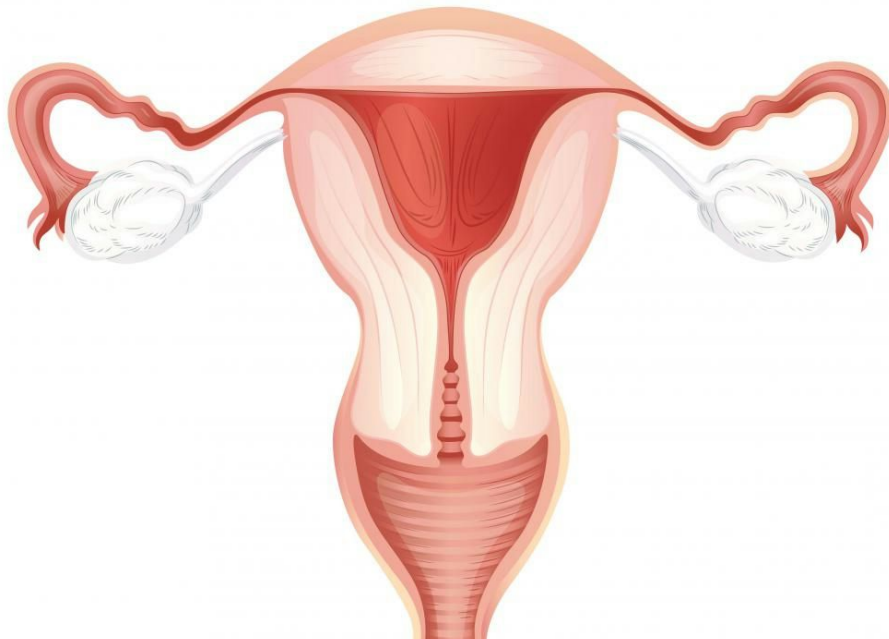


UTERINE CORPUS



Lecture Outlines:

- 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.

Important note: Please check out this link before viewing the file to know if there are any additions or changes. The same link will be used for all or our work: [Pathology Edit](#).

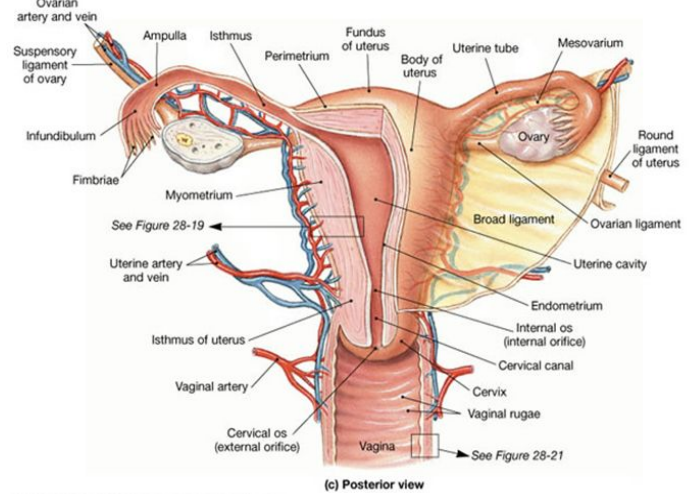
Grey = Extra
Red = Important

Introduction. (Extra)

Anatomy.

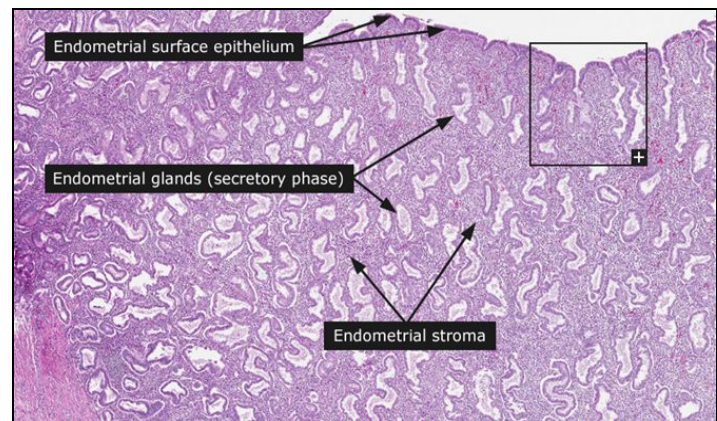
Uterus with bilateral tube and ovaries.

- **The uterus:** Is a thick-walled muscular organ that lies in the midline between *Rectum* and *Urinary bladder*, consisting of a body and Cervix, inferiorly. Cervix connects uterus with the vaginal canal.
- **The Uterine Tubes:** (known as Fallopian Tubes) arises laterally from each side of the uterus and has an indirect contact with the lateral side of the ovary and transports the ovum to the *ampulla where normal fertilization occurs*, and implantation of the fertilized ovum occurs in the body of the uterus.



Histology.

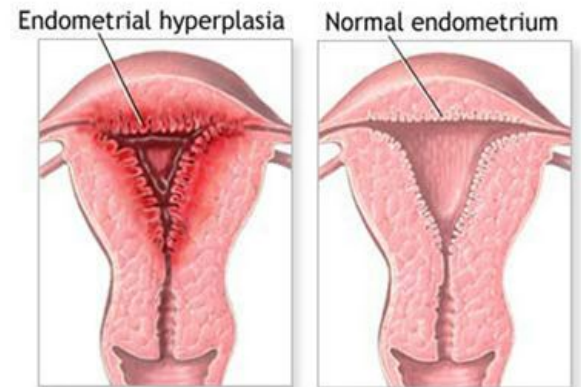
- **Body & fundus of the Uterus: (three layers)**
 - a. **Endometrium:** Partially ciliated simple columnar epithelium.
 - b. **Myometrium:** consisting mainly of three thick muscular layers:
 - The longitudinal Stratum Submucosum
 - The Circular Stratum Vasculare
 - The Longitudinal Supravasculare
 - c. **Perimetrium:** outer serosa.
- **Supplied by Two types of Arteries Derived from the ones that supply Myometrium:**
 - **Coiled Arteries** That extends to the functional zone.
 - **Straight Arteries** that stays where they are and terminate in the basal lamina.
- **Cervix:**
 - Internal OS & The Cervical canal → **Simple columnar epithelium**
 - External OS → **Non Keratinized Stratified Squamous Epithelium**
- **Stroma:** Dense fibrous tissue containing tubulo alveolar glands that secretes the Cervical mucus.



Endometrial Hyperplasia.

Endometrial hyperplasia is a process in which there is a proliferation of endometrial gland resulting in an **increase in gland/stroma ratio** when compared to the proliferative endometrium (i.e. there is more gland and less stroma when compared to normal).

- It is induced by persistent, prolonged **estrogenic stimulation** of the endometrium.
- The endometrial hyperplasia may progress to **endometrial carcinoma**.
- The development of cancer is based on the level and duration of the estrogen excess.
- The risk is of developing carcinoma depends on the severity of the **hyperplastic changes** and **associated cellular atypia**.



Causes:

Any condition in which there is **high estrogen level** can lead to endometrial hyperplasia.

Some of them are as follows:

- Anovulatory menstrual cycles (*failure of ovulation*). (LH surge does not occur so ovulation do not take place and estrogen is always elevated.)
- Excessive **endogenous** (by the body) production of estrogen, e.g. in:
 - Polycystic ovary syndrome (**Stein-Leventhal syndrome**).
 - Granulosa cell tumors of the ovary.
 - Excessive ovarian cortical function (**cortical stromal hyperplasia**).
- **Exogenous** administration of estrogenic steroids without counter balancing progestins, over a long period of time. i.e. Taking estrogen without progesterone

Clinical: Here it depends on the status of the woman and age mainly.

- **Mild type** of hyperplasia tends to occur in **younger patients**. The great majority of mild hyperplasia regress, either spontaneously or after treatment.
- **Severe type** of hyperplasia occur mainly in **perimenopausal** (several years before menopause) & **postmenopausal women**. This form has a **significant premalignant potential**.
- Patients with endometrial hyperplasia usually present with:
 - Abnormal uterine bleeding.
 - Menorrhagia¹, polymenorrhagia², menometrorrhagia³.
 - Postmenopausal bleeding.



¹ abnormally heavy bleeding at menstruation.

² A shortening of the menstrual cycle (more frequent periods)

³ is a condition in which prolonged or excessive uterine bleeding occurs irregularly and more frequently than normal.

Classification:

In endometrial hyperplasia there is proliferation of both glands and stroma but the proliferation of the **glandular component is much more**. Therefore over crowding of glands occur.

Endometrial hyperplasia is histologically classified based on:

- 1) **Gland architecture:** into → **simple** or **complex**, depending on the degree of glandular complexity and crowding.
- 2) **Cytologic features:** into → **with** or **without atypia**.
 - **Atypia (pleomorphism):** loss of polarity⁴, vesicular nuclei, prominent nucleoli, rounded cells.

Therefore the classification is as follows:

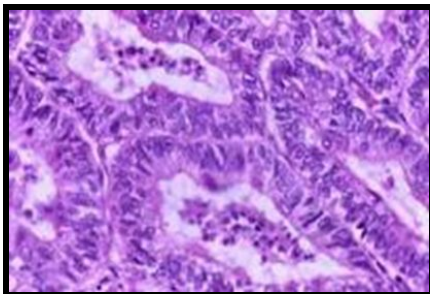
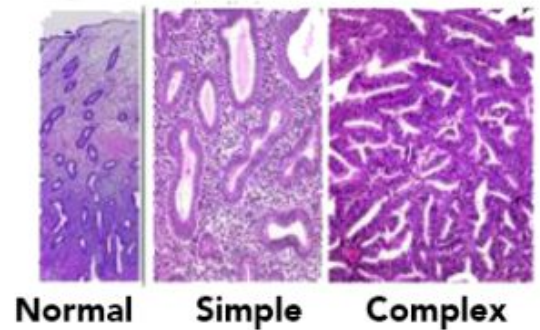
1. Simple hyperplasia

- a. Without atypia
- b. With atypia

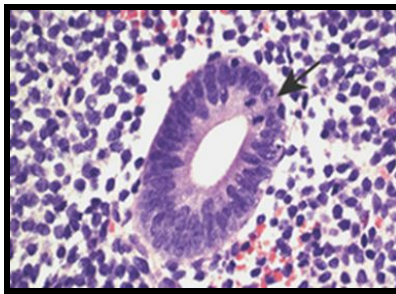
2. Complex hyperplasia

- a. Without atypia
- b. With atypia

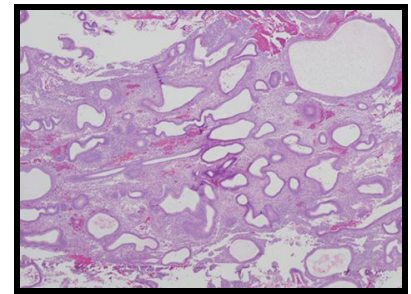
- The most important predictor for progression to carcinoma is **cellular atypia**.



No hyperplasia and no atypia



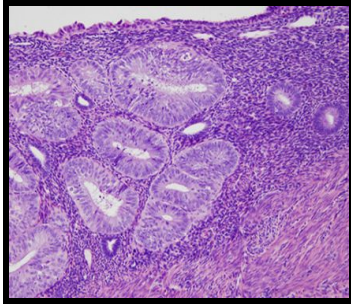
Hyperplasia with atypia



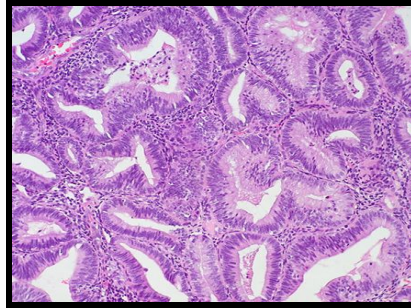
Simple hyperplasia without atypia

⁴ refers to spatial differences in the shape, structure, and function of cells.

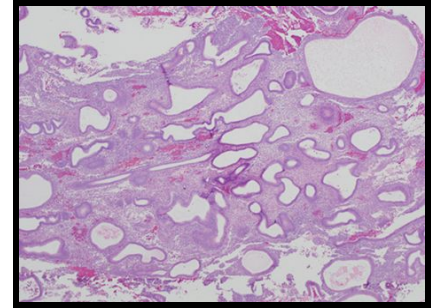
Simple hyperplasia without atypia	Simple hyperplasia with atypia	Complex hyperplasia without atypia	Complex hyperplasia with atypia
<ul style="list-style-type: none"> ● Simple hyperplasia (cystic hyperplasia): glands are <u>variably</u> shaped and sized and cystically dilated with <u>abundant cellular stroma</u> and give a "Swiss Cheese" appearance. ● mild increase in the gland-to-stroma ratio 	<p>It has the Architecture of simple hyperplasia, but there is cytologic atypia within the glandular epithelial cells.</p>	<ul style="list-style-type: none"> ● Proliferation of endometrial glands resulting in complex crowded glands with papillary infoldings and irregular shapes. The crowded glands are <i>back-to-back</i> with <u>very little intervening stroma</u>. ● epithelial cells remain cytologically normal. 	<ul style="list-style-type: none"> ● Complex proliferation of endometrial glands (<i>back-to-back irregular glands</i>) with atypia. ● The nuclei show <u>loss of polarity and are enlarged and rounded</u> and may have irregular nuclear membranes.
<p>1% rarely progress to adenocarcinoma</p>	<p>10% of such lesions progress to carcinoma</p>	<p>3% progression to carcinoma</p>	<p>About 30% progress to carcinoma.</p>
<p>Simple hyperplasia may progress to cystic atrophy</p>	<p>Uncommon</p>		<p>Commonly about 30% of women with this diagnosis have carcinoma somewhere in the uterus when a hysterectomy is performed.</p>



Complex hyperplasia with atypia



Complex hyperplasia without atypia



Simple hyperplasia without atypia

Clinical behavior and premalignant potential:

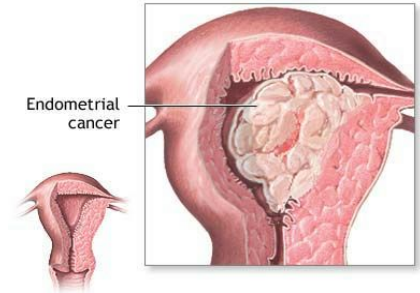
- Some endometrial hyperplasia revert to normal spontaneously or with medical treatment, others persist as hyperplasia, and a **few progresses to endometrial adenocarcinoma**.
- Generally, patients who have **hyperplasia with atypia are more likely to develop carcinoma** than those without atypia.
- Atypical hyperplasia in postmenopausal women appears to **have a higher rate** of progression to adenocarcinoma.

Risk Factors:

1. Obesity. i.e. Increased aromatization of androgens to estrogen in adipose tissue.
2. Western diet (junk food)
3. Nulliparity: a state in which a woman has never given birth to a child, or never had pregnancy. **Why?** As we know high estrogen levels are the leading cause of the hyperplasia which may has malignant potential. During pregnancy estrogen levels drop → lower risk of hyperplasia & malignancy.
4. Diabetes Mellitus.
5. Hypertension.
6. Hyperestrinism. (high estrogen)
7. Early menarche or late menopause
8. Hereditary nonpolyposis colorectal cancer

Endometrial adenocarcinoma

- This is a common neoplasm in women. Overall it is the fifth commonest cancer in women.
- It generally appears in **postmenopausal women** and is uncommon before age 40.
- They cause **postmenopausal bleeding**.
- Early detection and cures are possible (if we detect tumor before metastasis we do hysterectomy and send patient home).



Classified into two broad categories:

- A. **Type I carcinomas (endometrioid⁵ carcinoma)**: accounts for **80%** of endometrial cancers. It is the most common type.
- B. **Type II carcinomas**: e.g. → **papillary serous carcinoma** (most common form of type II carcinoma) and clear cell carcinoma.

Clinical features:

- Most patients are between 50 and 60 years.
- Many of the patients tend to be **nulliparous⁶** and **obese**.
- Endometrial adenocarcinoma manifests as **abnormal vaginal bleeding** and **excessive leukorrhea⁷**.
- The diagnosis of endometrial cancer must be confirmed by biopsy or curettage and histologic examination of the tissue.

Basic morphology:

- **Grossly**: Closely resemble normal endometrium and may be exophytic⁸ or infiltrative.
- **Microscopy**:
 - Mucinous, tubal (ciliated), and squamous (occasionally adenosquamous) differentiation.
 - 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.
 - **Serous carcinoma** has **much greater cytologic atypia** and are **more poorly differentiated** and therefore more aggressive



⁵ Endometrioid tumors are a class of tumor characterized by a resemblance to endometrium/ endometrial carcinoma

⁶ A woman who has never given birth

⁷ a whitish or yellowish discharge of mucus from the vagina.

⁸ tending to grow outward beyond the surface epithelium from which it originates—used of tumors; compare endophytic.

Prognosis:

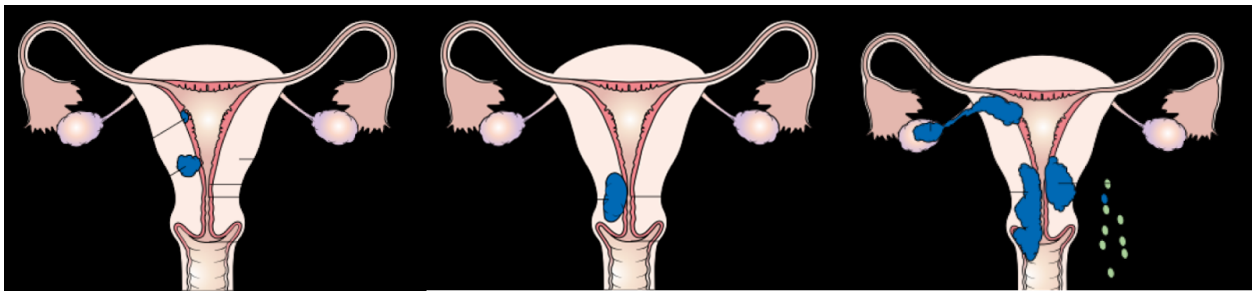
- Clinical behavior of endometrial adenocarcinoma depends on the **histologic type**, the **grade** (degree of differentiation) and the **stage** (extent of spread).
- Endometrioid carcinoma (type I) has a **better prognosis** than the other histologic types.
- Serous carcinomas (type II) have **poorer prognosis**.
- Stage is the major determinant of survival.

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**
-

How endometrial carcinoma can spread?

(stages 1, 2 and 3 of endometrial carcinoma)



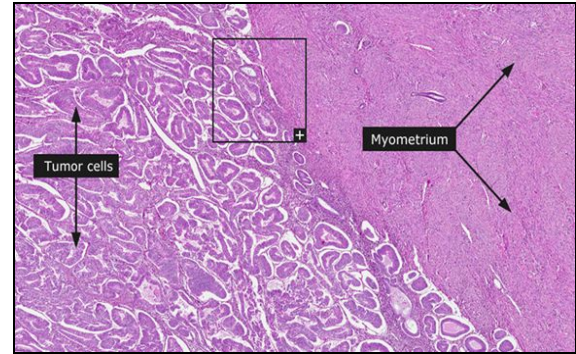
- **Stage 1:** The cancer is only growing in the body of the uterus. It may also be growing into the glands of the cervix, but is not growing into the supporting connective tissue of the cervix. The cancer has not spread to lymph nodes or distant sites.
- **Stage 2:** The cancer has spread from the body of the uterus and is growing into the supporting connective tissue of the cervix. The cancer has not spread outside of the uterus. The cancer has not spread to lymph nodes or distant sites.
- **Stage 3:** Either the cancer has spread outside of the uterus or into nearby tissues in the pelvic area.
- **Stage 4:** The cancer has spread to the inner surface of the urinary bladder or the rectum, to lymph nodes in the groin, and/or to distant organs

Type I Endometrial Carcinoma (Endometrioid Carcinoma).

Endometrioid carcinoma is associated with **estrogen excess** and **endometrial hyperplasia**. The majority are well differentiated.

Risk factors: for type I are the same as that of endometrial hyperplasia and include:

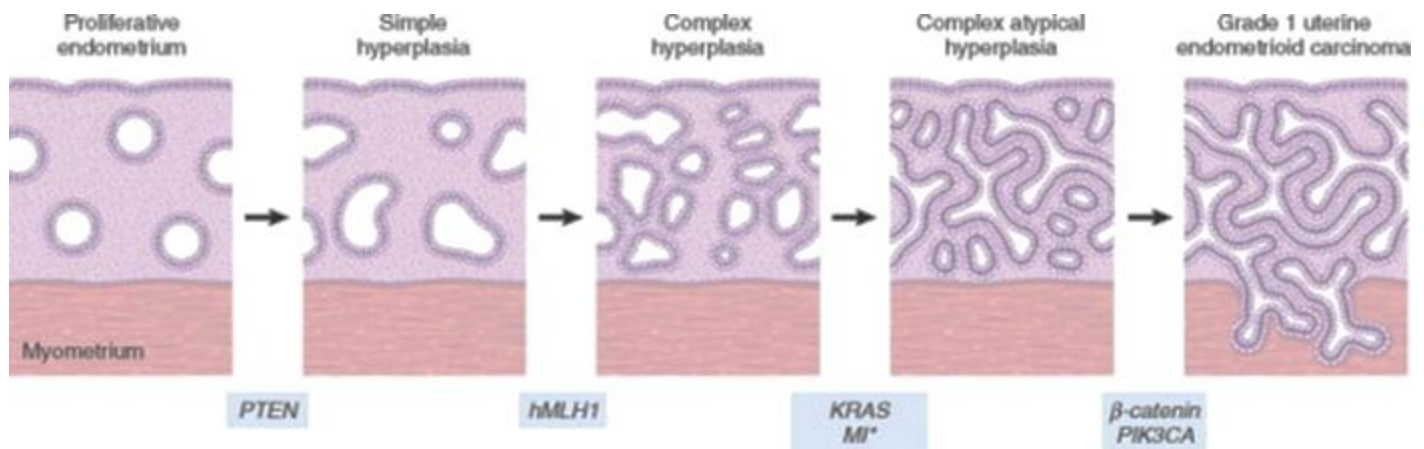
1. **Endometrial hyperplasia**
2. Obesity
3. Estrogen therapy
4. Nulliparity
5. Chronic anovulation
6. Late menopause
7. Hypertension
8. Diabetes
9. Tamoxifen therapy
10. High socioeconomic status



Note:

- The disease may follow atypical hyperplasia **but** may occur independently especially in older patients.
- Precursor lesion/Carcinoma in situ is **hyperplasia with atypia**.

Usual sequence of events in Type I endometrioid carcinoma

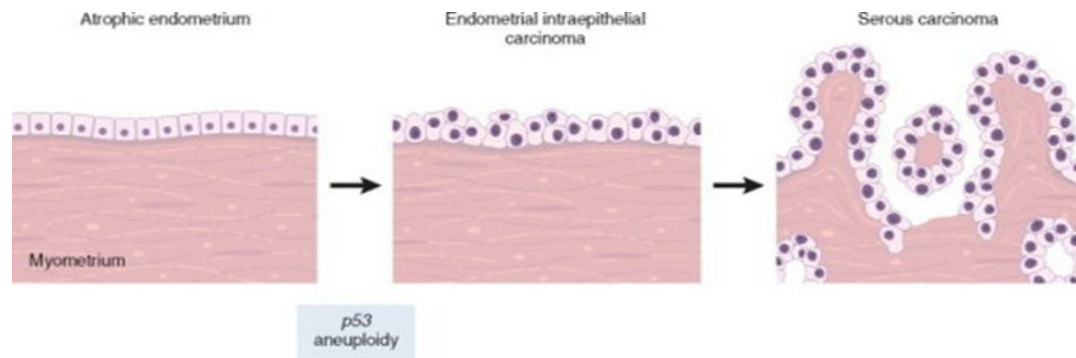


Genetics:

- Mutations in the **PTEN** gene have been identified in 30% to 80% of endometrioid carcinomas
- Women with germline mutations in **PTEN (Cowden syndrome)** are at high risk for this cancer
- 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.

Type II endometrial carcinomas (Serous carcinoma).

- *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.
- Extruterine extension is common.



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	High
MYOMETRIAL INVASION	Usually superficial	Usually deep
PROGNOSIS	Favorable	Poor

GENETIC ALTERATIONS NOTED	PTEN, microsatellite instability	P53 mutations
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LEIOMYOMA.

Leiomyoma (fibroid) of uterus:

- Leiomyoma is a **benign tumor** of **smooth muscle origin**. That is located in the myometrium of uterus. With **no appreciable malignant potential** (incidence of malignant transformation to sarcoma is 0.1-0.5%).
- It is the **most common neoplasm** of the female genital tract and probably the **most common neoplasm in women**.
- The tumor is **estrogen responsive** and often **increases in size during pregnancy** and **decreases in size during menopause**.
- Estrogens and possibly oral contraceptives **stimulate** their growth.
- About 40% of leiomyomas have an **associated chromosomal abnormality**
- Management is symptom based, usually tumor is not taken off because it rarely transform into malignant.

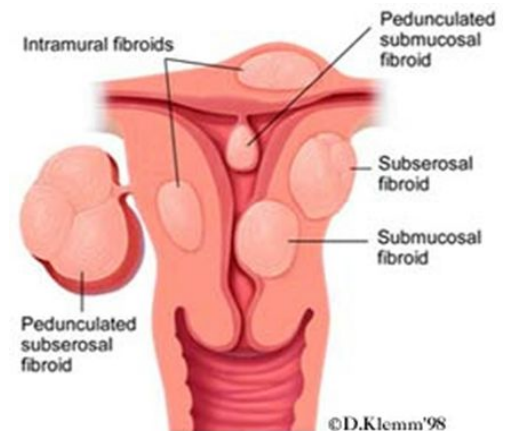
Clinical features:

- It can be **single or multiple**. Mostly it is **multiple**. Common in premenopausal women
- Alternatively it maybe entirely **asymptomatic**.
- Patients may present with **irregular abnormal bleeding, pelvic pain, pelvic mass, infertility**.
- It may cause **anemia** due to → heavy bleeding.
- Can have **urinary frequency** if the fibroid is compressing the urinary bladder.
- It may **interfere with implantation** → **infertility**.

In **pregnant women** → **abortion, obstructed labor, postpartum hemorrhage** etc.

Leiomyoma may be located anywhere in the myometrium as:

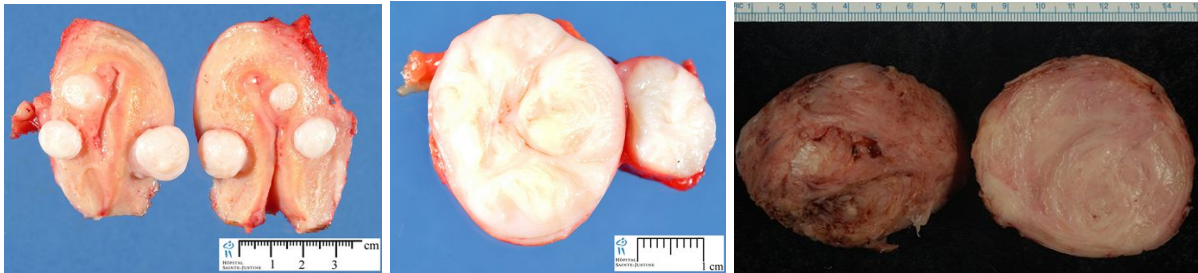
- **Submucosal tumors:** are present immediately below the endometrium.
- **Intramural tumors:** the most common, lie **within the myometrium**.
- **Subserosal fibroids:** lie beneath the serosal surface of the uterus or are pedunculated and attached to the serosa.
- **Pedunculated Submucosal fibroids:** ones may **lose their connection** to the uterus forming a "**parasitic leiomyoma**".



Morphology:

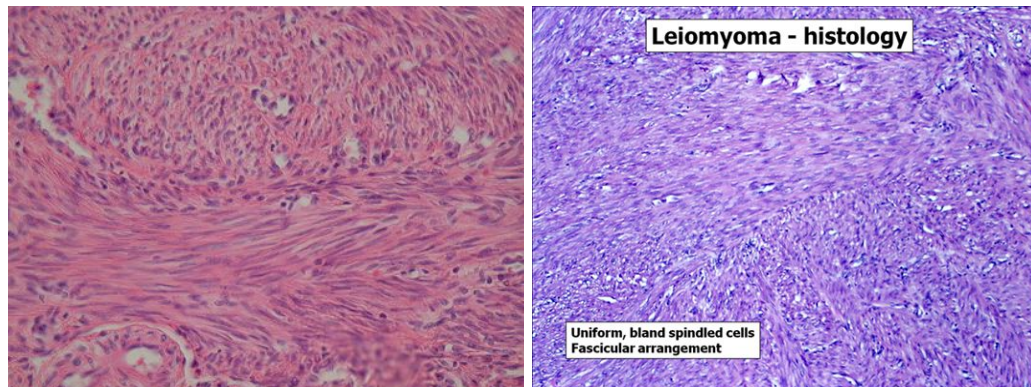
● Leiomyoma gross:

- **Well circumscribed**, spherical, dense and firm-to-hard masses.
- Cut section shows **whorled, tan-white cut surfaces**.



● Leiomyoma microscopically:

- There are **interlacing⁹ bundles** of smooth muscle cells with **collagenous stroma** between bundles.
- The individual muscle cells are **uniform in size and shape**. With **oval to elongated nucleus**.
- Mitotic figures are **scarce**.



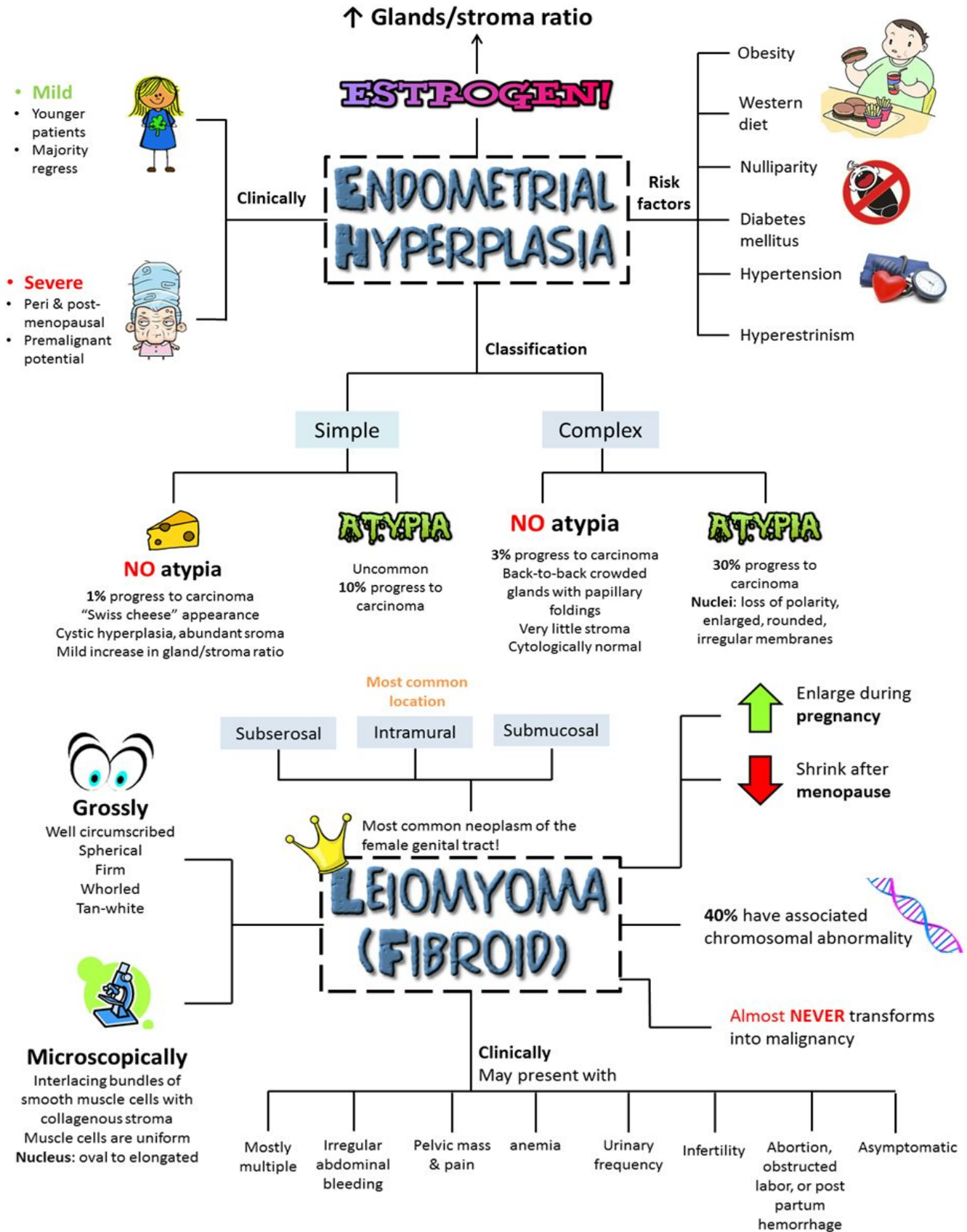
Leiomyosarcoma.

- It is the **malignant tumor** of the **smooth muscle** Usually in postmenopausal women
- It is rare.
- Sites include the uterus and soft tissue.
- **Poor prognosis**.
- Arises de novo¹⁰;

⁹ cross or be crossed intricately together

¹⁰ leiomyosarcomas do not arise from leiomyomas.

Summary.



Most common location

Subserosal

Intramural

Submucosal

Most common neoplasm of the female genital tract!

LEIOMYOMA (FIBROID)

Grossly

- Well circumscribed
- Spherical
- Firm
- Whorled
- Tan-white



Microscopically

- Interlacing bundles of smooth muscle cells with collagenous stroma
- Muscle cells are uniform
- Nucleus:** oval to elongated

Clinically

May present with

Mostly multiple

Irregular abdominal bleeding

Pelvic mass & pain

anemia

Urinary frequency

Infertility

Abortion, obstructed labor, or post partum hemorrhage

Asymptomatic

↑ Enlarge during pregnancy

↓ Shrink after menopause

40% have associated chromosomal abnormality 

Almost NEVER transforms into malignancy

MCQ's.

- 1. Leiomyoma of the uterus is the most common neoplasm of the female genital tract**
 - a. True
 - b. False
- 2. An 45 years old women having Endometrial hyperplasia what are the possible predisposing factors to her condition**
 - a. Obesity
 - b. Hypertension
 - c. Diabetes Mellitus
 - d. All of the above
- 3. Which of the following endometrial lesions carries the greatest risk of progression to endometrial carcinoma**
 - a. Polyp
 - b. Simple hyperplasia
 - c. Atypical hyperplasia
 - d. Complex hyperplasia
- 4. The following statements about uterine leiomyomata are true except**
 - a. May present with dysmenorrhoea and menorrhagia
 - b. Transform into leiomyosarcomas in up to 5% of cases
 - c. Are benign smooth muscle neoplasms
 - d. May enlarge during pregnancy
- 5. Granulosa cell tumours may cause all of the following except**
 - a. Precocious puberty
 - b. Endometrial hyperplasia
 - c. Postmenopausal bleeding
 - d. Chronic endometritis
- 6. Endometrial hyperplasia may be caused by all of the following except**
 - a. Granulosa cell tumour of the ovary
 - b. Treatment with oestrogenic agents
 - c. Failure of ovulation
 - d. Dysgerminoma
- 7. A 50-year-old woman complains of having intermenstrual bleeding for 4 months. A Pap smear is normal. An ultrasound examination shows a mass in the endometrial cavity. The patient elects to undergo a hysterectomy. A large polyp is found upon opening the endometrial cavity. Histologic examination of this polyp will most likely show which of the following pathologic findings?**
 - a. Atypical endometrial hyperplasia
 - b. Chronic endometritis
 - c. Complex endometrial hyperplasia
 - d. Endometrial glands and fibrous stroma

Answers: 1-A 2-D 3-C 4-B 5-D 6-D 7-D

For any suggestions or questions please don't hesitate to contact us on: Pathology434@gmail.com

Twitter: @Pathology434

Ask us: www.ask.fm/Pathology434

GOOD LUCK !!

خالد الدريبي
عبدالرحمن الحربي
عبدالله العماري
خالد الشهري
فيصل أبو نهية
حسين الكاف

مها الربيعة
رزان الصبحي
لينة الجرف
ريم لبني

