



# Endometriosis

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# Introduction

- ▶ Endometriosis is defined as the presence of normal endometrial mucosa (glands and stroma) abnormally implanted in locations other than the uterus (outside the endometrium and myometrium).
- ▶ This endometrial tissue possesses the same steroid receptors as normal endometrium and is capable of responding to the normal cyclic hormonal changes.
- ▶ This results in microscopic internal bleeding, with the subsequent inflammatory response, neovascularization, and fibrosis formation.
- ▶ Resulted changes are responsible for **the clinical consequences of this disease**.



# Etiology

- The exact cause and pathogenesis of endometriosis is ***not clear.***
- Several theories (***implantation theory following retrograde menstruation, metaplasia of coelomic epithelium, hematogenous or lymphatic spread, direct transplantation of endometrial cells***) exist that attempt to explain this disease, although none have been entirely proven.

# Implantation theory following retrograde menstruation

- The implantation theory proposes that endometrial tissue desquamated during menstruation passes through the fallopian tubes and once it reaches pelvic cavity, the tissue became implanted on peritoneal surfaces and grew into endometriotic lesions.
- This theory is simple, attractive, and easily explains why endometriosis is most commonly found on the peritoneal surfaces of the ovaries, culde-sac, and bladder and why lesions may develop in episiotomies and other incisions
- However, this concept fails to explain the low rate of disease compared to such a common event **(90% of menstruating women will manifest retrograde flow)**.

# Immunologic dysfunction

- ▶ An altered immune response to the displaced endometrial tissue has been shown to play **an important role** as well.
- ▶ Studies have suggested that deficient cellular immunity results in an inability to recognize the presence **of endometrial tissue in abnormal locations.**
- ▶ Women with this disorder appear to exhibit increased humoral immune responsiveness and macrophage activation while showing diminished cell-mediated immunity with decreased T-cell and ***natural killer cell responsiveness.***
- ▶ Humoral antibodies to endometrial tissue have also been found in sera of women with endometriosis.



# METAPLASIA

- ❖ Metaplasia, or the changing from one normal type of tissue to another normal type of tissue, **is another theory**.
- ❖ The endometrium and the peritoneum are derivatives of the same coelomic wall epithelium.
- ❖ Transformation of coelomic epithelium into **endometrial-type glands** in response to as yet unknown stimuli could explain endometriosis in unusual sites.



# Remnant müllerian cells

- ▶ Another theory states that remnant müllerian cells may remain in the pelvic tissues during development of the müllerian system.
- ▶ Under situations of estrogen stimulation, they may be induced to differentiate into functioning **endometrial glands and stroma**.
  
- ▶ **Vascular and lymphatic dissemination**
- ▶ suggested by presence of endometriosis **in thoracic cavity**.



# Genetics

- ▶ Some women may have a genetic predisposition to endometriosis.
- ▶ Studies have shown that **first-degree relatives of women with this disease are more likely to develop it as well.**
- ▶ The search for an endometriosis gene **is currently under way.**

# Risk factors

- ❖ **Risk factors for endometriosis include the following:**
  - Inverse relationship to parity.
  - Family history of endometriosis.
  - Early age of menarche.
  - Short menstrual cycles (**< 27 d**).
  - Long duration of menstrual flow (**> 7 d**).
  - Heavy bleeding during menses.
  - Delayed childbearing.
  - Defects in the uterus or fallopian tubes.

# Pathophysiology:

- ▶ Endometriosis is an estrogen-dependent disease and, thus, usually affects reproductive-aged women.
- ▶ Ectopic endometrial tissues are most commonly located in the dependent portions of the female pelvis (e.g., **posterior and anterior cul-de-sac, uterosacral ligaments, tubes, ovaries**), but any organ system is potentially at risk .
- ▶ Transtubal dissemination is the most common route, although other routes, such as **lymphatic and vascular channels**, have been observed.
- ▶ This may explain how endometrial tissue can be found at distant, noncontiguous locations in the body.
- ▶ The endometriotic implants are often functional **causing pain during patient's menses.**
- ▶ Over time, inflammation and scarring may ensue, which may distort the pelvic anatomy causing pain and infertility.
- ▶ As inflammation and scarring progresses patient's pain may be noted at any time during the cycle, not confined to menses



# Types of endometriosis

- **There are three typical types of endometriotic lesions:**
  - **1.** Superficial peritoneal and ovarian implants.
  - **2.** Endometriomas or chocolate cysts (ovarian cysts that are lined with endometrioidm mucosa).
  - **3.** Deep infiltrating endometriosis (complex nodules comprised of endometriotic tissue, adipose tissue, and fibromuscular tissue).
- *iatrogenic deposition of endometrial tissue has been found in some cases following gynecologic procedures and cesarean sections.*

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- **The ovary** is the most common site for endometriosis.
  - Lesions can vary in size from spots to large endometriomas.
  - Endometriomas **are cystic endometrial lesions contained within the ovary.**
  - The classic lesion is a chocolate cyst of the ovary that contains old blood that has undergone hemolysis.
  - It has an appearance of smooth walled, brown cyst, may be unilocular but often multilocular **when >3 cm in diameter.**
  - The cyst may undergo rupture following rise in intra cystic pressure, spilling its contents within the peritoneal cavity.
  - This can cause the severe **abdominal pain typically** associated with endometriosis exacerbations.
  - The inflammatory response causes adhesions that further increase the morbidity of the disease.



# Clinical presentation

- Women are usually **nullipara and in reproductive age**.
- There may be family history of endometriosis.
- The most common symptoms associated with endometriosis are pelvic pain, infertility, and abnormal uterine bleeding.
- Women usually present with regular, although short, menstrual cycles with prolonged flow of **8 or more days**.
- Onset of pain usually precedes flow by a few days and begins to resolve **1-2 days** into the menses.
- Occasionally women may present with endometriotic cyst of one or both ovaries.
- These masses can become quite painful, and patients with rupture present with an acute surgical abdomen.

# Symptoms

## Pain

- ▶ Although pain is common, a significant number of women with endometriosis remain asymptomatic **30%**.
- ▶ The most important point to remember is that the degree of visible endometriosis has **no correlation with the degree of pain** or other symptomatic impairment.
- ▶ However, pain does correlate with the depth of tissue infiltration, as pain is thought to be related to the degree of peritoneal inflammation rather than the volume of implants.
- ▶ Associated intra pelvic/intra-abdominal adhesions are also important determinants of the degree of pain experienced.
- ▶ **Midline disease** is general believed to be more painful than lateral disease.
- ▶ In addition to pain, patients present with nonspecific symptoms of fatigue, generalized malaise, and sleep disturbances.



❖ Pain related to endometriosis may present as any of the following:

- Dysmenorrhea.
- Dyspareunia (painful intercourse).
- Painful defecation (**dyschezia**).
- Lower back or abdominal pain.
- Chronic pelvic pain (**noncyclic abdominal pelvic pain of at least 6 months duration**).
- Painful micturition (**dysuria**).
- Inguinal pain.
- Pain during exercise.



- **Infertility**

The next most common symptom **is infertility**.

In women with moderate and severe endometriosis, there is adhesion of ovaries and fallopian tubes with adjacent structures resulting in decreased fertility rates.

Interestingly, women with only minimal or mild disease may also **have decreased fertility** when compared to those without clinical evidence of endometriosis.

In the absence of anatomic distortion of the pelvis, the mechanism of infertility associated with endometriosis implants alone **is poorly understood**.



❖ There are three other major theories that may explain the decreased monthly fecundity rates seen in women with endometriosis:

1. Increased incidence of luteinized unruptured ovarian follicle syndrome **(trapped oocyte)**
2. Increased peritoneal prostaglandin production or peritoneal macrophage activity **(resulting in oocyte phagocytosis)**.
3. Non receptive endometrium **(because of luteal phase dysfunction or other abnormalities)**.



## ➤ Abnormal Uterine Bleeding

- Abnormal uterine bleeding frequently has been associated with endometriosis.
- Abnormal uterine bleeding may be due to associated anovulation or coexisting pathology.



# Other symptoms

- ▶ Uncommon symptoms are usually attributable to endometriosis involvement of atypical locations.
- ▶ In addition to bowel implants that can cause rectal bleeding or obstruction, endometriosis can be located in the bladder, causing suprapubic pain, frequency, urgency, dysuria, and hematuria.
- ▶ Ureteral involvement may cause upper urinary tract symptoms such as flank pain or backaches.
- ▶ Pulmonary involvement can result in pleuritic pain, pleural effusion, cough, hemoptysis, or pneumothorax.
- ▶ Cyclic headaches or seizures may indicate brain lesions.
- ▶ Sciatica has been reported from endometriosis in the retroperitoneal space .



# Sings

## ► Inspection

- Endometriosis of the vagina, perineum umbilicus, inguinal area, or surgical scars may be visible as pigmented lesion that have cyclic pain and swelling.

## ► Speculum Examination

- Unfortunately, due to the diffuse and often varying nature of endometriotic lesions, the physical examination may not reveal any abnormality.
- Occasionally, bluish or red powder-burn lesions may be seen on the cervix or the posterior fornix of the vagina.
- These lesions may be tender or bleed with contact.



## ► **Bimanual Examination**

- Tender nodules may be palpable along the uterosacral ligaments, rectovaginal septum, or within the cul-de-sac, especially if the examination is performed just before menses.
  - A fixed, retroverted uterus and thickened parametrial areas may indicate more advanced disease.
  - Significant cystic formation may be detected as adnexal enlargement or tenderness.
  - Because much disease is found in the dependent areas of the pelvis, a rectovaginal examination is particularly helpful in evaluating the posterior cul-de-sac structures.
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# Staging

- At the time of laparoscopy, the extent of endometriosis lesions should be assessed to stage the disease.
- Surgically, endometriosis can be staged I-IV.
- The process is a complex point system that assesses lesions and adhesions in the pelvic organs.
- For the purpose of planning treatment, stages I and II can be combined as **“early stage endometriosis”** and Stage III and IV can be combined as **“advanced endometriosis”**.
- However, it is important to note staging assesses physical disease only, not the level of pain or infertility.
- A patient with Stage I endometriosis may have little disease and severe pain, while a patient with Stage IV endometriosis may have severe disease and no pain or vice versa.



## ► **Stage I (Minimal)**

- Findings restricted to only superficial lesions and possibly a few filmy adhesions.

## ► **Stage II (Mild)**

- In addition, some deep lesions are present in the cul-de-sac.

## ► **Stage III (Moderate)**

- As above, plus presence of endometriomas on the ovary and more adhesions.

## ► **Stage IV (Severe)**

- As above, plus large endometriomas, extensive adhesions.



# Differential Diagnosis

**The differential diagnosis of endometriosis includes:**

- pelvic inflammatory disease, tuboovarian abscess,
- ectopic pregnancy, interstitial cystitis, adenomyosis, pelvic adhesions,
- uterine fibroids, chronic or acute endometritis,
- ovarian neoplasms, musculoskeletal disease,
- gastrointestinal neoplasms, appendicitis,
- diverticular disease.



# Investigations

- **Clinical suspicion of endometriosis usually is based on the history and physical examination.**
- **Confirmation of endometriosis, however, requires direct visualization and occasionally biopsy, if the surgeon is uncertain of the diagnosis.**
- **The initial clinical assessment identifies patients at risk for endometriosis who should undergo further evaluation by laboratory tests, diagnostic imaging, and laparoscopy.**

# 1. Imaging Techniques

## ➤ a. Ultrasonography:

- Ultrasound examination is the first line investigational tool for suspected endometriosis.
- It allows detection of ovarian cysts and other pelvic disorders such as uterine fibroids.
- The usefulness of ultrasonography in detecting focal implants is poor.
- Endometriomas have several different ultrasonographic appearances.
- They usually appear as cystic masses with thick walls and scattered internal echoes.
- Some endometriomas contain septations, a combination of cystic and solid elements, or primarily solid components and may be indistinguishable from an ovarian abscess or neoplasm.
- The diagnostic accuracy can be improved by Doppler flow studies.



## ➤ **b. Magnetic resonance imaging (MRI):**

- At present, magnetic resonance imaging is the best imaging for identifying endometriosis, and can identify implants as small as 3 mm in size.
- It can also differentiate benign from malignant lesions, with excellent sensitivity and specificity.
- Because of the large disparity in cost of an MRI versus a transvaginal ultrasound, physicians may resort to using an MRI in cases of ultrasonographically indeterminate pelvic masses.

## 2. Laparoscopy

- Laparoscopy is the gold standard for the diagnosis of endometriosis.
- Endometriosis has wide variation in appearance.
- The classic lesions are blue-black or have a powderburned appearance.
- However, the lesions can be red, white, or nonpigmented.
- Peritoneal defects and adhesions are also indicative of endometriosis.
- An advantage of surgical diagnosis of endometriosis at the time of laparoscopy is that therapeutic excision or ablation of endometriosis implant can occur at the same time of diagnostic surgery.



## 3. Histologic Features

- ▶ Histologic demonstration of both endometrial glands and stroma in biopsy specimens obtained from outside the uterine cavity is required to make the diagnosis of endometriosis.
- ▶ Occasionally, the finding of fibrosis in combination with hemosiderinladen macrophages is sufficient for a presumptive diagnosis.

## 4. Laboratory Tests

- ▶ CA 125—Although serum level of cancer antigen 125 (CA 125) **is elevated** in moderate to severe endometriosis, its determination is not recommended as part of routine investigation.
- ▶ However, an undiagnosed pelvic mass may be evaluated with **CA 125 level as a component of risk malignancy index.**



# Treatment

- ❖ **Treatment for endometriosis depends on symptom or clinical presentation of the patient.**
- *Most women with endometriosis typically present with one or more of the following three complaints:*
  1. *Pelvic pain that interfere with daily activities*
  2. *Infertility*
  3. *A complex adnexal mass due to an ovarian cyst of ovary (endometrioma or chocolat cyst).*

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- Treatment is either aimed at pain reduction, fertility restoration, or evaluating a mass, such as in the case of an endometrioma or chocolate cyst.
  - Unfortunately, there are very few options for treatment of the patient who, both desires fertility and has pelvic pain.
  - Sometimes **pregnancy itself will relieve the pain of endometriosis.**

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- There are general points which should be considered when treating a woman to decide which treatment option will be most suitable for her.

- ▶ *These should include:*

The severity of the symptoms

The type of symptoms

The age of the patient

The desire to get pregnant or not

Length of treatment

Coping with side-effects of drug treatment

Cost

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- Endometriosis is an estrogen dependent lesion.
  - The aim of some treatments is to reduce or stop the estrogen being produced in a woman's body, so that it does not continue to feed the endometriotic deposits.
  - This is achieved by hormone drug therapy.
  - This type of treatment is only successful for milder cases of endometriosis where the growths are relatively small and few in number.
  - In more severe cases, treatment with surgery is usually needed to remove the endometriotic lesions.
  - ❖ **The options for treatment include:**
    - Observation with no medical intervention
    - Medical treatment with NSAID or hormone medication
    - Surgery
    - Combined treatment

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- A dark red arrow points to the right at the top left. Below it, several thin, dark grey lines curve downwards and to the left, resembling a stylized plant or abstract graphic.
- **Observation with No Medical Intervention.**
  - **This approach can be used for milder cases of endometriosis.**
  - **Analgesics may be prescribed to help with any pain.**

# Medical Treatment

Medical treatment is indicated in patients **with pain or dyspareunia**, because no pharmacologic method appears to restore fertility.

Since endometriosis is a chronic disease, it would be most beneficial to use drugs that can be safely used long-term.

**Dysmenorrhea** is one of the most common complaints in women with endometriosis, so many of the hormonal agents aim to cause amenorrhea.

These treatments may also relieve deep dyspareunia, non-cyclic pelvic pain, and dyschezia.

The drugs that can be used, include Oral contraceptives, progestins, danazol, gestrinone, medroxyprogesterone acetate, and GnRH agonists, aromatase inhibitors and are all supported by clinical trials showing approximately equal benefit .

**Their side-effect profiles and costs lead one agent to be preferred over another.**

However, once the agent is discontinued, the symptoms tend to recur.

## NSAIDs (non steroidal Anti inflammatory drugs)

- ▶ prostaglandin inhibitors are relatively safe, have a tolerable side-effect profile, and can generally be taken on a long-term basis by most patients, so they remain part of the first line therapy for the treatment of endometriosis-associated pain.

## Oral contraceptive pills

- ▶ OCPs suppress LH and FSH and prevent ovulation.
- ▶ They also have direct effects on endometrial tissue, rendering it thin and compact.
- ▶ The decidualization of endometrial implants, coupled with reduced reflux related to lower menstrual volume, is the probable mechanism of pain relief with OCPs, making them comparable to other treatments in effect.



# Progestational Agents:

- Progestins are similar to combination OCPs in their effects on FSH, LH and endometrial tissue.
- They may be associated with more bothersome adverse effects than OCPs.
- Cheaper than GnRH and Danazol.
- The levonorgestrel releasing intrauterine device releases 20 µg/day and induces amenorrhea by causing the endometrium to become atrophic and inactive.
- It has been shown to improve dysmenorrhea, relieve deep dyspareunia .
- Reasons for discontinuation include irregular bleeding, pelvic pain, breast tenderness, and weight gain.

# Danazol

- synthetic androgen (**17 $\alpha$  ethinyl testosterone**) that inhibits leuteinizing hormone (**LH**) and follicle-stimulating hormone (FSH), and inhibits ovarian steroidogenesis resulting in a relatively hypoestrogenic state.
- Danazol occupies receptor sites on sex hormone binding globulin (**SHBG**) to increase serum free testosterone level and also binds directly to androgen and progesterone receptors.
- As a result a hyper androgenic, hypoestrogenic state is created resulting in endometrial atrophy and relieving pain from endometriosis.
- Adverse effects related to estrogen deficiency include headache, flushing, sweating and atrophic vaginitis.
- Androgenic side effects include acne, edema, hirsutism, deepening of the voice and weight gain.

# GnRH Agonists

- These inhibit the secretion of gonadotropin and are comparable to danazol in relieving pain.
- GnRH agonists are contraindicated in pregnancy and have hypoestrogenic side effects.
- In particular, they have been shown to produce a mild degree of bone loss, although this condition reverses after the medication is discontinued.
- Because of concerns about osteopenia, “**add-back**” therapy with low-dose estrogen has been recommended.
- The dosage of leuprolide is a single monthly **3.75 mg depot injection** given intramuscularly.
- Gosarelin, in a dosage of **3.6 mg**, is administered subcutaneously every 28 days.
- A nasal spray (**nafarelin**) is used twice daily.
- The response rate is similar to that with danazol about **90 percent of patients experience pain relief.**

**Table 17.1: Medical treatment of endometriosis**

<i>Drug</i>	<i>Dosage</i>	<i>Adverse effects</i>
Danazol	800 mg per day in 2 divided doses	Estrogen deficiency, androgenic side effects
Oral contraceptives	1 tablet per day (continuous or cyclic)	Headache, nausea, hypertension
Medroxyprogesterone suspension in Injection (Depo-Provera)	100 mg IM every 2 weeks for 2 months; then 200 mg IM every month for 4 months or 150 mg IM every 3 months	Weight gain, depression, irregular menses or amenorrhea
Medroxyprogesterone	5 to 20 mg orally per day	Same as with other oral progestins
Norethindrone acetate	5 mg per day orally for 2 weeks; then increase by 2.5 mg per day every 2 weeks up to 15 mg per day	Same as with other oral progestins
Leuprolide	3.75 mg IM every month for 6 months	Decrease in bone density, estrogen deficiency
Gosarelin	3.6 mg SC (in upper abdominal wall) every 28 days	Estrogen deficiency

# Surgery

➤ **Surgical treatment of endometriosis is based on two concepts:**

**1. Surgical treatment of endometriosis lesions can reduce the pain and may improve fertility associated with disease.**

**2. Surgical removal of both ovaries permanently stops 95% of the endogenous production of estrogen, which will cure the disease but cause surgical menopause.**

❖ *Surgical treatment for endometriosis is usually indicated in one of the following situations:*

At the time of diagnosis for mild to moderate endometriosis with symptoms

If medical treatment has not worked or Contraindicated

If infertility is a problem and associated factors like pain or pelvic mass is present

If there is moderate to severe endometriosis involving bladder, bowel, ureter, pelvic Nerves.

If the patient is having acute adnexal torsion or ovarian cyst rupture

When endometriosis recurs

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- Surgery can either be **conservative** or **radical**.
  - The aim of conservative surgery is to return the appearance of the pelvis to as normal as possible.
  - This means destroying any endometriotic deposits, removing ovarian cysts, dividing adhesions and removing as little healthy tissue as possible.
  - Radical surgery means doing a hysterectomy with removal of both ovaries and is reserved for women with very severe symptoms, who have not responded to medical treatment or conservative operations.

## ❖ Laparoscopic Surgery

- Because primary method for diagnosis of endometriosis is laparocopy, surgical treatment at the time of diagnosis is an attractive option.
- The endometriosis spots are destroyed by diathermy.
- Fine adhesions can be cut using small scissors.
- Bleeding is usually minimal and having avoided an open operation means that the risk of subsequent adhesion development is reduced.
- Laparoscopic management also has the advantage of needing a minimal hospital stay, it is usually possible to go home the same or following day.
- The aim of laparoscopy, as usual, is to restore anatomy back to normal.



# Radical Surgery

- ❖ **Definitive surgery involves hysterectomy with bilateral salpingo-oophorectomy to induce menopause and ideally removal of all visible endometriotic nodule or lesions.**
  
- ❖ ***This is indicated in:***
  - 1.** Women who have significant pain and other symptoms despite conservative treatment and do not desire future pregnancy.
  
  - 2.** Women undergoing hysterectomy because of some other condition such as fibroid uterus



# Combined Treatment

- This form of treatment involves combining surgery and drug therapy.
- An example is when **Danazol or GnRH** is taken for 6 weeks prior to an operation to shrink the endometrial growths and ease the surgical removal.
- Following surgical removal of endometrial tissue, birth control pills may be prescribed that contain **both estrogen and progesterone**, to be taken continuously for up to nine months.
- This will induce a pseudo-pregnancy, with the aim to allow the body time to rest and heal.



# Prognosis

- As all form of current therapies offer relief but no cure, long term concerns are more guarded.
  - The course of endometriosis is impossible to predict at present, and future treatment options should greatly be improved what can now be offered.
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ATTENTION !!