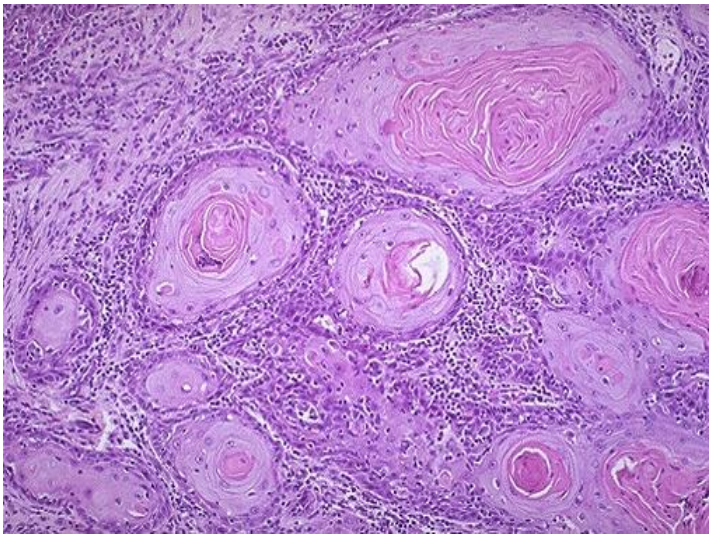
- Many of cervical cancers are diagnosed in early stages, and the vast majority is diagnosed in the pre-invasive phase.
- More advanced cases are seen in women who either have never had a Pap smear or have waited many years since the prior smear.

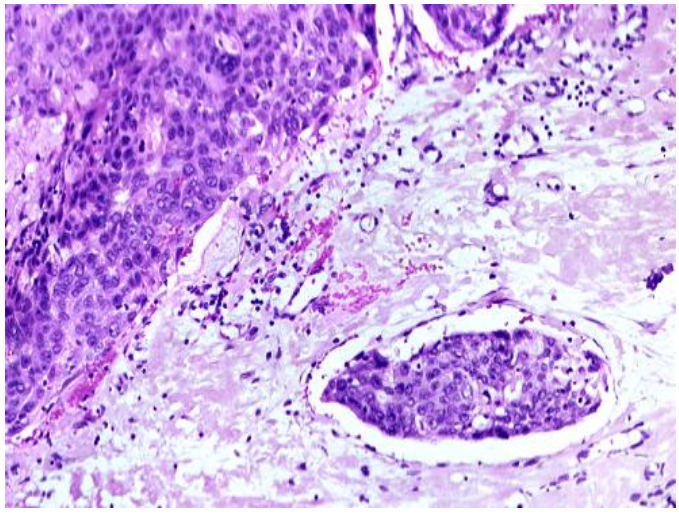
Cervical Carcinoma, Survival

- Laser or cone biopsy is the most effective method of managing patients with High grade SIL in cancer prevention.



A, Carcinoma of the cervix, well advanced.B, Early stromal invasion occurring in a cervical intraepithelial neoplasm.





Summary

- The most common site for dysplasia and cancer of the cervix is the Transformation Zone (the Squamo-Columnar Junction)

- **Erosion/Ectropion** Characterized by columnar epithelium replacing squamous epithelium, grossly resulting in an erythematous area. It is a typical response to a variety of stimuli including hormones. It is benign and has no malignant potential.

- **Cervical Polyp** They are inflammatory proliferations of cervical mucosa and are not true neoplasms.

- **Noninfectious (Nonspecific) Cervicitis** Caused by chemical irritation or mechanical irritation it is often acute but may be chronic. It is clinically, asymptomatic with red and swollen appearing cervix.

- **Infectious Cervicitis** Can caused by various organisms; e.g. Candida albicans, Trichomonasvaginalis, Chlamydia trachomatis. Most often involves the endocervix. Is often asymptomatic, may manifest as vaginal discharge

- **Candidiasis (moniliasis)** Common form of vaginitis /cervicitis. Caused by Candida albicans, a normal component of the vaginal flora. Associated with diabetes mellitus. Clinical Presentation: white patchy mucosal lesions with thick white.
- **Chlamydial cervicitis** is the most common sexually transmitted disease in the developed countries. It is a frequent cause of pelvic inflammatory disease.

- **Condyloma** can be caused by any HPV serotype but more commonly by types 6 and 11.
- **High- grade dysplasia** Caused by "high risk" HPV (types16 and 18) and "moderate-risk" HPV (types 31, 33, 35).

Cervical Neoplasia (ROBBINS summary)

- Risk factors for cervical carcinoma include early age at first intercourse, multiple sexual partners, cigarette smoking, immunodeficiency, and infection by "high-risk" papillomaviruses.
- Nearly all cervical carcinoma is HPV related, particularly certain HPV subtype (16, 18, 45, 31, and others). HPV vaccine can prevent the occurrence of cervical cancer.
- HPV virus E6 and E7 proteins cause inactivation of P53 and R B genes, respectively, resulting in increased cell proliferation and suppression of apoptosis.
- High-grade cervical dysplasias (CIN II and III) contain HPV incorporated into the cell genome, and cytologically have increased chromatin abnormality and an increased nuclear-to-cytoplasmic ratio.
- Not all HPV infections progress to CIN III or invasive carcinoma. The time course from infection to invasive disease may be 10 years or more.
- The Pap smear is a highly effective screening tool in the detection of cervical dysplasia and carcinoma, and has reduced the incidence of cervical carcinoma.

Question

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 agains 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.