Reproductive Team of Pathology

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Endometrial hyperplasia, uterine cancer and fibroids

3ed Lecture

The Uterine Corpus

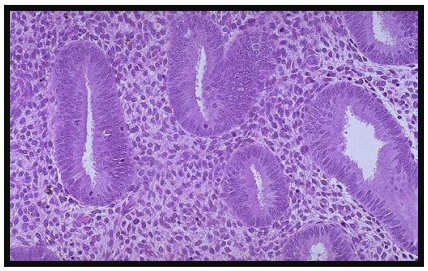
- The uterus is composed of : fundus , body and cervix.
- A cut section of the uterus shows layers: endometrium , myometrium and serosa .
- Endometrium: The inner most layer and it is composed of glands and stroma.
- Myometrium: main bulk composed of smooth muscles.
- Fallopian tube: simple columnar **ciliated**
- Ovary: surface epithelium (germ cells and stroma)

Proliferative endometrium: / secretary endometrium:

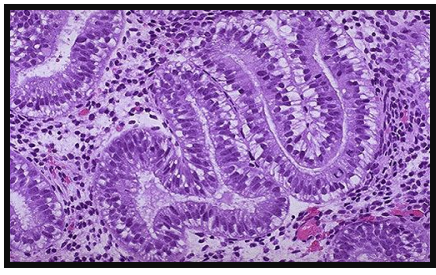
Menstrual cycle: Cyclic changes in the endometrium under the influence of hormones (estrogen and progesterone)

First half of the cycle is proliferative phase , the second half is the secretary phase and ovulation is in between.

- Proliferative endometrium: mainly controlled by estrogen
  On section: more gland which are growing with **compact stroma**



- Secretary endometrium : mainly controlled by progesterone
  On section: **stroma is loose** , subnuclear vaculation in the glands.



Anovulatory cycle: the progesterone is not released only estrogen , absence of ovulation.

1-Endometritis:

A- Acute Endometritis : short period

Acute endometristis is not very common as compared to chronic.

Etiology :-

- **Is most often related to intrauterine trauma e.g. after an abortion either spontaneous or induced, complications of pregnancy, medical instrumentation or intrauterine contraceptive devices (They cause chronic more than acute).**
- **Is most often caused by Staphylococci, Streptococci.**
- **Others like N. gonorrhoeae, gram-negative bacilli and occasionally fungi and viruses can also cause infection.**

B- Chronic endometritis : very common

- **Chronic endometritis is associated with**
  - **Intrauterine contraceptive device use**
  - **pelvic inflammatory disease**
  - **retained products of conception following an abortion or delivery.**
- **<u>The etiologic agent</u> : is often not apparent and the patient is said to have non-specific chronic endometritis**
- **<u>Clinical presentation :</u> Patients present with irregular bleeding**
- **Histologically:**
  - **the presence of plasma cells in the endometrium is diagnostic.**
  - **The stromal cells become spindled and swirl around the glands.**
  - **Sometimes granulomatous endometritis is noted in patients with tuberculosis.**

2-Endometrial polyp

- **<u>Definition</u> : Is a localized benign overgrowth of endometrial tissue covered by epithelium.**
- **Endometrial polyps are most common in women between 40 and 50 years.**

Around the time of menopause

- **<u>Clinical significant :</u> The polyp may cause irregular bleeding.**
- **<u>Characteristic :</u>**
  - **It may be *broad-based and sessile, *pedunculated or attached to the endometrium by a slender stalk.**
  - **The size is variable from 1mm to a mass that fills the endometrial cavity.**
  - **Occasionally a polyp may protrude through the external os.**

***broad-based and sessile**= the polyp is without a stalk

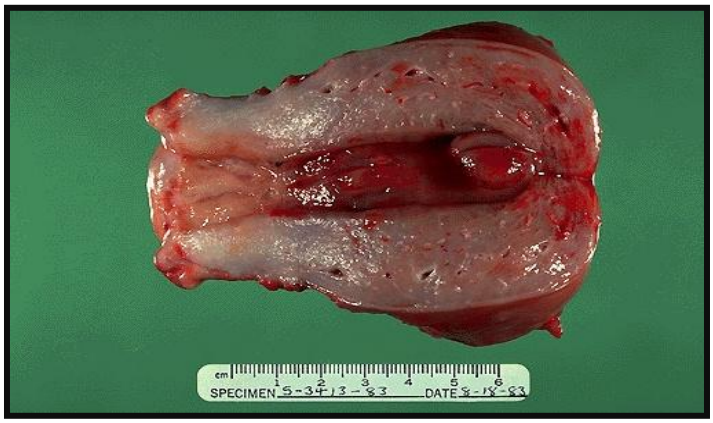
* **pedunculated** = with a stalk.

- **Histology :**
  - **Composed of glands of variable size and shape** (in contrast to the proliferative endomertium which shows growing glands with almost the same size. Proliferative endometrium is a normal condition while polyps are not)
  - **fibrotic stroma .**
  - **Thick-walled blood vessels.**
- **Clinical behavior :**

Endometrial polyps are benign with no malignant potential but Sometimes malignant tumors may be found in them.

-It might be a single polyp or multiple polyps most Commonly single .

-It does not transform into cancer but cancer may be found sometimes(coexistent) .



3-Leiomyoma (Fibroid)

- **Definition : Leiomyoma is a benign tumor of smooth muscle origin.**
- **Epidemiology:**
  - **It is the most common neoplasm of the female genital tract and probably the most common neoplasm in women.**
  - **Is more common in women of African lineage.**
- **Clinical and gross appearances**
  - **Patients may present with irregular bleeding, pelvic pain, pelvic mass, infertility.**
  - **The tumor is estrogen responsive and often increases in size during pregnancy and decreases in size during menopause.**
  - **It can be single or multiple. Mostly it is multiple.**

*Anything growing in the myometrium can alter the shape of the uterus resulting in pelvic pain because of the compression.

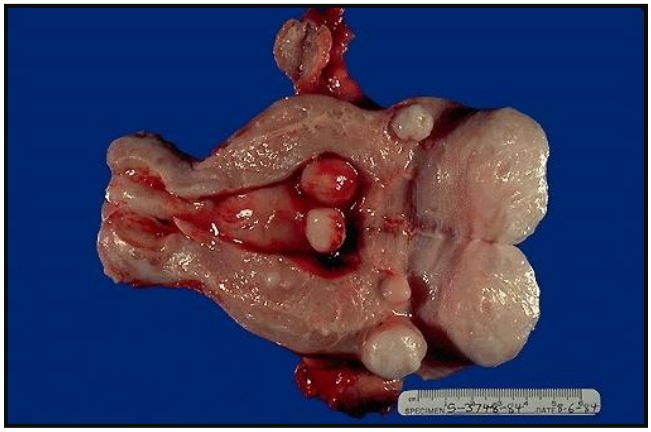
*infertility: The uterus isn't smooth, it is irregular.

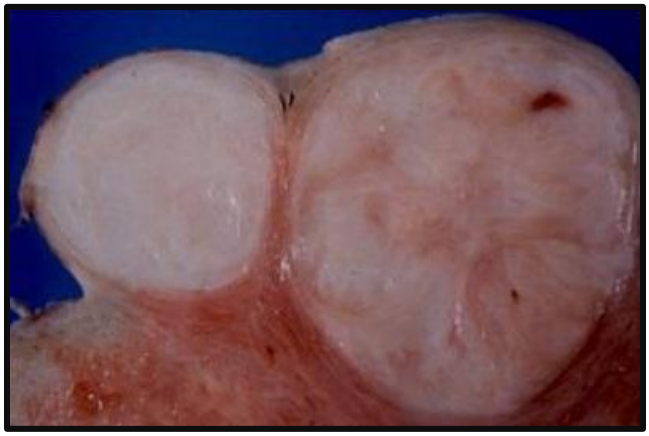
Leiomyoma may be located anywhere in the myometrium : (imp)

- Submucosal tumors are present immediately below the endometrium, may be pedunculated and occasionally protrude though the cervix. Under the mucosa/ protruding in the lumen covered by endometrium / it is the most common cause of bleeding or increased (irregular)periods because the surface area of endometrium is increased .
- Intramural tumors, the most common, lie within the myometrium. In the wall of the uterus / destroy the shape.
- Subserosal fibroids lie beneath the serosal covering of the uterus or are pedunculated and attached to the serosa. Under the serosa

  Pedunculated ones may undergo torsion and infarction or loose their connection to the uterus and become attached to another pelvic organ forming a "parasitic leiomyoma".

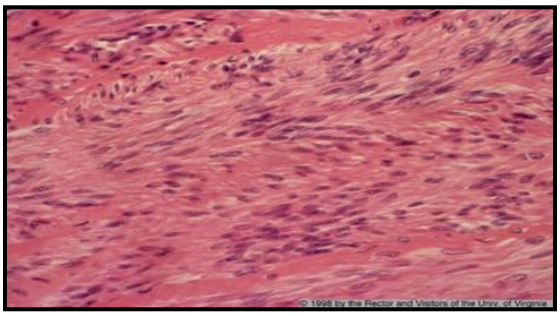
- **Grossly** : the tumors appear as well circumscribed, spherical, dense and firm-to-hard masses with whorled, tan-white cut surfaces, areas of hemorrhage can be seen





- **Histological :**

Composed of interlacing fibers of bland smooth muscle with collagenous stroma between bundles



- **Leiomyoma (Fibroid) Degenerative changes** (changes with long standing fibroid)
  - Atrophy — the tumor reduces in size at menopause or after pregnancy following drop in estrogen level.
  - Hyaline change (hyalinization) — Usually occurs as the tumor "ages".
  - Myxoid and cystic change.
  - Calcification — common in menopausal women.
  - Necrosis of the center due to circulatory inadequacy.

- Red degeneration— venous thrombosis and congestion with interstitial hemorrhage may occur, most commonly in pregnancy. This is usually accompanied by pain, which may produce a clinical picture of acute abdominal pain.

❖ **Clinical behavior**

- This is a benign tumor with no appreciable malignant potential (incidence of malignant transformation (Lieomyosarcoma) is 0.1-0.5%).
- It may cause anemia from heavy bleeding, or urinary or bowel obstruction (subserosal or parasitic tumors)
- In pregnant women it may cause spontaneous abortion, precipitate labor, obstructed labor ,post partum hemorrhage (due to interference with uterine contraction), and red degeneration.

4- Endometrial Hyperplasia

❖ **Definition :**

- It refers to a process in which there is a proliferation of endometrial glands.

❖ **General information :**

- The glands are irregular size and shape with an increase in gland/stroma ratio compared to proliferative endometrium. The glands are more than the stroma , resulting in crowding of the glands.
- 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 depends on the severity of the hyperplastic changes and associated cellular atypia.

❖ **Causes** :

- A common cause is a succession of anovulatory cycles (failure of ovulation).
- It may also be caused by excessive endogenously produced estrogen in :

1- -polycystic ovary syndrome including Stein-Leventhal syndrome,
2- -granulosa cell tumors of the ovary
3- -excessive ovarian cortical function (cortical stromal hyperplasia)

- Prolonged exogenous administration of estrogenic steroids without counter balancing progestins

❖ **Clinically :**

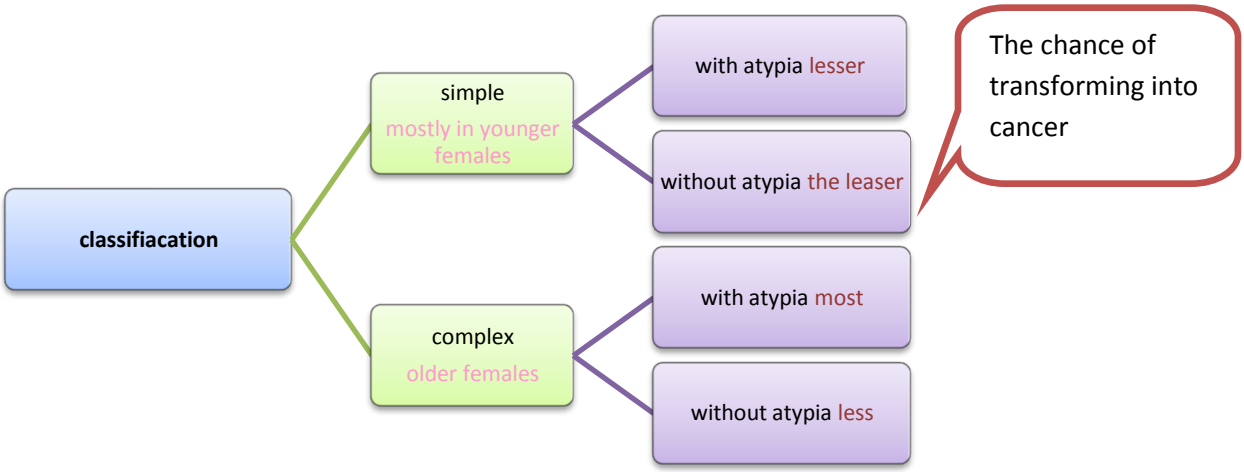
- Milder forms of hyperplasia tends to occur in younger patients
- The great majority of mild hyperplasia regress , either spontaneously or after treatment .
- The more severe forms ,occur predominantly in peri- and postmenopausal women .This form has a significant premalignant potential.
- Patients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

❖ **Histology :**

- Characterized by proliferation of both glands and stroma.
- In spite of proliferation of both components, glandular overcrowding occurs.
- Endometrial hyperplasia is histologically classified according to: types of hyperplasia are based on microscopic features

1) Architecture shape as: simple (regular or round) or complex (irregulat) depending on the degree of glandular complexity and crowding, and

2) Cytologic features as: with or without atypia. (depending on the lining of the glands)



❖ **Histology** :

- Simple hyperplasia (cystic hyperplasia) : glands are cystically dilated and dispersed within abundant cellular stroma and give a "Swiss Cheese" appearance.
- Complex hyperplasia :Characterized by complex crowded glands with papillary infoldings , budding and irregular shapes.

- The crowded glands are back-to-back with very little intervening stroma.

- Both simple and complex hyperplasia can be with or without atypia.

❖ **Clinical behavior and premalignant potential :**

- Some endometrial hyperplasia revert to normal spontaneously or with medical treatment (Sometimes as a treatment option they perform hysterectomy which is an operation where the uterus is taking out) 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:

  - Complex atypical — 30%

  - Simple atypical — 10%

  - Complex — 3%

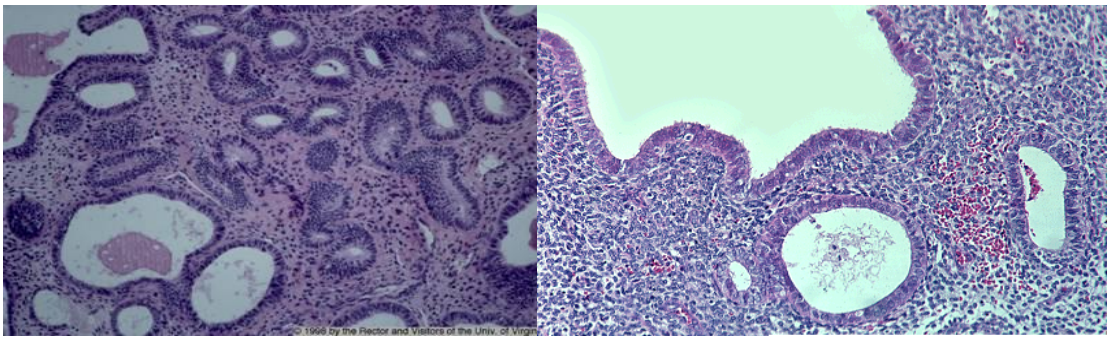
  - Simple — 1%

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

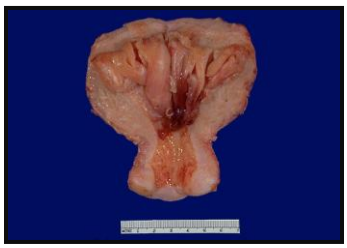
1. Obesity
2. Western diet
3. Nulliparity
4. Diabetes Mellitus
5. Hypertension
6. Hyperestrinism

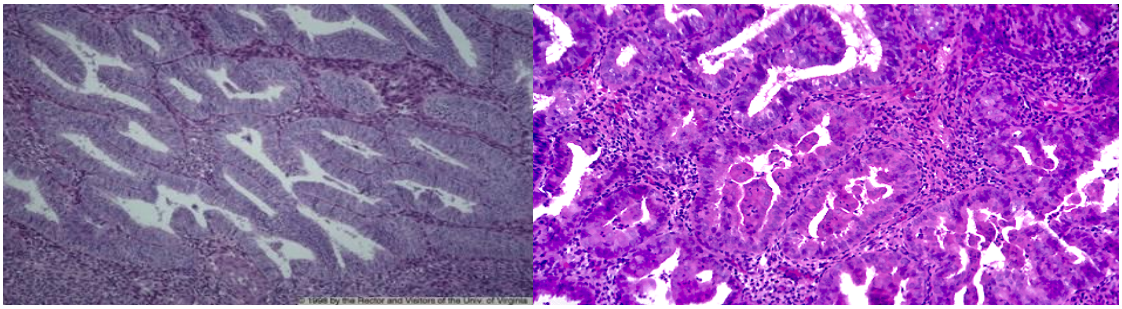
Nulliparity : woman who has never born a child

Hyperestrinism : condition marked by the presence of excess estrins (estrogenic hormone) in the body and often accompanied by functional bleeding from the uterus



Simple hyperplasia with dilated glands





Complex atypical hyperplasia with back-to-back arrangement of glands and papillary tufting

5- Endometrial adenocarcinoma

- **Epidemiology:**
  - It is the most common invasive tumor of the female genital tract in the U.S.
  - Worldwide, it is the fifth commonest cancer in women.
- **Risk Factors, Adenocarcinoma**
  - Obesity (women with upper body fat have 3 times the risk of women with lower body fat),
  - Estrogen therapy
  - Nulliparity (as a result of infertility due to chronic anovulation),
  - Chronic anovulation
  - Late menopause
  - Hypertension
  - Diabetes
  - Tamoxifen therapy side effect (breast cancer drug of choice , patients should be followed up).
  - High socioeconomic status.

Mutations in the **PTEN** tumor suppressor gene have been identified in 30% to 80% of endometrioid carcinomas and in approximately 20% of endometrial hyperplasias, both with and without atypia.

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

- **Clinical presentation**
  - Most patients are between 50 and 59 years.
  - Endometrial adenocarcinoma manifests as marked leukorrhea and abnormal vaginal bleeding.
  - The tumor may grow in a diffuse or polypoid pattern usually at the fundus however any site can be involved.
  - It often involves multiple areas of the endometrium
- **morphology:**
  - May closely resemble normal endometrium
  - May be exophytic
  - May be Infiltrative (infiltrating the myometrium)
  - May be polypoid (Localized radiologically detected)

❖ **histology:**

- The commonest type is : Endometrioid adenocarcinoma.
- Other types include:
    1- Clear cell
    2- Adeno-squamous : both glandular and squamous components appear malignant.
    3- Papillary serous carcinoma.
- Endometrioid carcinoma may show areas of benign looking squamous epithelium also known as (adenoacanthoma).
- In adenosquamous carcinoma both glandular and squamous components appear malignant.

❖ **prognosis:**

- Clinical behavior 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 histological types, which tend to occur at a higher stage.

❖ **Staging is based on:**

1- degree of myometrial invasion, cervical, adnexal and adjacent pelvic organ invasion,

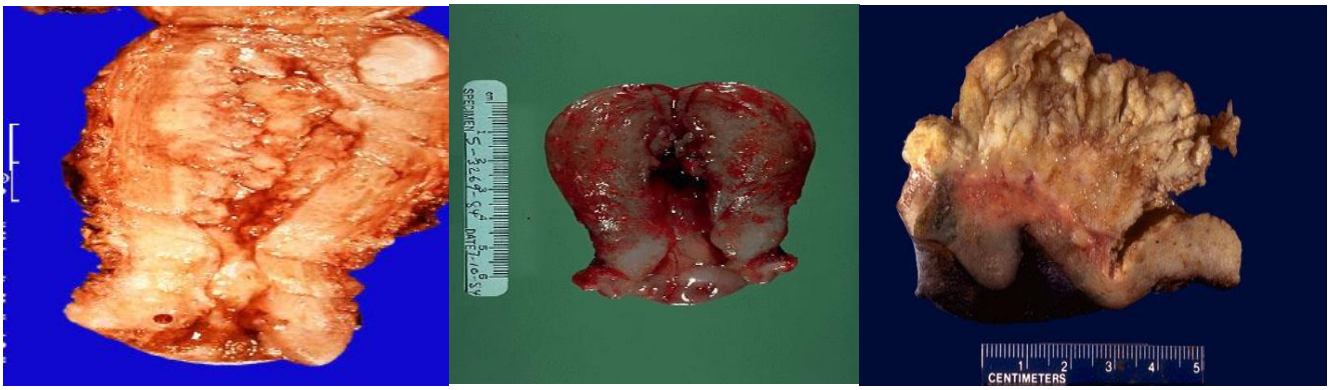
2- result of peritoneal fluid cytology and

3- distant organ metastasis.

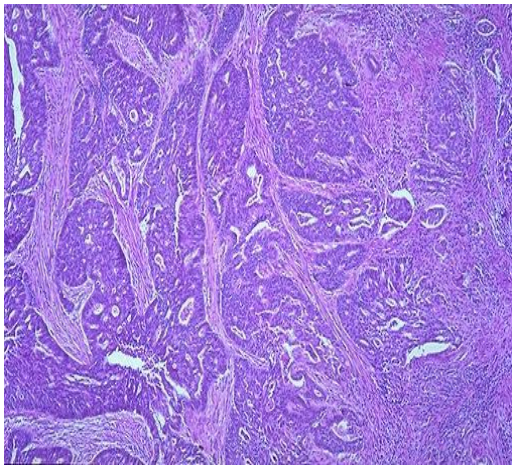
4- Lymph node status is an important prognostic factor.

❖ **prognosis:**

- 75% of patients present with stage I disease and these have 95% 5-year survival.
- The tumors associated with unopposed estrogen tend to have low histologic grade and clinical stage, hence tend to have better prognosis.
- These usually occur in young women.
- 20% of endometrial carcinoma there is no association with hyperestrinism or preexisting hyperplasia ,these cancers tend to occur late in life and have a poor prognosis.



- **Endometrial Carcinoma , Grading and staging**
  - Grading is from 1 to 3
  - Staging is from 1 to 4
    - Stage 1 : Confined to uterus corpus
    - Stage 2 : Cervix involvemen
    - Stage 3 : beyond the uterus ,but within the true pelvis
    - Stage 4 : Distant metastasis/ extrapelvic extension.



Summery:

Acute Endometritis	Rare , as a result of a trauma , mainly caused by Staphylococci, Streptococci.
Chronic Endometritis	Common , irregular bleeding , Intrauterine contraceptive device use, plasma cells in the stroma
Leiomyoma (Fibroid)	the most common neoplasm of the female genital tract , estrogen responsive , 3 types according to the location: submucosal – intramural – subserosal , grossly it is well circumscribed and shows areas of hemorrhage , histology bland smooth muscle with collagenous stroma between bundles
Endometrial polyp	Around the time of menopause , irregular bleeding , Composed of glands of variable size and shape , thick walled blood vessles , benign with no malignant potential
Endometrial Hyperplasia	Hyperplasia that hyperplasia may progress to endometrial carcinoma , an increase in gland/stroma ratio, persistent, prolonged estrogenic stimulation , might be simple or coplex with atypia or without.

Endometrial adenocarcinoma	the most common invasive tumor of the female genital tract , marked leukorrhea and abnormal vaginal bleeding , histological types: Endometrioid adenocarcinoma,Clear cell , Adeno-squamous , Papillary serous carcinoma

Questions:

1- Which of the following endometrial adenocarcinimas has the best prognosis?

a-clear cells adenocarcinoma

b-adeno-sqaumous adenocarcinoma

c-endometrioid adenocarcinima

d-they all have the same prognosis

2- Huda , a 30 year old female was concerned because of an irregular bleeding , on histology plasma cells were seen in the stroma of the endometrium , what is the diagnosis ?

a-leiomyoma

b-chronic endometritis

c-endometrial hyperplasia

d-endometrial polyp

3-which of the following has the highest incidence to develop endomatrium adenocarcinoma?

a-simple with atypia

b-complex without atypia

c-complex with atypia

d-simple without atypia

Answers:

c-b-c