Lecture 4:
Endometrial Hyperplasia, Uterine Cancer & Fibroids

▫ Important ▫ Notes ▫ Explanation

Objectives

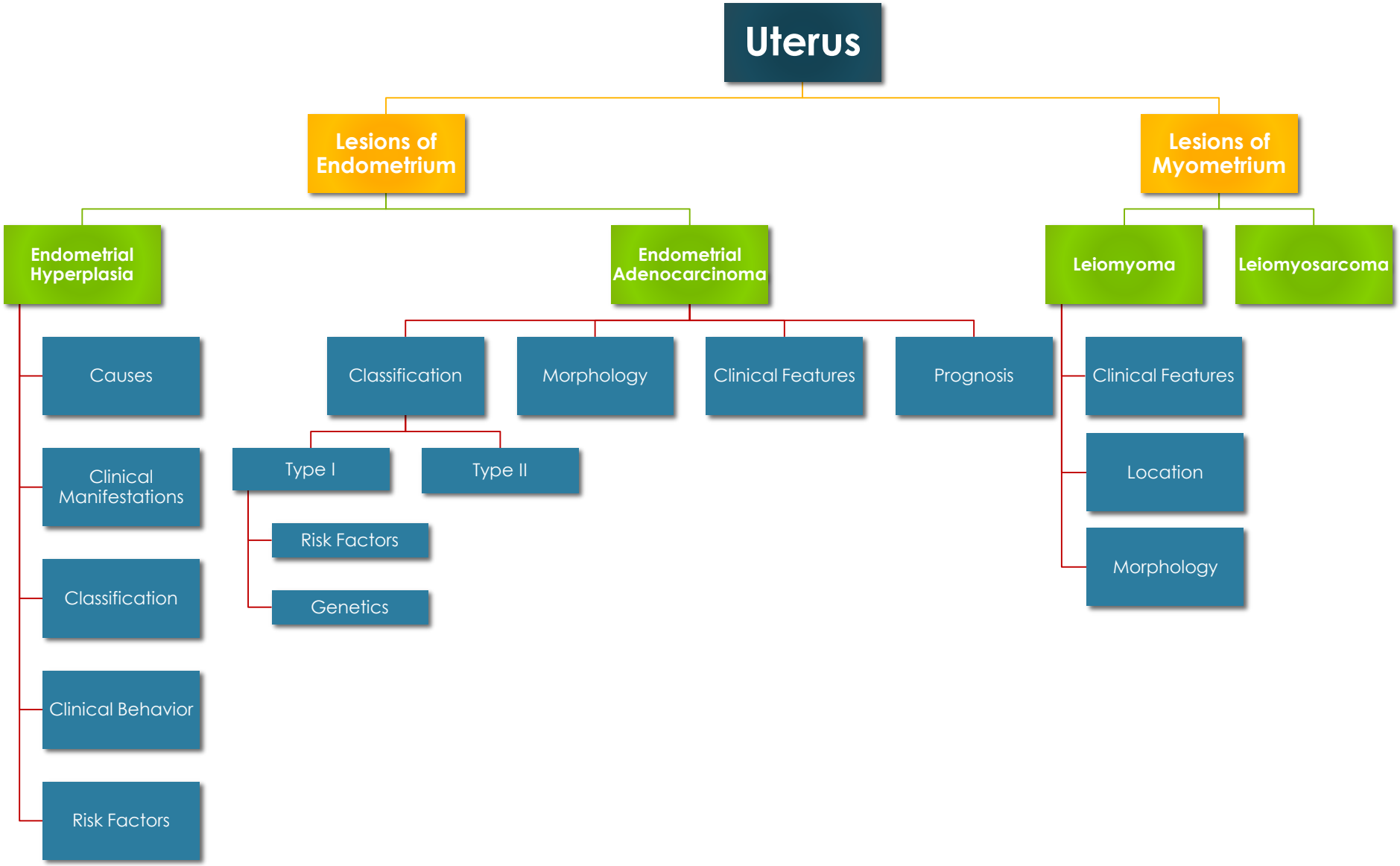
The student should know :

Lesions of endometrium of uterus:

- Endometrial hyperplasia
- Endometrial carcinoma

Lesions of myometrium of uterus:

- Leiomyoma
- Leiomyosarcoma


Uterus
Lesions of Endometrium
Lesions of Myometrium
Endometrial Hyperplasia
Endometrial Adenocarcinoma
Leiomyoma
Leiomyosarcoma
Causes
Clinical Manifestations
Classification
Clinical Behavior
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Classification
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Clinical Features
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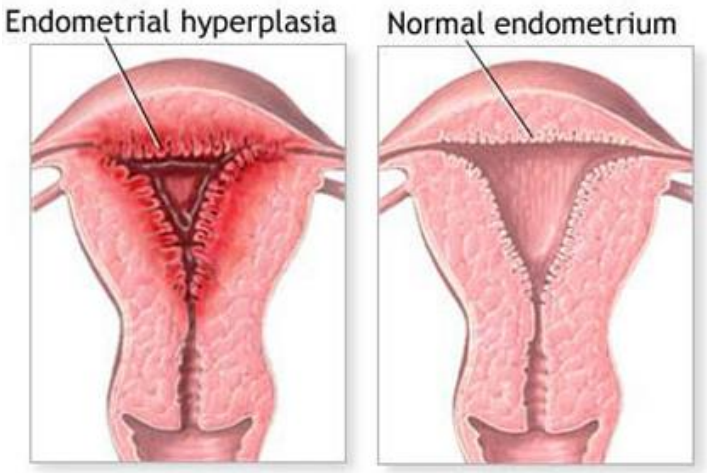
Endometrial Hyperplasia

- A process in which there is a proliferation of endometrial glands resulting in an increase in gland/stroma ratio compared to 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 depending on the severity of the hyperplastic changes and associated cellular atypia.

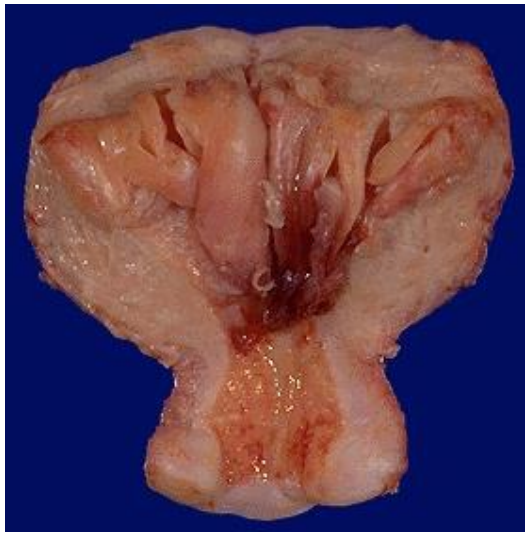


Causes :

Any condition in which there is high estrogen level. Some of them are as follows :

- **Anovulatory menstrual cycles** (failure of ovulation).
  (If the ovulation didn't occur, the estrogen phase will remain → high estrogen level)
- **Excessive endogenous 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.

Clinical Manifestation :

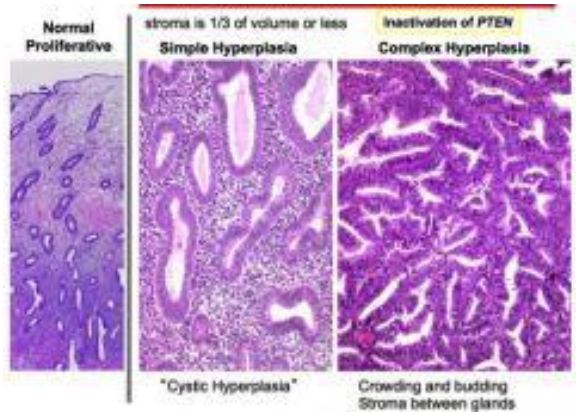


- Milder forms of hyperplasia tends to occur in younger patients.
- The great majority of mild hyperplasia **regress**, either spontaneously or after treatment.
- The more severe forms, occur predominantly in peri- and postmenopausal women. This form has a significant premalignant potential.
- **Patients usually present with abnormal uterine bleeding.**

Classification :

There is proliferation of both glands and stroma but the glandular component is more. Therefore over crowding of glands occur. Endometrial hyperplasia is histologically classified according to:

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



Therefore the classification is as follows:

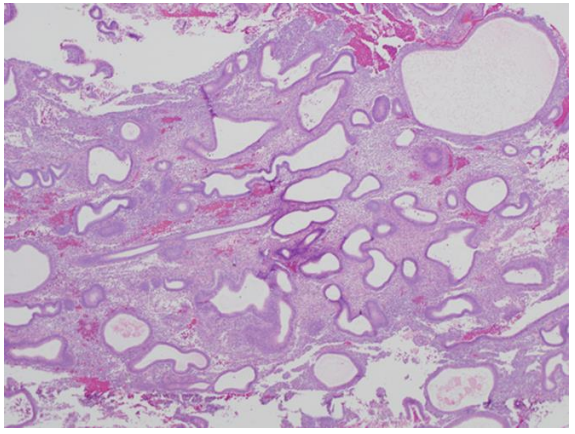
I. Simple hyperplasia
- Without atypia
- With atypia

II. Complex hyperplasia
- Without atypia
- With atypia

So, simple hyperplasia without atypia has the least probability to progress to carcinoma (1%). While, complex hyperplasia with atypia has the most (30%)

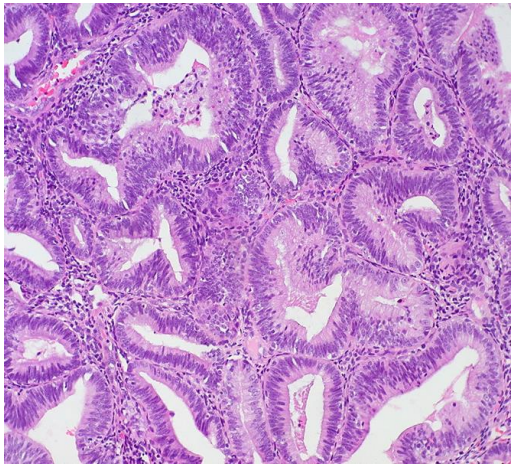
1- Simple hyperplasia without atypia (figure 1)

- Simple hyperplasia (cystic hyperplasia): glands are varibly shaped and sized and cystically dilated with abundant cellular stroma and give a "Swiss Cheese" appearance.
- Mild increase in the gland-to-stroma ratio.
- Uncommonly progress to adenocarcinoma.
- May progress to cystic atrophy.



2- Simple hyperplasia with atypia

- Uncommon, has the Architecture of simple hyperplasia, but there is cytologic atypia within the glandular epithelial cells.
- 10% of such lesions progress to carcinoma.

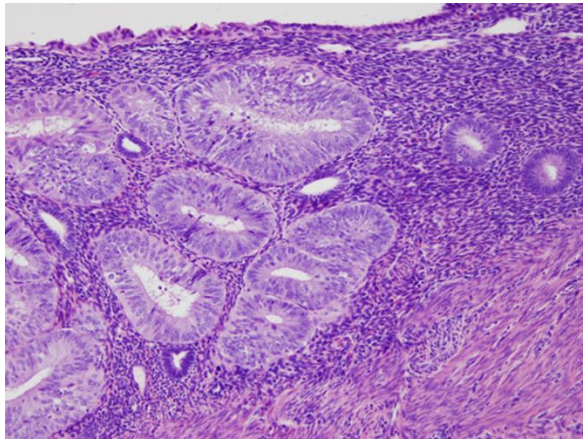


3- Complex hyperplasia without atypia (figure 2)

- 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

4- Complex hyperplasia with atypia (figure 3)

- 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.
- 23% to 48% of women with this diagnosis have carcinoma somewhere in the uterus when a hysterectomy is performed.
- 30% progress to carcinoma



Clinical Behavior and Premalignant Potential of Endometrial Hyperplasia :

- Some endometrial hyperplasias 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. 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.

Risk Factors :

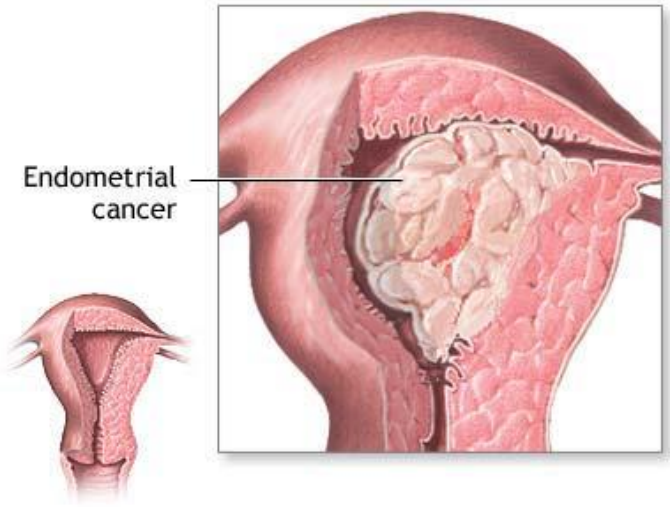
- Obesity
- Western diet
- Nulliparity (women never delivered a baby)
- Diabetes Mellitus
- Hypertension
- Hyperestrinism (increase amount of estrogen)

Perimenopausal women + Bleeding = Endometrial Hyperplasia
Postmenopausal women + Bleeding = Carcinoma

Endometrial Adenocarcinoma

Worldwide **5th** commonest cancer in women.

- Endometrial cancers arise mainly in postmenopausal women.
- Cause postmenopausal bleeding.
- Early detection and cures are possible.
- These tumors are classified into two broad categories:
  - **Type I carcinomas**: **Also known as endometrioid carcinoma**. It is the most common type.
  - **Type II carcinomas (the most common type II carcinoma is serous carcinoma)**



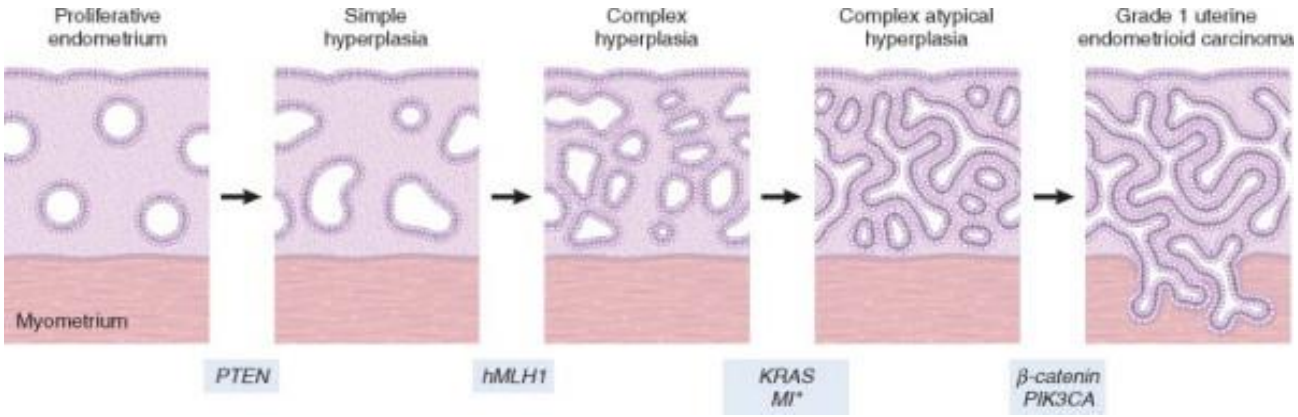
1- Type I Endometrial Carcinoma (Endometrioid Carcinoma) :

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

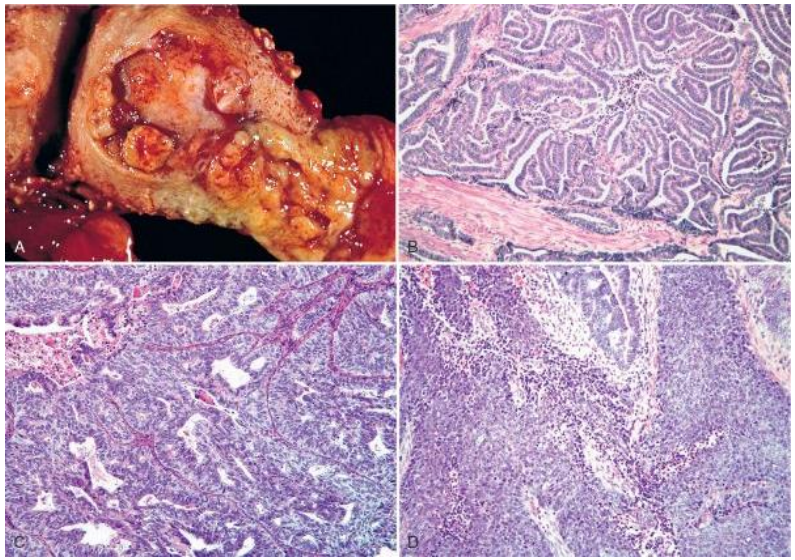
Risk factors for type I are the same as that of endometrial hyperplasia and include:

- **Endometrial hyperplasia** is a precursor to endometrioid carcinoma.
- **Obesity** (women with upper body fat have 3 times risk than women with lower body fat).
- **Chronic anovulation**
- **Nulliparity** (as a result of infertility due to chronic anovulation).
- **Hypertension, diabetes, estrogen therapy, late menopause, tamoxifen therapy**.
- **High socioeconomic status**. (While cervical cancer is the low socioeconomic status' cancer).
- The disease may follow atypical hyperplasia but may occur independently of it especially in older patients.

Type I endometrioid carcinoma: Genetics :



- Mutations in the **PTEN gene** have been identified in 30% to 80% of endometrioid carcinomas.
- There maybe 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.



2- Type II Carcinomas (Serous Carcinoma) :

- *Serous carcinoma* of the endometrium arises in older women, with endometrial atrophy (small atrophic uteri).
- 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 invaded early into the myometrium and have a poor prognosis.
- Extrauterine extension is common.

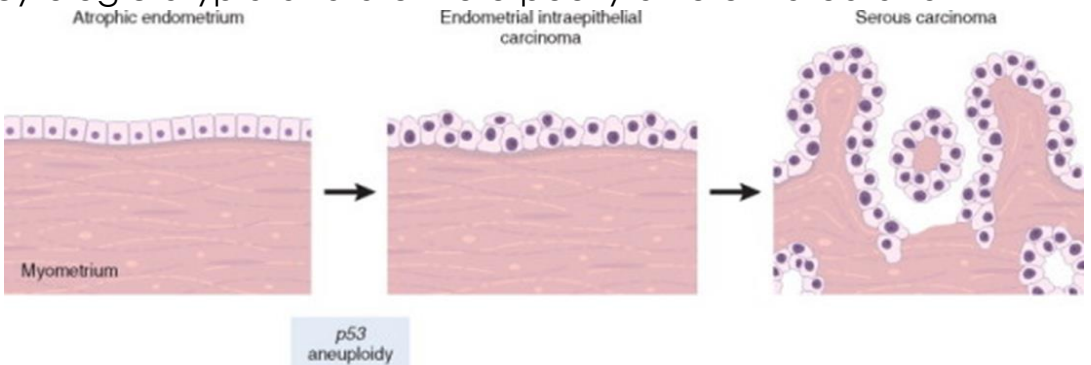
Endometrial Carcinoma: Basic morphology :

Grossly :

- May look close to normal or exophytic or infiltrative

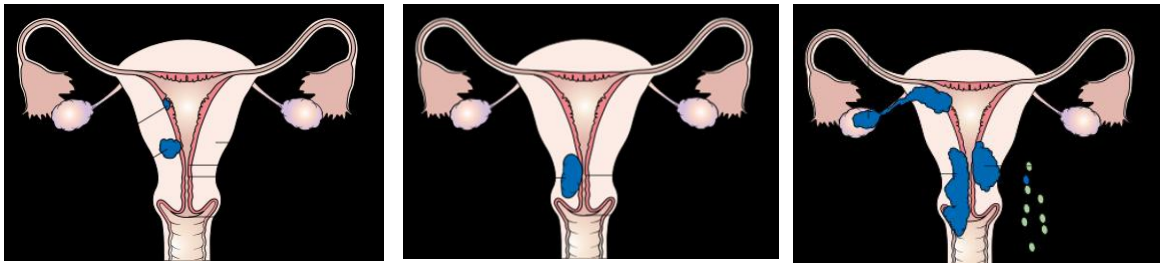
Microscopy :

- Both 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.



Tumor 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.



Clinical Features :

- Most patients are between 50 and 59 years.
- 50% of the women who are under 40 years are nulliparous and more than 75% of them are obese.
- Endometrial adenocarcinoma manifests as **abnormal vaginal bleeding and excessive leucorrhea** (thick, whitish-yellowish vaginal discharge).
- In elderly women the bleeding is postmenopausal.
- The diagnosis of endometrial cancer must be confirmed by biopsy or curettage and histologic examination of the tissue.

Prognosis :

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

Leiomyoma (Fibroid) of Uterus :

- Leiomyoma is a benign tumor of smooth muscle origin.
- 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; they shrink postmenopausally.
- About 40% of leiomyomas have an associated chromosomal abnormality.
- This is a benign tumor with no appreciable malignant potential (incidence of malignant transformation to Leiomyosarcoma is 0.1-0.5%).

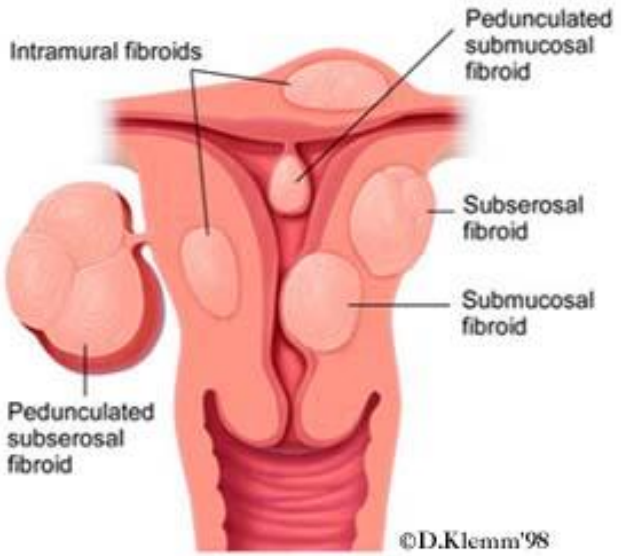
Clinical Features :

- It can be single or multiple, but **Mostly multiple**.
- Patients may present with irregular abnormal bleeding, pelvic pain, pelvic mass, infertility.
- It may cause anemia from heavy bleeding.
- Urinary frequency if fibroid compressing urinary bladder.
- It may interfere with implantation and therefore cause infertility.
- In pregnant women it may cause abortion, obstructed labor, post partum hemorrhage etc
- *Alternatively it maybe* entirely asymptomatic

Location :

Leiomyoma may be located anywhere in the myometrium.

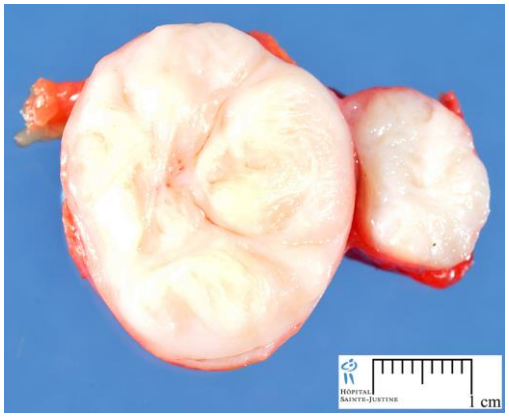
- **Submucosal** tumors are present immediately below the endometrium.
- **Intramural** tumors, the most common, lie within the myometrium.
- **Subserosal** fibroids lie beneath the serosal surface of the uterus or are pedunculated and attached to the serosa.
- Pedunculated ones may loose their connection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



Morphology :

Grossly :

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



Microscopy :

- Interlacing bundles of smooth muscle cells with collagenous stroma between bundles.
- The individual muscle cells are uniform in size and shape, they have the characteristic oval to elongated nucleus.
- Mitotic figures are scarce.

Leiomyosarcoma :

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

Summary

(from Robbin's basic pathology)

SUMMARY

Uterine Smooth Muscle Neoplasms

- Benign smooth muscle tumors, called leiomyomas, are common and frequently multiple; they may manifest with menorrhagia or as a pelvic mass or may be detected as a cause of infertility.
- Malignant smooth muscle tumors, called leiomyosarcomas, arise de novo, not from leiomyomas.
- Criteria of malignancy include necrosis, cytologic atypia, and mitotic activity.

SUMMARY

Endometrial Hyperplasia and Endometrial Carcinoma

- Endometrial hyperplasia results from excess endogenous or exogenous estrogen.
- Risk factors for developing endometrial hyperplasia include anovulatory cycles, polycystic ovary syndrome, estrogen-producing ovarian tumor, obesity, and estrogen therapy without counterbalancing progestin.
- The severity of hyperplasia is graded on the basis of architectural (simple versus complex) and cytologic (normal versus atypical) criteria. The risk of developing carcinoma is predominantly related to cytologic atypia.
- On the basis of clinical and molecular data, two major types of endometrial carcinoma are recognized:
  - *Endometrioid carcinoma* is associated with estrogen excess and endometrial hyperplasia. Early molecular changes include inactivation of DNA mismatch repair genes and the *PTEN* gene.
  - *Serous carcinoma* of the endometrium arises in older women and usually is associated with endometrial atrophy. Mutations in the *TP53* gene are an early event.
- Stage is the major determinant of survival in both types. Serous tumors tend to manifest more frequently with extrauterine extension and therefore have a worse prognosis than endometrioid carcinomas.

Thank You!

We hope you found this helpful and informative.

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