



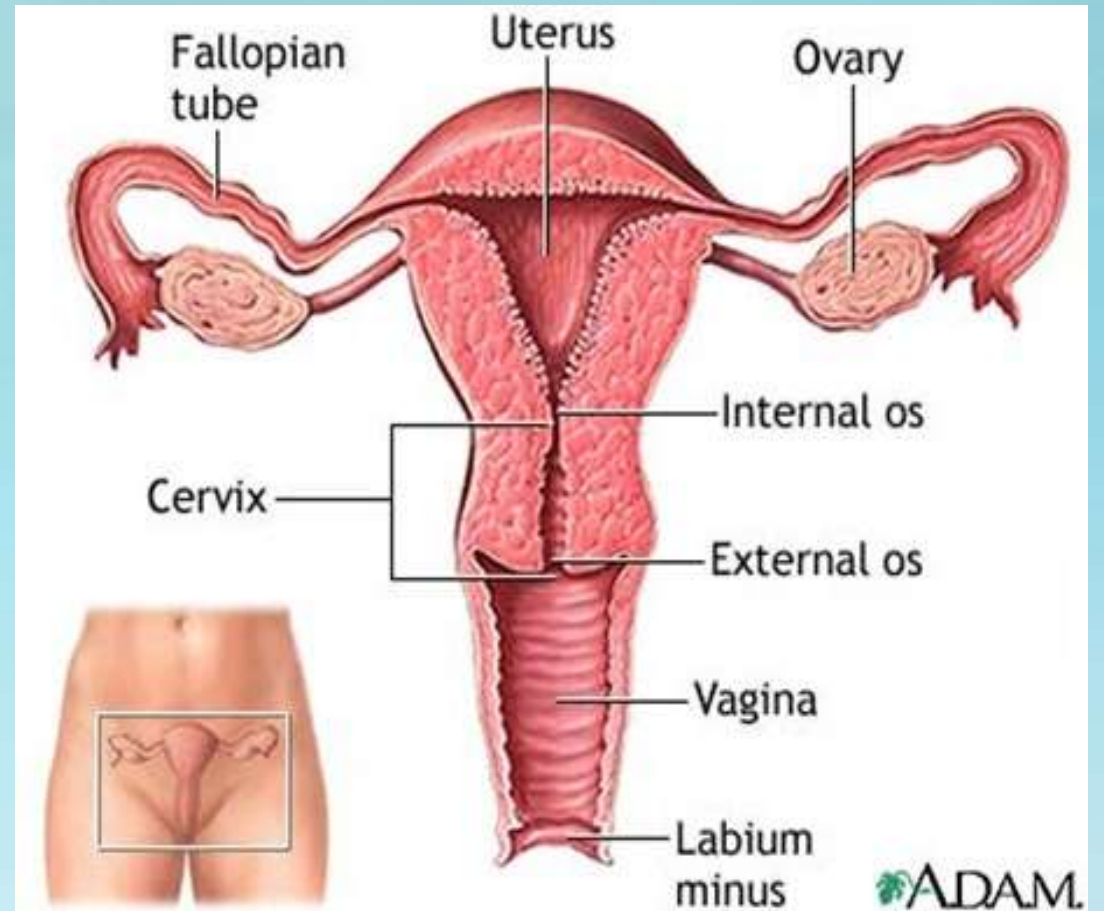
Female Genital Tract Pathology

LEC 1

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Major Organs of FGT

- Vulva
- Vagina
- Cervix
- Uterus
- Fallopian tubes
- Ovaries



Vulva

- The vulva is the external female genitalia and includes the hair-bearing skin (labia majora) and mucosa (labia minora).
- **Normal histology:** The vulva has **both keratinized and nonkeratinized squamous epithelium with appendageal structures** (hair follicles, sebaceous glands, eccrine and apocrine glands) vary in their localization.
- **Diseases of vulva:**
 1. Vulvitis (more common but not serious).
 2. Non-Neoplastic epithelial disorders.
 3. Tumors; Carcinomas (uncommon but life threatening).

1. Vulvitis

- Inflammation of vulva; It could be **infectious** or **non-infectious**

❖ A. Infectious;

A large variety of organisms can infect the female genital tract, which often are **sexually transmitted**.

- *The most important infectious agents are:*

1. Human papillomavirus (HPV); the causative agent of **condyloma acuminatum**, **vulvar intraepithelial neoplasia (VIN)**, and **vulvar squamous carcinoma**

2. Herpes simplex virus (HSV-1 or HSV-2); the agent of **genital herpes** (vesicular eruption and painful genital ulcerations).

3. *N. gonorrhoeae*; a cause of **suppurative** infection of the vulvovaginal glands.

4. **Syphilis**; (*Treponema pallidum*), which causes **primary chancre** at vulvar sites of inoculation; or **Secondary syphilis (Condyloma lata)**: hyperplasia of epithelium with underlying chronic inflammation rich in plasma cells & endarteritis obliterans.

5. **Candida**; also is a cause of vulvitis, but is **not** sexually transmitted.

- An important complication of vulvitis is obstruction of the excretory ducts of Bartholin glands. This blockage may result in painful dilation of the glands (*Bartholin cyst*) and abscess formation.

❖ B. Non infectious;

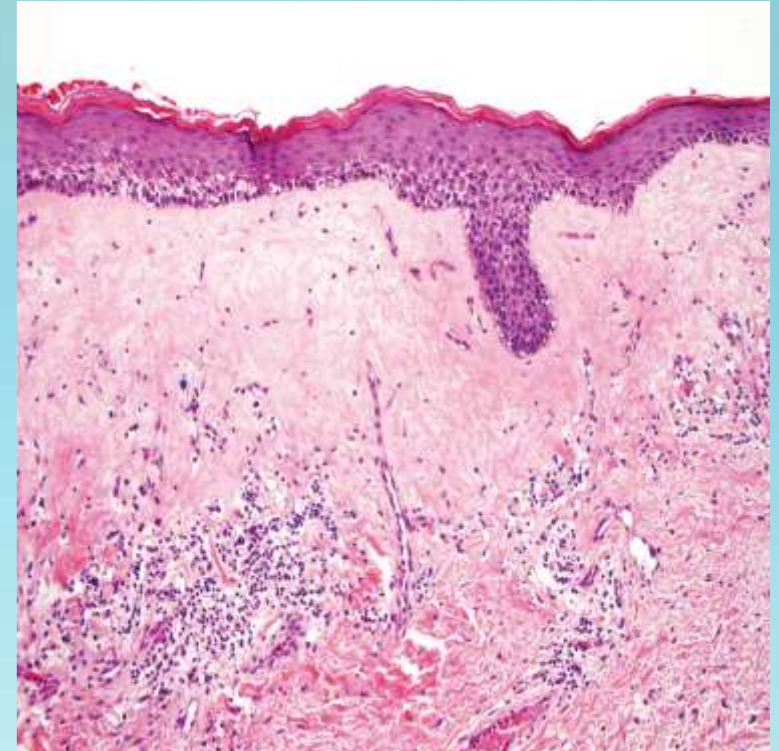
- One of the most common causes of vulvitis is **reactive inflammation** in response to an exogenous stimulus, which may be an irritant (**contact irritant dermatitis**); presents as **well- defined erythematous weeping and crusting papules and plaques**. May be a reaction to urine, soaps, detergents, antiseptics, or alcohol) or an allergen (**contact allergic dermatitis**; may result from allergy to perfumes and other additives in creams, lotions, and soaps, chemical treatments on clothing and other antigens).
- Many **inflammatory diseases** that affect skin elsewhere on the body also occur on the vulva, such as **psoriasis, eczema, and others.**

2. Non-Neoplastic epithelial disorders

- The epithelium of vulvar mucosa may undergo atrophic thinning or hyperplastic thickening
- There are two forms of non-neoplastic epithelial disorders: **lichen sclerosus** and **lichen simplex chronicus**.
- Both may coexist in **different areas** in the same person, and both may appear macroscopically as **depigmented white lesions, referred to as leukoplakia**.
- **Leukoplakia (white patches or plaques)** also are seen in a variety of other benign dermatoses, such as **psoriasis** and **lichen planus** as well as in **malignant lesions** of the vulva, such as squamous cell carcinoma in situ and invasive squamous cell carcinoma. **Thus**, biopsy and microscopic examination are often needed to differentiate these clinically similar-appearing lesions.

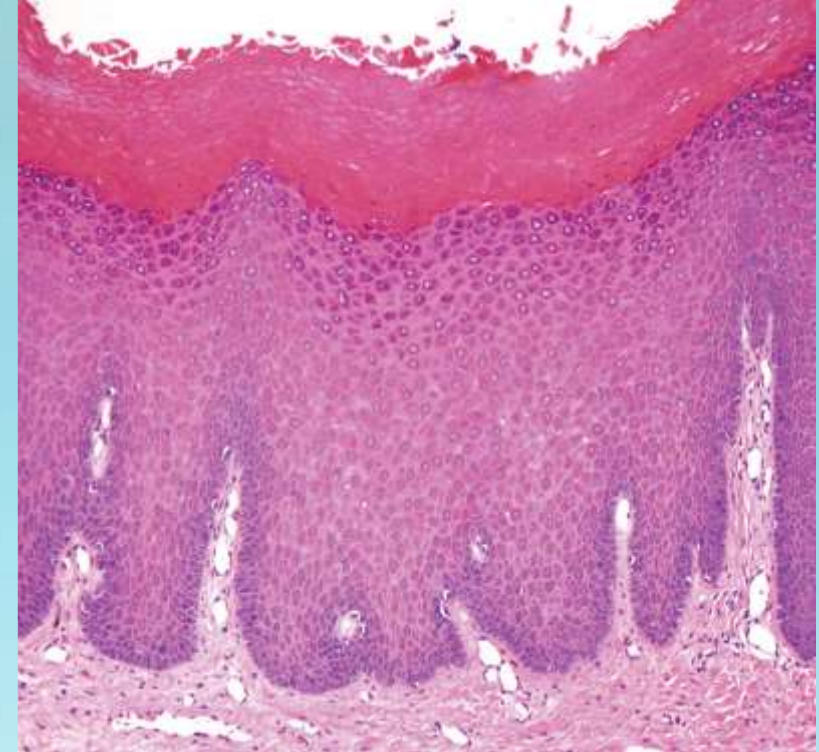
A. Lichen Sclerosus:

- **Clinical presentation:** smooth, white plaques or macules that in time may enlarge and coalesce.
- **Mic.:** the lesion is characterized by:
 1. Thinning of the epidermis,
 2. Disappearance of rete ridges,
 3. A zone of acellular, homogenized, dermal fibrosis,
 4. A band like mononuclear inflammatory cell infiltrate
- **Age:** It is most common in postmenopausal women but it can occur in any age.
- **Cause:** the exact cause is unknown , An autoimmune reaction in a genetically susceptible patient due to previous skin damage or irritations probably involved in its pathogenesis.
- **Risk:** there is an 1% to 5% increased risk of vulvar squamous cell carcinoma.



B. Lichen Simplex Chronicus

- **Clinically:** it presents as leukoplakia
- **Mic.:**
 - 1-Hyperkeratosis .
 - 2- **Epithelial thickening (particularly of the stratum granulosum) ,**
 - 3-Increased mitotic activity in the basal and suprabasal layers; but **no epithelial Atypia**
 - 4-Lymphocytic infiltration of the dermis is sometimes present.
- **Cause:** Nonspecific condition resulting from rubbing or scratching of the skin to relieve pruritus. is the end stage of many inflammatory dermatoses
- **Risk:** Generally, there is **no increased predisposition to cancer**, but suspiciously, lichen simplex chronicus is often present at margins of established cancer of the vulva.



3. Tumors

❖ Benign tumors

➤ Condylomas

- Any raised (exophytic) or wartlike lesions.
- There are **two main types**:

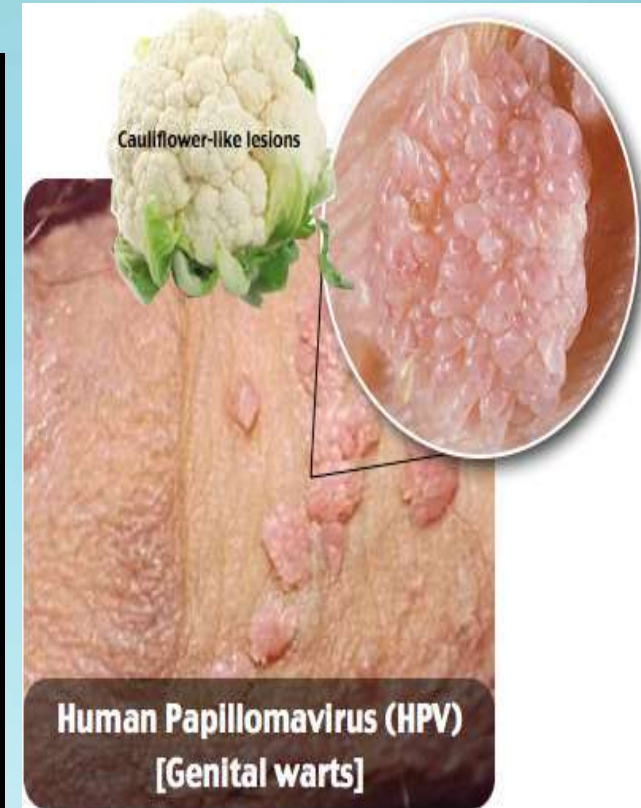
1. Condyloma acuminatum:

- The most common type.
- **Location:** They may occur anywhere on the **anogenital surface** (vulva, perineum, and perianal regions, vagina and, less commonly the cervix).
- **Cause:** HPV subtypes 6 and 11. (HPV is **sexually transmitted**, and identical lesions occur in men on the penis and around the anus in men and women; HPV 6 and 11 are low-risk viral types, and hence, **vulvar condylomas do not commonly progress to cancer**. However, women with condyloma acuminatum are at risk of having other HPV-related lesions in the vagina and cervix).
- **HPV vaccines** provide excellent protection against infection by low-risk HPV and genital warts.

2. Condyloma lata: seen in **secondary syphilis**.

➤ **Gross of Condyloma acuminatum:**

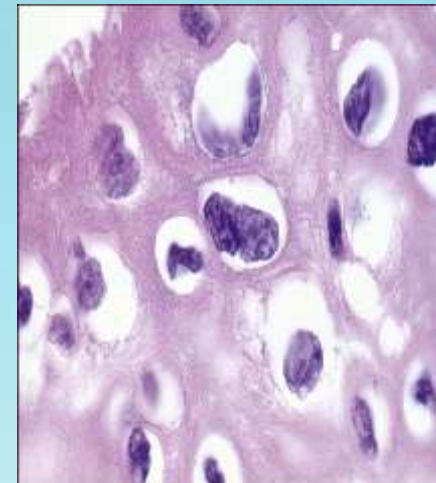
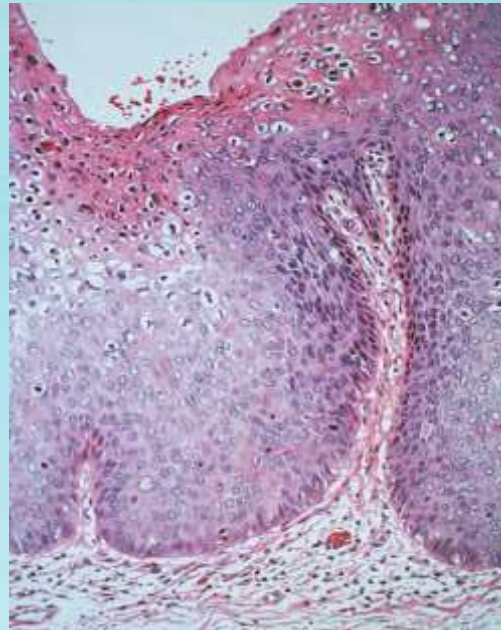
- **Papillary and distinctly elevated, they are often multiple, are red-pink to pink-brown lesions that measure range from a few millimeters up to several centimeters in diameter.**



- **Microscopical features of Condyloma acuminatum:**

- **Papillary (papillomatosis), exophytic, treelike cores of stroma covered by thickened squamous epithelium .**

The surface epithelium shows characteristic viral cytopathic changes referred to as *koilocytic atypia* (nuclear enlargement, hyperchromasia, and a wrinkled nuclear contour and a cytoplasmic perinuclear halo).



❖ Malignant tumors

➤ Carcinoma of the Vulva

- Represents about **3%** of all female genital tract cancers, occurring mostly in women older than age 60.
- Approximately **90%** of carcinomas are squamous cell carcinomas; most of the other tumors are adenocarcinomas or basal cell carcinomas.
- There are **two distinct forms** of vulvar squamous cell carcinomas that differ in pathogenesis and course
 1. **HPV-negative carcinoma**
 2. **HPV-positive carcinoma**
- **Both** forms of vulvar carcinoma tend to **remain confined** to their site of origin for a few years but ultimately invade and spread, usually **first to regional lymph nodes**. The risk of metastasis correlates with the depth of invasion. As with most carcinomas, **prognosis** is dependent on tumor stage.
- The **overall 5-year survival** is 70% to 93% for patients with negative lymph nodes but decreases to 25% to 41% for patients with lymph node metastases.

HPV-negative carcinoma

HPV-positive carcinoma

More common.

These are **less** common

Occur in **older women** (average 75 years of age).

Occur in **younger women** (average 60 years of age).

Unrelated to HPV infection

Related to infection with high-risk HPVs, most commonly HPV-16.

Sometimes following a long history of reactive epithelial changes (**lichen sclerosus**).

Is often preceded by precancerous changes in the epithelium termed vulvar intraepithelial neoplasia (**VIN**).

Unifocal and typically are **well-differentiated** keratinizing squamous cell carcinomas

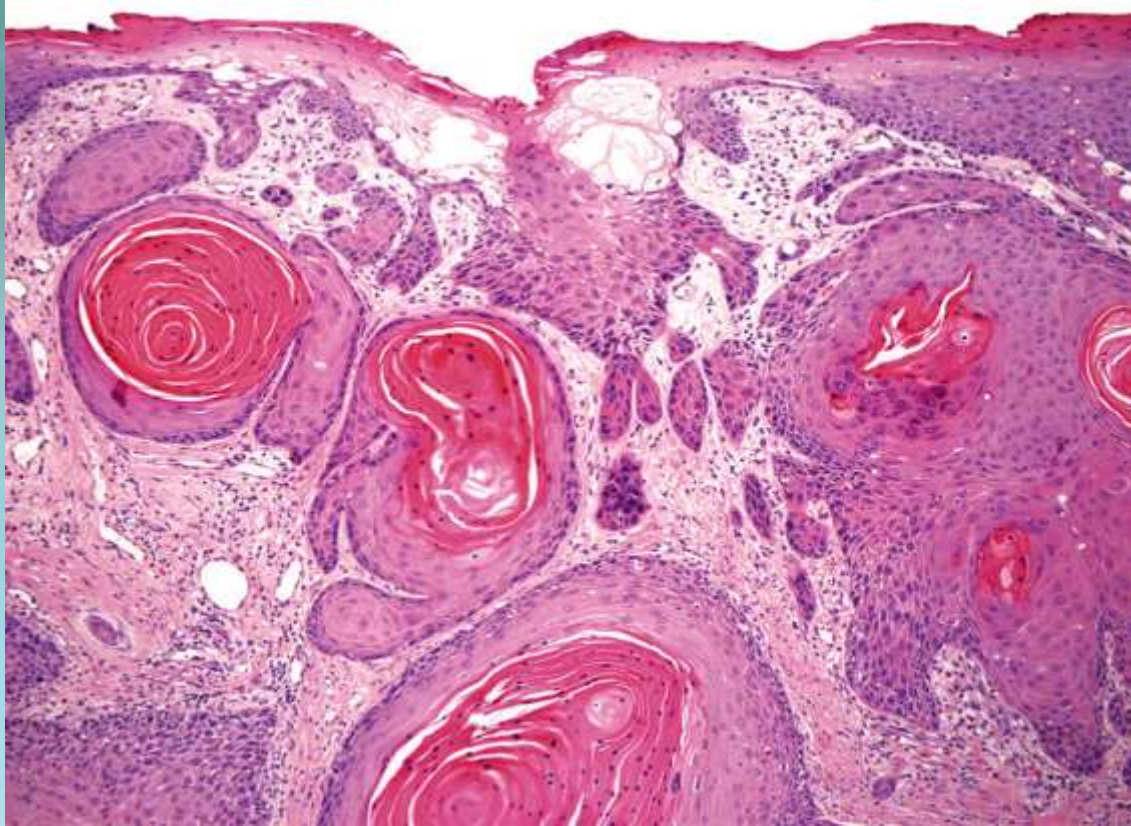
Often **multifocal** and warty and tend to be **poorly differentiated** squamous cell carcinomas

➤ Gross:

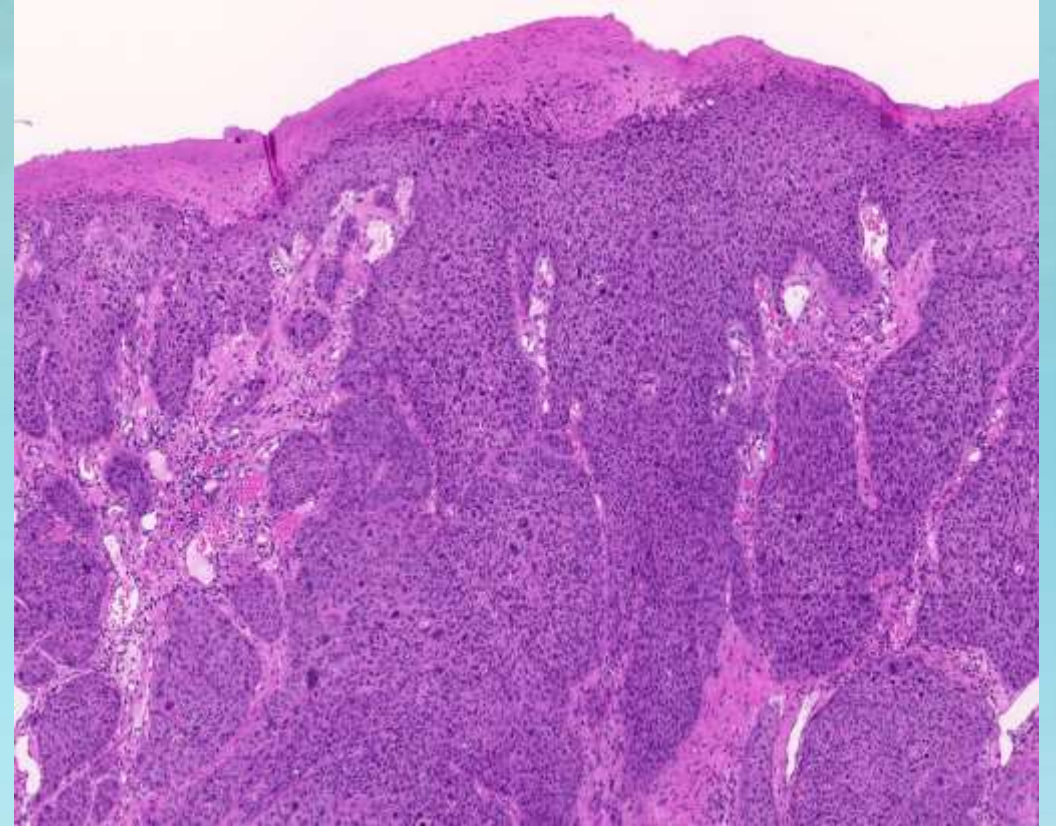
- Early vulvar carcinomas commonly manifest as areas of **leukoplakia**. In about one-fourth of the cases, the lesions are pigmented owing to the presence of melanin. **With time**, these areas are transformed into **overt exophytic or ulcerative endophytic tumors**.



Mic.:



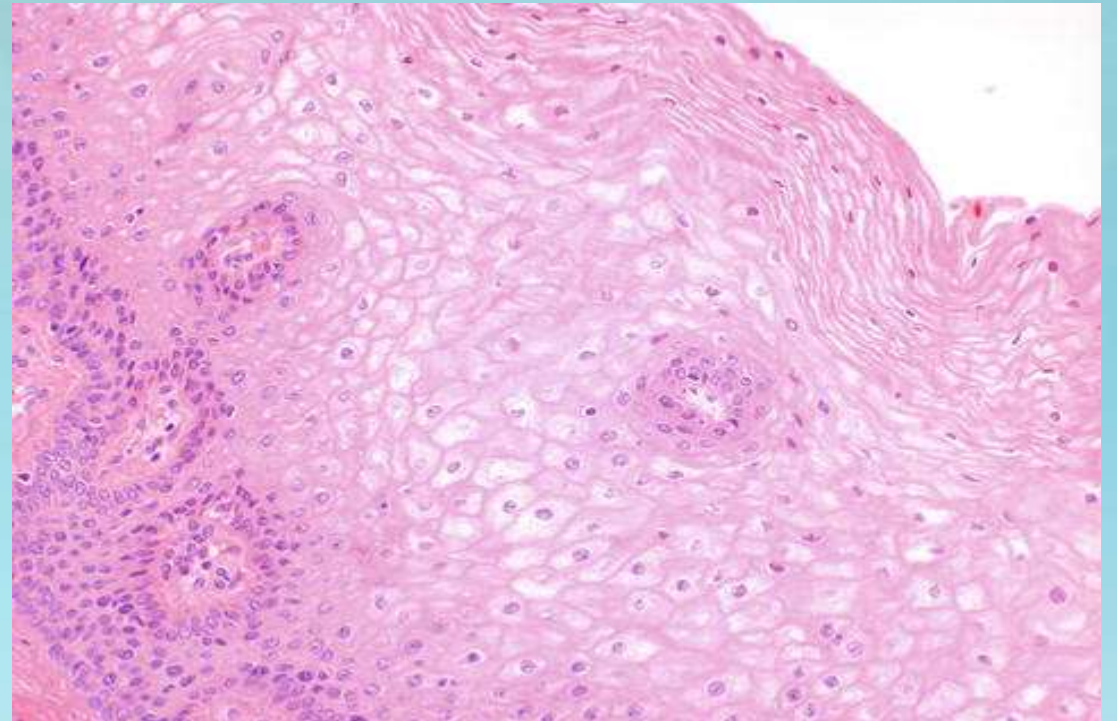
- **Well-differentiated, keratinizing squamous cell carcinoma of the vulva (HPV negative)** composed of invasive nests of malignant squamous cells with central keratin pearls.



- **Poorly differentiated (Nonkeratinizing) squamous cell carcinoma (HPV-positive)**

Vagina

- The vagina is seldom the site of primary disease; **more often it is secondarily involved** in the spread of cancer or infection arising in cervix, vulva, bladder, or rectum.
- The only primary disorders discussed here are **vaginitis, and primary tumors.**



- **Normal histology of the vagina:** is lined by **non-keratinized stratified squamous epithelium.** During reproductive life, the epithelium is highly glycogenated due to the effect of estrogen

❖ Vaginitis

- Is a common condition that is usually **transient** and of **no clinical consequence**.
- It is associated with the production of a vaginal discharge (**leukorrhea**).
- Usually caused by normal commensals that become pathogenic in **predisposed individuals** e.g.

➤ Diabetes

➤ Systemic antibiotic therapy

➤ After abortion or pregnancy

➤ elderly with compromise immune response & AIDS.

- The frequent organisms are **Candida Albicans** and **Trichomonas vaginalis**.

❖ **Candida vaginitis:**

- Cause vulvovaginal pruritus, erythema, swelling, and **curdlike vaginal discharge**.
- Severe infection may result in mucosal ulcerations.

❖ **Trichomonas vaginalis:**

- Produces a watery, copious **green discharge**, in which parasite can be identified microscopically.

However, *T. vaginalis* can also be identified in 10% of asymptomatic women.

❖ Malignant Tumors of the vagina

1. Squamous cell carcinoma

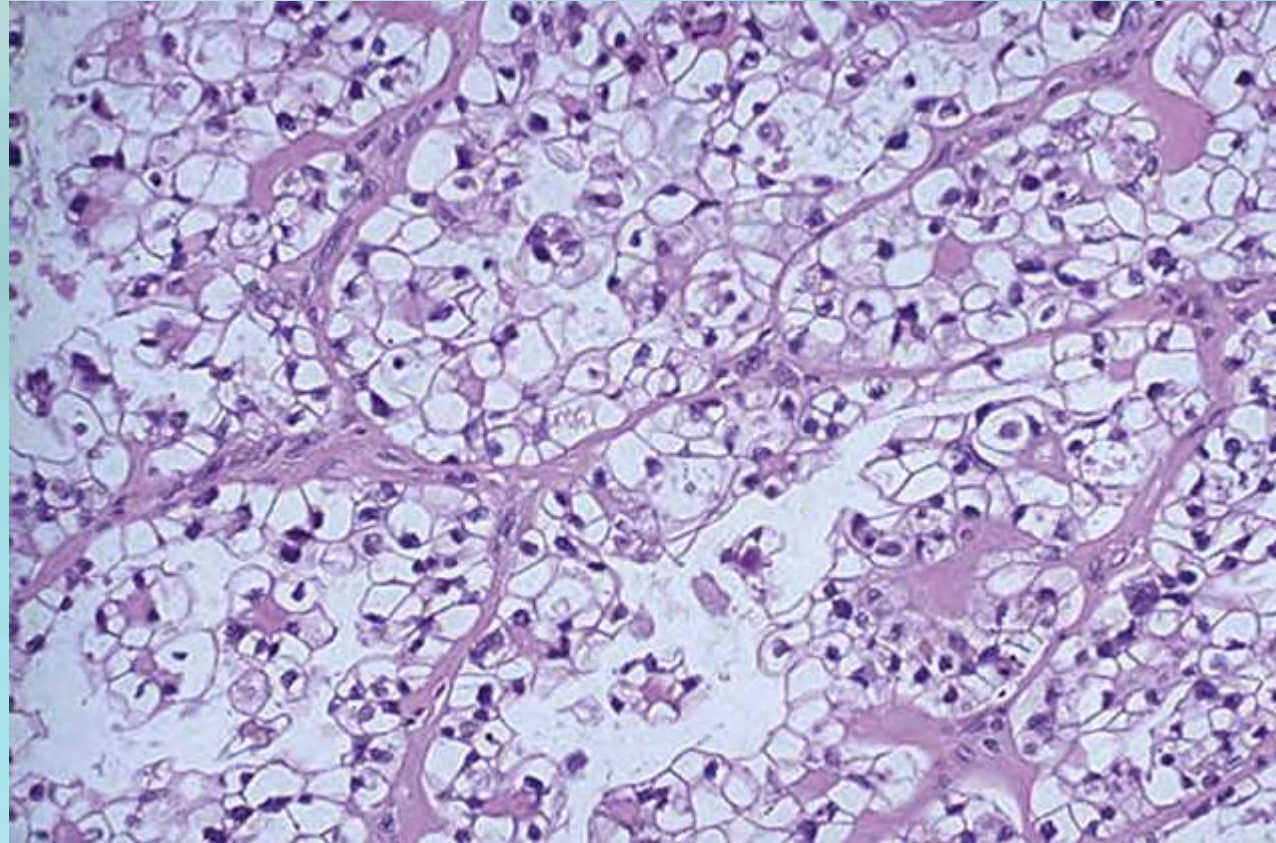
- Is very rare (it accounts for about 1% of malignant neoplasms in the female genital tract).
- Usually occurs in **elderly women**.
- Vaginal intraepithelial neoplasia (**VIN**) is a precursor lesion associated with **HPV infection**.

2. Clear cell adenocarcinoma

- Usually affects **adolescent and young females** whose **mothers took diethylstilbestrol during pregnancy**. (This medication used widely in the past(1940-1970) to prevent miscarriage).
- The tumor may arise from the cervix rather than the vagina in a third of the cases.
- It is preceded by increase in gland number (**adenosis**)

3. Embryonal rhabdomyosarcoma (**Sarcoma botryoides**)

- Produces **soft polypoid masses (grape like)** and is usually seen in **infants and children** younger than 5 years of age.

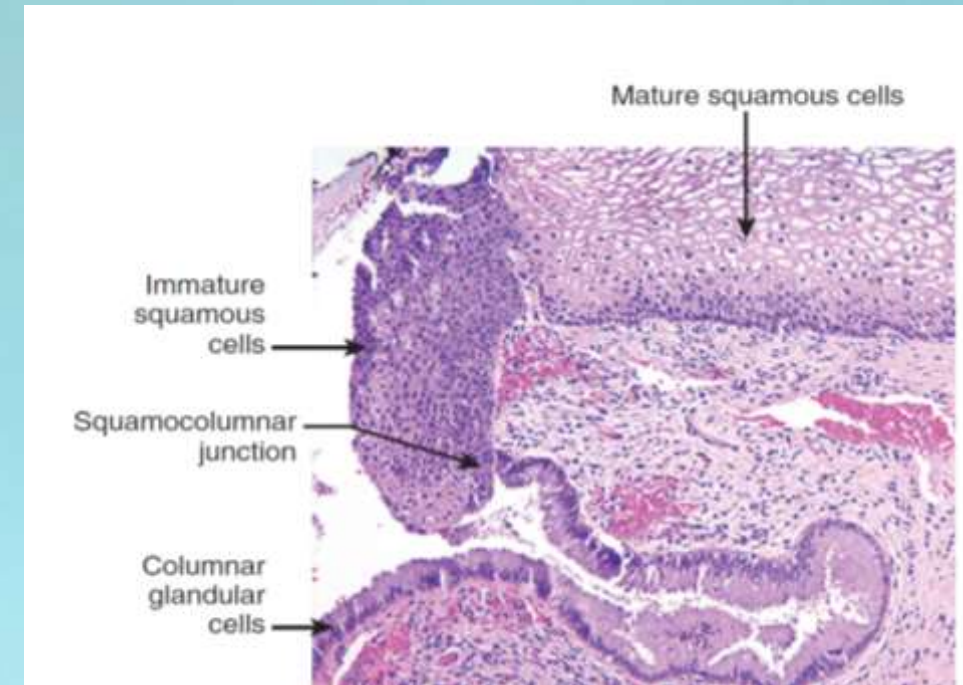


- **Clear cell adenocarcinoma of vagina:**

Vacuolated cells forming irregular clusters with ill-defined glandular lumens.

Cervix

- Consists of **ectocervix** (covered by squamous epithelium that is continuous with vaginal wall) and **endocervical canal** (lined by columnar mucinous epithelium). The position of the squamocolumnar junction (**transformation zone [TZ]**) is variable and changes with age and hormonal influence.
- **TZ** are most susceptible to HPV infection, and hence this is where cervical precursor lesions and cancers develop.
- 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.



Cervical **transformation zone** showing the transition from mature glycogenated squamous epithelium, to immature metaplastic squamous cells, to columnar endocervical glandular epithelium.

❖ Cervicitis:

- Inflammation of the cervix are **extremely common**, and are associated with **purulent vaginal discharge**.
- These inflammation can be infectious or noninfectious cervicitis.
- **Microorganisms** often present are indigenous, incidental vaginal aerobes and anaerobes, streptococci, staphylococci, enterococci, Escherichia coli, **Chlamydia trachomatis**, Ureplasma urelyticum, T. vaginlais, Candida spp., Neisseria gonorrhoeae, herpes simplex genitalis, and HPV.
- Many of these organisms **are transmitted sexually**, so cervicitis may represent sexually transmitted disease.
- Among these organisms, **C. trachomatis** represent **40 % of cases** of cervicitis encountered in sexually transmitted disease clinics.

➤ **Acute cervicitis:**

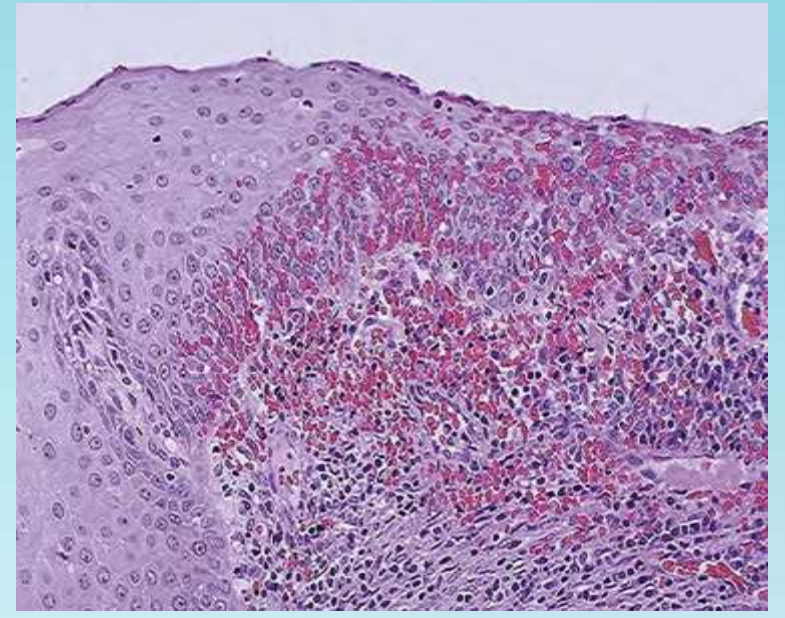
- Rare (postpartal and nonspecific)
- **Neutrophilic** infiltration beneath the lining mucosa

➤ **Chronic cervicitis:**

- More common, Bacterial growth & alteration in pH
- Common cause of leucorrhoea
- **Predisposing factors;**
 - Trauma of child birth
 - Instrumentation
 - Excess or deficiency of estrogen.

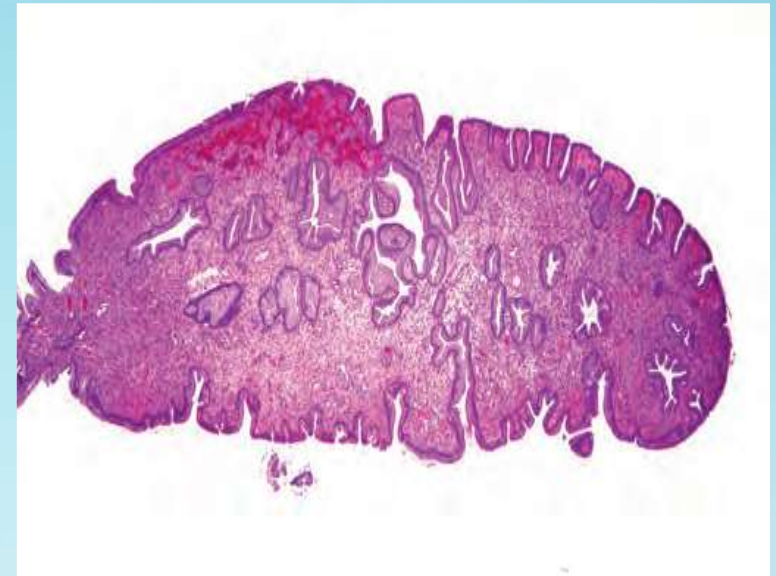
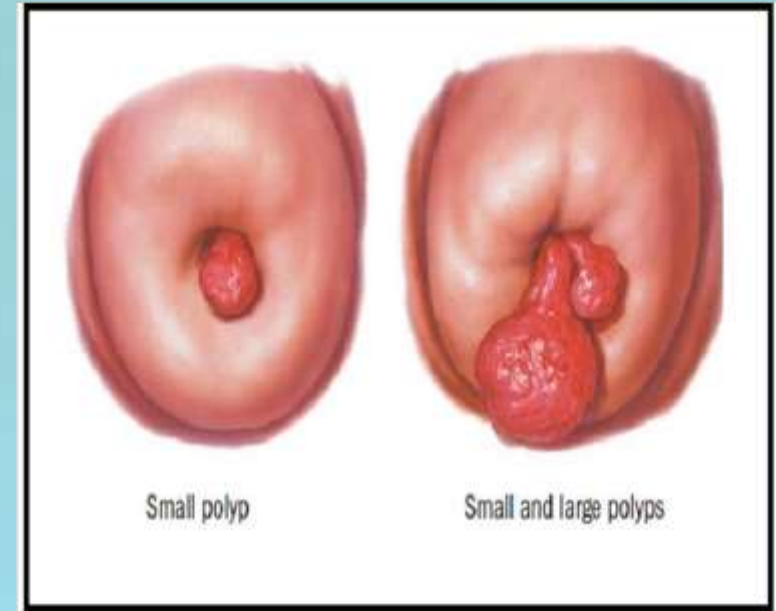
➤ **Morphology:**

- **Gross:** Hyperemia, edema around margin of external os., **Nabothian cyst** may be grossly visible (translucent, filled with a clear fluid) caused by obstruction of submucosal cervical glands so that glandular cystic dilation occurs.
- **Microscopically:** **chronic inflammatory cell infiltrate (lymphocytes)** in the submucosa; there is also hemorrhage.



❖ Endocervical Polyp

- **Benign exophytic growth** that arise within the endocervical canal .
- **Pathogenesis** may be **inflammatory in origin**.
- **Gross:** range up to few cm in diameter, **soft, covered by smooth glistening surface**
- **Mic.:**
- Polypoid lesion composed of a **fibrous stroma covered by mucus-secreting endocervical columnar epithelium**, often accompanied by **inflammation and cystically dilated endocervical glands filled with mucin secretion**
- **Clinical significance:** they may be the source of **irregular vaginal “spotting” or bleeding**, but have **No malignant potential**
- **Treatment:** surgical excision is curative.



NEOPLASIA OF THE CERVIX

❖ Premalignant and malignant neoplasm of the Cervix

➤ Pathogenesis:

- High-risk HPV is the causative agent of cervical neoplasia, **it has a tropism for the immature squamous cells of the transformation zone.**
- **Most** HPV infections are **transient** and are eliminated within months by the host immune response.
- **A subset of infections persists**, however, and some **cause** cervical intraepithelial neoplasia (**CIN**), which are **precursors** from which most **invasive cervical carcinomas** develop.
- **Important risk factors for the development of CIN and invasive carcinoma** thus are directly related to **HPV exposure** and include:
 - Early age at first intercourse
 - Multiple sexual partners
 - Male partner with multiple previous sexual partners
 - Persistent infection by high-risk strains of papillomavirus.
- **HPV alone is insufficient to cause cancer; other factors** e.g. **exposure to co-carcinogens and host immune status** determine whether an HPV infection regresses or persists and eventually progresses to cancer.

■ Human papilloma virus (HPV):

- DNA viruses more than 100 type HPV types have been identified that are grouped into those of **high** and **low oncogenic risk** based on their genotypes.
- There are **15 subtype** of **high-risk** HPVs that are currently identified (16, 18, 31, 33, 45, 51, 52, 56, 58, 59, 68, 73, and 82).
- **HPV-16** alone accounts for almost **60%** of cervical cancer cases, **HPV-18** accounts for another **10%** of cases; other HPV types contribute to less than **5%** of cases.
- **High-risk HPVs:** implicated in **squamous cell carcinomas** arising at many sites, including the vagina, vulva, penis, anus, tonsil, and other oropharyngeal locations.
- **Low risk HPVs:** (**HPV 6 and HPV 11**) are the cause of sexually transmitted vulvar, perineal, and perianal warts (**condyloma acuminatum**). the **viral DNA does not integrate into the host genome**.
- By contrast, **HPV types 16 & 18** usually **integrate** into the host genome...they start to **produce** the **viral E6 and E7 proteins**, which **interfere** with the activity of the **tumor suppressor proteins, p53 and RB**, respectively.
- The result is a **transformed cell**, capable of **autonomous growth** and susceptible to the acquisition of further mutations (cancer progression).
- The recently introduced HPV vaccine is very effective in preventing HPV infections and hence cervical cancers.

➤ **Premalignant: Cervical Intraepithelial Neoplasia (CIN):**

- **Precancerous cervical epithelial changes** are the precursor lesion for squamous cell carcinoma of the cervix.
- **Nearly all** invasive cervical squamous cell carcinomas arise from cervical intraepithelial neoplasia (CIN) or squamous intraepithelial lesion (SIL).
- Detection of CIN by the **Pap smear** at an early stage permits curative treatment.
- Cytological examination can detect CIN long before any abnormality can be seen grossly.
- Precancerous changes **usually take many years to evolve into overt carcinomas.**
- The **peak age** of CIN incidence is about **30 years**, whereas that of invasive carcinoma is about 45 years .

- ***Based on histology, precancerous changes are graded as-***
 - ***CIN I:*** Mild dysplasia
 - ***CIN II:*** Moderate dysplasia
 - ***CIN III:*** Severe dysplasia/carcinoma in situ

➤ **The current *Bethesda system* divides the precancerous lesions into only two groups:**

➤ **Low-grade SIL (LSIL):**

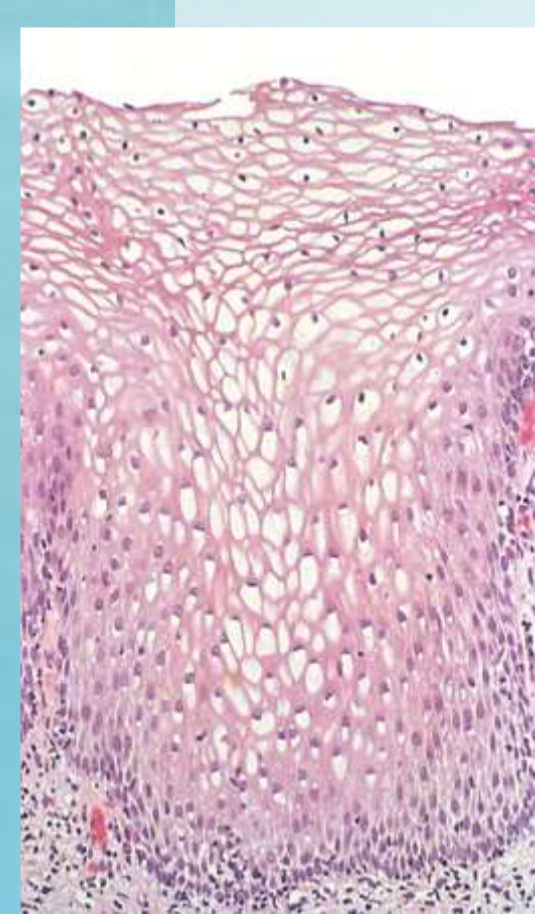
- Refers to lesions of **mild dysplasia (CIN1)**
- 10 times more common than HSIL.
- Associated with a productive HPV infection in which there is **high level of viral replication and only mild alterations in the growth of host cells**
- **Most regress; 10% progress to HSIL. Does not progress directly to invasive carcinoma**

Histology: dysplastic changes (nuclear atypia characterized by nuclear enlargement, hyperchromasia, coarse chromatin granules, and variation in nuclear size and shape **in the lower third of the squamous epithelium and koilocytotic change** in the superficial layers of the epithelium.

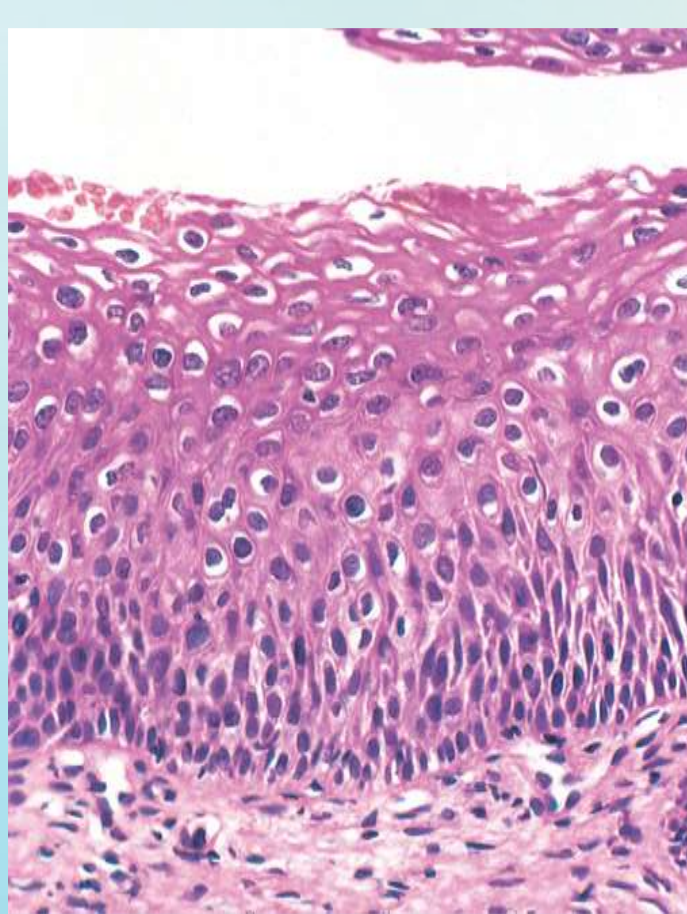
- **Can be followed-up +/- local ablation**

➤ **High-grade SIL (HSIL):**

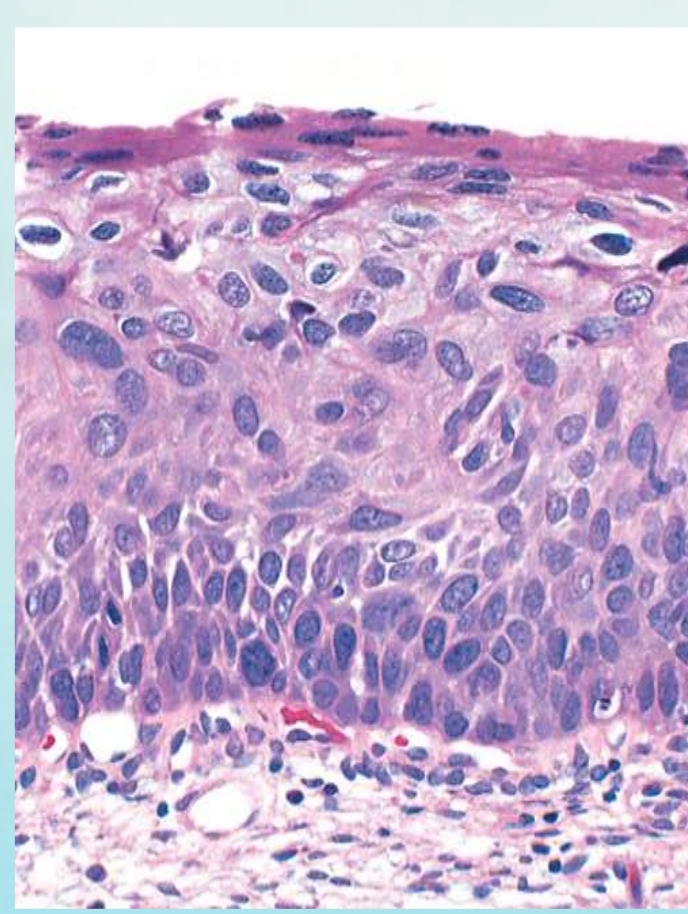
- Refers to lesions of **moderate dysplasia (CIN2) or severe dysplasia (CIN3)**
- Majority develop from LSIL; 20% are de-novo.
- Progressive deregulation of the cell cycle by HPV results **in increased cellular proliferation, decreased or arrested epithelial maturation and a lower rate of viral replication**
- Considered **high risk for progression to carcinoma (~10% progress to cancer within 2-10 yrs)**
- **Histology:** In HSIL (CIN II), dysplastic changes extends to the **middle third** of the epithelium. In HSIL (CIN III) dysplastic changes **affect all layers** of the epithelium. Koilocytotic change usually is absent.
- **Treated with cervical conization (superficial excision)**



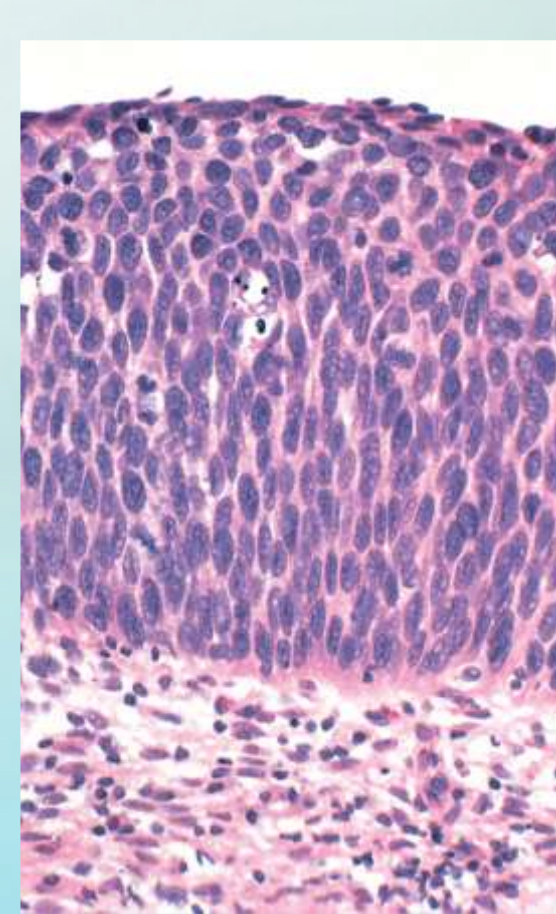
Normal



(CIN I)



(CIN II)



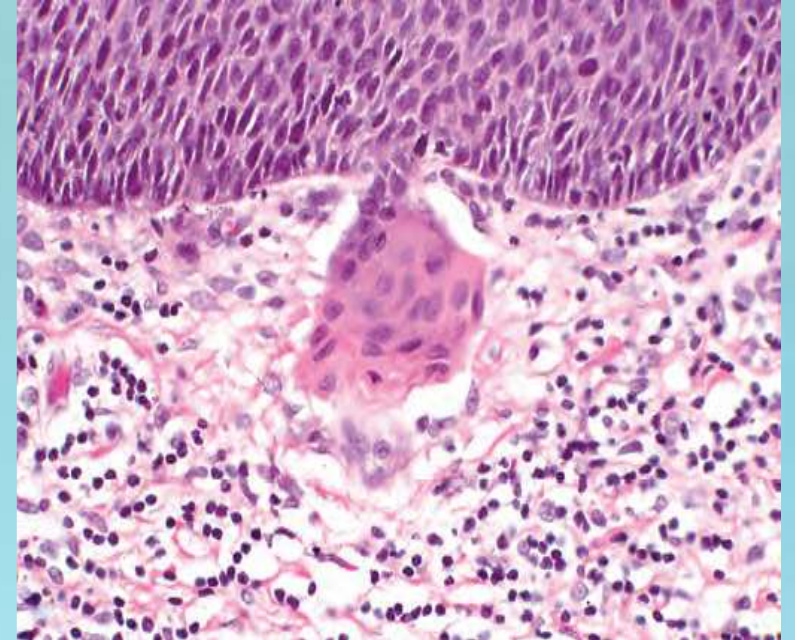
(CIN III)

Spectrum of CIN: normal squamous epithelium for comparison; **low-grade** squamous intraepithelial lesion (cervical intraepithelial neoplasia (CIN I); dysplastic changes in the lower third of the squamous epithelium with koilocytic changes; **high-grade** squamous intraepithelial lesion (HSIL) (CIN II); dysplastic changes extends to the middle third of the epithelium. HSIL (CIN III); dysplastic changes affect all layers of the epithelium. Koilocytotic change usually is absent.

Natural history of squamous intraepithelial lesions

Lesion	Regress	Persist	Progress in 10 years
LSIL (CIN I)	60%	30%	10% to HSIL
HSIL (CIN II, III)	30%	60%	10% to carcinoma

- With time, dysplastic changes become more atypical, but the alterations are confined to the epithelial layer. These changes constitute ***carcinoma in situ***.
- The next stage is ***invasive carcinoma*** (the basement membrane is no longer intact and atypical/malignant epithelial cells **invade deeply into the stroma**)
- **Note:**
 - The above progression sequences do not occur in all the cases.
 - **Cervical cytology** and **cervical colposcopy** remain the basis of cervical cancer prevention.



Early invasion in squamous cell carcinoma showing an invasive nest breaking through the basement membrane of a high-grade squamous intraepithelial lesion.

Malignant:

➤ Invasive Carcinoma of the Cervix

- Worldwide , cervical cancer is the **fourth cancer** in female after breast, colorectal and lung.
- It is one of the **major** causes of cancer-related deaths in women in the **developing world**. While, **in developed countries** HPV incidence and prevalence is decreasing due to **screening programmes** and **vaccination** leading to dramatic **improvement** in patient survival due to early diagnosis , detection of precancerous conditions by using **Pap smear** and **treatment** confirming that the cervical carcinoma is a preventable disease.

- **The most common cervical carcinomas are:**

1. Squamous cell carcinomas (75%), followed by

2. Adenocarcinomas and mixed adenosquamous carcinomas (20%) and

3. Small cell neuroendocrine carcinomas (<5%).

- All of these types of carcinomas are **associated with high-risk HPV**.

- **Age:** Squamous cell carcinoma has a peak incidence at the age of **about 45 years**, some 10 to 15 years after detection of precursor SIL.

- As already discussed, **progression of SIL to invasive carcinoma is variable and unpredictable and requires HPV infection as well as mutations in tumor suppressor genes and oncogenes.**

- **Risk factors for progression** include cigarette smoking and human immunodeficiency virus (HIV) infection, the latter finding suggesting that **immune surveillance plays a role in preventing progression.**

- Although risk factors may help identify patients who are likely to progress from SIL to carcinoma, the only reliable way to monitor the disease course is with **frequent physical examinations coupled with Pap smears and biopsy of suspicious lesions.**

Gross:

Invasive carcinomas of the cervix develop in the region of the **transformation zone** and range from **invisible** microscopic foci of early stromal invasion to grossly visible **exophytic** ulcerating masses or **deeply infiltrative** cancer that **encircle the external os** .



The tumor is a **red to tan to yellow mass that is exophytic** (growing outward and extending above the surrounding normal smooth epithelium).

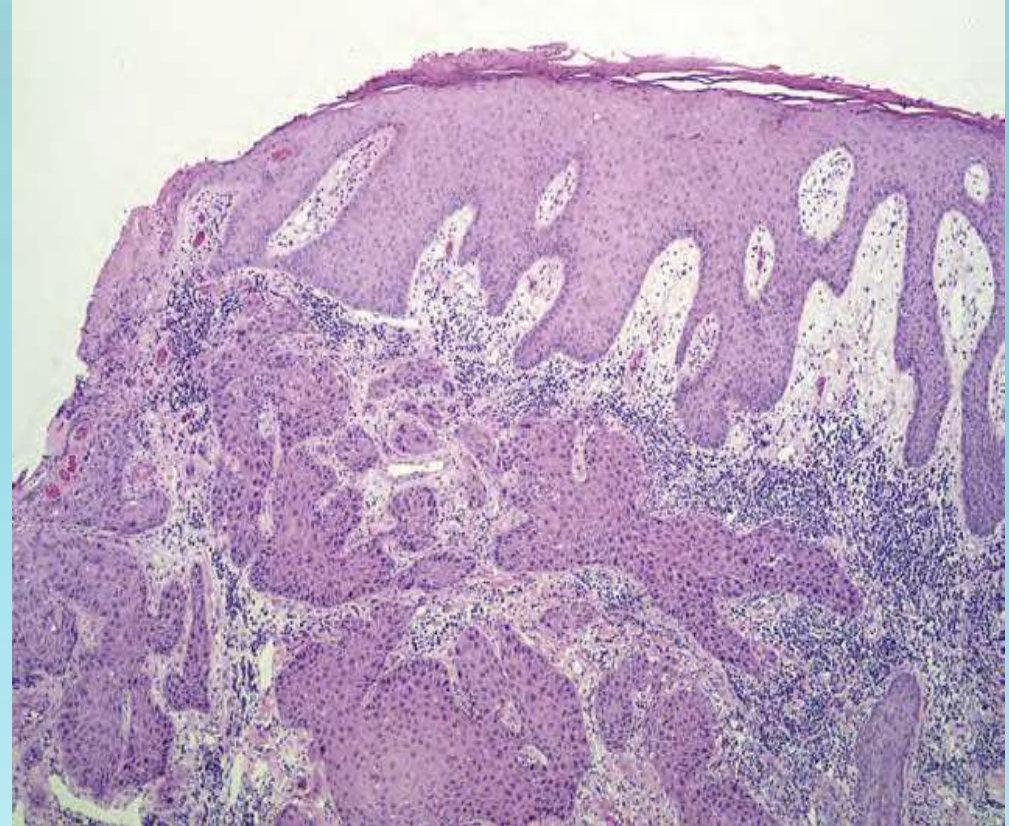


This total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH-BSO) on sectioning in half shows an **advanced cervical squamous cell carcinoma**

Mic.:

Squamous cell carcinoma is composed of **nests of malignant squamous epithelium, either keratinizing or nonkeratinizing, which invade the underlying cervical stroma**

- **Grading:** cervical carcinomas are **graded from 1 to 3** based on the degree of cellular differentiation
- **Staging:** from 1 to 4 depending on the extent of clinical spread.



➤ Clinically:

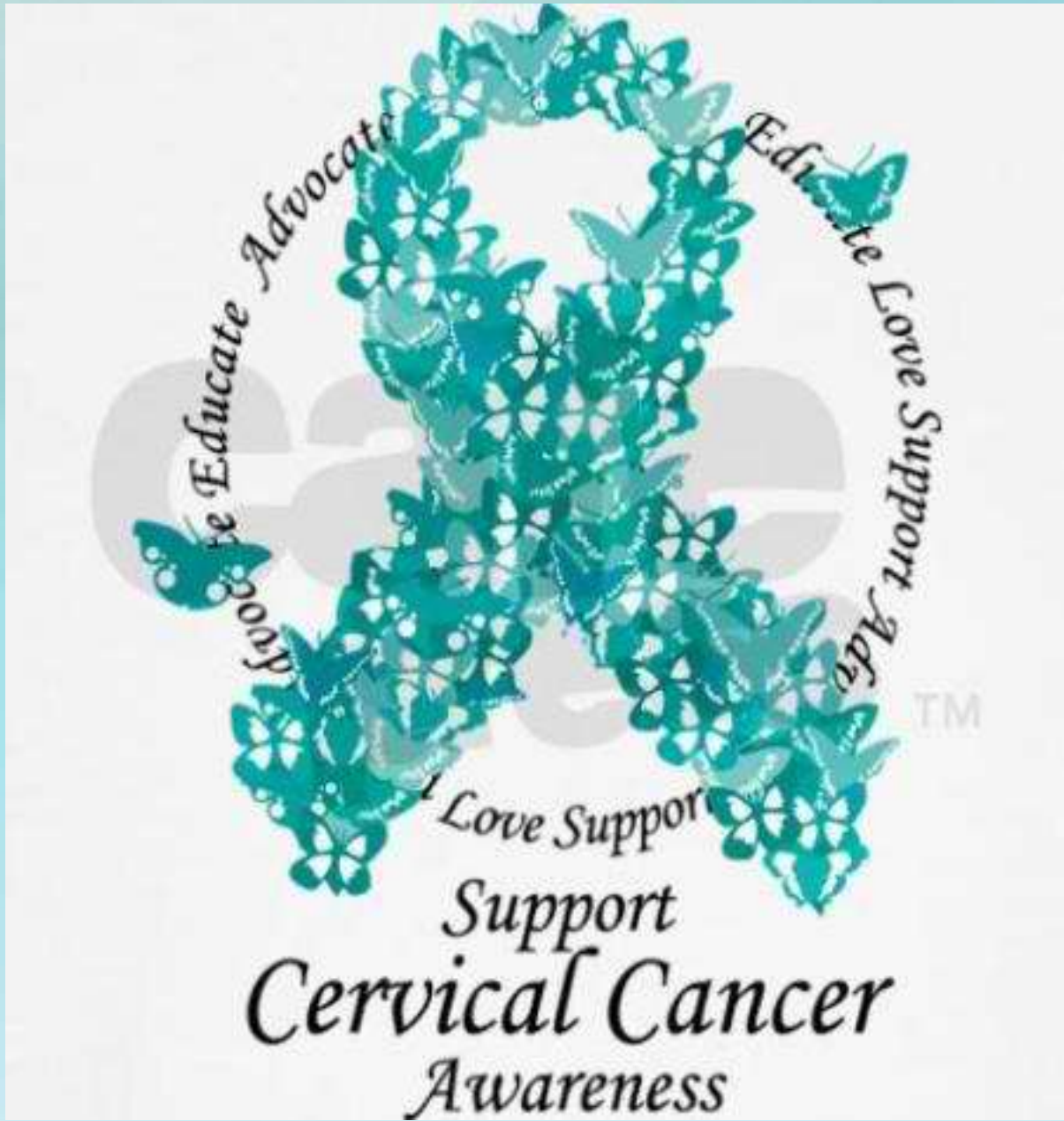
- Vaginal bleeding, leukorrhea (whitish vaginal discharge), painful coitus (dyspareunia), postcoital bleeding or dysuria.

➤ Treatment:

- Early invasive carcinomas (microinvasive carcinomas) can be treated by **cervical cone excision**; most other invasive carcinomas require **hysterectomy with LN dissection +/- radiation and chemotherapy**

➤ Prognosis:

- Depends on **stage** of cancer at diagnosis, and to some degree, **histologic subtype** (small cell neuroendocrine carcinoma have a very poor prognosis).
- Advanced cervical carcinoma **spreads by** (i) **direct extension** to contiguous tissues, including paracervical soft tissue, bladder, ureters, rectum and vagina (ii) **lymphovascular invasion** to lymph nodes and (iii) **distant metastases**.



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Educate Love Support
Love Support
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Awareness