Reviewed By
RAAOUM M. JABOR

Video Case

Endometriosis

Objectives:

- → Define endometriosis
- → Explain the pathogenesis of endometriosis theories
- → List the common sites of occurrence of endometriosis
- → Describe the symptoms and physical examination findings of endometriosis
- → List the investigations required to confirm the diagnosis of endometriosis
- → Describe the medical and surgical management options for endometriosis
- → Describe the symptoms and signs of adenomyosis
- → Define adenomyosis and describe its gross pathological appearance.
- → Describe the treatment options for adenomyosis.

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Female presentation

Video Case | Editing File

Endometriosis

Definition:

Endometriosis is a benign condition in which endometrial glands and stroma are seen outside the endometrial cavity. While it is associated with increased risks of epithelial ovarian carcinoma, it is not a premalignant condition.

Prevalence:

- Endometriosis affects 7-10% of female in their reproductive age.
- The prevalence of endometriosis in infertile women is 38%.
- 71-87% of women with chronic pelvic pain have endometriosis.

Pathogenesis:

- Islands of endometriosis respond cyclically to ovarian steroid hormone production. The implants proliferate under estrogenic stimulation and slough when support from estrogen and progesterone is removed with involution of the corpus luteum. Endometriotic implants **result in:**
  - ↑ Production of inflammatory and pain mediators
  - Anatomical changes (e.g., pelvic adhesions) ⟶ infertility
  - Nerve dysfunction
- Although the etiology is not known, but genetic predisposition clearly plays a role. The most accepted theory of explanation is that of Sampson.

- Theories:

Retrograde flow (Sampson theory): most acceptable theory

Endometrial fragments of endometrial tissue, which is normally shed at the time of menstruation **transported through the fallopian tubes** at the time of menstruation then implant and grow in various intra abdominal sites.

Vascular-lymphatic dissemination:

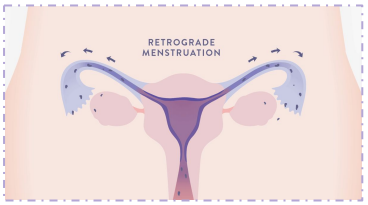
Endometrial cells travel **through vessels and lymph** to distal places like: kidney, pleural cavity, brain, lungs, nose.

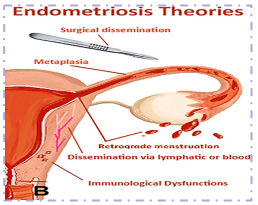
Coelomic metaplasia (mullerian metaplasia theory): 2nd most acceptable theory

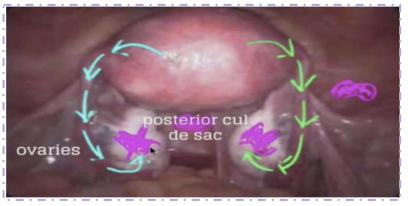
- **Multipotent stem cells** in peritoneal cavity that develop to functional endometrial tissue.
- This theory explains the presence of endometriosis in adolescence (Before menarche).

Immunological factor

The cause of the endometriosis **depends on the age and location**. if the patient is pre-menarche, the cause of her endometriosis would be **dysplasia of coelomic epithelium.** If the endometriosis in the brain for instance, the cause would be **lymphatic-vascular dissemination.**







Cervical erosion is an ulcer T or F? F it's metaplasia stratified into columnar / AKA cervical ectopia

Endometriosis

Risk factors:

- Female in their productive age.
- **First degree** family history **(Genetic predisposition)**
- Prolonged exposure to endogenous estrogen (early menarche, late menopause)
- Menorrhagia (> 1 week)
- Nulliparity

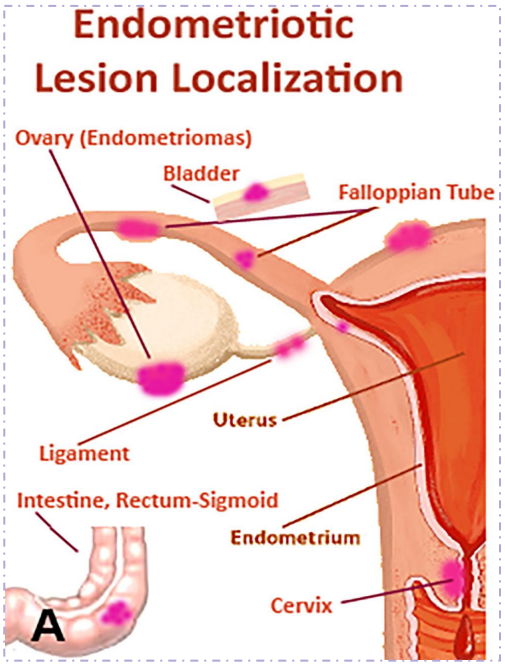
Sites of occurrence:

Common sites:

- **Ovaries (most common site** and its usually bilateral).
  - Because this is functioning endometrium, it bleeds on a monthly basis and can create adnexal enlargements known as endometriomas, also known as a **chocolate cyst.**
- **Pelvic peritoneum:** Posterior cul-de-sac (uterosacral ligament and rectovaginal septum), vesicovaginal space (space between bladder & uterus), Round ligament, fallopian tube.
  - **Cul-de-sac: The second most common site,** in this area the endometriosis nodules grow on the **uterosacral ligaments,** giving the characteristic uterosacral ligament nodularity and tenderness appreciated by the rectovaginal examination.
  - Menstruation into the cul-de-sac creates **fibrosis** and **adhesions** of bowel to the pelvic organs and a rigid cul-de-sac, which accounts for dyspareunia.
- Cyclic hematuria indicates an endometriotic lesion in the urinary tract
- Rectal bleeding indicates an endometriotic lesion in the intestines

Less common sites:

- In rare cases can occur in brain, lung, upper ureter, sites of surgical scars.



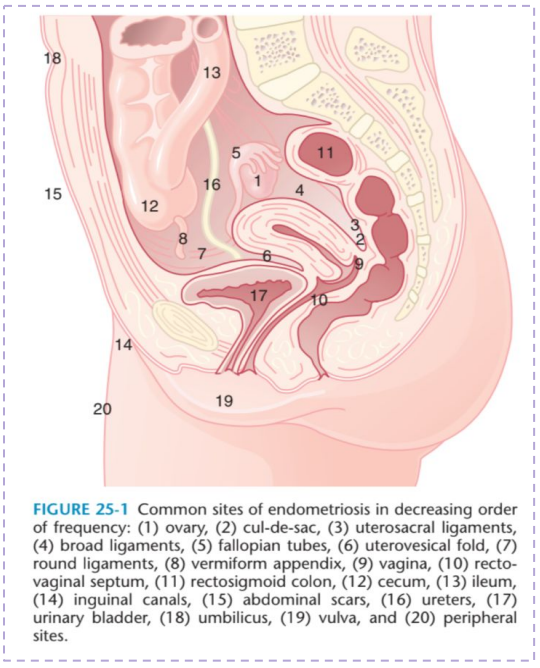


FIGURE 25-1 Common sites of endometriosis in decreasing order of frequency: (1) ovary, (2) cul-de-sac, (3) uterosacral ligaments, (4) broad ligaments, (5) fallopian tubes, (6) uterovesical fold, (7) round ligaments, (8) vermiform appendix, (9) vagina, (10) recto-vaginal septum, (11) rectosigmoid colon, (12) cecum, (13) ileum, (14) inguinal canals, (15) abdominal scars, (16) ureters, (17) urinary bladder, (18) umbilicus, (19) vulva, and (20) peripheral sites.

Endometriosis

Signs:

Sometimes there is no signs because it's either small or not clear, but we may see:

- Fixed non-Mobile uterus, secondary to adhesions.
- **Ovarian endometriosis (chocolate cysts)** **functional cysts**, tender but not palpable.
- **Uterosacral nodularity (classic sign).**

In PEx:

- **Pelvic tenderness** is common.
- A **fixed, retroverted uterus** is often caused by cul-de-sac adhesions.
- **Uterosacral ligament nodularity** is characteristic.
- **Enlarged adnexa** may be found if an endometrioma is present, appreciated on bimanual examination. In more than half the patients who are noted to develop endometriosis during childhood and adolescence, varying degrees of genital tract obstruction may be found.
- Lateral displacement of the cervix (due to uterosacral scarring)

Symptoms:

Symptoms triad: 3Ds

1. **Dysmenorrhea:** medical term for a painful menses.
    a. **Cyclical pelvic pain** 1 to 2 weeks before menstruation and peaks 1 to 2 days before menstruation pain end with menstruation.
        i. Pain is usually **dull ache not colicky**
        ii. Pelvic-abdominal pain is not necessarily related to the extent of disease.
2. **Dyspareunia.**
3. **Dyschezia.** (Pain during defecation, due to ectopic endometrial tissues on the bowel or rectal area)
4. **Infertility** (The association between mild to moderate endometriosis and infertility is not clear. When more advanced stages of endometriosis distort the pelvic structures, the role of endometriosis in infertility is more predictable). Endometriosis causes inflammation and adhesions that can change pelvic anatomy, altering egg quality and impairing implantation

- Endometriosis is often asymptomatic and may be an incidental finding during surgery for other conditions.
- Also abnormal bleeding is common.
- There is no clear relationship between the size or stage of endometriosis and the frequency and severity of pain.
- (If any patient presents with abnormal uterine bleeding, we should not think of endometriosis because heavy bleeding is not a hallmark of endometriosis)
- Adenomyosis occurs when tissue of uterine lining grows into your uterine wall, leading to doubling uterine wall patient can present with menorrhagia is more common among multiparital.

Complications:

- Causes inflammatory reaction → formation of **adhesions & scarring.** frozen pelvic
- Not malignant but associated with higher risk of ovarian carcinoma mechanism unclear.
- Infertility
- anemia

Endometriosis

Diagnosis

- The definitive diagnosis is generally made on the basis of the characteristic **gross** and **histologic** findings obtained at laparoscopy or laparotomy ultrasound used to exclude other causes.
- **Laparoscopy** (most definitive diagnostic tool/confirmatory): may show endometriotic implants and adhesions.
- **Laparotomy identification of endometriosis nodules or endometriomas.**
- Findings: (2 out of 4 is diagnostic)
    - Endometrial stroma
    - Endometrial gland
    - Endometrial epithelium
    - Hemosiderin-laden macrophages
- **Transvaginal ultrasound** (best initial test)
    - The uterus is generally not enlarged (endometriotic implants are extrauterine). But the uterus is uniformly enlarged in adenomyosis.
    - Evidence of ovarian cysts (**chocolate cysts**).
    - Nodules in bladder or rectovaginal septum
- WBC and erythrocytes sedimentation rate (ESR) are normal. CA-125 may be elevated.
- OCP trial if they get better that the diagnosis.

Management:

Goal: Seeks to prevent shedding of the ectopic endometrial tissue, thus decreasing adhesion formation and pain.

1. Decrease pelvic pain, **by giving NSAID.**
2. Decrease surgical intervention.
3. Preserve fertility.

- **Pregnancy**: can be helpful to endometriosis because during this time there is no menstruation; also, the dominant hormone throughout pregnancy is progesterone, which causes atrophic changes in the endometrium. However, infertility may make this impossible.

- **Pseudopregnancy (preventing Progesterone withdrawal):**
    1. **First line therapy:** oral contraceptive. Easy to use and inhibit functional endometriosis.
    2. Progesterone therapy (Visanne): implants, oral or injection, inhibit GnRh which suppress endometriosis.

Endometriosis

Management:

- **Pseudomenopause:**
  - achieves this goal by making the ectopic endometrium atrophic. The treatment is based on inhibition of the hypothalamic–pituitary–ovarian axis to decrease the estrogen stimulation of the ectopic endometrium.

1. **GnRh agonist: down regulate pituitary gland. Can cause <u>menopause like symptoms.</u> It can't be used as a long term therapy in young patients bc of low estrogen (It will cause osteoporosis).** **Patients on leuprolide therapy for >3-6 months** can complain of menopausal symptoms such as **hot flashes**, sweats, **vaginal dryness**, and personality changes. An alternative to leuprolide is depot medroxyprogesterone one acetate (DMPA), which also suppresses FSH and LH does not result in vasomotor symptoms.
2. **Danazol: suppresses LH/FSH secretion. Menopause-like symptoms. It has androgenic properties. So, women may have breast atrophy, hirsutism, acne, deepening of the voice** most imp irreversible and it's disaster if she gets pregnant with female fetus.
   i. Not used frequently due to its side effects) Danazol is an androgen similar to testosterone. "Zol" = زول = (صفات رجولية) رجل

Surgical therapy:

Large endometriomas (>3 cm) are usually amenable only to surgical resection or failure of medical therapy.

1. **Conservative (fertility-preserving treatment):** By laparoscopy
   a. Excision. (of the endometriod)
   b. Cauterization or ablation of vestal endometriosis.
   c. Lysis of peritubal adhesions.
   d. Ovarian cystectomies as well as oophorectomies can be treatment for endometriomas.

2. **Extirpative or aggressive:**

If medical and conservative is **not feasible or** if **fertility is not desired**, particularly if **severe pain** is present because of diffuse adhesions.

   a. Total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO). Estrogen replacement therapy is then necessary.

Why do they have infertility?
1- Scarring and adhesions will result in blockage of the tube and the fimbrial end.
2- Bleeding into the pelvis cavity will result in inflammation and release of cytokines that will inhibit the fertilization of the egg.
3- May affect the ovulation and prevent the release of the egg.

Adenomyosis

Definition:

- **Adenomyosis or "endometriosis interna" is the extension of endometrial glands and stroma into the uterine musculature more than 2.5 mm beneath the basalis layer.**
- The most common presentation is diffuse involvement of the myometrium.
- Occasionally, the adenomyosis may be confined to one portion of the myometrium and take the form of a fairly well-circumscribed adenomyoma.
- Contrary to the situation with a uterine leiomyoma (fibroid), no distinct capsular margin can be detected on cut sections between the adenomyoma and the surrounding myometrium.

Diagnosis:

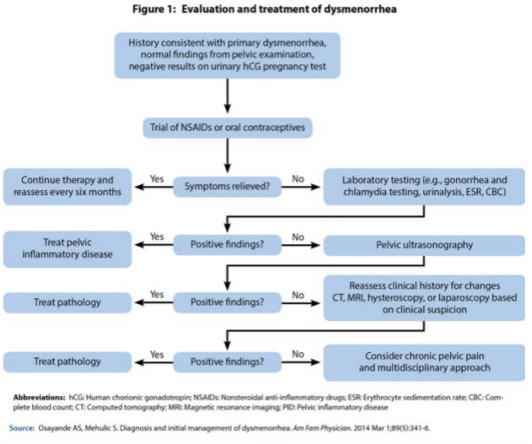
- In most cases the diagnosis is made **clinically** by identifying an **enlarged, symmetric, tender uterus** with **cystic areas found within the myometrial wall** in the absence of pregnancy.
- U/S showed uniformly enlarged uterus/ on US there was heterogeneity texture of the myometrium.
- A 48 years old lady comes with menorrhagia and dysmenorrhea. What is the next step? Transvaginal ultrasound
- Histology serves to confirm the diagnosis after hysterectomy **not** endometrial biopsy.

Symptoms:

- The majority of women are asymptomatic.
- The most common symptoms are secondary dysmenorrhea and **menorrhagia =** painful heavy menstrual bleeding with regular cycle (heavy and painful periods)
- **Uterus is generally clinically and symmetrically enlarged and may be mildly tender; dysmenorrhea is associated with a dull pelvic dragging sensation.**

Management:

- Conservative, to reduce heavy bleeding
  - Combined oral contraceptives
  - Progestin-only contraception (e.g., IUD, levonorgestrel intrauterine system (LNG-IUS), continuous-use contraceptive pill)
  - NSAIDs for pain relief
  - GnRH agonists
- Surgical
  - Hysterectomy is the definitive treatment.
  - Excision of single, organized adenomyoma.



Teaching case

A 28-year-old woman G0P0 woman is seen because of the inability to conceive for the past two years. She has never used oral contraceptives and she and her husband have not used any form of birth control for over two years. Her menarche occurred at the age of 12 and her menses became very painful in her late teens. She has had chronic cyclical pelvic pain, which has progressively worsened over the years. This pain is incapacitating at times. She describes the location of the pain to be in the lower abdomen and pelvis that radiates into the lower back. In addition to the pain, her menstrual periods have become increasingly frequent and heavy. She experiences deep dyspareunia that began with her first sexual partner and has continued with her husband. She denies any non-cyclical vaginal bleeding, discharge and weight loss. (this is important because we can rule out oncological causes and other causes of abnormal uterine bleeding). She states that her 22-year-old younger sister has always had very painful menses. On physical examination the patient looks her age. She is 138 lbs and is 5'6". Her BP is 110/76 mm Hg with a heart rate of 85 bpm. Her head and neck examination is negative. Cardiac and respiratory systems are also normal. Examination of the abdomen reveals that it is flat with no scars. On palpation she has generalized tenderness of the lower abdomen. There are no signs suggesting evidence of a surgical abdomen and she has no costovertebral angle tenderness. The pelvic exam showed a fixed, retroverted uterus. The uterosacral ligaments on both sides are nodular. A 5 cm right adnexal mass is palpated and tender.
Transvaginal ultrasound of the pelvis showed a 5.5 cm cystic mass with low-level echoes in the right ovary. The left ovary was reported as normal. The uterus is retroverted and is of normal size and contour. There is no evidence of fibroids and the endometrial lining is normal.

Q1: What symptoms does this patient present with that would lead to a suspicion of endometriosis?

- Infertility.
- Dysmenorrhea.
- Cyclic lower abdominal and pelvic radiate to lower back.
- Dyspareunia. (deep not superficial)
- Dyschezia.(painful defecation)
- Possible family history.
- **Key Learning Point:** Endometriosis can manifest in many ways. Patients may have no symptoms to significant symptoms. It is a painful syndrome with no heavy menses usually.

Q2: Describe the physical findings for this patient that helps confirm a possible diagnosis of endometriosis?

- Tender nodular uterosacral ligaments on pelvic exam.
- Fixed, retroflexed uterus. (Scar tissue is attached to the uterus and prevents it from moving)
- Palpable and tender right adnexal mass.

Q3: After discussing the possibility of endometriosis, the patient asks, "How did I get this disease?" How do you answer the patient?

1. Attachment and implantation of endometrial glands and stroma to peritoneal tissue from retrograde menstrual flow. Through fallopian tube.
2. Hematogenous and lymphatic spread. Which explains sites as brain, lung, nose.
3. Stem cells in peritoneal cavity that develop to functional endometrial tissue (celiomic).

Teaching case

Q4: What alternative diagnoses would you consider in this patient (DDx)?

- Chronic pelvic pain: chronic pelvic inflammatory disease, adhesions, gastrointestinal conditions (IBD & Diverticulosis), interstitial cystitis and benign or malignant ovarian neoplasm.
- Dysmenorrhea: causes of primary and secondary dysmenorrhea
- Dyspareunia: chronic pelvic inflammatory disease, or ovarian cysts.
- Adenomyosis (the tissue that normally lines the uterus (endometrial tissue) grows into the muscular wall of the uterus). (leads to heavy bleeding & pain)

Q5: How is the diagnosis of endometriosis made?

- **First step:** History and physical examination (Ask about dysmenorrhea and family history)
- Direct visualization (AKA laparoscopy) is needed for establishing a diagnosis.
- **Definitive diagnosis:** tissue biopsy (stroma & endometrial glands are important factors in the biopsy to diagnose endometriosis). US is suggestive but we need histopathology for diagnosis. (We can see chocolate cyst on US)
- Pelvic sonogram cannot make diagnosis, but can exclude other conditions.
- MRI (Nowadays, the sensitivity of MRI in the diagnosis of endometriosis is much better than before)

Q6: What protocols are used to stage endometriosis?

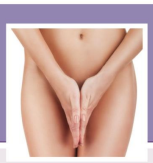
- **The American Society of Reproductive Medicine (ASRM)** protocol correlates fertility potential with a quantified stage of disease. The staging includes the color of lesions, the percentage of surface involved and a detailed description of endometriomas.
- **The revised American Fertility Society (AFS)** staging system is generally used to stage endometriosis in the infertile patient. In the AFS system, points are assigned for size and depth of implants and for the severity of adhesions in various locations . Stages I through IV are assigned on the basis of points. Management can be guided by stage and desire for fertility.
- Staging is important for communication between physicians for research purposes and to measure disease progression. Staging is also important for the treatment.

Q7:What are the treatment options for endometriosis?

- **Depends on** presenting symptoms and severity, location and severity, desire for fertility, US and MRI findings, age, and possible gastrointestinal or urinary tract involvement.
- **Conservative management** may be considered for patients with minimal symptoms and disease and/or patients who are trying to conceive.
- Medical therapy includes:
  1. NSAIDs (First line): (for it to work, it needs to be taken before the pain reaches it peak) .
  2. Combined estrogen and **progestin** contraceptive (Second line): (progestin especially will cause continuous shedding, so the lining will be thin with less inflammation, adhesions, bleeding, and prostacyclins).
  3. Progestins alone. (Visanne).
  4. Danazol. (Testosterone derivative so can have androgenic effects, CI when fertility is the goal)
  5. Gonadotropin- releasing hormone agonist (GnRH). (not given for more than 6 months as it causes osteoporosis) For this patient OCP is not an option, so NSAIDs then laparoscopy and conservative therapy.

Reference

CHAPTER 25



Endometriosis and Adenomyosis

JOSEPH C. GAMBONE

CLINICAL KEYS FOR THIS CHAPTER

- *Endometriosis* is defined as the presence of endometrial glands and stroma in extrauterine locations. An accurate prevalence for endometriosis is not known, but it is estimated that about 10% of women of reproductive age have the disease. Most women are without symptoms, but some have severe pain often manifested by dysmenorrhea, dyspareunia, and, less often, dyschezia. Infertility is often the initial sign of endometriosis.
- Retrograde menstruation, metaplastic transformation of peritoneal mesothelium, and lymphatic spread are the three most often cited hypotheses for the origins and locations of endometriosis. An immunologic factor is presumed to explain why some women who have risk factors similar to those that are affected do not develop the disease. Genetic predisposition is highly likely, based on polygenetic, multifactorial inheritance.
- The staging of endometriosis is based upon the location, extent, and appearance of the lesions. Implants of glands and stroma may be dark red, brown, bluish gray, or even white. The lesions are frequently surrounded by fibrosis, which results in puckering. Ovarian cysts filled with hemosiderin-laden, "chocolate"-colored fluid may form metaplastic endometriomas.
- The amount of endometriosis does not always correlate with the severity of symptoms. Women with minimal or no symptoms may be managed expectantly. Medical treatments consist of initial trials of nonsteroidal antiinflammatory drugs (NSAIDs) and low-dose progestins, including oral contraceptives (OCs). More advanced medical therapy includes the androgenic danazol and gonadotropin-releasing hormone (GnRH) analogues. When fertility is desired but is not occurring spontaneously and medical therapy has failed, conservative laparoscopic surgery to reduce the amount of endometriosis and reactive adhesions is indicated. More definitive extirpative surgery involves removal of all endometriosis and adhesions, along with the uterus and adnexal tissues. One or both ovaries may be preserved if they are completely free of endometriosis.
- Adenomyosis is the extension of endometrial glands and stroma into the uterine musculature more than 2.5 mm beneath the basalis layer. The uterus is homogeneously enlarged. Although many women with adenomyosis are without symptoms, some have severe dysmenorrhea, and the disorder may adversely affect fertility. Medical therapy with NSAIDs is indicated initially for the pain and uterine bleeding. Endometrial ablation may be performed for heavy bleeding, and hysterectomy is sometimes indicated when more conservative treatment has failed.

It is estimated that 5-15% of women of reproductive age have some degree of endometriosis, defined as the presence of endometrial glands and stroma in extrauterine locations. **Both endometriosis and adenomyosis** (growth of endometrial glands and stroma into the uterine muscle) **are associated with pelvic pain and infertility.** Endometriosis and adenomyosis often present difficult diagnostic and therapeutic challenges. In the case of endometriosis, few gynecologic conditions can require such difficult surgical dissections.

Endometriosis

Endometriosis is a benign condition in which endometrial glands and stroma are present outside the uterine cavity and walls. Endometriosis is important

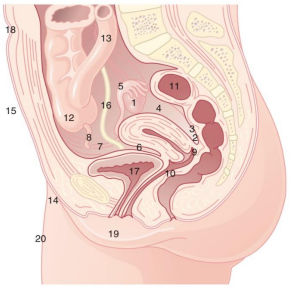


FIGURE 25-1 Common sites of endometriosis in decreasing order of frequency: (1) ovary, (2) cul-de-sac, (3) uterosacral ligaments, (4) broad ligaments, (5) fallopian tubes, (6) uterovesical fold, (7) round ligaments, (8) vermiform appendix, (9) vagina, (10) rectovaginal septum, (11) rectosigmoid colon, (12) cecum, (13) ileum, (14) inguinal canals, (15) abdominal scars, (16) ureters, (17) urinary bladder, (18) umbilicus, (19) vulva, and (20) peripheral sites.

appearance. These older, inactive lesions have been called the tattooing of endometriosis.

Endometriomas of the ovary are cysts filled with thick, chocolate-colored fluid that sometimes has the black color and tarry consistency of crankcase oil. This characteristic fluid represents aged, hemolyzed blood and desquamated endometrium. Usually, endometrial glands and stroma are present in the cyst wall. Sometimes, however, the pressure of the enclosed fluid destroys the endometrial lining of the endometrioma, leaving only a fibrotic cyst wall infiltrated with large numbers of hemosiderin-laden macrophages. Generally, ovarian implants are associated with significant scarring of the ovary to the pelvic sidewall or broad ligament. **Histologically, two of four characteristics must be found in the endometrioma specimen to confirm the diagnosis: endometrial epithelium, endometrial glands, endometrial stroma, and hemosiderin-laden macrophages.**

Although endometriosis is a benign process, it shares many characteristics with malignancy. It is locally infiltrative, invasive, and widely disseminated. It is also curious that cyclic hormones tend to induce growth, whereas continuous hormonal exposure, especially in high doses, generally induces significant regression.

STAGING

The American Society of Reproductive Medicine employs a staging protocol in an attempt to correlate fertility potential with a quantified stage of endometriosis. This staging, which was initially based on the allocation of points depending on the sites involved and the extent of visualized disease (Figure 25-3), was modified to include a description of the color of the lesions and the percentage of surface involved in each lesion type, as well as a more detailed description of any endometrioma. The lower portion of Figure 25-3 provides sketches of normal and abnormal uterine and adnexal anatomy where mapping of implants of endometriosis and adhesions can be documented for accurate staging.

SYMPTOMS

The characteristic triad of symptoms associated with endometriosis is dysmenorrhea, dyspareunia, and, less frequently, dyschezia. The pain that women experience with endometriosis varies with the time since the onset of the disease. Early in the clinical course, women tend to have cyclic pelvic pain, which starts 1 to 2 days before the menstrual flow and resolves at the end of the menses. This secondary dysmenorrhea is thought to be related to the premenstrual swelling and extravasation of blood and menstrual debris, which induces an intense inflammatory reaction in the surrounding tissue mediated by prostaglandins and cytokines that are more directly responsible for triggering the pain sensation. Deep, infiltrating implants, especially those in the retroperitoneal space, are associated with more pain than are superficial lesions. Over time, the pain may become more chronic, with exacerbations at the time of the menses. Interestingly, **there is no clear relationship between the stage of endometriosis and the frequency and severity of pain symptoms.**

Dyspareunia is generally associated with deep-thrust penetration during intercourse and occurs mainly when the cul-de-sac, uterosacral ligaments, and portions of the posterior vaginal fornix are involved. Deep-thrust dyspareunia can also result from uterine immobility caused by significant internal scarring caused by endometriosis. Endometriomas in these circumstances may be exquisitely tender to palpation.

Dyschezia is experienced with uterosacral, cul-de-sac, and rectosigmoid colon involvement. As the stool passes between the uterosacral ligaments, the characteristic dyschezia is experienced.

Premenstrual and postmenstrual spotting is a characteristic symptom of endometriosis. Heavy menstruation is uncommon, with the amount of flow usually diminishing with endometriosis. If the ovarian capsule is involved with endometriosis, ovulatory pain and midcycle vaginal bleeding often occur. Rarely, as

in gynecology because of its frequency, distressing symptomatology, association with infertility, and potential for invasion of adjacent organ systems, such as the gastrointestinal and urinary tracts.

OCCURRENCE

The prevalence of endometriosis in the general population is not known, but **it is estimated that 5-15% of women have some degree of the disease.** At least one-third of women with chronic pelvic pain have visible endometriosis, as do a significant number of infertile women. Interestingly, endometriosis is noted in 5-15% of women undergoing gynecologic laparotomies, and it is an unexpected finding in approximately half of these cases.

The typical patient with endometriosis is in her 30s, nulliparous, and infertile. However, in practice, many women with endometriosis do not fit the classic picture. Occasionally, endometriosis may occur in infancy, childhood, or adolescence, but at these early ages, it is usually associated with obstructive genital anomalies such as a uterine or vaginal septum. Although endometriosis should regress following menopause unless estrogens are prescribed, 5% of new cases develop in that age group. In addition, the scarifying involution from preexisting lesions may result in obstructive problems, especially in the gastrointestinal and urinary tracts.

PATHOGENESIS

The pathogenesis of endometriosis is not completely understood. Genetic predisposition clearly plays a role. The following three hypotheses have been used to explain the various manifestations of endometriosis and the different locations in which endometriotic implants may be found:

1. **The retrograde menstruation theory** of Sampson proposes that endometrial fragments transported through the fallopian tubes at the time of menstruation implant and grow in various intraabdominal sites. Endometrial tissue, which is normally shed at the time of menstruation, is viable and capable of growth in vivo or in vitro. To explain some rare examples of endometriosis in distant sites, such as the lung, forehead, or axilla, it is necessary to postulate hematogenous spread.
2. **The müllerian metaplasia theory** of Meyer proposes that endometriosis results from the metaplastic transformation of peritoneal mesothelium into endometrium under the influence of certain generally unidentified stimuli.
3. **The lymphatic spread theory** of Halban suggests that endometrial tissues are taken up into the lymphatics draining the uterus and are transported to the various pelvic sites where the tissue grows ectopically. Endometrial tissue has been found in pelvic lymphatics in up to 20% of patients with the disease.

Most authorities believe that several factors are involved in the initiation and spread of endometriosis, including retrograde menstruation, coelomic metaplasia, immunologic changes, and genetic predisposition. A fundamental question is why all menstruating women do not develop endometriosis, given that most, if not all, women have retrograde flow into the pelvic peritoneum during menstruation. The amount of exposure to retrograde flow and the woman's immunologic response seem to be critical. Researchers have identified differences in the chemical composition and biologic pathways of endometrial cells from women with endometriosis compared with those of unaffected women. They have also found significant differences in the inflammatory and growth factors in the peritoneal fluid of affected women. A clearer understanding of the pathophysiology of endometriosis would provide insights into more effective strategies for prevention and treatment.

SITES OF OCCURRENCE

Endometriosis occurs most commonly in the dependent portions of the pelvis. Specifically, implants can be found on the ovaries, the broad ligament, the peritoneal surfaces of the cul-de-sac (including the uterosacral ligaments and posterior cervix), and the rectovaginal septum (Figure 25-1). Quite frequently, the rectosigmoid colon is involved, as is the appendix and the vesicouterine fold of peritoneum. **Endometriosis is occasionally seen in laparotomy scars,** developing especially after a cesarean delivery or myomectomy in which the endometrial cavity has been entered. It is probable that endometrial tissue is seeded into the surgical incision. **Two of three women with endometriosis have ovarian involvement.**

PATHOLOGY

Islands of endometriosis respond cyclically to ovarian steroidal hormone production. The implants proliferate under estrogenic stimulation and slough when support from estrogen and progesterone is removed with involution of the corpus luteum. The sloughed material induces a profound inflammatory response, resulting in pain immediately and fibrosis in the longer term. The macroscopic appearance of endometriosis depends on the site of the implant, the activity of the lesion, the day of the menstrual cycle, and the time since implantation.

Lesions may be raised and flat with red, black, or brown coloration; fibrotic, scarred areas that are yellow or white in hue; or vesicles that are pink, clear, or red (Figure 25-2). The color of the implant is generally determined by its vascularity, the size of the lesion, and the amount of residual sloughed material. Newer implants tend to be red, blood-filled, active lesions. Older lesions tend to be much less active hormonally, scarred, and bluish gray in color, with a puckered

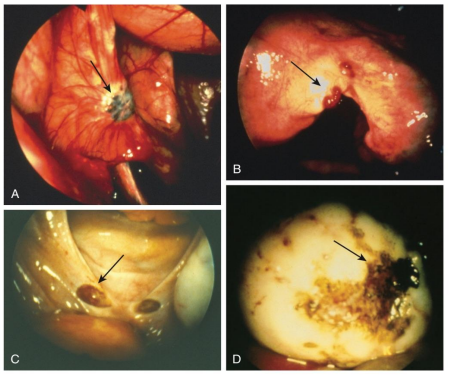


FIGURE 25-2 Appearance of red **(B),** brown **(C),** and black **(D)** raised lesions *(arrows)* of active endometriosis at the time of laparoscopy. The common finding of blue-gray lesions **(A)** represents less active "tatooing" of old endometriosis.

other organ systems are involved, menstrual hematochezia, hematuria, and other forms of endometriotic sloughing become evident.

The association between mild to moderate endometriosis and infertility is not clear. When more advanced stages of endometriosis distort the pelvic structures, the role of endometriosis in infertility is more predictable.

SIGNS

Endometriosis presents with a wide variety of signs, ranging from the presence of a small, exquisitely tender nodule in the cul-de-sac or on the uterosacral ligaments to a huge, relatively nontender, cystic abdominal mass. Occasionally, a small, tender, mulberry-like spot may be seen in the posterior fornix of the vagina. **Characteristically, a tender, fixed adnexal mass is appreciated on bimanual examination.** The uterus is fixed and retroverted in a substantial number of women with endometriosis. **Occasionally, no signs at all are appreciated during a physical examination.**

DIFFERENTIAL DIAGNOSIS

The main differential diagnoses in the acute phase of endometriosis are (1) chronic pelvic inflammatory disease or recurrent acute salpingitis, (2) hemorrhagic corpus luteum, (3) benign or malignant ovarian neoplasm, and, occasionally, (4) ectopic pregnancy.

DIAGNOSIS

The diagnosis of endometriosis should be suspected in an afebrile patient with the characteristic triad of pelvic pain; a firm, fixed, tender adnexal mass; and tender nodularity in the cul-de-sac and uterosacral ligaments. The characteristic sharp, firm, exquisitely tender "barb" (so called because it is reminiscent of barbed wire) felt in the uterosacral ligament is the diagnostic sine qua non of endometriosis, but this finding is generally present only in severe cases. An ultrasonic evaluation may indicate an adnexal mass of complex echogenicity, with internal echoes consistent with old blood. Imaging studies are of limited value in most cases. Serum levels of the cancer antigen CA-125 are frequently elevated in women with endometriosis. However, the positive predictive value of CA-125 for detecting endometriosis is low (about 20%), and this test should not be used to diagnose endometriosis.

The definitive diagnosis is generally made on the basis of the characteristic gross and histologic findings obtained at laparoscopy or laparotomy. Unfortunately, even the most experienced surgeon may fail to identify endometriotic implants visually,

Reference

American Society for Reproductive Medicine
Revised Classification of Endometriosis

Patient's name _____ Date _____

Stage I (minimal) — 1 – 5
Stage II (mild) — 6 – 15
Stage III (moderate) — 16 – 40
Stage IV (severe) — > 40

Laparoscopy____ Laparotomy____ Photography____
Recommended treatment _____

Total_____ Prognosis _____

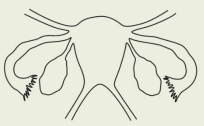
Peritoneum	Endometriosis	<1 cm	1-3 cm	>3 cm
	Superficial	1	2	4
	Deep	2	4	6
Ovary	R Superficial	1	2	4
	Deep	4	16	20
	L Superficial	1	2	4
	Deep	4	16	20
	Posterior cul-de-sac obliteration	Partial	Complete	
		4	40	
Ovary	Adhesions	<1/3 Enclosure	1/3 –2/3 Enclosure	>2/3 Enclosure
	R Filmy	1	2	4
	Dense	4	8	16
	L Filmy	1	2	4
	Dense	4	8	16
Tube	R Filmy	1	2	4
	Dense	4*	8*	16
	L Filmy	1	2	4
	Dense	4*	8*	16

*If the fimbriated end of the fallopian tube is completely enclosed, change the point assignment to 16.
Denote appearance of superficial implant types as red [(R), red, red-pink, flamelike, vesicular blobs, clear vesicles], white [(W), opacifications, peritoneal defects, yellow-brown], or black [(B), black, hemosiderin deposits, blue]. Denote percent of total described as R__%, W__%, and B__%. Total should equal 100%.

Additional endometriosis: _____

Additional pathology: _____

To be used with normal tubes and ovaries



To be used with abnormal tubes and/or ovaries

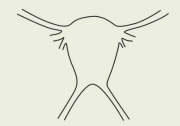


FIGURE 25-3 Modification of the revised American Society for Reproductive Medicine classification of endometriosis. (Reprinted with permission from American Society for Reproductive Medicine: Revised American Society for Reproductive Medicine classification of endometriosis: 1996. *Fertil Steril* 67:819–820, 1997.)

more conservative laparoscopic or open surgical approach is designed to destroy all endometriotic implants and remove all adhesive disease. This usually involves excision (not lysis) of all adhesions and laser ablation or electrocautery of suspected implants. Endometriomas present a challenge when fertility is desired. Any surgery on the ovary, particularly in women with low ovarian reserve, could adversely affect follicular function and decrease fertility (see Chapter 34). **Large endometriomas (>3 cm) are usually amenable only to surgical resection.** Because of extensive adhesive disease that generally surrounds these cysts, cystectomy is not always possible, and an oophorectomy may be necessary. Extensive tubal disease, with or without ovarian involvement, may be treated by removal of the affected organs but with uterine preservation for in vitro fertilization when at least one ovary remains or for donor embryo transfer when both have been removed. **Preoperative treatment with medical agents such as GnRH agonists for 3 to 6 months can improve surgical success.**

The role of medical therapy postoperatively remains controversial, although it is indicated to treat women who have known residual disease diagnosed at surgery. **There is a risk of recurrence of endometriosis throughout a woman's life,** so measures should be taken to reduce the risk of retrograde menstruation or cyclic ovarian sex steroid production. Depot medroxyprogesterone acetate (DMPA), continuous OCs, and the levonorgestrel-releasing intrauterine device (IUD) are all attractive long-term options. Medical and surgical treatment options for endometriosis are summarized in Box 25-1.

BOX 25-1

OPTIONS FOR TREATING ENDOMETRIOSIS

Watchful Waiting

There is a limited role for expectant management without any medical or surgical intervention. Women who are attempting pregnancy with little or no symptoms may consider this option. In addition, women who are approaching menopause and have minimal symptoms may choose to wait for the cessation of cyclic ovarian function, at which stage endometriosis is usually far less active.

Medical Treatment

First-line therapy: Nonsteroidal antiinflammatory drugs, low-dose oral contraceptives, or progestins (e.g., medroxyprogesterone acetate). ***Note:*** This treatment should be given an adequate trial of 3 to 6 months before initiating second-line therapy.

Second-line therapy: Higher-dose progestins (e.g., medroxyprogesterone acetate or megestrol acetate [Megace]), danazol, or gonadotropin-releasing hormone analogues appear to be equally effective. ***Note:*** Laparoscopic confirmation of the diagnosis of endometriosis before initiation of second-line treatment is usually performed, but it is not required according to some guidelines. Biopsy of visualized lesions, however, is the only definitive way to diagnose endometriosis.

Surgical Treatment

Most definitive therapy: Total abdominal hysterectomy with bilateral salpingo-oopherectomy with destruction and/or removal of all peritoneal endometriotic implants and adhesions. ***Note:*** There is always a risk of recurrence, even with "definitive" treatment.

Fertility-preserving treatment: Laparoscopic or open surgery (laparotomy) with destruction and/or removal of all peritoneal endometriotic implants and adhesions. ***Note:*** Removal of endometriomas may decrease fertility potential, especially in women with already-reduced ovarian reserve (see Chapter 34). Large endometriomas >3 cm in diameter should be removed surgically. Preoperative suppressive treatment for 3 to 6 months may improve surgical success.

PREVENTION

Whenever severe dysmenorrhea occurs in a young patient, the possibility of varying degrees of obstruction to the menstrual flow must be considered. The possibility of a blind uterine horn in a bicornuate uterus or an obstructing uterine or vaginal septum should be kept in mind. **In more than half the patients who are noted to develop endometriosis during childhood and adolescence, varying degrees of genital tract obstruction may be found.** Whenever a congenital abnormality of the urinary or intestinal tract is detected, the genital tract should be investigated for an obstructive lesion. Infants with genital tract obstruction have been noted to develop endometriosis even in the first year of life. **In all women, minimization of menstrual flow and suppression of ovarian cycling can reduce the risk of endometriosis.**

Adenomyosis

***Adenomyosis* is defined as the extension of endometrial glands and stroma into the uterine musculature more than 2.5 mm beneath the basalis layer.** Often this is an incidental finding during a pathologic examination, where it is seen in up to 60% of women in their 40s. **About 15% of patients with adenomyosis have associated endometriosis.** Islands of adenomyosis do not participate in the proliferative and secretory cycles induced by the ovary.

PATHOLOGY

Generally, the gross appearance of the uterus consists of diffuse enlargement with a thickened myometrium containing characteristic glandular irregularities, with implants containing both glandular tissue and stroma (Figure 25-4). The endometrial cavity is also enlarged. Occasionally, the adenomyosis may be confined to one portion of the myometrium and take the

because the older implants may have a very subtle appearance and the deeper infiltrating lesions may not be visible at the peritoneal surface. Biopsy of any suspicious lesions improves diagnostic accuracy.

MANAGEMENT

The management of endometriosis depends on certain key considerations: (1) the certainty of the diagnosis, (2) the severity of the symptoms, (3) the extent of the disease, (4) the desire for future fertility, (5) the age of the patient, and (6) the threat to the gastrointestinal or urinary tract or both.

Treatment is indicated for endometriosis-associated pelvic pain, dysmenorrhea, dyspareunia, abnormal bleeding, ovarian cysts, and infertility caused by gross distortion of tubal and ovarian anatomy. Surgical intervention is required for an endometrioma larger than 3 cm, gross distortion of pelvic anatomy, involvement of bowel or bladder, and adhesive disease. Surgery may improve fertility for women with severe endometriosis. Medical therapy is generally the first-line treatment for other symptomatic women. **There is no convincing evidence that treatment significantly improves fertility in women with mild endometriosis.**

Asymptomatic women found incidentally to have endometriosis may not require any therapy. Some women who have minimal symptoms may choose to be managed expectantly if they are trying to conceive or if they are approaching menopause, when endometriosis generally becomes less symptomatic.

Medical Treatments

Therapy should be targeted toward relieving the patient's individual complaints and reducing the risk of disease progression. **Dysmenorrhea** that results from endometriosis **can be approached** as outlined in Chapter 21, using **nonsteroidal antiinflammatory drugs (NSAIDs) and reduction of menstrual flow with hormonal regimens such as low-dose oral contraceptives (OCs).**

For relief of noncyclic pelvic pain, short-term medical treatment may be used. **NSAIDs, OCs, and progestins (e.g., medroxyprogesterone acetate) should be considered the appropriate first-line medical treatments for symptomatic endometriosis. When an inadequate response occurs, second-line medical treatment with a gonadotropin-releasing hormone (GnRH) agonist, higher-dose progestins, or danazol appears to be equally effective.** Cost, individual patient response, and potential side effects generally guide selection of one agent or the other.

Danazol is an androgenic derivative that may be used in a "pseudomenopause" regimen to suppress symptoms of endometriosis if fertility is not a present concern. It is given over a period of 6 to 9 months, and doses of 600 to 800 mg daily are generally necessary to suppress menstruation. Through its weak androgenic properties, danazol decreases the plasma levels of sex hormone–binding globulin. The resulting increase of free testosterone may cause hirsutism and acne. **Three years after cessation of danazol, 40% of patients will have recurrence of endometriosis. After a full course of danazol therapy, use of a cyclic OC may help to delay or prevent such recurrence.**

GnRH agonists cause a temporary medical castration, thereby bringing about a marked, albeit temporary, regression of endometriosis. Treatment of women with endometriosis with GnRH agonists usually produces relief of pain and involution of implants. The disadvantages of these agonists are related to cost, hot flashes, and side effects, including vaginal dryness. They also cause calcium loss from bone and an unfavorable lipid profile. If treatment with a GnRH agonist is effective in relieving chronic pelvic pain and if surgery is not indicated, low-dose estrogen-progestin add-back therapy can permit longer-term use of GnRH agonists by mitigating the adverse impact of estrogen deficiency without reducing the efficacy of GnRH agonists.

OCs and oral medroxyprogesterone acetate are more effective than placebos in treatment of endometriosis-associated pelvic pain. The levonorgestrel-releasing intrauterine system reduces dysmenorrhea and may be helpful for inducing regression of cul-de-sac implants without diminishing circulating estrogen levels in the serum.

Surgical Treatments

The most comprehensive procedure (extirpative surgery) includes total abdominal hysterectomy, bilateral salpingo-oophorectomy with destruction of all peritoneal implants, and dissection of all adhesions. Usually, an appendectomy is also performed. A single ovary or both ovaries may be spared only if they are free of endometriosis and all other implants have been resected. Because of extensive adhesions, surgery for endometriosis is often technically very challenging. If the patient's endometriosis involves the cul-de-sac or uterosacral ligaments, the proximity to the ureter, bladder, and sigmoid colon must be considered. If the endometriosis obstructs the ureter, resection and ureteroplasty may be necessary to preserve renal function. **Nearly 25% of kidneys are lost when endometriosis blocks the ureter.** Obstruction of the rectosigmoid, and even obstruction of the small intestine, may require resection of the involved intestinal segment. The surgical risks must be explained carefully to the woman, as well as her subsequent need for treatment for loss of ovarian steroids. She also needs to understand that, postoperatively, there is a 20% recurrence rate for endometriosis, usually involving the bowel.

Often the desire for future fertility precludes this extirpative surgical option. In such circumstances, a

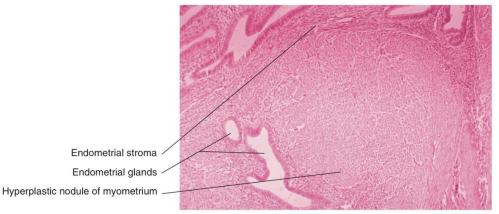


FIGURE 25-4 Histologic illustration of adenomyosis causing enlargement of the uterus. A hyperplastic nodule of myometrium can be seen. Note the endometrial glands and stroma.

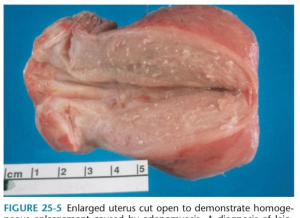


FIGURE 25-5 Enlarged uterus cut open to demonstrate homogeneous enlargement caused by adenomyosis. A diagnosis of leiomyomata may be incorrectly made at the time of pelvic examination. (Courtesy Dr. Sathima Nataratan, Ronald Reagan—UCLA Medical Center.)

form of a fairly well-circumscribed adenomyoma. Contrary to the situation with a uterine leiomyoma (fibroid), no distinct capsular margin can be detected on cut sections between the adenomyoma and the surrounding myometrium. The distinction between adenomyosis and a uterine fibroid may not always be clear on ultrasonic examination. Figure 25-5 illustrates the typical gross appearance of an enlarged uterus with extensive adenomyosis.

SYMPTOMS

Although many women with adenomyosis are asymptomatic, those who have this condition typically complain of severe secondary dysmenorrhea and heavy menstrual bleeding. Even though the islands do not cycle in response to ovarian hormonal stimulation, prostaglandin release and local inflammatory changes persist that can induce pain and tenderness and may disrupt the vasoconstriction of the arterial arcade supplying the endometrium. Deep-thrust dyspareunia, especially premenstrually, can be caused by adenomyosis.

SIGNS

Pelvic examination reveals the uterus to be generally symmetrically enlarged and somewhat boggy and tender if the examination is conducted premenstrually. Occasionally, it may enlarge asymmetrically, which makes it very difficult to distinguish adenomyosis from a myomatous uterus. The consistency of the enlarged adenomyomatous uterus is generally softer than that of a fibroid uterus.

TREATMENT

The treatment of adenomyosis depends entirely on the patient's symptoms and the possibility of other diagnoses. Any history of new onset or worsening of uterine bleeding, particularly in a woman with risk factors for endometrial cancer, should be investigated by endometrial biopsy or fractional dilation and curettage and/or hysteroscopy to rule out malignancy. **Conservative management with NSAIDs and hormonal control of the endometrium are mainstays of therapy.** Combination OCs or hormone-containing patches and vaginal rings may be used to reduce cyclic blood loss and menstrual pain. DMPA, levonorgestrel IUD, and continuous OC pills can be used to try to achieve amenorrhea. If the woman is not a candidate for any of these medical interventions or if medical treatments do not sufficiently control her symptoms, **hysterectomy may be indicated. Endometrial ablation to control the bleeding is another option.**

Med 441 Team:

Leaders:

Leen Alrajhi - Yara Almufleh

Members:

Dana Alsagheir

Good Luck!

Med 438 Team:

Leaders:

Ateen Almutairi - Lama ALzamil - Lina Alosaimi

Members:

Deana Awartani - Norah Alharbi - Alhanouf Alhaluli

Med 439 Team:

Leader:

Bushra Alotaibi - Renad Alhomaidi

Members:

Rand AlRefaei - Muneerah Alsadhan - Sarah AlQuwayz