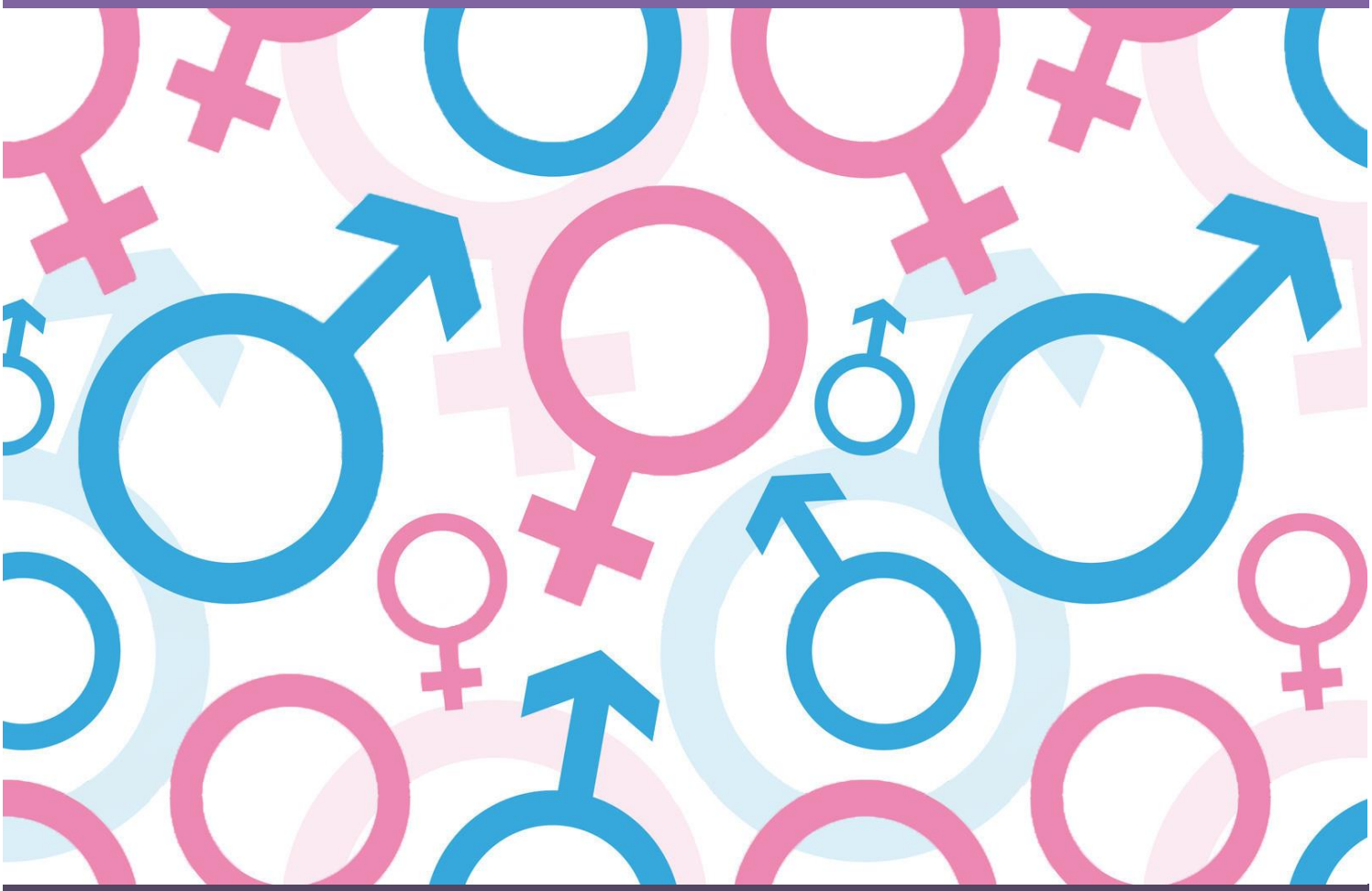


SUMMARY OF

Reproductive Pathology (L1-L9)

*432 **Pathology** Team*

Done By: Fahad Al-Dhahri

Reproductive Block

NOTE: THIS IS JUST A SUMMARY; PLEASE STUDY ORIGINAL LECTURES BEFORE READING IT.

LECTURE ONE:

Testicular tumors:

1- Seminoma:
   a. Age → 30s
   b. **PLAP positive**
   c. **Massive leukocyte infiltration in the septa.**
   d. Morphology:
      i. Unilateral
      ii. **No Necrosis or Hemorrhage**
      iii. Homogenous
      iv. Nodular

2- Spermatocytic seminoma:
   a. Age > 65
   b. Spermatic in origin.
   c. Excellent in prognosis.

3- Embryonic:
   a. Age → 20s-30s
   b. High incidence of mixed tumors(Could be present with other neoplasm in 45%)
   c. Morphology :
      i. **Necrosis and hemorrhage.**
      ii. Undifferentiated cells.
      iii. Glandular differentiation
      iv. Cells grow in alveolar or tubular pattern
      v. Large hyperchromatic nuclei.

4- Yolk sack tumor:
   a. Mainly affects infants and children up to 3 years.
   b. **AFP positive**
   c. Morphology:
      i. Non encapsulated, Homogenous, Mucinous.
      ii. **Schiller – Duval bodies**(central vessel surrounded by tumor cells)
      iii. Hyaline–pink globules.

5- Choriocarcinoma:
   a. Origin from trophoblasts.
   b. HCG positive.

6- Teratoma:
   a. Heterogenous appearance .
   b. In **children** → mature Teratoma is **benign**.
   c. In **adults** → We should always treat a Teratoma as **a malignant** neoplasm.

LECTURE TWO :

Prostate:→ Men > 50years

Normal prostate → weight: 20g \ diameter: 3-4cm

1- Hyperplasia → Transitional zone.
    a. Hyperplasia of glands and stroma
    b. **Related to the action of androgen(Dihydrotestesterone)**
    c. Main manifestation →*lower urinary tract obstruction.*
        i. urinary urgency, frequency, and nocturia
        ii. Difficulty in starting the stream of urine (hesitancy) and intermittent interruption of the urinary stream while voiding
    d. Morphology →appears nodular
2- Malignancy → Peripheral zone.
    a. **Absence of the basal layer is a main histological feature of malignancy**
    b. (symptoms of obstruction appear late)
    c. Palpable in rectal exam
    d. cross-section of the prostate the neoplastic tissue is **gritty and firm**
    e. Morphology:
        i. No intervening stroma
        ii. Nuclei are hyperchromatic
        iii. Prominent nucleoli and absent basal cells
    f. Invasion:
        i. Local → Seminal vesicles
        ii. Hematogenous→ chiefly bones, mainly **Osteoblastic.**
    g. Early detection :
        i. PSA (prostatic specific antigen)
        ii. Biopsy
        iii. imaging
    h. **localized→radical surgery**
    i. **advanced cancers →radiotherapy**

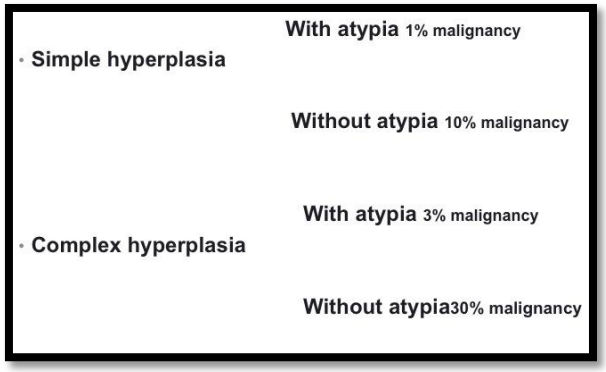
LECTURE THREE: Uterine Corpus:

1- Endomertitis:
   a. Acute:
      i. Caused usually by trauma.
      ii. Staphylococci \ Streptococci.
   b. Chronic:
      i. Etiology often not apparent.
      ii. **Histology: Plasma in the endometrium** is diagnostic.
      Granuloma → TB
      iii. Around the age of menopause + Irregular bleeding.

2- Endometrial Polyp:
   a. Histology:
      i. Glands of variable sizes and shapes.
      ii. Fibrotic stroma.
      iii. Thick walled blood vessles.
      iv. Occasionally some malignant activity could be seen in the polyp.
   b. Clinical behavior:
      i. Benign, however malignant tumors could be found within the polyp.

3- Leiomyoma:
   a. Clinicla behavior:
      i. Benign.**with no appreciable malignant potential (o.1-o.5%)**
      ii. Can be single or multiple.
      iii. **The tumor is estrogen responsive(increases in pregnancy, decrease in menopause.**
      iv. **In pregnant women it may cause spontaneous abortion, precipitate labor, obstructed labor ,post partum hemorrhage (due to interference with uterine contraction), and red degeneration**
   b. Location:
      i. Submucosal (below endometrium)
      ii. Intramural (Myometrium)
      iii. Subserosal(Parasitic) could cause→**urinary or bowel obstruction**
   c. Morphology:
      i. Gross → Firm or hard \Pale\Well circumscribed\whorled cut-surface.
      ii. **Histo →Bundles of smooth muscle fibers with in between collagen.**
   d. **Degenerative changes(read slides)**

4- Endometrial hyperplasia:
   a. Clinical behavior:
      i. Some revert to normal, other persist as hyperplasia and **few progress to endometrial adenocarcinoma:**
         1. The **risk depends on** the severity of the hyperplastic changes and associated cellular **atypia**, and level and duration of estrogen excess.
         2. Hyperplasia with atypia are more likely to develop carcinoma than those without atypia. 10x



ii. Any state of **Excess body Estrogen** is a risk factor

b. proliferation of endometrial glands.

c. **glands are irregular size and shape** → increase in gland/stroma ratio.

d. induced by persistent, prolonged estrogenic stimulation

5- Endometrial Adenocarcinoma:

a. **Abnormal bleeding 50-59 years is very indicative.**

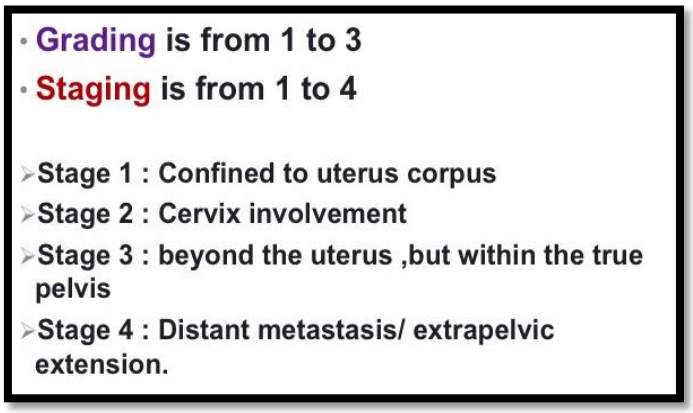
b. **Any cause of excessive estrogen production (tamoxifentreatment)**

c. Manifests as marked leukorrhea and abnormal vaginal bleeding.

d. most common invasive tumor of the female genital tract in the U.S

e. **High socioeconomic status women have a higher incidence.**

f. **The disease may follow atypical hyperplasia but may occur independently, especially in older patients.**



LECTURE FOUR: Ovarian cysts & Ovarian tumors:

- Silent growth of ovarian tumors make them so dangerous →high mortality

1. ***NON NEOPLASTIC CYSTS***:
   a. **Corpus Luteum cyst**→Results from delayed resolution → Hemorrhage into persistent mature corpus luteum→self limited
   b. **Follicular cyst**→distension of un-ruptured graafian follicle:
      i. Thin walled fluid filled structure
      ii. **Lined internally by granulosa cells and externally by theca interna cells**.
      iii. Less than 5 cm.
   c. **Chocolate cyst** is a blood containing cyst (from endometriosis with hemorrhage)

2. ***NEOPLASMS***→ Divided by cells of origin to:
   a. Epithelial surface tumors→ Most common (90%) →**types can be(see table) :**

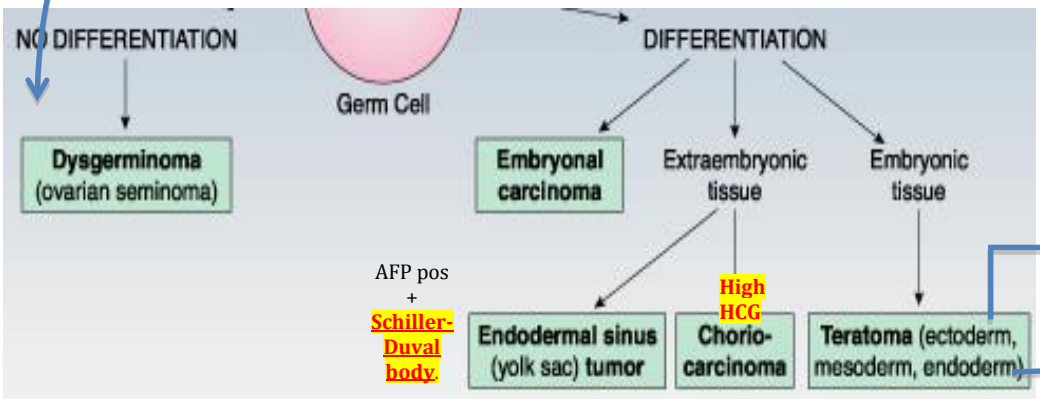
Type	Gross	Microscope
Benign	No atypia + No invasion	Cystic
Borderline	atypia + No invasion	Cystic / solid foci
Malignant	atypia + invasion	mostly solid & hemorrhage / necrosis

      i. **Serous**(tubal) →From Fallopian tube →**Serous columnar cells**
         1. Serous cystadenoma: single layer of columnar ciliated epith.+ **Fine papillae**
         2. Serous cystadenocarcinoma:
            a. **Papillary complexity**
            b. **stromal invasion**
            c. **Psammoma bodies**
      ii. **Mucinous**→(endocervical or intestinal)→**Rarely bilateral**→Cells: **columnar + apical mucin +Partially ciliated if intestinal**
         1. Mucinous cystadenoma:
            a. Multilocular
            b. single layer of columnar cells with basally placed nuclei and apical mucin
      iii. **Endometrioid→cells look like endometrium→many are associated with endometrial cancer**
         1. Endometrioid adenocarcinoma→
            a. Gross: Solid / cyst filled by **hemorrhage & necrosis**
            b. Microscope →stromal invasion **by irregular malignant endometrial glands**
      iv. **Transitional cell - Brenner's**
   b. **Sex cord tumor**→often produces steroid hormones
      - **Adult** form→postmenopausal→**endometrial hyperplasia and carcinoma**
      - **Juvenile** type→ First 20 years →**precocious sexual development**

      i. Granulosa Cell Tumor→Call-Exner bodies
      ii. Thecoma-fibroma→producing estrogen
      iii. Sertoli-Leydig cell tumors→androgenic→defeminization→Tubules lined by Sertoli cells and sheet of Leydig cells

      High risk of endometrial hyperplasia and cancer

   c. **Germ Cell tumors**→in children and teens
   d. Metastatic →**Krukenberg tumor**



Monodermal teratoma→one tissue element→Stroma ovarii (thyroid tissue)

Immature teratoma→ immature or embryonal tissues ,mainly neuroepithelium

LECTURE 5: Ectopic Pregnancy, Abortion, GTD

ECTOPIC PREGNANCY

implantation of a fertilized ovum in any site other than the the endometrium of the uterine cavity →**90% occur in the fallopian tubes**→majority will present as an emergency with tubal rupture and hemorrhagic shock (Maybe mistaken for Appendicitis)

→ Other presentations: pelvic pain or abnormal bleeding following a period of amenorrhoea

Diagnosis :

- **Ultrasound**→a mass within fallopian tube
- **Positive hCG** levels
- **Microscopic**→ placental tissue or fetal parts

SPONTANEOUS ABORTION/ MISCARRIAGE:

- **Miscarriage**→ end of a pregnancy when the embryo or fetus is still incapable of surviving →Most during the first 13 weeks
    1. before the sixth week →**early pregnancy loss or chemical pregnancy**
    2. after the sixth week →**spontaneous abortion**
- **Causes:**
    1. **Chromosomal abnormalities→Half of the 1st trimester miscarriages→ more common > 35 years old →genetic problem has a 95% probability of ending in miscarriage**
    2. **Hormonal problems→Cusning \ Hypothyroid \ luteal phase defect**[1]
    3. **Infections**
    4. **Maternal health problems→Collagen vascular diseases\antiphospholipid antibody syndrome**
    5. **Lifestyle→ Smoking, drug abuse…**
    6. **Abnormal structural anatomy** of the uterus→fibroids\uterine septum
- **Diagnosis**→ultrasound + examination of the passed tissue microscopically + Genetic exam

GTD:

1. **Benign non-neoplastic trophoblastic lesions**
2. **Hydatidiform mole(HM)**
    a. Complete
    b. Partial

HM	Paternal Ch.	Maternal chro.	HCG	Villi	Treatment	Fetal tissue	Choricarcinoma
Complete	46XX	Absent	Very High	Large villi	Evacuation, and sometimes Chemotherapy	Present	2% of patients
Partial	46X	23X	High	Mixture of large and small		No Fetal tissue	Never

    c. Invasive\chorioadenoma→ 15% of complete HM →villi extends into the myometrium →Can cause hemorrahge and uterine perforation.
3. **Gestational trophoblastic neoplasia (GTN)→Choriocarcinoma**
    - Malignant tumor
    - proliferation of malignant cytotrophoblast and syncytiotrophoblast(placental tissue), without villi formation
    - **Sky high serum concentration of HCG**
    - **50% preceded by complete hydatidiform mole**

HCG level is a very good marker for persistent trophoblastic division, thus, it's important to follow up the patient's levels of HCG, after miscarriage, hyditform mole and through and after the treatment of choriocarcinoma

[1] inadequate function of the corpus luteum in the ovary.

LECTURE6 : Polycystic Ovarian Disease & Endometriosis

PCOD:

bilaterally enlarged ovaries, with thickened cortex and multiple cortical cysts.

Histologically → **Absent Corpus Luteum**

Abnormalities:

1. High LH + Low FSH
2. No Corpus Luteum→ Anovulation → Irregular menses + Infertility
3. High Androgens → Hirsutism, Villiremia.
4. High estrogen → Endometrial hyperplasia and carcinoma.

ENDOMETRIOSIS:

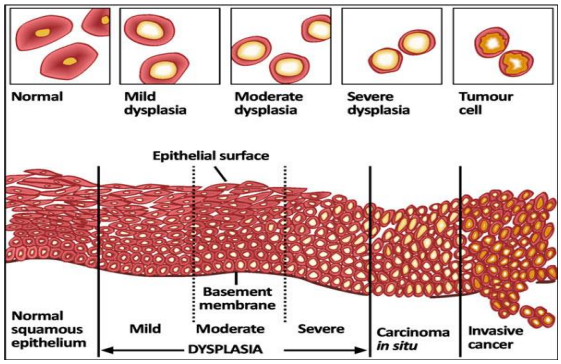
- Ectopic endometrial **glands** **and** **stroma** outside the uterus.
- Frequent locations:
  - 1st Ovary→ Hemorrhage into ovarian foci causes **chocolate cyst formation**
  - 2nd Pouch of Douglas
  - 3rdUterine ligaments
- Non-neoplastic.
- responsive to the hormonal variations (Cyclical)
- **Presentation**→ Usually severe menstrual pain + Infertility.
- **Gross** →**multiple, red or brown nodules**, sometimes with surrounding fibrous adhesions**.**
- **Clinically** →Present as a **benign abdominal mass**, sometimes after surgery (excision or C-section)

ADENOMYOSIS:

- **Endometrial glands and stroma in the myometrium**
- When extensive the lesions produce myometrial thickening
- Small yellow or brown cystic spaces containing fluid or blood.
- Benign→regresses after the menopause

LECTURE 7: Crvical Pathology And Cancer

1. ***EROSION\ ECTOPION***→columnar epithelium replacing squamous epithelium →benign
2. ***CERVICAL POLYP***→**a small, pedunculated, often sessile mass→originate from the endocervix→inflammatory proliferations→benign stroma**
3. ***CERVICITIS:***
   a. **Non-infectious**(Chemical or mechanical irritation) → asymptomatic →cervix appears red and swollen
   b. **Infectious**→If symptomatic it manifest as **vaginal discharge**
      i. **Candidiasis** → Patient usually Pregnant or diabetic →**Thick white discharge**→vulvovaginalpruritis→ Histology + Pseudohyphae
      ii. **Trichomoniasis**→**motile trophozoites are seen**→ inflammatory infiltrate of lymphocytes and plasma cells
      iii. **Chlamydia**→mucopurulent cervical discharge with a reddened, congested and edematous cervix
      iv. **HPV**→May cause the following:
         a. **Condyloma (genital warts)→ HPV 6,11**
         b. **Mild dysplasia "low risk" → HPV 6, 11**
         c. **High grade dysplasia →HPV 16,18,31,33,35**
4. ***PRE-INVASIVE CERVICAL LESIONS***:
   a. **There are no visible symptoms that you have dysplasia of the cervix →Pap smear and annual Pap exam is very important, and decreases cancer risk markedly.**
   b. **HPV infection**is now known to be a preceeding factor to cervical dysplasia and carcinoma**.**
   c. Precancerous lesion (CIN\SIL[1]) → Non invasive →may begin as Low Grade CIN and progress to High Grade CIN, or they might start as HG lesion:
      i. **CIN I** :**Mild** Dysplasia →**koilocytotic** atypia→ Cytology: big hyperchromatic nuclei
      ii. **CIN II** :**Moderate** Dysplasia →progressive **atypia in all layers** of the epithelium→Cytology : Huge nuclei
      iii. **CIN III** :**Severe** Dysplasia and Carcinoma in situ→**diffuse atypia and loss of maturation→Cytology: Crowded hyperchromatic nuclei**



5. ***CERVICAL CARCINOMA***:
   a. **Most common** cervical cancer**is squamous cell carcinoma→Remember: Histologically, it could produce keratin .**
   b. **Cause**→**HPV virus, mainly 16,18,31,33,35**
   c. **Morphology**→Range from microscopic foci of early stromal invasion to frank tumors encircling the Os
   d. **Grading**→ based on cellular differentiation
      1. Well 2. Moderate 3. Poor
   e. **Staging** → Based on clinical spread (carcinoma in citu = Stage 0)
      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 or distant organs**
   f. **Treatment**→**laser or cone biopsy**

[1] CIN = Cervical Intraepithelial Neoplasia(Histology) \ SIL =Squamous Intraepithelial Lesion(Cytology)

LECTURES 8-9: Breast Pathology

CLINICAL PRESENTATION OF BREAST DISEASES:

1. **Pain (mastalgia)**
2. **Palpable mass**
3. **Nipple discharge**
   a. Milky→ Benign lesion
   b. Bloody →most commonly with benign lesions, rarely **can be due to a malignancy**
4. **Mammographic screening: (Very important after the age of 40)**
   a. Densities → Can be benign or malignant.
   b. Calcification→Can be benign or malignant
      →**small, irregular, numerous, and clustered calcifications**→very alarming for DCIS

INFLAMMATORY LESIONS:

1. **Acute mastitis →during the first month of breastfeeding**
   a. Staphylococcus aureus
   b. **erythematous and painful (Acute inflammation)**
2. **Periductal mastitis** →not associated with lactation→**strong association with cigarette smoking**
3. **Mammary duct ectasia**(dilated ducts)→**(nipple discharge –Comido- that look like CIS lesions)**
   Old age + Breast mass + Comido discharge

BENIGN LESIONS:

1. **Non proliferative**breast changes **(fibrocystic changes)**→**Normal cancer risk.**
   a. Most common disorder of the breast.
   b. Between 20-55yrs, decreases progressively after menopause.
   c. Presentation →**Palpable breast mass with multiple nodules**, mammographic densities, calcifications ,or nipple discharge
      i. **Cysts formation**
      ii. **Fibrosis**→Causes firmness.
      iii. **Adenosis**→Increase in the number of acini per lobule (note:adenosis can be seen in pregnancy).
   d. **Cyclical**(Mass characters, size and pain vary through menstrual cycle)
2. **Proliferative**breast disease**without atypia**→**1.5 – 2 times risk of cancer**
   A. Epithelial hyperplasia
      I. **The presence of more than 2 histological layers**(Normally only 2: epithelial and myoepthelial layers) →**Both layers proliferate.**
      II. **No Atypical features.**
   B. Sclerosing adenosis
      I. Most often occurs as an **incidental** microscopic finding
      II. May manifest as a palpable mass that **may be mistaken clinically for cancer**
      III. **Diffuse microcalcifications are commonly seen in the lesion, which may mimic carcinoma in situ on mammography.**
   C. Complex sclerosing lesions/radial scar
      I. **stellate lesions**

II. **IRREGULAR** mammographic density→closely mimic an invasive carcinoma both mammographically(irregular and dense)and on gross examination(firm mass lesion)

D. Papillomas

I. arises from the duct epithelium→ age is around 40

II. Commonly solitary →Sub aleolar + Bloody nipple discharge

III. Multiple lesions (papillomatosis) → Increased risk of cancer → Rarely causes nipple discharge

E. *Proliferative variant of fibrocystic disease*.

3. Proliferative breast disease with atypia (Atypical hyperplasia)→3 – 5 times risk of cancer. Cellular and architectural changes resemble -but- lack sufficient qualitative or quantitative features for a diagnosis of carcinoma in situ

I. Atypical ductal hyperplasia (ADH)

II. Atypical lobular hyperplasia (ADL)

BREAST CARCINOMA:

❖ The most common malignancy of breast is carcinoma.

1. Risk Factors:

A. Age:

a. (77%) of cases occur in women >50 yrs old

b. Rare before 25 yrs→except familial forms→ more agressive

c. **Younger** age at **menarche, and older menopause→higher** her risk.

d. **Earlier** first **birth,→lower** lifetime risk.

B. ***First Degree relative with Breast Cancer→Multiplies the risk (Very imp.)***

C. **Atypical hyperplasia**→increases the risk

D. Longer breast feeding→decreases risk

E. Geographic influence

F. Estrogen Exposure

G. Radiation exposure

H. History of breast cancer

I. History of Other Cancer (especially ovarian)

J. Bad Diet(fat, alchohol..)

K. Obesity

L. Low Exercise

M. Exposure toToxins

N. Tobacco

All Increase The Risk

2. Etiology →Usually unknown

3. Types:

a. Heriditary(Remember BRCA1 and BRCA2 mutations)

b. Sporadic→Majority of these cancers are **postmenopausal→ Related to hormone exposure (menarche, pregnancy, breast feeding, HRT…)**

4. Majority are **Adenocarcinoma**, and are classified to:
   a. CIS: (Ductal/ Lobular)
   b. Invasive

❖ **Carcinoma In Citu**→**doesn't** invade basement membrane(**precancerous\non-invasive**)

A. Ductal Carcinoma In situ (DCIS) → 80% of breast CIS

I. **P**roliferating malignant cells **within the duct system, not yet invaded BM[1].**
II. Patient are**x10 susceptible to invasive carcinoma** than normal individuals.
III. Age →mostly50 and 59 years
IV. ***Multifocal, widely spread through the ductal system.***
V. **Mammography (Golden standard)→Microcalcifications (Fine calcification[2]) (72%-98%)→ Usually no mass lesion.**
   i. ***comedo: Lesions with large central zones of necrosis with calcified debris→worst type → 100% risk of invasion***
   ii. ***cribiform***(cells arranged around "punched-out" spaces); ***papillary,***
   iii. ***micropapillary***
   iv. ***solid*** (cells fill spaces)
VI. of ***different grades*** i.e. low, intermediate and high grade (e.g. comedo=high)→Incidence of invasion in high grades is higher.
VII. Treatment → Local excision or total mastectomy.

B. Paget's disease→ Presence of **malignant cells in the epidermis**→Orange eczematous like skin change

C. Lobular Carcinoma In City (LCIS) → 20%
Multicentric(multifocal) and bilateral→Malignant cells fill and expand the acini of a lobule.

❖ **Invasive Breast Carcinoma**→extended across the basement membrane

1. **Features**:

[1]BM → Basement membrane.
[2] Dr. Emad used this term throughout the 2 lectures instead of microcalcification.

a. **Palpable mass** → Firm →Larger carcinomas may be **fixed** to the chest wall or cause **dimpling of the skin**
b. By the time a cancer becomes palpable→over half the patients will have **axillary lymph node metastases** → could block lymph drainage → lymphedema
c. **Mammography** → most commonly present as a **density**
d. A carcinoma extensively involving dermal lymphatics→**enlarged erythematous breast**→**inflammatory carcinoma**

2. Diagnosis→**histopahtologic examination is the only confirmative test.**
3. Types:
   a. **NOS Ductal 80% (Non Otherwise Specified):**
      i. Classical presentation →palpable mass with hard consistency.
      ii. Gross →firm ,hard, and have an irregular border.
      iii. Calcifications→grating **sound** when cut or scraped.

   b. Lobular 10%
      i. **(Multifocal / Bilateral)→ Patient with only one breast affected has to check up very often**
      ii. Histopathology:
         1. indian file pattern
         2. No tubules or papillary formation
   c. Tubular 6%
   d. Mucinous (Colloid) 2%
      i. Occur in **older women**.
      ii. Sharply circumscribed
      iii. **Tumor cells floating**in **pools of Extracellular mucin**
   e. Medullary 2%
      i. **well circumscribed**
      ii. soft mass
      iii. **Lymphocytes and plasma cells surround the tumor cells.**
   f. Papillary 1%
   g. Metaplastic Carcinoma 1%

Prognosis is better than NOS

4. **Treatment**:
    a. Wide local excision
    b. Radical mastectomy

5. Prognostic factors:
    a. **Invasive(bad) or In situ (will become invasive if not treated properly)**
    b. **Distant metastasis (poor)**
    c. **Lymph node metastasis (poor)**
    d. **Tumor Size→less than 2 cm is →better prognosis**
    e. **Locally advanced disease (invasion of surrounding skin or muscle(poor).**
    f. **Inflammatory Carcinoma (very bad prognosis)**
    g. **Histologic Subtype (ductal and lobular are the worst)**
    h. ***HER2 mutation(poor)***
    i. **Lymphovascular invasion: either with or without lymph node metastasis (poor)**
    j. **Proliferative rates**

❖ STROMAL TUMORS:

1. Fibroadenoma:
    a. (Most common mass lesion in the breast)
    b. Usually young age group<30
    c. **firm, mobile lump ("breast mouse")**
    d. benign + sharply demarcated
    e. proliferation of intralobular stroma surrounding
2. Phylloides tumor:
    a. Can be benign, border line or malignant.
    b. Age → 50s
    c. **Phyllodes tumors must be excised with wide margins to avoid the high risk of local recurrences.**

تم بحمد الله