Sheets Pathology

Number: 5

Doctor: Mousa Al-Abbadi

Done By: Ola Al-juneidi & Obada Zalat

Correction: Ahmad Al-Tarefe

Abnormal Uterine Bleeding (AUB)

AUB is a very common scenario or symptom where women complain of **menorrhagia** (heavy and/or for long periods), **metrorrhagia** (irregular bleeding) or **post-menopausal bleeding**. All of these complaints are serious which have to be investigated.

Causes:

There are multiple causes depending on age and the situation of the patient.

- **Dysfunctional uterine bleeding (DUB)** where there is no uterine organic pathology, i.e. uterus is normal. The cause could be hormonal or extra-uterine pathology.
- **Endometrial polyps**: benign proliferations.
- **Leiomyomas (fibroids)** "تليف": benign smooth muscle neoplasm. It is very common
- **Endometrial hyperplasia** is a precursor of endometrial carcinoma.
- **Endometrial carcinoma**
  Endometrial hyperplasia and carcinoma are serious that's why we investigate very well to make sure they are not present.

This table is very important. It shows the causes of AUB for each age group:

TABLE 19.2 Causes of Abnormal Uterine Bleeding by Age Group

Age Group	Cause(s)
Prepuberty	Precocious puberty (hypothalamic, pituitary, or ovarian origin)
Adolescence	Anovulatory cycle
Reproductive age	Complications of pregnancy (abortion, trophoblastic disease, ectopic pregnancy) Proliferations (leiomyoma, adenomyosis, polyps, endometrial hyperplasia, carcinoma) Anovulatory cycle Ovulatory dysfunctional bleeding (e.g., inadequate luteal phase)
Perimenopause	Anovulatory cycle Irregular shedding Proliferations (carcinoma, hyperplasia, polyps)
Postmenopause	Proliferations (carcinoma, hyperplasia, polyps) Endometrial atrophy

- ✓ Around the age of puberty, it is mainly **hormonal**; hypothalamic, pituitary or ovarian problems (abnormality of hypothalamic-pituitary axis or pituitary-ovarian axis).
- ✓ In adolescence (after menarche= the first occurrence of menstruation) the most common cause is **anovulatory cycles**. The cycles begin but the ovary doesn't spell out ova.
- ✓ In reproductive age, causes are **related to pregnancy** like:
  - Abortion: she was pregnant and then she experienced AUB.
  - Trophoblastic disease: she aborted and then had a D&C procedure (dilation & curettage عمليات التنظيف) but AUB didn't stop. In this case we have to rule out trophoblastic disease.
  - Ectopic pregnancy: there are pregnancy symptoms but the ultra sound shows empty uterus! Pregnancy could be outside the uterus.

  *We will discuss these complications in detail later in this lecture.

  Other causes include **proliferations**:
  - Leiomyoma: benign neoplasm.
  - Adenomyosis: discussed last lecture.
  - Polyps.
  - Endometrial hyperplasia and carcinoma: the more serious causes.
- ✓ When we reach perimenopause and postmenopause, AUB becomes more serious and more intense to be investigated. Here, it is more urgent to do endometrial evaluation by D&C to take a biopsy because this is the age where endometrial hyperplasia and carcinoma occurs and we have to catch it early. This does not mean there are no benign causes in this age group, but it becomes more important to rule out hyperplasia and carcinoma.

Now we will discuss these causes in more details:

1) Dysfunctional uterine bleeding (DUB)

One of the causes of AUB is what we call dysfunctional uterine bleeding (you will be asked a lot about the difference between the two terms).

AUB is abnormal bleeding of any type, shape or cause. DUB is abnormal bleeding where there is no organic uterine pathology; endometrium and myometrium are normal (no adenomyosis, no fibroid…). It is caused by hormonal imbalance or an extra-uterine pathology. It is very common.

Causes

Many are due to **anovulation** around menarche and perimenopause because of **hormonal imbalances**. Sometimes we cannot exactly determine the hormonal imbalance. It could be treated by short course of contraceptive pills followed by evaluation.

Less common causes are **pathologies outside the uterus** like:

- Endocrine diseases.
- Ovarian tumors like granulosa cell tumor (GCT) which arises from granulosa/ follicular cells. Most of these tumors are estrogen producing (functional). Estrogen causes endometrial hyperplasia and then endometrial bleeding. Ovaries are examined using ultra sound.
- Polycystic ovary syndrome (PCOS). It is mostly seen in **young** patients.
- Obesity: obese females have more adipose tissue, thus more conversion to active estrogen. More estrogenic on the endometrium → more bleeding
- Malnutrition, chronic diseases and inadequate luteal phase.

In DUB, when take a biopsy (if there is a need) it turns out to be normal which indicated there is no uterine pathology.

2) Proliferative lesions of the endometrium and myometrium

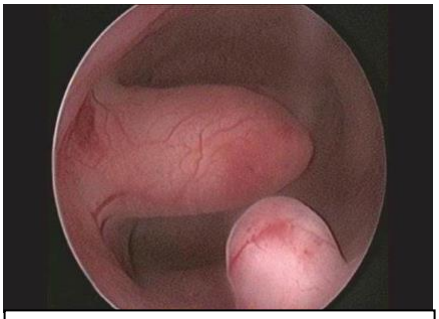
a. Endometrial polyps
b. Leiomyomas “fibroids”
c. Endometrial hyperplasia
d. Endometrial carcinoma

Endometrial hyperplasia and carcinoma are more serious. We should not miss these two and we should diagnose them early. However, all of these (a-d) can cause AUB.

a. Endometrial polyps:

Polyps are a common finding in endometrial curettings. Almost all are benign (99.9%) and they can cause AUB. Very rarely, we find cancer inside these polyps arising from stroma or glands (uterine stromal sarcoma or adenocarcinoma, respectively).
They are most common around menopause (around 52-55 yrs).

00:00-10:00



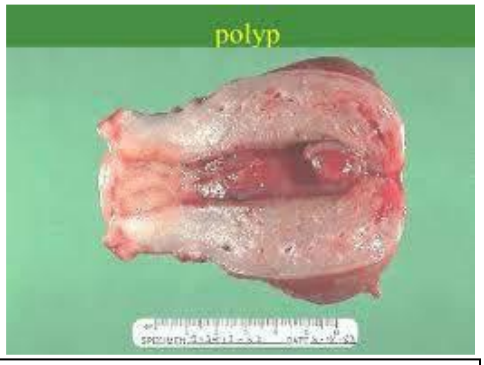
Hysteroscopic picture showing 2 polyps

They are shining and have smooth mucosa.

Microscopic appearance

There are several histological types but they are all benign.

They have smooth lining. They are ovoid in shape and not infiltrative.



This uterus was removed for some reason.

You can see adenomyosis in the myometrium and a large polyp.

b. Leiomyomas (fibroids)

Leiomyoma is a benign smooth muscle tumor of myometrium. Smooth muscles of the myometrium acquire mutations that cause their proliferation. It is a common cause of AUB.

Most common tumor of females, 30-50% of women in reproductive age have fibroids. More common in Blacks (African-Americans).

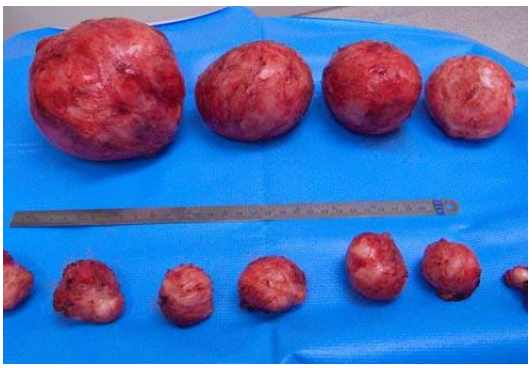
These tumors have chromosomal abnormalities (Ch6 and 12 rearrangements) and MED12 gene mutations.

They are characterized by their ability to grow with estrogens and Oral contraceptive pill and shrink post-menopausally. Most leiomyomas have estrogen receptors. A female who has one fibroid will be found to have 6 or 7 fibroid because of the use of OCP.

Most of them are asymptomatic; many females in reproductive age have asymptomatic leiomyomas. When they are bigger and more in number, they become symptomatic resulting mainly in AUB (mostly **menorrhagia**).

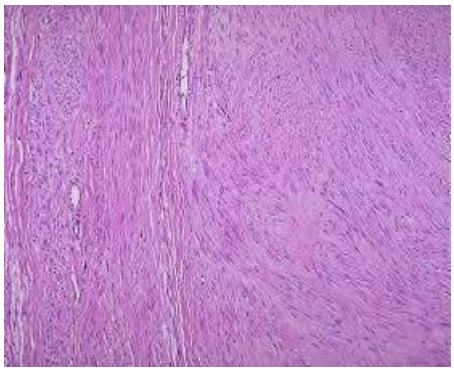
Pathologic Features

Complete hysterectomy because of multiple fibroids
They are benign but when they are abundant they cause bleeding and anemia so they must be removed.
Every mass of those is a leiomyoma (the plural is leiomyomata uteri).
They can be in different places; submucosal, intramural or subserosal.
Because of the multiple fibroids, the uterine cavity is distorted and abnormal.



11 leiomyomas that were removed laparoscopically (they were able to be removed laparoscopically because they were close to the surface).

The characteristic pathologic features: well circumscribed (they are benign and do not infiltrate surrounding tissue) and have shiny and smooth external surface.



Microscopic features:

Smooth muscle neoplasm
There is no increased intra-Leiomyomas hemorrhage or mitoses , No infiltration of the surrounding tissue
I.e.>> no features of malignancy

***Remember*: Leiomyomas are benign tumors and they don't transform to malignancy (i.e.they don't transform into leiomyosarcoma).

If you find a leiomyosarcoma in the uterus (which is rare) it definitely was leiomyosarcoma from the beginning (didn't arise from a leiomyoma).
Leiomyosarcoma has different features: there is infiltration, hemorrhage, necrosis and mitosis.

Side note:

- If the bleeding was because of hypogoagulative state you can easily know; there is bleeding in other places like gums etc.

- In a 35 year old female who has 10 fibroids that are causing anemia, you perform simple hysterectomy (without removing ovaries and tubes) because you don't want to castrate her surgically (early surgical menopause). Menopause is not easy.
If she is already menopausal, you can remove the tubes (to avoid ovarian cancer).

- If the fibroid is small and didn't distorte the uterine cavity, she can get pregnant. Whereas uteri with multiple fibroids are more prone to have abnormal pregnancies (early abortions, ectopic pregnancy, etc).

10:00-23:00

c. Endometrial Hyperplasia

This is an important topic.

Endometrial hyperplasia is defined as increased number of endometrial cells.

Usually, endometrial hyperplasia is due to an excess of estrogen in relation to progestins. Any situation where there is more estrogen than progesterone (whether endogenous or exogenous) there will be endometrial hyperplasia. It is also called ***hyper-proliferative endometrium*** or ***disordered proliferative endometrium with increased estrogenic effect***.

We always like to protect from endometrial hyperplasia by giving opposing progesterone. That's why the most natural contraceptive pills are the combined contraceptive pills.

Causes

- Obesity; because it increases the peripheral conversion of androgen to estrogen .
- Anovulation(no ovulation means persistent presence of estrogen).
- Unopposed estrogen intake.
- Estrogen producing ovarian tumors; such as granulosa cell tumor of the ovary. This excess estrogen will go to the uterus and induce endometrial hyperplasia.

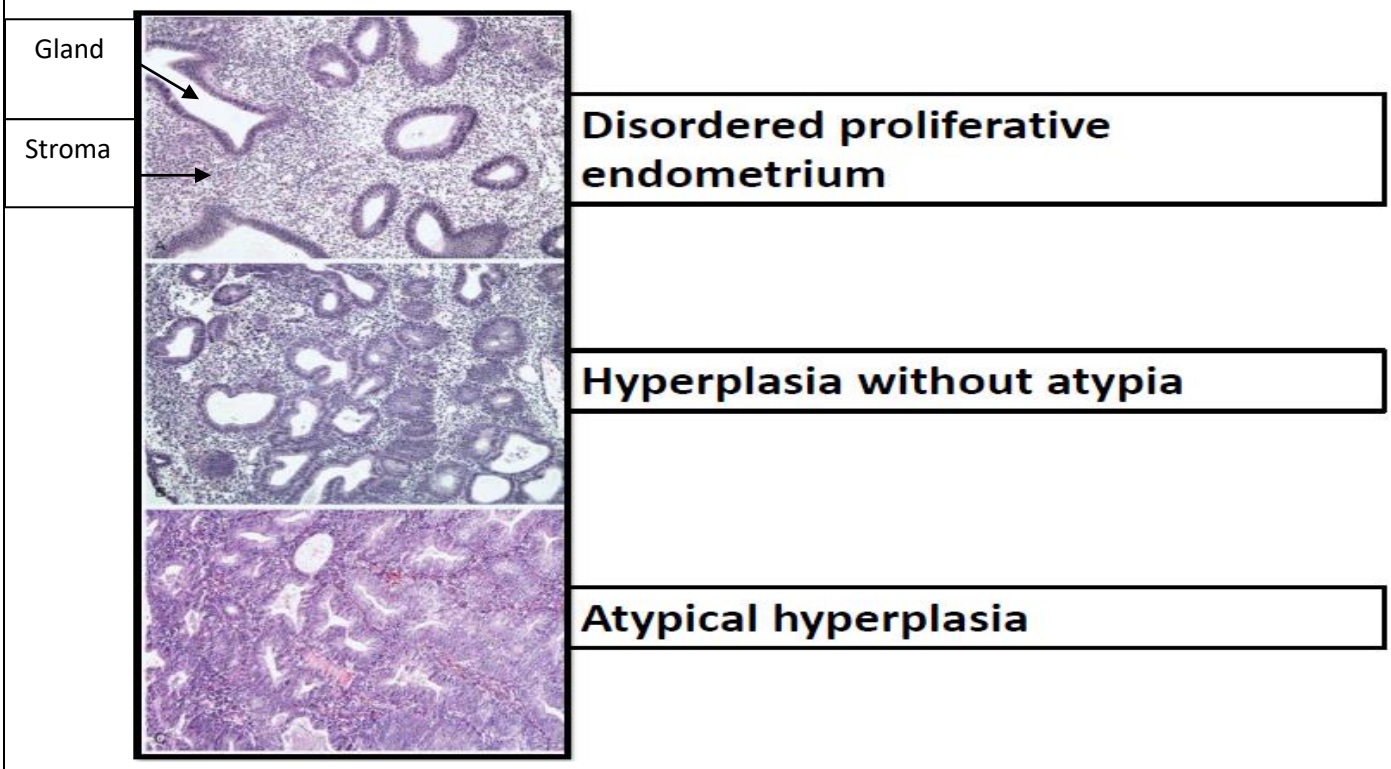
Endometrial hyperplasia can exist as Hyperplasia without atypia or Hyperplasia with atypia (EIN).

• **Hyperplasia without atypia**

- No atypical cellular features
- Less complex, more cystic
- Risk of carcinoma is 1-3%, almost close to normal female
- No PTEN tumor suppressor gene abnormalities; which is commonly associated with the development of **endometrial** carcinoma (especially the **endometriod** carcinoma)

- **Hyperplasia with atypia**
  - Atypical cellular features present
  - More complex glands
  - Risk of carcinoma is 20-50%, and this why we need to catch it before the cancer occur
  - Inactivation of PTEN tumor suppressor gene
  - This is the step which precede the development of the endometroid carcinoma, so when hyperplasia with atypia is discovered, we discuss hysterectomy with the patient.

Under the microscope, if we see glands <u>more than</u> the stroma, then the diagnosis will be disordered proliferative endometriam without evidence of hyperplasia. This is not a danger condition, but we afraid from the progression to the hyperplasia, so we can give the patient progestin 3-6 months, and do evaluation after that.



If this condition wasn't treated, it may progress to hyperplasia without atypia

Hyperplasia without atypia is characterized by the presence of much more glands than the stroma and the glands are more complex than than previous one. Remember that there is 2-3% risk to develop carcinoma, so in this case we allow the patient to choose if she wants hysterectomy or progestin.

If we have hyperplasia with atypia, then this is a very serious condition. Sometimes, we can't distinguish between the complex hyperplasia with atypia from the grade- 1 endometriod carcinoma, so it is a very serious condition, and must be treated aggressively with follow up or hysterectomy.

d. Endometrial carcinoma

It is the **most frequent cancer (malignant)** in FGT, with peak incidence 55-65 years . There are 2 main types:

1) **Endometrioid carcinoma (80%),** those with good prognosis and could be treated by hysterectomy. Histologicaly, it is similar to the normal endometriam (In pathology, **oid** means similar).
2) **Serous carcinoma (15%),** it has a bad prognosis with different pathogenesis of the endometriod type. It doesn't associate with hyper-estrogenic effect .
3) There are others less common: clear cell Ca and MMT (carcinosarcoma)

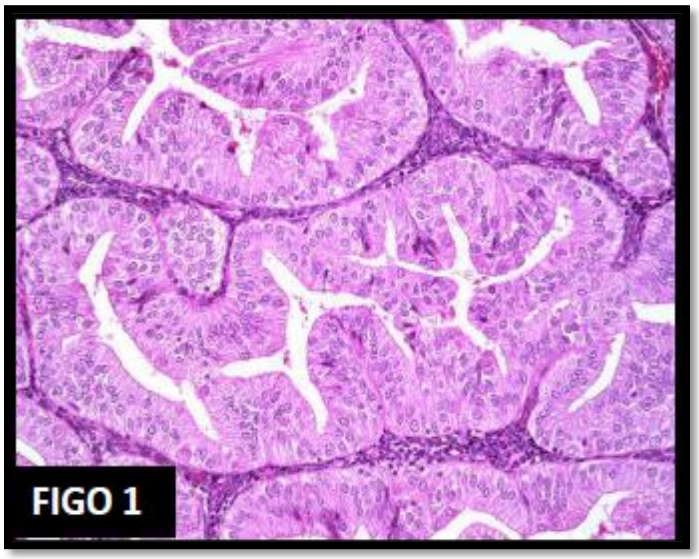
•Endometroid carcinoma

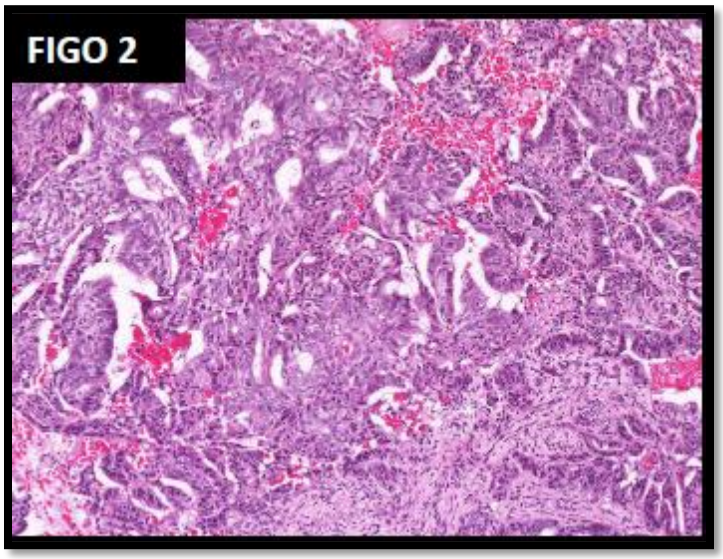
- Histology similar to normal endometrium, thus we call them endometr**oid.**
- Risk factors (important): Obesity, hypertension, DM, infertility, & unopposed estrogen exposure.
- Associated and preceded by atypical hyperplasia**.**
- Mutations:

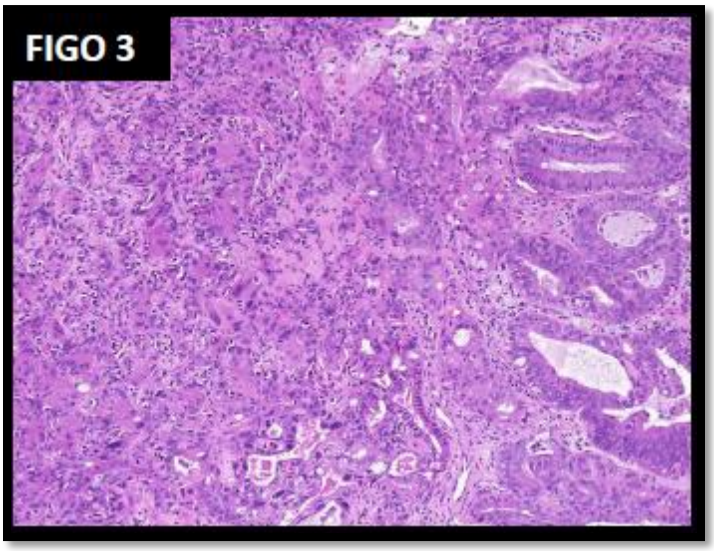
  – Early: mutation in the mismatch DNA repairs genes mainly in Lynch syndrome increasing the risk of endometroid tumors as well as GI tumors. Also, mutation PTEN tumor suppressor gene, mainly in Cowden syndrome is found in the endometroid tumor.

– Late: TP53 mutations, less common and late event. It's very important in diagnosis (we will take about that later on).

- Histologicaly, there is a very high number of glands with little stroma to the extent that the glands lies close to each others, and this by definition grade 1 endometroid carcinoma. If the cells are poorly differentiated with little glands, this is FIGO 3.







FIGO stand for *International Federation of Gynecology and Obstetrics*; which is a system for grading the tumors.

FIGO 1; a well- differentiated tumor

FIGO 3; a poorly-differentiated tumor

Most of the endometroid tumors are FIGO 1 and FIGO 2; so it carries a good prognosis.

If we have FIGO 3 carcinoma, then one of the possibilities that it is a **serous carcinoma**.

- **SEROUS CARCINOMA**

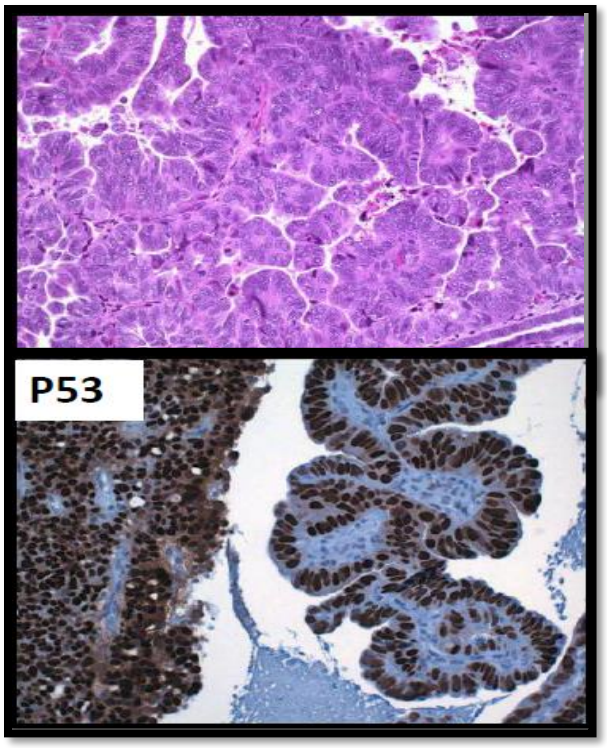
Serous carcinoma is serious (aggressive carcinoma). Not associated with hyperplasia or unopposed estrogen exposure

The main mutation is mutation in the TP53.

Maybe preceded by serous endometrial intraepithelial carcinoma (SIEC) with TP53 mutations.

Morphologically, it is bad with abnormal nucleus and high mitotic figure. So, it is very close to the FIGO 3 endometroid carcinoma and to distinguish between them, we stain the TP53

In the serous carcinoma TP53 mutation is significant and very predominant than in FIGO 3 endometroid carcinoma, so in the serous carcinoma almost all the cells will be stained with brown color (the stain of the TP53)



FIGO staging measures the depth and burden of the tumor. Dr.Mousa focused on stage 1 +2+ 4.

Table 1: 2009 FIGO staging system for carcinoma of the endometrium

Stage I[a]			Tumor contained to the corpus uteri
	IA		No or less than half myometrial invasion
	IB		Invasion equal to or more than half of the myometrium
Stage II			Tumor invades the cervical stroma but does not extend beyond the uterus[b]
Stage III[a]			Local and/or regional spread of tumor[c]
	IIIA		Tumor invades the serosa of the corpus uteri and/or adnexas
	IIIB		Vaginal and/or parametrial involvement
	IIIC		Metastases to pelvis and/or para-aortic lymph nodes
		IIIC1	Positive pelvic nodes
		IIIC2	Positive para-aortic lymph nodes with or without positive pelvic lymph nodes
Stage IV[a]			Tumor invades bladder and/or bowel mucosa and/or distant metastases
	IVA		Tumor invasion of bladder and/or bowel mucosa
	IVB		Disant metastases, including intra-abdominal metastases and or inguinal lymph nodes

FIGO = International Federation of Gynecology and Obstetrics
[a] Includes grades 1, 2, or 3
[b] Endocervical glandular involvement only should be considered as stage I and no longer as stage II.
[c] Positive cytology has to be reported separately without changing the stage.

- **CLINICALLY**
  - Irregular or postmenopausal bleeding
  - Endometrioid carcinoma is slow growing, late progression with no treatment .
  - Early stage after hysterectomy, 5-year survival is >90%
  - Untreated: metastasis to lymph nodes and surrounding structures
  - Serous carcinoma is more aggressive, present with advanced stage and have bad prognosis.

Good luck