Reviewed By
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Fibroid & Uterine Malignancy

Objectives:

- → Mention the differential diagnosis of post-menopausal bleeding.
- → List the risk factors for endometrial hyperplasia and endometrial cancer.
- → Mention types of endometrial hyperplasia.
- → Discuss diagnosis and management of endometrial hyperplasia.
- → Describe the signs and symptoms of endometrial cancers.
- → Discuss the diagnostic work up for a patient with postmenopausal bleeding.
- → Describe the staging of endometrial carcinoma.
- → Discuss management of endometrial cancer according to stage.
- → Discuss the prognosis of endometrial carcinoma versus sarcoma.

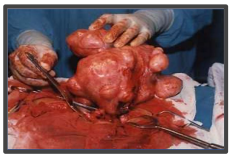
- → Slides
- → **Important**
- → **Golden notes**
- → Extra
- → **Doctor's notes**
- → **Previous Doctor's notes**
- → **Reference**

Kaplan Video

Editing File

Uterine Fibroids

Introduction:



→ **Uterine Fibroids (leiomyomas or leiomyomata):** benign monoclonal tumors arising from the smooth muscle cells of the myometrium.
→ The **most common pelvic tumor** in women.
→ **Contents:** extracellular matrix (collagen - proteoglycan - fibronectin).
→ **Surrounded by:** thin pseudocapsule of areolar tissue + compressed muscle fibers.

Pathogenesis: *still not that clear*

Components Contribute to Leiomyoma Development:
→ Transformation of normal myocytes into abnormal myocytes.
→ Growth of abnormal myocytes into clinically apparent tumors.

Genetics[1]:
→ **Somatic mutations:**
  → **Mediator complex subunit 12 (MED12):** most common group.
  → High mobility group AT-hook (HMGA2 and HMGA1).
  → Collagen type IV alpha-5 (COL4A5).
  → Collagen type IV alpha-6 (COL4A6).
→ **Inherited mutations:**
  → **Fumarate hydratase gene (FH):** a risk of hereditary cutaneous and uterine leiomyomatosis and papillary renal cell carcinoma syndrome (**HLRCC**).
    → Rare autosomal dominant.
    → ↑ uterine sarcoma risk.

Steroid Hormones:
→ **Fibroid are estrogen dependent:**
  → **Child bearing age:** ↑ estrogen hormone = ↑ fibroids size.
  → **Around the age of menopause:** ↓ estrogen hormone = ↓ fibroids size.
→ **Receptor upregulation of:** aromatase - estrogen - progesterone.
→ Potential role of gonadotropins.
→ ↑ type 1 isotype of 17-beta hydroxysteroid dehydrogenase.

Stem Cells:
→ Key role in fibroid pathogenesis.

Uterine Vascular Abnormalities:
→ ↑ arterioles and venules.
→ Venular dilation
→ Angiogenic growth factors (fibroblast growth factor-2).

Hypoxia:
→ Injury during menstruation → myometrial cells hypoxia → ↑ transformation of normal myocytes to abnormal myocytes → leiomyomas.

Vitamin D:
→ Vitamin D deficiency and uterine fibroids may be mediated in part by the effect of vitamin D on the transforming growth factor-beta pathways.

1. Which is why it's seen in young patient even before having babies.

Uterine Fibroids

Clinical Features:

→ Most women with fibroids (50%-65%) have no clinical symptoms → discovered incidentally.
→ **Symptoms vary depending on tumor:** number - size - location.

Symptoms:

→ **Assess:** duration - severity - impact on quality of life.
→ Ethier pressure symptoms or bleeding.

Heavy / prolonged menses (menorrhagia):
→ Lead to iron deficiency anemia (**Hb:** 4 - 5 g/dl).
→ Most common, especially in **sub-mucosal**.
→ Blood loss is assessed with 5 questions (based on normal):
1. Change pads at ≥ 3 hours.
2. < 21 pads per cycle.
3. Rarely change at night.
4. Clots < 1 inch.
5. Not anemic.

Pelvic Pressure Symptoms:
→ **Urinary tract obstruction (anterior fibroid):** frequency - difficulty emptying - complete urinary obstruction - hydronephrosis - renal failure **(**lateral fibroid**)**
→ **Bowel obstruction (posterior fibroid):** constipation.
→ **Venous compression:** thromboembolism.

Pain:
→ Least common symptom
→ Noncyclic, intermittent, dull and gradual onset.
→ Degeneration or torsion → acute pain.
→ **Assess:** location - severity - characteristics.

Infertility or Obstetric Complications:
→ Depends on size & location.
→ Submucosal or intramural with an intra-cavitary component → miscarriage - placental abruption[1] - fetal growth restriction[2] - malpresentation - preterm labor[3].
→ Subserosal → far to the outside → don't affect fertility unlike submucosal (unless huge → compress cavity).
→ 1 - 2% of infertility cases are related to fibroids.
→ **Dysmenorrhea:** pain during menstrual period.
→ **Dyspareunia:** pain during sexual intercourse in anterior fibroids & fundal.
→ **Degeneration:** carneous or red degeneration.
→ Pregnancy → fibroid enlarges → hypoxic & necrotic center → cytokines (IL + TNF) → pain (red degeneration).
→ **Treatment:** analgesia, surgical intervention are contraindicated in pregnancy.
→ Torsion.
→ Prolapsed fibroid.
→ Endocrine effects → secrete ectopic hormones:
→ Erythropoietin → polycythemia.
→ Parathyroid hormone → hypercalcemia + hyperprolactinemia.

1. The wall has no healthy tissue.
2. With huge fibroid.
3. If the fibroid occupies the lower segment of the uterus.

Uterine Fibroids

Risk Factors:

- → ↑ with age during reproductive years.
- → **Black:** more common due to ↓ vitamin D.
- → Hypertension.
- → **History of uterine fibroids:** 50% reoccur.
- → **Nulliparous:** no exposure to pregnancy progesterone levels.
  - → Progesterone shrinks fibroids.
  - → Estrogen grow fibroids (*estrogen dependent*).
- → Early menarche & late menopause → ↑ estrogen exposure.
- → Early exposure to OCPs (13 - 16 years old):
  - → Diethylstilbestrol.
  - → Clomiphene.
  - → Plastic bottles (phthalates - polychlorinated biphenyl - bisphenol).
- → ↑ BMI.
- → **Diet:** red meats - ↑ dietary glycemic index product.
- → Alcohol → liver damage → ↓ SBG → ↑ free estrogen → fibroid stimulation.
- → Family history.

Protective Factors:

- → **Type 2 diabetes:** a risk factor for endometrial cancer.
- → Low physical activity.
- → **Smoking:** degrade estrogen rapidly → heavy smokers age quickly.
- → **Progesterone modulator ulipristal acetate:** emergency OCP, still under investigation.
- → **Long-acting progestin-only contraceptives (depot medroxyprogesterone - merina):** protect against development of leiomyomas + inhibit postpartum fibroid regression.

Physical Examination:

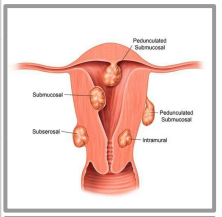
- → General examination.
- → **AbdomenoPelvic Examination:** abdominal examination or bimanual pelvic examination.
  - → Palpated on (if large).
  - → Nontender irregularly enlarged uterus with lumpy-bumpy or cobblestone protrusions that feel firm or solid on palpation.
- → The size of the myomatous uterus is described in menstrual weeks as pregnancy.

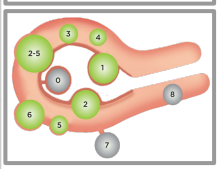
Uterine Fibroids

Classification: *FIGO*[1]

→ Classification helps with management planning.

Submucous	**0**	**Pedunculated intracavity**
	1	**< 50% intramural**
	2	**≥ 50% intramural**
Others	**3**	**100% intramural** **Contact endometrium**
	4	**Intramural:** *not even at the endometrium border*
	5	**Subserous** **≥ 50% intramural**
	6	**Subserous** **< 50% intramural**
	7	**Subserous pediculated**
	8	**Other (cervical - parasitic):** *not related to muscle at all*





Subserosal
Outside uterus (*towards the peritoneum / abdomen*)

→ Located beneath the uterine serosa.
→ Grow → distort uterine external contour → firm, non-tender asymmetry.
→ **Depending on location:** put pressure on bladder, rectum, or ureters.
→ **If pedunculated:** if it becomes parasitic → broken stalk → stalk float around in abdomen & attach to mesentery → get blood supply.

Intramural
Inside the uterine wall

→ Located within the uterus wall (most common).
→ Small → usually asymptomatic + cannot be felt on examination.
→ Enlarged → uterine external contour is altered → symptomatic & felt.

Submucosal
In the lining of the uterus *(inside the organ itself)*

→ Located beneath the endometrium.
→ Can distort the uterine cavity.
→ Distorted overlying endometrium → inappropriate response to normal hormonal fluctuations → unpredictable intermenstrual bleeding.
→ **Most common symptom:** abnormal vaginal bleeding → anemia.

Pedunculated

→ Subserosal or submucosal with a big peduncle (stalk).
→ Excised easily by cutting the pedicle.

Parasitic
Originates in the uterus but found in another location or organ "*no peduncle*"

→ Break away from uterus.
→ Blood supply from another abdominal organ (omentum - mesentery).
→ Size changes depend on the reproductive life stage of the woman.
  → Slow growth.
  → **Rapid growth:** ↑ estrogen receptors in leiomyomas → rapid enlargement during in high estrogen levels (pregnancy).

1. Patients can have multiple fibroids with different locations and that depends on some risk factors including: ethnicity (African American have higher number of fibroids and bigger in size) as well as the age (size & number increase with age, within reproductive age and then decrease after menopause).

Uterine Fibroids

Diagnostic Evaluation:

→ Exclude pregnancy.
→ Exclude submucosal fibroids.
→ Exclude adenomiosis.
→ Exclude benign or malignant uterine neoplasms.

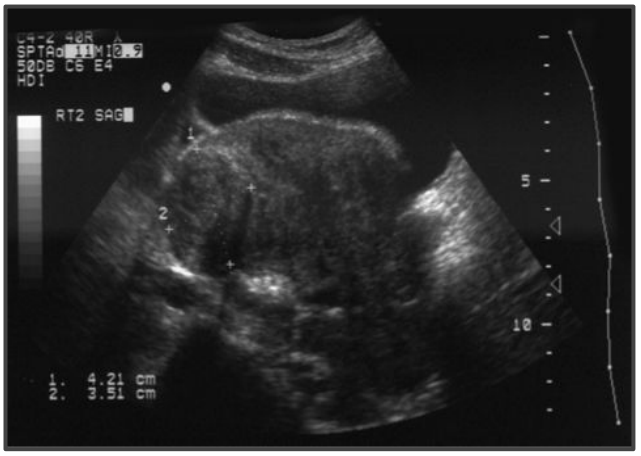
→ **Determine:** number - location - volume.
→ Alarming signs.
→ Hydronephrosis?

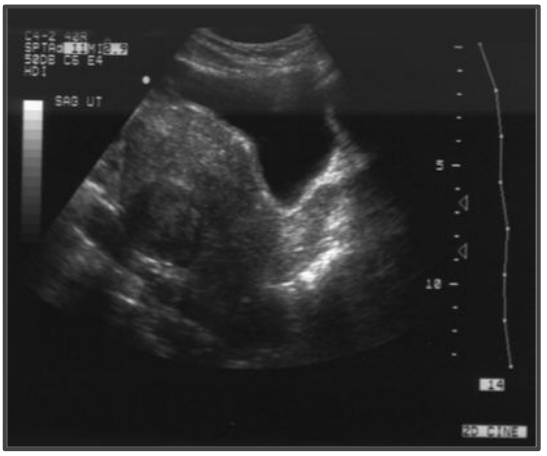
Differential Diagnosis:

→ **Main sarcoma[1] that may resemble a leiomyoma:** leiomyosarcoma (very aggressive).
  → **Risk factors:**
    → Postmenopausal status.
    → Black race.
    → Tamoxifen.
    → Pelvic radiation.
    → Hereditary leiomyomatosis.
    → Renal cell carcinoma.

Diagnosis:

→ **Pelvic ultrasound (test of choice / gold standard):** areas of **hypoechogenicity**.
→ Hysterosalpingography **(HSG):** saline infusion sonogram and hysteroscopy.
  → **Additional tools for:** location - size - submucosal fibroid - distinguishing fibroids from polyps.
  → Stopped period after surgery → perform HSG to diagnose asherman syndrome.
    → **Asherman syndrome:** intrauterine adhesions preventing endometrial shedding.
→ **MRI:** distinguishing fibroids from adenomyosis - surgical planning - location.
  → Best imaging modality for leiomyosarcoma showing sarcomatous changes.





Prognosis:

→ Fibroids are benign tumors and the risk of transforming to malignancy is very low.
→ **Malignant transformation sign:** RAPID ↑ size from small regular to irregular with calcifications.

1. It's not clear who may develop sacome but there is signs, e.g. MRI findings (sarcomatous changes: irregular border, heterogeneous), rapidly enlarging tumor, and growing tumor after menopause.

Uterine Fibroids

Management:

→ **The type and timing of any intervention should be individualized, based upon:**
- → Type and severity of symptoms.
- → **Size of the myoma(s):** 3 cm vs 30 cm.
- → **Location of the myoma(s):** subserosal - submucosal - intramural.
- → **Patient age:** in postmenopausal we push for hysterectomy.
  - → Old patient → wait till menopause → regress.
    - → **After menopause or GnRH agonist use (↓ FSH → ↓ estrogen):** ↓ estrogen levels & estrogen receptors are no longer stimulated → ↓ leiomyomas size.
  - → Young patient → surgery is the mainstay of treatment.
- → Reproductive plans.
- → Obstetrical history.

A. Expectant Management:

→ Most cases of uterine fibroids grow slowly and **don't require treatment**.
- → Annual pelvic exam (to check the size) + CBC (to check for anemia) for follow up.
- → Actively growing → follow up every 6 months to monitor the size and growth.
  - → 7 - 40% of fibroids regress over 6 months to 3 years.

B. Medical Therapy:

→ Generally has limited help, it fails most of the time.
→ Used to treat the symptoms not the disease , it can shrink but never completely resolve.

Nonhormonal Treatment	Hormonal Treatment

→ For pain and bleeding.
→ NSAID.
→ **Antifibrinolytics:** tranexamic acid.
  → ↓ bleeding.
  → Used temporary till the surgery.
	→ Combined OCPs.
	→ **Progestins:** medroxyprogesterone acetate - mirena IUD - norethindrone acetate.
	→ **Progesterone receptor modulators (PRMs):** mifepristone - ulipristal acetate → liver toxicity.
	  → Prevention of growth & symptoms by intermittent use of ulipristal acetate is under investigation, shows promise as a medical therapy for fibroids.
	→ **Androgenic steroids:** danazol - gestrinone.
	  → Frequent menopausal side effects → not used for more than 6 months.
	  → **Gestrinone:** ↓ myoma volume + ↑ amenorrhea in women with leiomyomas.
	  → **Advantage:** carry-over effect after it is discontinued.
	→ **GnRH agonists:** nafarelin acetate - leuprolide acetate - depot - goserelin acetate.
	  → Approved for administration for 3 - 6 months prior to leiomyoma-related surgery in conjunction with iron supplementation → facilitate procedure + anemia correction.
	  → **New generation of oral GnRH antagonists:** more acceptable, effective & well tolerated.
	→ **Aromatase inhibitors:** letrozole.
	→ **GnRH antagonists (elagolix):** commonly added with OCPs → rapid onset without flare-up.

Uterine Fibroids

Management:

C. Surgical Management:

→ **Mainstay therapy** for leiomyomas.

→ **Indications:**

→ Abnormal uterine bleeding.

→ Bulk-related symptoms.

→ Infertility.

→ Recurrent pregnancy loss.

→ Presurgical GnRH for 3 - 6 months → shrinkage up to 70% of its size (regrowth happen after stopping treatment).

Hysterectomy *Gold standard*	→ **Definitive treatment** for myomas along with removal of fallopian tubes (most common area for ovarian cancer). → Most utilized procedure (70% of all fibroid procedures). → **Method:** → Small myomas → vaginal and laparoscopic. → Large or multiple myomas → abdominal. → **Indications:** 1. Acute hemorrhage + do not respond to other therapies. 2. Completed childbearing + current or ↑ future risk of (CIN - endometriosis - adenomyosis - endometrial hyperplasia - uterine cancer - ovarian cancer). 3. Failed prior minimally invasive therapy for leiomyomas. 4. Completed childbearing + significant symptoms - multiple leiomyomas - desire for a definitive end to symptomatology.
Myomectomy *Best option for women desire fertility*	→ Most commonly practiced. → **Indications:** symptomatic fibroids & wish to preserve fertility. → **Method:** → Hysteroscopically. → Laparoscopically with and without robotic assistance. → Laparotomy. → **Fibroids recurrence:** > 60% of patients in 5 years (recurrence can happen). → **Complications:** adhesions frequently form → pain & infertility.
Endometrial Ablation	→ With or without hysteroscopic myomectomy. → **Purpose:** stop bleeding for a while, 2 - 3 weeks before surgery. → **Indications:** → Completed childbearing. → Bleeding abnormalities (submucosal). → **NO** bulk or pressure symptoms. → **Types:** → **Microwave ablation:** < 3 cm. → **Rollerball ablation:** > 3 cm.

Uterine Fibroids

Management:

Myolysis	→ **Method:** → Laparoscopic thermal. → Radiofrequency. → Cryoablation (cryomyolysis) of leiomyoma tissue. → Easier to master than myomectomy (requires suturing). → Localized tissue destruction without repair → ↑ subsequent adhesion adhesions or rupture during pregnancy.
Uterine Artery Occlusion	→ **Method:** → Laparoscopy. → Vaginally-placed clamp. → UAE is preferable to laparoscopic uterine artery occlusion.
Uterine Artery Embolization	→ **Fibroid shrinkage:** 50 - 80%. → Minimally invasive option for preserving uterus and no future fertility. → **Advantages**: → ↓ hospital stay. → ↓ pain. → ↑ return to work. → **NO** anesthesia required. → **Disadvantages:** → Complications. → Unscheduled visits. → Readmissions. → ↑ reintervention risk. → Failure risk. → Studies suggest laparoscopic myomectomy rather than embolization. → Not advisable in young patients. → Poking the uterine artery → compromised ovaries blood supply → ovarian failure (irreversible). → **Uterus blood supply:** uterine artery (70%) + ovarian artery (30%). → **Ovarian blood supply:** ovarian artery (mainly) + ascending branches of uterine artery (some). → **Good for:** → 45 years old patients. → P6 patient. → Patient with anesthesia reaction (because it is a local procedure).
Magnetic Resonance Guided Focused Ultrasound Surgery (MRgFUS)	→ **Indications:** premenopausal women who have completed childbearing. → More recent option for the treatment of uterine leiomyomas. → Noninvasive thermoablative technique converges multiple waves of ultrasound energy on a small volume of tissue → thermal destruction. → Can be performed as an **outpatient procedure**. → **Consider:** → **Size:** ≤ 10 cm is accepted. → **Number:** ≤ 4 is accepted. → Vascularity. → Access. → **Not indicated for:** → Leiomyomas resectable with a hysteroscope. → Heavily calcified, severe adenomyosis. → 5 ≥ fibroids. → Non enhancement with gadolinium. → Symptomatic improvement in 3 months.

Uterine Fibroids

Prolapsed Fibroids:

Symptoms:

- → Vaginal bleeding.
- → Watery vaginal discharge.
- → **Pelvic pain / contractions / cramping:** significant during the cervical fibroid expulsion process.
- → Vaginal pressure.
- → Extensive + no clear pedicle lesion → consider uterine sarcoma

Examination:

- → **Speculum examination:** firm consistency.

Imaging:

- → **Ultrasound:** size + location.
- → **MRI without contrast:** size + location.

Pathology:

- → Presentation consistent with benign lesions (polyp - fibroid) → removed entirely.
- → Presentation **not** consistent with benign lesions (polyp - fibroid) → take biopsy.

Differentials:

- → Cervical polyp (common).
- → Prolapsed endometrial polyp.
- → Prolapsed uterine sarcoma.
- → Polypoid form of uterine adenomyosis.

Management:

Vaginal Myomectomy:

- → **Location:** office (mainly).
- → With paracervical block.
- → Symptomatic → relief symptoms.
- → Asymptomatic → pathological diagnosis + 🚫symptoms & infections.
- → **Contraindications**:
  - → Anesthesia complications.
  - → Bleeding diathesis.
  - → Anticoagulants use.
- → **In OR if:**
  - → > 4 cm.
  - → Pedicle cannot be visualized or palpated.
  - → Broad-based (pedicle > 2 cm).
  - → Not pedunculated cervical fibroid.
- → **Complications:**
  - → **Excessive bleeding:** pressure (*uterine pack - ballon - suture*).
    - → Bleeding persists → hysteroscopy.
  - → **Recurrence:** infrequent.
  - → Vaginal spotting.
  - → **Cramping:** acetaminophen - NSAIDs.
  - → **Advise patient to watch:** fever - purulent vaginal discharge - bleeding > 2 weeks - profuse.

Uterine Fibroids

Prolapsed Fibroids:

Excision in pregnancy:

- → **Indications:**
  - → Excessive bleeding.
  - → Infection.
  - → Pain.
  - → Urinary retention.

Management:

Obstruction of labor (occured or predicted):

- → Cesarean section.
- → Fibroid can be removed at a later time.

Antibiotic Prophylaxis:

- → **Indications:**
  - → Necrotic.
  - → Obviously infected.
  - → Intermittent pneumatic compression device (thromboprophylaxis).

Fibroids' Degeneration:

- → Rare.
- → Happens when fibroids are not treated → ↑ size → lack of blood supply → degeneration.
- → Times of rapid growth → myomas outgrow their blood supply → fibroid ischemic degeneration.
- → Most common during pregnancy.
- → **Types:**
  - → Hyaline degeneration.
  - → Myxomatous degeneration.
  - → **Calcific degeneration:** starting sarcoma (bad sign) → remove it.
  - → **Red (carneous) degeneration:** important for MCQs
  - → Happens in **pregnancy**.
  - → **Symptoms:** extreme, acute pain → hospitalization and narcotics.
  - → ↑ size → central necrosis → more **pain**.
  - → **Treatment in pregnancy:**
    - → **Analgesia** + wait until it regresses and excise it.
    - → Myomectomy is contraindicated (high vascularity → potential bleeding).
  - → Fatty degeneration.
  - → Cystic degeneration.
  - → Necrosis.

Fibroids in Pregnancy:

- → **Size:** ⅓ ↑ in size - ⅓ stay the same size - ⅓ ↓ in size.
- → **Can cause:**
  - → Obstruction of labour, especially if it is in the lower uterine segment on the cervix.
  - → ↑ abdominal pain.
  - → Cause abnormal fetal presentation
- → Should not be removed.
- → Undergo red degeneration.

Endometrial Cancer

Introduction:

→ **Fourth** most common cancer after breast, lung, and colorectal cancer.
→ **Most common gynecological cancer** followed by ovarian, cervical and valvular.
→ **Lifetime risk of developing uterine cancer:** 2.6 %.
→ **Average age of uterine cancer diagnosis in the US:** 61 years old (postmenopausal > premenopausal).
→ 80% of cases consist of endometrioid histology (most cases).
→ 20% of cases consist of non-endometrioid.
→ Usually has a good prognosis (fortunately, 90% of the patient presenting in stage 1).
→ **Classic symptom (90%): abnormal uterine bleeding**.

Clinicopathological Subtypes:

Type 1

→ Most common.
→ E_2 dependent.
→ **Histologic subtypes:**
  → Grade 1 endometrioid.
  → Grade 2 endometrioid.
→ **Average age:** 63 years old.
→ 73% confined to the uterus → better prognosis.
→ **Presentation:** postmenopausal women with uterine bleeding

Type 2

→ Non E_2 dependent → unknown risk factors.
→ **Histologic subtypes:**
  → Sero pap.
  → Ccc.
  → Carcinosarcoma.
  → Grade 3 endometrioid.
→ **Average age:** 67 years old.
→ 50% of patients present with metastasis (more aggressive than Type 1).
→ **Presentation:** 45 year old, not diabetic, hypertensive, or obese, presenting with uterine bleeding

Risk Factors:

01 **Unopposed estrogen** Type 1 mostly
02 **Postmenopausal** ***Median diagnosis age:*** *61.*
03 **Nulliparity**
04 **Early menarche - Late menopause**
05 **Obesity - Diabetes - HTN** Adipose tissue rich in estrogen → endometrial thickening
06 **Tamoxifen**

Endometrial Cancer

Tamoxifen:

→ Potent antiestrogenic agent (selective estrogen receptor modulator), compete with estrogen for binding sites in breast and other tissues, but not in the uterus (agonist in the uterus).
→ **Risk of endometrial cancer:** ↑ by 2 - 3 folds.
→ **Changes are:**
  → Cystic glandular dilatation.
  → Stromal edema.
  → Myometrial hyperplasia and edema.
→ Thick endometrium alone is not indication to evaluate the endometrium.

Hyperplasia:

→ Proliferation of endometrial glands → ↑ gland-to-stroma ratio.
→ Glandular pattern can be either simple or complex with or without nuclear atypia (*% = endometrial cancer risk of in 5 years*).
  → Simple hyperplasia without atypia 1%..
  Multiply by 10 → Complex hyperplasia without atypia 3%.
  Multiply by 10 → Simple atypical hyperplasia 8%.
  → Complex atypical hyperplasia 29%.
→ **Most important risk factor:** presence of atypia.

Diagnosis:
→ Made by **endometrial biopsy NOT** US.
  → **Why?** type 2 doesn't come always with thick endometrium (can present with normal endometrial thickness) + early grade have the same thickness as a normal endometrium → high false negative.
→ If you found "biopsy" and "hysteroscopy D and C", go for "**hysteroscopy D and C**".

Treatment:
→ Hormonal management.
  → **Progestins:** usual therapy, oppose the effect of estrogen on endometrium.
    → To treat hyperplasia without atypia & young females who wants to preserve fertility.
→ Hysterectomy.
→ **EIN:**
  → Used in any lesion with cytologic **atypia**.
  → Only 50% respond to MPA.
  → **Concurrent endometrial cancer:** 40%.

PostMenopausal Bleeding (PMB):

→ 20 - 30% of women with **postmenopausal bleeding (PMB) will have uterine cancer**.
→ A **"red flag" symptom** for gynecological cancer → always taken seriously.
→ **Physical examination:**
  → External genitalia inspection & speculum exam → exclude valval, vaginal & cervical cancer.
  → May be normal in women with endometrial cancer .
    → **Endometrial cancer can be excluded by:** transvaginal ultrasound scan (TVUSS) - hysteroscopy and/or **endometrial biopsy**.
→ **Differential diagnosis:**

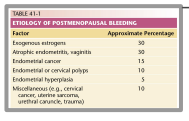


TABLE 41-1
ETIOLOGY OF POSTMENOPAUSAL BLEEDING

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

  → **Endometrial carcinoma:** most important/serious diagnosis to rule out → biopsy is a must.
  → **Vaginal or endometrial atrophy:** most common cause, benign cause.
  → **Postmenopausal hormone replacement therapy (HRT):** benign cause.

Endometrial Cancer

Diagnosis:

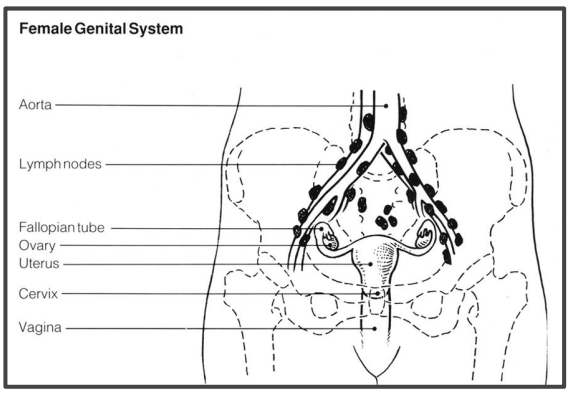
→ **Classic symptom (90%): abnormal vaginal bleeding**.
→ **Hysteroscopy with D & C: gold standard**, nowadays we only do it if we fail to take a biopsy (but choose it in the exam).
  → **Allows direct visualization of:**
    → Endocervical canal.
    → Endometrial cavity.
  → **Lesions that can be removed at the time of hysteroscopy:**
    → Endocervical polyps.
    → Endometrial polyps.
    → Submucosal leiomyomas.
  → **Take a biopsy** from the most suspicious lesion.

→ **EndoMetrial Sample/Biopsy office EMB:**
  → 10 % false negative rate.
  → Any symptomatic patient with –ve biopsy → Hysteroscopy + D & C.
  → Office procedure.
  → ↑ sensitivity + ↓ complication rate + ↓ cost → historically been the initial diagnostic test for postmenopausal bleeding.
  → Ideal for global lesions but not very sensitive for diagnosing localized structural lesions such as polyps or submucous leiomyomas.
→ US.
→ CT.
→ MRI.
→ Colonoscopy.
→ Ca 125.
→ **Detection rates of endometrial cancer by pipelle:** 91 - 99%.
→ **Detection of hyperplasia:** 81%.

→ **Recommendation:** EMB as initial test, hysteroscopy with D & C if EMB inconclusive / failed (*due to pain or bleeding*) or high suspicion (hyperplasia with atypia - pyometra - presence of necrosis – persistent bleeding).

Treatment:

→ **Standard staging procedure for endometrial carcinoma:** total extrafascial hysterectomy with bilateral salpingo-oophorectomy with pelvic and para-aortic lymph node dissection (in type 2) +/- omentectomy (in type 2).
→ Staging can be performed via a minimally invasive route or laparotomy.



Endometrial Cancer

Staging: *FIGO 2010*

→ **Stage:** the spread of the cancer.
→ All gynecological cancers are surgically staged (except cervical).

Stage	Invasion
IA	Tumor confined to the uterus, no or **< ½ myometrial** invasion → no adjuvant therapy
IB	Tumor confined to the uterus, **> ½ myometrial** invasion → vaginal brachytherapy
II	**Cervical** stromal **invasion**, but not beyond uterus → treated like cervical cancer (*radical hysterectomy OR simple hysterectomy & external beam radiation*)
IIIA	Tumor invades serosa or adnexa
IIIB	Vaginal and/or parametrial involvement tissue lateral to the cervix
IIIC1	Pelvic node involvement
IIIC2	Para-aortic involvement
IVA	Tumor invasion bladder and/or bowel mucosa
IVB	Distant metastases (abdominal metastases and/or inguinal lymph nodes) → palliative

Chemo & radiotherapy

Grading:

→ **Grade:** cancer aggressiveness, it is what actually kills the patient.
  → **G1:** ≤ 5% of solid pattern → less aggressive.
  → **G2:** 6 - 50% → moderately aggressive.
  → **G3:** > 50 % → very aggressive.

H Receptors:

→ ER + PR levels are inversely proportional to the histologic grade.
→ Positive ER or PR or both → better prognosis.
→ HER 2 NEU.

Endometrial Cancer

Management:

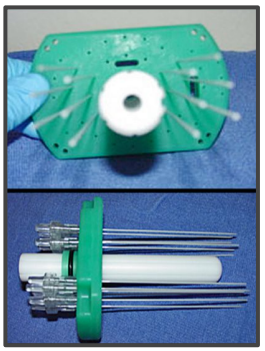
Adjuvant Therapy:

→ **Decisions are based upon clinicopathologic factors:** grade - tumor size - patient's age.

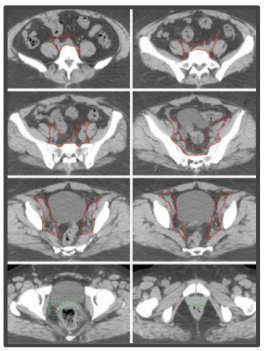
→ **Usual components:** brachytherapy (through the vagina) + external beam radiation therapy (EBRT) +/- chemotherapy.

CLINICAL FINDINGS	ADVERSE RISK FACTORS[m]	HISTOLOGIC GRADE/ADJUVANT TREATMENT[b,n] G1	G2	G3
Completely surgically staged: Stage I — Stage IA (< 50%) myometrial invasion	Adverse risk factors not present	Observe	Observe or Vaginal brachytherapy	Observe or Vaginal brachytherapy
	Adverse risk factors present	Observe or Vaginal brachytherapy	Observe or Vaginal brachytherapy and/or pelvic RT (category 2B for pelvic RT)	Observe or Vaginal brachytherapy and/or Pelvic RT
Stage IB (≥ 50%) myometrial invasion	Adverse risk factors not present	Observe or Vaginal brachytherapy	Observe or Vaginal brachytherapy	Observe or Vaginal brachytherapy and/or Pelvic RT
	Adverse risk factors present	Observe or Vaginal brachytherapy and/or Pelvic RT	Observe or Vaginal brachytherapy and/or Pelvic RT	Pelvic RT and/or Vaginal brachytherapy ± chemotherapy[o,p] (category 2B for chemotherapy) or Observe (category 2B)

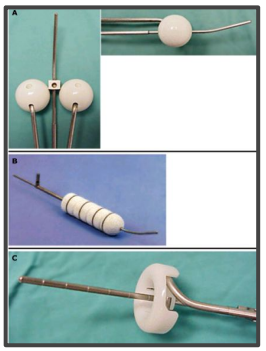
CLINICAL FINDINGS	HISTOLOGIC GRADE/ADJUVANT TREATMENT[b,n,p] G1	G2	G3
Completely surgically staged: Stage II[q,r]	Vaginal brachytherapy and/or pelvic RT	Pelvic RT + vaginal brachytherapy	Pelvic RT + vaginal brachytherapy ± chemotherapy[o,p] (category 2B for chemotherapy)
Completely surgically staged: Stage IIIA	Chemotherapy ± RT or Tumor-directed RT ± chemotherapy or Pelvic RT ± vaginal brachytherapy	Chemotherapy ± RT or Tumor-directed RT ± chemotherapy or Pelvic RT ± vaginal brachytherapy	Chemotherapy ± RT or Tumor-directed RT ± chemotherapy or Pelvic RT ± vaginal brachytherapy



Syde-type interstitial implant for **cervical interstitial brachytherapy**.

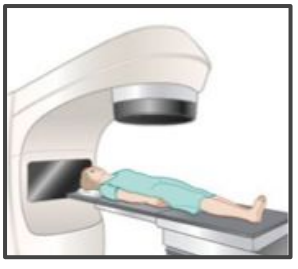


Pictures of cervical brachytherapy



High dose rate (HDR) cervical brachytherapy applicators: intrauterine tandem with either:

- **A.** Vaginal ovoids.
- **B.** Vaginal cylinders.
- **C.** Vaginal ring.



EBRT

Endometrial Cancer

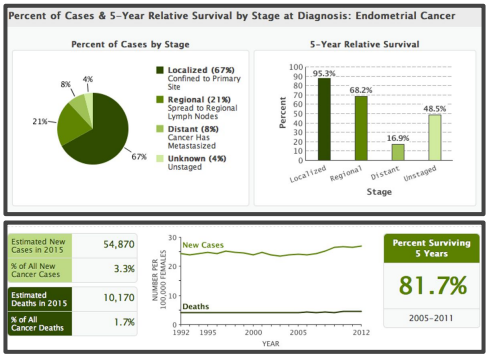
Complications: *of both surgery and radiation*

- → **TAH/BSO complications:** mortality (<1%) - infection - wound.
- → Dehiscence.
- → Fistula.
- → Bleeding.
- → Frequency and urgency of urine and/or stool.
- → Vaginal stenosis → use dilators.
- → Thrombocytopenia with WART.

Fertility Preservation:

- → Women with low-risk endometrial carcinoma who wish to preserve fertility may be candidates for treatment with **progestin** therapy.
- → Evaluation prior to medical therapy (dilation and curettage - imaging studies) is necessary to try to confirm that the lesion is **confined to the uterus** and is **grade 1**.
- → **Criteria for fertility preservation:** grade 1 + type 1 + **MRI findings:** confined to the uterus, limited to the endometrium & no lymph node enlargement or invasion. **If fulfilled, treat with:**
  1. High dose of progesterone.
  2. **Repeat biopsy after 3 months:**
     - → Negative biopsy → IVF.
     - → Positive biopsy (remained) → double progesterone dose.
  3. **Repeat the biopsy after 6 months:**
     - → Negative biopsy → IVF.
     - → Positive biopsy (remained) → repeat MRI.
       - → Did not progress → double progesterone dose again.
  4. **Repeat biopsy after 3 months:**
     - → Positive biopsy (remained for total 9 months) → surgery, no rule for fertility preservation.
     - → Negative biopsy → IVF.

Survival & Prognosis:



- → **Rate of five-year for stage I disease:** ~ 80 - 90%.
- → **Rate of five-year for stage II disease:** 70 - 80%.
- → **Rate of five-year for stages III and IV disease:** 20 - 60%.
- → **Stage I or II carcinosarcomas 5-year survival**: ~ 70% if treated (*surgical staging + adjuvant radiation + chemotherapy*).
- → **Poor prognosis:**
  - → Grade 3.
  - → **Non endometrioid types:** seropaplary - clear cell carcinoma - carcinosarcoma.
  - → Lymphovascular invasion.
  - → **Peritoneal cytology:** first thing we do in surgery is to wash the abdomen & take a sample.
  - → T size.
- → **Uterine leiomyosarcomas & endometrial sarcomas prognosis:** poor.
  - → **Cause:** propensity for hematogenous dissemination.
  - → **Overall 5-year survival rate:** ~ 35%.
- → **Endometrial stromal sarcomas prognosis:** good.

Endometrial Cancer

Lymphadenectomy:

→ Lymph node metastases found in about 10% of patients with endometrial cancer clinically confined to the uterus.
→ Lymph node evaluation is **part of FIGO staging** for endometrial cancer.

Advantages

→ Assigning patients to their proper **FIGO stage**.
→ Useful in planning postoperative treatment.

Complications

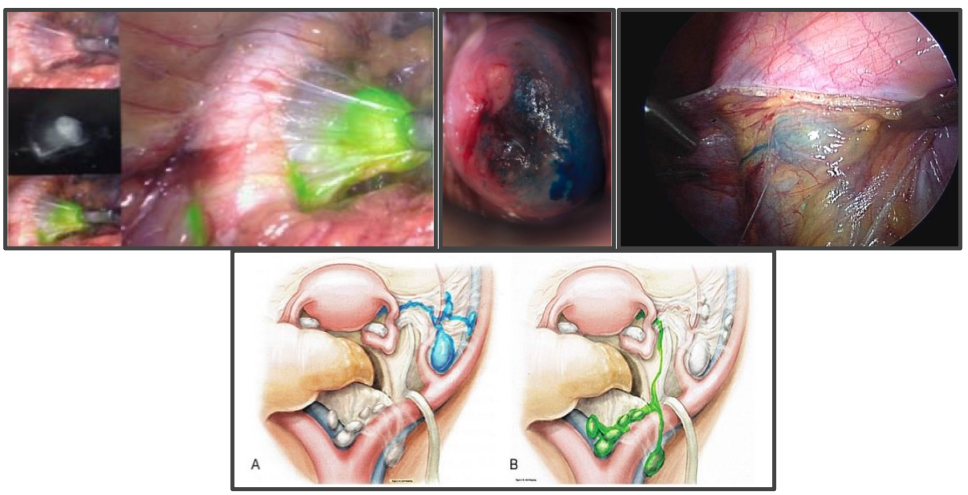
→ **Prolonged operative** time.
→ ↑ **blood** loss.
→ **Injury** to adjacent structures.
→ **Lymphocele** and **lymphedema**.

Sentinel Lymph Nodes (SLN):

→ Injecting a dye in the cervix → drains through lymphatics → first lymph node draining the tumor will be colored → excised and tested:
  → Negative biopsy → don't remove them.
  → Positive biopsy → others need to be removed and vice versa.
→ SLN is considered the **standard of care** in many **solid** tumors (breast - melanoma - vulva).
→ Precise and **less invasive** than complete lymphadenectomy.
→ Allow identification of aberrant **drainage sites**.
→ Detect more metastases (**ultra-staging**).

Goals of SLN:
→ **Avoid complete lymphadenectomy** if SLN is negative bilaterally.
→ ↓ **morbidity** of lymphadenectomy.
→ Avoid under/over treatment.

Sentinel Lymph Node Napping in Endometrial Cancer:
→ Colorimetric detection with Patent Blue (PB) and/or radio-isotopic detection with Technetium (TC99) to identify SLN.
→ **Injection site:** cervix at 3 and 9 o'clock



Uterine Fibroids

Summary from Doctor's Slides:

→ Asymptomatic fibroids may regress, continue to grow or new may develop.
→ Management depends on patient's age, symptoms, obstetrical history, future childbearing, size and location.
→ Account for 1 to 2 percent of infertility " the key factor is the location, not size".
→ Subserosal fibroids do not impact fertility.
→ Medical therapy before pregnancy is unsuccessful due to side effects and rebounding.
→ Do not postpone pregnancy with fibroids "fertility declines with age, especially after age 35 years.
→ No need for prophylactic myomectomy if asymptomatic and no history of infertility or recurrent miscarriages.
→ Ulipristal "selective progesterone modulator" decrease uterine bleeding and myoma size (has minimal menopausal symptoms) **5 mg orally per day for three months interrupted by menstruation**.
→ Myomectomy is better for those who wish to conceive / preserve fertility.
→ UAE is better in high surgical risk "previous multiple laparotomies or diffuse uterine leiomyomas".
→ Post myomectomy should wait 6-12 months before conceiving to allow the uterus to heal (risk of rupture).
→ If post myomectomy has difficulties in conceiving (HSG).
→ **In case of pregnancy:** an elective cesarean delivery at early term 37-38 weeks "risk of rupture".
→ Hysteroscopy myomectomy is the procedure of choice for submucosal myomas.
→ **Multiple Myomas (treatment of choice):** abdominal myomectomy or TAH if childbearing is completed.
→ **Pregnancy rates after abdominal myomectomy:** 42 - 87%.
→ MIS has a role but needs experience.
→ **Laparoscopic myomectomy:** <18 weeks' size, with ≤3 intramural or subserous leiomyomas of ≤5 cm. open procedure include size ≥5.0 cm, intramural or anterior location, and preoperative use of a GnRH-agonist.
→ Myoma coagulation or myolysis cause adhesion ↑risk of uterine rupture.

439 Summary

Uterine fibroids/leiomyoma

Definition	• Also known as leiomyomas/ leiomyomata • They are benign monoclonal tumors arising from the smooth muscle cells of the myometrium (risk of transforming to malignancy is very low) • The most common pelvic tumors in women.

Etiology/Predisposing factors	• **Nulliparity:**
	  ○ Estrogen→ fibroid grows
	  ○ Progesterone→ fibroid shrinks
	• **Early menarche** (< 10 years of age)
	• Age: 25–45 years
	  ○ Fibroids are largely found in women of reproductive age. (it increases with age during the reproductive years)(VC: Fibroids usually become symptomatic in the 5th decade of life)
	  ○ Influenced by hormones (i.e., estrogen, growth hormone, and progesterone)
	  ○ During menopause, hormone levels begin to decrease and leiomyomas begin to shrink.
	• Ethnicity: African American
	• Family history
	• Obesity: Increased BMI
	• Alcohol
	• Hypertension
	• Prior history of uterine fibroids

Protective factors	• Smoking • Emergency OCP: progestin modulator • POP: long-acting progestin-only contraceptive
Classification	Classified according to their location.

Subserosal leiomyomas	Located in the outer uterine wall beneath the peritoneal surface (Outside the uterus (towards the peritoneum "abdomen")
Intramural leiomyomas (most common)	Growing from within the myometrium wall
Submucosal leiomyoma	Located directly below the endometrial layer (uterine mucosa)
Pedunculated leiomyoma	Can either be subserosal or submucosal with a stalk
Parasitic leiomyoma	Can be any one of the above (originating from the uterus) that then breaks away from the uterus and receives their blood supply from another abdominal organ.

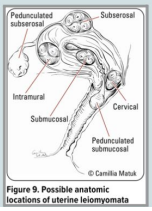


Figure 9. Possible anatomic locations of uterine leiomyomata

Clinical features	**Symptoms:** depends on the number, size, and location of leiomyomas. **Most women have small, asymptomatic fibroids.**
	• Abnormal menstruation (possibly associated with anemia especially in sub-mucosal): **menorrhagia**, dysmenorrhea, metrorrhagia
	• Features of mass effect:
	  ○ Enlarged, firm and irregular uterus during bimanual pelvic examination
	  ○ Back or pelvic pain/discomfort
	  ■ Noncyclic, intermittent, dull pain, with gradual onset.
	  ■ Could be acute onset in cases of degeneration or torsion.
	  ○ Urinary tract symptoms: urinary frequency/retention, features of hydronephrosis
	  ○ Bowel symptoms: constipation
	• Reproductive abnormalities
	  ○ Infertility (difficulty conceiving and increased risk of pregnancy loss)
	  ○ Dyspareunia
	Signs on palpation:
	• Non-tender, irregularly/asymmetrically enlarged uterus, with a lumpy-bumpy or cobblestone protrusions, firm or solid on palpation.
	• Size of fibroids is described in menstrual weeks as pregnancy.

Diagnostics	• Bimanual exam:
	  ○ Fibroid uterus may be enlarged or irregularly shaped
	• Laboratory studies:
	  ○ Beta HCG: exclude pregnancy
	  ○ CBC: could show anemia
	• Imaging studies:
	  ○ **Pelvic US: initial test.** Supportive findings:
	  ■ Well-circumscribed hypoechoic solid mass
	  ■ Calcifications and/or cystic areas due to **degeneration**
	  ■ Mass effect (e.g., hydronephrosis) may be seen in patients with large leiomyomas.
	  ○ Hysteroscopy:
	  ■ Allows direct visualization of endocervical canal and endometrial cavity.
	  ■ Diagnostic and serves as a method of **surgical intervention** *(check hysteroscopic myomectomy)*.
	  • Endocervical/endometrial polyps or submucosal leiomyomas can be removed at time of hysteroscopy
	  ○ Sonohysterography: to evaluate endometrial cavity
	  ○ Hysterosalpingogram (HSG)
	  ○ MRI: not routinely done.
	  ■ Helps further characterize leiomyomas before surgery
	  ■ Can rule out comorbid conditions or differential diagnoses of uterine leiomyomas
	• Mass characteristics:
	  ○ Well circumscribed lesion with a thin pseudocapsule of areolar tissue
	  ○ Compressed smooth muscle cells and fibrous connective tissue
	  ○ Contain extracellular matrices (collagen, proteoglycan, fibronectin)

Management

Expectant management (Observation)

• Indication:
  ○ Symptoms absent or minimal
  ○ Fibroids <6-8 cm or stable in size
  ○ Not submucosal (submucosal fibroids are more likely to be symptomatic)
  ○ Currently pregnant due to increased risk of bleeding (follow-up U/S if symptoms progress)
  ○ If actively growing, follow up every 6 months to monitor the size and growth → 7 to 40 percent of fibroids regress over 6 months to 3 years.
• Follow up:
  ○ Annual pelvic exam and CBC to check for anemia
  ○ Monitor symptoms

Medical therapy (generally has limited help)	
Non-hormonal	• NSAIDs • Tranexamic acid (to decrease bleeding, used temporality before surgery)

Hormonal	• Contraceptives such as: combined OCP, progestins
	• **GnRH agonists (e.g. leuprolide):**
	  ○ **Used primarily as a short-term bridge therapy:**
	  ■ Before planned surgery
	  • Given for 3 - 6 months prior to surgery
	  • Decreases up to 70% of leiomyoma size and vascularization and overall uterine size
	  ■ Before interventional therapy or additional pharmacotherapy
	  ○ Not suitable as long-term therapy because of the risk of hypoestrogenic effects (e.g., osteoporosis, hot flashes, altered lipid profile)
	• Androgenic steroids (e.g. danazol):

Non-surgical interventional therapy	

Uterine artery embolization (UAE)	• A minimally invasive, interventional radiology procedure that occludes both uterine arteries that supply the leiomyoma, causing it to shrink and therefore significantly reduces leiomyoma size and bleeding
	• Option for preserving uterus and no future fertility.
	• Complications
	  ○ Postembolization syndrome
	  ■ Common complication of transarterial embolization
	  ■ Clinical features: fever, pain, nausea, and vomiting < 72 hours of UAE in the absence of infection
	  ■ Typically self-limited
	  ○ Thromboembolic events (e.g., pulmonary embolism, uterine ischemia and necrosis)
	  ○ Bleeding/blood-tinged vaginal discharge: typically self-limited
	  ○ Endometritis
	  ○ Treatment failure

Endometrial ablation	To stop the bleeding for awhile 2-3 wks before surgery (± hysteroscopic myomectomy) for: • Completed childbearing • Bleeding abnormalities: does not shrink the fibroid(s) but can help to decrease heavy menstrual bleeding caused by fibroids. • NOT for bulk or pressure symptoms.
Radiofrequency ablation (RFA)	• Ultrasound-guided targeted coagulative necrosis of leiomyoma • **Significant decrease in leiomyoma size and symptoms** • Low risk of further surgical intervention • Unknown effects on fertility

439 Summary

Uterine fibroids/leiomyoma

Surgical therapy (mainstay therapy for fibroids)		
Indications	• Abnormal uterine bleeding or Bulk-related symptoms • Infertility • Recurrent pregnancy loss	
Procedures	**Hysterectomy**	**Myomectomy**
Indications	• **Desire a definitive treatment** • Do not desire fertility and/or have had an insufficient response to alternative treatments • Suspected leiomyosarcoma • With acute hemorrhage who do not respond to other therapies	• Symptomatic fibroids who wish to **preserve fertility** (childbearing/younger age, nulliparous) (Adhesions frequently form that which might complicate pain and infertility)
Approach	• Vaginal or laparoscopic → small fibroids • Abdominal → large or multiple fibroids	• Hysteroscopic → **submucosal leiomyomas** • Laparoscopic → **subserosal** and most **intramural** leiomyomas • Abdominal

Complications

- Infertility
- Iron deficiency **anemia** (due to heavy menstruation); especially in submucosal leiomyomas
- Malignant transformation to **uterine leiomyosarcoma**
  - **Very rare chance of transformation (<1%)**
  - Sarcoma risk factors: postmenopausal status, black race, **tamoxifen**, pelvic radiation, and hereditary leiomyomatosis and renal cell carcinoma.

Special cases of uterine fibroids

Degeneration of fibroids	• **During times of rapid growth,** myomas may outgrow their blood supply, resulting in ischemic degeneration of a fibroid. This is most common during pregnancy.
	• Types of degeneration
	  ○ Hyaline degeneration
	  ○ Myxomatous degeneration
	  ○ Calcific degeneration → A bad sign, that's how the sarcoma starts. We have to remove it bc it is the start of sarcoma
	  ○ Red degeneration (also known as carneous degeneration):
	  ■ Happens in pregnancy
	  ■ Can cause such extreme, acute pain that the patient requires hospitalization and **narcotics**
	  ■ It increases in size causing central necrosis.
	  ○ Fatty degeneration
	  ○ Cystic degeneration
	  ○ Necrosis

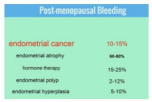
Fibroids in pregnancy	• **Undergo red degeneration**
	• ↑ in size.
	  ○ ⅓ will increase in size
	  ○ ⅓ will stay the same size
	  ○ ⅓ will decrease in size
	• **Management:**
	  ○ **IV Analgesia only** (If analgesia is not an option = Reassure)
	  ○ CI: **Should not be removed** due to high vascularity of fibroid and its potential to bleed in this period.
	• Pregnancy complications of fibroids:
	  ○ Increase abdominal pain
	  ○ Obstructed labor
	  ○ Abnormal fetal presentation

Prolapsed fibroids	Symptoms:
	• Vaginal bleeding
	• Watery vaginal discharge
	• Pelvic pain or contractions or cramping → significant during the process of fibroid expulsion through the cervix
	• Vaginal pressure
	Management:
	• Vaginal myomectomy → mainly in the office with paracervical block to relieve symptoms and for pathological diagnosis even in asymptomatic to prevent symptoms and infections.
	  ○ Contraindications: complication with anesthesia, bleeding diathesis or on anticoagulants.
	  ○ In OR if:
	  ■ Larger than 4 cm
	  ■ Pedicle cannot be visualized or palpated.
	  ■ Broad-based (pedicle >2 cm)
	  ■ Not pedunculated cervical fibroid.

Postmenopausal bleeding (PMB)

DDx of PMB

It's a red flag and should always be taken very seriously as there is risk of cancers. DDx includes:

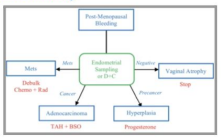


Genital Atrophy (vaginal or endometrial)	• **Most common cause** of PMB • Managed by estrogen
Gynecological malignancies	• **Endometrial cancer** (20-30% of women with post-menopausal bleeding will have uterine cancer) • Vulval, vaginal, cervical cancer
Benign proliferative disorders	• **Endometrial hyperplasia** • **Endometrial polyps** • Endometriosis • Uterine leiomyoma
Hormonal replacement therapy	

Investigation of PMB

- Endometrial sampling (office endometrial biopsy): **initial diagnostic test**
  - If we fail due to pain/bleeding we go for hysteroscopy
- **Hysteroscopy with dilation and curettage (D&C): gold standard**
  - Allows direct visualization of the endocervical canal and endometrial cavity
  - Can be diagnostic and therapeutic (surgical excision) in cases of: endocervical or endometrial polyps, or submucosal leiomyomas.
  - Indications:
    - Inconclusive Endometrial Bx (EMB)
    - High suspicion of: hyperplasia with atypia, pyometra, presence of necrosis, or persistent bleeding

Simplified Approach to PMB (Online MedEd)



Endometrial Cancer

- CC: Abnormal uterine bleeding, postmenopausal bleeding

Endometrial Hyperplasia

- Proliferation of endometrial glands resulting in a greater gland-to-stroma ratio
- May progress to endometrial carcinoma
- Risk factors: same as endometrial cancer risk factors.
  - Most significant risk factor to endometrial hyperplasia is exposure to unopposed estrogen (exogenous or endogenous). Example of endogenous estrogen exposure: **granulosa ovarian cell tumor.**
- Classification of hyperplasia based on growth pattern (simple/complex) and atypia (with/without). Percentage represents the risk of endometrial cancer in 5 years.

	Simple hyperplasia without atypia	Complex hyperplasia without atypia	Simple hyperplasia with atypia	Complex hyperplasia with atypia
Risk of progression to carcinoma	1% with atypia 10%	3% with atypia 10%	8%	**29%**

- Diagnosis:
  - Endometrial sampling (office endometrial biopsy): **initial diagnostic test**
  - **Hysteroscopy with dilation and curettage (D&C): gold standard**
    - DR: In questions if you found (a) biopsy (b) hysteroscopy and D&C, then go for (b) D&C
      - Biopsy is best initial, D&C is gold standard
  - Transvaginal US:
    - endometrial stripe that is <4 mm: low probability of endometrial cancer
    - endometrial stripe that is >4 mm: higher probability of endometrial cancer

439 Summary

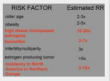
Endometrial Cancer

- Treatment:
  - **Hormonal management–Progestins** are the usual therapy, since they oppose the effect of estrogen on the endometrium.
    - Usually the method of treatment in endometrial hyperplasia without atypia
  - Hyperplasia without atypia→ progesterone tx
  - Hyperplasia with: atypia, old patient, completed family, or has RF for endometrial cancer → be proactive and tx
  - No role of U/S in premenopausal. US is only used in post-menopausal where normal endometrial thickness is is less than 5mm. If more than 5mm(=hyperplasia) → hysteroscopic Bx (in real life we do endoscopic bx).
  - Most important investigation in post menopausal bleeding? Endometrial BIOPSY!!!! US has no role (don't pick it in exam)!!! We have to do biopsy regardless of US results.
  - Most common cause of post meno bleeding? Atrophic. Most serious cause? atrophic.
  - **Hysterectomy**
    - Usually the method of treatment in endometrial hyperplasia with atypia
    - Desire for fertility: long term high dose progestin therapy
    - No desire for fertility: hysterectomy

Endometrial carcinoma

Endometrial carcinoma	
Epidemiology	• Prevalence: 4th most common cancer in women. **Most common gynecological cancer.** ○ 1st: breast, 2nd: lung, 3rd: colorectal • Age: Median age of diagnosis is at 61 years in US • Majority of patients (90%) are diagnosed in early stage (stage I), therefore it has a good prognosis • **Endometrial hyperplasia** is the most common precursor to endometrial carcinoma
Subtypes	

Type I (most common)	Type II
More common	Less common
Estradiol (E2) dependant	E2-independent. Doesn't follow any RF.
Endometrioid (80%)	Serous, **clear cell** (20%)
Low grade (grade 1 and 2)	High grade (grade 3) Agressive.
Superficial myometrial invasion (73% confined to uterus)	Usually deep myometrial invasion and extrauterine extension is common (50% develop metastasis)
Better prognosis	Worse prognosis

Risk factors
"COLD NUT"
 
	• Cancer (ovarian, breast, colon) - Lynch syndrome (HNPCC syndrome)
	• Obesity: (BMI > 40)
	  ○ Conversion of androstenedione to estrone in fat tissue
	• Late menopause/early menarche
	• Diabetes mellitus, HTN
	• Nulliparity
	• **Unopposed estrogen:**
	  ○ **PCOS, anovulation** (infertility)
	  ○ **Unopposed estrogen in HRT (Without progesterone)** - high risk (which is why progesterone must be given with estrogen to all patients with a uterus).
	  ○ Ovarian granulosa cell tumor
	• Tamoxifen therapy (chronic use)

Protective factors	• Multiparity • Combination OCP • Smoking

Clinical features	• **Abnormal uterine bleeding - Main symptom:**
	  ○ Postmenopausal: any amount of bleeding; including spotting or staining
	  ○ Perimenopausal: menorrhagia, intermenstrual bleeding
	• Later stages may present with:
	  ○ Pelvic pain, palpable abdominal mass
	  ○ Weight loss

Endometrial carcinoma

Diagnostics	• Endometrial sampling (office endometrial biopsy):
	  ○ **Initial test:** confirmed cancer? Next step is surgical staging
	  ○ 10% false negative rate, so any symptomatic pt with **-ve biopsy** should undergo **hysteroscopy with D&C**
	• Hysteroscopy with D&C:
	  ○ **Gold standard** in the books choose it in exam but nowadays we only do it if we fail to take biopsy
	  ○ Considered in patients with inconclusive sampling or high suspicion of malignancy (hyperplasia with atypia, **pyometra**, presence of necrosis, or persistent bleeding)
	• Imaging studies:
	  ○ **Transvaginal US:** initial imaging (not initial test!)
	  ▪ endometrial stripe that is <4 mm: low probability of endometrial cancer
	  ▪ endometrial stripe that is >4 mm: higher probability of endometrial cancer
	  ○ Abdominal US: to exclude metastasis
	  ○ CT/MRI: assessment of metastasis
	• Laboratory studies:
	  ○ Tumor marker: Ca-125
	  ○ CBC: anemia
	  ○ Coagulation studies: to assess for other possible causes of heavy uterine bleeding

Staging	Surgically staged. Represents the spread of cancer. Check FIGO 2010 classification below.

Fertility preservation treatment	• Criteria:
	  ○ Type I endometrial cancer
	  ○ Confined to uterus, grade 1
	  ○ No lymph node invasion/enlargement
	Treatment:
	1. High dose of progesterone
	2. Repeat biopsy after 3 months if -ve send them to IVF, if still +ve double the dose of progesterone
	3. Repeat the biopsy after 6 months, still +ve repeat MRI, if it didn't progress → again double the progesterone dose
	4. Repeat biopsy after 3 month, if in the total 9 months it's still +ve then no role for fertility preservation

Endometrial carcinoma

Treatment	• Based on lymph involvement and staging.		
	FIGO 2010		**Treatment**
Stage 1	IA	Tumor confined to the uterus, no or < 1/2 myometrial invasion	• TAH/BSO • No therapy
	IB	Tumor confined to the uterus, > 1/2 myometrial invasion	TAH/BSO + Vaginal brachytherapy **Surgical therapy is the most accepted mode of treatment in stage 1**
Stage 2	II	Cervical stromal invasion, but not beyond uterus reached cervix (and parametria)	Treated like cervical cancer: radical hysterectomy OR simple hysterectomy and external beam radiation
Stage 3	IIIA	Tumor invades serosa or adnexa	Chemotherapy and radiation
	IIIB	Vaginal and/or parametrial involvement	
	IIIC1	Pelvic node involvement	
	IIIC2	Para-aortic involvement	
Stage 4	IVA	Tumor invasion bladder and/or bowel mucosa	
	IVB	Distant metastases including abdominal metastases and/or inguinal lymph nodes	Palliative care

439 Summary

Endometrial carcinoma

Treatment	**Progestin therapy**	• Women with low-risk endometrial carcinoma who wish to preserve fertility may be candidates for treatment with progestin therapy.
		• Criteria for fertility preservation:
		  ○ Grade 1, type 1
		  ○ MRI finding: No lymph node enlargement or invasion, confined to the uterus, and limited to the endometrium.
		• Fulfilled criteria → High dose of progesterone → Repeat biopsy after 3 months if - ve send them to IVF, if still +ve double the dose of progesterone
		  ○ Repeat the biopsy after 6 months, still +ve repeat MRI, if it didn't progress → again double the progesterone dose
		  ○ Repeat biopsy after 3 month, if in the total 9 months it's still +ve then no rule for fertility preservation has to undergo surgery. If -ve send them to IVF

	Lymphadenectomy	• Lymph node evaluation is part of FIGO staging for endometrial cancer.
		• Advantages:
		  ○ Assigning patients to their proper FIGO stage.
		  ○ Useful in planning post operative treatment.

	Sentinel node (SLN)	• Done by injecting dye in the cervix → drains through the lymphatics → the first lymph node draining the tumor will be colored → excised and tested → if +ve then the others are and all need to be removed and vice versa if negative we don't remove them.
		• Advantages:
		  ○ Avoid complete lymphadenectomy if SLN is negative bilaterally.
		  ○ Reduce the morbidity of lymphadenectomy.
		  ○ Avoid under/over treatment.

	Simplified treatment:
	• **Amboss**
	  ○ **Surgical:** indicated that women do not wish to preserve fertility. Done by TAH/BSO.
	  ○ **Non-surgical:**
	  ■ Progestins: Indicated for women with early stage endometrial carcinoma and who wish to preserve fertility
	  ■ Radiotherapy and/or chemotherapy (adjuvant or palliative)
	• **OME**
	  ○ Hyperplasia: progestins.
	  ○ Adenocarcinoma: total hysterectomy with bilateral salpingo-oophorectomy (TAH/BSO) with or without lymph node removal
	  ○ Metastasis: TAH/BSO + chemotherapy (usually carboplatin and paclitaxel)	

Endometrial carcinoma

Grading/ Prognosis	Good prog bc 90% are stage 1 Grade: represent the **cancer aggressiveness**, it's what actually kill the patient • G 1: 5% or less of solid pattern → less aggressive • G 2: 6-50% → moderately aggressive • G 3: more than 50 % → very aggressive Poor prognosis characteristics: • Grade 3 • Non-endometrioid types (common in type II): sero-paplary, clear cell carcinoma, carcinosarcoma. • + Lymphovascular invasion • + Peritoneal cytology → the first thing we do in surgery is to wash the abdomen and take a sample • T size
Complications of surgery/radiation	• TAH/BSO complications: mortality (<1%), infection, wound dehiscence, fistula, bleeding • Frequency and urgency of urine and/or stool • Vaginal stenosis – use dilators • Thrombocytopenia with WART
Screening/ Prevention	No routine screening test.

Uterine Sarcoma

- Arise from stromal components (endometrial stroma, mesenchymal, or myometrial tissue). Includes: leiomyosarcoma and endometrial sarcoma
- Behave more aggressively and are associated with worse prognosis than endometrial carcinoma.
- Has the potential to spread hematogenously. Mostly to: lungs.
- 5-year Survival rate: 35%

Quiz

Question 1:

→ **A 56-year-old postmenopausal African-American woman comes to the gynecology office because of abnormal vaginal bleeding for the past week. Imaging of the uterus shows a single bulky, oval mass originating deep to the endometrium. Biopsy reveals areas of necrosis and hemorrhage, with a high degree of cellular atypia and mitotic index. It is characterized as non-estrogen sensitive and appears to have arisen de novo. Which of the following is the best classification for such a tumor?**

A. Endometrial carcinoma
B. Germinoma
C. Leiomyosarcoma
D. Leiomyoma

Question 2:

→ **A 51-year-old woman came to the emergency department for abdominal pain. She was discharged later that day with a diagnosis of gastroenteritis and her symptoms have since resolved. She comes to the gynecology clinic today and brings the report from an ultrasound she had done while she was in the emergency department. The report notes a 3 cm posterior uterine fibroid. The patient believes she is nearing menopause because her periods have become irregular and infrequent with minimal bleeding. What is the most appropriate management of this patient?**

A. Obtain a biopsy
B. Schedule this patient for hysterectomy
C. Schedule this patient for myomectomy
D. Advise this patient that no treatment is needed at this time

Question 3:

→ **A 30-year-old woman comes to the office for a routine gynecologic appointment. Over the past year, her menses have become significantly heavier, to the point where she fills a pad every two hours. She has also experienced pain with intercourse. Her menses last 10 days and come regularly every 27 days. Prior to this year, she had a normal menses that lasted four days with a 27-day cycle. Her flow was lighter to the point where she would fill a pad every four to five hours on the first day of her menses. She denies any pain during menstruation and she takes no medications. Urine pregnancy test is negative. Physical examination shows an irregularly shaped uterus of a size consistent with 20 weeks' gestation. Which of the following is the most likely diagnosis?**

A. Endometrial hyperplasia
B. Endometriosis
C. Leiomyoma
D. Leiomyosarcoma

Question 4:

→ **A 60-year-old woman comes to the office because of vaginal bleeding for the past 2 days. Her last menstrual period was 7 years ago and she has not had any bleeding until now. Pelvic examination shows no abnormalities. An endometrial biopsy is performed and reveals grade I endometrial adenocarcinoma, and staging is done via a CT scan. Which of the following is the most appropriate initial step in management?**

A. Chemotherapy
B. Dilation and curettage
C. Hysterectomy
D. Radiation therapy

1	2	3	4
C	D	C	C

Quiz

Question 1:

→ **A 58-year-old woman comes to the office because of vaginal bleeding. She experienced an episode of bleeding two months ago for the first time since menopause five years ago. The episode lasted for two days and was lighter in flow than her previously normal menses. She experienced another episode of bleeding this week that lasted three days that was similar in flow to her normal menstrual cycles. Other than some minimal cramping, she denies pain with these episodes. In the past she had normal menstrual cycles and gave birth to one full-term boy via spontaneous vaginal delivery at 32 years old. She went through menopause at the age of 54 and was treated with hormonal replacement therapy for nine months due to severe hot flashes. Her past medical history is otherwise noncontributory. Her BMI is 35 kg/m2. Which of the following is the most likely diagnosis?**

A. Endometrial hyperplasia
B. Endometriosis
C. Leiomyoma
D. Leiomyosarcoma

Question 2:

→ **A 60-year-old woman comes to the office because of post-menopausal bleeding for the last two weeks. She states that the flow was initially similar to that of her prior menses, but over the last week she only experienced intermittent spotting. Endometrial biopsy shows complex hyperplasia without atypia. Which of the following, if present, is a risk factor associated with her condition?**

A. Combination estrogen/progestin hormonal therapy
B. Menopause at age 45
C. Polycystic ovarian syndrome
D. Serous cystadenocarcinoma of the ovary

Question 3:

→ **A 53-year-old woman comes to the clinic because of post-menopausal vaginal bleeding. She has no complaints of pelvic pain and has not had intercourse in years. She stopped menstruating aged 49. Her last pap smear 2 years ago was negative. She is currently undergoing medical treatment for "ER positive breast cancer." Based on this history, which of the following options is the most likely cause of her post-menopausal bleeding?**

A. Gonorrhea
B. Endometrial polyp
C. Recurrence of periods
D. Cervical cancer

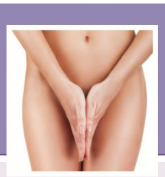
Question 4:

→ **A 40-year-old Asian-American woman, gravida 4, para 4, comes to the office because of irregular menstrual bleeding for the past week. History shows menarche occurred at age 16 and menses had previously occurred every 28 days. For the past four years, she has experienced painless vaginal bleeding every 10-60 days. Her BMI is 35 kg/m2. Pelvic examination shows no abnormalities. An endometrial biopsy is obtained and reveals endometrial carcinoma. Which of the following is the most likely risk factor for this diagnosis?**

A. Age of menarche
B. Obesity
C. Parity
D. Younger age

1	2	3	4
A	C	B	B

CHAPTER 19



Benign Conditions and Congenital Anomalies of the Uterine Corpus and Cervix

WILLIAM H. PARKER • JOSEPH C. GAMBONE

CLINICAL KEYS FOR THIS CHAPTER

- Uterine fibroids (also called leiomyomas) are benign smooth muscle tumors, and about 80% are asymptomatic. They are very common, with an estimated prevalence of 70% by the sixth decade of life. Uterine tumors presenting as fibroids are rarely malignant, with less than 1 in 1000 leiomyosarcomas found at the time of surgical removal. Fibroids may cause abnormal uterine bleeding, pelvic discomfort, and pressure when they enlarge. They can cause pain (sometimes severe) if degeneration and infarction occur.
- Fibroids arise within the myometrium (intramural) but may grow near the serosal surface (subserosal) or near the endometrium (submucosal). Some fibroids are pedunculated. About 40% of fibroids enlarge during the first trimester of pregnancy, but rarely thereafter.
- Medical treatment with progestins, gonadotropin-releasing hormone (GnRH) analogues, or other hormones may be indicated initially for uterine bleeding and fibroid enlargement. Uterine artery embolization (UAE) and magnetic resonance directed ultrasound may be used as alternatives to surgery. Surgical treatment ranges from myomectomy (removal of one or several fibroids) for women who desire fertility or uterine preservation to hysterectomy when less invasive treatments fail.
- Endometrial and cervical polyps may cause uterine bleeding and must be biopsied to rule out cancer. Complex atypical endometrial hyperplasia progresses to endometrial cancer in about 20-30% of cases. Simple hyperplasia may be treated medically.
- Congenital anomalies of the uterus and cervix are most often due to incomplete fusion of the paramesonephric (müllerian) ducts, incomplete dissolution of the midline fusion of those ducts, or formation failures. Diagnosis of uterine defects can be made by hysterosalpingogram or magnetic resonance imaging. Some defects may be diagnosed and treated by hysteroscopy.

Congenital anomalies of the uterus and cervix are most often caused by incomplete fusion of the paramesonephric (müllerian) ducts, incomplete dissolution of the midline fusion of those ducts, or formation failures. Diagnosis of uterine defects can be made by hysterosalpingogram (HSG) or magnetic resonance imaging (MRI). Some defects may be diagnosed and treated by hysteroscopy.

Benign conditions of the uterine corpus and cervix are commonly encountered in gynecologic practice, because they may adversely affect a woman's fertility, cause abnormal uterine bleeding, or cause pelvic pain. In this chapter, benign neoplasms, epithelial changes, functional disorders of the uterus (corpus and cervix), and congenital anomalies are discussed along with both conventional and emerging therapies. Cervical dysplasia along with cervical cancer is covered in Chapter 38.

Benign Neoplastic Conditions

UTERINE FIBROIDS (LEIOMYOMAS)

Uterine fibroids are benign tumors derived from the smooth muscle cells of the myometrium. They are also referred to as leiomyomas or myomas, but "fibroid" is most often used today. Fibroids are the most common neoplasm of the uterus. Estimates are that more than 70% of women have fibroids by the age of fifty, but most are asymptomatic. However, **fibroids may be associated with heavy menstrual bleeding or infertility, pelvic pressure related to uterine bulk and, rarely, pain secondary to degeneration.** Fibroids are the primary indication for as many as one-third of the 500,000 hysterectomies performed in the United States each year. Although fibroids have the potential to grow to be large, **they rarely become malignant.** Leiomyosarcomas occur in less than 1 per 1000 women operated on for presumed fibroids. Rapid growth is not always a reliable sign of leiomyosarcoma.

Risk factors associated with developing fibroids include increasing age during the reproductive years, ethnicity, nulliparity, and family history. African American women have a 2- to 3-fold increased risk of developing fibroids compared with white women, and they may develop more numerous fibroids and at a younger age. Some studies have suggested that higher body mass index (BMI) may be associated with a greater risk of developing fibroids. In other studies, oral contraceptive pills have been associated with a reduced risk.

Pathogenesis of Fibroids

Factors that initiate fibroids are not known. **These benign growths are monoclonal, and about 40% are chromosomally abnormal.** The remaining 60% may have as yet undetected mutations or epigenetic changes. Genetic differences between fibroids and leiomyosarcomas indicate that leiomyosarcomas do not result from malignant degeneration of fibroids. Ovarian sex steroids, both estrogen and progesterone, are important for the growth of fibroids. Fibroids rarely develop before menarche and seldom develop or enlarge after menopause, unless stimulated by exogenous hormones. **Approximately 40% of fibroids enlarge during pregnancy.** Most of the growth occurs in the first trimester and they seldom interfere with the course of the pregnancy.

Fibroids have increased levels of estrogen and progesterone receptors compared with other smooth muscle cells. Estrogen stimulates the proliferation of smooth muscle cells, whereas progesterone increases the production of proteins that interfere with programmed cell death (apoptosis). Many growth factors are over-expressed in fibroids, including those that stimulate the production of fibronectin and collagen, both of which are major components of the extracellular matrix that characterizes fibroids. Other growth factors include those that increase smooth muscle proliferation and DNA synthesis, as well as those that promote mitogenesis and angiogenesis.

Characteristics of Fibroids

Fibroids are usually elliptical or spherical, well-circumscribed, white, firm lesions with a whorled appearance on cut section. Although the fibroid appears discrete, it does not have a true cellular capsule. Compressed smooth muscle cells on the tumor's periphery provide the false impression of a true capsule. **This pseudocapsule contains a rich network of blood vessels, but few blood vessels and lymphatics actually traverse the pseudocapsule into the fibroid.**

Fibroids can undergo degenerative changes, **most commonly hyaline acellularity,** in which the fibrous and muscular tissues are replaced with hyaline tissue. If the hyaline substance breaks down from a further reduction in blood supply, **cystic (fluid) degeneration may occur. Calcification may occur in degenerated fibroids,** particularly after the menopause. **Fatty degeneration may also occur** but is rare. **During pregnancy, 5-10% of women with fibroids undergo a painful red or carneous degeneration** caused by hemorrhage into the tumor.

Fibroids always arise within the myometrium **(intramural)** but may develop near the serosal surface **(subserosal)** or the endometrium **(submucosal),** as depicted in Figure 19-1. Fibroids very near the serosal or endometrial surfaces may develop pedicles. The submucosal fibroids can be propelled by uterine contractions until they extend through the endocervical canal and deliver through the cervical os. This process can be associated with significant bleeding and cramping pain. A subserosal fibroid on a long pedicle can present as a mass that feels separate from the uterus. MRI is often helpful to differentiate a pedunculated fibroid from other types of pelvic masses. Very rarely, pedunculated subserosal fibroids attach to the blood supply of the omentum or bowel mesentery and lose their uterine connections to become **parasitic growths.** Fibroids can also arise in the cervix, between the leaves of the broad ligament (intraligamentous), and very rarely in the various supporting ligaments (round or uterosacral) of the uterus.

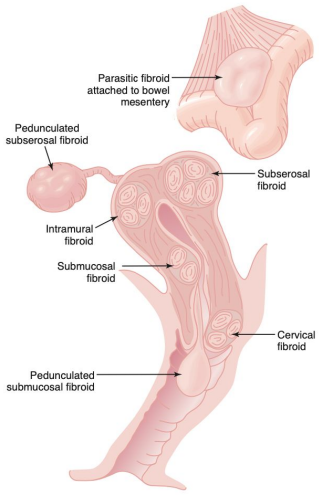


FIGURE 19-1 Uterine leiomyomas (fibroids) in various anatomic locations.

Symptoms of Fibroids

The majority of uterine fibroids (approximately 80%) cause no symptoms. Occasionally, a woman may be able to feel a lower abdominal mass when the fibroid protrudes above the pelvis. For women with fibroids that are asymptomatic or mildly to moderately symptomatic, "watchful waiting" may allow treatment to be deferred, perhaps indefinitely. Symptomatic women **may complain of pelvic pressure, congestion, bloating, or a feeling of heaviness in the lower abdomen. Rarely, lower back pain may be associated with fibroids.** If the fibroid presses upon the bladder, it may cause frequency of urination or nocturia. A large fibroid in the lower uterine segment or near the cervix may compress the vesicourethral junction and lead to urinary retention. Compression of the ureters with resultant hydronephrosis is very rare and, if suspected, can be ruled out with a renal ultrasound.

Prolonged or heavy menstrual bleeding may be associated with submucosal fibroids. Growth factors secreted by fibroids interfere with the blood-clotting cascade. Intermenstrual bleeding is not characteristic of these tumors but may occasionally occur with submucosal fibroids ulcerating through the endometrial lining. Excessive bleeding may result in anemia, weakness, and even dyspnea.

Fibroids do not usually cause pain, but **severe pain may occur when degeneration (acute infarction) occurs within a fibroid.** Dyspareunia can occur with posterior fibroids near the vaginal cul-de-sac. There is an increased incidence of secondary dysmenorrhea in women with uterine fibroids, generally caused by heavy menstrual bleeding. Although many women with uterine fibroids become pregnant and carry their pregnancies to term, **submucosal fibroids may be associated with an increased incidence of infertility,** possibly due to growth factor secretion by the fibroid that may interfere with implantation.

Signs of Fibroids

Fibroids smaller than a 12- to 14-week gestation are usually confined to the pelvis, but larger fibroids can be palpated abdominally. Before examination, the bladder should be emptied because a full bladder will alter the examiner's impression of uterine size. **On bimanual pelvic examination, a firm, irregularly enlarged uterus with smoothly rounded or bossellated protrusions may be felt if the fibroids are subserosal or intramural.** The tumors are usually nontender, although degenerating fibroids can be tender to palpation. Their consistency may vary from rock hard, as in the case of a calcified postmenopausal leiomyoma, to soft or even cystic, as in the case of cystic degeneration. In general, the fibroid uterus is in the midline, but sometimes a large portion of the fibroid lies in the lateral aspect of the pelvis and may be indistinguishable from an adnexal mass. **If the mass moves with the cervix, it is suggestive of a fibroid.** Often the presence of a fibroid precludes a proper evaluation of the adnexa, but ultrasonic imaging, as seen in Figure 19-2, can help to distinguish adnexal masses from laterally placed fibroids.

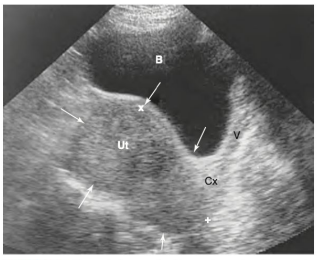


FIGURE 19-2 Ultrasonic image of a uterus enlarged and irregularly distorted by multiple fibroids *(arrows)*. Such studies are useful to help rule out ovarian enlargement too. *B,* Bladder; *Cx,* cervix; *Ut,* uterus; *V,* vagina. (From Mettler FA: *Essentials of radiology,* ed 2, Philadelphia, 2005, Saunders.)

Differential Diagnosis for Fibroids

Fibroids present as pelvic masses and thus the differential diagnosis is extensive and includes other uterine pathology. This includes adenomyosis (see Chapter 25), uterine sarcoma (rarely), and other pelvic processes, such as **an ovarian neoplasm, a tubo-ovarian inflammatory mass, a pelvic kidney, a diverticular or inflammatory bowel mass, or cancer of the colon.** Ultrasonography may be helpful to visualize the fibroids and identify normal ovaries apart from the fibroids. MRI is the most accurate way to diagnose uterine fibroids if the diagnosis is uncertain. Figure 19-3 shows the gross appearance of an irregularly enlarged uterus with multiple fibroids and Figure 19-4 is an MRI of a similarly deformed uterus preoperatively.

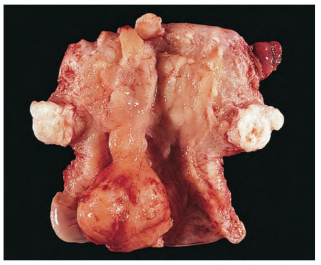


FIGURE 19-3 Gross appearance of an irregularly enlarged uterus with multiple fibroids. (From Voet RL: *Color atlas of obstetric and gynecologic pathology,* St Louis, 1997, Mosby.)

Management of Fibroids

In general, when asymptomatic fibroids are detected, treatment is not necessary. If the fibroid uterus is causing bothersome symptoms or is implicated as a cause of infertility in a woman seeking pregnancy, then some treatment is indicated. Traditionally, rapid growth has been listed as an indication for removal but recent studies show that rapid growth is not a reliable predictor of uterine sarcoma.

Medical Management

Heavy or prolonged menstruation presumed to be caused by fibroids can initially be managed hormonally in some cases. Many women with symptomatic fibroids are in the age group of women who may also have anovulation as the cause of the bleeding. **Progestin-only therapies** (oral or injected medroxyprogesterone acetate, progestin-only oral contraceptive pills, or levonorgestrel-releasing intrauterine devices) **or combination hormonal contraceptive methods** (oral contraceptive pills, vaginal rings, or patches) **are usually the first therapeutic option.** The goal is to reduce monthly menstrual blood loss with cyclic hormonal methods or to eliminate menses with extended or continuous use of these methods. Dysmenorrhea is also markedly reduced by these measures.

Gonadotropin-releasing hormone (GnRH) analogues (agonists and antagonists) block ovarian steroidogenesis, which reduces the volume of the myometrium and fibroids and stops menstrual bleeding. However, because of the intense vasomotor symptoms and the deleterious effect the GnRH-analogues may have on bone mineral density, only short courses of these agents can be administered. Usually their use is confined to decreasing uterine size and/or increasing hemoglobin levels for women preparing for surgical treatments, such as endometrial ablation, myomectomy, or hysterectomy.

Surgical Management Options

When uterine fibroids are not amenable to the less invasive medical therapies, surgery or embolization should be considered (Table 19-1). Even after childbearing is complete, many women desire uterine preserving treatment for symptoms of fibroids. **Myomectomy should be considered as a safe alternative to hysterectomy.** Case-controlled studies suggest that there may be less risk of intraoperative injury to the bladder, bowel, and ureters with myomectomy when compared with hysterectomy.

The surgical approach depends on the size, number, and location of the various fibroids. MRIs are the best way to localize and estimate the volume of each fibroid, and to determine its position relative to the endometrium and other anatomical structures in the pelvis. Submucosal fibroids less than 5 cm may be resected at the time of hysteroscopy. Pedunculated, subserosal, and many intramural fibroids may be removed laparoscopically or with robotic assistance. Laparotomy is generally reserved for larger or more numerous tumors. If the endometrial cavity is entered during myomectomy, future births are usually recommended to be by cesarean delivery even though the risk of rupture is reported to be very low. In skilled hands, myomectomy may often avoid hysterectomy.

Although new fibroids may form following myomectomy, only 11% of women with three or fewer fibroids and about 25% of women with four or more fibroids will require a subsequent operation because of new fibroid growth. Less invasive techniques using laparoscopy and hysteroscopy for the removal of fibroids, including morcellation, have significantly reduced the hospital stay necessary for myomectomy as well as the morbidity associated with larger incisions and longer operating times. Although this may be of great benefit to the large majority of appropriate patients, any fast growing fibroid in a premenopausal woman or enlarging fibroid in a postmenopausal woman should be removed at open operation. At least, women in these two circumstances should be warned about the possibility of a sarcoma and the potential lethal dangers of spread caused by open morcellation.

For women desiring uterine preservation but not future fertility, surgical management of excessive bleeding is possible using procedures that ablate the endometrium. **With endometrial ablation, over 70% of women have a significant and satisfactory decrease in menstrual blood loss after one treatment, while others require repeat ablation or undergo hysterectomy. Uterine artery embolization (UAE) is a**

Reference

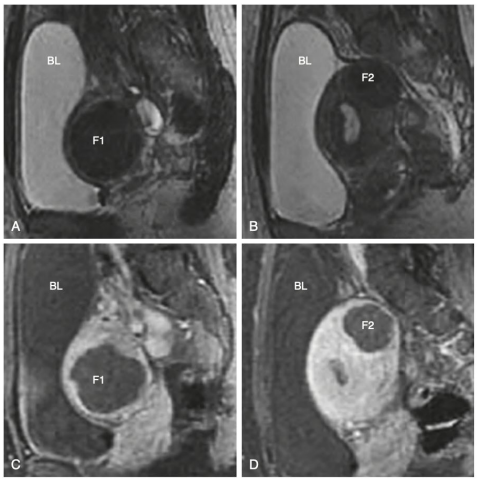


FIGURE 19-4 Two magnetic resonance imaging views of two uterine fibroids F1 (**A** and **C**) and F2 (**B** and **D**). Significant uterine deformity due to fibroids can result in symptoms such as abnormal uterine bleeding when the fibroids are submucosal (entering the uterine cavity) or pelvic pressure and a feeling of fullness. Large fibroids may put pressure on the bladder (BL) resulting in urinary frequency. Fibroids rarely cause pain except when they undergo degeneration (infarction). (From Bouwsma EV, Gorny KR, Hesley GK, et al: Magnetic resonance-guided focused ultrasound surgery for leiomyoma-associated infertility. *Fertil Steril* 96:e9-e12, 2011, Figure 1.)

TABLE 19-1

INTERVENTION FOR PATIENTS WITH FIBROIDS NOT AMENABLE TO MEDICAL THERAPY*

Clinical Presentation	Nonmedical Options	Comments
Desired fertility or uterine preservation	Myomectomy or uterine artery embolization (UAE)†	Usually used for a limited number of fibroids
Poor surgical risk	Endometrial ablation or UAE	UAE only for a limited number of fibroids
No desired fertility or uterine preservation	Endometrial ablation or hysterectomy	Hysterectomy is definitive therapy
Rapidly growing uterus (double in size in 6 months)	Exploratory laparotomy, abdominal hysterectomy	More extensive surgery if malignancy discovered

*Generally failed medical therapy or large (>12 to 14 weeks' gestational size) uterus.
†Pregnancies after UAE are at higher risk.

procedure performed under conscious sedation using microspheres or small coils introduced into the uterine artery via a transcutaneous femoral approach. These coils and/or particles occlude the artery feeding the fibroid, leading to necrosis of the myoma. Fibroids often shrink in volume, and bleeding is successfully reduced in 90% of women. After UAE is performed, pregnancy may still be possible, but there is a higher risk of placental complications (accreta), postpartum hemorrhage, premature delivery, and malpresentation.

Hysterectomy provides definitive therapy for uterine fibroids. Approximately 200,000 hysterectomies are done annually in the United States to treat fibroids. If the uterus is very large or bulky, laparotomy is generally the preferred approach. Vaginal hysterectomy or total laparoscopic hysterectomy are both excellent options for women with smaller uteri. If a woman desires a supracervical hysterectomy, the vaginal approach is not possible but laparoscopic supracervical hysterectomy may be used. Usually ovarian preservation is encouraged unless the woman is over age 60, or has risk factors for ovarian carcinoma (see Chapters 20 and 39).

Other technologies have been developed recently to offer newer treatment options. **Magnetic resonance-guided focused ultrasonography** (seldom used) produces energy that penetrates through soft tissue to produce regions of protein denaturation and necrosis, with minimal (20%) reduction of fibroid volume. **Radio frequency ablation** through a laparoscope, aided by intraoperative ultrasonic guidance, can also be used to treat individual fibroids.

ENDOMETRIAL POLYPS

Endometrial polyps (named for their shape and not their histology) form from the endometrium to create abnormal protrusions of friable tissue into the endometrial cavity. They can cause irregular menstrual bleeding during the reproductive years and postmenopausal bleeding after menopause. On ultrasound, endometrial polyps may appear as a focal thickening of the endometrial stripe. **They can be more clearly recognized on saline infusion sonography (SIS)** or **visualized directly by hysteroscopy** (see Figure 34-1). Endometrial polyps may evade detection by endometrial aspiration or dilation and curettage (D&C) because they are too large to be aspirated through the sampling orifice and are very flexible and can be pushed out of the path of the sharp curette. Histologic evaluation of the polyp is imperative, because although most are benign, endometrial hyperplasia, endometrial carcinoma, and carcinosarcomas may also present as polyps. Malignant or hyperplastic polyps are significantly more common in postmenopausal compared with premenopausal women (5% versus 2%), and more common in women with abnormal bleeding compared to those without bleeding (4% versus 2%).

CHAPT 41

Uterine Corpus Cancer

NEVILLE F. HACKER

CLINICAL KEYS FOR THIS CHAPTER

- There are two different clinicopathologic types of endometrial cancer. Type I endometrial cancers are caused by unopposed estrogenic stimulation, are endometrioid in histologic type, and generally have a good prognosis. Type II endometrial cancers are unrelated to estrogenic stimulation, are often nonendometrioid histologically (serous or clear cell), and have a poor prognosis.
- About 5% of endometrial cancers occur in women with Lynch syndrome, which is also called *hereditary nonpolyposis colon cancer* (HNPCC) *syndrome.* This syndrome is caused by germline mutations in the DNA mismatch repair genes. Women with HNPCC syndrome have about a 40% risk of developing endometrial cancer, which is similar to their risk of developing bowel cancer.
- The commonest presenting symptom of patients with endometrial cancer is postmenopausal bleeding. A transvaginal ultrasound will reveal an endometrial stripe that is wider than 4 mm, and an endometrial biopsy done in the office will usually allow histologic diagnosis. If the office biopsy is negative or shows endometrial hyperplasia, hysteroscopy and uterine curettage will be necessary to definitively exclude endometrial cancer.
- Total hysterectomy and bilateral salpingo-oophorectomy is the basic treatment for stage I endometrial cancer, and this is usually performed by laparoscopic or robotic surgery. Any enlarged pelvic or paraaortic lymph nodes should be resected in all patients. Formal surgical staging, including at least pelvic lymphadenectomy, should be performed in high-risk patients, including those with serous, clear cell, or grade 3 histology, outer-half myometrial invasion, or cervical extension.
- For patients with advanced disease, treatment must be individualized. The uterus, tubes, and ovaries should be removed, if possible, for palliation of bleeding and other pelvic symptoms. Some cases of advanced disease are a result of delayed diagnosis. If the patient has an advanced grade 1 or 2 tumor with positive estrogen or progesterone receptors, good responses and prolonged survival may be seen with the use of high-dose progestins or tamoxifen.

Cancer of the endometrium is the most common gynecologic malignancy in the United States. For 2013, it was estimated that there would be 45,560 new cases and 8190 deaths. It is the fourth most common malignancy found in American women after breast, colorectal, and lung cancers, and it is predominantly a disease of affluent, obese, postmenopausal women of low parity.

Epidemiology and Etiology

There are two different clinicopathologic types of endometrial carcinoma (Table 41-1): an estrogen-dependent and a non–estrogen-dependent type.

Any factor that increases exposure to unopposed estrogen increases the risk for type I endometrial cancer. If the proliferative effects of estrogen are not counteracted by a progestin, endometrial hyperplasia and possibly adenocarcinoma can result.

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.

Unopposed estrogenic stimulation from anovulatory cycles occurs in patients who have polycystic ovarian syndrome (Stein-Leventhal syndrome) **and in patients with a late menopause.** In postmenopausal women taking estrogen replacement without a progestin for menopausal symptoms, the risk of cancer developing appears to be both dose-dependent and duration-dependent. This increased risk varies from 2- to 14-fold compared with nonusers. The addition of progestin in a cyclic fashion for 10 to 14 days of the month or in a continuous fashion daily throughout the month eliminates this increased risk. **Women taking tamoxifen for breast cancer have a two- to threefold increased risk of endometrial cancer.** Young women who use oral contraceptives have been shown to have a lower incidence of subsequent endometrial cancer.

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. Their risk of developing bowel cancer is also about 40%.

TABLE 41-1

CLINICOPATHOLOGIC TYPES OF ENDOMETRIAL CARCINOMA

Type I	Type II
Endometrioid	Non endometrioid (serous, clear cell)
Mean age 63 yr	Mean age 67 yr
Estrogen-related	Non–estrogen-related
Microsatellite instability	Chromosomal instability
Mutations in *PTEN, PIK3CA, KRAS*	*TP53* mutations
Good prognosis	Poor prognosis

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

Screening of Asymptomatic Women

Population screening for endometrial cancer is not feasible, because there is no simple method of cancer detection available. However, screening may be justified for high-risk women, including those with a family history of HNPCC syndrome, those with polycystic ovarian disease, and any woman with an intact uterus taking unopposed estrogen. **Only about 50% of women with endometrial cancer will have malignant cells on a Papanicolaou smear.**

Since the 1990s, transvaginal ultrasonography has increasingly been used for endometrial evaluation. Almost all women with endometrial hyperplasia or carcinoma will have an endometrial thickness of 5 mm or more. **Tamoxifen produces a confusing ultrasonic image, which leads to frequent false-positive reports.**

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.** The most common conditions associated with postmenopausal bleeding are listed in Table 41-2. In the premenopausal or perimenopausal patient, diagnosis is often delayed because frequent or heavy bleeding is usually thought to be dysfunctional in nature.

As menopause approaches, menstruation often becomes lighter and less frequent. If the bleeding becomes heavier or more frequent, it should 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. The adnexa should be palpated carefully for evidence of extrauterine metastases or an ovarian neoplasm. **A granulosa cell tumor or an endometrioid ovarian carcinoma may occasionally coexist with endometrial cancer.**

Reference

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.** Specimens from the endometrium and endocervix should be submitted separately for histologic evaluation to determine whether the tumor has extended to the endocervix.

In a premenopausal patient with high-risk factors and abnormal uterine bleeding, the endometrium must be sampled. If there are no high-risk factors present, failure to respond to medical management or a suspicious transvaginal ultrasound is also an indication for hysteroscopy and uterine curettage.

STAGING

In 1988, the International Federation of Gynecology and Obstetrics (FIGO) changed from a clinical to a surgical staging system for endometrial cancer. This surgical staging system was further revised in 2009. The latest FIGO staging system is shown in Table 41-3.

TABLE 41-3

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

From Pecorelli S: Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. *Int J Gynaecol Obstet* 105:103-104, 2009.
*Either Grade 1, Grade 2, or Grade 3.
†Endocervical glandular involvement should be considered only as stage I and no longer as stage II.
‡Positive cytology has to be reported separately without changing the stage.

Preoperative Investigations

In addition to a thorough physical examination, blood studies should include a complete blood count; determinations of hepatic enzymes, serum electrolytes, blood urea nitrogen, and serum creatinine; and a coagulation profile. A routine urinalysis should be performed. **It is usual to perform computed tomography (CT) of the chest, pelvis, and abdomen, particularly in high-risk cases,** to detect any enlarged lymph nodes, liver or lung metastases, hydronephrosis, or adrenal masses. **Magnetic resonance imaging is useful for differentiating superficial from deep myometrial invasion or detection of cervical involvement.** It may be useful for triaging patients to a gynecologic oncologist.

Pathologic Features

About 75% of endometrial cancers are pure adenocarcinomas. When squamous elements are present, the tumor is called an *adenocarcinoma with squamous differentiation*. Such tumors are graded on the glandular component of the lesion. Less often, **clear cell, squamous, or serous carcinomas occur, and all carry a worse prognosis.**

Invasive adenocarcinoma of the endometrium demonstrates proliferative glandular formation with minimal or no intervening stroma. Tumor grade is determined by both the degree of abnormality of the glandular architecture and the degree of nuclear atypia. A lesion that is well differentiated (grade 1) forms a glandular pattern similar to normal endometrial glands (Figure 41-1). A moderately well-differentiated lesion (grade 2) has glandular structures admixed with papillary, and occasionally solid, areas of tumor. In a poorly differentiated lesion (grade 3), the glandular structures have become predominantly solid with a relative paucity of identifiable endometrial glands (Figure 41-2).

Pattern of Spread

Endometrial cancer spreads by (1) direct extension, (2) exfoliation of cells that are shed through the fallopian tubes, (3) lymphatic dissemination, and (4) hematogenous dissemination.

The most common route of spread is direct extension of the tumor to adjacent structures. The tumor may invade through the myometrium and eventually penetrate the serosa. It may also grow downward and involve the cervix. Although uncommon, progressive growth may eventually involve the vagina, parametrium, rectum, or bladder.

Exfoliated cells may pass through the fallopian tubes and implant on the ovaries, the visceral or parietal peritoneum, or the omentum.

Lymphatic spread occurs most commonly in patients with deep myometrial penetration. **Spread occurs mainly to the pelvic nodes and subsequently to the paraaortic nodes, although simultaneous spread to both nodal groups may occur.** About 50% of patients with positive pelvic nodes will have positive paraaortic nodes, but isolated paraaortic nodal metastases occur in only about 2-3% of cases.

In stage I endometrial cancer, the overall incidence of pelvic lymph node metastases is about 12%, and paraaortic metastases occur in about 8% of cases. **In patients with deeply invasive, poorly differentiated stage I adenocarcinomas, pelvic lymph node metastases occur in up to 40%** of cases. Lymphatic spread is also responsible for vaginal vault recurrences.

Hematogenous dissemination is less common, but it results in parenchymal metastases, particularly in the lungs or liver, or both.

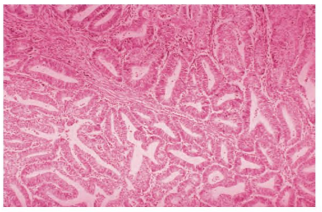


FIGURE 41-1 Well-differentiated endometrial adenocarcinoma. Note the back-to-back glands with minimal intervening stroma and the gland-within-gland pattern.

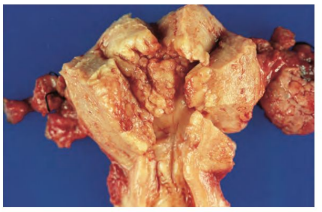


FIGURE 41-3 Specimen from a total abdominal hysterectomy and bilateral salpingo-oophorectomy. The uterus has been opened to reveal an exophytic carcinoma on the posterior wall of the corpus.

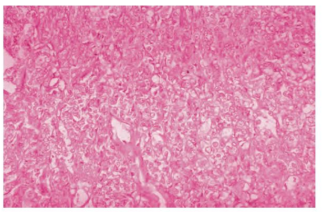


FIGURE 41-2 Poorly differentiated endometrial adenocarcinoma. Note the predominantly solid nature of the tumor with minimal gland formation.

Treatment

STAGE I

Surgery

Total hysterectomy and bilateral salpingo-oophorectomy are performed on all patients, unless there are absolute medical contraindications (Figure 41-3). This is usually performed by laparoscopic or robotic surgery, although some cases will still require open laparotomy. Upon entering the abdomen, peritoneal washings are taken with normal saline for cytologic evaluation, although the status of the washings is no longer part of the FIGO staging. Retroperitoneal spaces should be opened and evaluated, and any enlarged pelvic or paraaortic lymph nodes should be resected. **Formal surgical staging, including at least pelvic lymphadenectomy, should be performed on high-risk patients, including those with serous, clear cell, or grade 3 histology; outer-half myometrial invasion; or cervical extension.**

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.

Recommendations are as follows (Figure 41-4):

1. Patients with grade 1 or 2 endometrioid carcinomas confined to the inner half of the myometrium may be followed **without adjuvant therapy** (i.e., **stage IA, grade 1 or 2**).

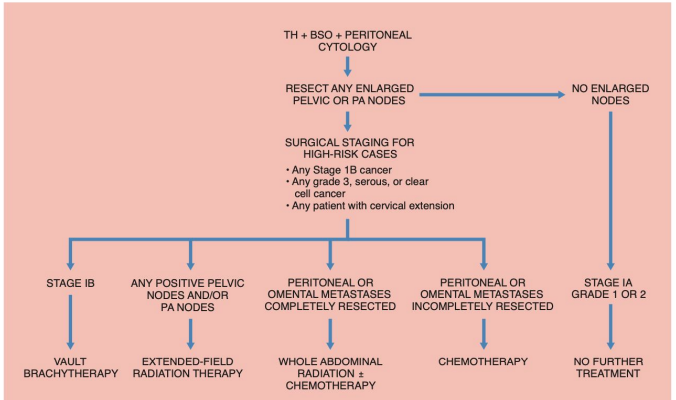


FIGURE 41-4 Algorithm for the treatment of stage I and occult stage II endometrial cancer. *BSO,* Bilateral salpingo-oophorectomy; *PA,* paraaortic; *TH,* total hysterectomy.

2. Patients with **high-risk carcinomas with negative pelvic nodes** (i.e., any stage IB cancer; any grade 3, clear cell, or serous cancer; or any stage II cancer) may have **vault brachytherapy** (without external beam pelvic radiation).
3. Patients with any positive pelvic nodes or proven positive paraaortic nodes should receive **extended-field radiation** (i.e., pelvic and paraaortic).
4. For patients with pelvic peritoneal or upper abdominal metastases completely resected, whole abdominal radiation may be given.

In patients medically unfit for surgery, radiation therapy alone may be employed. A combination of intracavitary plus external beam radiation is used. The overall 5-year survival rate is about 20% lower than that for patients treated with hysterectomy.

Hormone Therapy

Endometrial cancer occasionally occurs **in women younger than 40 years of age.** These tumors are usually at an early stage and of low grade, and there is frequently a desire to preserve fertility. **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. A levonorgestrel-releasing intrauterine device (Mirena) may also be useful in these patients.

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. If the lymph nodes are negative, no brachytherapy is required. If they are positive, postoperative external beam extended-field radiation is required.

ADVANCED STAGES

For advanced disease, treatment must be individualized. The uterus, tubes, and ovaries should be removed, if possible, for palliation of bleeding and other pelvic symptoms. If gross disease is present in the upper abdomen, tumor metastases that are readily removable, such as an omental "cake," should be extirpated in an attempt to improve the patient's quality of life by temporarily decreasing abdominal discomfort and ascites. In addition, patients with advanced disease will also require chemotherapy and/or radiation therapy.

Some cases of advanced disease are a result of delayed diagnosis. **If the patient has an advanced grade 1 or 2 tumor with positive estrogen receptors (ERs) or progesterone receptors (PRs), good responses and prolonged survival may be seen with high-dose progestin or tamoxifen therapy.**

Chemotherapy

The role of chemotherapy in patients with advanced endometrial cancer remains controversial. **Platinum-based regimes are the most effective,** but increased pelvic recurrence rates have been reported when adjuvant chemotherapy is used alone in patients with high-risk or advanced disease.

RECURRENT DISEASE

Seventy-five percent of recurrences develop within 2 years of treatment. If recurrent disease is detected, the patient should undergo a complete physical examination and metastatic workup. Careful follow-up is particularly important for patients treated without adjuvant therapy. The majority of recurrences in these patients are at the vaginal vault, and 70-80% of isolated vault recurrences can be salvaged by radiation therapy.

Metastases in other sites, such as the upper abdomen, lungs, or liver, are treated initially with high-dose progestins or antiestrogens. About one-third of recurrent endometrial carcinomas contain ERs and PRs, with the more well-differentiated tumors more likely to contain such receptors. As with breast cancer, the likelihood of response to progestin treatment is increased in patients whose tumor contains ERs and PRs. Approximately 80% of such patients respond to progestin therapy, compared with fewer than 10% of patients whose tumor is receptor-negative.

Medroxyprogesterone acetate (Provera 50 mg three times daily; Depo-Provera 400 mg intramuscularly weekly) or megestrol acetate (Megace 80 mg twice daily) may be given. **If disease progresses while the patient is receiving progestins, chemotherapy may be offered.** The combination of carboplatin and paclitaxel (Taxol) gives a response rate of about 50%.

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%.**

TABLE 41-4

CARCINOMA OF THE CORPUS UTERI: PATIENTS TREATED FROM 1999 TO 2001 WITH SURVIVAL RATES BY FIGO SURGICAL STAGE (*N* = 7990)

		Overall Survival (%)		
Strata	Patients	1-Year	3-Year	5-Year
IA	1054	98.2	95.3	90.8
IB	2833	98.7	94.6	91.1
IC	1426	97.5	89.7	85.4
IIA	430	95.2	89.0	83.3
IIB	543	93.5	80.3	74.2
IIIA	612	89.0	73.3	66.2
IIIB	80	73.5	56.7	49.9
IIIC	356	89.9	66.3	57.3
IVA	49	63.4	34.4	25.5
IVB	206	59.5	29.0	20.1

Modified from Creasman WT, Odicino F, Maisonneuve P, et al: Carcinoma of the corpus uteri. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer. *Int J Gynaecol Obstet* 95(Suppl 1):S105-S143, 2006.
These results are based on the 1988 FIGO staging system. Stages IA and IB are now officially combined as stage IA, and there is no stage IIA.

Five-year survival rates for each FIGO stage of endometrioid endometrial cancer are presented in Table 41-4.

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.

Uterine Sarcomas

Uterine sarcomas account for about 3% of uterine cancers. They are mesodermal tumors, which have a tendency for hematogenous dissemination and a poor prognosis.

CLASSIFICATION

A classification system for uterine mesodermal tumors is presented in Table 41-5.

Uterine sarcomas may also be classified as homologous, implying that the tissue that is malignant is normally present in the uterus (e.g., endometrial stroma, smooth muscle), **or heterologous,** implying that the tissue that is malignant is not normally present in the uterus (e.g., bone or cartilage). The majority of pure uterine sarcomas are leiomyosarcomas and endometrial stromal sarcomas.

Reference

TABLE 41-5

UTERINE MESODERMAL TUMORS WITH MALIGNANT POTENTIAL

Tumor Type	Percentage of Tumors
Smooth Muscle Tumors	30-40%
Leiomyosarcomas	
Smooth muscle tumors of uncertain malignant potential	
Endometrial Stromal Tumors	15-25%
Endometrial stromal sarcomas	
Undifferentiated uterine sarcomas	
Carcinosarcomas	40-50%
Homologous	
Heterologous (malignant mixed müllerian tumors)	
Adenosarcomas	5%

TABLE 41-6

INTERNATIONAL FEDERATION OF GYNECOLOGY AND OBSTETRICS STAGING FOR LEIOMYOSARCOMAS (2009)

Stage	Definition
I	Tumor limited to uterus
IA	<5 cm
IB	>5 cm
II	Tumor extends to the pelvis
IIA	Adnexal involvement
IIB	Tumor extends to extrauterine pelvic tissue
III	Tumor invades abdominal tissues (not just protruding into the abdomen)
IIIA	One site
IIIB	More than one site
IIIC	Metastasis to pelvic and/or paraaortic lymph nodes
IV	
IVA	Tumor invades bladder and/or rectum
IVB	Distant metastasis

From FIGO Committee on Gynecologic Oncology: FIGO staging for uterine sarcomas. *Int J Gynaecol Obstet* 104:179, 2009.

LEIOMYOSARCOMA

Leiomyosarcomas usually arise de novo from the uterine muscle, although rarely they may arise from a preexisting leiomyoma. The risk of malignant transformation in a benign fibroid is less than 1%. **The histologic criteria for distinguishing leiomyosarcomas from leiomyomas are the mitotic count (usually >10 per 10 high-power fields), the presence or absence of coagulative necrosis, and the presence or absence of cellular atypia.** Leiomyosarcomas were officially staged by FIGO in 2009 (Table 41-6).

Clinically, the mean age of patients with leiomyosarcoma is about 55 years. Patients with this disease may present with pelvic pain, abnormal uterine bleeding, or a pelvic or lower abdominal mass. A sensation of pressure on the bladder or rectum may also be noted.

Most cases are not diagnosed preoperatively; they are often discovered at the time of exploratory surgery for a probable fibroid. Curettings are usually normal. **If a known fibroid uterus appears to be rapidly enlarging, especially postmenopausally, malignancy should be suspected.**

The treatment of a uterine leiomyosarcoma consists of total abdominal hysterectomy and bilateral salpingo-oophorectomy. Adjuvant pelvic radiation appears to decrease local pelvic recurrence; it does not prolong survival, however, because most patients die with distant metastases.

Response rates to chemotherapy are very low.

TABLE 41-7

INTERNATIONAL FEDERATION OF GYNECOLOGY AND OBSTETRICS STAGING OF ENDOMETRIAL STROMAL SARCOMAS AND ADENOSARCOMAS (2009)

Stage	Definition
I	Tumor limited to uterus
IA	Tumor limited to endometrium/endocervix with no myometrial invasion
IB	Less than or equal to half myometrial invasion
IC	More than half myometrial invasion
II	Tumor extends to the pelvis
IIA	Adnexal involvement
IIB	Tumor extends to extrauterine pelvic tissue
III	Tumor invades abdominal tissues (not just protruding into the abdomen)
IIIA	One site
IIIB	More than one site
IIIC	Metastasis to pelvic and/or paraaortic lymph nodes
IV	
IVA	Tumor invades bladder and/or rectum
IVB	Distant metastasis

From FIGO Committee on Gynecologic Oncology: FIGO staging for uterine sarcomas. *Int J Gynaecol Obstet* 104:179, 2009.
Note: Simultaneous tumors of the uterine corpus and ovary/pelvis in association with ovarian/pelvic endometriosis should be classified as independent primary tumors.

ENDOMETRIAL STROMAL TUMORS

The three types of stromal tumors are (1) endometrial stromal nodule; (2) endometrial stromal sarcoma, previously known as endolymphatic stromal myosis; and (3) high-grade endometrial sarcoma. The first of these, **the stromal nodule, is a rare, benign condition.** There are typically 3 or fewer mitoses per 10 high-power fields. A hysterectomy is curative. These tumors were officially staged by FIGO in 2009 (Table 41-7).

Endometrial stromal sarcoma is a low-grade lesion. Histologically, there is minimal to no cellular atypia, with usually fewer than 5 mitoses per 10 high-power fields. There is always evidence of vascular channel invasion. These patients usually present with abnormal vaginal bleeding and often with pelvic pain.

Most patients are cured with total abdominal hysterectomy and bilateral salpingo-oophorectomy. Local and distant recurrences may occur, even 10 to 20 years later, and require reexploration and resection of disease. Prolonged survival is possible after resection of recurrent disease, and response to progestins is good. Pelvic disease may respond to radiation therapy.

Undifferentiated endometrial sarcoma generally causes abnormal uterine bleeding, and more than half the patients are premenopausal. **The diagnosis can often be made by endometrial biopsy or uterine curettage.** Histologically, there are 10 or more mitoses per 10 high-power fields, and the lesion is composed of very poorly differentiated cells. Aggressive myometrial invasion occurs, and hematogenous spread is common at the time of diagnosis.

The treatment of high-grade endometrial sarcoma is total abdominal hysterectomy and bilateral salpingo-oophorectomy. A thorough exploration of the peritoneal cavity and retroperitoneum should be done for evidence of metastases. **Postoperative pelvic irradiation improves local control but does not improve survival.** In patients with metastatic disease, progestogens or chemotherapy may be offered. The best chemotherapeutic agents are cisplatin, doxorubicin, and ifosfamide, but the prognosis is poor.

ADENOSARCOMAS

Adenosarcomas are typically low-grade tumors characterized by a benign epithelial component and a malignant mesenchymal component. The latter is commonly a low-grade endometrial stromal sarcoma. These tumors are usually seen in postmenopausal women, and the treatment and prognosis are consistent with that of the mesenchymal component.

MALIGNANT MIXED MESODERMAL TUMORS

Malignant mixed mesodermal tumors or carcinosarcomas are believed to be metaplastic carcinomas, and they behave, and should be managed, as a grade 3 endometrioid carcinoma. They usually occur in postmenopausal patients and present with vaginal bleeding or discharge. About one-third of patients have tumors growing through the cervix into the vagina as a polypoid mass. The tumors aggressively invade the myometrium and disseminate via the lymphatics and the bloodstream. **Up to 50% of patients have evidence of metastatic disease at the time of diagnosis if surgically staged.**

Prognosis

The prognosis for uterine leiomyosarcomas and endometrial sarcomas is poor because of the propensity for hematogenous dissemination. The overall 5-year survival rate is about 35%. Patients with endometrial stromal sarcomas have a good prognosis, whereas patients with stage I or II carcinosarcomas have a 5-year survival of about 70% if treated with surgical staging and adjuvant radiation and chemotherapy.

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Good Luck!

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