جامعة الملك سعود
King Saud University

PATHOLOGY 438

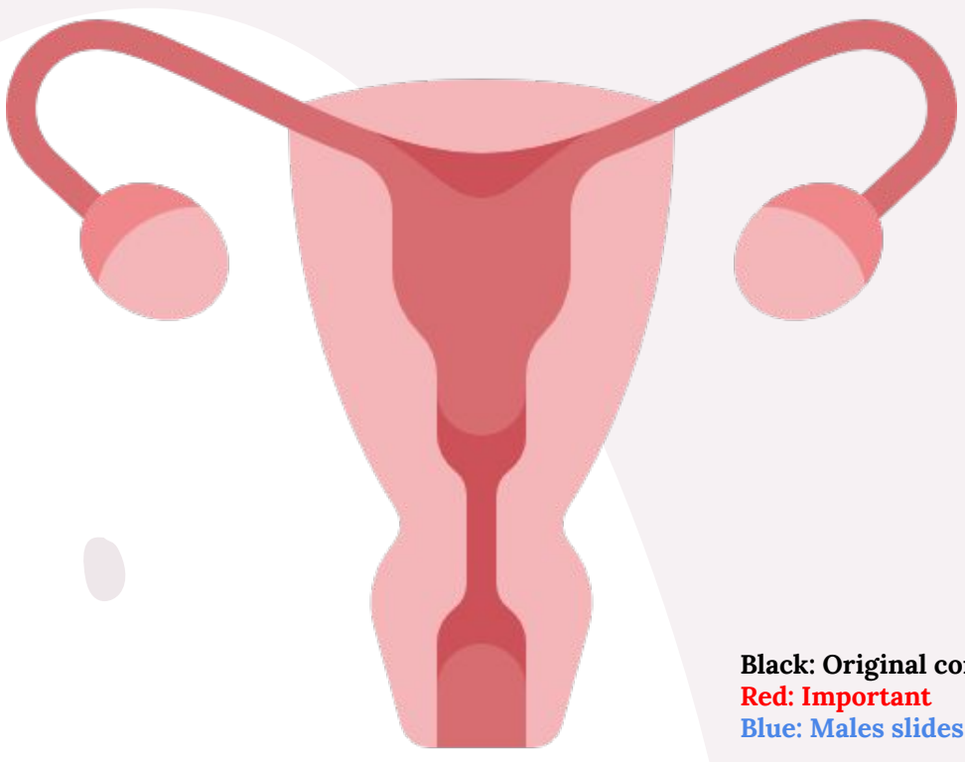
Editing file

Pathoma Video

Pathology of Cervix

Objectives

- 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 program.
- Know the incidence, risk factors, clinical presentation, pathological features and prognosis of cervical squamous cell carcinoma.

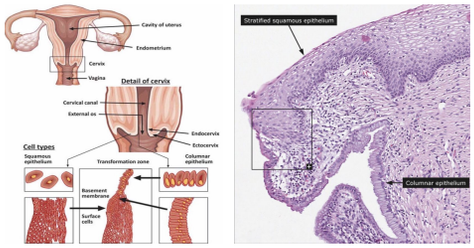


Black: Original content
Red: Important
Blue: Males slides
Orange: Doctor notes
Grey: Extra/Robbins
Green: Females slides

Reviewed by Razan AlRabah & Ibrahim AlDakhil

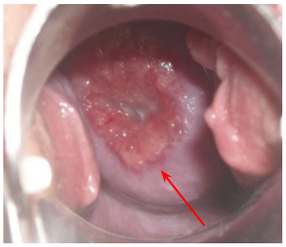
Pathology of Uterine Cervix

Introduction



- **Endocervix:** lined by columnar epithelium.
- **Ectocervix:** lined by Stratified squamous epithelium.
- **Transformation zone:** the area in between. Most common place of cervical pathology.

Cervical Ectropion (Erosions) (Female slides)



- **Squamous Epithelium is replaced by columnar epithelium.**
- Resulting in an erythematous area[1].
- **Benign**, with no malignant potential.
- It occurs in response to (causes):
  - Hormones, irritation, oral contraceptives and inflammation (chronic cervicitis).

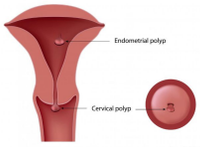
Squamous Metaplasia

- **The columnar cells are replaced by squamous cells[2].**
- It is seen in the cervix at the **squamocolumnar junction** (transitional zone).
- Squamous metaplastic epithelium is a sensitive area that is most affected by human papillomavirus (**HPV**) infection.
- The area where dysplasia and malignant transformation starts.
  - However, it is **benign** and by itself not considered premalignant.

Cervical polyp

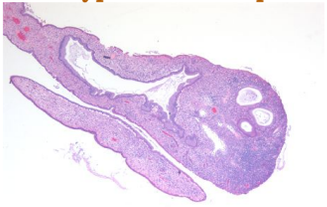
- This is a **small, pedunculated mass** (not a true neoplasm)
- **Types:**

1. **Endocervical polyps:**
   - Originate from endocervix
   - Most common polyps.



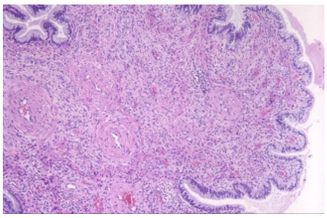
2. **Ectocervical polyps:**
   - Originate from ectocervix.
   - Less common.

Polypoidal in shape



Morphology

- Overgrowth of **benign** cervical stroma covered by cervical epithelium:
  - **The epithelium covering the polyp:** can be **columnar** (**most common**) or stratified squamous or sometimes partly both.
  - **The stroma:** is made up of fibrous tissue with thick-walled blood vessels and inflammatory cells.



1. Extending distally out of the external OS.
2. Extend proximal.

Cervicitis

Non-infectious Cervicitis

- Is inflammation (acute or chronic) of the cervix caused by:
  - Chemical irritation (e.g. douche).
  - Mechanical irritation (e.g. tampon, diaphragm).

Clinical appearances

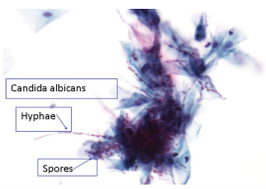
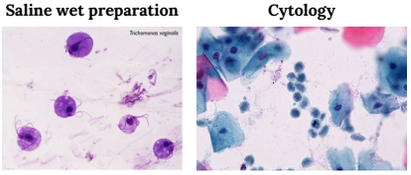
- Often **asymptomatic**.
- The cervix appears red and swollen.

Histology

- Inflammatory cells: neutrophils in acute, plasma cells and lymphocytes in chronic.
- Squamous metaplasia is common in chronic cervicitis.

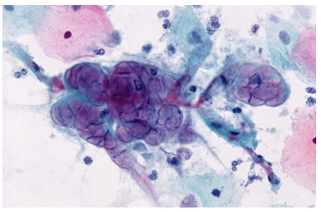
Infectious cervicitis

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

	1. Candidiasis (moniliasis)	2. Trichomoniasis	3. Chlamydia trachomatis
Organism	- **Candida Albicans.** - Fungal colonies. - Vaginal flora.	- **Trichomonas vaginalis**: unicellular flagellated protozoa.	- Obligate, gram -ve intracellular pathogen. - May coexist with N. gonorrhoeae.
Transmission/ Association	**Immunosuppression**: DM, pregnancy, antibiotic therapy, oral contraceptives.	**Sexually transmitted disease** involves the vagina and cervix.	**Most common sexually transmitted disease** in the developed countries.
Clinical Features	- Involve cervix & vagina. - **White patchy mucosal lesion.** - **Thick curdy white discharge.** - Vulvovaginal pruritus (itching). - Ulcers in severe cases.	- **Greenish-yellow frothy** and **foul smelling** vaginal discharge. - Painful urination, - Vulvovaginal itching. - Dyspareunia.	- Most often asymptomatic. - **Mucopurulent cervical discharge.** - Reddened, congested and edematous cervix. - Maybe associated with **urethritis**. - Common cause of pelvic inflammatory disease which leads to ectopic pregnancy and infertility. - Can cause *lymphogranuloma venereum* (ulcerative disease of the genital area caused by the L1,L2,L3 serotypes).
Pap smear (Cytology)	- Appear as spores. - Branching pseudohyphae on the cervical epithelium. - Chronic inflammatory cells. 	- Seen in a background of inflammatory cells. **- Saline wet preparation**: motile trophozoites are seen. **Saline wet preparation** **Cytology** 	

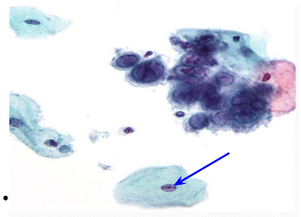
Cervicitis

4. Herpes simplex virus (HSV)



- HSV **Type 2** infection (most common cause of genital herpes)
- Sexual transmission.
- It produces vesicles and **ulcers** that can involve the cervix, vagina ,vulva, urethra, and perianal skin.

Pap smears (cytology):



- **3 Ms: Multinucleation, molding of nuclei and margination of chromatin.**
- **Intranuclear "Cowdry type A" viral inclusions.**
- Nucleic Ground glass appearance due to accumulation of viral particles.

5. Human papillomavirus infection (HPV)

- HPV infection of the cervix is common.
- **Over 20 serotypes** of HPV infect the female genital areas.

Clinical behavior

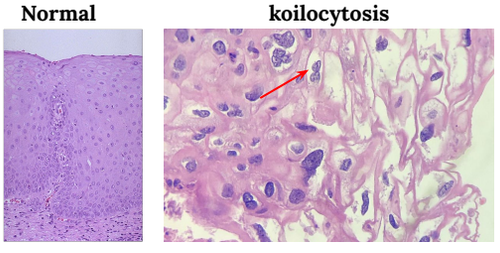
- **koilocytic** atypia in the cervical squamous epithelium.
- Associated with increased risk of subsequent **cervical cancer**.

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

1. Condyloma	2. Low grade (Mild) dysplasia	3. High-grade dysplasia
- In the **squamous epithelium** of the ectocervix. - The lesions may be **flat** or **exophytic** (called *exophytic condyloma acuminatum*). - Usually caused by serotypes **6** & **11**.	usually caused by: - **Low risk** HPV serotypes, **6** and **11**. - Usually associated with condyloma.	usually caused by: - **High risk** HPV (types **16** and **18**). - **Moderate risk** HPV (types **31, 33 and 35**).

4. Koilocytes: are squamous epithelial cells that have undergone **structural change** due to infection of the cell by HPV.

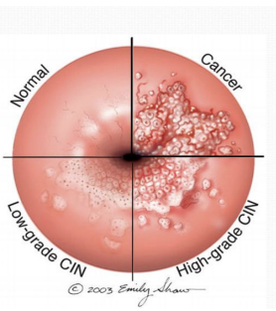
- They show koilocytosis or **koilocytic atypia** which include the following cellular changes:
  - Nuclear enlargement.
  - Irregular nuclear membrane.
  - Nuclear hyperchromasia (Dark nuclei).
  - **Perinuclear halo (clear area around the nucleus).**



Neoplasia of the cervix

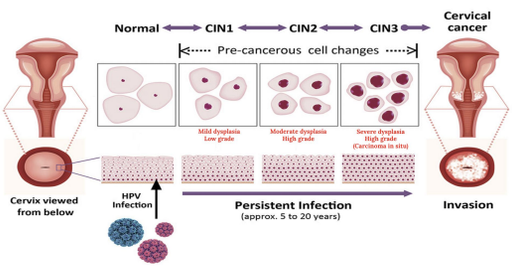
CIN - SIL

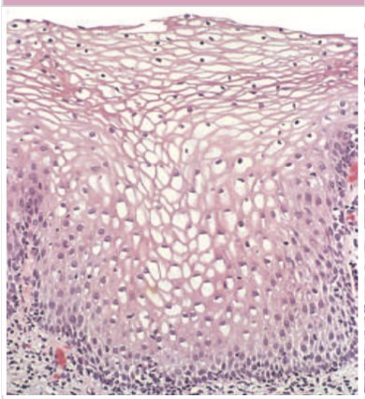
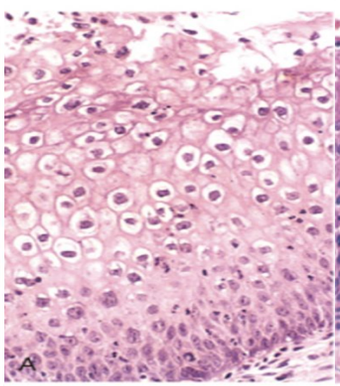
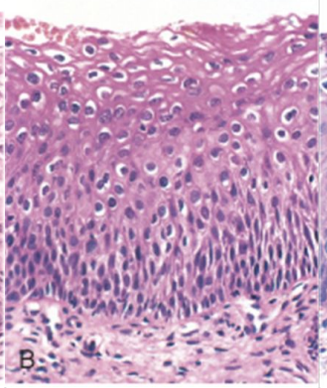
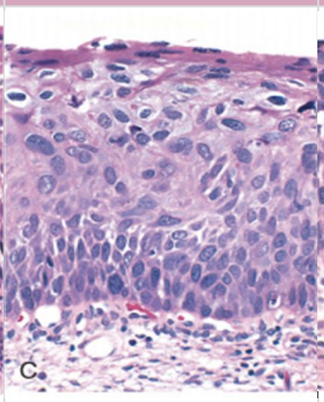
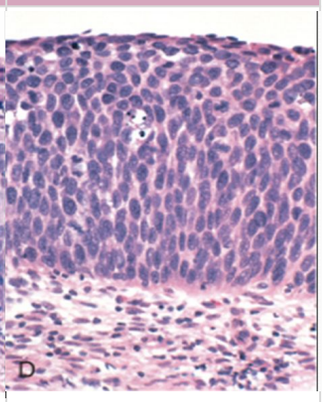
- The most common cervical cancer is **squamous cell carcinoma**.
- All invasive squamous cell carcinomas arise from non invasive **precancerous** cervical squamous epithelium called: **cervical intraepithelial neoplasia (CIN) or squamous intraepithelial lesions (SIL).**
- **NOT** all cases of CIN/SIL progress to invasive cancer, some cases may spontaneously regress.
- Cases of **high grade** CIN/SIL are associated with:
  - **High-risk HPV** serotypes and a **higher risk** of progression to cancer.
- Timely detection and diagnosis of CIN/SIL is essential in preventing the development of invasive carcinoma.



CIN Histological Reporting

- Terminology used for histological reporting is **Cervical intraepithelial neoplasia (CIN).**
- CIN lesions may **begin as Low Grade** CIN and progress to High Grade.
- Or they might **begin straight away as High Grade** CIN.
- Based on histology, pre-cancer lesions are graded as:
  - **CIN I**: Mild Dysplasia.
  - **CIN II**: Moderate Dysplasia .
  - **CIN III**: Severe Dysplasia and **Carcinoma in situ** (CIS).

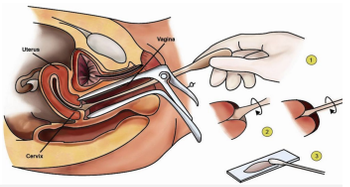


Normal	Koilocytes of HPV	CIN I	CIN II.	CIN III (CIS)
				
		Mild dysplasia	**Moderate dysplasia**	**Severe dysplasia**
	To differentiate	- Koilocytes in the upper part. - In the lower ⅓ of epithelium the maturation is lost and the cells are replaced by pleomorphic cells.	- Progressive koilocytic atypia in the upper layers. - In the lower ⅔ of the epithelium the maturation is lost and the cells are replaced by pleomorphic cells.	- There is **diffuse** koilocytic atypia and **- All** of the epithelium lost its maturation and the cells are replaced by pleomorphic cells, (full thickness).

Neoplasia of the cervix

PAP Screening Test

- Cytological examination (**PAP screening test)** can detect **SIL long before any abnormality** can be seen grossly.
- Deaths from cervical carcinoma are decreasing and there is an improvement of treatment due to the early diagnosis by PAP screening test.
- **PAP test** is the cytological examination of the cells of cervix.



1. The cells lining the cervical wall at the **transformation zone** are scrapped off (sampled) with a spatula.

→

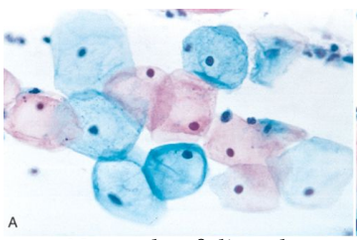
2. Then transferred onto a slide, processed, stained (Papanicolaou stain).

→

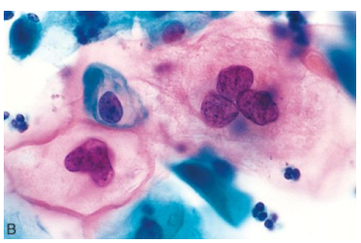
3. Then examined under a light microscope to look for squamous intraepithelial lesions (SIL) and a diagnosis is made.

Cytology Pap Smear

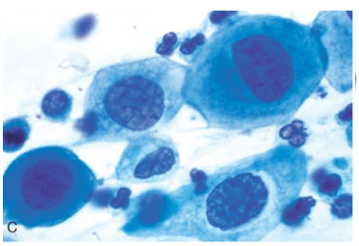
- Terminology used in Pap smears is **squamous Intraepithelial lesions (SIL)**.
- In cytology smear report these are few of the possible diagnoses:
  - **Normal cells**: Negative for squamous intraepithelial lesion.
  - **Low Grade SIL** (LSIL): CIN 1 (mild dysplasia on histology).
  - **High Grade SIL**[1] (HSIL): CIN 2 and CIN 3 (moderate to severe dysplasia on histology).
- 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.



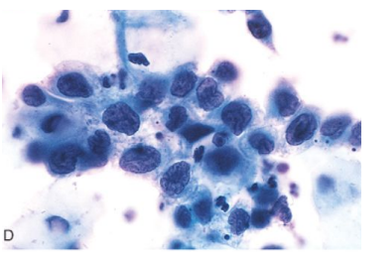
Normal exfoliated superficial squamous epithelial cells



CIN I = low grade SIL



CIN II = high grade SIL



CIN III = high grade SIL

Cytoplasmic staining in superficial cells (PIC A&B) may be either red or blue.

- In **higher grade lesions:** there is reduction in cytoplasm and increase in the nucleus to cytoplasm ratio.
- This reflects the progressive **loss of cellular differentiation** on the surface of the lesions from which these cells are exfoliated.

1. Difficult to differentiate CIN 1 from CIN 2 on cytology, easier on histology.

Neoplasia of the cervix

Rules for PAP TEST

- Women may not show visible signs or symptoms so it is difficult to diagnose SIL/CIN without a Pap smear.
- Therefore a regular pap exams should be done on women, to detect any SIL.
- It is a common testing procedure for HPV infection. it detects HPV infection early.

General rules of pap smear test are:

- Should start pap test by the age of **21**.
- For women between age **21 to 29**: pap test should be done every 3 years.
- For women between age **30-64** : there are **2 possibilities.**
    - Either do **only pap test** once every **3 years**.
    - Or do **two tests** (co-testing) at the same time the pap test **+ DNA in-situ hybridization (ISH)** HPV testing, **every 5 years**.

Side note: ISH is done to identify the serotype of the HPV. This test will determine whether you carry high or low risk strains of the virus. It should not be used before age 30 if pap test is normal.

Risk Factors

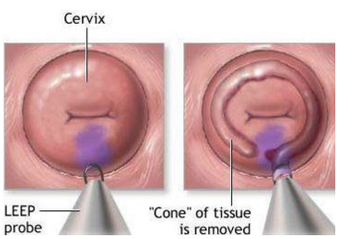
- Smoking.
- Early age at first intercourse.
- Multiple sexual partners.
- Male partner with multiple previous sexual partners.
- Persistent infection by high risk papillomaviruses.
- Other risk factors: low socioeconomic groups.
- Rare among virgins and multiple pregnancies[1].

Causes

- **The HPV virus** is the **number one cause.**
- 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**.

Treatment

- **Laser or cone biopsy[2]:** is the most effective method of managing patients with High grade SIL in cancer prevention.



1. Protective factor.
2. By removing part of cervix (transformation zone).

Invasive Cervical Carcinoma

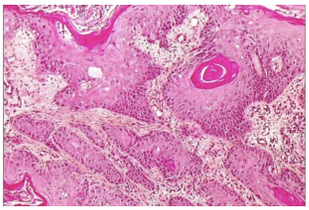
Invasive Cervical Carcinoma

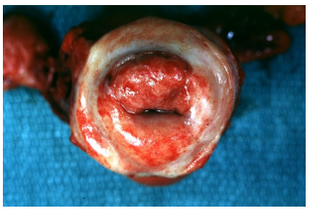
- About **75-90%** of invasive cancers are **squamous cell carcinomas (ectocervix).**
- The remainder are **adenocarcinoma (endocervix)**, and neuroendocrine carcinoma.
- Reduction in the West is due to PAP smear test which detects premalignant lesions.

Morphology

- The tumors may be invisible or present as an exophytic mass.
- **Cervical carcinomas are:**
  - **Graded** from **1 to 3**[1] (i.e. well, moderately and poorly differentiated) based on cellular differentiation.
  - **Staged** From **1 to 4** depending on clinical spread.

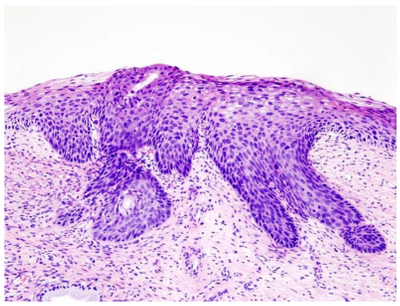
Well differentiated

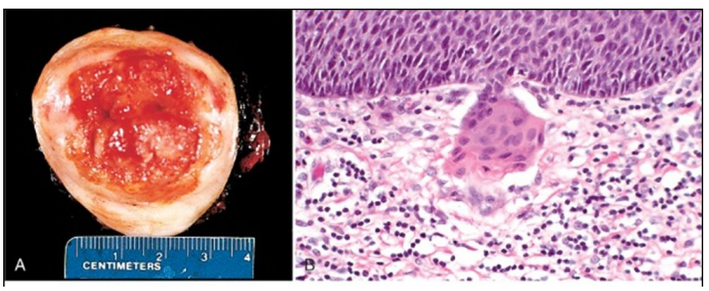




Invasive Squamous Cell Carcinoma

- **Squamous cell carcinomas typically arise from pre-cancer CIN/SIL lesions at the transformation zone.**
- Peak incidence at the age of about **45 years**, some 10 to 15 years after detection of precursor SIL.
- Majority are diagnosed in the pre-invasive CIN/SIL phase due to pap test.
- **Advanced cases** of Squamous cell carcinoma are seen in:
  - Women who either have never had a PAP smear.
  - Have waited many years since the last PAP smear.





1. Sometimes 4 = undifferentiated.

Invasive Cervical Carcinoma

Clinical features

- The early stages may be completely **asymptomatic (invisible lesions)**.
- On **colposcopy**: cervix shows a **mosaic[1] vascular pattern** and the lesions appear as **white patches** after application of acetic acid to cervix.
- **Vaginal bleeding, contact bleeding, or cervical mass.**
- 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.

Mosaic vascular pattern

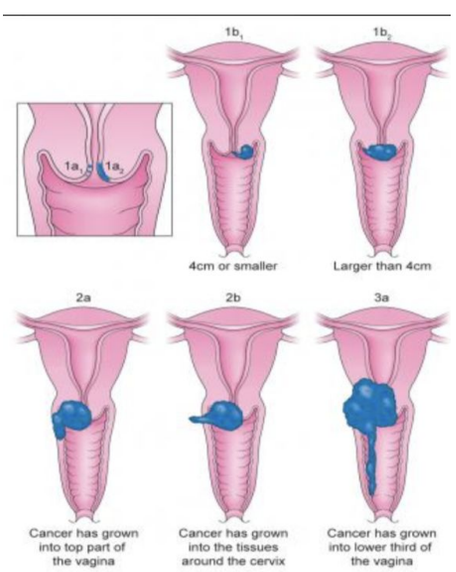
Treatment

Depending on the stage there are different treatment options: .

1. If patient wants 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. **Chemotherapy and radiotherapy** maybe needed in advanced cases.

Cervical Carcinoma Staging[2]

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.



1. Heterogenous.
2. Dr Maria: for your knowledge.

Summary

Pathology of Uterine Cervix	
Cervical erosions	- **Benign,** Squamous Epithelium is replaced by columnar epithelium. - Causes **erythematous** area.
Squamous metaplasia	- **Benign,** The columnar cells are replaced by squamous cells. - Seen at the squamocolumnar junction. - Most affected area by **HPV**.
Cervical polyp	- Non neoplastic small, pedunculated mass, can be endo or ectocervix. - Overgrowth of **benign** cervical stroma covered by cervical epithelium (commonly **columnar**).
Cervicitis	
Infectious	
Candidiasis (moniliasis)	**- Common** and Involves both of the cervix and vagina. - In immunosuppression. - Characterized by **white patchy mucosal lesions with thick curdy white discharge.**
Trichomoniasis	- It is **sexually transmitted disease** and Involves the vagina and cervix. - Greenish-yellow frothy and foul smelling vaginal discharge + Painful urination.
Chlamydia trachomatis	- Chlamydia trachomatis is an obligate, gram -ve **intracellular** pathogen. **- Most common sexually transmitted disease also** coexist with Neisseria gonorrhoeae infection. - Mucopurulent cervical discharge + associated urethritis.
Herpes simplex virus (HSV)	- It produces vesicles and ulcers. **- Cytology: intracellular "Cowdry type A" viral inclusion and the 3 Ms** → multinucleated cells, molding of nuclei, margination of chromatin.
Human papillomavirus (HPV)	- Most important because it increases the risk of cervical cancer. - **Pathology:** - **Condyloma:** caused by serotypes 6 & 11. - **Low grade dysplasia:** caused by **low risk** serotypes 6 & 11. **- High grade dysplasia:** caused by **moderate risk** serotypes 31, 33 & 35 and **high risk** serotypes 16 & 18. - **Koilocytosis.**

Summary

Neoplasia of the cervix	
Grading	- **CIN:** Terminology used for **histological** reporting. - **SIL:** Terminology used in **Pap smears (cytology).** - **Low grade SIL (LSIL):** - **CIN I:** low dysplasia, loss of maturation in the lower ⅓ epithelium on histology. - **1-5%** become invasive. - **High grade SIL (HSIL):** - **CIN II:** moderate dysplasia, loss of maturation in the lower ⅔ epithelium. - **CIN III and CIS:** severe dysplasia, loss of maturation in all epithelium on histology. - **6-74%** become invasive.
Risk Factors	- Early age at first intercourse, Multiple sexual partners, Persistent infection.
Causes	- **The HPV virus number one** cause for abnormal cells of the cervix.
Treatment	- **Laser or cone biopsy.**

Invasive Cervical Carcinoma	
Introduction	- **75-90%** of invasive cancers are ectocervical **squamous cell carcinomas** which arise from CIN/SIL lesions at the transformation zone. - The remainder are endocervical **adenocarcinoma.**
Morphology	- **Invisible or visible as an exophytic mass.**
Clinical features	- **Vaginal bleeding**, **contact bleeding**, or **cervical mass** In **advanced disease**, **metastases** may be present.
Treatment	• **Simple hysterectomy** • **Radical hysterectomy** • **Chemotherapy and radiotherapy**

Quiz

1) A 31-year-old, sexually active woman has had a mucopurulent vaginal discharge for 1 week. On pelvic examination, the cervix appears reddened around the os, but no erosions or mass lesions are present. A Pap smear shows numerous neutrophils, but no dysplastic cells. A cervical biopsy specimen shows marked follicular cervicitis. Which of the following infectious agents is most likely to produce these findings?
A- Candida albicans
B- Chlamydia trachomatis
C- Gardnerella vaginalis
D- Herpes simplex virus

2) A 31-year-old woman has had vulvar pruritus along with a thick, whitish, odorless, globular vaginal discharge for the past week. On pelvic examination, the cervix appears erythematous, but there are no erosions or masses. A Pap smear shows budding cells and pseudohyphae. No dysplastic cells are present. Which of the following infectious agents is most likely to produce these findings?
A- Candida albicans
B- Chlamydia trachomatis
C- Neisseria gonorrhoeae
D- Trichomonas vaginalis

3) A healthy 30-year-old woman comes to the physician for a routine health maintenance examination. No abnormalities are found on physical examination. A screening Pap smear shows cells consistent with a low-grade squamous intraepithelial lesion (LSIL). Subsequent cervical biopsy specimens confirm the presence of cervical intraepithelial neoplasia (CIN) I. Which of the following risk factors is most likely related to her Pap smear findings?
A- Diethylstilbestrol (DES) exposure
B- Multiple sexual partners
C- Oral contraceptive use
D- Prior treatment for a malignancy

4) A 33-year-old woman comes to her nurse practitioner for a routine health maintenance examination. On physical examination, there are no abnormal findings. A Pap smear reveals Dysplasia extending to the middle third of epithelium with some pleomorphism and mitosis. In which stage is she?
A- CIN I
B- CIN II
C- CIN III
D- SCC

5) A 42-year-old woman has a Pap smear as part of a routine health maintenance examination. There are no remarkable findings on physical examination. The Pap smear shows cells consistent with a high-grade squamous intraepithelial lesion (HSIL) with human papillomavirus type 18. Cervical biopsy specimens are obtained, and microscopic examination confirms the presence of extensive moderate dysplasia (CIN II) along with intense chronic inflammation with squamous metaplasia in the endocervical canal. What is the most likely explanation for proceeding with cervical conization for this patient?
A- Her reproductive years are over
B- HPV infection cannot be treated
C- Risk for invasive carcinoma
D- Presence of chronic cervicitis

6) A 43-year-old woman has had postcoital bleeding for 6 months. She experienced menarche at age 11 years and has had 12 sexual partners during her life. She continues to have regular menstrual cycles without abnormal intermenstrual bleeding. Pelvic examination shows a focal, slightly raised area of erythema on the cervix at the 5 o'clock position. A Pap smear shows a high-grade squamous intraepithelial lesion (HSIL), also termed severe cervical intraepithelial neoplasia (CIN III). Analysis of cells from the cervix shows the presence of human papillomavirus type 16. Which of the following malignancies is she at greatest risk of developing if the lesion is not treated?
A- Clear cell carcinoma
B- Immature teratoma
C- Krukenberg tumor
D- Squamous cell carcinoma

7) A 34-year-old woman has a routine Pap smear for the first time. The results indicate that dysplastic cells are present, consistent with a high-grade squamous intraepithelial lesion (HSIL), also called cervical intraepithelial neoplasia (CIN) III. She is referred to a gynecologist, who performs colposcopy and takes multiple cervical biopsy specimens that all show CIN III. Conization of the cervix shows a focus of microinvasion at the squamocolumnar junction. Based on these findings, what is the next most likely step in treating this patient?
A- Bone scan for metastatic lesions
B- Course of radiation therapy
C- No further therapy
D- Vaginal hysterectomy

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

Thank You!

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Done by the brilliant minds

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