Endometriosis

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Main Reference

- Comprehensive Gynecology, 7th ed. (2017), Lentz GM, Lobo RA, Gershenson DM, Katz VL ; Chapter 19

Endometriosis: Outline

Definition

Pathology

Clinical diagnosis

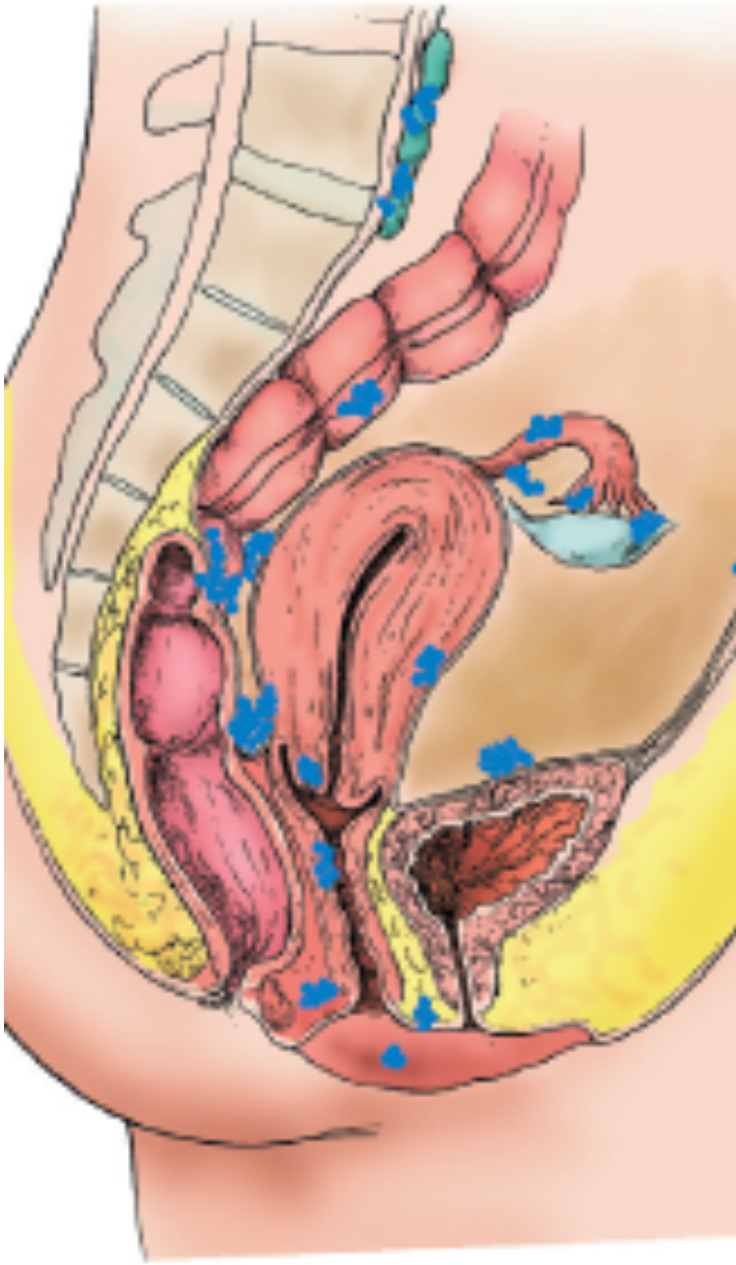
Differential diagnosis

Etiologies/theories

Treatment

Definition

Endometriosis is the presence and growth of the glands and stroma of the lining of the uterus in an aberrant or heterotopic location.



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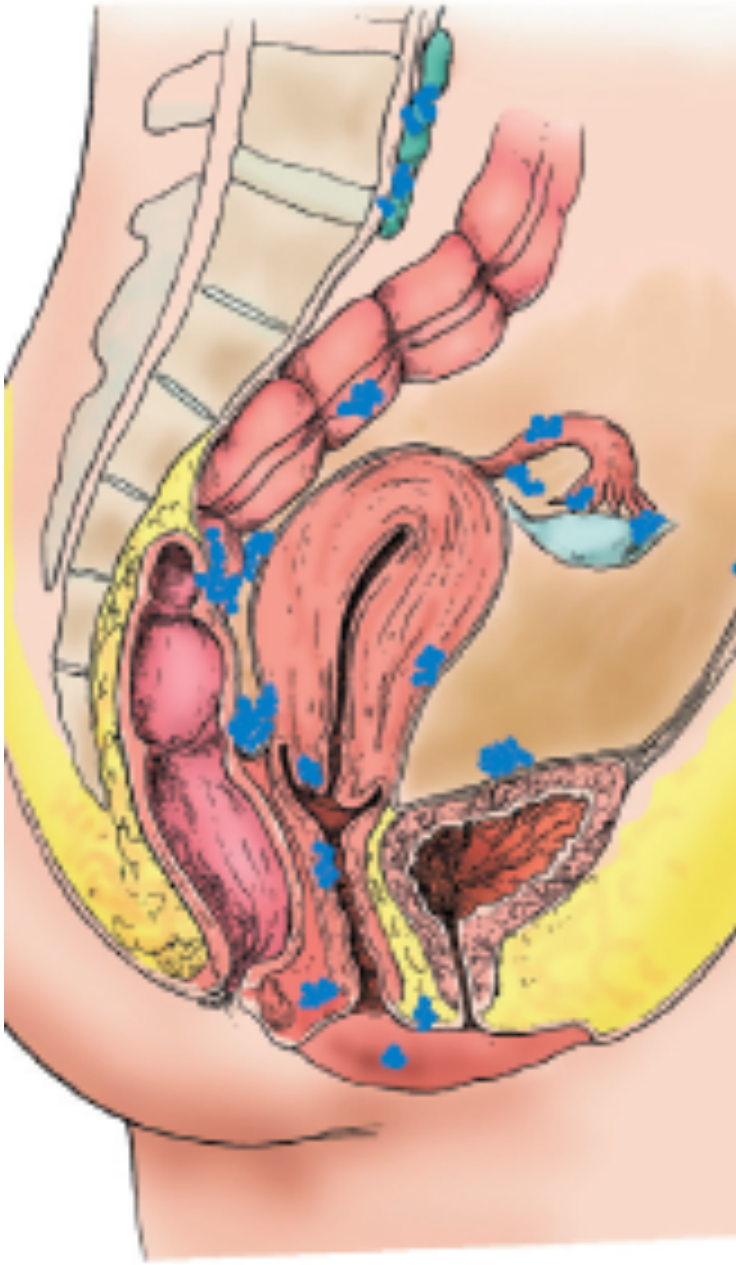
Endometriosis

It is a benign disease, yet it has the characteristics of a malignancy— that is, it is **locally infiltrative, invasive, and widely disseminating.**

growth of ectopic endometrium is stimulated by physiologic levels of **estrogen**



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Endometriosis

- Mostly seen in dependent portions of female pelvis
- **Ovaries**: most common site
- **three cardinal histologic features** of endometriosis are (1)ectopic endometrial glands, (2)ectopic endometrial stroma, and (3) hemorrhage into the adjacent tissue

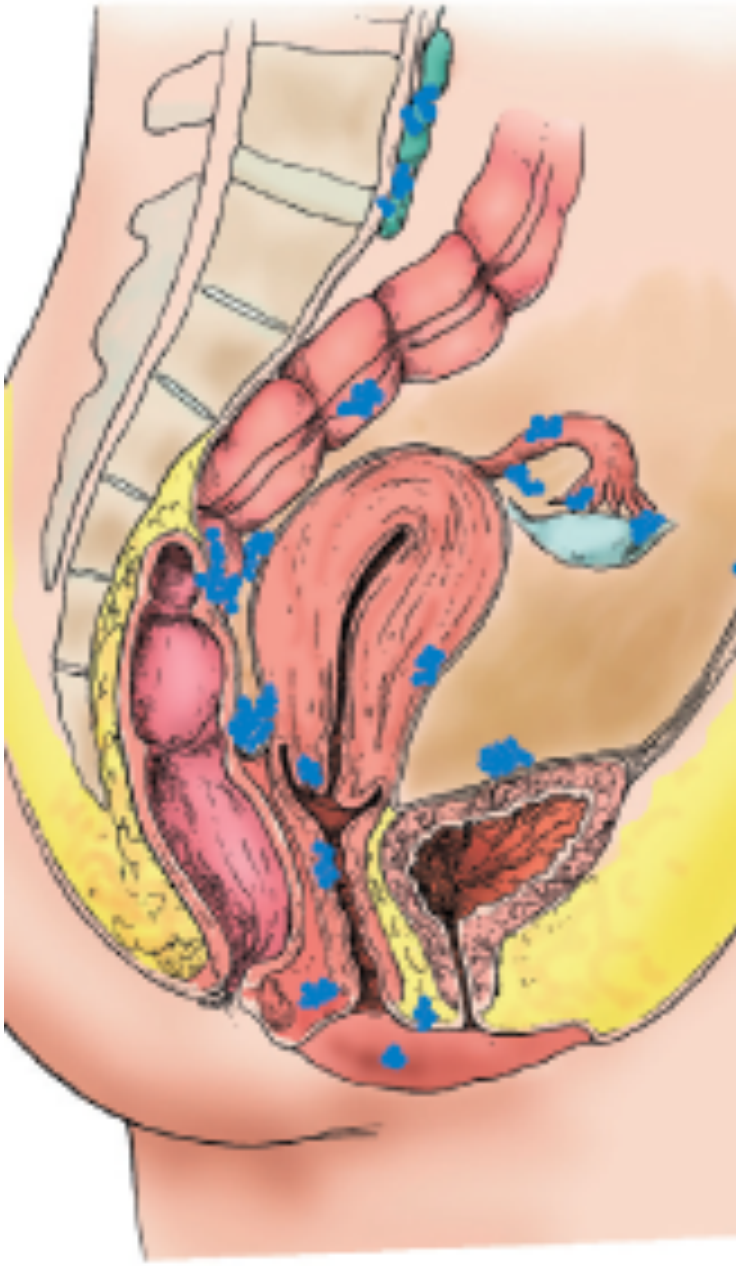

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Table 19.1 Anatomic Distribution of Endometriosis

Common Sites	Rare Sites
Ovaries	Umbilicus
Pelvic peritoneum	Episiotomy scar
Ligaments of the uterus	Bladder
Sigmoid colon	Kidney
Appendix	Lungs
Pelvic lymph nodes	Arms
Cervix	Legs
Vagina	Nasal mucosa
Fallopian tubes	Spinal column

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Endometriosis: epidemiology

- 10 percent of reproductive-age women
- Endometriosis has been reported in up to 40 percent of adolescents with genital tract anomalies , up to 50 percent of women with infertility, and up to 70 percent of women and adolescents with pelvic pain

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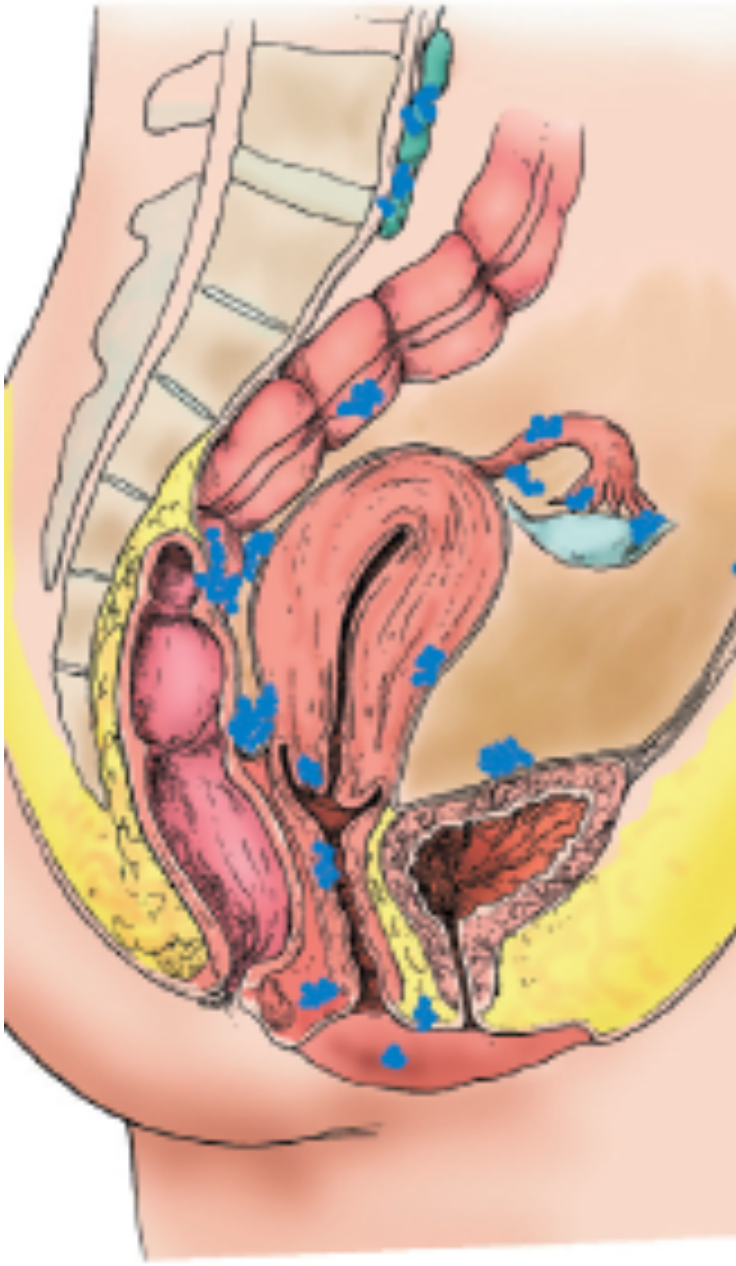
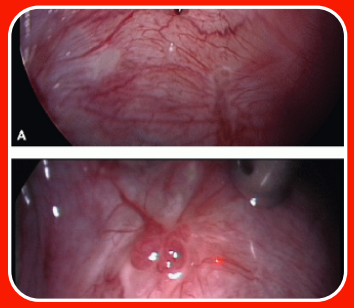
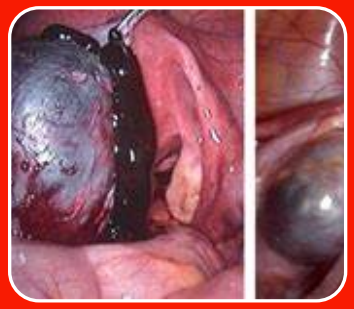


3 phenotypes:



Superficial (peritoneal) lesions

- The color of the lesion varies widely and may be red, brown, black, white, yellow, pink, clear, or a red vesicle.
- The predominant color depends on the blood supply and the amount of hemorrhage and fibrosis.
- The color also appears related to the size of the lesion, the degree of edema, and the amount of inspissated material



Endometriomas (“oma”)

- Ovarian cysts may range from < 1cm to large chocolate cysts greater than 8 cm in diameter
- The associated adhesions may be filmy or dense. Larger cysts are usually densely adherent to the surrounding pelvic sidewalls or broad ligament.

Deep infiltrating endometriosis (DIE)

- penetrations of greater than 5 mm, represent a more progressive form of the disease

Pathogenesis: Theories on development of endometriosis

Etiology

Theories:

1. Retrograde menstruation
2. Coelomic metaplasia
3. Benign metastases (Lymphatic and vascular metastasis)
4. Iatrogenic dissemination
5. Immunologic changes
6. Genetic predisposition

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1. Retrograde Menstruation

- **Sampson's theory**
- Most popular theory
- Reflux of menstrual blood and viable endometrial cells in the pelvis leads to implantation of endometrial cells in the pelvic peritoneum and under hormonal influence, grow as homologous grafts.

- Examples/evidence:

1. Endometriosis is discovered most frequently in areas immediately adjacent to the tubal ostia or in the dependent areas of the pelvis.
2. Endometriosis is frequently found in women with outflow obstruction of the genital tract.

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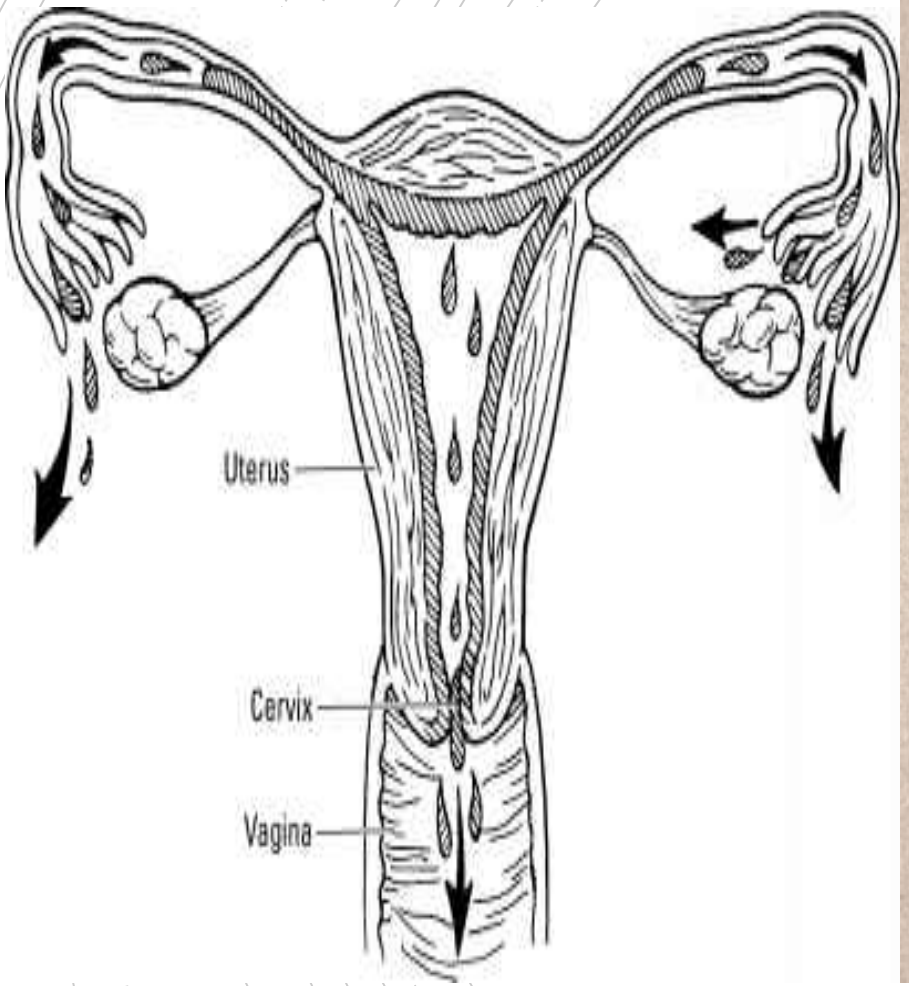
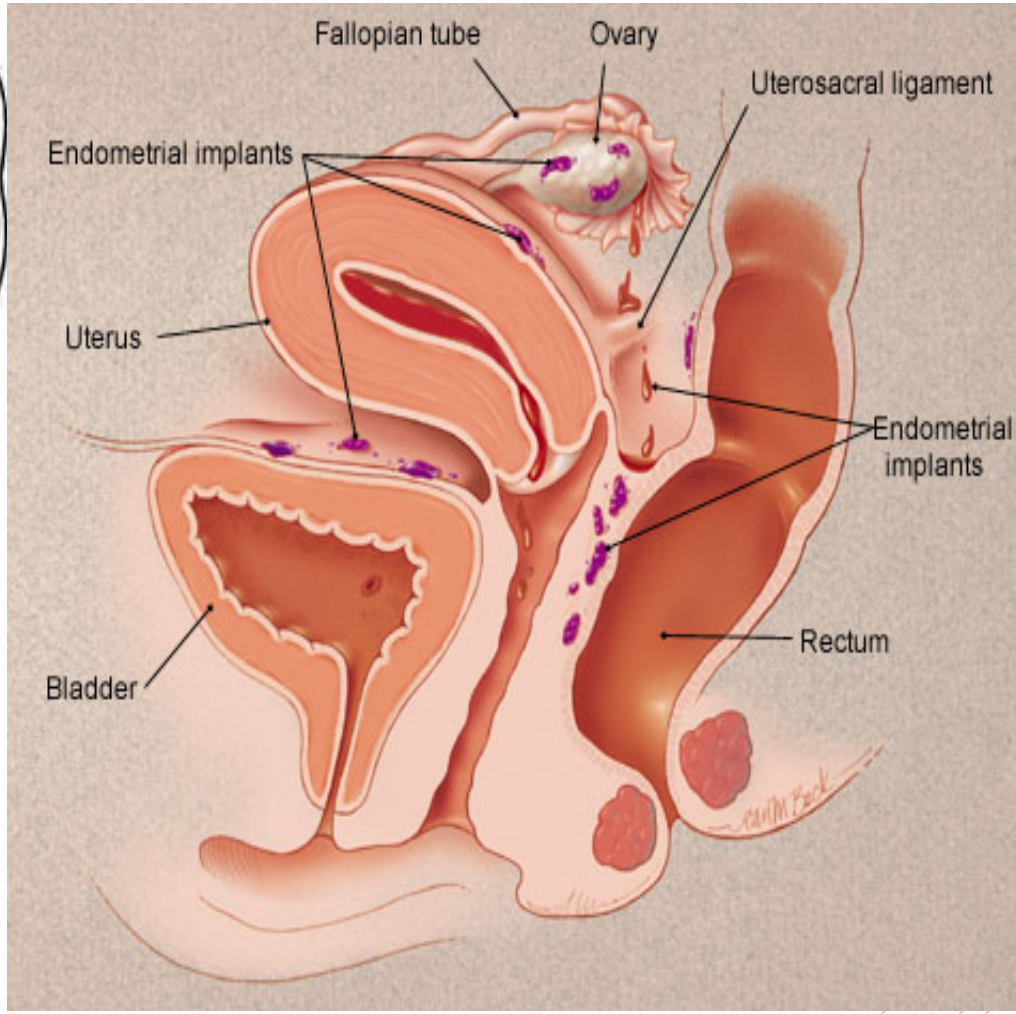

Uterus
Cervix
Vagina


Fallopian tube
Ovary
Uterosacral ligament
Endometrial implants
Uterus
Endometrial implants
Rectum
Bladder

Retrograde menstruation

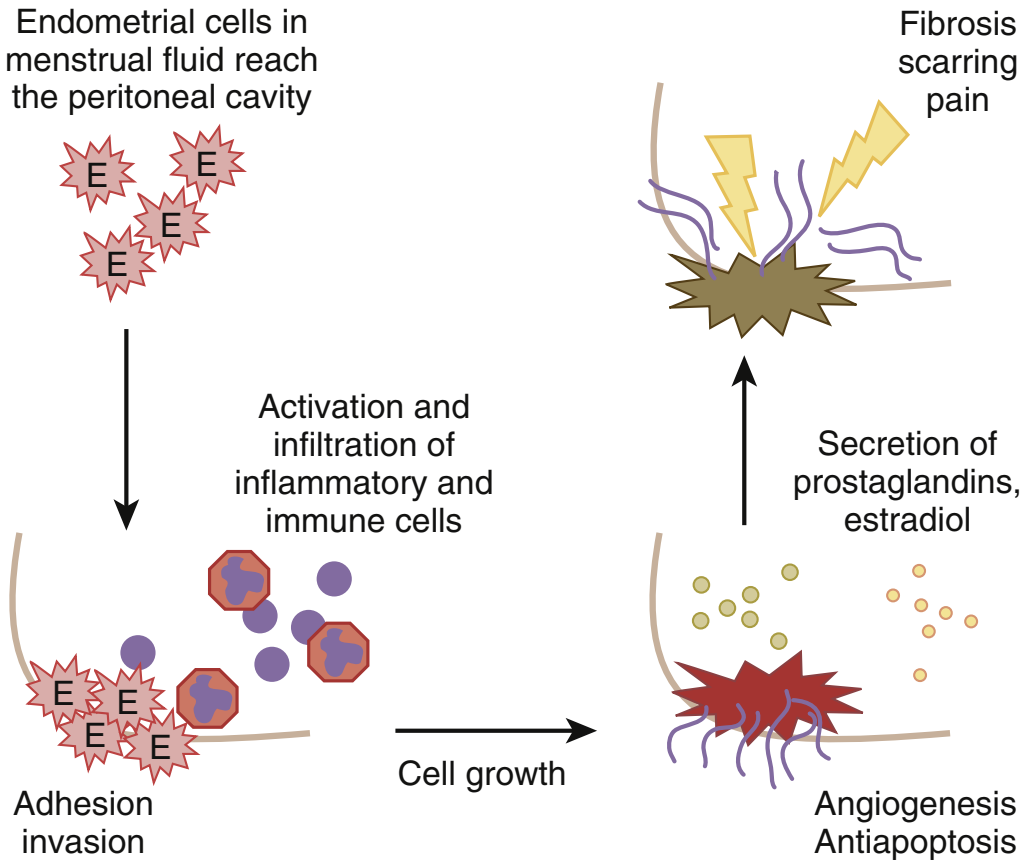


Figure 19.1 Proposed establishment of peritoneal endometriotic implants via retrograde menstruation, attachment, proliferation, migration, neovascularization, inflammation, and fibrosis. *E*, Endometrial cell. (From Flores I, Rivera E, Ruiz LA, et al. Molecular profiling of experimental endometriosis identified gene expression patterns in common with human disease. *Fertil Steril.* 2007;87[5]:1180-1199.)

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Endometrotic implants

- The gross appearance of the implant depends on the site, activity, relationship to the day of the menstrual cycle, and chronicity of the area involved.
- The color of the lesion may be red, brown, black, white, yellow, pink, or a clear/reddish vesicle.
- The color depends on the blood supply, amount of hemorrhage, fibrosis, size of the lesion, the degree of edema, and the amount of inspissated material
- New lesions are small, bleblike implants that are less than 1 cm in diameter

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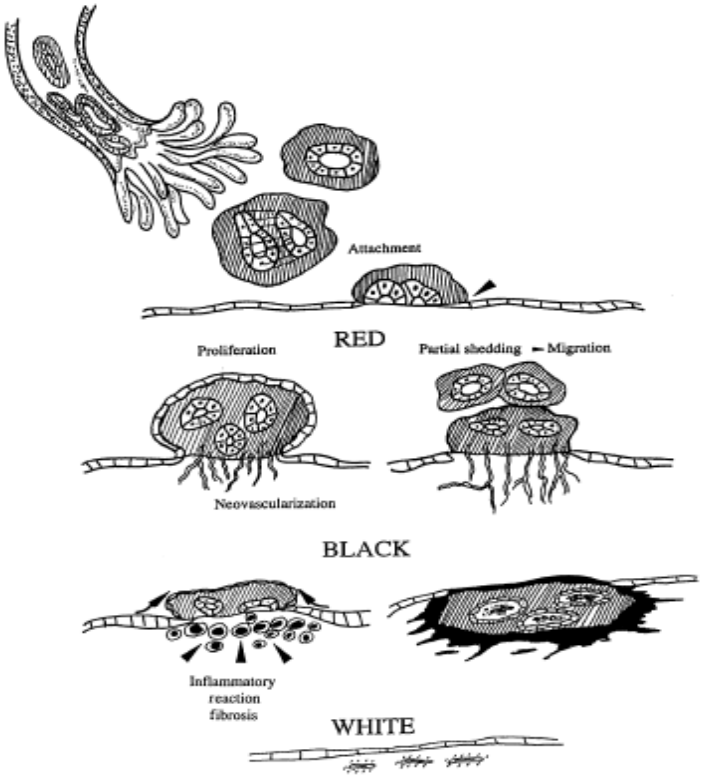

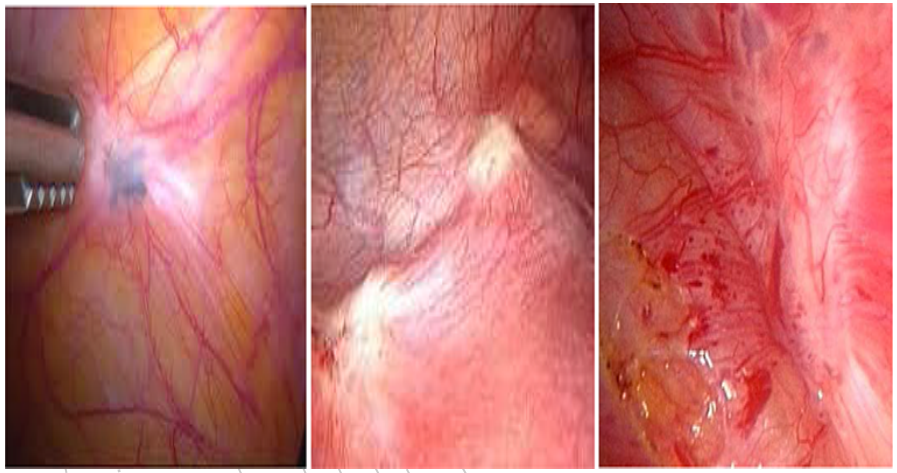

- New lesions are small, bleblike implants that are less than 1 cm in diameter.
- Red, blood-filled lesions are the most active phase of the disease
- dark brown/dark blue/black color, are described as “powder burn” areas
- The older lesions are white, have more intense scarring, and are usually puckered or retracted from the surrounding tissue.
  - White or mixed colored lesions are *more likely to provide histologic confirmation of endometriosis.*

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2. Coelomic metaplasia

- metaplasia of the coelomic epithelium or proliferation of embryonic rests.
- theory of embryonic Mullerian rests, or mullerianosis
- The metaplasia hypothesis postulates that the coelomic epithelium retains the ability for multipotential development

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2. Coelomic metaplasia

- Metaplasia occurs after an "induction phenomenon" has stimulated the multipotential cell.
- The induction substance may be a combination of menstrual debris and the influence of estrogen and progesterone.

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2. Coelomic metaplasia

- Examples: Endometriosis has been discovered:

1. in prepubertal girls
2. women with congenital absence of the uterus
3. very rarely in men.
4. Decidual reaction of isolated areas of peritoneum during pregnancy

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3. Lymphatic and vascular metastasis

- Helps to explain rare and remote sites of endometriosis, such as

1. the spinal column
2. nose
3. pelvic lymph nodes
4. Forearm
5. thigh
6. multiple lesions in the lung/

"***catamenial hemothorax***"= bloody pleural fluid occurring during menses.

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4. Iatrogenic Dissemination

- Hypothesis: endometrial glands and stroma are implanted during a surgical procedure.

- Examples:

1. CS scar endometriosis (subcutaneous layer)
2. Episiotomy scar endometriosis

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5. Immunologic changes

- **altered function of immune-related cells**, are directly related to the pathogenesis of endometriosis
- abnormalities in cell-mediated and humoral components of the immune system in both peripheral blood and peritoneal fluid.

Box 19.1 Cytokines and Growth Factors in Peritoneal Fluid

Concentrations Increased in Endometriosis
Complement
Eotaxin
Glycodelin
IL-1
IL-6
IL-8
MCP-1
PDGF
RANTES
Soluble ICAM-1
TGF-β
VEGF

Concentrations Unchanged in Endometriosis
EGF
Basic FGF
Interferon-γ
IL-2
IL-4
IL-12

Concentrations Decreased in Endometriosis
IL-13

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5. Immunologic changes

- primary immunologic change involves an alteration in the function of the **peritoneal macrophages** prevalent in the peritoneal fluid of patients with endometriosis.
- Women with no endometriosis have monocytic-type macrophages in their peritoneal fluid that have a short life span and limited function.
- Women who develop endometriosis have more peritoneal macrophages that are larger. These hyperactive cells secrete multiple growth factors and cytokines that enhance the development of endometriosis

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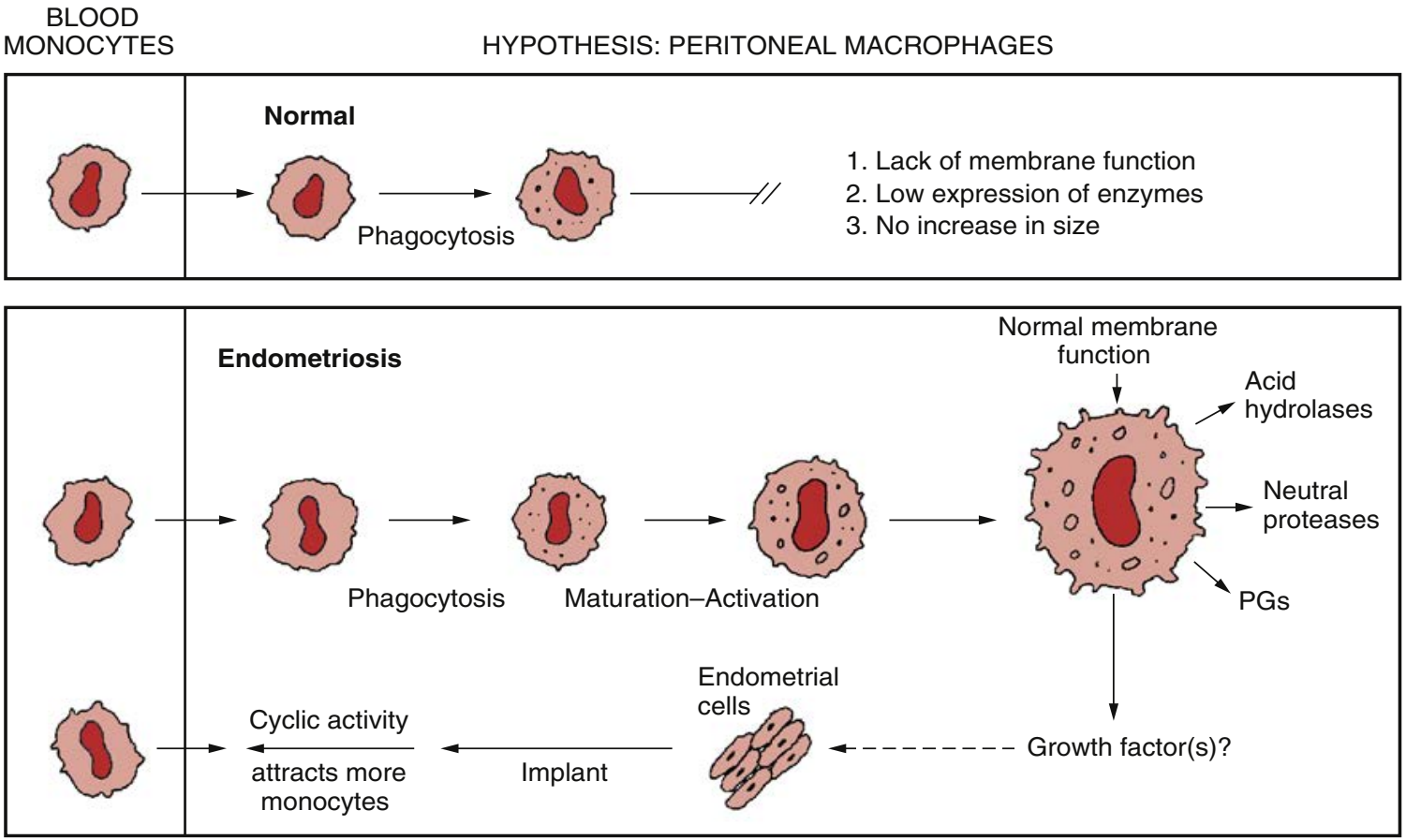

Figure 19.4 Hypothesis regarding pathophysiologic characteristics of human peritoneal macrophages in endometriosis. *PG*, Prostaglandins. (Modified from Halme J, Becker S, Haskill S, et al. Altered maturation and function of peritoneal macrophages: possible role in pathogenesis of endometriosis. *Am J Obstet Gynecol.* 1987;156:787.)

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5. Immunologic changes

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- natural killer (NK) cells have decreased cytotoxicity against endometrial and hematopoietic cells in women with endometriosis.
- Peritoneal fluid of women with endometriosis has less influence of NK activity than is found in fertile women without endometriosis

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5. Immunologic changes

- Endo 1 protein (chemoattractant protein) found in endometriotic tissues enhanced local production of interleukin-6 (IL-6) and self-perpetuates lesion/cytokine interactions.
- expression of basic fibroblast factor, IL-6, IL-8, platelet- derived growth factor (PDGF), and vascular endothelial growth factor (VEGF) are all increased, further compounding the proliferative activity of endometriosis lesions

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5. Immunologic changes

- Steroid interactions also enhance the progression of disease.
- Estrogen production is enhanced locally, and there is evidence for upregulation of aromatase activity, increased COX-2 expression, and deficiency in 17β-dehydrogenase II activity favoring local estradiol production

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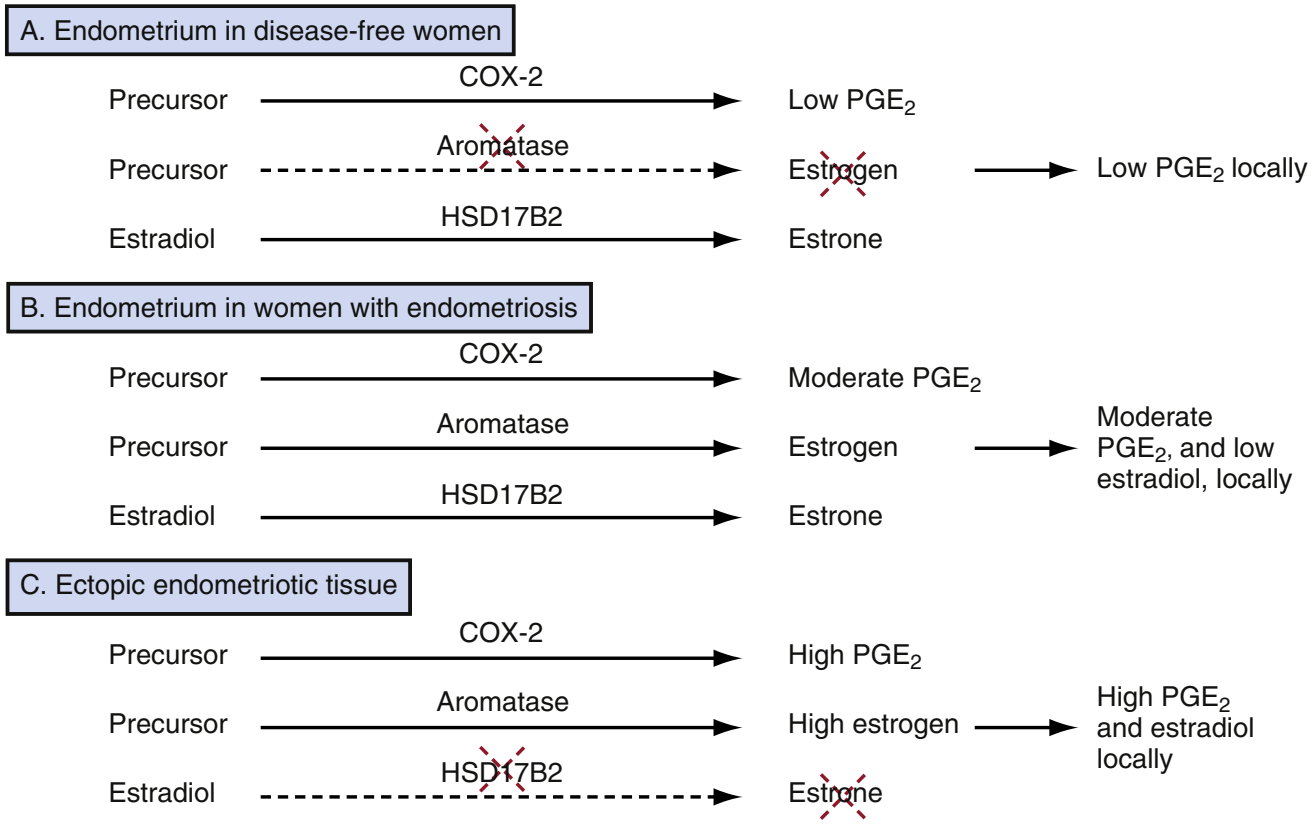
Normal Endometrium and Endometriosis.



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5. Immunologic changes

- Enhanced aromatase activity appears to be the result of overexpression of the orphan nuclear receptor steroidogenic factor-1 (SF-1) in lesions.
- The local production of estrogen through aromatase activity explains why progression of lesions may occur even with ovarian suppression.

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5. Immunologic changes

- there is evidence for progesterone "resistance"

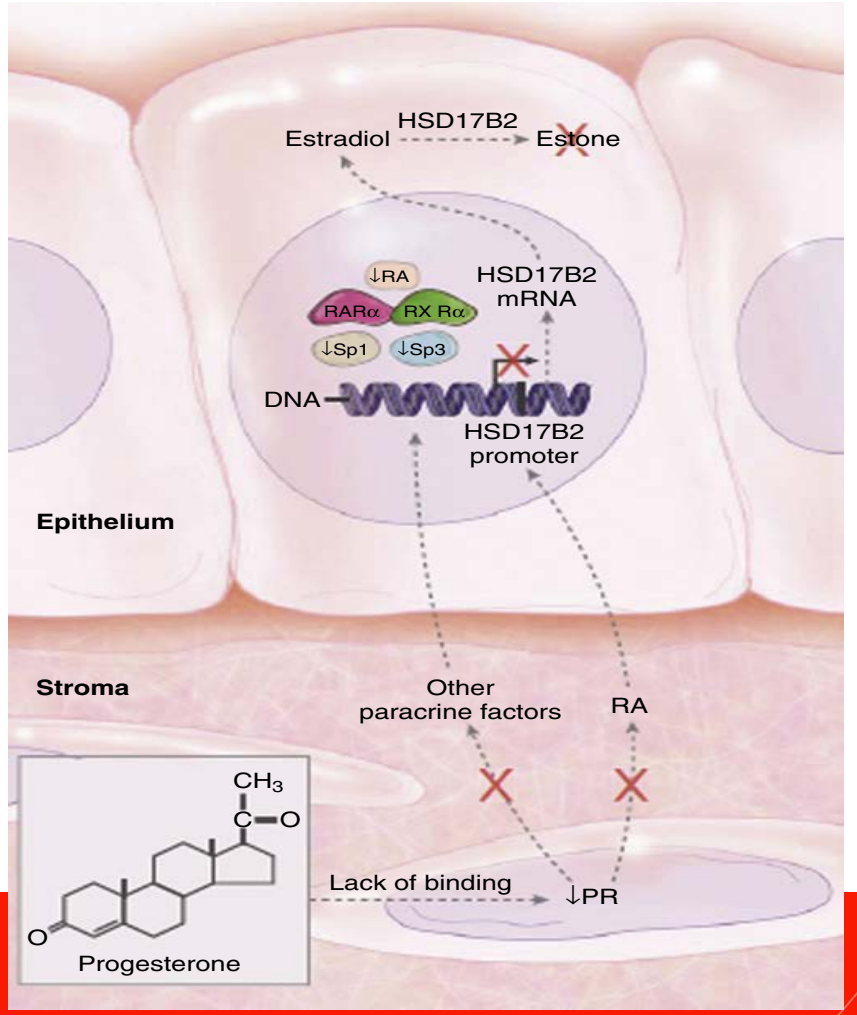

Figure 19.6 Disrupted paracrine action of progesterone in endometriotic tissue. (Modified from Bulun SE. Mechanisms of disease: endometriosis. *N Engl J Med.* 2009;360[3]:268-279.)

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5. Immunologic changes

- Autoimmunity may well exist in women with endometriosis
- there are reports of increased B and T cells, and serum immunoglobulin (IgG, IgA, and IgM) autoantibodies in endometriosis.
- evidence of the higher prevalence of other autoimmune diseases.

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6. Genetic predisposition

- familial predisposition to endometriosis with grouping of cases of endometriosis in mothers and their daughters.
- The incidence of endometriosis in first-degree relatives, women with severe endometriosis, has been thought to be **7%**.
- Women who have a family history of endometriosis are likely to develop the disease earlier in life and to have more advanced disease
- deletions of genes, most specifically increased heterogenicity of chromosome 17 and aneuploidy, in women with endometriosis compared with controls

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Clinical Diagnosis

Clinical diagnosis: history

- The classic symptoms of endometriosis are **cyclic pelvic pain** and **infertility**
- chronic pelvic pain usually presents as secondary dysmenorrhea or dyspareunia (or both).
- Secondary dysmenorrhea usually begins 36 to 48 hours prior to the onset of menses.
- approximately one third of patients with endometriosis are asymptomatic

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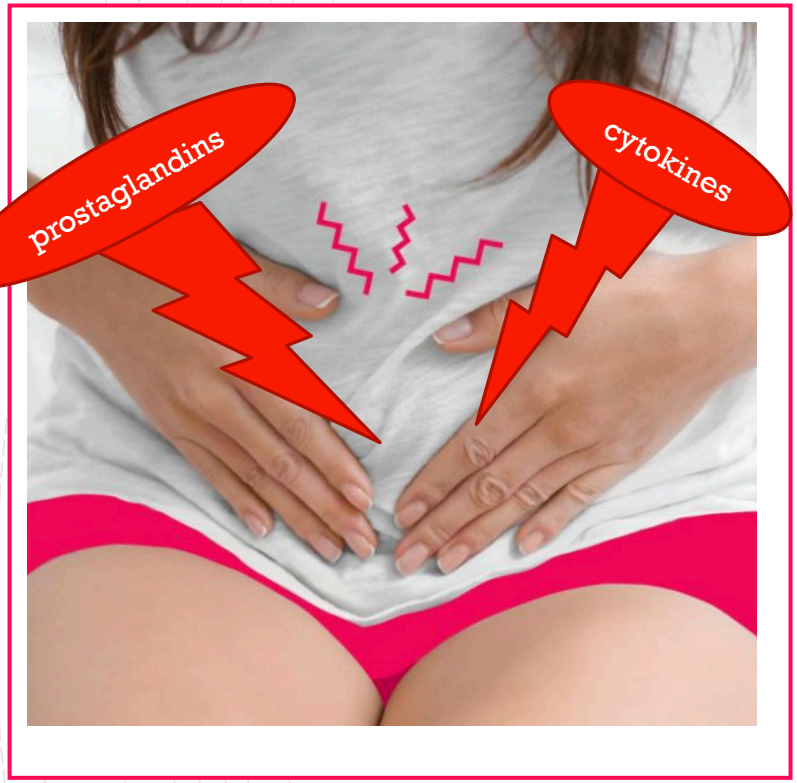
Clinical diagnosis: history



- The **cyclic pelvic pain** is related to the sequential swelling and the extravasation of blood and menstrual debris into the surrounding tissue.
- The chemical mediators of this intense sterile inflammation and pain are believed to be **prostaglandins and cytokines**
- the extent of pelvic pain is often **inversely related** to the amount of endometriosis in the female pelvis.

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Clinical diagnosis: history

- dyspareunia associated with endometriosis is described as pain deep in the pelvis.

- The cause of this symptom
- . seems to be immobility of the pelvic organs during coital activity or direct pressure on areas of endometriosis in the uterosacral ligaments or the cul-de-sac (‘nodular culdesac’)

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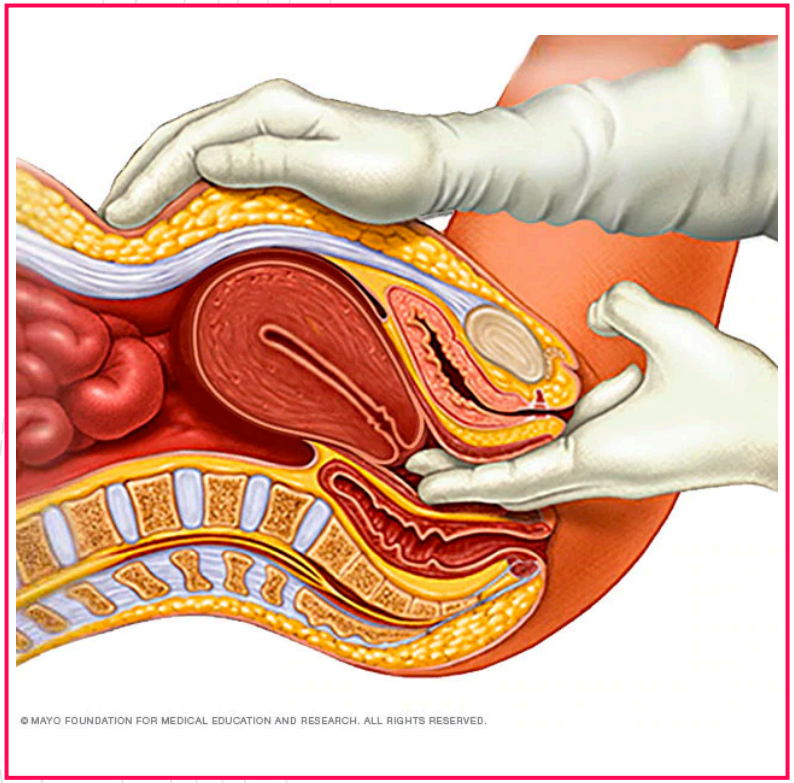
Table 19.2 Preoperative Symptoms in 130 Patients Undergoing Colorectal Resection for Endometriosis

Symptom	No. of Patients	(%)
Pelvic pain	111	(85)
Rectal pain	68	(52)
Cyclic rectal bleeding	24	(18)
Diarrhea	55	(42)
Constipation	53	(41)
Diarrhea and constipation	18	(14)
Dyspareunia	83	(64)

From Bailey HR, Ott MT, Hartendorp P. Aggressive surgical management for advanced colorectal endometriosis. *Dis Colon Rectum*. 1994;37(8):747-753.

Clinical diagnosis:



- The classic pelvic finding of endometriosis is a fixed retroverted uterus, with scarring and tenderness posterior to the uterus.
- The characteristic tender nodularity of the uterosacral ligaments and cul-de-sac, and induration of rectovaginal septum may be palpated on RVE.
- The ovaries may be enlarged and tender and are often fixed to the broad ligament or lateral pelvic sidewall

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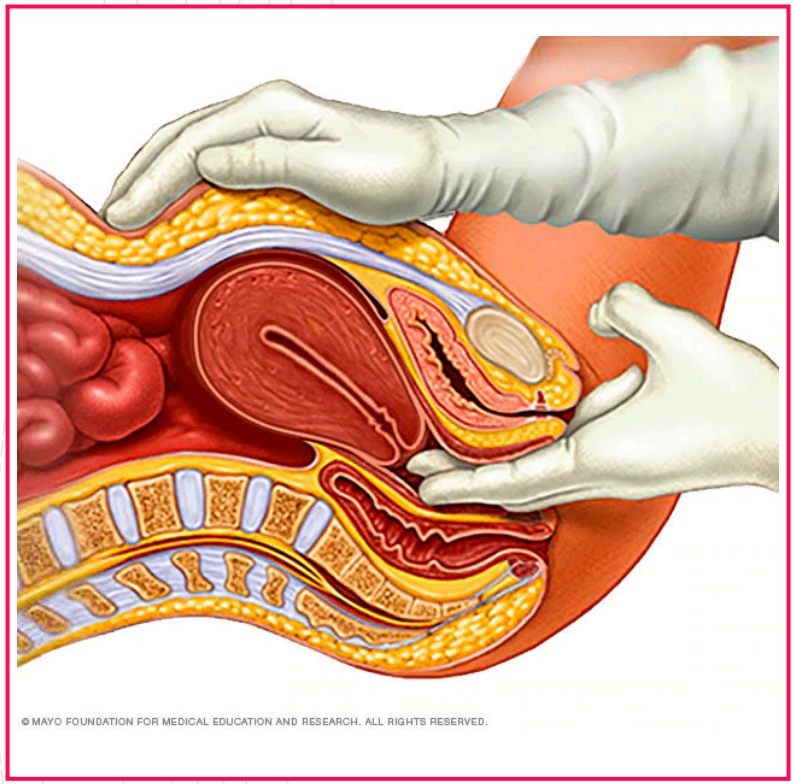
Clinical diagnosis:



- Best time to do PELVIC EXAM → first or second day of her menstrual flow → This is the time of maximum swelling and tenderness in the areas of endometriosis.

- Diagnosis can be confirmed in most cases by direct laparoscopic visualization of endometriosis
- Biopsy of selected implants confirms the diagnosis

- GOLD STANDARD of diagnosis: DIRECT VISUALIZATION + BIOPSY

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Imaging

- Imaging can be a useful adjunct to the clinical presentation and physical exam for evaluation of endometriosis.
- Transvaginal Ultrasound examination: first line diagnostic imaging;
  - has the highest sensitivity and specificity in identifying ovarian endometriomas
  - helpful in differentiating solid from cystic lesions and may help distinguish an endometrioma from other adnexal abnormalities.
  - Because the lesions are vascular, increased Doppler flow may be demonstrated in endometriosis

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Imaging

- 4 ultrasonographic steps to the evaluation of the pelvis with suspected endometriosis:

1. traditional evaluation of the uterus and adnexa for adenomyosis or endometriomas.

   (Adenomyosis is observed more frequently in women with deep endometriosis lesions compared with those with superficial lesions)

2. ultrasound probe is used to determine the location of specific tender spots that may reflect disease-specific sites to be investigated at the time of surgery.

Falcone T and Flyct R. Clinical Management of Endometriosis. (Obstet Gynecol 2018;0:1–15

Imaging

3. evaluate the cul de sac (pouch of Douglas) to determine whether there is deeply infiltrating disease or obliteration by the "sliding sign," in which pressure is placed on the cervix with the probe to see whether the anterior rectum moves freely across the area of the vagina next to the posterior cervix and upper uterus.
4. evaluation for nodules of the anterior compartment (bladder) and posterior compartment.

   The posterior compartment includes the uterosacral ligaments (which are not seen by ultrasonography unless there is a nodule) the rectovaginal septum, vaginal wall, and rectum.

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Imaging

- Modified techniques such as **rectal water contrast transvaginal ultrasound** can increase the probability of detecting a DIE lesion, which is now considered to be the more sensitive technique for the diagnosis of DIE.
- Magnetic resonance imaging (MRI) provides the best over-all diagnostic tool for endometriosis but is not always a practical modality for its diagnosis.
  - The use of magnetic resonance imaging seems logical for equivocal ultrasound findings, especially if surgery is planned for excision of deeply infiltrating endometriosis, possibly requiring rectal or bladder resection

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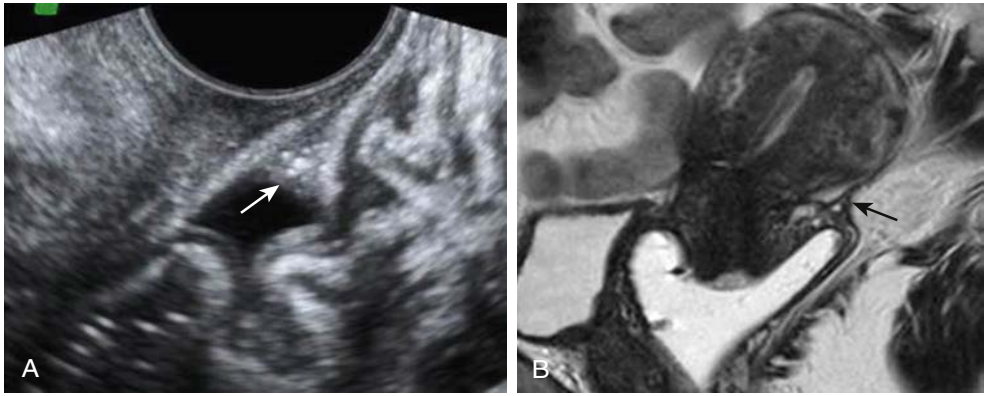

Figure 19.13 Retrocervical endometriosis attached to posterior vaginal fornix on vaginal ultrasound (**A**) and by MRI (**B**). Arrows show the lesions in different patients. (Courtesy of Manoel Goncalves, MD, Clinica Medicina da Mulher and RDO Medicina Diagnostica, and Mauricio Abrao, MD, University of Sao Paulo, Sao Paulo, Brazil.)

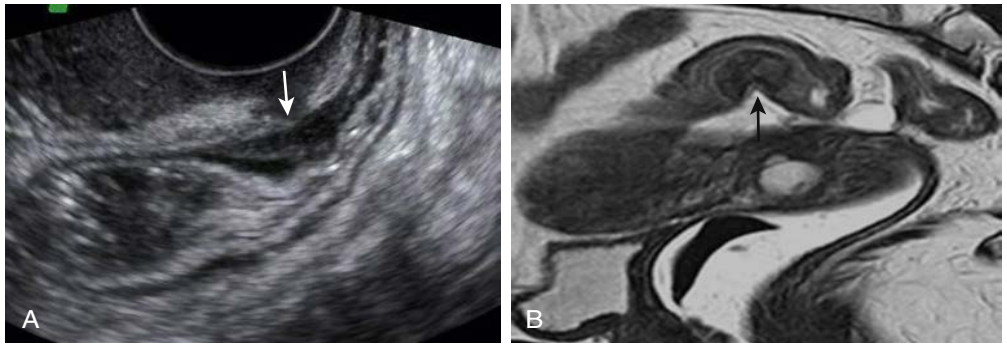

Figure 19.14 Rectal endometriosis infiltrating part of the muscular wall of the intestine by vaginal ultrasound (**A**) and sigmoid endometriosis infiltrating part of the muscular wall of the intestine by MRI (**B**). Arrows show the lesions. (Courtesy of Manoel Goncalves, MD, Clinica Medicina da Mulher and RDO Medicine Diagnostica, and Mauricio Abrao, MD, University of Sao Paulo, Sao Paulo, Brazil.)

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Diagnostic Laparoscopy

- When laparoscopy is undertaken to establish the diagnosis of endometriosis, it is important to describe systematically the extent of the pathology.
- The American Society for Reproductive Medicine developed a point-scoring designed primarily to record the extent of the disease in fertility patients
  - The focus here was intended to provide characterization of disease extent for fertility and not for pain assessment.
- the Endometriosis Fertility Index (EFI): focuses on the fertility potential of patients with endometriosis, and it has been shown in prospective evaluation to correlate with pregnancy rates

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Differential Diagnoses

- Although a benign disease, endometriosis exhibits characteristics of both malignancy and sterile inflammation.
- Therefore, the common considerations in the differential diagnosis include chronic pelvic inflammatory disease, ovarian malignancy, degeneration of myomas, hemorrhage or torsion of ovarian cysts, adenomyosis, primary dysmenorrhea, and functional bowel disease.

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Differential Diagnoses

- Occasionally a large endometrioma of the ovary may rupture into the peritoneal cavity.
- This results in an acute surgical abdomen and brings into the differential diagnosis conditions such as ectopic pregnancy, appendicitis, diverticulitis, and a bleeding corpus luteum cyst.

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Biomarkers for Endometriosis

Biomarkers

- cancer antigen-125 (CA-125) :levels are elevated in most patients with endometriosis and increases incrementally with advanced stages
  - low specificity: increase with other pelvic conditions such as leiomyomas, acute pelvic inflammatory disease, and the first trimester of pregnancy.
- Glycodelin, previously known as *placental protein 14,* has been shown to be elevated in endometriosis and is produced in endometriotic lesions.
- The most predictive markers appear to be IL-1 (most useful marker), chemoattractant protein-1 and interferon gamma

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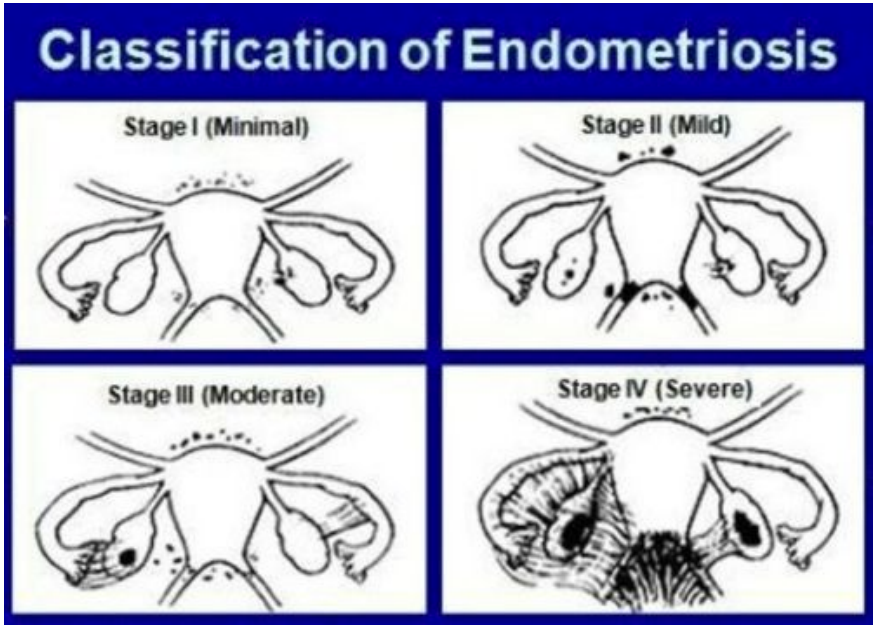
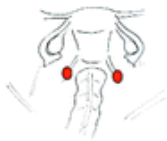
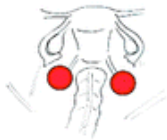
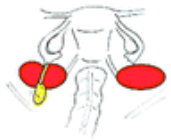
Staging for Endometriosis

ASRM (AFS) STAGING



Stage	Progression	Tissue Description
I	Minimal	Presentation of 2-3 superficial implants.
II	Mild	Appearance of more implants that occur within deeper layers of tissue.
III	Moderate	Many deep implants in combination with minor/small endometriomas on one or both ovaries. May also present filmy adhesions.
IV	Severe	Persistance of deep implants, enlargement of endometriomas on one or both ovaries, development of dense adhesions.

ENZIAN STAGING

Pelvic compart-ment / Level	A rectovaginal space vagina	B sacrouterine ligaments cardinal ligaments, pelvic sidewall external ureter compresression	C lower bowel rectum / sigmoid
1 <1cm	 A 1	 B 1	 C 1
2 1-3 cm	 A 2	 B 2	 C 2
3 >3cm	 A 3	 B 3	 C 3

FA
uterine adenomyosis

FB
bladder

FU
intrinsic ureter

FI
intestine
sigma, coecum,
term. Ileum

FO
other localisations
Diaphragma,....

link.springer.com

EFI STAGING

ENDOMETRIOSIS FERTILITY INDEX (EFI) SURGERY FORM

LEAST FUNCTION (LF) SCORE AT CONCLUSION OF SURGERY

Score		Description		Left	Right
4	=	Normal	Fallopian Tube		
3	=	Mild Dysfunction			
2	=	Moderate Dysfunction	Fimbria		
1	=	Severe Dysfunction			
0	=	Absent or Nonfunctional	Ovary		

To calculate the LF score, add together the lowest score for the left side and the lowest score for the right side. If an ovary is absent on one side, the LF score is obtained by doubling the lowest score on the side with the ovary.

Lowest Score	Left	+	Right	=	LF Score

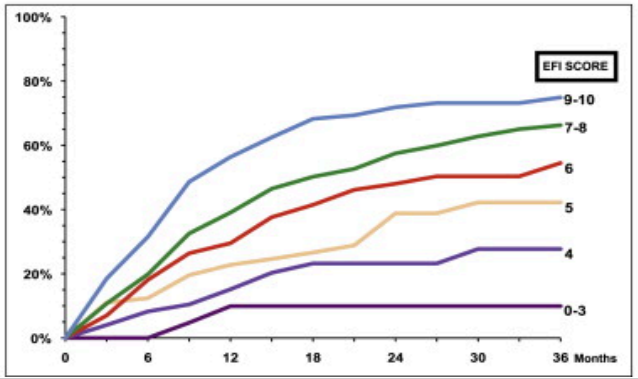
ENDOMETRIOSIS FERTILITY INDEX (EFI)

Historical Factors			Surgical Factors		
Factor	Description	Points	Factor	Description	Points
Age			LF Score		
	If age is ≤ 35 years	2		If LF Score = 7 to 8 (high score)	3
	If age is 36 to 39 years	1		If LF Score = 4 to 6 (moderate score)	2
	If age is ≥ 40 years	0		If LF Score = 1 to 3 (low score)	0
Years Infertile			AFS Endometriosis Score		
	If years infertile is ≤ 3	2		If AFS Endometriosis Lesion Score is < 16	1
	If years infertile is > 3	0		If AFS Endometriosis Lesion Score is ≥ 16	0
Prior Pregnancy			AFS Total Score		
	If there is a history of a prior pregnancy	1		If AFS total score is < 71	1
	If there is no history of prior pregnancy	0		If AFS total score is ≥ 71	0
Total Historical Factors			Total Surgical Factors		

EFI = TOTAL HISTORICAL FACTORS + TOTAL SURGICAL FACTORS:

Historical	+	Surgical	=	EFI Score

ESTIMATED PERCENT PREGNANT BY EFI SCORE



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Treatment: Medical and Surgical

TREATMENT

The two primary short-term goals in treating endometriosis are: 1) relief of pain 2) promotion of fertility

primary long-term goal in the management of endometriosis is attempting to prevent progression or recurrence of the disease process.

Treatment of endometriosis can be medical, surgical, or usually a combination of both.

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TREATMENT

- selection of an optimal treatment is based on multiple factors including:

1. patient age
2. patient preference
3. reproductive plans
4. pain severity
5. degree of disease
6. treatment cost and intended duration
7. treatment risks/side effect profiles
8. accessibility.

Falcone T and Flyct R. Clinical Management of Endometriosis. (Obstet Gynecol 2018;0:1–15

TREATMENT: Medical

- The main objective of medical management is to prevent recurrence and reduce symptoms, thereby eliminating the need for surgery (or repeat surgery) or prolonging the time between surgeries.

Falcone T and Flyct R. Clinical Management of Endometriosis. (Obstet Gynecol 2018;0:1–15

TREATMENT: Medical

- **Aim**: suppression of lesions and associated symptoms, particularly pain.
- The goal of hormonal treatments is to induce a local hypoestrogenic state by suppressing ovulation (menstrual suppression) → amenorrhea
- the resulting amenorrhea or hypomenorrhea reduces the conversion of arachidonic acid to prostaglandins with menses and subsequently lessens dysmenorrhea and pelvic pain.

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TREATMENT: Medical

- medical therapy usually suppresses symptomatology and prevents progression of endometriosis, but it does not provide a long-lasting cure of the disease.
- Unfortunately, once suppressive therapy is stopped, symptoms tend to recur at variable rates.

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MEDICAL TREATMENT: Oral contraceptives

- "Pseudopregnancy effect"
- It has been accepted that the most economical regimen for the treatment of women with mild or moderate symptoms of endometriosis has been continuous daily oral contraceptives for 6 to 12 months.
- Continuous dose regimens are aimed at more complete suppression and the only concern is with breakthrough bleeding

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MEDICAL TREATMENT: Oral contraceptives

- One potential risk of using oral contraceptives or progestogens is that there is some risk of rupture if a large endometrioma is present.
- Rupture of large endometriomas may result in an acute surgical abdomen during the first 6 weeks of oral contraceptive therapy.
- During prolonged therapy the endometrial glands atrophy and the stroma undergoes a marked decidual reaction.
- Some smaller endometriomas (≤3 cm) can undergo necrobiosis and resorption.

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MEDICAL TREATMENT: Oral contraceptives

- Most common side effects:

weight gain and breast tenderness.

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MEDICAL TREATMENT: Progestogens

- For women who fail combined hormone therapy, smokers older than 35 years, and women with predisposing risk factors for myocardial infarction, stroke, or thrombolic events
- May be given through oral, intrauterine, parenteral, or implantable routes and all have breakthrough bleeding as their most common side effect.
- Breakthrough bleeding can be ameliorated with a 7- to 14-day course of oral estrogen.

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MEDICAL TREATMENT: Progestogens

- some authors suggest that progestin-only methods such as norethindrone acetate and dienogest may be superior to COCs and can be considered first-line, especially in women with rectovaginal and extrapelvic endometriosis
- Examples:

1. Medroxyprogesterone acetate (Provera): 20-30 mg PO daily
2. Depot medroxyprogesterone acetate (Depo-Provera): 150 mg IM every 3 months to a maximum of 200 mg every month will produce a prolonged amenorrhea.

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TREATMENT: Progestogens

3. Norethindrone acetate: 10-40 mg OD; has a similar symptom profile to that of continuous medroxyprogesterone.
4. Gestrinone: 2.5 - to 7.5 mg/week. Gestrinone acts as an agonist–antagonist of progesterone receptors and an agonist of androgen receptors; binds weakly to estrogen receptors.
5. Dienogest: 2mg OD is a selective progestogen that causes anovulation, has an antiproliferative effect on endometrial cells, and may inhibit cytokine secretion.

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TREATMENT: GnRH agonists

- "medical oophorectomy."
- A dramatic reduction occurs in serum estrone, E2, testosterone, and androstenedione to levels similar to the hormonal levels in oophorectomized women.
- GnRH agonists have no effect on sex hormone-binding globulin. Thus, the androgenic side effects from danazol caused by the increase in free serum testosterone are not observed.
- Similarly, no significant changes occur in total serum cholesterol, HDL, or LDL levels during therapeutic periods of as long as 6 months.

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MEDICAL TREATMENT: GnRH agonists

- Examples:

1. leuprolide acetate: 3.75 mg IM qmonthly or a 11.25-mg depot injection every q 3months.
2. Nafarelin acetate nasal spray is given in a dose of one spray (200 mg) in one nostril in the morning and one spray (200 mg) in the other nostril in the evening up to a maximum of 800 mg daily.
3. Goserelin acetate: 3.6 mg every 28 days SQ

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MEDICAL TREATMENT: GnRH agonists

- The side effects associated with GnRH agonist therapy are primarily those associated with estrogen deprivation, similar to menopause.
- The three most common symptoms are hot flushes, vaginal dryness, and insomnia.

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MEDICAL TREATMENT: NSAIDS

- Pain relief and control of bleeding
- Rationale: lesions of endometriosis have been found to express high levels of Cox-2

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TREATMENT: DANAZOL

- Attenuated androgen (active when given orally)
- Produces a hypoestrogenic and hyperandrogenic effect
- Androgenic and anabolic effects has limited its modern-day use.
- Induces atrophic changes in the endometrium of the uterus and similar changes in endometrial implants.
- It may also modulate immunologic function.
- Dose: 400 – 800 mg daily for 6-9 months, but many clinicians reduce the total daily dosage of the drug down to 200, and even 100 mg daily because of side effects.

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TREATMENT: DANAZOL

- Danazol is usually begun during menses (days 1 to 5).
- Because the relief of the symptoms is directly related to the incidence of amenorrhea, the lower dosages of danazol are not as effective but may be tried.
- Unfortunately, symptoms will recur in 15% to 30% of women within 2 years following therapy.

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CLASS	MECHANISM OF ACTION	DRUG	DOSE	SIDE EFFECTS
1. Estrogen–progestin combinations	• Ovulation inhibition • Decidualization or atrophy of lesions	Monophasic estrogen–progestin	Continuous orally daily	Breakthrough bleeding, breast tenderness, nausea, headaches, mood changes
2. Progestins	• Decidualization or atrophy of lesions • Inhibition of angiogenesis • Suppression of matrix metalloproteinase-facilitated growth and implantation of ectopic endometrium	1. Depo Provera 2. Etonogestrel-releasing implant 3. Norethindrone acetate 4. Levonorgestrel-releasing IUS 5. Medroxyprogesterone acetate 6. Dienogest	150mg IM q3mos 1 for 3 yr 5mg OD 1 for 5 yr 30mg OD x 6mos 2mg OD	Acne, weight gain, mood changes, headache, breakthrough bleeding, breast tenderness, lipid abnormalities (norethindrone)
3. GnRH agonists	Inhibition of gonadotropin secretion and subsequent downregulation of ovarian steroidogenesis	1. Leuprolide acetate 1. Goserelin 1. Nafafelin	3.75mg IM monthly (11.25mg IM q3mos) 3.6m mg SC monthly (10.8mg IM q3mos) 200 micrograms intranasally 2x/day	Decreased bone density, atrophic vaginitis, hot flashes, headache, joint pain

Falcone T and Flyct R. Clinical Management of Endometriosis. (Obstet Gynecol 2018;0:1–15

CLASS	MECHANISM OF ACTION	DRUG	DOSE	SIDE EFFECTS
4. GnRH antagonists	Inhibition of gonadotropin secretion and subsequent downregulation of ovarian steroidogenesis	Elagolix	150 mg OD	Hot flushes, lipid abnormalities, decreased bone density
5. Aromatase inhibitors	Local blockade of enzymatic (aromatase) conversion of androgens to estrogens	1. Letrozole 2. Anatrozole	2.5mg OD 1 mg OD	Hot flushes, headaches, decreased bone density
6. Androgenic steroids	• Inhibition of pituitary gonadotropin secretion • Local growth inhibitor • Inhibition of estrogenic enzymes	Danazol	100-400mg PO BID	Hair loss, weight gain, acne, hirsutism
7. Selective progesterone receptor modulators	Inhibition of ovulation, agonist or antagonist at progesterone receptor	1. Mifepristone 2. Ulipristal acetate	50mg OD 15mg orally every other day	Spotting, cramping, dizziness, headache, nausea

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TREATMENT: Surgical

- Surgical management is indicated for the following:

1. after failure of empiric therapy
2. failure, or intolerance of medical management
3. For purposes of diagnosis and immediate treatment
4. for diagnosis and treatment of an adnexal mass and treatment of infertility in some patients.

Falcone T and Flyct R. Clinical Management of Endometriosis. (Obstet Gynecol 2018;0:1–15

TREATMENT: Surgical

- Surgical therapy is divided into conservative and definitive operations.
- Conservative surgery involves the resection or destruction of endometrial implants, lysis of adhesions, and attempts to restore normal pelvic anatomy.
- Definitive/extirpative surgery involves the removal of both ovaries, the uterus, and all visible ectopic foci of endometriosis.
  → analogous to cytoreductive surgery in ovarian carcinoma.

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TREATMENT: Surgery

- foundation of treatment for women with moderate or severe endometriosis, especially those with adhesions and when the disease involves nonreproductive organs.
- Preferably done by laparoscopy
- Conservative surgery has as its goal the removal of all macroscopic, visible areas of endometriosis with the preservation of ovarian function and restoration of normal pelvic anatomy.
- Conservative operations include removal or destruction of implants, removal of endometriomas, lysis of adhesions, appendectomy, and sometimes presacral neurectomy.

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TREATMENT: Surgery

- If the patient has midline pain, such as dysmenorrhea or dyspareunia → presacral neurectomy or resection of the uterosacral ligaments may be performed.
- Ablation of the uterosacral nerves when performed via the laparoscope is called laser uterosacral nerve ablation (LUNA).
- presacral neurectomy relieves only midline pain and does not diminish pain in other areas of the pelvis..

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TREATMENT: Surgery

- Ovarian cystectomy/ oophorocystectomy (for endometriotic cysts)
- Total hysterectomy with bilateral salpingooophorectomy (THBSO)

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Endometriosis: Summary

- Definition
- Pathology
- Etiologies/theories
- Differential diagnosis
- Clinical diagnosis
- Treatment

Thank you!

- *youtube channel: Ina Irabon*
- *www.wordpress.com: Doc Ina OB Gyne*

Thank you for your kind attention