Female genital tract pathology

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Vulva

- The vulva is the external female genitalia and includes the hair-bearing skin (labia majora) and mucosa (labia minora).
- **Diseases of vulva:**

1. Vulvitis (more common but not serious).
2. Non-NeopIastic epithelial disorders.
3. Tumors; Carcinomas (uncommon but life threatening).

1. . Vulvitis

- **Inflamation 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. **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 & end arteritis obliterans.
5. **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. Noninfectious;**

- 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-Neoplasic 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 an1% 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 acuminate 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 (HPV-negative carcinoma and 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.

❖ **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^{o}/ 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)
- **MIC.:** vacuolated cells forming irregular clusters with ill-defined glandular lumens.

3. Embryonal rhabdomyosarcoma (Sarcoma botrryoides)

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

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.

❖ Cervicitis:

- Inflammation of the cervix are **extremely common**, and are associated with purulent vaginal discharge.
- These inflammations 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, Candidaspp., Neisseria gonorrhea, 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^{O}/o 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 and 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.

❖ 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 or 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)
- **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.*

❖ 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
- **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.
- **Mortality** is most strongly related to the tumor stage. The 5-year survival in stage 1 is 90% but this figure drops to 10% in stage 4.