Uterine Malignancies

Objectives:

1- Mention the differential diagnosis of postmenopausal bleeding.
2- List the risk factors for endometrial hyperplasia and endometrial cancer.
3- Mention types of endometrial hyperplasia
4- Discuss the diagnosis and management of endometrial hyperplasia
5- Describe the signs and symptoms of endometrial cancer
6- Discuss the diagnostic work up for a patient with postmenopausal bleeding.
7- Describe the staging of endometrial carcinoma
8- Discuss management of endometrial cancer according to the stage.
9- Discuss the prognosis of endometrial carcinoma VS sarcoma

★ **Resources used:**

Doctor's important notes (check the last pages!)
(Lecture not given)
Hacker and Moore Essentials Book

★ **Editing file**

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1- Mention the differential diagnosis of post-menopausal bleeding.

TABLE 41-2

ETIOLOGY OF POSTMENOPAUSAL BLEEDING

Factor	Approximate Percentage
Exogenous estrogens	30
Atrophic endometritis, vaginitis	30
Endometrial cancer	15
Endometrial or cervical polyps	10
Endometrial hyperplasia	5
Miscellaneous (e.g., cervical cancer, uterine sarcoma, urethral caruncle, trauma)	10

2- List the risk factors for endometrial hyperplasia and endometrial cancer.

Endometrial hyperplasia:

- Over abundant growth of the endometrium generally caused by persistent levels of estrogen unopposed by progesterone.
- Hyperplasia is most frequently seen at the extremes of a woman's reproductive years when ovulation is infrequent.

Risk factors:

1. **PCOS:** Unopposed estrogenic stimulation from anovulatory cycles occurs in patients who have polycystic ovarian syndrome (Stein-Leventhal syndrome) and in patients with a late menopause.
2. **Obesity:** results in an increased extraovarian aromatization of androstenedione to estrone. Androstenedione is secreted by the adrenal glands, whereas the increased peripheral conversion occurs predominantly in fat depots, as well as in the liver, kidneys, and skeletal muscles. Granulosa-theca cell tumors of the ovary produce estrogen, and up to 15% of patients with these tumors have an associated endometrial cancer.
3. Any factor that increases exposure to **unopposed estrogen** increases the risk for type I endometrial cancer.
4. Women taking **tamoxifen** for breast cancer have a two- to threefold increased risk of endometrial cancer.
5. About 5% of endometrial cancers occur in women with **Lynch syndrome**, which is also called the hereditary nonpolyposis colon cancer **(HNPCC)** syndrome. This syndrome is caused by germline mutations in the DNA mismatch repair genes. Women with the HNPCC syndrome have about a 40% risk of developing endometrial cancer, usually before the menopause.

3- Mention the types of endometrial hyperplasia.

- There are two categories are:
  - simple hyperplasia
  - complex hyperplasia
- And two subcategories:
  - With atypia
  - Without atypia
- Complex atypical hyperplasia has the greatest malignant potential; about 20-30% of cases progress to endometrial carcinoma, if untreated.

4- Discuss the diagnosis and management of endometrial hyperplasia.

Endometrial hyperplasia should be suspected when women develop intermenstrual bleeding, or when high-risk women develop unexplained heavy or prolonged bleeding. In premenopausal women, endometrial sampling is necessary to obtain a histologic diagnosis, especially for women at high risk of hyperplasia (chronic anovulation, obesity, diabetes mellitus). Office endometrial biopsy is easy to perform, but fractional D&C or hysteroscopically directed biopsy may be needed to rule out carcinoma or other pathology. Postmenopausal women who have bleeding can be evaluated with transvaginal ultrasound and a thin (<4 mm) endometrial stripe is reassuring. Those whose endometrial stripe is thicker should be sampled.

Treatment:

Treatment of simple hyperplasia in reproductive aged women without atypia generally consists of a thorough, coordinated sloughing of the hyperplastic endometrium and therapies directed at preventing recurrence.

Simple hyperplasia without atypia should be treated initially with a progestin, such as 10 days each month for 3 months, then biopsy should be repeated to confirm normalization of the endometrium.

Complex hyperplasia must be evaluated with a fractional D&C and should be initially treated with daily progestin therapy for 3 to 6 months. The levonorgestrel intrauterine system may also be successful in reversing hyperplasia. Test of cure with another biopsy is then needed.

Complex hyperplasia with atypia is best treated by hysterectomy once carcinoma has been excluded. Endometrial ablation is absolutely contraindicated in any of these situations until the endometrium normalizes.

5- Describe the signs and symptoms of endometrial cancer.

Symptoms:
The most common symptom of endometrial cancer is **abnormal vaginal bleeding**, which is present in 90% of patients. Postmenopausal bleeding is always abnormal and must be investigated.

Signs:
A general physical examination may reveal obesity, hypertension, and the stigmata of diabetes mellitus. Evidence of metastatic disease is unusual at initial presentation, but the chest should be examined for any effusion and the abdomen carefully palpated and percussed to exclude ascites, hepatomegaly, or evidence of upper abdominal masses.
On pelvic examination, the external genitalia are usually normal. The vagina and cervix are also usually normal, but they should be inspected and palpated carefully for evidence of involvement. A patulous cervical os or a firm, expanded cervix may indicate extension of disease from the corpus to the cervix.
The uterus may be of normal size or enlarged, depending on the extent of the disease and the presence or absence of other uterine conditions, such as adenomyosis or fibroids.

6- Discuss the diagnostic work up for a patient with postmenopausal bleeding.

Diagnosis:
Any woman who presents with postmenopausal bleeding should undergo transvaginal ultrasonography. If the endometrial thickness is greater than 4 mm, endometrial evaluation is necessary. An outpatient endometrial biopsy is usually feasible with a sampling device such as a Pipelle, GynoSampler, or Vabra aspirator. Outpatient endometrial biopsy has a diagnostic accuracy of about 95%. If the endometrial biopsy reveals endometrial cancer, definitive treatment can be arranged. If the endometrial biopsy is negative for cancer or reveals endometrial hyperplasia, a hysteroscopy and fractional dilation and curettage should be performed with the patient under general anesthesia.

7- Discuss the prognosis of endometrial carcinoma versus sarcoma

Prognosis:
The patient's prognosis is dependent on several variables, including histologic type, grade of tumor, depth of myometrial penetration, status of lymph nodes, and presence or absence of occult adnexal or upper abdominal metastases. Serous and clear cell endometrial carcinomas have a particularly poor prognosis, and both of these histologic types are prone to early dissemination. Five-year survival rates for these tumor types are less than 50%.

Follow-up:
Follow-up examinations should be performed every 3 months for 2 years, then every 6 months for a further 3 years. It is important to take a vault Papanicolaou smear from patients who have not had radiation therapy.

8- Describe the staging of endometrial carcinoma

"You don't have to know the stages" -doctor-

INTERNATIONAL FEDERATION OF GYNECOLOGY AND OBSTETRICS SURGICAL STAGING FOR CARCINOMA OF THE ENDOMETRIUM (2009)	
Stage	**Description**
I*	Tumor confined to the corpus uteri
IA*	No or less than half myometrial invasion
IB*	Invasion equal to or more than half of the myometrium
II*	Tumor invades cervical stroma, but does not extend beyond the uterus†
III*	Local and/or regional spread of the tumor
IIIA*	Tumor invades the serosa of the corpus uteri and/or adnexa‡
IIIB*	Vaginal and/or parametrial involvement‡
IIIC*	Metastases to pelvic and/or paraaortic lymph nodes‡
IIIC1*	Positive pelvic nodes
IIIC2*	Positive paraaortic lymph nodes with or without positive pelvic lymph nodes
IV*	Tumor invades bladder and/or bowel mucosa, and/or distant metastases
IVA*	Tumor invasion of bladder and/or bowel mucosa
IVB*	Distant metastases, including intraabdominal metastases and/or inguinal lymph nodes

9- Discuss management of endometrial cancer according to the stage.

Stage I:

- **Surgery:** Total hysterectomy and bilateral salpingo-oophorectomy are performed on all patients, unless there are absolute medical contraindications .
- **Radiation Therapy:** with the advent of surgical staging, less reliance has been placed on adjuvant radiation therapy in the management of patients with endometrial cancer.
- **Hormone Therapy:** High-dose medroxyprogesterone acetate (200 mg twice daily) for 3 to 6 months will reverse the changes in about 75% of patients, but recurrences are common, so careful monitoring is essential.

Stage II:

If the cervix is grossly normal and involvement is detected only on the histologic evaluation of the endocervical curettage material (occult stage II disease), treatment may be the same as that for stage I disease (i.e., total hysterectomy, bilateral salpingo-oophorectomy, surgical staging, and tailored postoperative radiotherapy).

Alternatively, regardless of the size of the cervix, primary radical hysterectomy, bilateral salpingo-oophorectomy, together with pelvic and paraaortic lymphadenectomy, may be performed.

Advanced stage: For advanced disease, treatment is individualized. The uterus, tubes, and ovaries should be removed, if possible, for palliation of bleeding and other pelvic symptoms.

Important notes!

Important notes taken during the 2 lectures (The doctor repeated some points more than once, the following notes cover most of them if not all)

Leiomyoma (Fibroids) notes:

- 2 out of 1000 (i.e. 0.2%) of leiomyomas progress to malignancy.
- Leiomyoma symptoms depend on the size and location of the tumor.
- The least problematic site is the **subserosal**.
- The most problematic is the **submucosal.**
- Smoking is a risk factor → hyperestrogenic status.
- Menorrhagia is when blood loss is > 80 cc.
- We do NOT operate during pregnancies unless seriously required.
- Most serious fibroid degeneration is the **sarcomatous**.
- Management of Fibroids: usually nothing is done (managed conservatively) but if we need medical intervention, GnRH agonists are given.
- Embolization management may cause ovarian failure.
- Embolization is a good option for elderly and a bad option for young females.
- Definitive cure is: hysterectomy.
- **MCQ:** Most common fibroid degeneration is the **hyaline**!!!

Uterine cancer notes:

- Mostly postmenopausal
- Risk factors related → factors that increase estrogen
- Obesity is a risk factor because fat aromatizes androgens to estrogens
- Fibrothecoma, granulosa cell tumors → secrete estrogen
- Tamoxifen, a selective estrogen receptor modulator (SERM), works as an antiestrogen in breast tissue but has estrogenic activity in the endometrium and can cause uterine malignancies.
- Treatment of uterine malignancies is:
  - Bringing back the balance of estrogen and progesterone, regular cycle
  - Reducing estrogen
- OCPs do NOT have any relation with breast and protect against ovarian, uterine cancer (don't ask, I found this in my written notes, I'm also confused but I think it's related to the following points about combined OCPs and hormonal replacement therapy)
- A female's risk of uterine cancer is 2-3%
- Tamoxifen adds 2.2% additional risk
- Continuous combined oral contraceptive use → decrease the risk (protective)
- Hormone replacement therapy → increases risk of breast cancer
- Breast cancer risk in females is 13%
- In complex endometrial hyperplasia with atypia, 30% progress to carcinoma
- Complex endometrial hyperplasia with atypia is treated by hysterectomy

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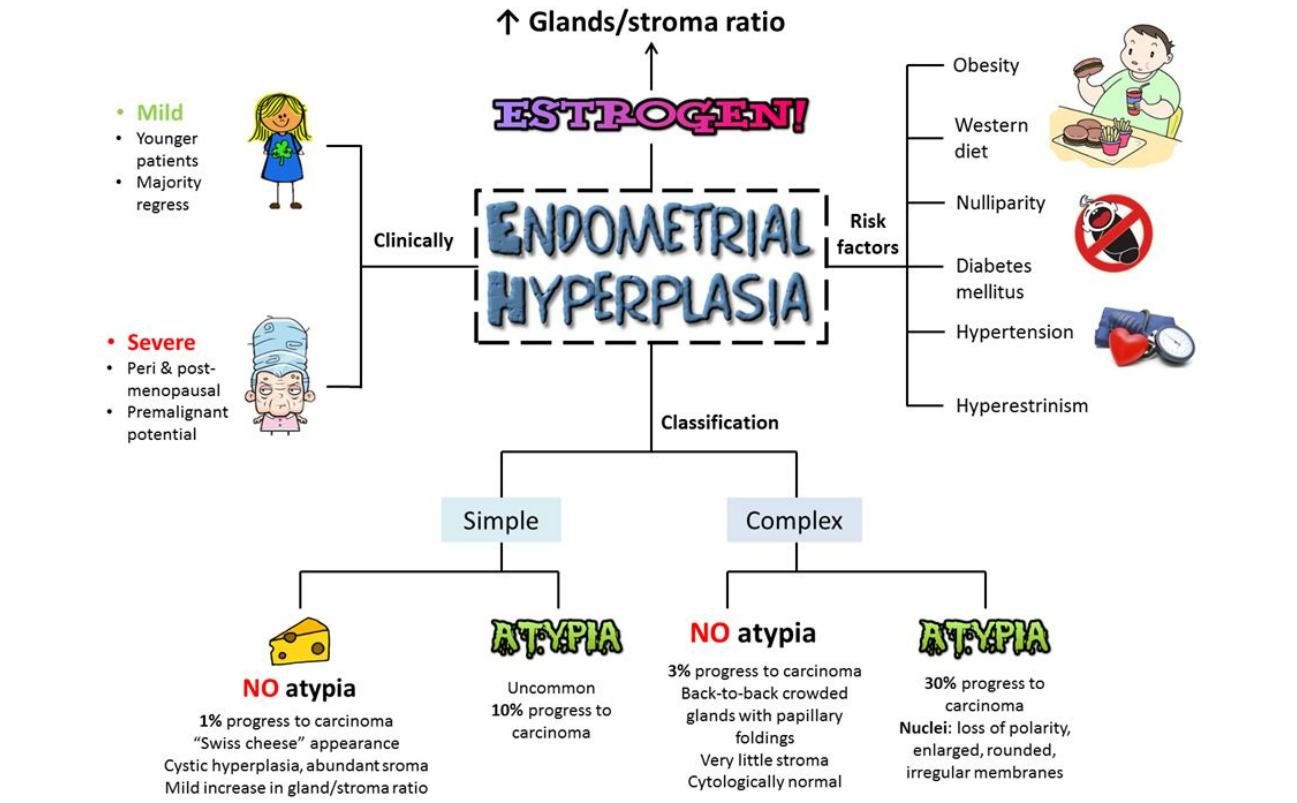
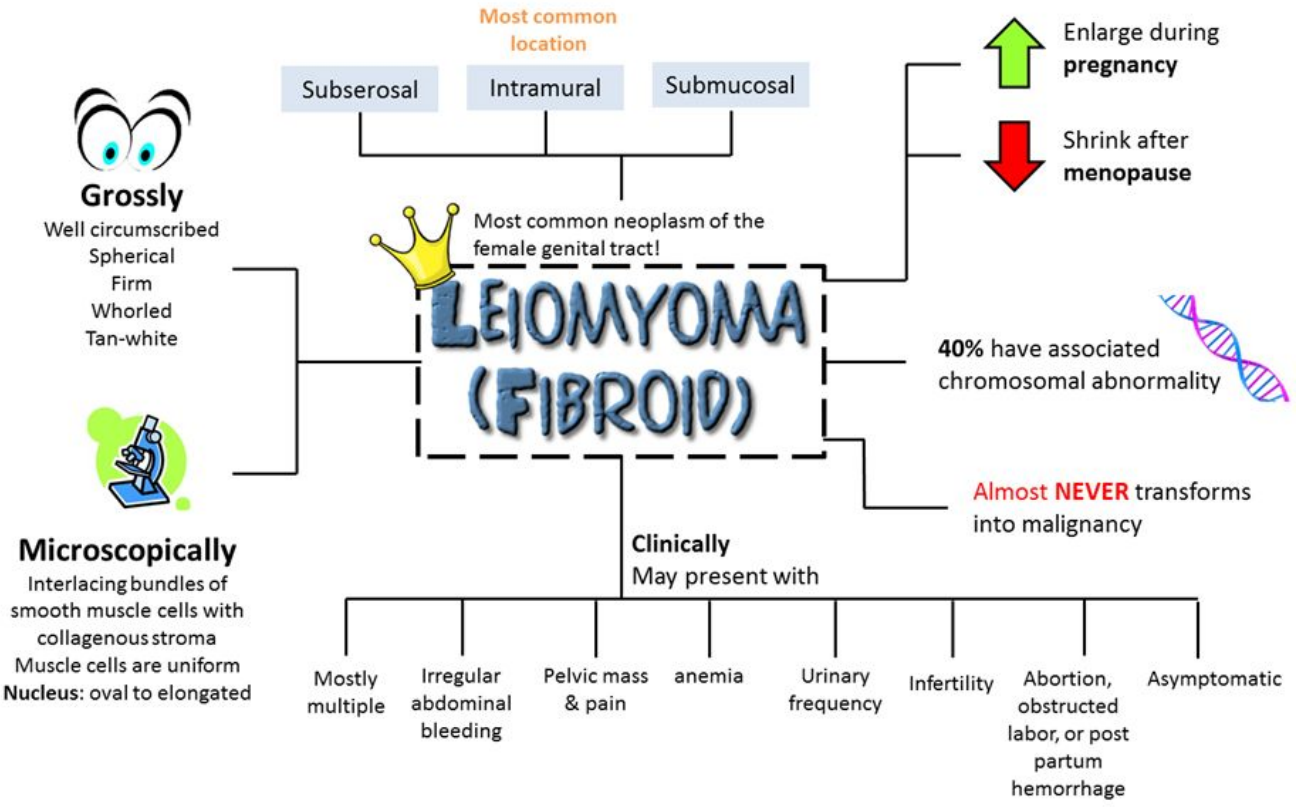
Uterine cancer notes (cont.):

- Postmenopausal bleeding is an important topic!
- Risk of cancer is 15-20% (in postmenopausal bleeding I think)
- Most common cause of postmenopausal bleeding is NOT cancer, it's vaginal or endometrial **atrophy**!
- Most important diagnosis to rule out in postmenopausal bleeding is endometrial carcinoma
- Basic workup:
    a. Pap smear
    b. Endometrial biopsy → cut off is 4 mm endometrial thickness
- Good type: related to estrogen and accounts for 90% of cases
- Bad type: not related to estrogen and accounts for 10%
- "No need to know the stages" -Doctor-
- Mainstay is surgical
- Recurrence is highest in 2 years, so follow up every 3 months then every 6 months then annually
- Early recurrence is in upper vagina
- Endometrial biopsy if the patient is symptomatic

Summary:


↑ Glands/stroma ratio
ESTROGEN!
ENDOMETRIAL HYPERPLASIA
Clinically
• Mild
• Younger patients
• Majority regress
• Severe
• Peri & post-menopausal
• Premalignant potential
Risk factors
Obesity
Western diet
Nulliparity
Diabetes mellitus
Hypertension
Hyperestrinism
Classification
Simple
Complex
NO atypia
1% progress to carcinoma
"Swiss cheese" appearance
Cystic hyperplasia, abundant sroma
Mild increase in gland/stroma ratio
ATYPIA
Uncommon
10% progress to carcinoma
NO atypia
3% progress to carcinoma
Back-to-back crowded glands with papillary foldings
Very little stroma
Cytologically normal
ATYPIA
30% progress to carcinoma
Nuclei: loss of polarity, enlarged, rounded, irregular membranes


Most common location
Subserosal
Intramural
Submucosal
Enlarge during pregnancy
Shrink after menopause
Most common neoplasm of the female genital tract!
LEIOMYOMA (FIBROID)
Grossly
Well circumscribed
Spherical
Firm
Whorled
Tan-white
40% have associated chromosomal abnormality
Almost NEVER transforms into malignancy
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