

UTERINE CERVIX

{ ومن لم يذق مرّ التعلّم ساعةً.. تجرع ذلّ الجهل طوال حياته }



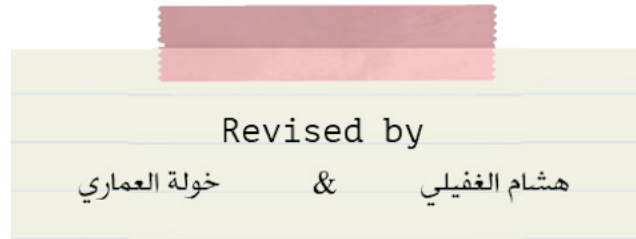
Lecture Five

Objectives:

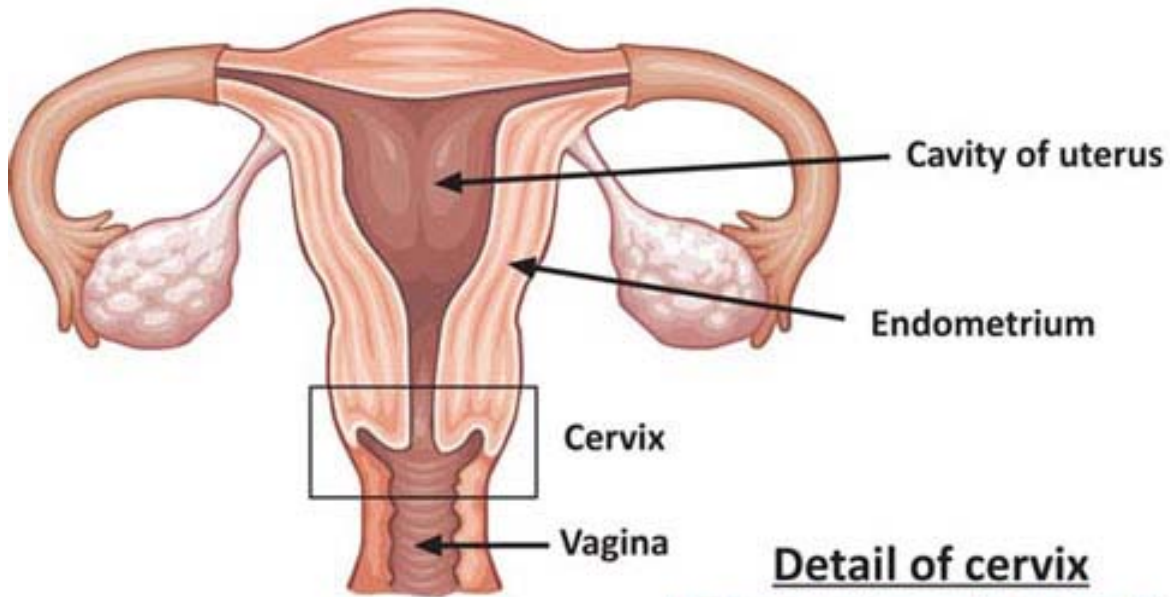
At the end of this lecture, the student should be able to:

- Know 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.

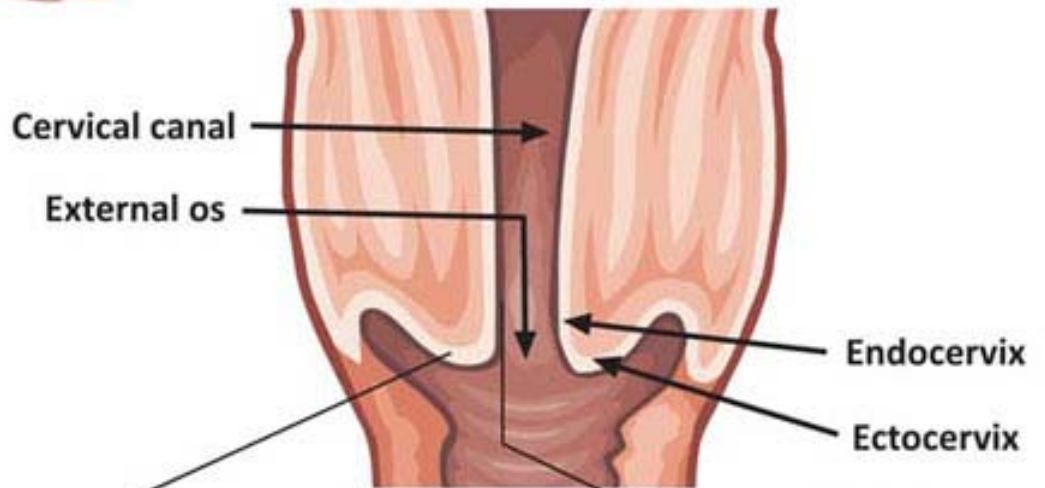
References: Lecture slides & Robbins



Uterus and cervix
in cross section (front view)

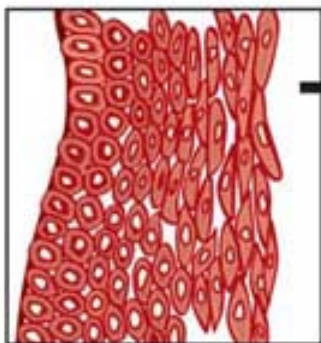


Detail of cervix

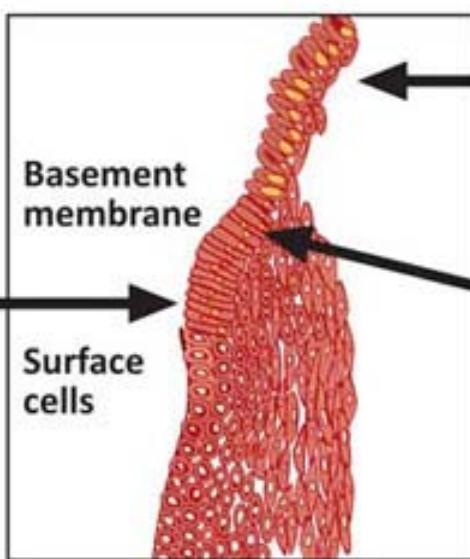


Cell types

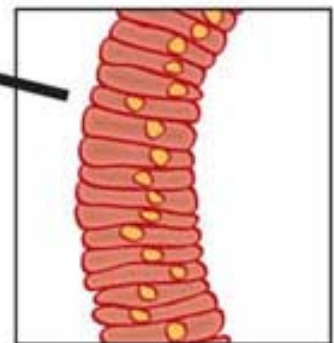
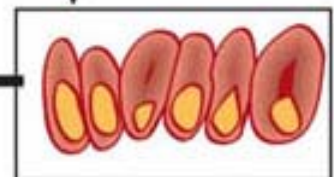
Squamous epithelium

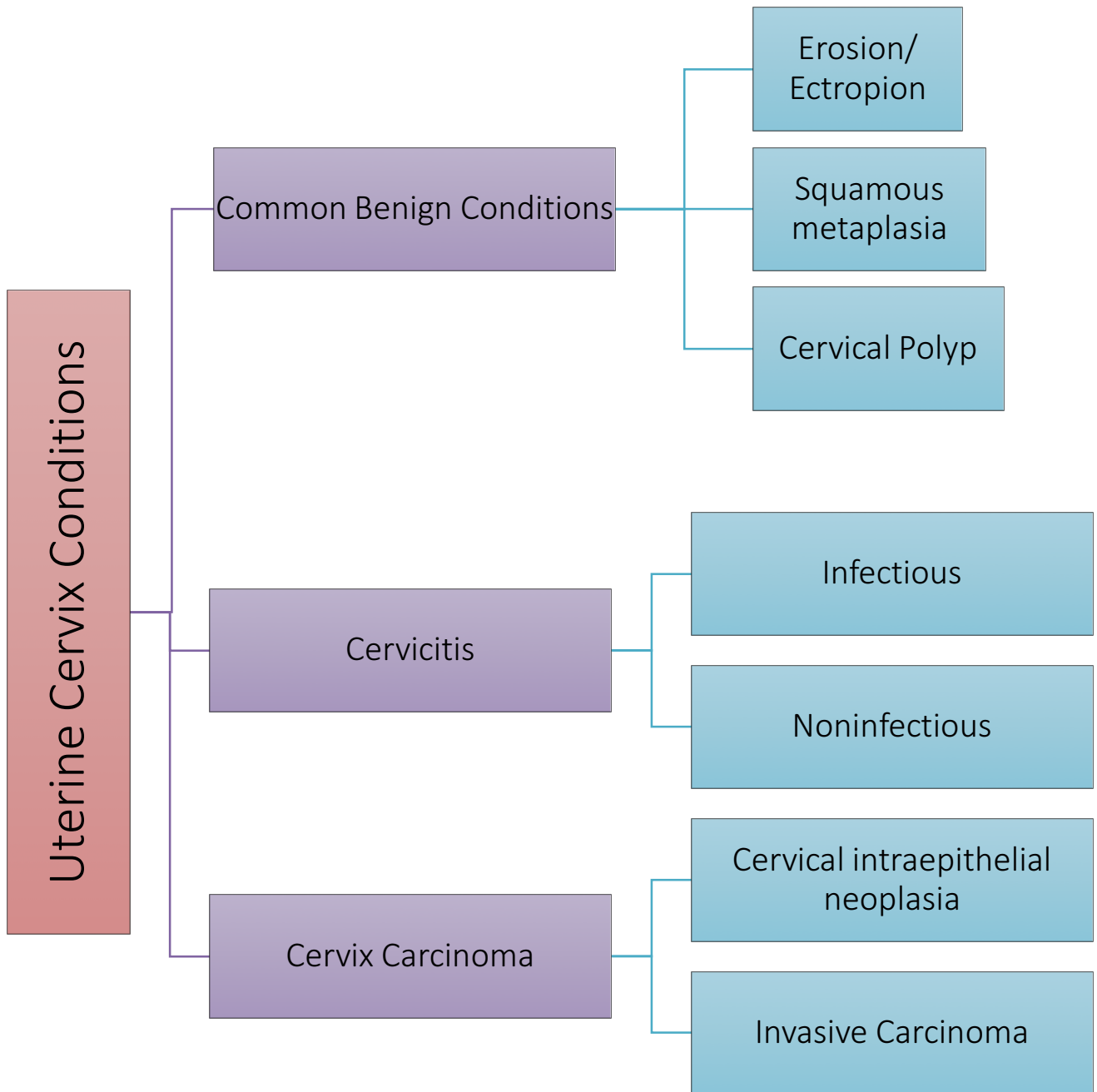


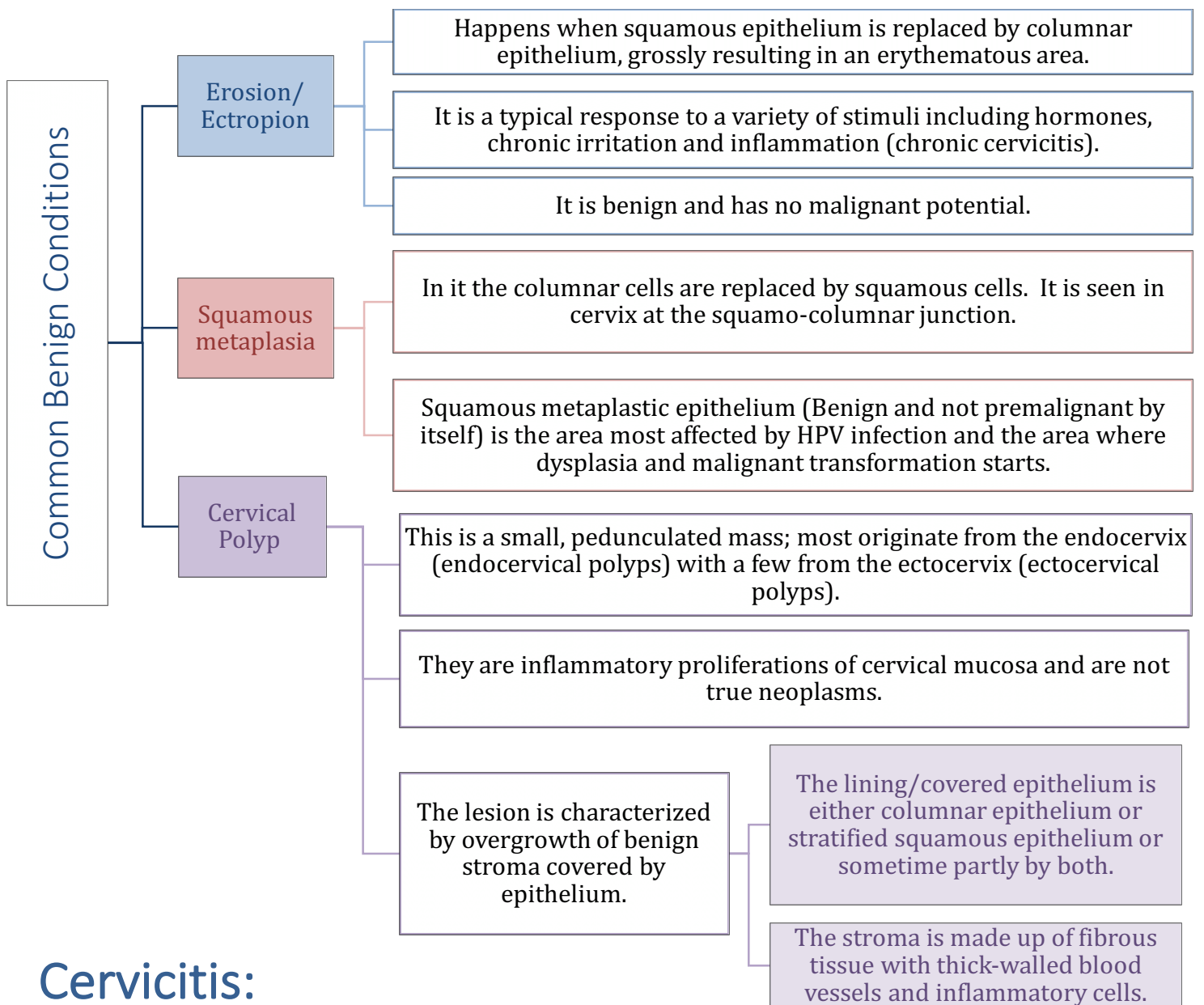
Transformation zone



Columnar epithelium







Cervicitis:

Inflammation of cervix; can be non-infectious or infectious. Extremely common and are associated with a purulent vaginal discharge.

Noninfectious (Nonspecific) Cervicitis:

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

| | |
|----------------------------|---|
| Clinical Appearance | <ul style="list-style-type: none"> • Noninfectious cervicitis is often asymptomatic. • The cervix appears red and swollen |
| Histology | <ul style="list-style-type: none"> ▪ 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. |

Infectious Cervicitis:

could be symptomatic or asymptomatic

- Can be caused by various organisms e.g. Staphylococci, enterococci, Gardnerella vaginalis, Trichomonas vaginalis, Candida albicans and Chlamydia trachomatis. (discussed below)
- Most often involves the endocervix.
- May be asymptomatic & may manifest as vaginal discharge or itching.

It's an important topic they always ask about it in exam (HPV, screening programs).



| | Candidiasis (moniliasis) | Trichomoniasis | Chlamydia trachomatis ¹ |
|-----------------|---|---|---|
| Info | Common involves cervix & vagina | Sexually transmitted (STD) | The most common STD in the developed countries. |
| Caused By | Candida albicans ² | Trichomonas vaginalis ³ | |
| Associated with | DM, pregnancy, antibiotic therapy , oral contraceptive use & immunosuppression. - Changing in hormones - Antibiotics (case: young patient with acne, then comes with vaginal discharge and itching) | <ul style="list-style-type: none"> • Greenish-yellow frothy and foul smelling vaginal discharge • Painful urination, dyspareunia. • vulvovaginal itching or irritation. | <ul style="list-style-type: none"> • May coexist with Neisseria gonorrhoeae infection. • A frequent cause of pelvic inflammatory disease. • Can cause lymphogranuloma venereum |
| Characteristics | White patchy mucosal lesions with thick curdy white discharge and vulvovaginal pruritis. Ulcers may develop. | | Most often asymptomatic. But in symptomatic cases there is a mucopurulent cervical discharge with a reddened, congested and edematous cervix. It may be associated with urethritis. |
| Cytology Smear | Shows fungal colonies in the form of spores and branching pseudohyphae on the cervical epithelium. Chronic inflammatory cells are present. | Found in Pap-stained vaginal smears 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. | - |
| | HSV | Human papilloma virus (HPV) | |
| Info | Herpes simplex virus type 2 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. | It's a very common and prevalent disease. Common in cervix. Over 20 serotypes infect the female genital areas and cause a variety of different lesions depending on the serotypes. | |
| Associated with | | <ul style="list-style-type: none"> ▪ Associated with increased risk of subsequent cervical cancer. ▪ HPV infection causes koilocytic atypia⁴ in the cervical squamous epithelium ▪ May cause any of the following depending on the serotype: <ol style="list-style-type: none"> 1) Condyloma: develops in the squamous epithelium of the cervix. The lesions may be flat or exophytic condylomma acuminatum. Usually caused by HPV serotypes 6 and 11. 2) Mild dysplasia: usually caused by "low risk" HPV serotypes, 6 & 11. 3) High- grade dysplasia: caused by "high risk" HPV (types 16 and 18) and moderate risk HPV (types 31, 33 and 35). = carcinoma in situ, this is the bad one. It's very important to know the serotype and related disease. <p>Koilocytes: Squamous epithelial cells that have undergone structural change due to infection of the cell by HPV. They show koilocytosis or koilocytic atypia which is the following cellular changes:</p> <ul style="list-style-type: none"> - Nuclear enlargement. - Nuclear hyperchromasia. - Perinuclear halo (clear area around the nucleus). - Irregular nuclear membrane. | |

¹ An obligate, gram-negative intracellular pathogen.

² A normal component of the vaginal flora

Cervix Carcinoma:

- Most tumors of the cervix are of epithelial origin.
- Most common cervical cancer is **squamous cell carcinoma**. Other types are **adenocarcinoma**, **neuroendocrine carcinoma**, etc.
- Use of **PAP screening has lowered the incidence of invasive cancer** and deaths by it. Which remains the most successful cancer screening test ever developed.

What causes Cervical carcinoma?

HPV; it's 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 of HPV: 16, 18, 31, 33, 35, 39, 45, 52, 56, 58, and 59.**
- **Low risk types of HPV: 6, 11, 42, 44. These types result in condylomas.**

Risk Factors

- Early age at first intercourse or 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.

Precancerous lesion of cervical carcinoma:

Cervical intraepithelial neoplasia (CIN) or squamous intraepithelial lesions (SIL).

All invasive squamous cell carcinomas arise from noninvasive pre-cancer epithelial lesions called **cervical intraepithelial neoplasia (CIN)** or **squamous intraepithelial lesions (SIL)**⁵.

- Timely detection and diagnosis of CIN/SIL is essential in preventing the development of carcinoma (invasive lesion) and therefore providing curative treatment.
- **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 the ones associated with the high-risk HPV serotypes.

Cervical intraepithelial neoplasia (CIN): sometimes it starts as high grade without mild. Intraepithelial = squamous

- Precancerous lesions of the cervix.
- Pre-cancer changes can precede the development of an overt cancer by many years.
- Lesions may begin as Low Grade CIN and progress to High Grade CIN, or they might start straight off as High Grade CIN.
- CIN peaks in incidence at about 30 years of age, whereas invasive carcinoma peaks at about 45 years of age.

³ A unicellular flagellated protozoan

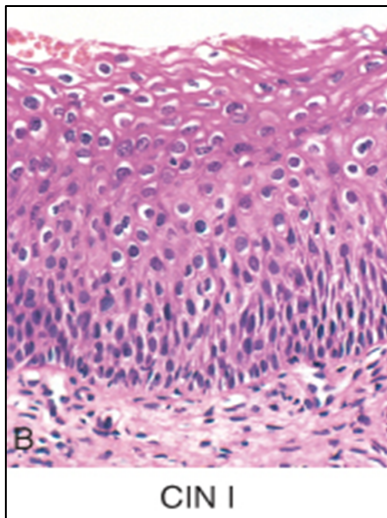
⁴ Keep that in mind, we'll discuss it further more below.

⁵ SIL is the terminology used in cytology (pap smears) and CIN is the terminology used in histology (biopsies)

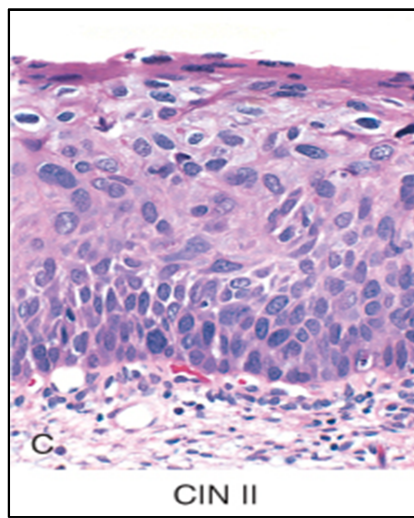


▪ **Based on histology, pre-cancer lesions are graded as follows⁶:**

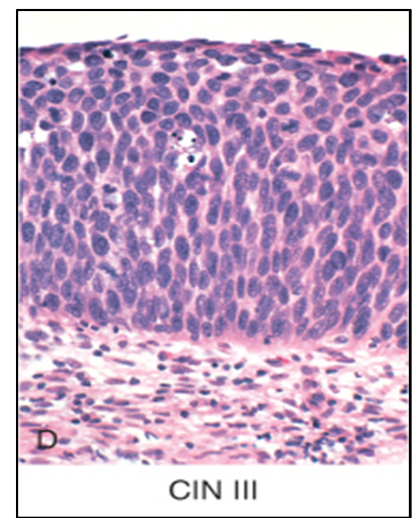
- CIN I: Mild Dysplasia. **Low grade**
- CIN II: Moderate Dysplasia
- CIN III: Severe Dysplasia and Carcinoma in situ (CIS). **(CIN II & CIN III both high grade)**



Mild dysplasia= CIN I with HPV associated koilocytotic atypia (in the superficial layers). Lower 1/3rd of the squamous epithelium is replaced by pleomorphic cells.



Moderate dysplasia= CIN II. There is progressive atypia in the layers of the epithelium; lower 2/3rd of the epithelium is replaced by pleomorphic cells. (takes the form of delayed keratinocyte maturation).



Severe dysplasia= CIN III (CIS). There is diffuse atypia and loss of maturation. All levels of the epithelium are replaced by pleomorphic cells, **(full thickness)**

Staging: additional information but they may become nasty and ask you about it.

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

Pap Screening Test: Cytology Screening for Precancerous Lesions:

identifies pre-cancer

- **Cytologic examination** can detect precancerous SIL long before any abnormality can be seen grossly, using the PAP test.
 - PAP test is the cytologic examination of the cells of cervix.
 - In it the cervix is examined and the cells lining the cervical wall at the transformation zone 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.

Only pap test could give us the hint, it won't show on radiological examination, it's mandatory for women

⁶ This three-tiered grading system has recently been simplified to a two-tiered system, with CIN I renamed low-grade squamous intraepithelial lesion (LSIL) and CIN II and CIN III combined into one category referred to as high-grade squamous intraepithelial lesion (HSIL).

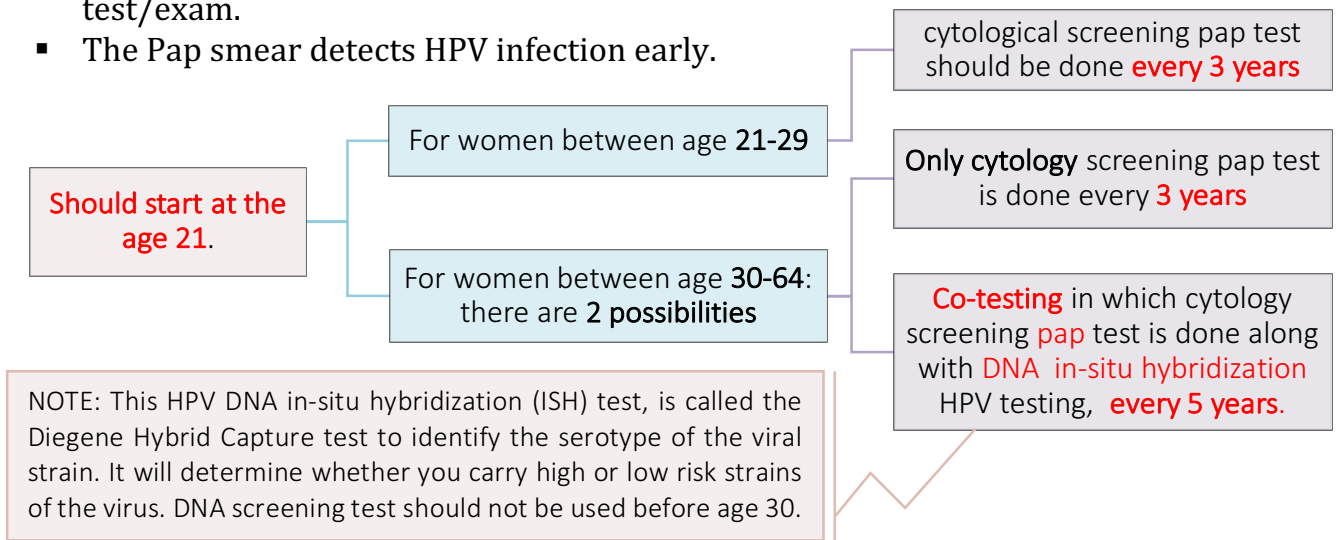
- **SILs are divided into low grade and high grade SIL:**
 - In cytology smear report these are few of **the possible diagnoses:**
 - a) Normal cells/ Negative for squamous intraepithelial lesion (SIL)
 - b) Low Grade SIL (= CIN1/mild dysplasia)
 - c) High Grade SIL (= CIN2 and 3/moderate to severe dysplasia)
 - 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**

- **Signs of CIN/ SIL:**

There are no visible symptoms of dysplasia of the cervix, and it is difficult to diagnose without a Pap test; so regular pap exams should be done to detect any abnormal cells.

- **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.



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

Invasive Cervical Carcinoma: normal cervix doesn't produce keratin but when you have carcinoma you get keratin

- About 75-90% of invasive cancers are **Squamous cell carcinomas (SCC)**, which generally evolve from pre-cancer CIN/SIL lesions. The remainder are Adenocarcinoma.
- SCC appears in increasingly younger women, now with a peak incidence at about 45 years, about 10-15 years after detection of their precursors.
- Keep in mind that the progression of CIN to invasive carcinoma is unpredictable and requires **HPV infection** as well as mutations in genes such as **LKB**. **Risk factors for progression include:**
 - Cigarette smoking.
 - HIV (suggests that immune surveillance has a role in holding CIN in check).
- Cervical carcinomas are graded from 1 to 3 (i.e. well, moderately and poorly differentiated) based on cellular "squamous" differentiation and staged from 1 to 4 depending on clinical spread.

Morphology:

- Mainly in 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 exophytic⁷.
- Tumors encircling the cervix and penetrating the underlying stroma **produce a barrel cervix**, which can be identified by direct palpation.

Clinical Course:

Patients on schedule with their PAP screening test

HPV is detectable by molecular methods in nearly all cases of CIN and cervical carcinoma.

Many of cervical cancers are diagnosed in early stages, and the vast majority are diagnosed in the pre-invasive phase.

Patients who have never had a PAP screening test or haven't for years

More advanced cases are seen in those women.

Hence, it is often symptomatic, with patients coming to medical attention for unexpected vaginal bleeding, leukorrhea, painful coitus (dyspareunia), or dysuria.

Signs and symptoms:

- **Early stages of cervical cancer** → May be completely asymptomatic.
- **If symptomatic:**
 - **Vaginal bleeding, contact bleeding, or cervical mass.**
 - Leukorrhea.
 - Painful coitus which is known as **dyspareunia**, or dysuria.
- **Advanced Cervical Cancer symptoms:**
 - Loss of appetite & Weight loss.
 - Fatigue.
 - Pelvic, back & leg pain.
 - Swollen legs.
 - Heavy bleeding from the vagina.
 - Bone fractures.
 - **Leakage of urine or faeces from the vagina (rarely).**

Metastasis:

- In advanced disease, Metastases may be present in the abdomen, lungs or elsewhere.
- Extension into the parametrial soft tissues can affix the uterus to the surrounding pelvic structures.
- The likelihood of spread to pelvic lymph nodes correlates with the depth of tumor invasion and the presence of tumor cells in vascular spaces.

Mortality:

- Strongly related to tumor stage.
- Most patients with advanced disease die as a result of local invasion not distant metastasis (eg. renal failure).

⁷ Tending to grow outward beyond the surface epithelium from which it originates.



There's an **HPV vaccine for types 6, 11, 16, and 18** which is very effective in preventing HPV infections & is expected to greatly lower the frequency of genital warts and cervical cancers associated with these HPV serotypes. Despite its efficacy, the vaccine does not replace the need for routine cervical cancer screening— many at-risk women are already infected, and the vaccine protects against only some of the many oncogenic HPV serotypes.

Depending on the stage the treatment options are:

- If a patient **wants to be able to have children**, the cancer is removed with a **cone biopsy** (*cervical conization*), and then followed up regularly.
- **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.**

Extra Summaries, Pictures and helpful explanations

C. trachomatis is by far the most common of the mentioned pathogens, accounting for as many as 40% of cases of cervicitis encountered in sexually transmitted disease (STD) clinics. Morphology: Nonspecific cervicitis may be either **acute** or **chronic**. The relatively uncommon **acute form** is limited to women in the postpartum period and usually is caused by staphylococci or streptococci. Chronic cervicitis consists of inflammation and epithelial regeneration, some degree of which is common in all women of reproductive age. Cervicitis commonly comes to attention on routine examination or because of leukorrhea.

How will HPV lead to cancer?

HPV loves immature squamous cells of the transformation zone, so while keeping this in mind; when the infection takes place, it is usually eliminated by inflammatory responses. However, a subset of infections persists and some of these progress to cervical intraepithelial neoplasia (CIN); the precursor lesion for most invasive cervical carcinomas. HBV alone is not sufficient to drive the neoplastic process. The progression has been attributed to diverse factors such as immune and hormonal status, or co-infection with other sexually transmitted agents.



What is the transformation zone?

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.

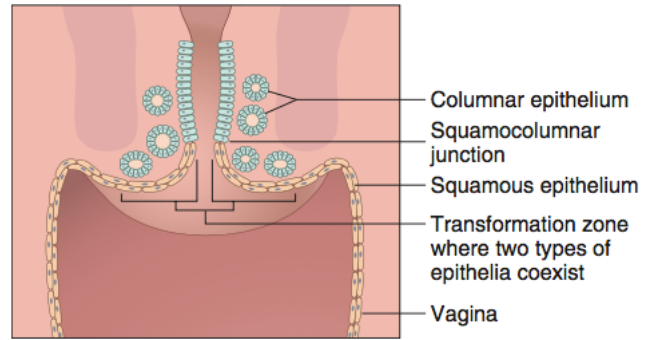
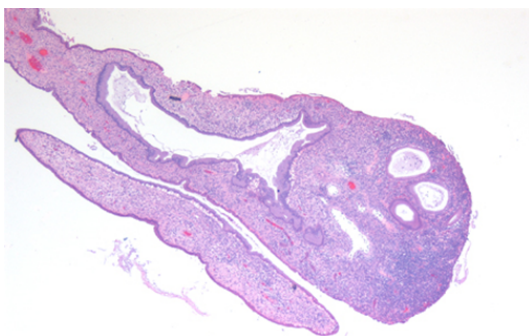


Figure 18-4 Development of the cervical transformation zone.

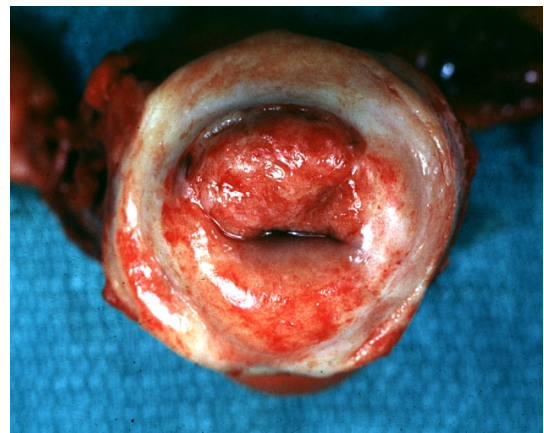
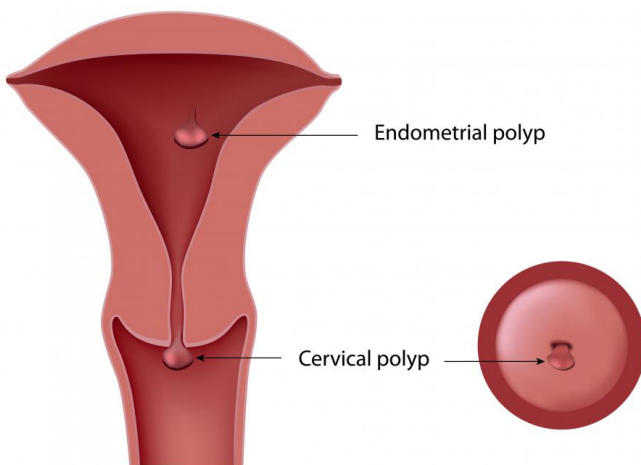
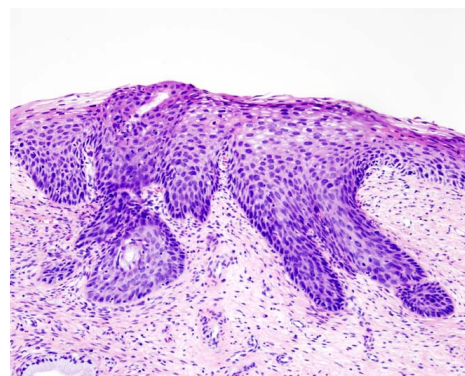
Genes:

More recently, somatically acquired mutations in the tumor suppressor gene LKB1 were identified in more than 20% of cervical cancers. LKB1 was first identified as the gene mutated in Peutz-Jeghers syndrome, an autosomal dominant condition characterized by hamartomatous polyps of the GI tract (Chapter 14) and a significantly elevated risk of epithelial malignancies at a variety of anatomic sites including the cervix. LKB1 is also frequently inactivated in lung cancer. The LKB1 protein is a serine-threonine kinase that phosphorylates and activates AMPK, a metabolic sensor. AMPK in turn regulates cell growth through the mTOR complex.

Cervical Polyp:

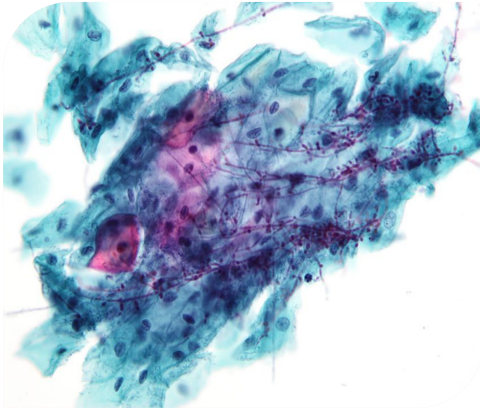


Cervical tumor:



wiseGEEK

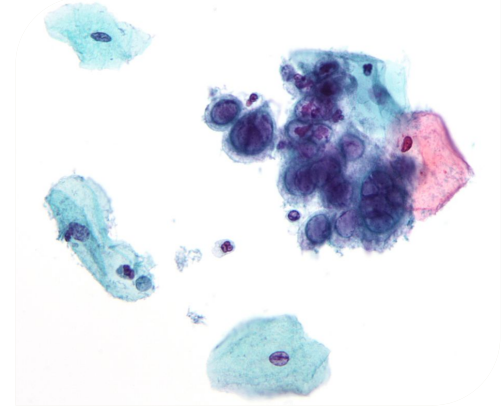
Candidiasis (moniliasis):



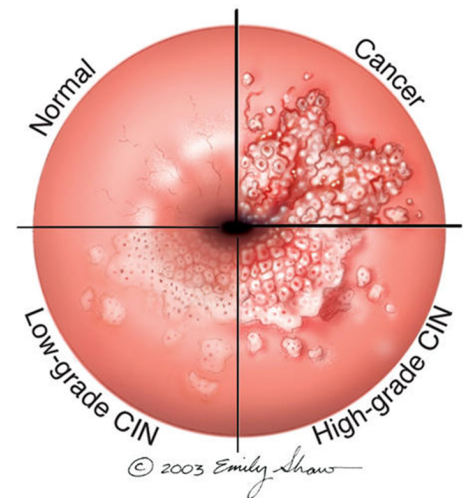
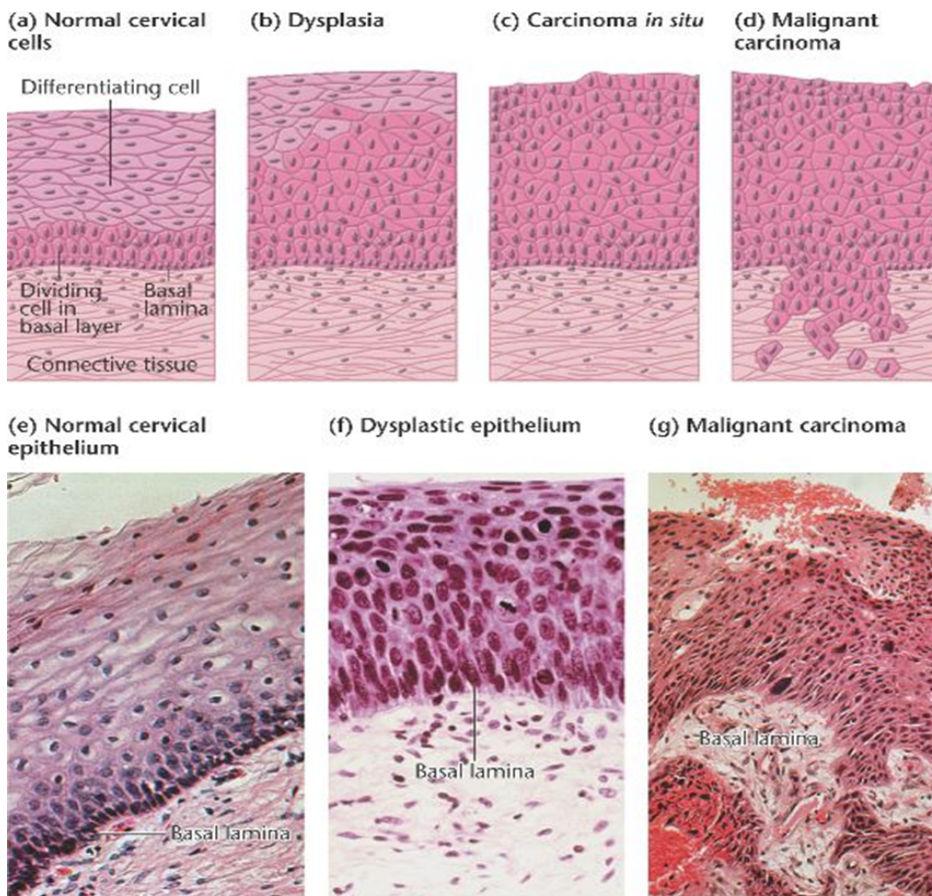
Trichomoniasis:



Herpes simplex virus (HSV):



Precancerous lesion of cervical carcinoma: cervical intraepithelial neoplasia (CIN) or squamous intraepithelial lesions (SIL).



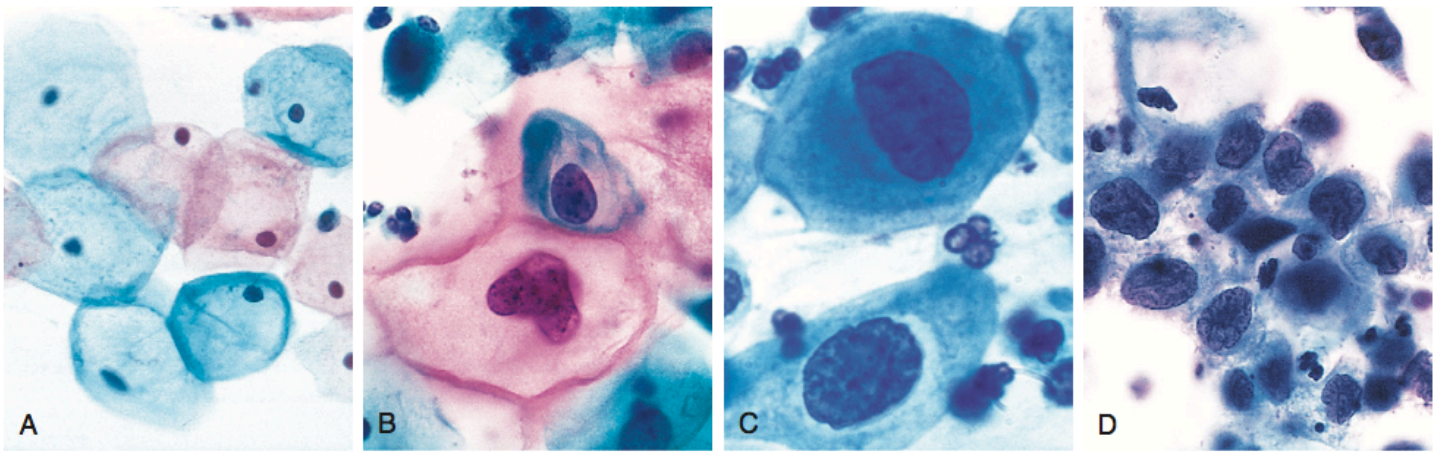


Figure 18-7 Cytologic features of cervical intraepithelial neoplasia (CIN) in a Papanicolaou smear. Superficial squamous cells may stain either red or blue. **A**, Normal exfoliated superficial squamous epithelial cells. **B**, CIN I—low-grade squamous intraepithelial lesion (LSIL). **C** and **D**, CIN II and CIN III, respectively—both high-grade squamous intraepithelial lesions (HSILs). Note the reduction in cytoplasm and the increase in the nucleus-to-cytoplasm ratio as the grade of the lesion increases. This observation reflects the progressive loss of cellular differentiation on the surface of the cervical lesions from which these cells are exfoliated (Figure 18-6).

(Courtesy of Dr. Edmund S. Cibas, Brigham and Women's Hospital, Boston, Massachusetts.)

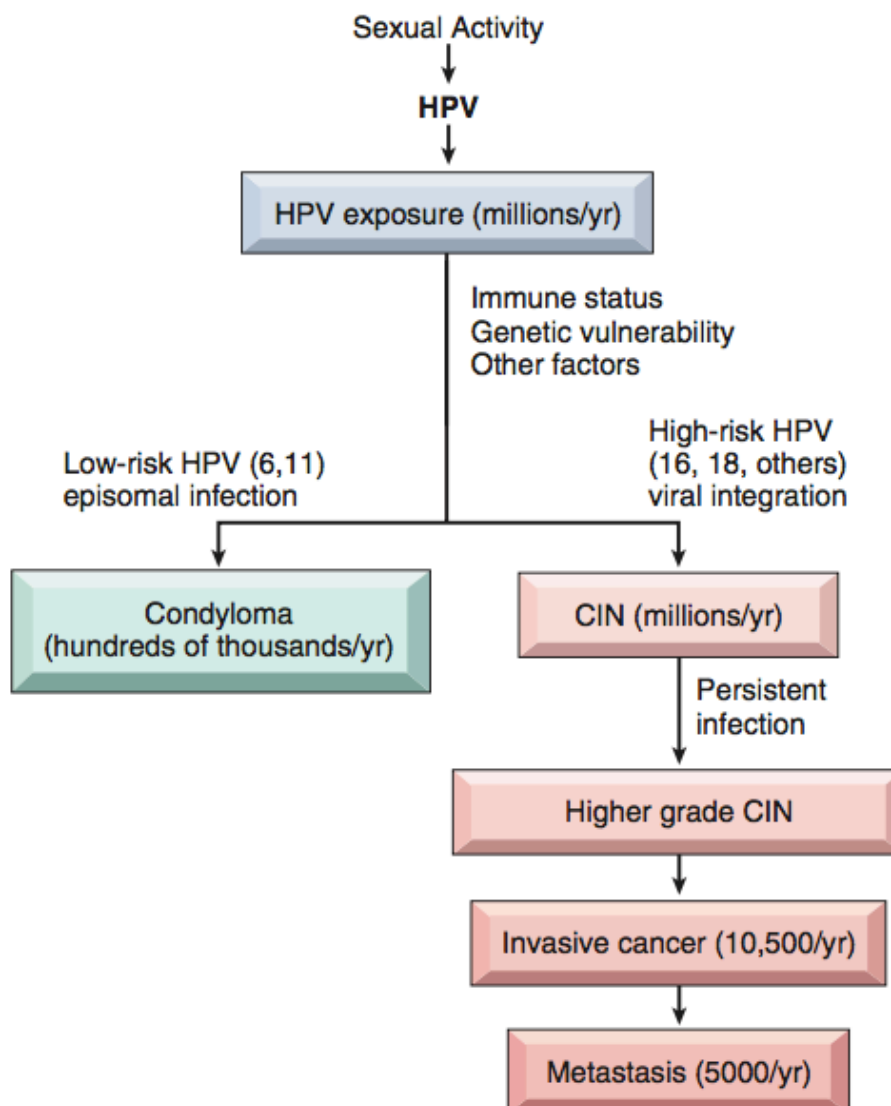


Figure 18-5 Possible consequences of human papillomavirus (HPV) infection. Progression is associated with integration of virus and acquisition of additional mutations as discussed in the text. CIN, cervical intraepithelial neoplasia.

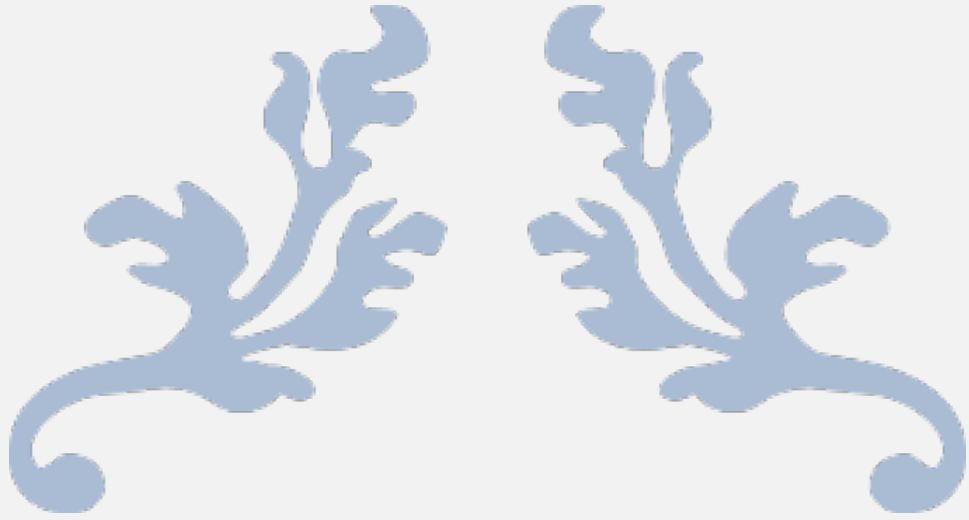
Now Check Your Understanding!

MCQs:

- 1. What are the risk factors for the development of CIN and invasive carcinoma?**
 - A. Early age at first intercourse.
 - B. Multiple sexual partners.
 - C. persistent infection by high risk papillomaviruses.
 - D. All of the above.
- 2. On the basis of histology, pre-cancer lesions are graded as follows:**
 - A. CIN I, CIN II, CIN III
 - B. CIN I, CIN VI, CIN V
 - C. CIN II, CIN X, CIN IX
 - D. None of the above
- 3. Which of the following statements is false?**
 - A. HPV is not detectable by molecular methods in cases of CIN and cervical carcinoma.
 - B. Due to the PAP screening screening test, many of cervical cancers are diagnosed in early stages.
 - C. The early stages of cervical cancer may be completely asymptomatic.
 - D. Symptoms of advanced cervical cancer may include loss of appetite.
- 4. Which one of the following is the most common cervical cancer?**
 - A. Squamous cell carcinoma
 - B. Adenocarcinoma
 - C. Neuroendocrine carcinoma
- 5. The usage of PAP screening has effect on which of the following?**
 - A. Lowered the incidence of invasive uterine cancer
 - B. Lowered the incidence of colon carcinoma
 - C. Lowered the incidence of breast cancer
- 6. Which of the following is the most common cause of cervical cancer?**
 - A. HIV
 - B. HPV
 - C. Hepatitis C virus

MCQs:
1: D 2: A 3: A 4: A 5: A 6: B





Thanks for checking our work! Good Luck.

Done by:

نوف التويجري & عمر آل سليمان

ساره القحطاني

نجود الحيدري

شمام السحيلي

{ قال صلى الله عليه وسلم: من سلك طريقًا يلتمس فيه علمًا سهل الله
له به طريقًا إلى الجنة }

