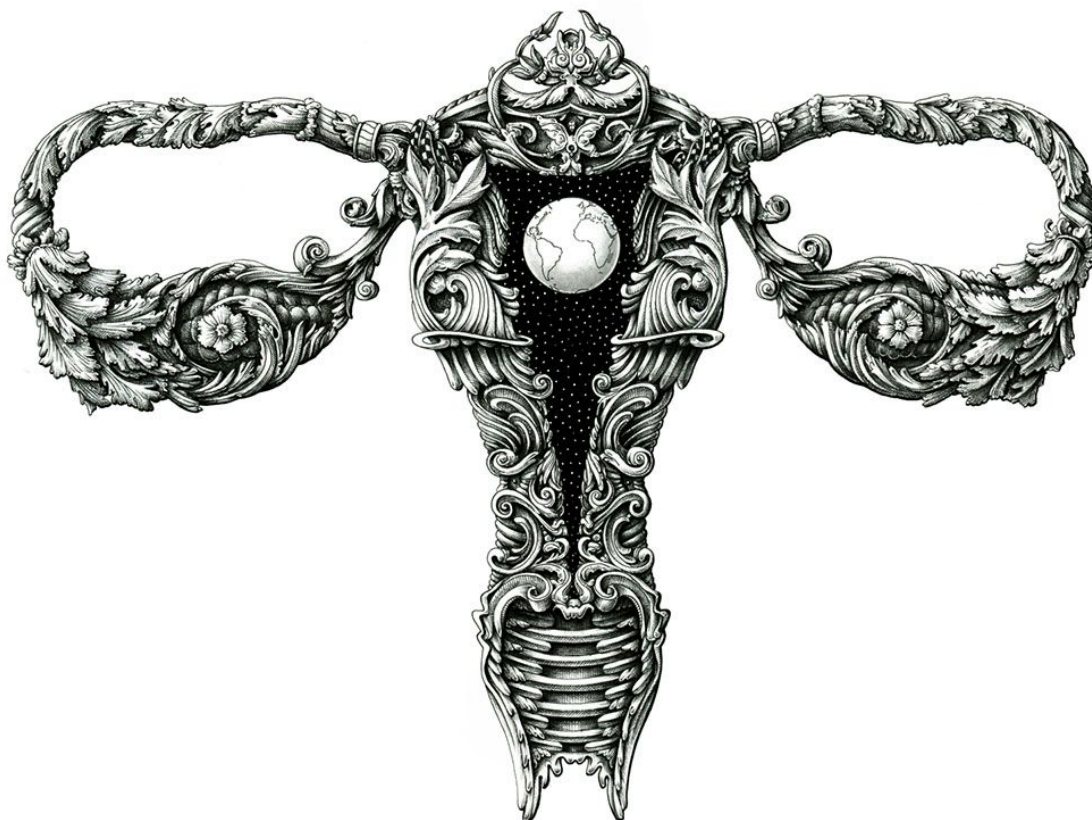


uterine cervix



Lecture Outlines:

- Some common benign conditions and infections
- Understand the concepts of dysplasia and intraepithelial neoplasia in the female genital tract and the role of a cervical screening programme.
- Know the incidence, risk factors, clinical presentation, pathological features and prognosis of cervical squamous cell carcinoma.

Important note: Please check out this link before viewing the file to know if there are any additions or changes. The same link will be used for all of our work: [Pathology Edit](#).

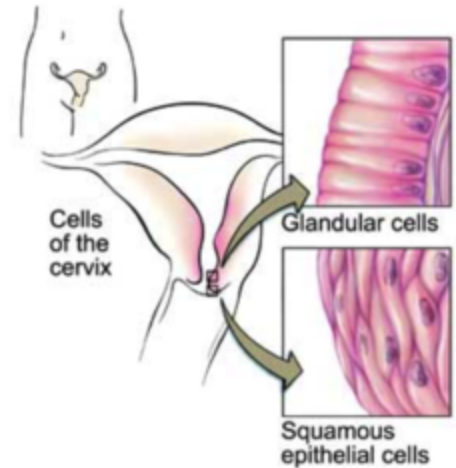
Grey = Extra
Red = Important

Introduction.

The cervix is the part of the uterus below the level of the isthmus.

Epithelium of the cervix:

1. **Endocervix (cervical canal):** simple columnar.
 2. **Exocervix (external os):** stratified squamous epithelium (non-keratinized).
- **Squamo-columnar junction (transformation zone):** is the region between the endocervix & the exocervix. It's important because most of diseases begin there.
 - **Substance of the cervix:** dense fibrous tissue with few smooth muscle fibers.
 - Cervical lesions are mostly mild inflammations (cervicitis), but the cervix also is the site of one of the most common cancers in women worldwide.



Erosion (Ectropion).

- When **squamous epithelium** is replaced by **columnar 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.



Squamous metaplasia.

- In it the **columnar cells** are replaced by **squamous cells**. It is seen in cervix at the **squamo-columnar junction**.
- Squamous metaplastic epithelium is the area most affected by **Human Papillomavirus (HPV)** infection and the area where dysplasia and malignant transformation **starts**.
- Note: squamous metaplastic epithelium is benign and by itself not considered premalignant.

Cervical polyp.

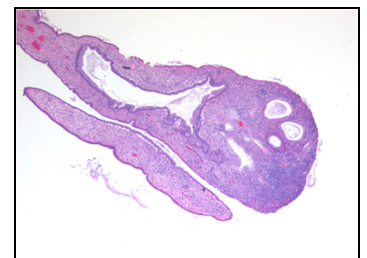
- Inflammatory proliferations of cervical mucosa, small, **pedunculated mass**.
- **Most originate from the endocervix** (endocervical polyps) with a few from the ectocervix (ectocervical polyps).
- They are inflammatory proliferations of cervical mucosa and are **not true neoplasms**.
- The lesion is characterized by **overgrowth of benign stroma covered by epithelium**.



Microscopically:

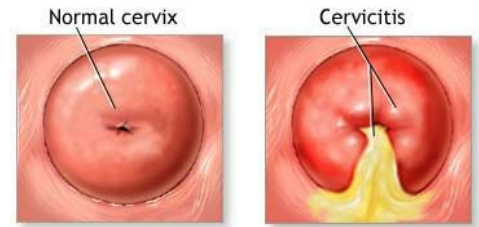
Lining/covered epithelium: is either columnar epithelium or stratified squamous epithelium or sometime partly by both.

Stroma: is made up of fibrous tissue with thick-walled blood vessels and inflammatory cells.



Cervicitis.

Inflammation of cervix, Can be infectious or noninfectious.



1- Noninfectious (Nonspecific)

Cervicitis:

inflammation of the cervix, it's often acute but it can be chronic.

It's caused by irritation either:

- Chemical (e.g. douche¹, deodorant)
- Mechanical (e.g. tampon, diaphragm)

Clinical appearances:

- Often **asymptomatic**.
- The cervix appears red and swollen.

Histology:

- The **inflammatory cells** are seen (neutrophils, plasma cells and lymphocytes).
- **Squamous metaplasia** is common in chronic cervicitis.
- Some glands dilate to form cysts filled with mucin 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** (cervical canal).
- May be asymptomatic or manifest as vaginal discharge and itching.

Candidiasis (moniliasis).

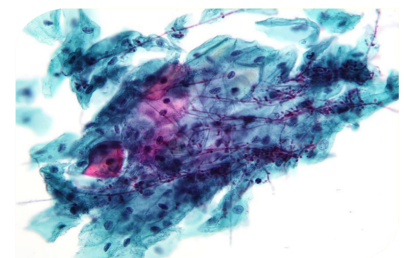
- **Common**. (majority of women develop it during their lives)
- Involves cervix and vagina.
- Caused by **Candida albicans**, a normal component of the vaginal flora.

Risk factors Associated with low immunity such as: **DM**, **pregnancy**, **oral contraceptive use**, **antibiotic therapy** (affect PH of vagina which causes candida growth), **immunosuppression**.

Clinical presentations: Characterized by white patchy mucosal lesions with **thick curdy (creamy) white discharge** and **vulvovaginal pruritis (itching)**, Ulcers may develop if itching is severe.

Cytology smears show:

- Fungal colonies in the form of **spores** and **branching pseudohyphae** on the cervical epithelium.
- Chronic inflammatory cells are present.



¹ a shower of water.

Trichomoniasis.

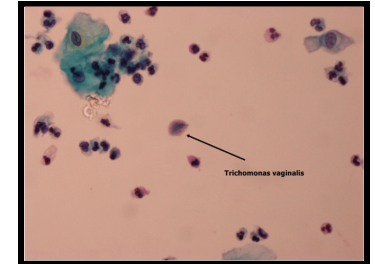
- It is sexually transmitted disease (STD).
- It is caused by a unicellular flagellated protozoan called *Trichomonas vaginalis*.
- Involves the vagina and cervix.

Clinical presentation:

- **Greenish-yellow frothy and foul smelling vaginal discharge.**
- Painful urination.
- vulvovaginal itching or irritation.
- Dyspareunia (painful sexual intercourse).

Cytology smears show: (Pap-stained vaginal smears)

- Shows the organism in a background of inflammatory cells.



Diagnosis can also be made by examination of a saline wet preparation in which the motile trophozoites are seen.

Chlamydia trachomatis Cervicitis.

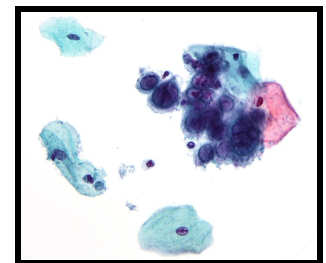
- Chlamydia trachomatis is an obligate, gram-negative intracellular pathogen.
- Chlamydial cervicitis is the **most common sexually transmitted disease in the developed countries**. It may coexist with *Neisseria gonorrhoeae* infection.
- It is a frequent cause of **pelvic inflammatory disease** and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

Clinical appearance:

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

Herpes simplex virus (HSV) Cervicitis.

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



Human papillomavirus (HPV) infection. (IMPORTANT)

- HPV infection of the cervix is common. *Sexual DNA transmitted diseases.*
- Over 20 serotypes infect the female genital areas and cause a variety of different lesions depending on the serotypes.

Clinical behavior:

- HPV infection is associated with **increased risk of subsequent cervical cancer**.
- HPV infection causes **koilocytic atypia** in the cervical **squamous epithelium** in the transformation zone.

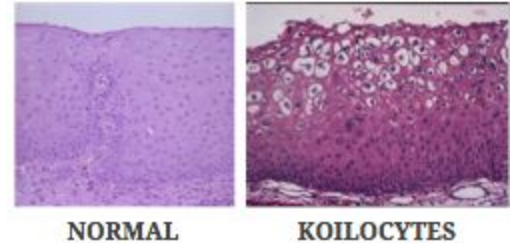
HPV infection may cause any of the following depending on the serotype: (memorize numbers)

1. **Condyloma**²: This develops in the squamous epithelium of the cervix. The lesions may be flat or exophytic condyloma acuminatum³. Usually caused by HPV serotypes **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** and **35**). (high levels of E6 & E7 → P53 & RB mutation → high grade dysplasia)

Koilocytes.

Are squamous epithelial cells that has undergone structural change due to infection of the cell by **HPV**. They show koilocytosis or koilocytic atypia which is the following cellular changes:

- Nuclear enlargement.
- Irregular nuclear membrane.
- Nuclear hyperchromasia.
- **Perinuclear halo** (clear area around the nucleus).



Summary.

Inflammation	Organism	Clinical presentation	Cytology	Notes
Candidiasis (moniliasis)	Candida albicans	- low immunity - white discharge - vulvovaginal pruritis	- spores - branching pseudohyphae	Common
Trichomoniasis	unicellular flagellated protozoan, <i>Trichomonas vaginalis</i> .	- foul smelling vaginal discharge - dysuria - irritation - Dyspareunia	- Pap-stained - motile trophozoites are seen	(STD)
Chlamydia trachomatis	Chlamydia trachomatis	- pelvic inflammatory disease - lymphogranuloma venereum 1- asymptomatic. 2- symptomatic: mucopurulent discharge & urethritis.	gram-negative intracellular pathogen	most common STD in the developed countries
(HSV) Cervicitis	HSV Type 2	vesicles and ulcers involve the cervix, vagina, vulva, urethra and perianal skin		spread by sexual contact
(HPV) infection	Over 20 serotypes	- koilocytic atypia - Condyloma: (6, 11) - Mild dysplasia: (6, 11) - High-grade dysplasia: (16, 18, 31, 33, 35).		- Common - increased risk of subsequent cervical cancer

² a raised growth on the skin resembling a wart (ثالول)

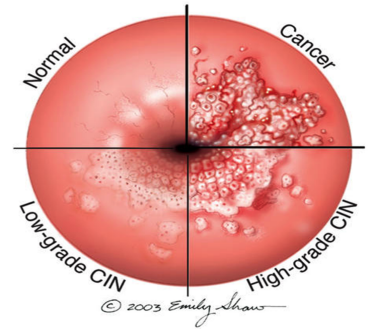
³ condyloma acuminatum= refers to an epidermal manifestation attributed to the epidermotropic human papillomavirus (HPV).

Cervical intraepithelial neoplasia (CIN)/Squamous intraepithelial lesion (SILs)

Cervical intraepithelial neoplasia (CIN): which is the terminology used in histology (**biopsies**).

OR:

Squamous intraepithelial lesions (SIL): the terminology used in cytology (**pap smears**).



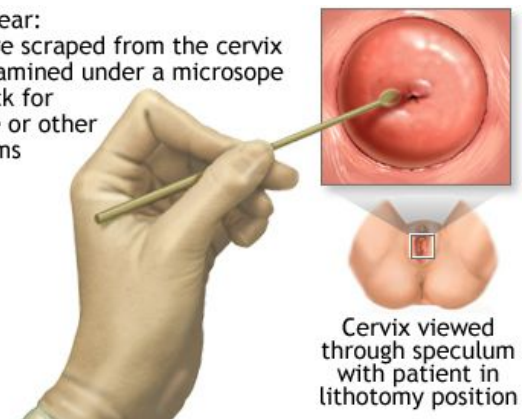
- CIN/ SIL are **precancerous lesions of the cervix**.⁴ Can precede the development of an overt cancer by many years.
- Characterized by koilocytotic change nuclear atypia and increased in mitotic activity of cervical epithelium.

PAP screening test.

Cytologic examination can **detect precancerous squamous intraepithelial lesions** long before any abnormality can be seen grossly, using the PAP test. SIL/CIN cannot be detected grossly, they are detected only by PAP smear, that's why this test is important.

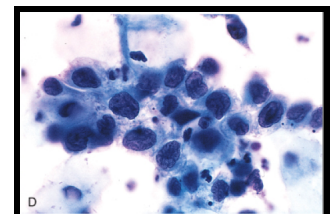
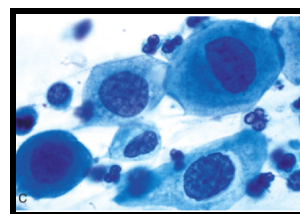
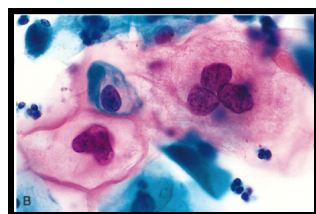
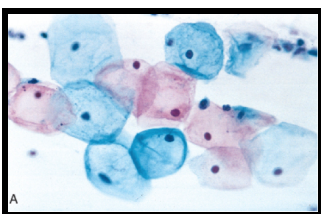
- PAP test is the cytologic examination of the cells lining the cervical wall **at the transformation zone** in which they are scrapped/sampled with a spatula and then transferred onto a slide, processed, stained (**Papanicolaou stain**) and examined under a light microscope to **look for squamous intraepithelial lesions and a diagnosis is made**.
- This screening for pre-cancer **should be done on all women usually from age of 21 years and onwards**.

Pap smear:
cells are scraped from the cervix and examined under a microscope to check for disease or other problems



In cytology smear they are divided into:

- A. Normal cells/ Negative for squamous intraepithelial lesion (SIL)
- B. **Low Grade SIL:** CIN 1 = *mild dysplasia*.
- C. **High Grade SIL:** CIN 2 & 3 = *moderate to severe dysplasia*.
 - About **1 to 5%** of low Grade SIL become invasive squamous cell carcinomas.
 - About **6 to 74%** of high Grade SIL become invasive squamous cell carcinomas.



⁴ Characterized by koilocytotic change, disordered cellular maturation, nuclear atypia and increased mitotic activity

Normal exfoliated SSI

CIN I/ low grade SIL

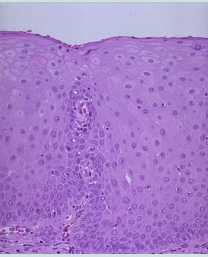
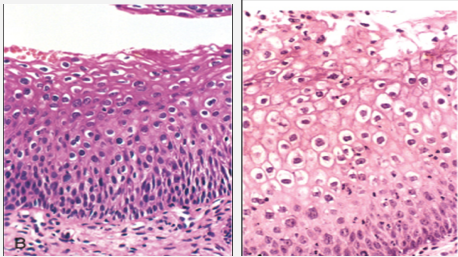
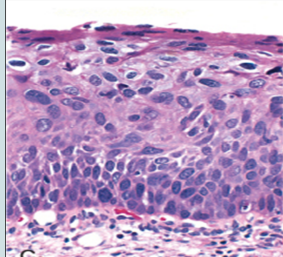
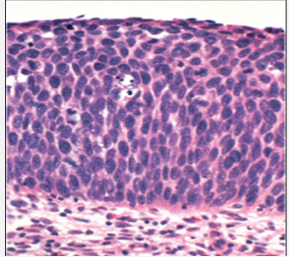
CIN II/ high grade SIL

CIN III/ high grade SIL

- Note the *reduction in cytoplasm* and the **increase in nucleus/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.
- **Not all cases of CIN/SIL progress to invasive cancer** and some cases of CIN/SIL may spontaneously regress.
- **The risk of progression to cancer is more in the high grade CIN/SIL and they are associated the high-risk HPV serotypes.**⁵

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

- **CIN I : Mild Dysplasia** has potential to reverse 66%
- **CIN II : Moderate Dysplasia** has potential to reverse 33 %
- **CIN III : Severe Dysplasia** rarely reverse
- **Carcinoma in situ (CIS)** no reversibility

Normal	Mild dysplasia = CIN I	Moderate dysplasia = CIN II	Severe dysplasia = CIN III (CIS)
			
	<p>HPV associated koilocytotic atypia.⁶</p> <p>Lower 1/3rd of the epithelium is replaced by pleomorphic cells.</p>	<p>There is progressive atypia in the layers of the epithelium</p> <p>lower 2/3rd of the epithelium is replaced by pleomorphic cells</p>	<p>There is diffuse atypia and loss of maturation.</p> <p>All levels of the epithelium are replaced by pleomorphic cells, (full thickness)</p>

- Once the basement membrane is ruptured it's called invasive carcinoma → able to metastasize.

Signs

- There are no visible symptoms of dysplasia of the cervix, and it is difficult to diagnose without a Pap smear/exam .
- Therefore regular pap exams should be done to detect any abnormal cells.

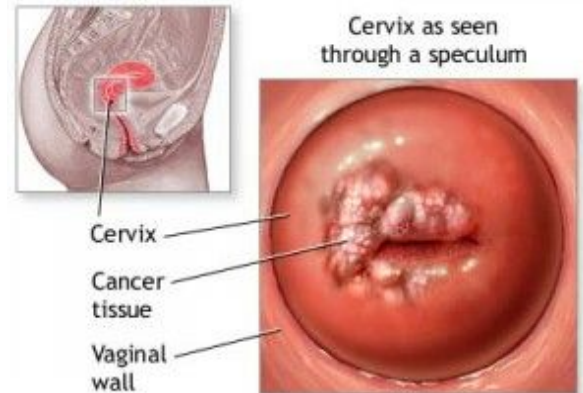
⁵ Human Papillomavirus-Related Gynecologic Neoplasms

⁶ A **Koilocyte** is a squamous epithelial cell that has undergone a number of structural changes, which occur as a result of infection of the cell by human papillomavirus. **Koilocytotic atypia** is used to describe the presence of koilocytes in a specimen.

Treatment: laser or cone biopsy is the most effective method of managing patients with High grade SIL in cancer prevention.

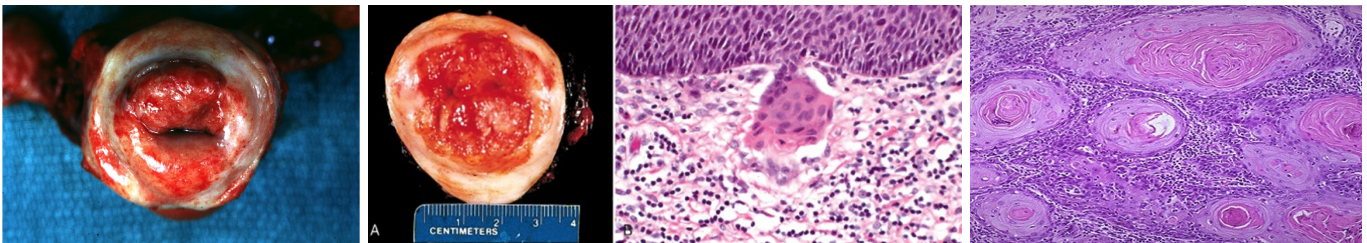
Cervical cancer (Cervix Carcinoma) [PATHOMA VIDEO](#)

- Most common cervical cancer is **squamous cell carcinoma** (75-90%), followed by **adenocarcinoma, neuroendocrine carcinoma** etc.
(Presents as vaginal bleeding or cervical discharge, key risk factor is high-risk HPV inf. Followed by smoking and HIV inf.)
- Cervical carcinoma used to be a major causes of cancer-related death in women. But Nowadays there is dramatic improvement in management of this disease because of early diagnosis treatment and use of **PAP screening test**. Therefore the incidence and the deaths associated to cervical cancer are decreasing.
- Squamous cell cancers are appearing more in *younger women*, more common in middle aged women (45 years +/- 10 years). (this cancer takes about 10 years to develop)



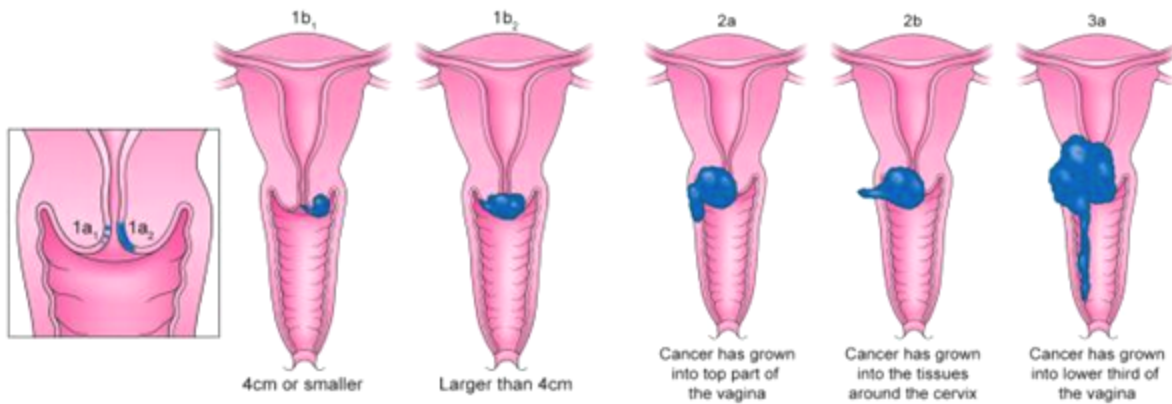
Morphology:

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



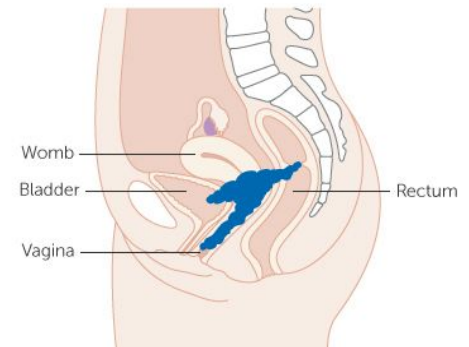
Staging: (not important)

- 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.



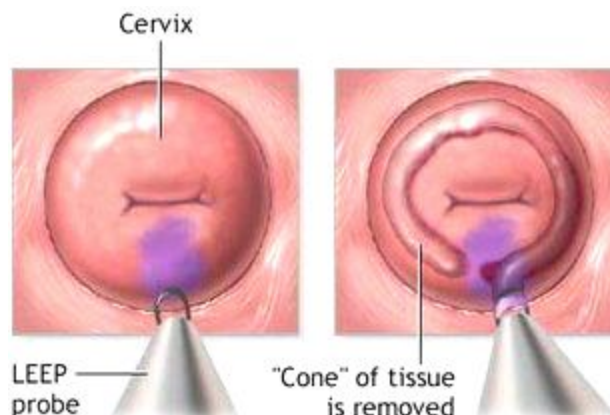
Clinical Course:

- The early stages of cervical cancer may be completely asymptomatic.
- **Vaginal bleeding**, contact bleeding, or cervical mass.
- Dyspareunia⁷.
- Dysuria (Urinary obstruction).
- In advanced disease, metastases may be present in the abdomen, bones, lungs, **bladder** (urine come out of bladder or hematuria appear), **rectum** (feces with urine).
- **Symptoms of advanced cervical cancer may include:** loss of appetite, weight loss, fatigue, pelvic pain, back pain, leg pain, swollen legs, **heavy bleeding from the vagina**, bone fractures, and/or (rarely) **leakage of urine or faeces from the vagina**.
- Advanced tumors can invade the ureter and cause **hydronephrosis** with **postrenal failure** (common cause of death in advanced cervical carcinoma).



Treatment. Depending on the stage the treatment options are:

1. If patient wants to be able to have children, the cancer is removed with **a cone biopsy (cervical conization)**, and then followed up regularly.
2. **Simple hysterectomy** (removal of the whole uterus including part of the vagina).
3. **Radical hysterectomy** (removal of the whole uterus including part of the vagina along with the removal of lymph nodes in the pelvis).
4. Adjunct chemotherapy & radiotherapy.



⁷ Dyspareunia = painful coitus

Risk Factors and causes of CIN/ SIL & cervical carcinoma.

Risk Factors:

- Early age at first intercourse.
- Multiple sexual partners.
- A male partner with multiple previous sexual partners.
- Persistent infection by high risk **papillomaviruses**.
- Other risk factors: low socioeconomic groups.
- Rare among **virgins** and **multiple pregnancies**.
- Smoking and immunodeficiency.

Causes:

- **HPV virus** is the most common cause of abnormal cells of the cervix (85-90 % of precancerous lesions).
- HPV is a skin virus, which results in warts, such as flat warts, genital warts (condylomas), planter warts, and precancerous 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.



How does HPV Cause Malignant Transformation? (robbins page 686)

HPV-infected squamous cells do, as a consequence of expression of two potent oncoproteins encoded in the HPV genome called E6 and E7. The E6 and E7 proteins bind and inactivate two critical tumor suppressors, p53 and Rb, respectively, and in doing so promote growth and increased susceptibility to additional mutations that may eventually lead to carcinogenesis.

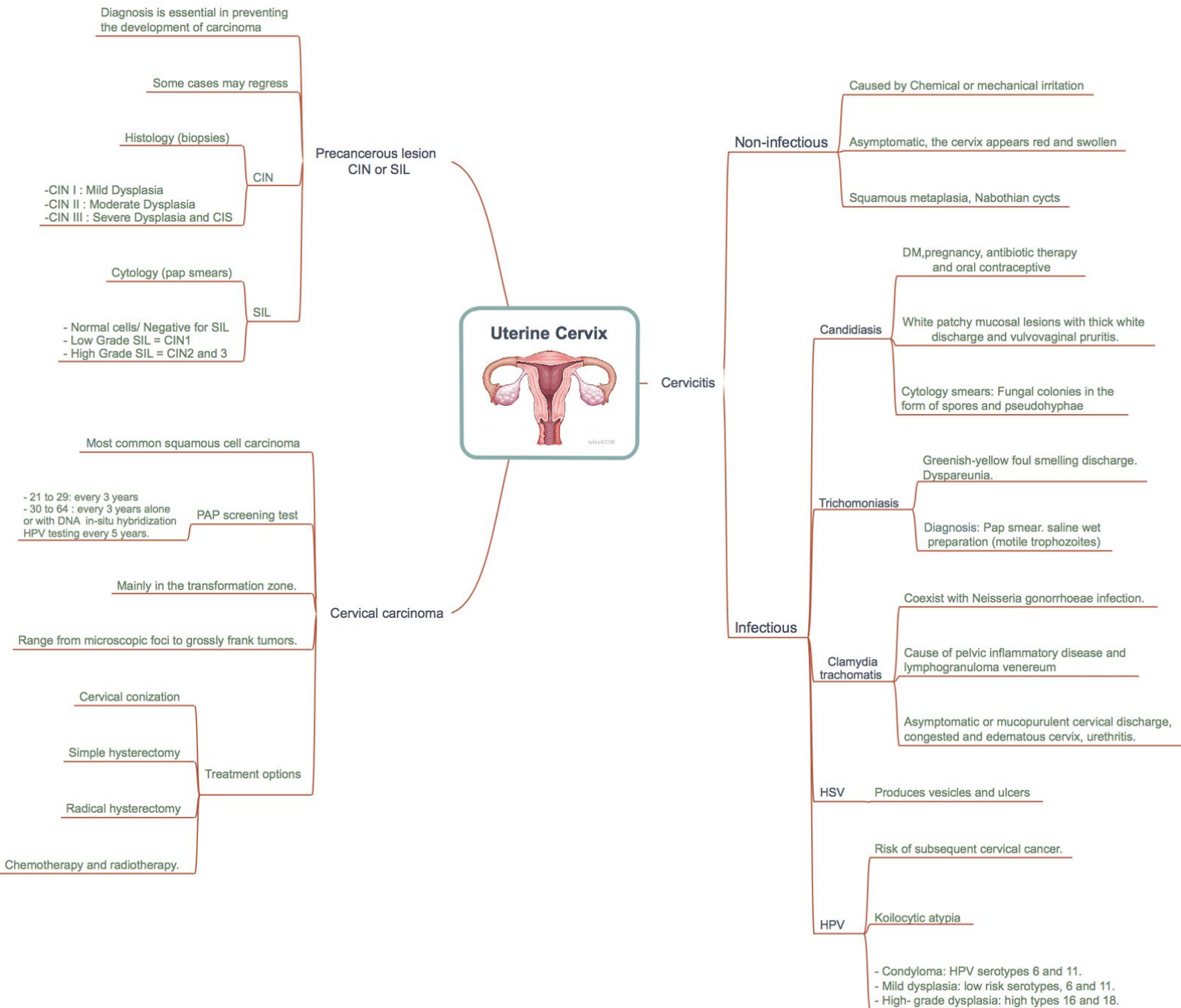
General rules of Pap Screening for CIN/SIL and carcinoma cervix via pap smear are:

The common testing procedure for HPV infection is a cytology pap smear screening test/exam.

- The Pap smear detects HPV infection early.
- **For women between age 21 to 29:** cytological screening pap test should be done every 3 years.
- **For women between age 30 to 64:** there are 2 possibilities:
 - A. Either only cytology screening pap test is done every **3 years**.
 - B. Or there is co-testing (2 tests are done) in which cytology screening pap test is done along with DNA in-situ hybridization HPV testing, every **5 years**.

NOTE: This HPV DNA **in-situ hybridization (ISH)** test, is called the **Digene Hybrid Capture** test to identify the serotype of the viral strain. This test will determine whether you carry high or low risk strains of the virus. DNA screening test should not be used before age 30.

Summary.



MCQ's.

1-A hysterectomy specimen is performed on a 38-year-old woman for resection of a large intramural leiomyoma, and the cervix is examined histologically by the pathologist. Microscopic sections of the cervix reveal atypical dysplastic squamous epithelial cells in the lower one third of the epithelium. These cells have condensed nuclei with perinuclear clearing. No papillary structures are found. Mitoses are present only in the basal one-third of the epithelium. No invasion into the underlying tissue is noted. Which of the following is the best pathologic diagnosis for this cervical biopsy specimen?

- A. Condyloma acuminatum
- B. Cervical intraepithelial neoplasia grade I
- C. Cervical intraepithelial neoplasia grade II
- D. Carcinoma in situ
- E. Invasive carcinoma

2- A 32-year-old woman with a previous history of abnormal Pap smears is lost to follow-up but presents with vaginal bleeding. Physical examination finds a 3-cm fungating lesion of the cervix. Histologic examination of this lesion is most likely to reveal which of the following abnormalities?

- A. Adenocarcinoma
- B. Clear cell carcinoma
- C. Small cell carcinoma
- D. Squamous cell carcinoma
- E. Verrucous carcinoma

3- in which one of these we can find Fungal colonies in the form of spores and branching pseudohyphae?

- a-Trichomoniasis
- b-Candidiasis
- c-Chlamydia trachomatis Cervicitis.

4- A 24-year-old woman is noted to have atypical cells on a Pap smear that are consistent with infection by human papillomavirus (HPV). Which of the listed abnormalities describes the characteristic cytopathic effect caused by infection with HPV?

- A. Acanthosis
- B. Apoptosis
- C. Hyperkeratosis
- D. Koilocytosis
- E. Parakeratosis

5/ A routine cervical Pap smear taken during a gynecologic examination of a 31-year-old woman shows numerous, loosely arranged cells with high nuclear-to-cytoplasmic ratio. Colposcopy shows white epithelium, punctuation, and a mosaic pattern in the transformation zone. Which of the following is the most likely diagnosis?

- (A) Adenocarcinoma of endocervix
- (B) Chronic cervicitis
- (C) Clear cell adenocarcinoma
- (D) Dysplasia of the cervix

6/ A 36-year-old woman is evaluated for an abnormal Pap smear. A cervical biopsy shows

atypical squamous cells throughout the entire thickness of the epithelium, with no evidence of epithelial maturation. The basal membrane appears intact. What is the appropriate diagnosis?

- (A) Clear cell adenocarcinoma
- (B) Invasive squamous cell carcinoma
- (C) Mild dysplasia (cervical intraepithelial neoplasia [CIN]-1)
- (D) Severe dysplasia (CIN-3)

7/ A 35-year-old woman presents with a 6-week history of vaginal discharge, which is occasionally blood tinged. Pelvic examination reveals a 2-cm pedunculated, lobulated, and smooth cervical growth; it is excised. Histologic examination of the specimen would most likely reveal which of the following?

- (A) Condyloma acuminatum
- (B) Embryonal rhabdomyosarcoma
- (C) Endocervical polyp
- (D) Leiomyosarcoma

Answers:

1-B 2-D 3-B 4-D 5-D 6-D 7-C

For any suggestions or questions please don't hesitate to contact us on: Pathology434@gmail.com

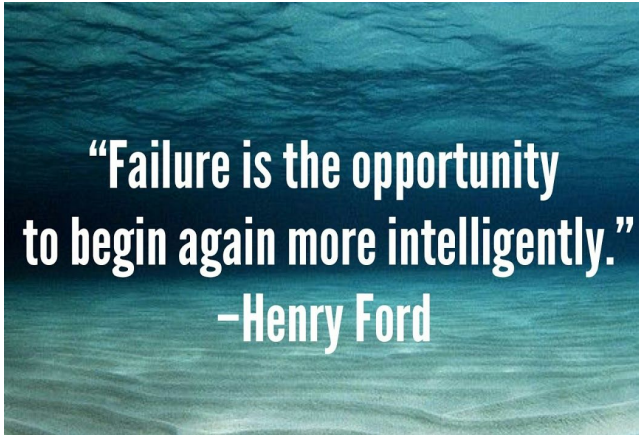
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GOOD LUCK !!

خالد الدريبي
محمد المحمود
عبدالإله المطيري
فيصل التويجري
عمر الرهيني
حسين الكاف

مها الربيعة
سارة الميرك
فتون المطيري
هديل السلمي
ريما الناصر
ريم لبنني



**“Failure is the opportunity
to begin again more intelligently.”
-Henry Ford**