Contact us: Pathology435@gmail.com

Uterine Corpus

{ ومن لم يذق مرّ التعلُّمِ **ساعةً**.. تجرع ذلّ الجهل **طوال** حياتهِ }

Lecture one

Objectives:

Lesions of endometrium of uterus: know the risk factors, clinical presentation, macroscopic and histological features of

- **Endometrial hyperplasia**
- **Endometrial carcinoma**

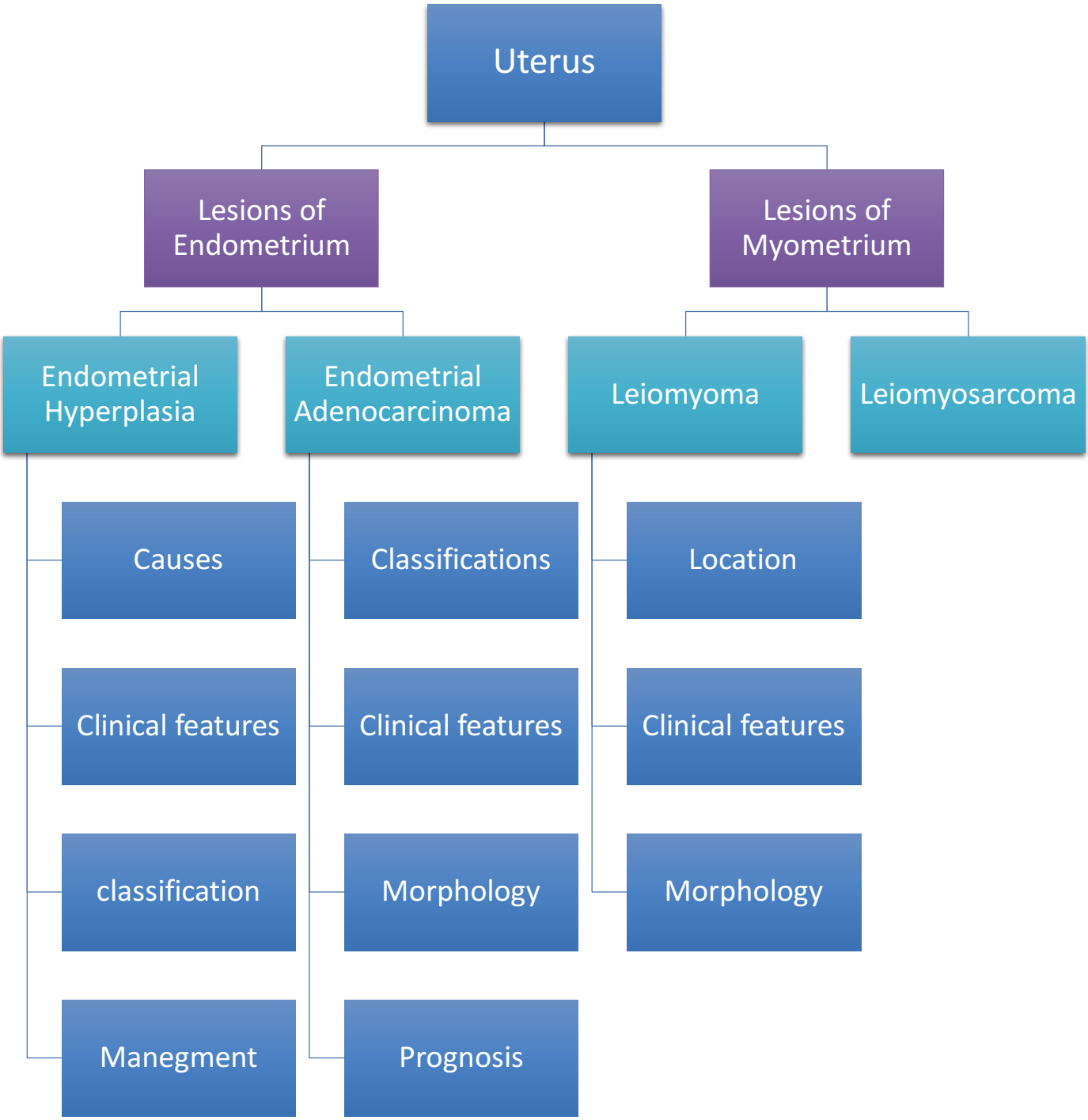
Lesions of myometrium of uterus:

- **Leiomyoma:** understand the pathology and clinical features of uterine leiomyomas and that leiomyoma (fibroid) is the commonest neoplasm arising in the female genital tract.
- **Leiomyosarcoma**

References: Lecture Slides & Robbins.

Revised by
خولة العماري & هشام الغفيلي

Red: Important. Grey: Extra Notes Doctors Notes

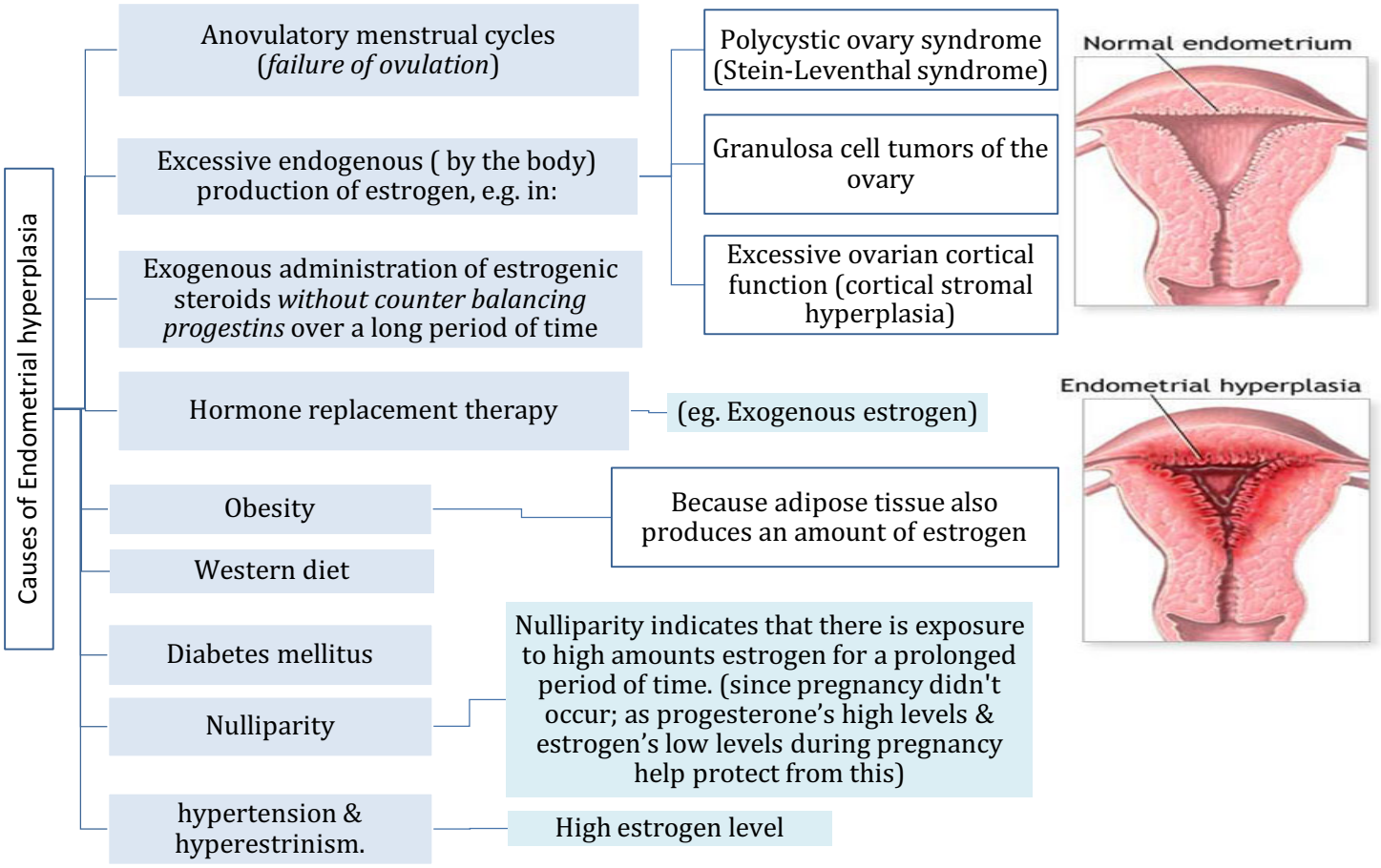

Uterus
Lesions of Endometrium
Lesions of Myometrium
Endometrial Hyperplasia
Endometrial Adenocarcinoma
Leiomyoma
Leiomyosarcoma
Causes
Clinical features
classification
Manegment
Classifications
Clinical features
Morphology
Prognosis
Location
Clinical features
Morphology

Endometrial Hyperplasia:

- It's an abnormal endometrial gland **proliferation** resulting in an **increase in Gland/stroma ratio** when compared to normal. The amounts of glands outnumber the stroma
- I t is induced by **persistent, prolonged estrogenic stimulation of the endometrium.**
- The endometrial hyperplasia may progress to **endometrial carcinoma.**
- The severity of hyperplasia is correlated with the level and duration of estrogen excess.
- The risk is of developing carcinoma depends on the severity of the **hyperplastic changes** and **associated cellular atypia.**

➢ Causes (Risk factors):

Any condition in which there are high estrogen levels can lead to endometrial hyperplasia. Some of them are as follows:



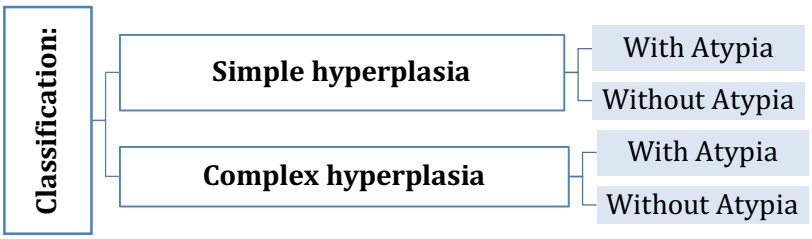
➢ Clinically:

- Mild type of hyperplasia tends to occur in **younger patients**. younger patients towards menopause, because changes in the cycle start to occur.
- The great majority of mild hyperplasia regress, either spontaneously or after treatment.
- The more severe type of hyperplasia occurs mainly in **peri- and postmenopausal women. This form has a significant premalignant potential.**
- Patients with endometrial hyperplasia usually present with **abnormal uterine bleeding.** In early stage hyperplasia, they have thick endometrium with bleeding due to excessive estrogen production.

Endometrial Hyperplasia is classified based on:

Gross: the cavity becomes folded and irregular due to proliferation of endometrial glands.

- **Gland architecture**: into → **simple or complex,** depending on the degree of glandular complexity and crowding.
- **Cytologic features**: into → **with or without atypia**[1].



Without atypia

Simple hyperplasia	Complex hyperplasia
▪ **Simple hyperplasia (cystic hyperplasia):** glands are varibly shaped and sized and cystically dilated with abundant cellular stroma and give a "Swiss Cheese" appearance. Why is it called cystic? Because the endometrial gland gets bigger (cystic changes) & when you do an ultrasound you will actually see the cyst. ▪ There is a mild increase in the gland-to-stroma ratio. ▪ These lesions rarely progress to adenocarcinoma. **(1%)** No hysterectomy is needed ▪ Simple hyperplasia may progress to **cystic atrophy.**	▪ Proliferation of endometrial glands resulting in complex **crowded glands** with papillary infoldings and irregular shapes. The crowded glands are back-to-back with very little intervening stroma. ▪ The epithelial cells remain cytologically **normal**. ▪ **3%** progression to carcinoma.

With Atypia

Simple hyperplasia	Complex hyperplasia
▪ Uncommon. ▪ It has the architecture of simple hyperplasia, but there is **cytologic atypia** within the glandular epithelial cells. ▪ **10%** of such lesions progress to carcinoma.	▪ Complex proliferation of endometrial glands (back-to-back irregular glands) with atypia. ▪ The nuclei show loss of polarity and are enlarged and rounded and may have **irregular nuclear membranes**. ▪ Commonly about 30% of women with this diagnosis have carcinoma somewhere in the uterus when a hysterectomy is performed. ▪ **About 30% progress to carcinoma.**

Genetics:

In a significant number of cases, the hyperplasia is associated with inactivating mutations in the PTEN tumor suppressor gene. (An important brake on signaling through the PI-3-kinase/AKT signaling pathway). you can also have mismatch repair

[1] Atypia (pleomorphism) = loss of polarity, vesicular nuclei, prominent nucleoli, rounded cells

➢ Management:

- Some revert to normal spontaneously or with medical treatment, others persist as hyperplasia, and a few progresses to endometrial adenocarcinoma.
- When hyperplasia with atypia is present, it must be carefully evaluated for the presence of cancer serial **endometrial biopsies**.

Behavior

Generally, patients who have hyperplasia with atypia are more likely to develop carcinoma than those without atypia**. The risks for developing adenocarcinoma in each are as follows:**

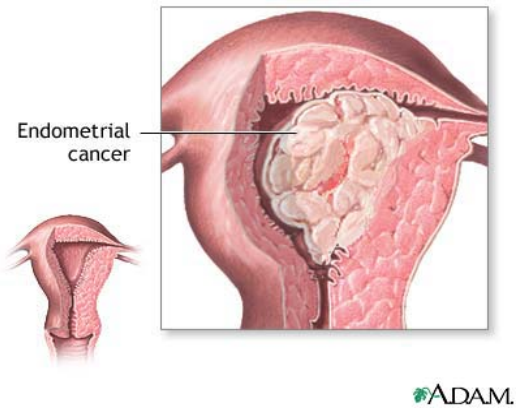
- Simple hyperplasia without atypia — 1%
- Complex hyperplasia without atypia — 3%
- Simple hyperplasia with atypia (simple atypical hyperplasia) — 10%
- Complex hyperplasia with atypia (complex atypical hyperplasia) — 30%

Notice that the atypia increases the risk 10-fold.

Atypical hyperplasia in postmenopausal women appears to have a higher rate of progression to adenocarcinoma.

Endometrial adenocarcinoma:

- A **common** neoplasm in women. Overall it is the fifth commonest cancer in women.
- Arise mainly in **postmenopausal** women.
- They cause **postmenopausal bleeding**; Early detection and cures are possible.
  Ovarian tumors which produce estrogen (eg, Thecoma, granulosa cell tumors) will present with bleeding.



These tumors are classified into two broad categories:

- **Type I carcinomas** (also known as **endometrioid carcinoma**): accounts for 80% of endometrial cancers. It is the most common type. e.g.→ endometrioid adenocarcinoma and its variants.
- **Type II carcinomas:** e.g.→ papillary serous carcinoma **(most common form of type II carcinoma)** and clear cell carcinoma. Type II are: - more aggressive -more associated with p53 -don't result from hyperplasia (type I does)

The good thing about uterine cancers is that they are picked up very early because the patient will have bleeding immediately and if you do hysterectomy you will cure the patient. It presents as postmenopausal bleeding. Type 1 is the good one and type 2 is the bad one. In type 2, papillary carcinoma is **more common** than clear cell carcinoma.

➢ Type I endometrial carcinoma/ endometrioid carcinoma:

- very crowded & similar to hyperplasia with atypia

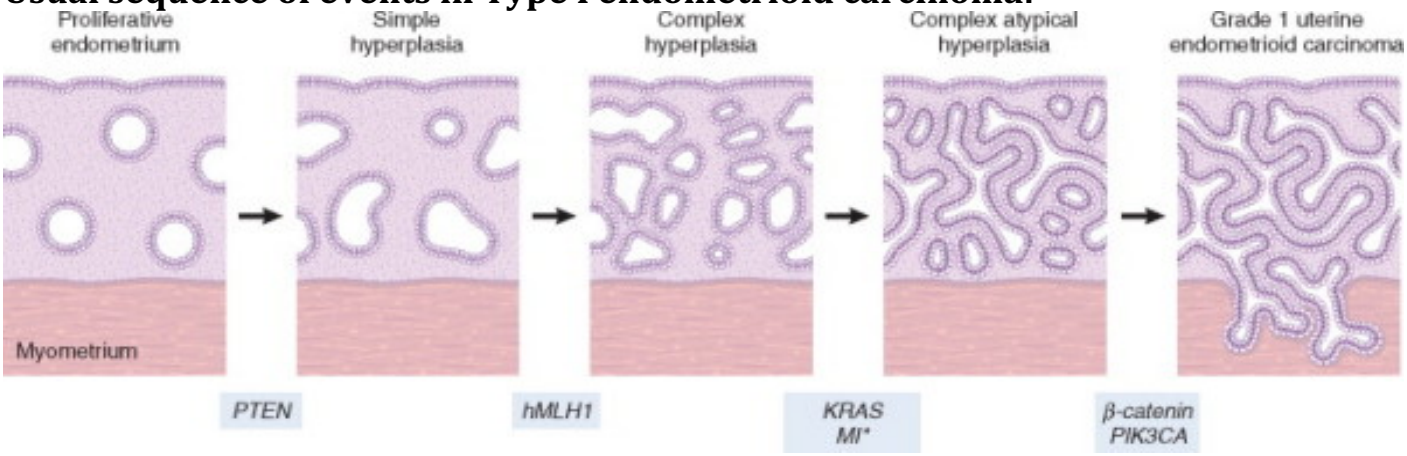
- Called endometrioid because of their histologic similarity to normal endometrial glands.
- Associated with **estrogen excess** and **endometrial hyperplasia**. The majority are well differentiated.

- **Risk factors are the same as that of endometrial hyperplasia and include:**
  - Endometrial hyperplasia is a precursor to endometrioid carcinoma.
  - Obesity (women with upper body fat have 3 times the risk of women with lower body fat).
  - The disease may follow atypical hyperplasia but may occur independently of it especially in older patients.
  - Nulliparity (as a result of infertility due to chronic anovulation).
  - Early menarche and Late menopause.
  - Lynch syndrome (colorectal, endometrial, and ovarian cancers)
  - Women with germline mutations in PTEN (Cowden syndrome) are at high risk for this cancer.
  - Breast carcinoma (which also is estrogen- dependent يعني الاستروجين سبب الثنتين)
  - Estrogen therapy or Estrogen-producing ovarian tumors (granulosa cell tumors)
  - High socioeconomic status.
  - Hypertension.
  - Chronic anovulation.
  - Tamoxifen therapy: a medicine given to a woman with breast cancer, people who take this medication are always referred from oncologist to gynecologist to follow them up for hyperplasia or adenocarcinoma.
  - Diabetes.

Genetics

- Mutations in the PTEN gene have been identified in 30% to 80% of endometrioid carcinomas
- There may be **inactivation** of DNA mismatch repair genes.
- In the more **poorly differentiated endometrioid carcinomas**, mutations in ***p53*** can be found in up to **50% of cases** (most common in Serous tumors ↓)
- **The serous type:** Nearly all cases have mutations in the TP53 tumor suppressor gene (TP53 mutations occur but are relatively uncommon and are believed to be late events in the genesis of this tumor type), whereas mutations in DNA mismatch repair genes and PTEN are rare.

Usual sequence of events in Type I endometrioid carcinoma:

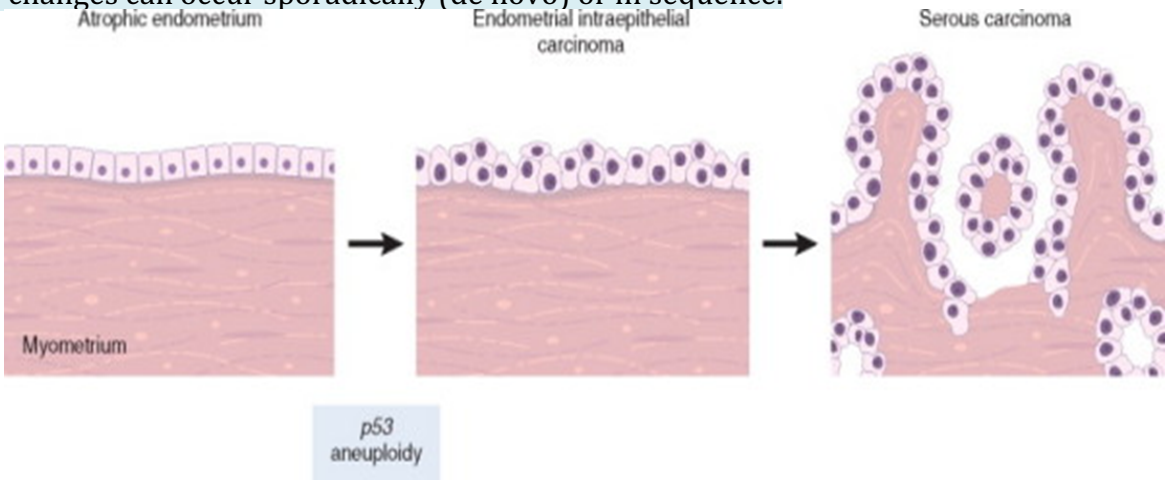


Schematic diagram depicting the development of type I endometrial carcinoma arising in the setting of hyperplasia. The **most common** molecular genetic alterations are shown at the time they are most likely to occur during the progression of the disease. *MI, microsatellite instability.

Type II endometrial carcinomas: Serous carcinoma:

- Arises in **older** women, with endometrial atrophy (small atrophic uterus).
- They occur in late in life, about one decade later than type I carcinoma.
- There **is no association with hyperestrinism or preexisting hyperplasia.**
- They represent 15% of cases of all endometrial carcinoma.
- Mutations in ***p53* are present** in at least 90% of serous endometrial carcinoma
- The **precursor of serous carcinoma is endometrial intraepithelial carcinoma** (like carcinoma in situ).
- These tumors are large bulky poorly differentiated tumors which invade early into the myometrium and have a poor prognosis. Extrauterine extension is common.

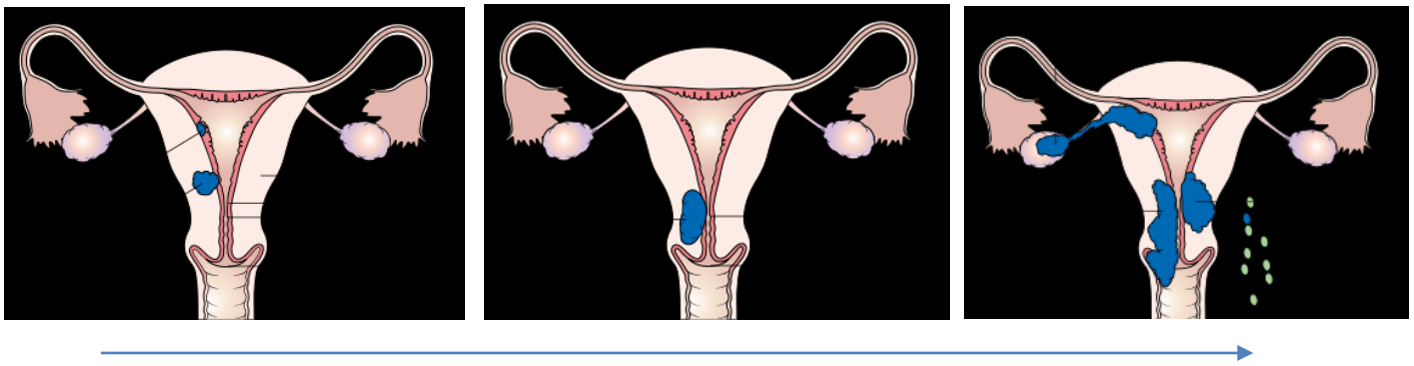
Genetic changes can occur sporadically (de novo) or in sequence.



CHARACTERISTICS OF TYPE I AND TYPE II ENDOMETRIAL CARCINOMAS

FEATURES	TYPE I	TYPE II
HISTOLOGIC TYPE	Endometrioid adenocarcinoma	Serous or clear cell carcinoma
AGE	Premenopausal and perimenopausal (50-60 yrs)	Post-menopausal (~ 70 yrs)
UNOPPOSED ESTROGEN	Present	Absent
PRECURSOR LESION	Hyperplasia with atypia	Endometrial intraepithelial carcinoma
GROWTH	Slow growing	Rapidly progressing
GRADE	Low (Endometrioid carcinomas are graded I to III, based on the degree of differentiation)	High
MYOMETRIAL INVASION	Usually superficial	Usually deep
PROGNOSIS	Favorable	Poor
GENETIC ALTERATIONS NOTED	PTEN, microsatellite instability	P53 mutations

How endometrial carcinoma can spread:



➢ Clinical Features of both:

- Most patients are between 50 and 60 years.
- Many of the patients tend to be **nulliparous and obese**.
- Abnormal menstrual cycle & abnormal uterine bleeding[2]
- Endometrial adenocarcinoma manifests as abnormal **vaginal bleeding** and **excessive leucorrhea**.
- Elderly women present with postmenopausal bleeding.
- With progression, the uterus **enlarges** and may become affixed to surrounding structures as the cancer infiltrates surrounding tissues.
- Usually slow to metastasize, but if left untreated, eventually disseminate to regional nodes and more distant sites.
- The **diagnosis** of endometrial cancer must be confirmed by **biopsy** or **curettage** and histologic examination of the tissue.

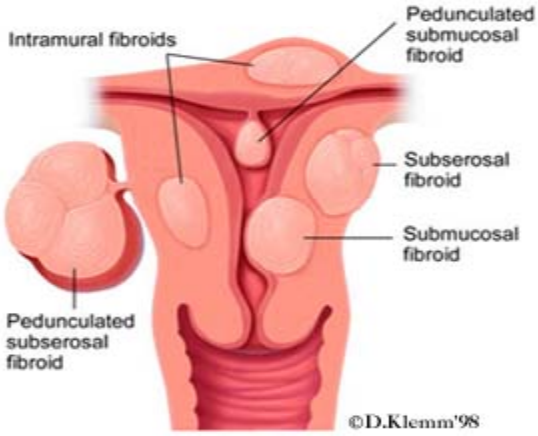
Morphology	**Gross:** May look close to normal or exophytic or infiltrative	
	Microscopic	▪ Both type I and II are adenocarcinomas. ▪ In both cases tumors originate in the endometrium and can eventually infiltrate the underlying myometrium and enter vascular spaces, with **metastases to regional lymph nodes.** ▪ **Endometrioid carcinomas** closely resemble normal endometrium and may be exophytic or infiltrative They include a range of histologic types, including those showing **mucinous**, **tubal** (ciliated), and **squamous** (occasionally adenosquamous) differentiation. ▪ **Serous carcinoma** on the other hand, form small tufts and papillae, rather than the glands seen in endometrioid carcinoma, and exhibit much **greater cytologic atypia** and are **more poorly differentiated** and therefore more aggressive
	Spreads by	▪ Direct myometrial invasion with extension to the periuterine structures. ▪ Through lymphatics to lymph nodes. ▪ In the late stages, metastasize to the lungs, liver, bones & others.

[2] So as somebody who has hyperplasia, endometrial polyps or someone who's going through normal menopause! so how do you distinguish between all of these? You must do biopsy and histological examination (light microscopy)

➢ Prognosis:

- Clinical behavior of endometrial adenocarcinoma **depends on** the histologic type, the grade (degree of differentiation) and the **stage**[3] (extent of spread).
- Endometrioid carcinoma (type I) has a better prognosis than the other histologic types.
- Serous carcinomas (type II) have **poorer prognosis**
- **Stage is the major determinant of survival** so is the type (1 or 2).
- These tumors with therapy, the 5-year survival rate for early-stage carcinoma is 90%, but survival drops precipitously in higher-stage tumors.

Leiomyoma (fibroid) of uterus:



- A benign tumor of smooth muscle in **myometrium.**
- The most common neoplasm of the **female** genital tract and probably the most common neoplasm in women.
- Affects African Americans more than white Americans.
- It is an **estrogen responsive** tumor; hence, estrogens and possibly oral contraceptives **stimulate** leiomyoma's Growth. Means if the patient has more estrogen in her body it will grow.
- Leiomyomas **shrink** in postmenopausal woman.
- About 40% of leiomyomas have an associated chromosomal abnormality; e.g., the rearrangement of chromosomes 6 and 12 are associated with leiomyomas, endometrial polyp and lipomas.
- They have **no** appreciable malignant potential (incidence of malignant transformation to leiomyosarcoma is 0.1-0.5%).

Submucosal tumors: are present immediately below the endometrium.
Intramural tumors: the most common, lie within the myometrium.
Subserosal fibroids: lie beneath the serosal surface of the uterus or are pedunculated and attached to the serosa.
Pedunculated ones: may lose their connection to the uterus forming a **"parasitic leiomyoma"**. Sometimes when the leiomyoma is in the sub-serosa it grows out and it's called pedunculated sub-serosa fibroid; and sometimes this peduncle gets disconnected and you will have this small round mass that floats around in the pelvic cavity and this is called parasitic leiomyoma.

[3] If it's detected early and the tumor is only in the uterus then you take out the uterus and send her home and follow her the next 3-4 days.

Clinical Features

It may be entirely **asymptomatic** (Accidentally discovered); If the patient doesn't have many symptoms you can leave the tumor but if she comes with symptoms and problems then you can treat the patient.

- **It can be:**
  1- Single.
  2- Multiple: Mostly
- **If it was symptomatic; patients may present with:** (15 days' period a month)
  1- **Irregular abnormal bleeding** (It may cause anemia from heavy bleeding)
    a- **Submucosal**: **most common**
    b- **Intramural**: happened if it is multiple and protrude into endometrial cavity
    c- **Subserosal**: less common
  2- Pelvic pain.
  3- Pelvic mass.
  4- **Infertility** (It may interfere with implantation and therefore cause infertility)
- Can have urinary frequency if the fibroid is compressing the urinary bladder.
- In pregnant women it may cause
  1- Abortion
  2- Obstructed labor
  3- Post-partum hemorrhage

- In pregnancy, enlargement + decrease in blood supply will lead to red/hemorrhagic change (infarction/necrosis)

Morphology

Gross	• Well-circumscribed, spherical, dense and firm-to-hard masses. They appear hard, if you take it out and hit it against the window you will probably break that window. • Cut section shows **whorled**, **grey-white** cut surfaces. If you get an MCQ saying a mass in myometrium of the uterus, cut section is grey white whorled you have to think of fibroid or leiomyoma.
Microscopic	1. There are **interlacing bundles of smooth muscle cells with collagenous stroma between bundles**. 2. The individual **muscle cells** are **uniform in size and shape**. 3. Muscle cells have the characteristic **oval to elongated nucleus**. 4. **No Mitotic figures** & usually no necrosis or atypia 5. **Foci of fibrosis** 6. **Calcification**
Spreads by	Direct myometrial invasion with extension to the periuterine structures Through lymphatics to lymph nodes In the late stages, metastasize to the lungs, liver, bones, others

Leiomyosarcoma:

- It is the **malignant tumor** of **the smooth muscle.**
- It is rare.
- Sites include the uterus and soft tissue
- Poor prognosis.

Now Check Your Understanding!

MCQs:

1- **What kind of carcinoma do you think endometrial gland will develop?** (Dr. Sufia's MCQ)
   A. Squamous cell carcinoma
   B. Transitional cell carcinoma
   C. Adenocarcinoma
2- **Which of the following is a malignant tumor of the smooth muscle?**
   A. Leiomyosarcoma
   B. Leiomyoma
   C. Fibroid of the uterus
   D. Endometrial carcinoma
3- **Endometrial hyperplasia can be caused by:**
   A. High progesterone
   B. Low estrogen
   C. High estrogen
   D. Low progesterone
4- **Which of the following is the major determinant of survival in endometrial carcinoma?**
   A. Histologic type
   B. Age
   C. Stage
   D. Grade
5- **A patient presented to the clinic with abnormal bleeding, she is worried because as she explained; her period stopped over 10 years ago. A biopsy was taken which revealed** small tufts, papillae **and great cytologic atypia. Which of the following could be the diagnosis?**
   A. Leiomyosarcoma
   B. Type II endometrial carcinoma
   C. Type I endometrial carcinoma
   D. B & C

T or F:

1- Mutations in the PTEN gene are most common in serous carcinoma.
2- Simple hyperplasia **gives a** "Swiss Cheese" **appearance.**
3- Atypical hyperplasia in postmenopausal women appears to have a lower rate of progression to adenocarcinoma.
4- A parasitic leiomyoma means there are infections and parasites.
5- Adipose tissue secretions can lead to endometrial hyperplasia in obese patients.

MCQs:
1: C, the patient can have any of them but the majority is adenocarcinoma because they are glands.
2: A 3: C 4: C 5: B

T or F:
1: F, type I 2: T
3: F, higher rate
4: F, they are pedunculated ones that lost their connections to the uterus
5: T

Thanks for checking our work! Good Luck.

* A huge thanks to Khawla Alammari for her help in simplifying the lecture.

Done by:

نوف التويجري & عمر آل سليمان

فهد العبداللطيف

معاذ باعشن

زكي الوطبان

فوزان العتيبي

رغده القاسم

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