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Summary file

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Pathology

Uterine Corpus Pathology



439

Color index

- Important
- Doctor's note
- Extra info
- Main text



Revised & Approved



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تجعل الحزن اذا شئت سهلا

Objective

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

- Endometrial hyperplasia.
- Endometrial carcinoma

02 Lesions of myometrium of uterus:

- Leiomyoma: pathology and clinical features and aware that leiomyoma (fibroid) is the commonest neoplasm arising in the female genital tract.
- Leiomyosarcoma

Overview

Uterine Corpus Pathology

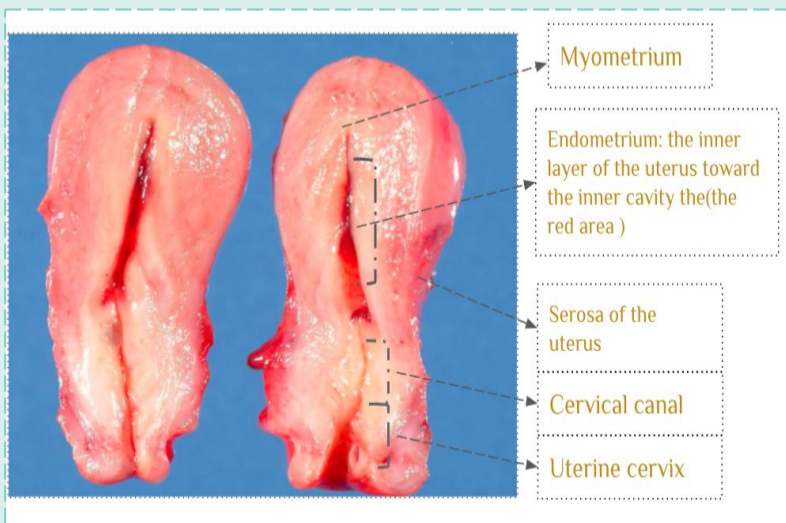
Endometrial hyperplasia

Endometrial Carcinoma

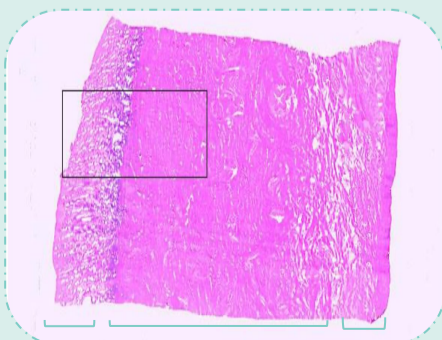
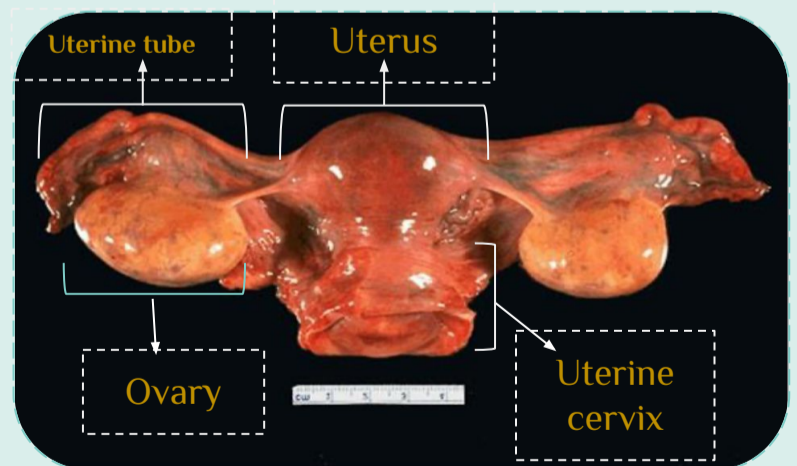
Leiomyoma

Leiomyosarcoma

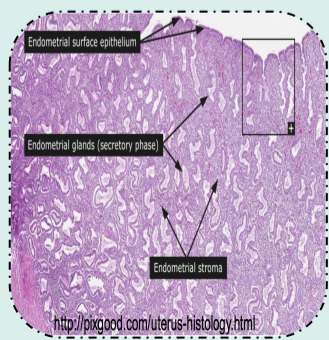
Intro.



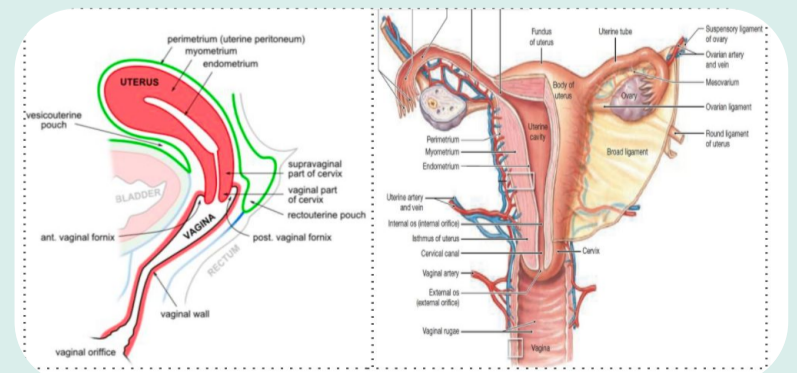
Uterus with bilateral tube and ovaries, posterior view



Myometrium Endometrium Serosa



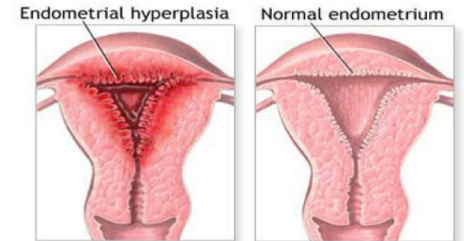
Morphology of endometrium is different according to the phase of the menstrual cycle



Endometrial hyperplasia

Introduction

- ❖ Is a process in which there's **abnormal** Proliferation of endometrial glands; resulting in **increased gland:stroma' ratio** of the endometrium relative to normal tissue.
- ❖ Induced by **persistent, prolonged** stimulation of the endometrium by **high levels of estrogen**.
- ❖ It may progress to **endometrial carcinoma** so it's important to recognize them before they progress to carcinoma.
 - Risk of developing to carcinoma depends on:
 - Level & duration of **estrogen excess**.
 - Severity of hyperplasia.
 - Presence of **cellular atypia**.



Causes Male doctor: very imp to know the causes of Endometrial Hyperplasia

1. Any condition where there is high estrogen.
2. **Anovulatory menstrual cycles (failure of ovulation)** such as in perimenopause. In anovulatory menstrual cycles, the level of estrogen is high due to low-level progesterone in the body.
3. Excessive endogenous production of estrogen:
 - a. **Polycystic ovary syndrome (Stein-Leventhal syndrome)**.
 - b. **Granulosa cell tumors** of the ovary. it's important to memorize it
 - c. Cortical stromal hyperplasia (excessive ovarian cortical function).
4. Exogenous administration or intake of estrogenic steroids without counter balancing progestin, over a long period of time.



Abnormal thickening of the endometrium with adjacent normal endometrium

Risk factors (Males slides)

- ❖ Obesity, western diet.
- ❖ Nulliparity (never having given birth).
- ❖ Diabetes mellitus. (Chronic disease)
- ❖ Hypertension (Chronic disease)
- ❖ **Hyperestrinism. The main cause**

Clinical features

- ❖ Most common: **abnormal uterine bleeding** (such as menorrhagia, excessive bleeding, irregular periods and postmenopausal bleeding),.
- ❖ Mild types occur in younger patients.
 - regress spontaneously or after treatment.
- ❖ Severe types occur in perimenopausal or postmenopausal women.
 - This form has a **significant premalignant potential**.

Endometrial hyperplasia

Before Classifications: Female doctor: Diagnosis of Endometrial Hyperplasia

- 1- Clinically (the abnormal bleeding)
- 2-Radiology (the US can measure the thickness of endometrium)
- 3-Endometrial curettage endometrial biopsy
- 4-Classification of the lesion

Classifications

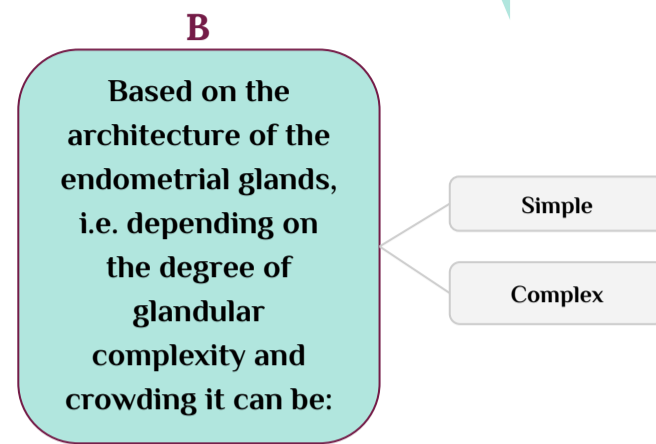
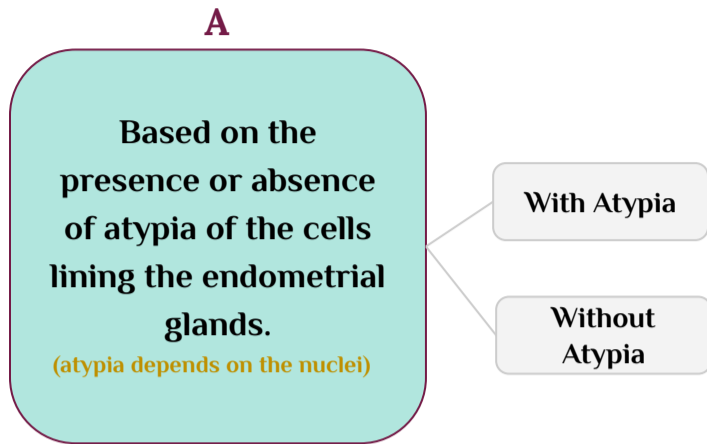
(old classification)

Simple hyperplasia

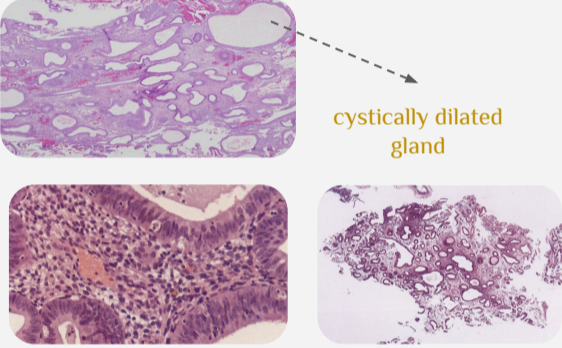
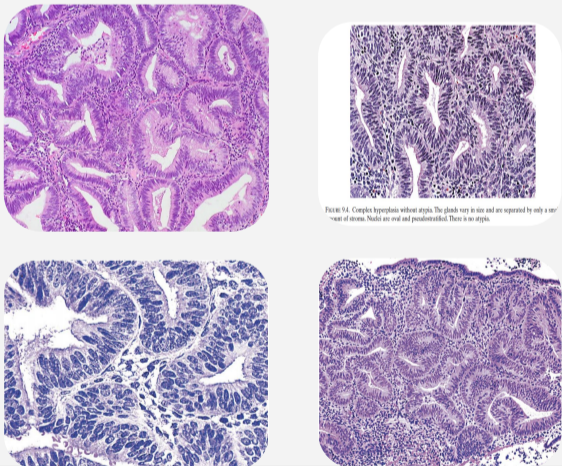
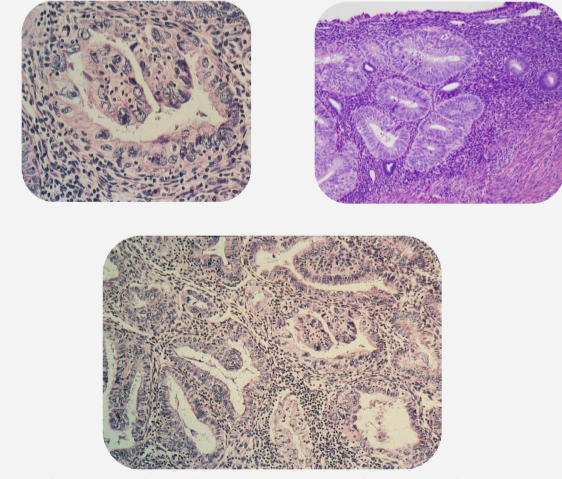
- A. Without atypia
- B. With atypia

II. Complex hyperplasia

- A. Without atypia
- B. With atypia

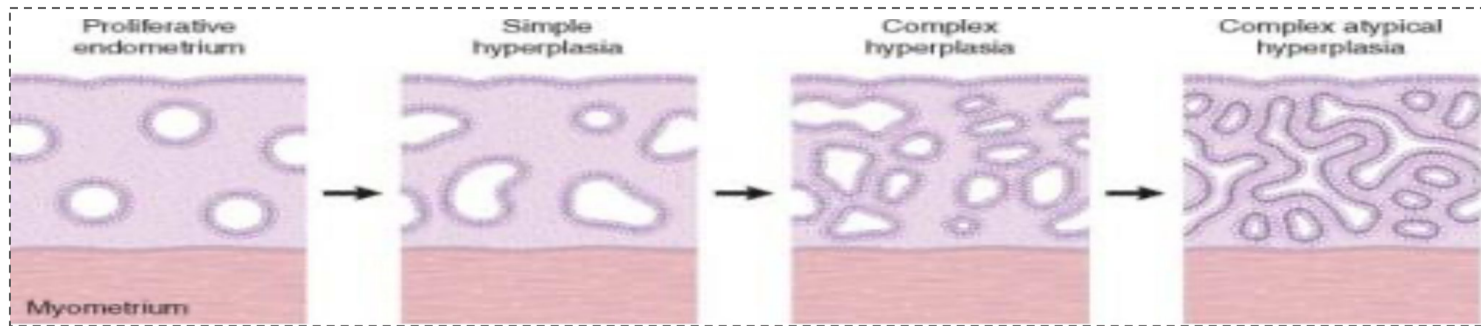


Atypia: loss of polarity, vesicular nuclei, prominent nucleoli, rounded cells. More progression to carcinoma if there's atypia

Simple hyperplasia	without atypia	<ul style="list-style-type: none"> ❖ Cystic hyperplasia: glands are variably shaped and sized, and are cystically dilated, with abundant stroma and gives a SWISS CHEESE APPEARANCE. ❖ Mild increase in gland to stroma ratio. ❖ May progress to cystic atrophy. ❖ Rarely (1%) progress to adenocarcinoma 	 <p>cystically dilated gland</p>
	with atypia	<ul style="list-style-type: none"> ❖ Uncommon. ❖ Architecture of simple hyperplasia, but there is atypia within the glandular epithelial cells. (less crowding than complex) ❖ 10% progress to carcinoma. 	
Complex hyperplasia	without atypia	<ul style="list-style-type: none"> ❖ Proliferation of endometrial glands resulting in Complex, crowded glands with papillary infoldings. ❖ Crowded glands: the glandular structures are close to each other “back-to-back” with little intervening stroma in between. ❖ However, epithelial cells are normal without atypia. ❖ 3% progress to adenocarcinoma. 	
	with atypia	<ul style="list-style-type: none"> ❖ Complex proliferation “back-to-back” with atypia. (back-to-back means very little stroma in between.) ❖ Nuclei are: <ul style="list-style-type: none"> ➢ Enlarged and rounded. ➢ Show loss of polarity! ➢ Have irregular nuclear membranes. ❖ Commonly about 30% of women with this diagnosis have carcinoma somewhere in the uterus when a hysterectomy is performed.¹ ❖ 30% progress to adenocarcinoma. 	 <p>Loss of polarity, vesicular nuclei, prominent nucleoli</p>

1: When perform endometrial curettage or endometrial biopsy the biopsy is not represented by the whole endometrium so if we see a Complex hyperplasia with atypia in the biopsy there's a 30% chance that she has carcinoma somewhere else in the endometrium but it's not represented in the biopsy so in this case you have to perform hysterectomy especially in post menopause or perimenopause (as they don't need for the uterus anymore)

Endometrial hyperplasia



Endometrial Hyperplasia: Clinical behavior and premalignant potential

- ❖ Some endometrial hyperplasia revert to normal spontaneously or with medical treatment (In a young patient start hormonal treatment (progesterone) , others persist as hyperplasia, and a few progresses to endometrial adenocarcinoma.
- ❖ 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%**
- ❖ Atypical hyperplasia in postmenopausal women appears to have a higher rate of progression to adenocarcinoma.

New classification Male and Female doctor: you have to know the new calcification

- ❖ Endometrial hyperplasia is placed into two categories based on presence of atypia:
 - **Non atypical endometrial hyperplasia**, which carries a low risk (1% - 3%) for progression to endometrial carcinoma.
 - **Atypical endometrial hyperplasia /Endometrioid intraepithelial neoplasia (EIN)**, associated with a much higher risk (20%–50%).
- ❖ The importance of this classification is that atypia correlates with presence endometrial carcinoma.
- ❖ When atypia is discovered it must be evaluated for the presence of cancer, and usually indicates a hysterectomy in patients no longer desiring fertility (If the patient is perimenopause, postmenopause or there's no desire to be pregnant) . In younger patients high dose progestin may be used to preserve the uterus.

This space is designated for the sole purpose of having more slides and making you feel the lecture is harder♥

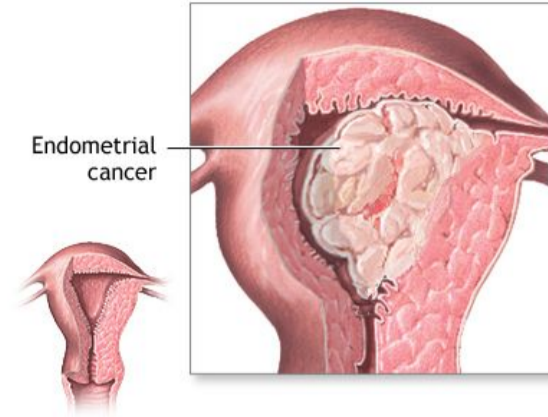


Here is a cookie to make you feel better

Endometrial carcinoma

Introduction

- ❖ The fifth most common cancer in women.
- ❖ Usually arise in postmenopausal women 50-70 years old causing bleeding.
- ❖ Postmenopausal bleeding always need to be investigated
- ❖ Early detection and cures are possible.
- ❖ Classified into:
 - Type 1: endometrioid carcinoma.
 - Type 2: serous carcinoma. it's a high grade tumor compared to type 1



Type 1: Endometrioid carcinoma

- ❖ Account for 80% of endometrial cancer (the most common type) e.g. → endometrioid adenocarcinoma and its variants.
- ❖ It is sequential to endometrial hyperplasia, however may occur independently, especially in older patients.
- ❖ It is associated with estrogen excess.
- ❖ The cells forming the tumor resembling the endometrial cells

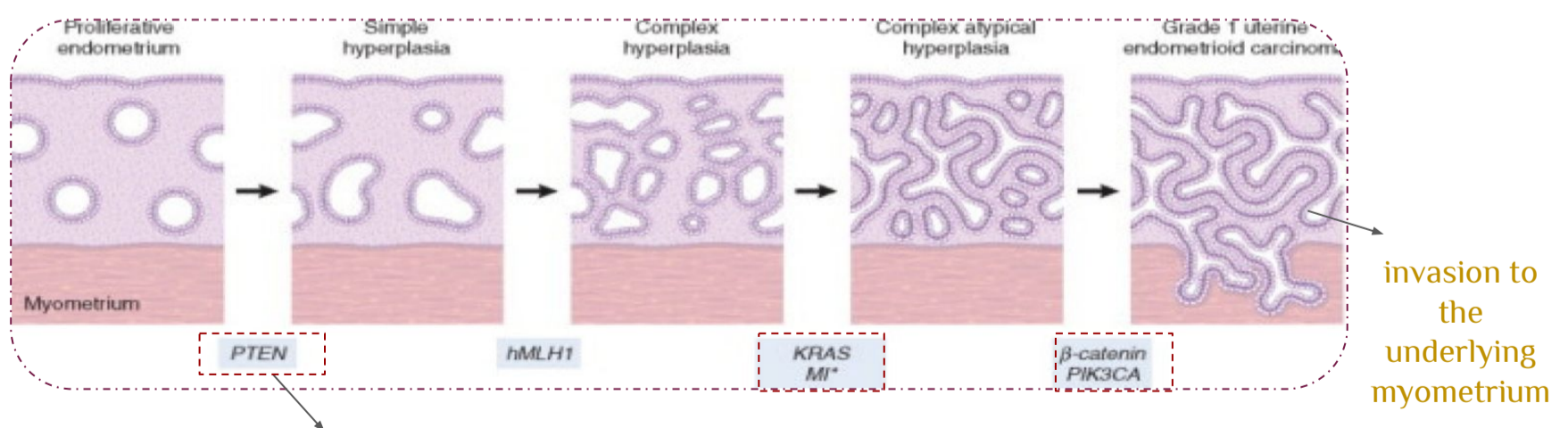
Male doctor: It is important to differentiate between the two types as it will affect the management, prognosis, and outcome

Risk factors

- ❖ Obesity, western diet, hypertension, DM.
- ❖ Nulliparity.
- ❖ Hyperestrinism.
- ❖ Chronic anovulation (the ovaries are not releasing an oocyte).
- ❖ Estrogen therapy.
- ❖ Late menopause.
- ❖ Tamoxifen therapy (in breast cancer).
- ❖ High socioeconomic status.

Genetics

- ❖ Women with germline mutation in **PTEN** (Cowden syndrome).
- ❖ Also germline mutation in DNA mismatch repair gene (Lynch syndrome)¹
- ❖ TP53 are uncommon, and are found in later stages of the development of this tumor. Seen in half of poorly differentiated endometrioid carcinoma.



Male doctor: the most important genetic mutation associated with type 1 endometrial carcinoma and you have to memorize very well is PTEN

(Lynch syndrome): type of inherited cancer syndrome associated with a genetic predisposition to different cancer types. This means people with Lynch syndrome have a higher risk of endometrioid carcinoma

Endometrial carcinoma

Clinical features

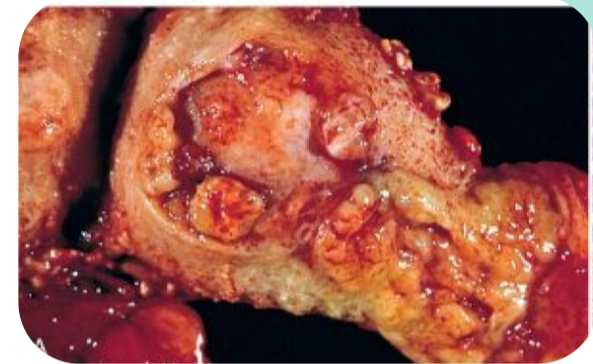
- ❖ Most patients are between 50 and 60 years.
- ❖ Patients tend to be obese and nulliparous.
- ❖ Patients have **abnormal vaginal bleeding** and excessive leucorrhoea. *vaginal discharge*
- ❖ Elderly women present with postmenopausal bleeding.
- ❖ Diagnosis confirmed by biopsy or curettage and histological examination of the tissue.
shouldn't perform hysterectomy until it's confirmed by biopsy



Morphology

Gross:

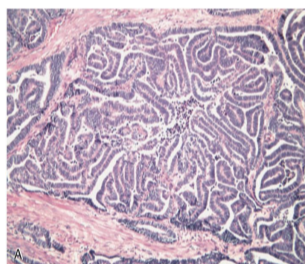
- ❖ Tumors are **large, bulky, and poorly differentiated** which invade into the myometrium. and have a poor prognosis. Extrauterine extension is common.
- ❖ May appear normal or **exophytic**¹ or **infiltrative**.



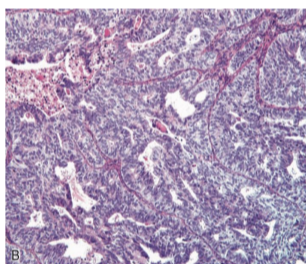
Coronal section of uterus filled with masses

Microscopy:

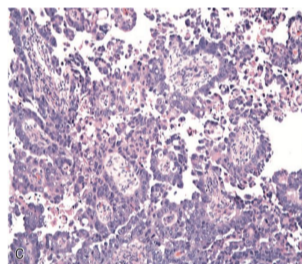
- ❖ Both type I and type II are adenocarcinomas.
- ❖ Tumor originate in the endometrium, and can infiltrate myometrium, and enter vascular and lymphatic spaces. (*inguinal lymph node - pelvic lymph node*)
- ❖ **Serous carcinoma** has a much greater cytological atypia and poorly differentiated; therefore more aggressive.



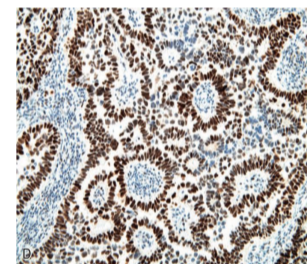
Endometrioid: infiltrating myometrium, growing in glandular pattern (stage I)



Endometrioid: stage 3; solid growth pattern



Serous carcinoma: papilla formation and marked cytological atypia



Immunohistochemistry show accumulation of P53

Prognosis

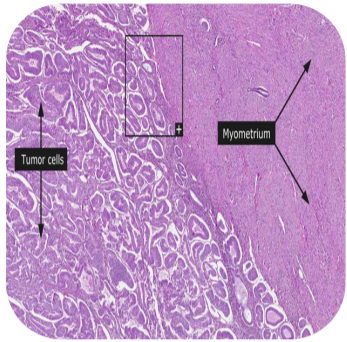
- ❖ **Tumor spread:**
 - **Direct** myometrial invasion followed by extension to periuterine structures. (*such as cervix, ovary, prostate, ligaments ...ect*)
 - **Lymphatic:** to lymph nodes
 - **By blood:** in late stages to lung liver, and bone.
- ❖ **Prognosis depend on:**
 - Histological type.
 - Stage (extent of spread). *Evaluate the cervix, myometrium, blood vessels and lymphatic invasion .*
 - Grade (degree of differentiation).
- ❖ **Endometrioid** (type 1) has **better prognosis** than other types.
- ❖ **Serous** (type 2) has **poorer prognosis**.
- ❖ However, stage is the major determinant factor of survival.

1- Grow beyond the surface. / growing inside the endometrial cavity or infiltrative to to the myometrium

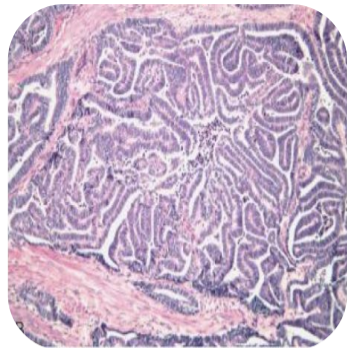
Endometrial carcinoma

Type 1: Endometrioid carcinoma

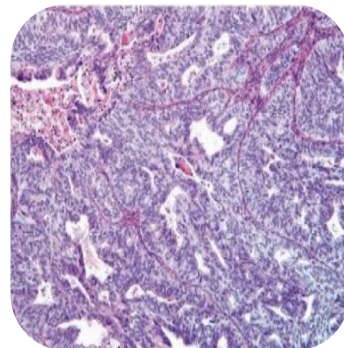
After naming the tumor we have to grade it based on the Figo grading system depend on glandular differentiation and the degree of cytological atypia



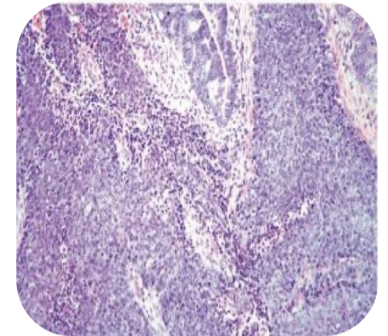
Well differentiated
No invasion



Invasion of myometrium



Moderately differentiated



Poorly differentiated

Complexed architecture
Back-to-back glands with
cytological atypia and
Myometrium invasion

It's a solid area, not forming
glands and more seen with
higher grade

Type 2: Serous Carcinoma

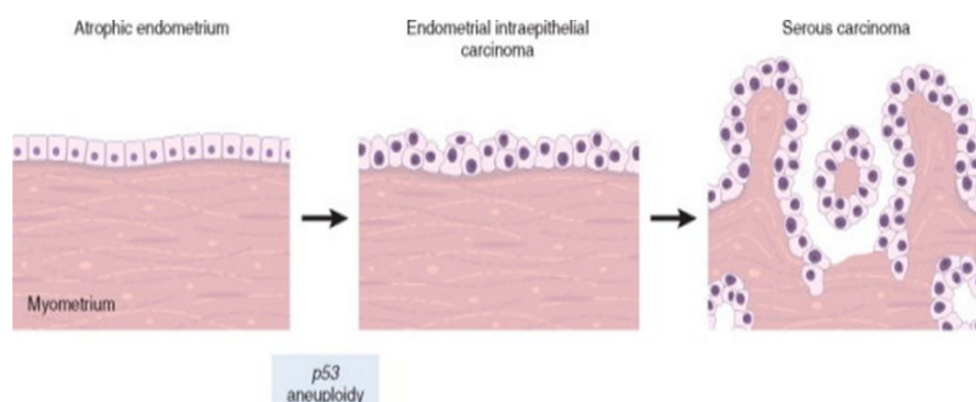
- ❖ Could be:
 - Serous papillary (**papillary is more common**).
 - Clear cell carcinoma.

Serous carcinoma

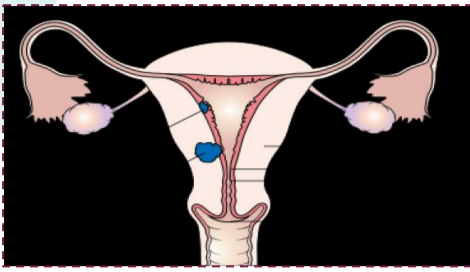
- ❖ Account for **15%** of endometrial cancer.
- ❖ Occur later in life, about one decade later than type 1 carcinoma, in older women with endometrial **atrophy** (small atrophic uterus).
- ❖ Not associated with hyperestrinism or preexisting hyperplasia.

Genetics

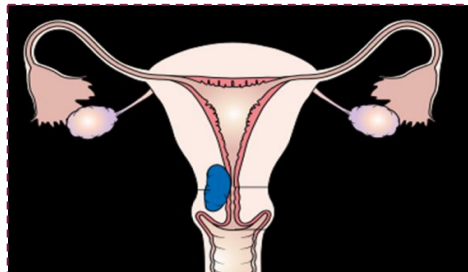
- ❖ Mutation in **p53** is present in at least 90% of serous endometrial carcinoma.
- ❖ It is preceded by Serous Endometrial Intraepithelial Carcinoma **SEIC** (similar to carcinoma in situ).
 - TP53 mutation is often detected in SEIC, giving the mutation a role in the development of the disease.



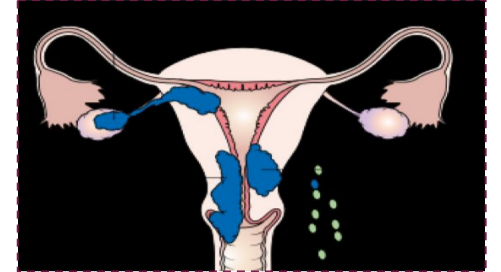
Endometrial carcinoma



Localized to the endometrium



Extension to the uterine cervix



Extension to the ovary and vaginal

IMPORTANT TABLE	Type 1	Type 2
Histological type	Endometrioid adenocarcinoma	Serous or clear cell carcinoma
Age	Premenopausal & perimenopausal (50-60 yrs)	Post menopausal (~ 70 yrs) usually in older patient
Unopposed estrogen	Present	Absent
Precursor lesion	Hyperplasia with atypia	Endometrial intraepithelial carcinoma
Growth	Slow growing	Rapidly progressing (aggressive)
Grade	Low	High
Myometrial invasion	Usually superficial	Usually deep
Prognosis	Favorable	Poor
Genetic alteration	PTEN , microsatellite instability	P53 mutations

Leiomyoma

Introduction

- ❖ **Benign** tumors that arise from smooth muscle cells of the myometrium.
- ❖ Clinically referred to as **fibroids**, due of their firmness.
- ❖ **Most common benign tumor** in female genital tract and propably the most common neoplasm in women, affecting 30-50% of female at the reproductive age. More common in **black women**.
- ❖ Estrogens and possibly oral contraceptives stimulate the growth of leiomyomas; conversely, these tumors shrink postmenopausally **because of a lack of estrogen**
- ❖ Stimulated by estrogen:
 - They **increase** in size during pregnancy or taking contraceptives.
 - **Decrease** in size after menopause.

Leiomyoma

Genetics

- ❖ 40% have chromosome abnormalities
- ❖ They are benign tumors with no appreciable malignant potential (incidence of malignant transformation to sarcoma is 0.1-0.5%).
- ❖ Rearrangement of chromosomes 6 & 12 which are also found in other benign neoplasms like lipomas and endometrial polyps.
- ❖ Mutation in the **MED12** gene has been found in 70% of leiomyomas, which encodes component of the RNA polymerase transcription complex. The mechanism by which MED12 mutations contribute to the development of leiomyomas is not presently understood.

Clinical features

- ❖ **Asymptomatic**, discovered incidentally on routine pelvic examination.
- ❖ It can be single or multiple (mostly multiple).
- ❖ **Menorrhagia** (Most common) with or without metrorrhagia (**bleeding occurring at irregular and/or frequent intervals**) which can cause anemia (**Decrease Hb level in the blood**)
- ❖ Sometimes pelvic pain.
- ❖ Urinary frequency (if the fibroid is compressing the urinary bladder).
- ❖ May cause infertility by interfering with implantation
- ❖ In pregnant women:
 - It may cause abortion.
 - Obstructed labor.
 - Postpartum hemorrhage.
- ❖ Leiomyomas rarely, if ever, transform into sarcomas, and the presence of multiple lesions does not increase the risk of malignancy.

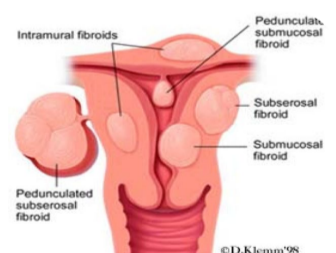
Sarcoma → in the connective tissue or mesenchymal tissue (such as smooth muscles, blood vessels, bones, and soft tissues)

Carcinoma → in the epithelial tissue (the glands)

Morphology

Gross:

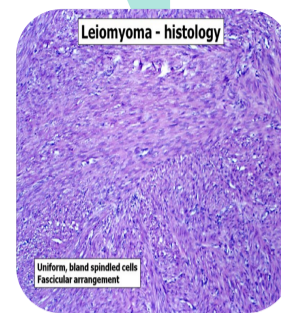
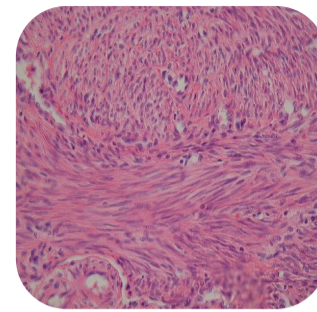
- ❖ Well circumscribed, firm, spherical mass.
- ❖ **Cut surface:** whorled, grey-white
- ❖ Could be single but more likely multiple scattered within uterus, ranging from small nodules to large that may dwarf the uterus. **Very huge fibroid compresses the uterus and makes it smaller**
- ❖ **Locations:**
 - **Intramural:** within myometrium (**most common**)
 - **Submucosal:** directly beneath endometrium
 - **Subserosal:** beneath serosa; may become attached to surrounding organs or are pedunculated and attached to the serosa
 - **Parasitic leiomyoma:** A pedunculated subserosal fibroid that undergoes torsion, detaches from the uterus, and sustains its growth through neovascularization from adjacent tissues.



Leiomyoma

Histopathology:

- ❖ Interlacing bundles of smooth muscle cells with collagenous stroma.
- ❖ Individual cells are uniform in shape and size.
- ❖ Characteristic oval to elongated nucleus.
- ❖ Mitotic figures are scarce.



Leiomyosarcoma

Introduction

- ❖ Rare, **malignant** tumor that almost always arises de novo¹ from the mesenchymal cells of the myometrium.
- ❖ Unlike leiomyomas. Leiomyosarcomas are **solitary** and arise in postmenopausal women.
- ❖ Poor prognosis:
 - Recurrence is common after surgery .
 - may metastasize, typically to the lung.

Morphology

- ❖ **Diagnostic features:**
 - Tumor necrosis.
 - Cytological atypia.
 - Mitotic activity.
- ❖ Because increased mitotic activity may be found in benign smooth muscle tumors; **all three features must be present** to make a diagnosis of malignancy.



Summary

Endometrial hyperplasia

Intro	Proliferation of endometrial glands, may progress to carcinoma Clinical features: menorrhagia, in young regress normally, in postmenopausal women.
Causes	Persistent prolonged estrogen stimulation: - anovulatory cycle - excessive production of estrogen: polycystic ovarian syndrome, granulosa cell tumor - Exogenous intake of estrogen steroids
Classification	Based on architecture of glands: - simple: abundant stroma, less crowded - complex: crowded glands, “back-to-back”, papillary infolding Based on Presence of Atypia: With Atypia: show loss of polarity, vesicular nuclei, prominent nucleoli, rounded cells. Without Atypia: does not show features of Atypia Atypia has the strongest correlation with development of carcinoma.

Uterine Tumors

Endometrial carcinoma	Malignancy of endometrium, usually in postmenopausal women 1- Endometrioid: it is sequential to endometrial hyperplasia, associated with estrogen excess. - genetic: PTEN mutation Better prognosis 2- Serous: occurs later than type one, associated with p53 mutation , - it is preceded by Serous endometrial intraepithelial carcinoma. Poorer prognosis
Leiomyoma	Benign tumors of smooth muscle cells, referred to as fibroids. Stimulated by estrogen: - It increase in size during <u>pregnancy or taking contraceptives</u> - Decrease in size after <u>menopause</u> Mutation in MED12 gene. Or chromosome 6 & 12 rearrangement Clinical features: Asymptomatic or menorrhagia, urinary frequency, infertility, rarely progress to sarcoma.
Leiomyosarcoma	- Malignant tumor of smooth muscle cells - Solitary and arise in postmenopausal women. - poor prognosis: recurrence & metastasis is common. Morphology: necrosis, Atypia, Mitotic activity.



QUIZ!

MCQs

01 A 42-year-old woman has had menometrorrhagia for the past 2 months. She has no history of prior irregular menstrual bleeding, and she has not yet reached menopause. On physical examination, there are no vaginal or cervical lesions, and the uterus appears normal in size, but there is a right adnexal mass. An abdominal ultrasound scan shows the presence of a 7-cm solid right adnexal mass. Endometrial biopsy shows hyperplastic endometrium, but no cellular atypia. What is the most likely lesion that underlies her menstrual abnormalities?			
A) Corpus luteum cyst	B) Endometrioma	C) Granulosa-theca cell tumor	D) Mature cystic teratoma
02 A 62-year-old childless woman noticed a blood-tinged vaginal discharge twice during the past month. Her last menstrual period was 10 years ago. Bimanual pelvic examination shows that the uterus is normal in size, with no palpable adnexal masses. There are no cervical erosions or masses. Her body mass index is 33. Her medical history indicates that for the past 30 years she has had hypertension and type 2 diabetes mellitus. An endometrial biopsy specimen is most likely			
A) Adenocarcinoma	B) Choriocarcinoma	C) Leiomyosarcoma	D) Malignant müllerian mixed tumor
03 A study of patients with postmenopausal uterine bleeding reveals that some of them have malignant neoplasms that arise from prior atypical hyperplastic lesions. The peak incidence is between 55 and 65 years of age in women who have obesity, hypertension, and/or diabetes mellitus. Molecular analysis reveals mutations of the PTEN tumor suppressor gene in most of them. Their malignancies tend to remain localized for years before spreading to local lymphatics. Which of the following neoplasms is most likely to have these characteristics?			
A) Clear cell carcinoma	B) Endometrioid carcinoma	C) Leiomyosarcoma	D) Serous carcinoma
04 A 62-year-old obese, nulliparous woman has an episode of vaginal bleeding, which produces only 5 mL of blood. On pelvic examination, there is no enlargement of the uterus, and the cervix appears normal. A Pap smear shows cells consistent with adenocarcinoma. Which of the following preexisting conditions is most likely to have contributed to the development of this malignancy?			
A) Adenomyosis	B) Chronic endometritis	C) Endometrial hyperplasia	D) Use of oral contraceptives
05 A 53-year-old woman whose last menstrual period was 3 years ago notes vaginal bleeding for a week. On physical examination, her uterus is markedly enlarged, but there are no adnexal masses. CT imaging reveals an irregular 8-cm mass in the body of the uterus. A total abdominal hysterectomy is performed, and microscopic examination of the soft, hemorrhagic mass shows spindle cells with atypia and numerous mitoses. There is coagulative necrosis of tumor cells. Which of the following is the most likely cell of origin for this mass?			
A) Cytotrophoblastic cells	B) Endometrial glandular	C) Germ cells	D) Smooth muscle cells
06 A 69-year-old woman has passed blood per vagina for a month. On pelvic examination no abnormal findings are noted. Which of the following diagnostic procedures should be performed next?			
A) Endometrial biopsy	B) Magnetic resonance imaging	C) Microbiologic culture	D) Pap smear

MCQs Answer key	01	02	03	04	05	06
	C	A	B	C	D	A

Thank You!

We kept 438 pathology theme in the credits to remind you that this wonderful work was originally done by them

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