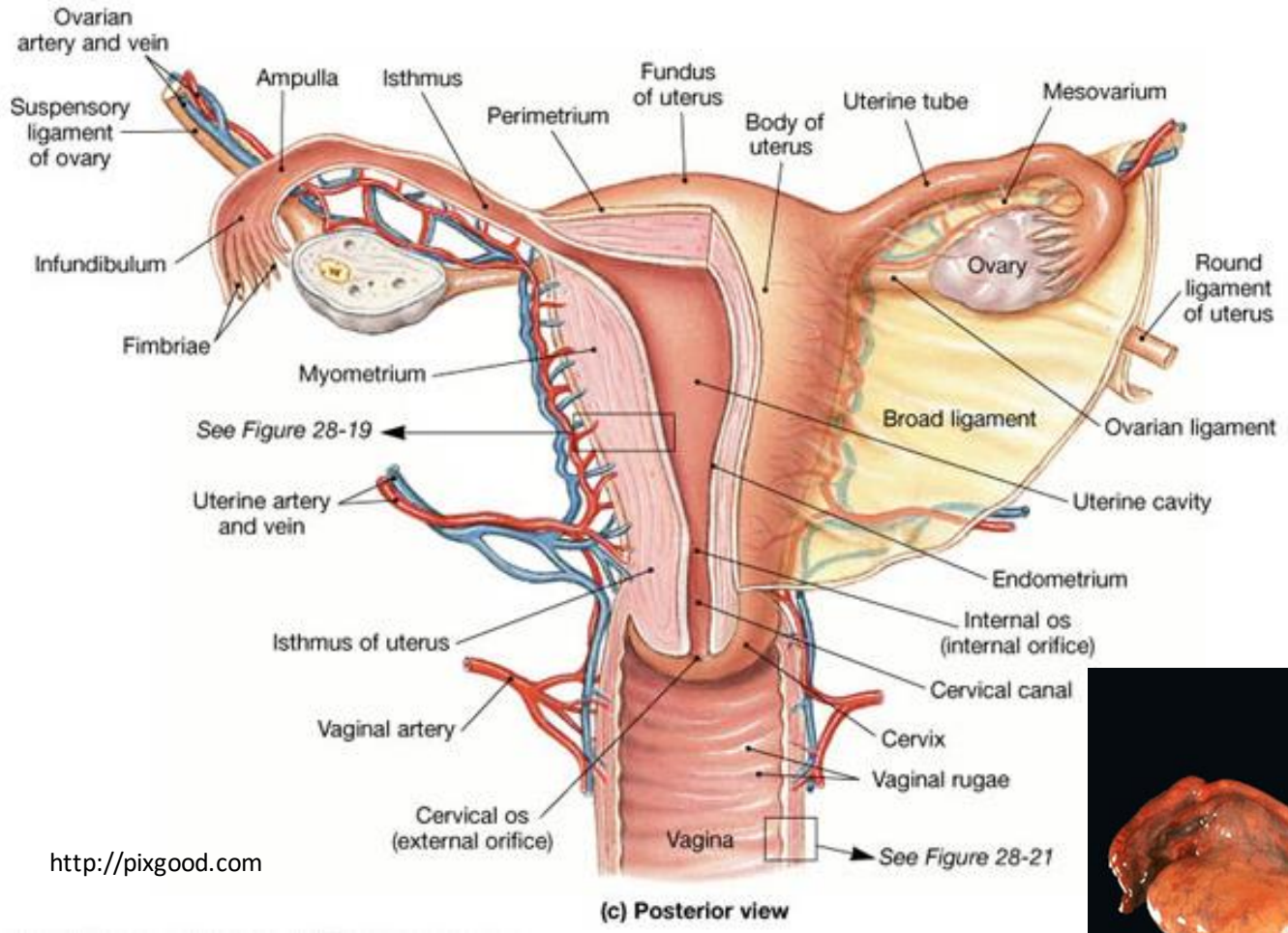
Endometrial hyperplasia, uterine cancer and fibroid.

Amany Fathaddin, MD

Uterus with bilateral tube and ovaries, posterior view



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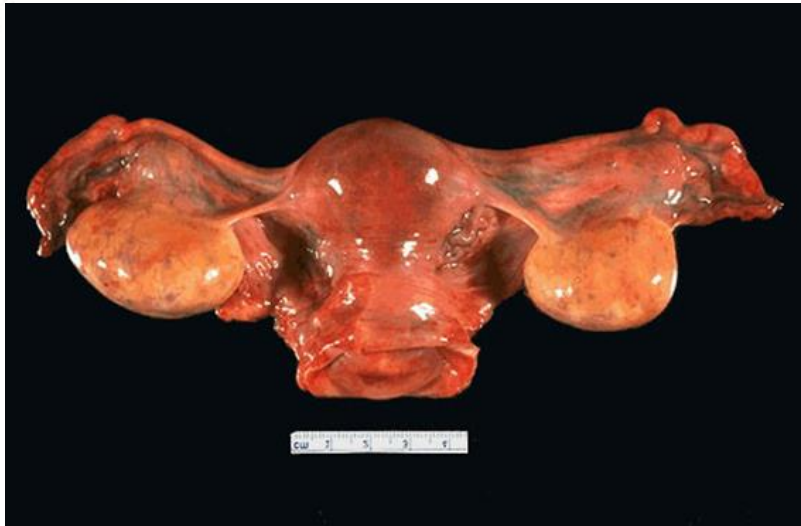

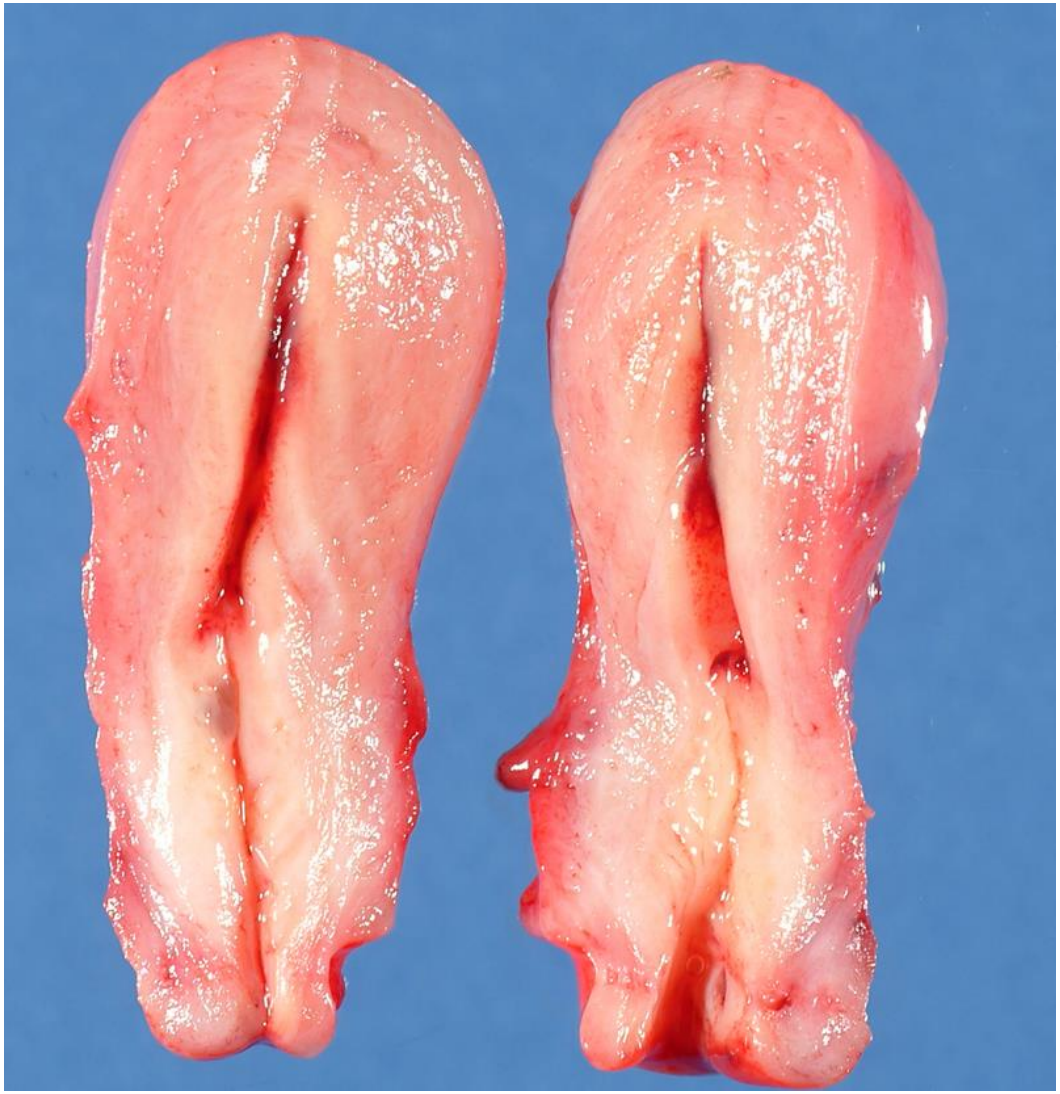

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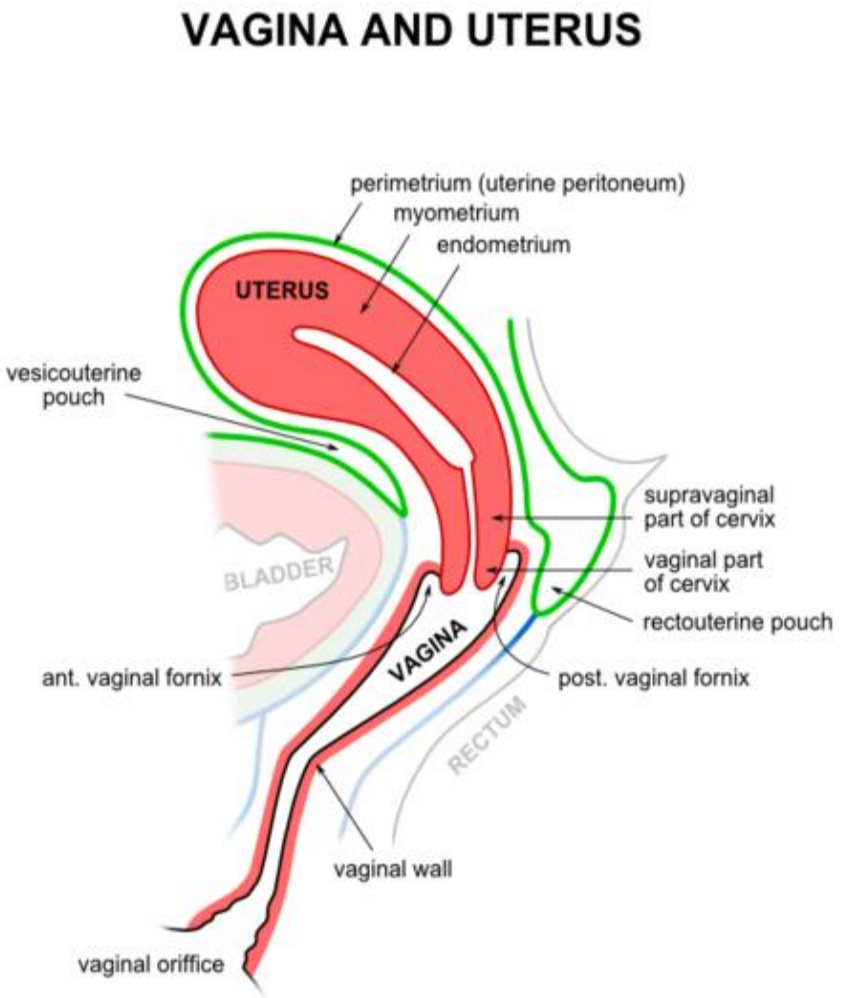

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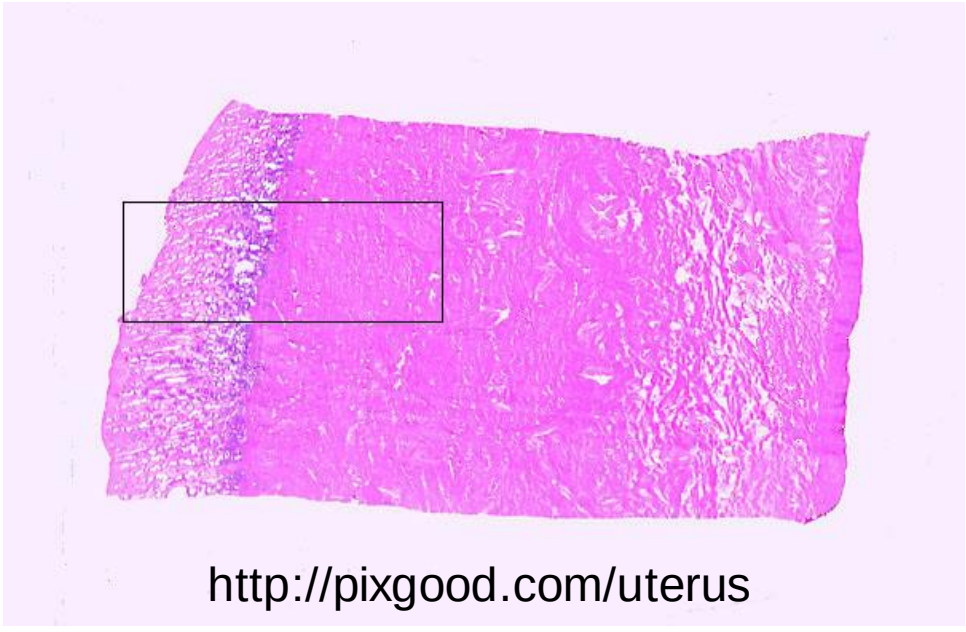

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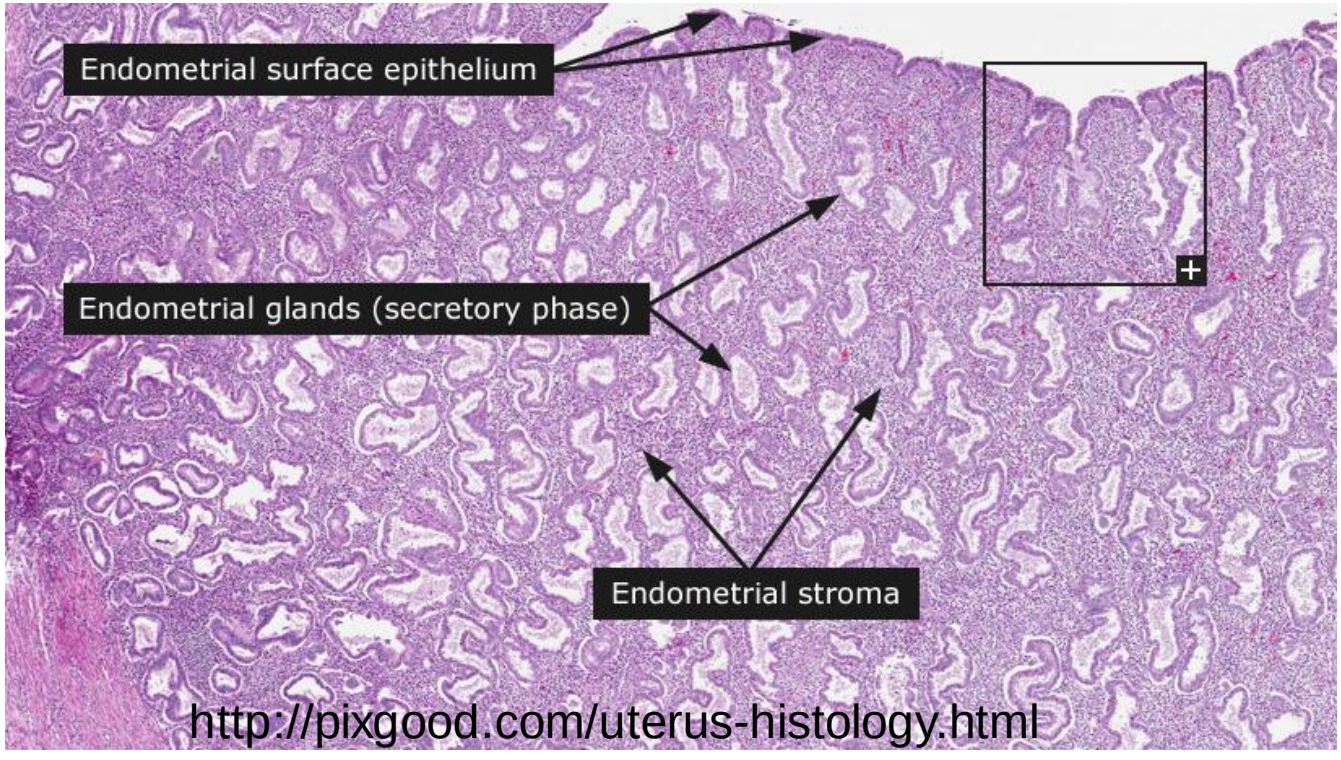

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Lecture Outline

Lecture: At the end of this lecture, the student should know:

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

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

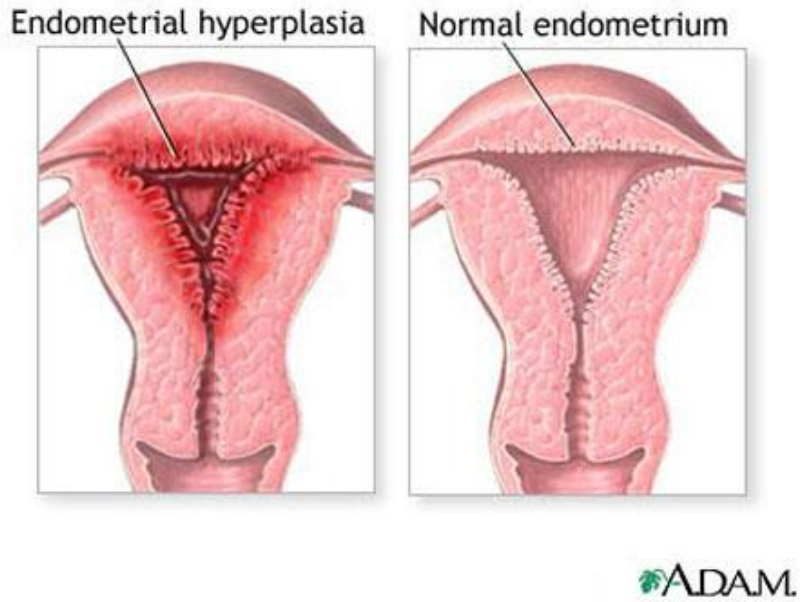
Lesions of myometrium of uterus:

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

Endometrial Hyperplasia

Endometrial Hyperplasia

- Endometrial hyperplasia is a process in which there is a proliferation of endometrial glands resulting in an increase in the gland/stroma ratio of the endometium when compared to normal.
- It is induced by persistent, prolonged stimulation of the endometrium by high levels of estrogen.
- The endometrial hyperplasia may progress to endometrial carcinoma.
- The risk of developing carcinoma depends on the level and duration of the estrogen excess, the severity of the endometrial hyperplasia and associated cellular atypia.



Endometrial Hyperplasia: causes

Causes of Endometrial Hyperplasia: **any condition in which there is high estrogen level can lead to endometrial hyperplasia e.g.**

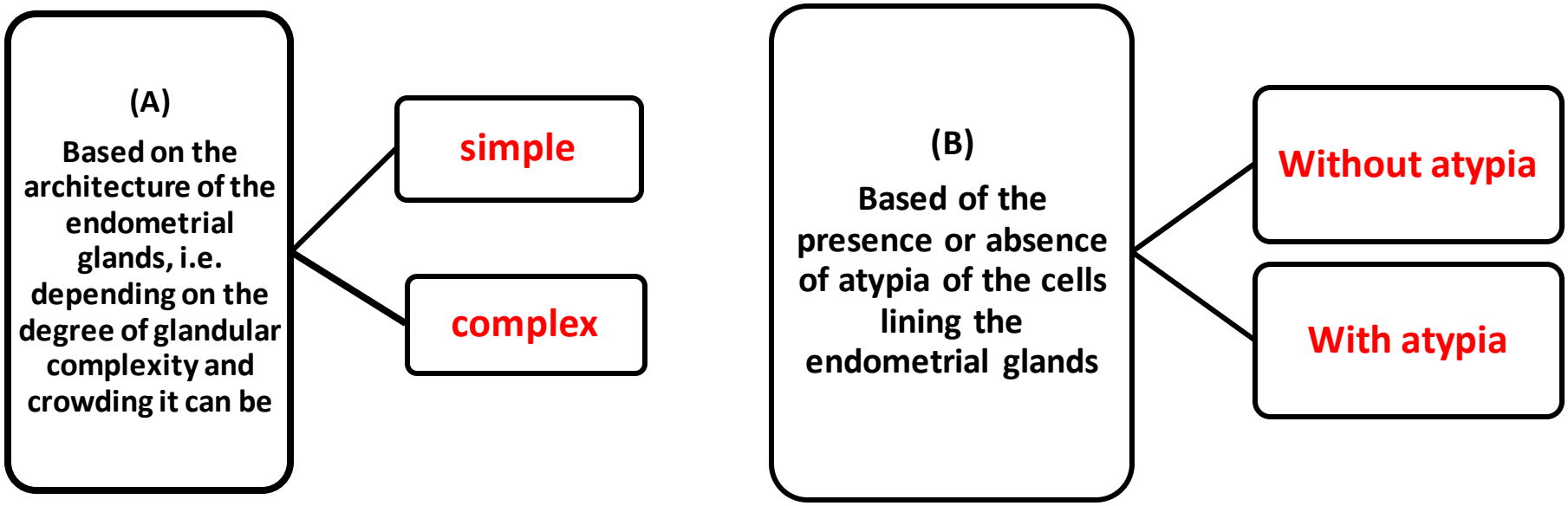
a. Anovulatory menstrual cycles (such as in perimenopause)
b. Excessive endogenous production of estrogen (by the body) e.g. in
   - polycystic ovary syndrome (Stein-Leventhal syndrome),
   - granulosa cell tumors of the ovary
   - cortical stromal hyperplasia (excessive ovarian cortical function)
c. Exogenous administration or intake of estrogenic steroids without counter balancing progestins, over a long period of time.

Endometrial Hyperplasia: clinical

- Mild type of hyperplasia tends to occur in younger patients. Most of the mild hyperplasia cases regress, either spontaneously or after treatment.
- The more severe type of hyperplasia occur mainly in perimenopausal or postmenopausal women. This form has a significant premalignant potential.
- Patients with endometrial hyperplasia usually present with abnormal uterine bleeding.

Endometrial Hyperplasia: classification

In endometrial hyperplasia there is proliferation of both glands and stroma but the proliferation of the glands is much more leading to over crowding of glands. Endometrial hyperplasia is classified based on (A) and (B):



CLASSIFICATION OF ENDOMETRIAL HYPERPLASIA:

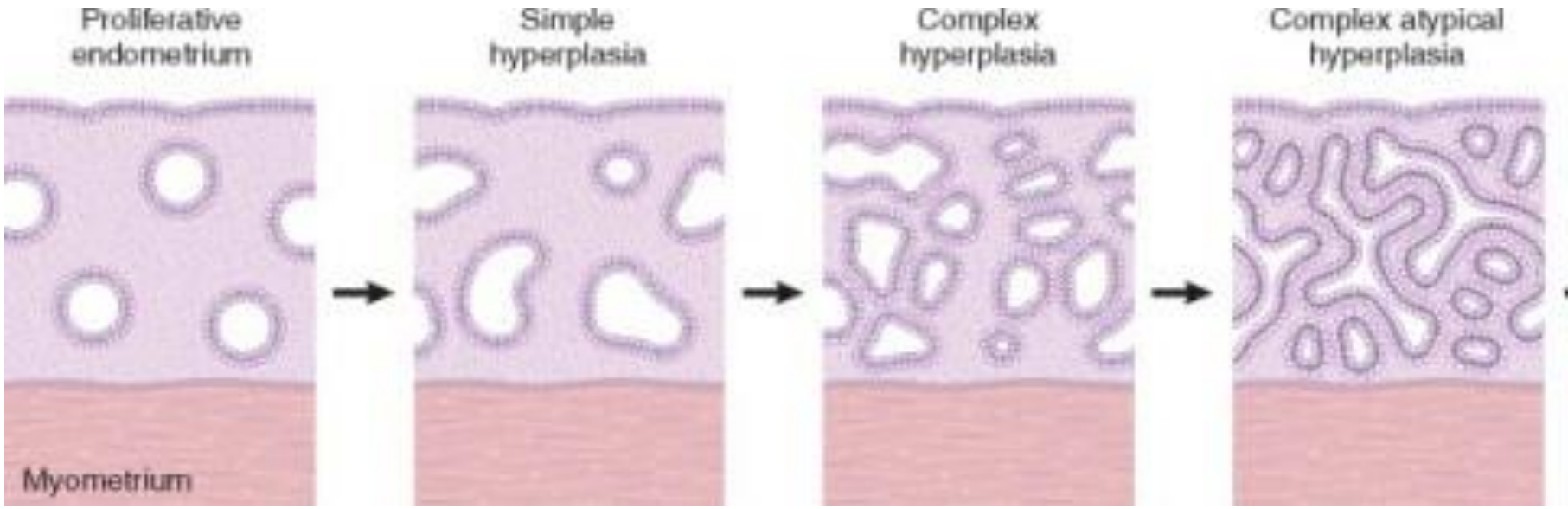
I. Simple hyperplasia

- Without atypia
- With atypia

II. Complex hyperplasia

- Without atypia
- With atypia

Note: atypia/ pleomorphism = loss of polarity, vesicular nuclei, prominent nucleoli, rounded cells.



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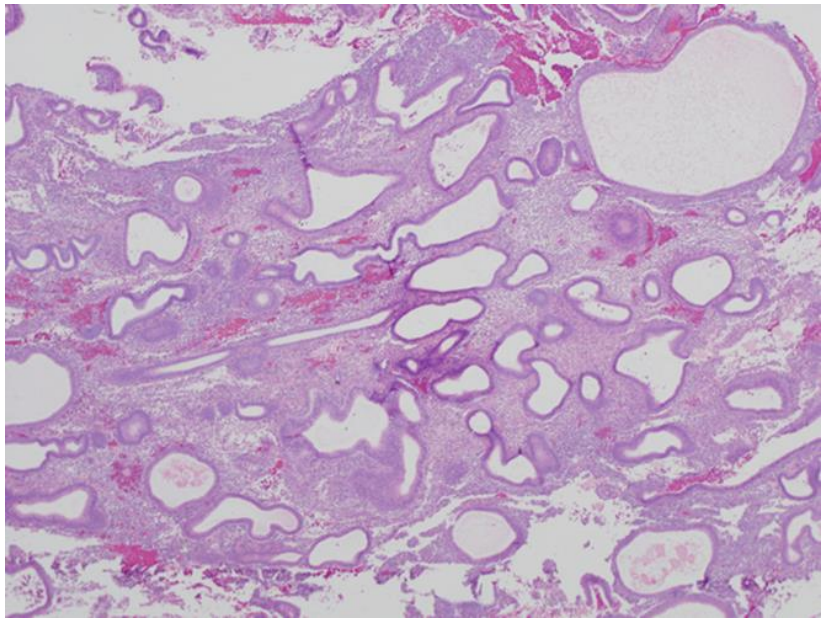
Simple hyperplasia without atypia

- Simple hyperplasia (cystic hyperplasia): glands are varibly shaped and sized and cystically dilated
- There is a mild increase in the gland-to-stroma ratio
- These lesions rarely progress to adenocarcinoma.



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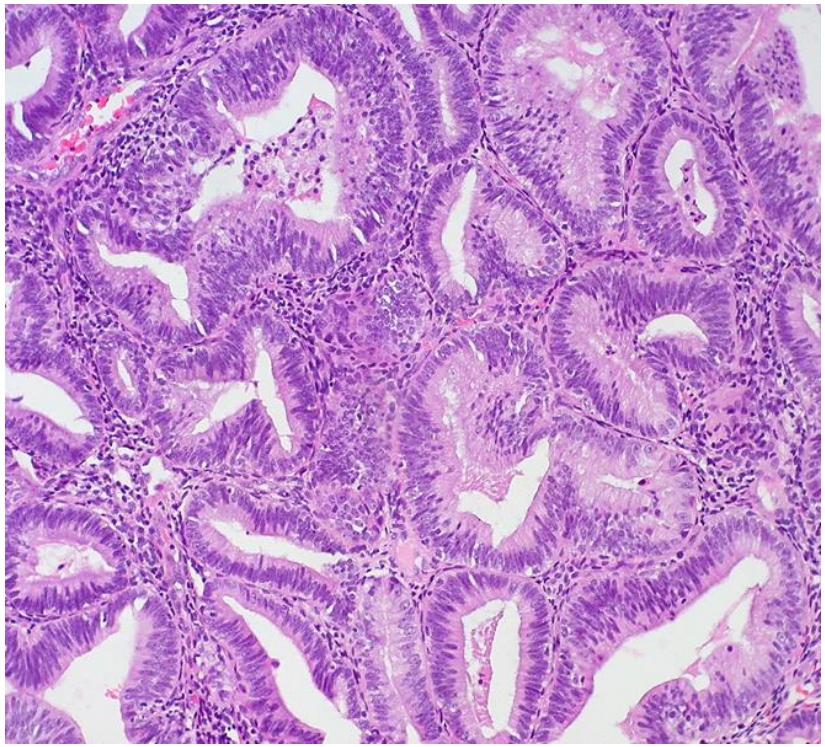
Simple hyperplasia with atypia

- 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 hyperplasia without atypia

- 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



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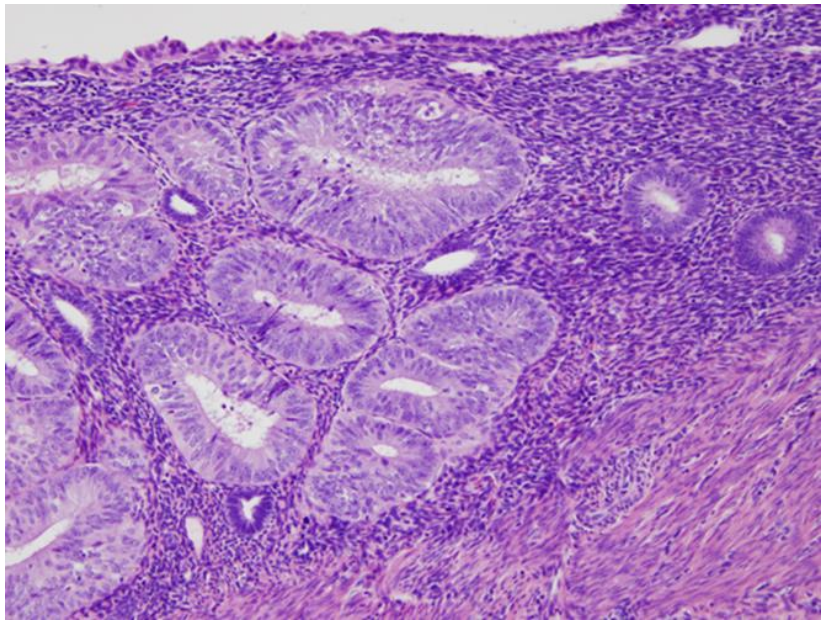
Complex hyperplasia with atypia

- 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



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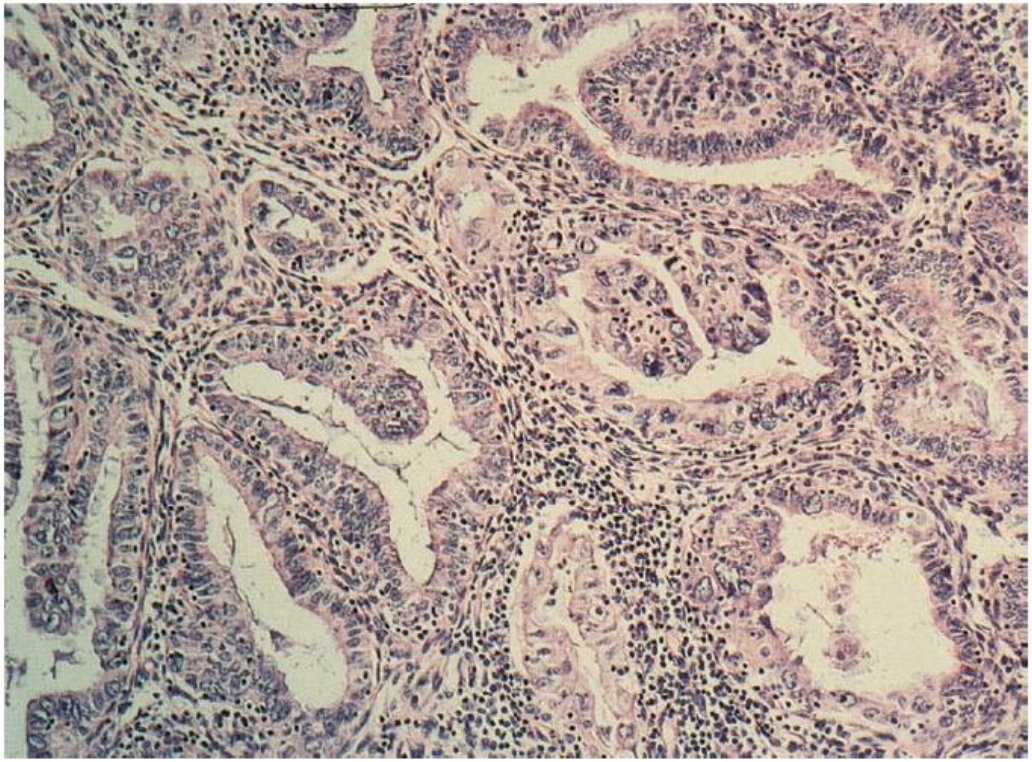


Fig. 6.31 Atypical hyperplasia with cytologic atypia. H & E, ×100

Gisela Dallenbach-Hellweg
Dietmar Schmidt · Friederike Dallenbach

Atlas of Endometrial Histopathology

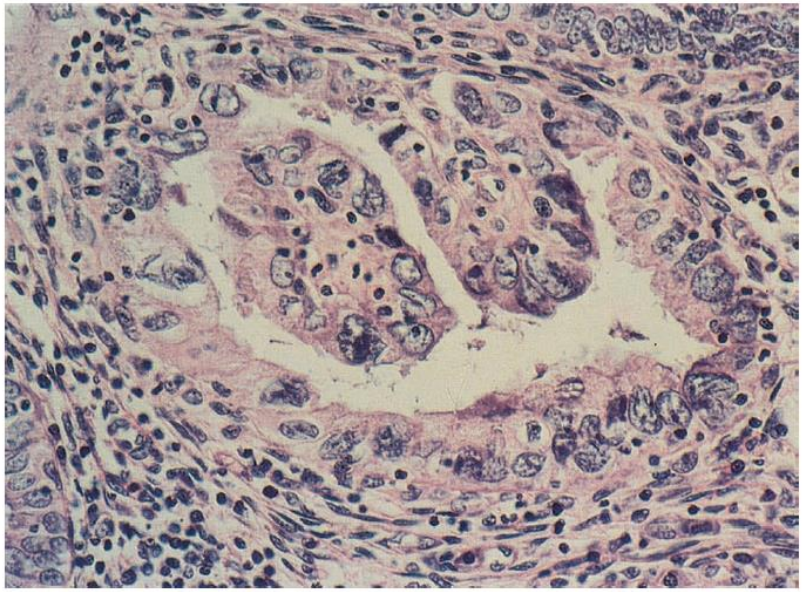


Fig. 6.32 Higher magnification of Fig. 6.31. H & E, ×350

Endometrial Hyperplasia: 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.
- 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.

Robbins 10the ed

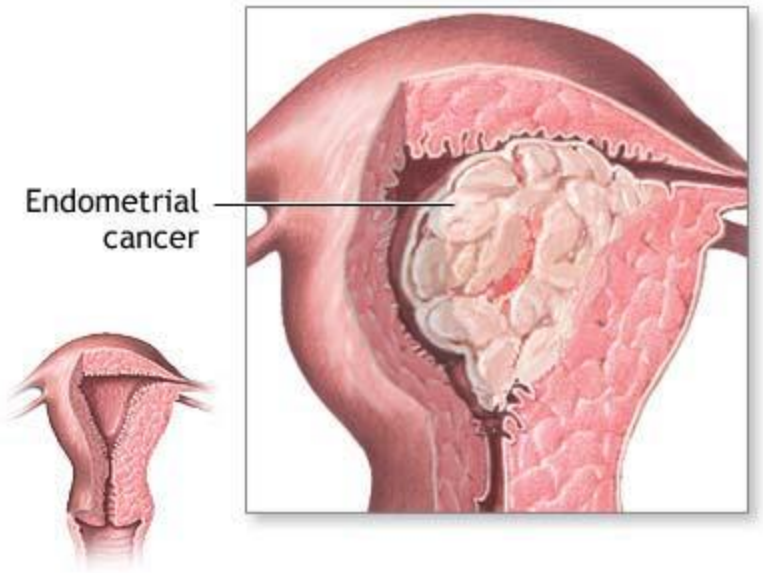
- Endometrial hyperplasia is placed in two categories based on the presence of cytologic atypia: hyperplasia without atypia and hyperplasia with atypia .
- The importance of this classification is that the presence of cytologic atypia correlates with the development or concurrent finding of endometrial carcinoma.
- Hyperplasia without cellular atypia carries a low risk (between 1% and 3%) for progression to endometrial carcinoma, whereas hyperplasia with atypia, also called endometrial intraepithelial neoplasia (EIN), is associated with a much higher risk (20%–50%).
- When hyperplasia with atypia is discovered, it must be carefully evaluated for the presence of cancer and usually warrants a hysterectomy in patients no longer desiring fertility. In younger patients, treatment with high-dose progestins may be used in an attempt to preserve the uterus.

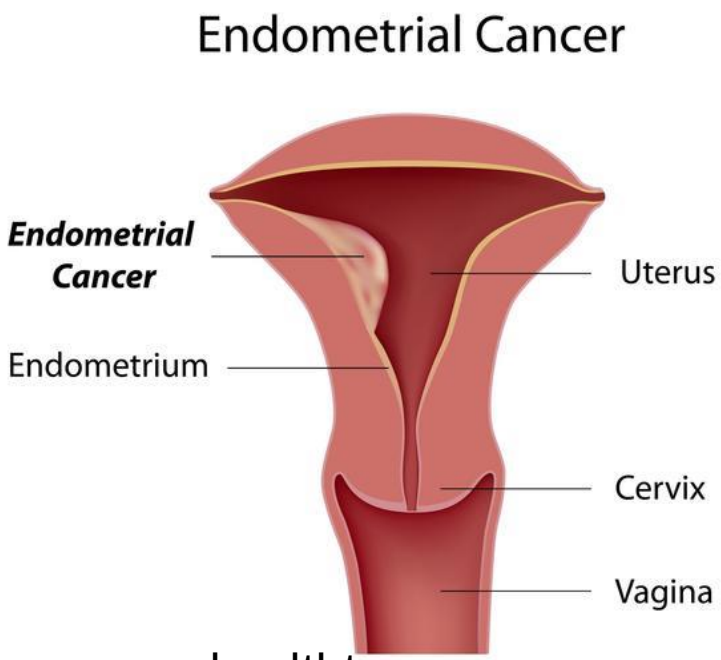
Endometrial adenocarcinoma

Endometrial adenocarcinoma

This is a common neoplasm in women. Overall it is the fifth commonest cancer in women.

- Endometrial cancers arise mainly in postmenopausal women
- They 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):** accounts for 80% of endometrial cancers. It is the most common type. e.g.→ endometrioid adenocarcinoma and its variants.
  - **Type II carcinomas:** they are serous carcinoma and clear cell carcinoma.





Type I endometrial carcinoma/ endometrioid carcinoma

- Endometrioid carcinoma is associated with estrogen excess and endometrial hyperplasia. The majority of the carcinomas are well differentiated.
- Endometrial hyperplasia is a precursor to endometrioid carcinoma
- Risk factors for type I are they same as that of endometrial hyperplasia and include:
    - Obesity
    - Western diet
    - Nulliparity
    - Diabetes Mellitus
    - Hypertension
    - Hyperestrinism
    - Estrogen therapy
    - chronic anovulation
    - Late menopause
    - Tamoxifen therapy

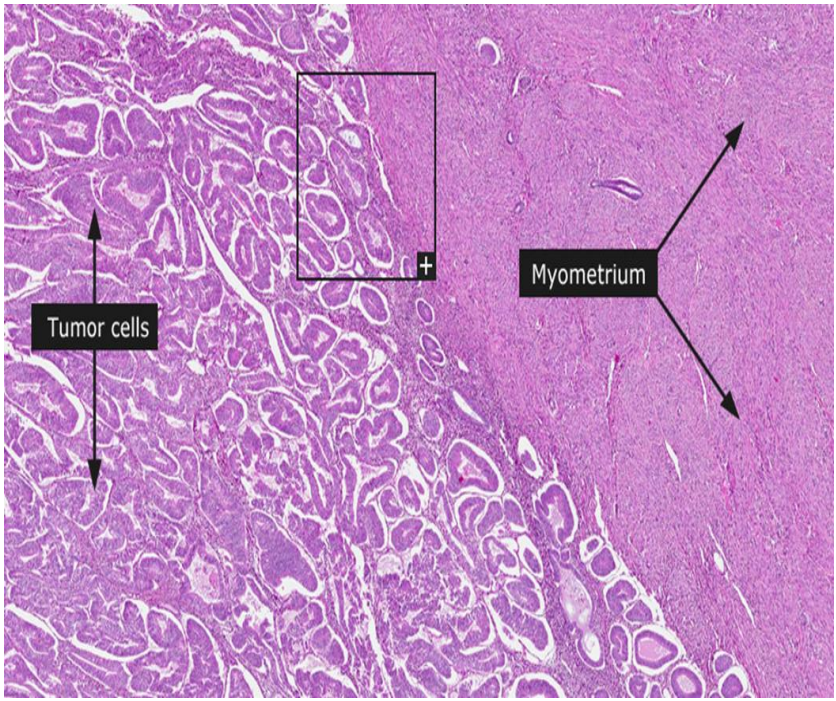
The disease may follow atypical hyperplasia but may occur independently of it especially in older patients.

Type I endometrioid carcinoma: genetics

*Mutations in mismatch repair genes and the tumor suppressor gene PTEN are early events in the stepwise development of endometrioid carcinoma.

*Women with germline mutations in PTEN (Cowden Syndrome) and germline alterations in DNA mismatch repair genes (Lynch Syndrome) are at high risk for this cancer.

*TP53 mutations occur but are relatively uncommon and are late events in the genesis of this tumor type.



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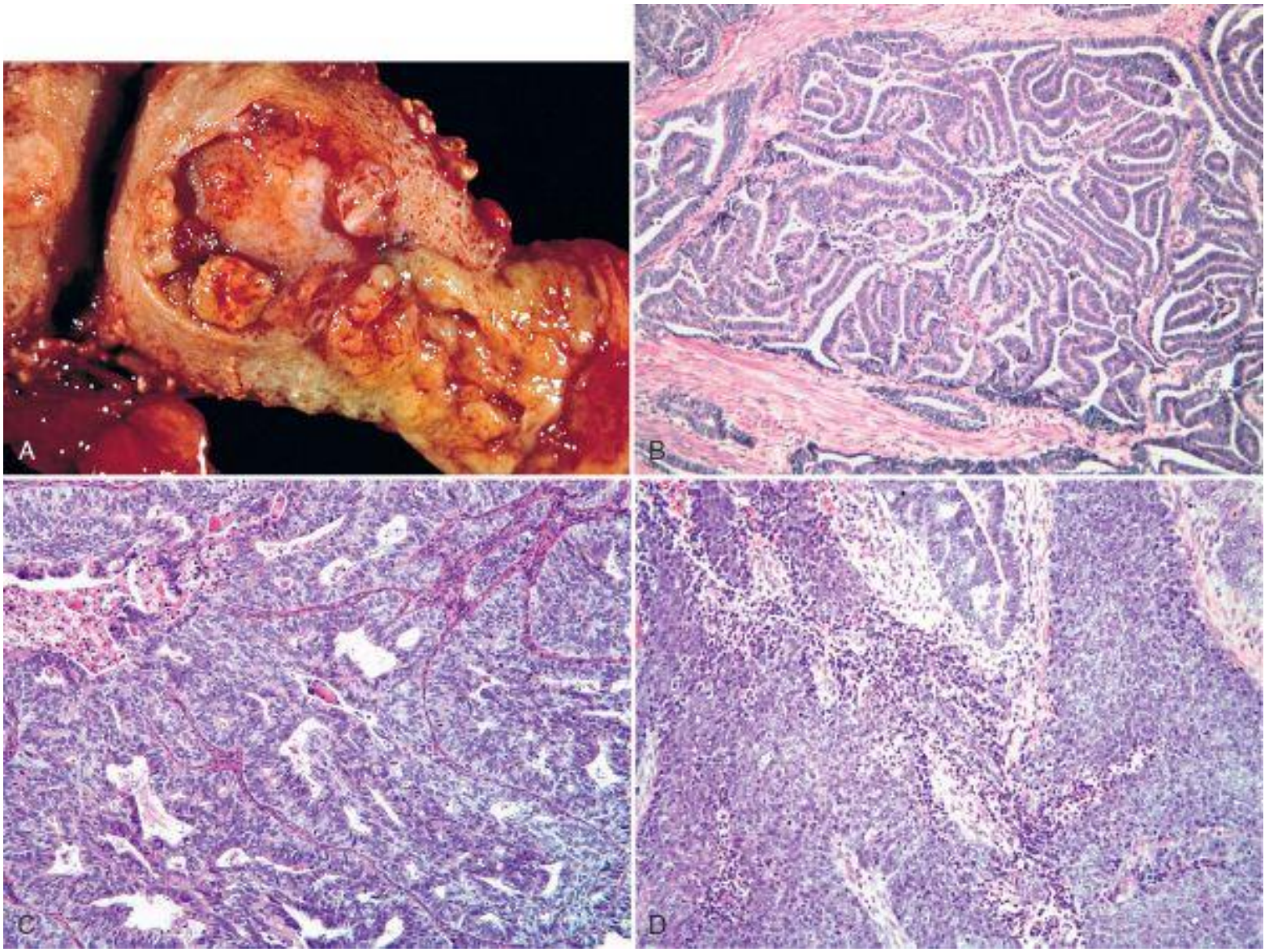
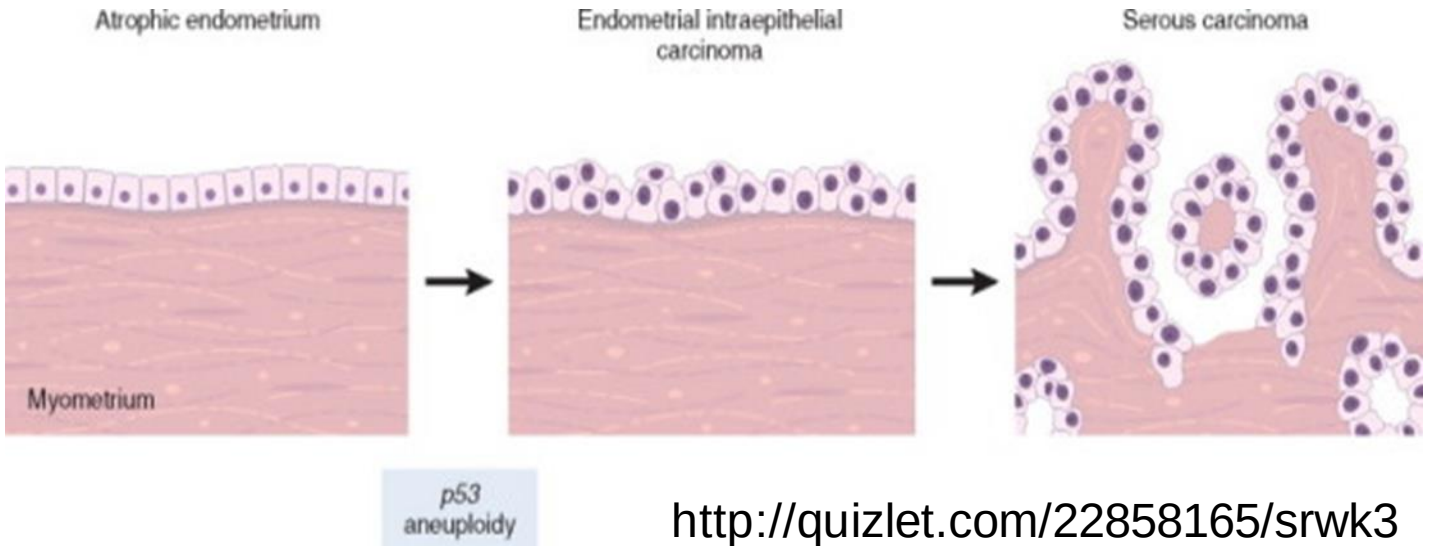
Endometrial carcinoma



Picture Taken from Robbins and Cotran Pathologic basis of disease. 8th edition, Chapter 21, 2010 Sanders

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 serous endometrial intraepithelial carcinoma (its like carcinoma in situ) (SEIC) in which TP53 mutations are often detected, suggesting an early role for such mutations in the development of this form of endometrial carcinoma.
- These tumors are large bulky poorly differentiated tumors which invade early into the myometrium and have a poor prognosis. Extrauterine extension is common.



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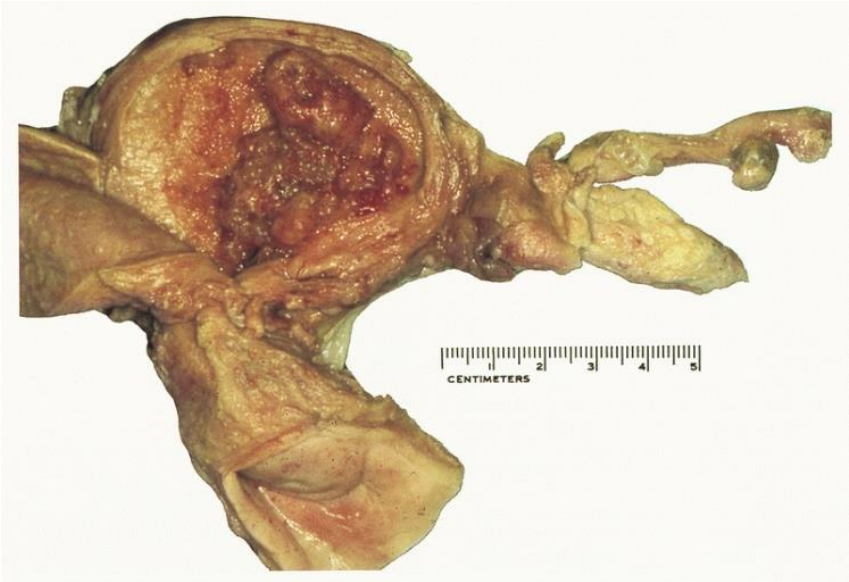
CHARACTERISTICS OF TYPE I AND TYPE II ENDOMETRIAL CARCINOMAS

FEATURES	TYPE I	TYPE II
HISTOLOGIC TYPE	Endometriod 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

Endometrial adenocarcinoma: clinical features

- Most patients are between 50 and 60 years.
- Many of the patients tend to be nulliparous and obese.
- Patients have abnormal vaginal bleeding and excessive leucorrhea.
- Elderly women present with postmenopausal bleeding.
- The diagnosis of endometrial cancer must be confirmed by biopsy or curettage and histologic examination of the tissue.



http://upload.w ikimedia.org/w ikipedia/commons/0/00/Endometrial_hyperplasia.jpg

Endometrial carcinoma: basic morphology

- **Grossly:**
  - May look close to normal or exophytic or infiltrative
- **Microscopy:**
  - Both type I and II are adenocarcinomas.
  - In both cases tumors originate in the endometrium and can eventually infiltrate the underlying myometrium, enter vascular spaces and metastasize to lymph nodes.
  - Serous carcinoma has much greater cytologic atypia and are more poorly differentiated and is 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

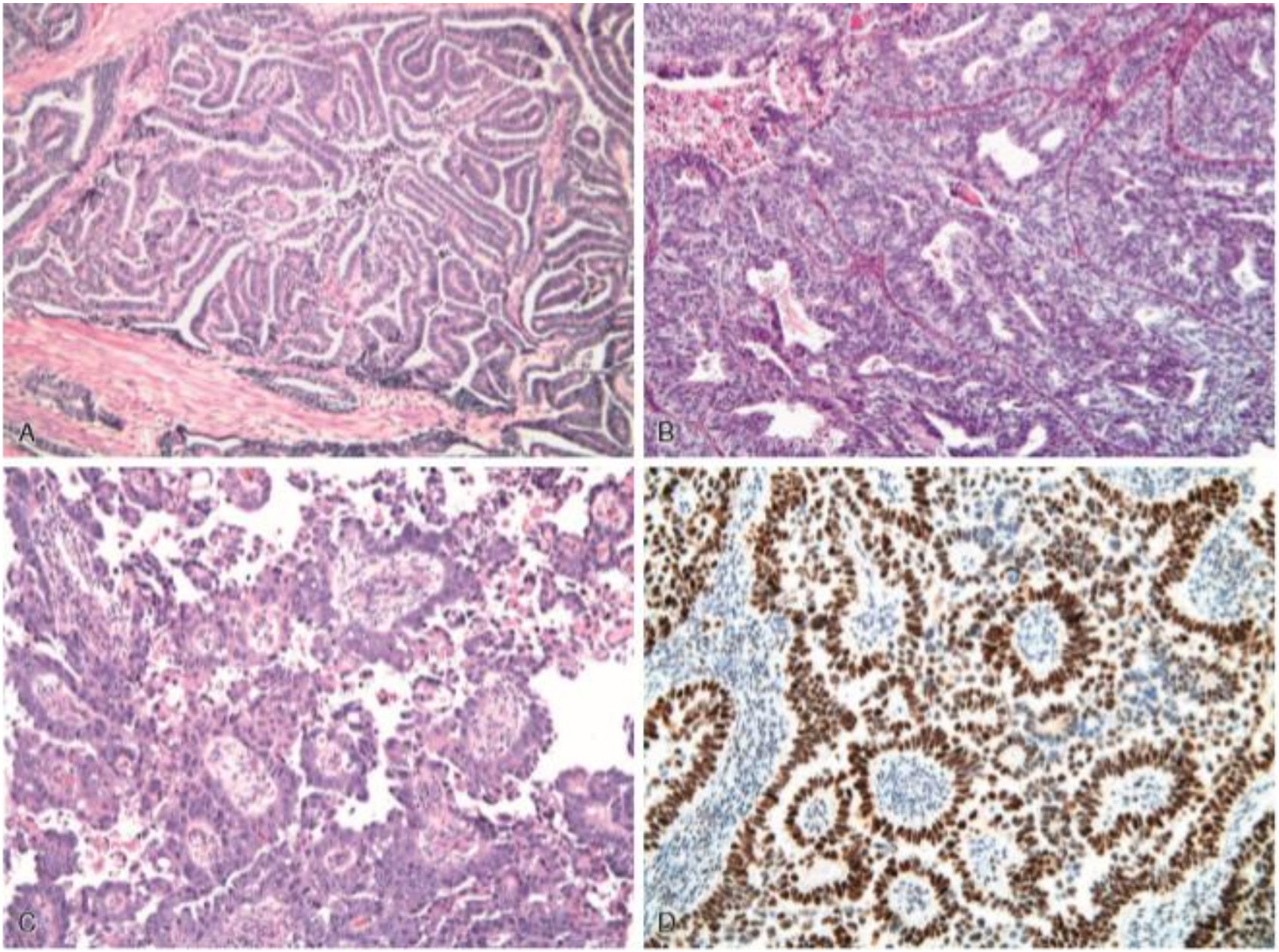


Fig. 19.12 Endometrial carcinoma. (A) Endometrioid type, grade 1, infiltrating myometrium and growing in a glandular pattern. (B) Endometrioid type, grade 3, has a predominantly solid growth pattern. (C) Serous carcinoma of the endometrium, with papilla formation and marked cytologic atypia. (D) Immunohistochemical staining shows accumulation of p53, a finding associated with *TP53* mutation.

Endometrial adenocarcinoma: 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.

LEIOMYOMA

Leiomyoma (fibroid) of uterus

- Benign tumors that arise from the smooth muscle cells in the myometrium are properly termed leiomyomas, but because of their firmness often are referred to clinically as fibroids.
- Leiomyomas are the most common benign tumor in females, affecting 30% to 50% of women of reproductive age, and are considerably more frequent in black women.

- These tumors are associated with several different recurrent chromosomal abnormalities, including rearrangements of chromosomes 6 and 12 that also are found in a variety of other benign neoplasms, such as endometrial polyps and lipomas.

- Mutations in the MED12 gene, which encodes a component of the RNA polymerase transcription complex, have been identified in up to 70% of leiomyomas. The mechanism by which MED12 mutations contribute to the development of leiomyomas is not presently understood.

- Estrogens and possibly oral contraceptives stimulate the growth of leiomyomas; conversely, these tumors shrink postmenopausally

Leiomyoma (fibroid) of uterus

Clinical features

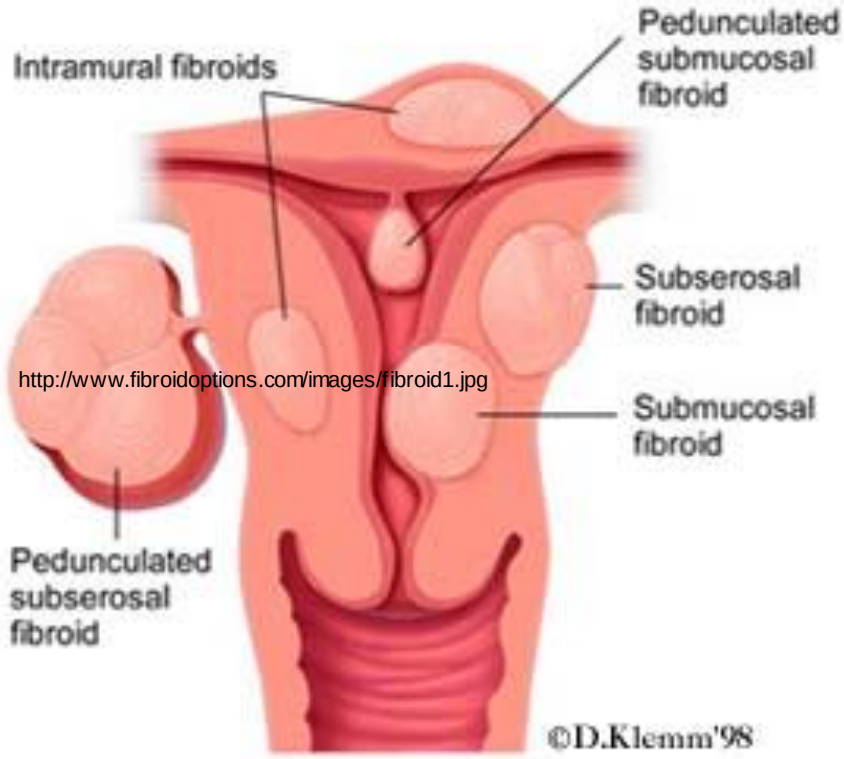
- Leiomyomas of the uterus often are asymptomatic, being discovered incidentally on routine pelvic examination.
- The most frequent presenting sign is menorrhagia, with or without metrorrhagia.
- Leiomyomas rarely, if ever, transform into sarcomas, and the presence of multiple lesions does not increase the risk of malignancy.

Uterine Leiomyoma

Leiomyomas are typically sharply circumscribed, firm gray white masses with a characteristic whorled cut surface.

They may occur singly, but more often occur as multiple tumors that are scattered within the uterus, ranging from small nodules to large tumors that may dwarf the uterus.

*Some are embedded within the myometrium (intramural), whereas others may lie immediately beneath the endometrium (submucosal or the serosa (subserosal). In the latter location, tumors may extend out on attenuated stalks and even become attached to surrounding organs, from which they may develop a blood supply (parasitic leiomyomas)

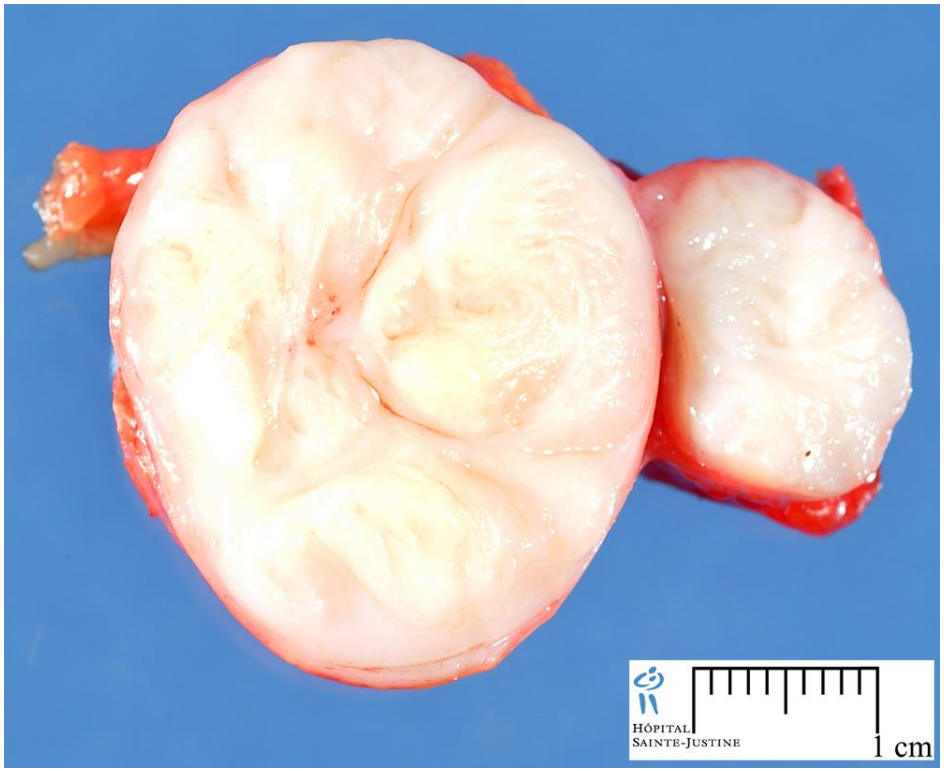


http://www.fibroidoptions.com/images/fibroid1.jpg

http://www.humpath.com/IMG/jpg/uterine_leiomyoma_0412_3.jpg

Leiomyoma gross:

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



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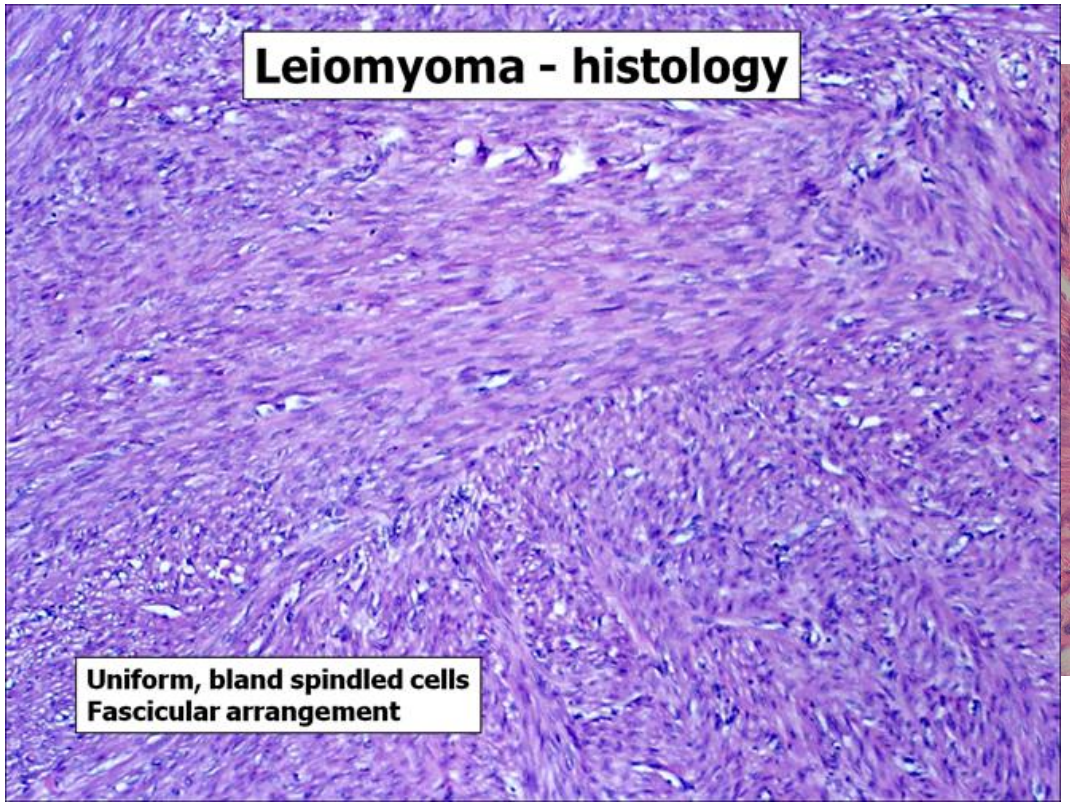
Leiomyoma: Microscopically, there are interlacing bundles of smooth muscle cells with collagenous stroma between bundles. The individual muscle cells are uniform in size and shape. They have the characteristic oval to elongated nucleus. Mitotic figures are scarce.



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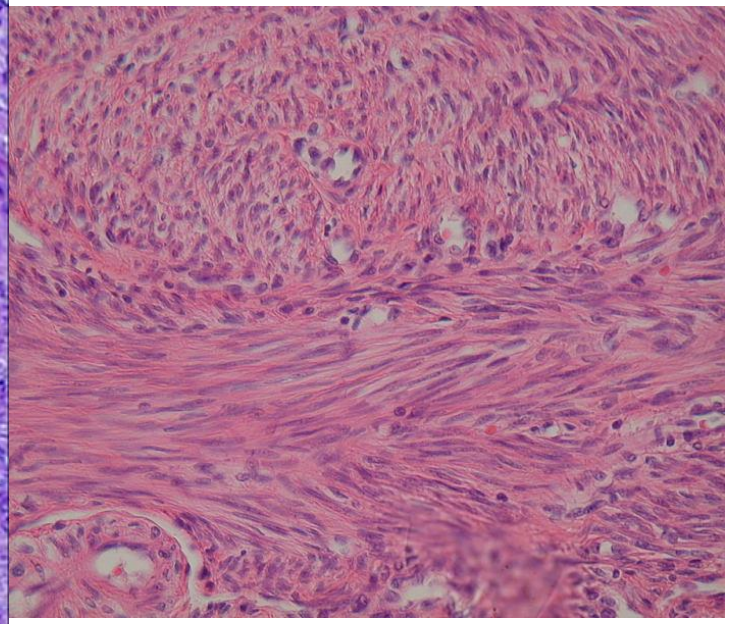

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Leiomyosarcoma

*Leiomyosarcomas of the uterus virtually always arise de novo from the mesenchymal cells of the myometrium.

*They are almost always solitary and most often occur in postmenopausal women, in contradistinction to leiomyomas, which frequently are multiple and usually arise premenopausally.

*Recurrence after surgery is common with these cancers, and many metastasize, typically to the lungs.

Morphology

- The diagnostic features of leiomyosarcoma include tumor necrosis, cytologic atypia, and mitotic activity.

- Because increased mitotic activity is sometimes seen in benign smooth muscle tumors, particularly in young women, an assessment of all three features is necessary to make a diagnosis of malignancy.

Summary

- Endometrial hyperplasia results from excess endogenous or exogenous estrogen.
- 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.

Reference

- Robbins basic pathology 10th edition.