

Lecture 6

Pathology of Uterine Cervix



432 Pathology Team

Done By: Abdulhameed Al-Saawy

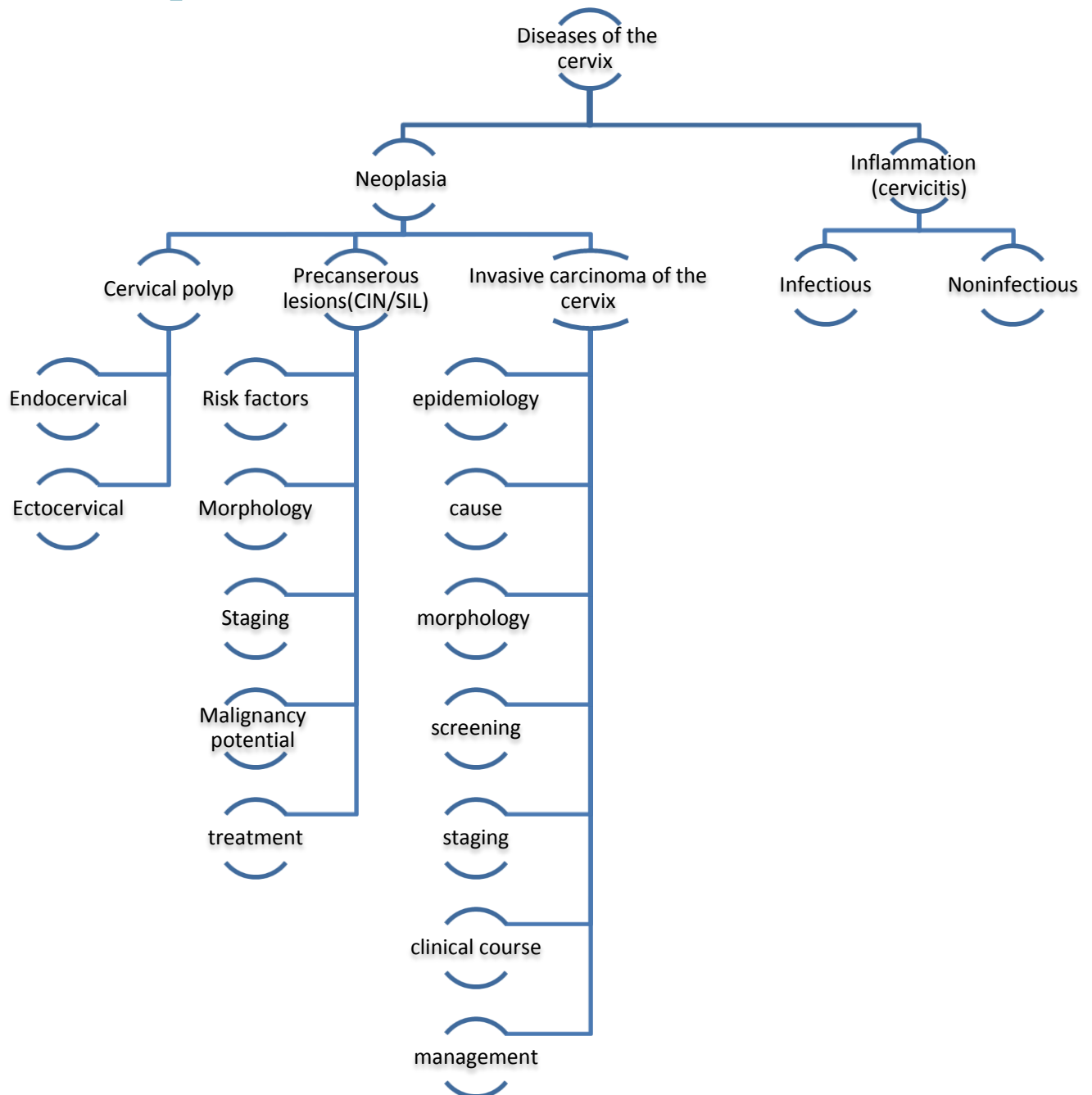
Reviewed By: Alanoud Al-Yousef & Rihaf Al-Gain

Reproductive Block



Pathology of the uterine cervix

Mind Map:

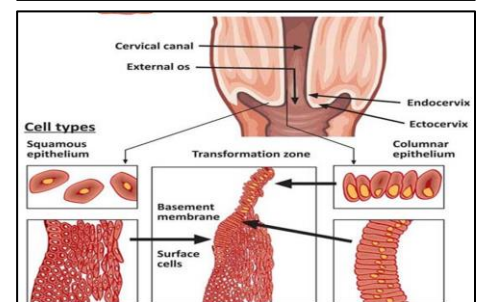
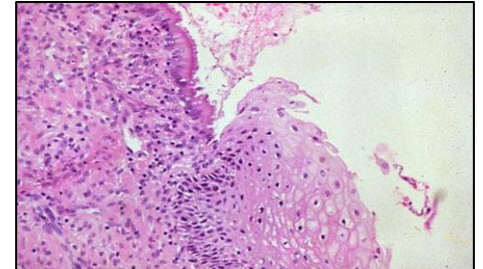


Helpful Video (Thanks to Heba Alsharif):
<https://drive.google.com/file/d/0B9J8xbkwItPIWWILd1I5QVNVaE/edit?usp=sharing>

Cervix

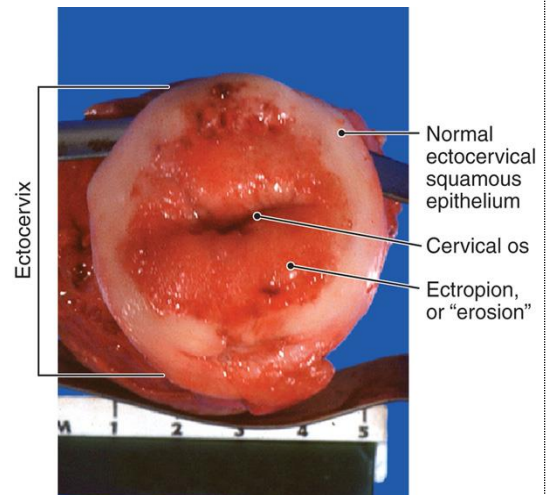
Introduction

- Most cervical lesions are relatively banal inflammations (**cervicitis**), but the cervix also is the site of one of the most common cancers in women worldwide.
- During development, the columnar, mucus-secreting epithelium of the endocervix is joined to the squamous epithelial covering of the exocervix at the cervical os.
- With the onset of puberty, the squamocolumnar junction undergoes eversion, causing columnar epithelium to become visible on the exocervix.
- The exposed columnar cells, however, eventually undergo squamous metaplasia, forming a region called the **transformation zone**.



Erosion/Ectropion

- Characterized by **columnar epithelium replacing squamous epithelium**, grossly resulting in an **erythematous area**. Figure. **The central (endocervical) columnar epithelium protrudes out through the external os of the cervix and onto the vaginal portion of the cervix, undergoes squamous metaplasia, and transforms to stratified squamous epithelium.**
- It is a typical response to a variety of stimuli including hormones, chronic irritation and inflammation (**chronic cervicitis**). **(A physiological response rather than a pathogenic process) Str. squamous epithelium is much more resistant to infections.**
- It is benign and has **no malignant potential**.



REMEMBER:

- Cervical ectropion: normal response to chronic irritation or hormonal stimulation with no malignant potential.
- It's indistinguishable from early cervical cancer, further diagnostic studies (e.g., Pap smear, biopsy) must be performed for a differential diagnosis.

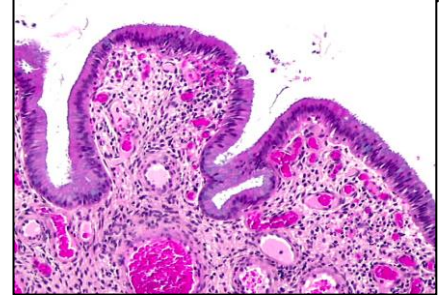
1- Cervical polyp

- **Most** originate from the endocervix (**endocervical polyps**) with a few from the ectocervix (ectocervical polyps).

Grossly: they are small, pedunculated, often sessile masses.

Microscopically: They are **inflammatory proliferations** of cervical mucosa and are **not true neoplasms**.

- 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 is edematous and contains thick-walled blood vessels, fibrous tissue and some inflammatory cells. (see figure)



REMEMBER:

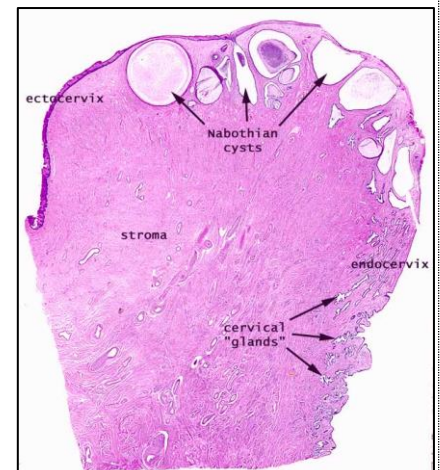
- These lesions may bleed, thereby arousing concern, but they have no malignant potential.

2- Cervicitis

- Inflammation of cervix.
- Can be subclassified as **infectious or noninfectious**, although differentiation is difficult owing to the presence of normal vaginal flora including incidental vaginal aerobes and anaerobes, streptococci, staphylococci, enterococci, and Escherichia coli.

A-Noninfectious (nonspecific) cervicitis:

- **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**.
- It is **often asymptomatic**.
- The cervix appears **red and swollen**.
- 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**.



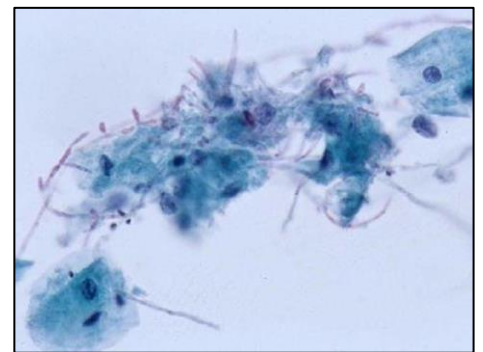
B- Infectious cervicitis:

- 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 (leukorhea)

I - Candidiasis (moniliasis)

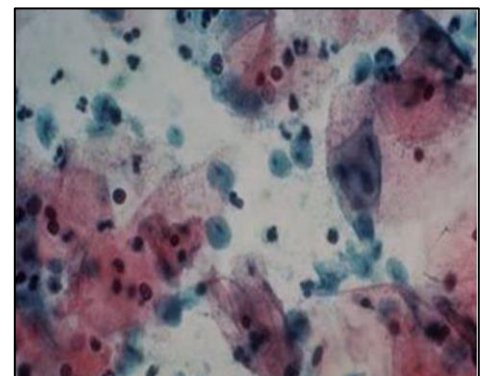
- Common form of *vaginitis* / cervicitis.
- Caused by *Candida albicans*, a normal component of the vaginal flora (in about 5% of women).
- Associated with diabetes mellitus, pregnancy, broad spectrum antibiotic therapy and oral contraceptive use and immunosuppression. (They all lower the immunity of the host).
- Characterized by white patchy mucosal lesions with thick white discharge and vulvovaginal pruritis. Itching

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 and branching pseudohyphae.



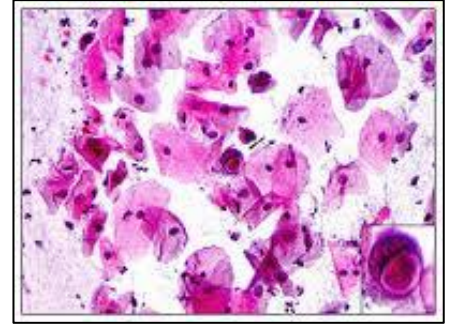
II- Trichomoniasis

- Caused by a unicellular flagellated protozoan, *Trichomonas vaginalis*. It is sexually transmitted disease
- Involves the vagina and cervix also.
- Most infections are asymptomatic and pass unnoticed. Occasionally, a copious, thin, frothy, yellow green to gray offensive discharge is produced. There may be vulvar itching or burning or dyspareunia (Painful coitus) bad odor
- 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.



III- Chlamydia trachomatis Cervicitis

- Chlamydia trachomatis is an **obligate, gram-negative intracellular pathogen**.
- Chlamydial cervicitis is the **most common sexually transmitted disease** (40%) in the developed countries.
- It may coexist with **Neisseria gonorrhoeae** infection.
- It is a frequent cause of **pelvic inflammatory disease**.
- Is most often asymptomatic.
- Chlamydial infection may also cause a condition known as **lymphogranuloma venereum**
- 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**.



IV- 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.



Extra note from Robbins:

- Although less common, herpetic infections are noteworthy because maternal-infant transmission during childbirth may result in serious, sometimes fatal systemic herpetic infection in the newborn.

V- 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.
- 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.

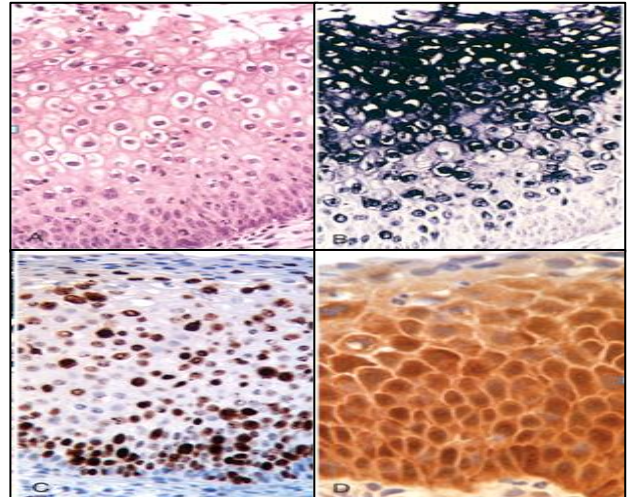
Morphology:

A. Flat condyloma with prominent **koilocytotic atypia** of HPV in the upper epithelial cells, as evidenced by the prominent perinuclear halos.

B. Nucleic acid in situ hybridization of the same lesion for HPV nucleic acids. The dark staining denotes HPV DNA, which is typically most abundant in the koilocytes.

C. Diffuse immunostaining of CIN II for Ki-67, illustrating widespread deregulation of cell cycle controls.

D. Up-regulation of p16ink4 (seen as intense immunostaining) characterizes high-risk HPV infections.



NOTE:

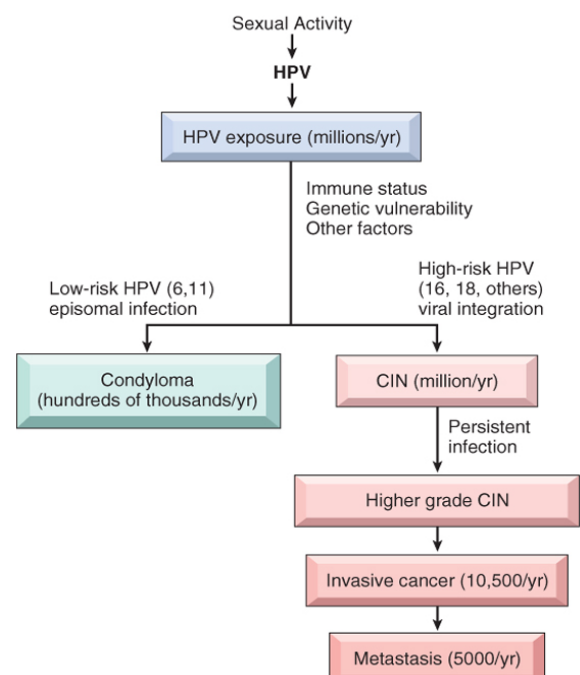
- Koilocytosis: A cytopathic change characterized by perinuclear cytoplasmic vacuolization and wrinkled nuclear contours that is a hallmark of HPV infection.

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 **condylomma acuminatum**. It 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**).



3-Cervical cancer

- One of the major causes of cancer-related death in women, especially in the developing world.
- **Most common cervical cancer is squamous cell carcinoma (75%).** Other types are **adenocarcinoma (20%),** neuroendocrine carcinoma (less than 5%) etc.
- Nowadays there is dramatic improvement because of early diagnosis and treatment.
- The **wide use of PAP screening lowered the incidence of invasive cancer.**

A. Precancerous lesion of cervical carcinoma (CIN/ SIL)

- **All invasive squamous cell carcinomas arise from pre-cancerous** (noninvasive lesions) epithelial changes referred to as **Cervical Intraepithelial Neoplasia (CIN)** or **Squamous intraepithelial lesions.**
- Squamous Intraepithelial Lesion (SIL) is the terminology used in cytology and CIN is the terminology used in histology(biopsies)
- Timely detection and diagnosis of CIN is essential in preventing the development of carcinoma (invasive lesion) and therefore providing curative treatment possible.
- **Not all cases of CIN progress to invasive cancer and some cases of CIN may spontaneously regress.**
- The **risk of persistence or progression to cancer is more in the high grade precancerous lesions** which are associated the high-risk HPV types.

Risk Factors (all of them are important)

- 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, multiple pregnancies.

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.
- 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.**

Pathogenesis from Robbins:

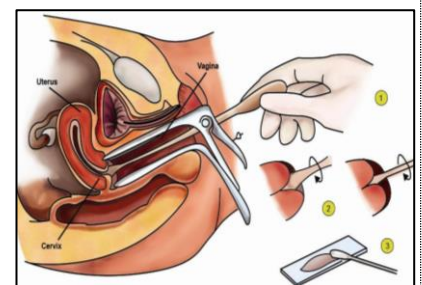
- HPV-infected squamous cells replicate HPV-DNA, as a consequence of expression of two potent oncoproteins encoded in the HPV genome called E6 and E7. These proteins inactivate two critical tumor suppressors, p53 and Rb, promoting growth and increased susceptibility to additional mutations that may eventually lead to carcinogenesis.
- HPV alone is not sufficient to drive the neoplastic process.
- The progression to cervical cancers has been attributed to diverse factors such as cigarette smoking and human immunodeficiency virus (HIV) infection, immune and hormonal status, or co-infection with other sexually transmitted agents. More recently, somatically acquired mutations in the tumor suppressor gene LKB1 were identified in more than 20% of cervical cancers.

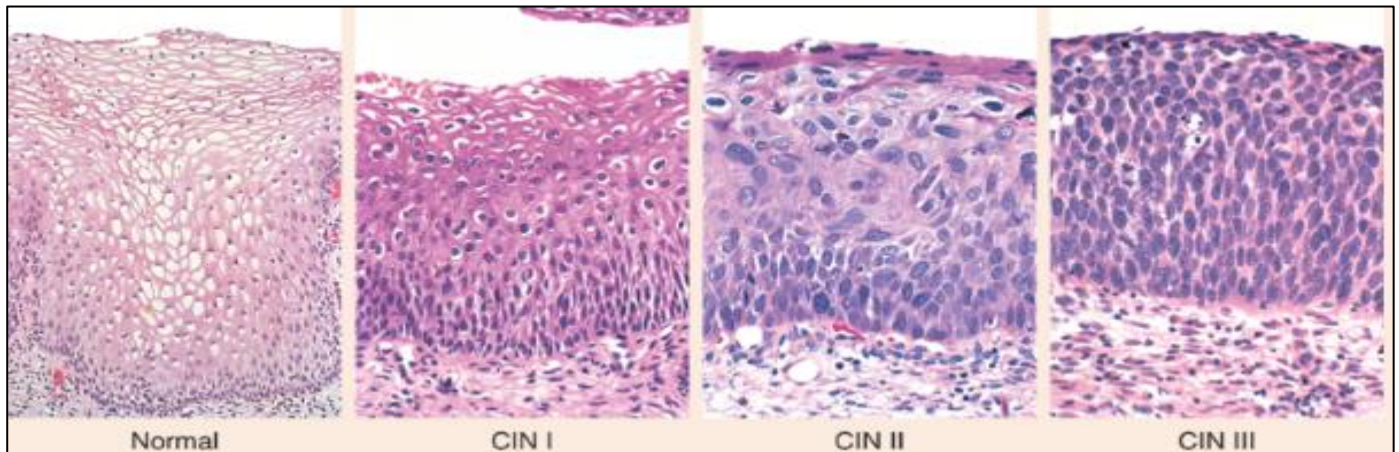
Cervical intraepithelial neoplasia (CIN)

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

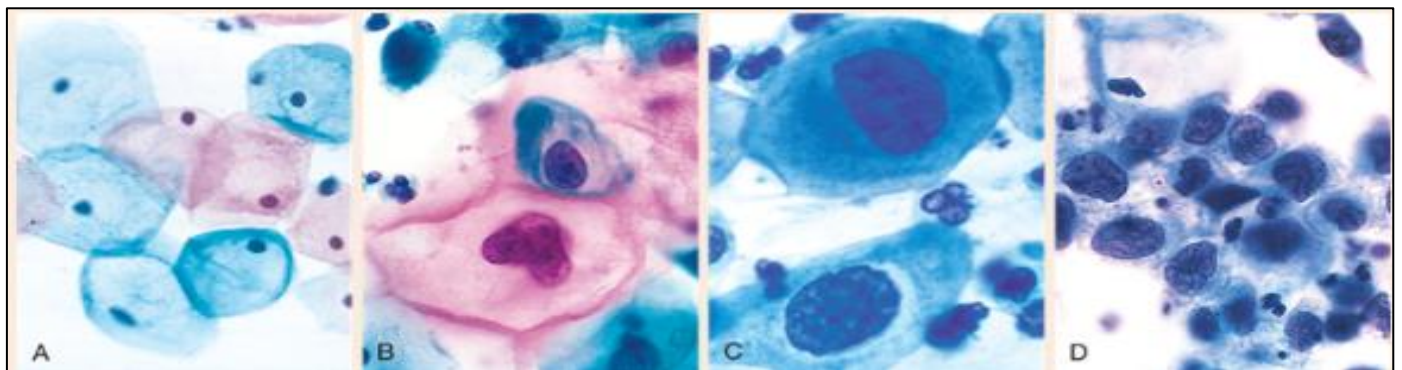
Cytology screening for precancerous lesions

- Cytologic examination can detect precancerous lesions long before any abnormality can be seen grossly
- For cytologic examination 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.**
- This screening for precancer should be done on all young and old women (usually from **age of 21 onwards**).
- In cytology smears we separate pre-cancer lesions into two groups :
 - **Low Grade SIL (= CIN1/mild dysplasia)**
 - **High Grade SIL (= CIN2 and 3/moderate to severe dysplasia)**
- Of Low Grade SIL 1-5 % become invasive
- Of High Grade SIL incidence is 6-74%





- HPV associated koilocytotic atypia
- Lower 1/3rd of the epithelium is replaced by pleomorphic cells
- Progressive atypia in the layers of the epithelium.
- Lower 2/3rd of the epithelium is replaced by pleomorphic cells
- carcinoma in situ with diffuse atypia and loss of maturation
- All levels of the epithelium are replaced by pleomorphic cells, (full thickness)



A Normal exfoliated superficial squamous epithelial cells.

B, CIN I/ low grade SIL

C, CIN II/ high grade SIL

D, CIN III/ high grade SIL

- Increase in the nucleus to cytoplasm (n/c) 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.

Signs of CIN/ SIL

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

Screening

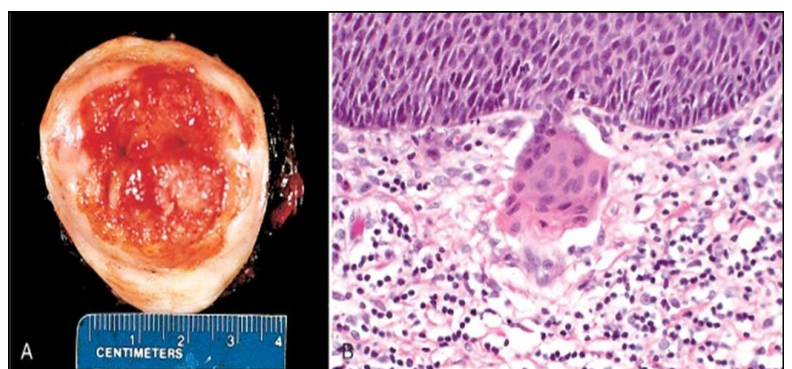
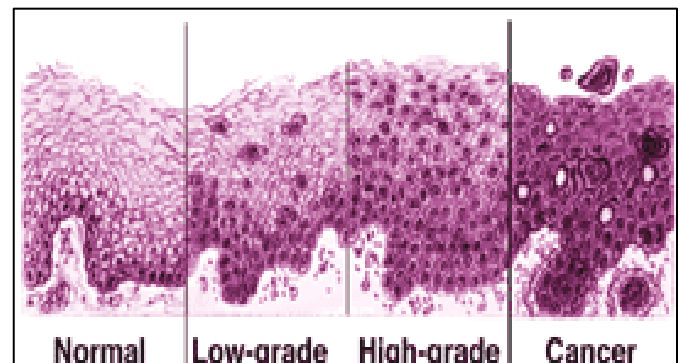
- The Pap smear detects early HPV infection.
- The common testing procedure for HPV infection is an annual pap exam. Should **start at the age 21**.
- Screening between age 21-29: Cytology screening test should be **done every 3 years**
- There is a **HPV DNA in-situ hybridization (ISH) test**, called the Digene Hybrid Capture test to identify 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.
- Screening between age 30-64: screening by Cytology + HPV test every 5 years (cytology every 3 years is acceptable).

Treatment

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

B. Invasive cervical carcinoma

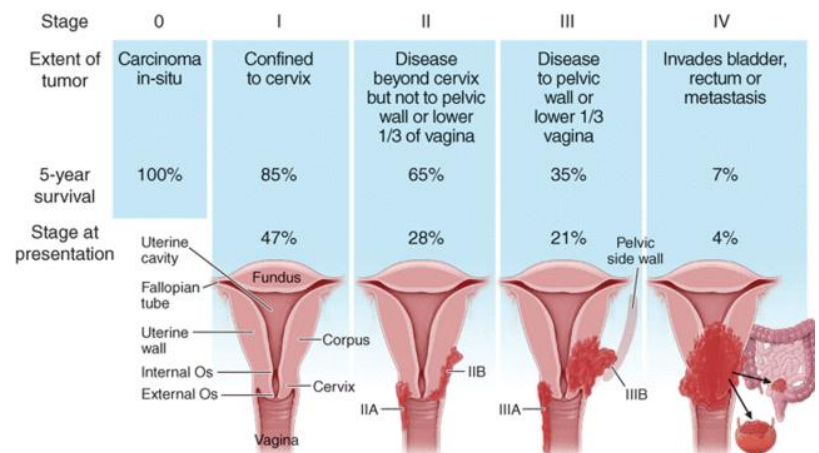
- **75 -90%** of invasive cancers are **Squamous cell carcinomas**, which generally evolve from pre-cancer CIN.
- The **remainders are Adenocarcinoma**.
- Squamous cell cancers are appearing in **increasingly younger women**, now with a **peak incidence at about 45 years**, about **10-15 years** after detection of their precursors.
- Mainly in the region of the **transformation zone**, and range from microscopic foci of early 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.



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

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



- 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.
- The early stages of cervical cancer may be completely asymptomatic.
- **Vaginal bleeding**, contact bleeding, or (rarely) a vaginal mass may indicate the presence of malignancy. Also, moderate **pain during sexual intercourse** and vaginal discharge are symptoms of cervical cancer. In advanced disease, metastases may be present in the abdomen, lungs or elsewhere.
- 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.

Treatment:

Depending on the stage the treatment options included are:

- If you still want to be able to have children, first the cancer is removed with a cone biopsy (cervical conization), and then you are watched closely to see if the cancer comes back.
- Simple hysterectomy (removal of the whole uterus including part of the vagina).
- Radical hysterectomy (removal of the whole uterus including part of the vagina along with the removal of lymph nodes in the pelvis).
- Adjunct chemotherapy and radiotherapy.

Summary

Summary from Robbins:

Cervical Neoplasia

- Risk factors for cervical carcinoma are related to HPV exposure, such as early age at first intercourse, multiple sexual partners, and other factors including cigarette smoking and immunodeficiency.
- Nearly all cervical carcinomas are caused by HPV infections, particularly high-risk HPV types 16, 18, 31, and 33; the HPV vaccine is effective in preventing infection due to HPV types 16 and 18.
- HPV expresses E6 and E7 proteins that inactivate the p53 and Rb tumor suppressors, respectively, resulting in increased cell proliferation and suppression of DNA damage–induced apoptosis. Loss of LKB1 gene is also involved.
- In high-grade cervical dysplasias (CIN II and III), HPV is incorporated into the genome of the host cell.
- Not all HPV infections progress to CIN III or to invasive carcinoma. The time course from infection to invasive disease is usually 10 years or more. In general, the risk of progression is proportional to the degree of dysplasia.
- The Pap smear is a highly effective screening tool for the detection of cervical dysplasia and carcinoma and has significantly reduced the incidence of cervical carcinoma.

Summary

		Gross	Microscopically	Comments
Cervical polyp		<ul style="list-style-type: none"> • Small. • Pedunculated. • Often sessile masses. 	<ul style="list-style-type: none"> • Overgrowth of benign stroma covered by epithelium. • Endocervical polyps are covered by endocervical, squamo-columnar or metaplastic squamous epithelium. • Ectocervical polyps are covered by stratified squamous epithelium. • The stroma is edematous and contains thick-walled blood vessels, fibrous tissue and some inflammatory cells. 	<ul style="list-style-type: none"> • Most originate from the endocervix • They are inflammatory proliferations of cervical mucosa and are not true neoplasms. • These lesions may bleed, thereby arousing concern, but they have no malignant potential
Cervicitis	A-Noninfectious cervicitis	- The cervix appears red and swollen .	<ul style="list-style-type: none"> • May comprise neutrophils or plasma cells and lymphocytes. • 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. 	<ul style="list-style-type: none"> • 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. • It is often asymptomatic.
	Comments			
	B-Infectious cervicitis	<ul style="list-style-type: none"> • Most often involves the endocervix. • Can be caused by Trichomonas vaginalis, Candida albicans, Chlamydia trachomatis, HPV and HSV. • Is often asymptomatic • May manifest as vaginal discharge (leukorhea) 		

Cervical Cancer:

	Comments	Treatment
A- Precancerous lesion of cervical carcinoma (CIN/SIL)	<ul style="list-style-type: none"> The HPV is the number one reason for abnormal cells of the cervix. HPV can be detected in 85 -90 % of pre-cancer lesions. High risk types HPV: <u>16, 18, 31, 33, 35, 39, 45, 52, 56, 58, and 59.</u> Low risk types HPV: <u>6, 11, 42, 44 .</u> These types result in condylomas. 	<ul style="list-style-type: none"> Laser or cone biopsy is the most effective method of managing patients with High grade SIL in cancer prevention.
B- Invasive cervical carcinoma	<ul style="list-style-type: none"> 75 -90% of invasive cancers are Squamous cell carcinomas, which generally evolve from pre-cancer CIN. Squamous cell cancers are increasing in younger women, now with a peak incidence at about <u>45 years.</u> 	<ul style="list-style-type: none"> Cancer is removed with a cone biopsy (cervical conization) if patient still wants to conceive. Simple hysterectomy. Radical hysterectomy. Adjunct chemotherapy and radiotherapy.

Questions

1/ 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, punctation, 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

2/ 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)

3/ 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- D
- 2- D
- 3- C

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If there is any mistake or feedback please contact us on: 432PathologyTeam@gmail.com

