Benign gynecologic lesions:
Endometriosis and Adenomyosis

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Obstetrics and Gynecology

Reproductive Endocrinology and Infertility
Laparoscopy and Hysteroscopy

Reference

- Comprehensive Gynecology 7th edition, 2017 (Lobo RA, Gershenson DM, Lentz GM, Valea FA *editors);* chapters 18 and 19

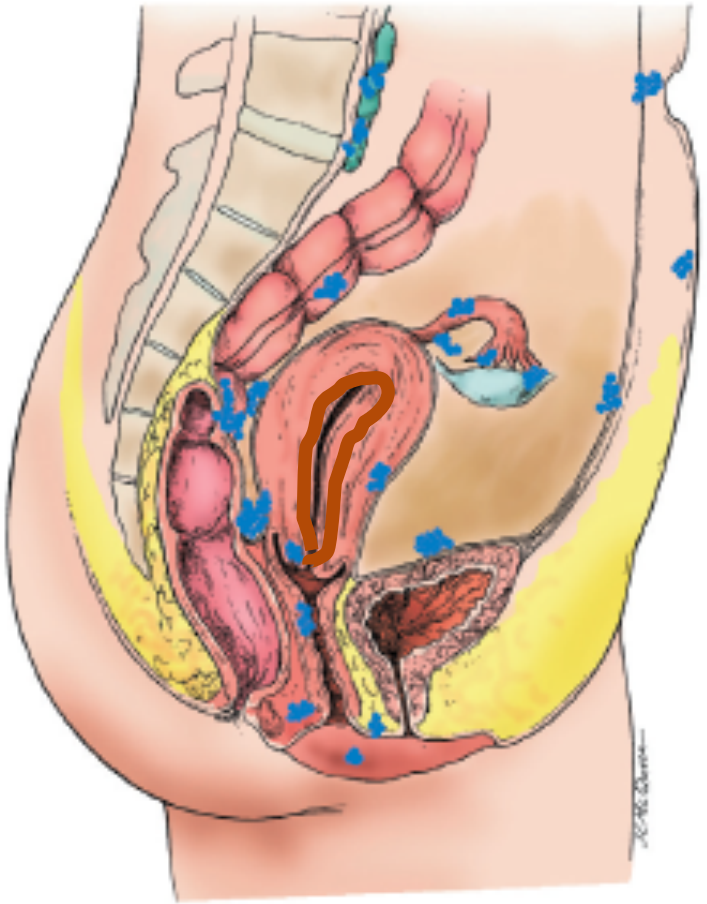
Endometriosis

Endometriosis: Outline

1. Definition
2. Pathology
3. Clinical diagnosis
4. Differential diagnosis
5. Endometriosis and ovarian cancer
6. Endometriosis and menopause
7. Etiologies/theories
8. 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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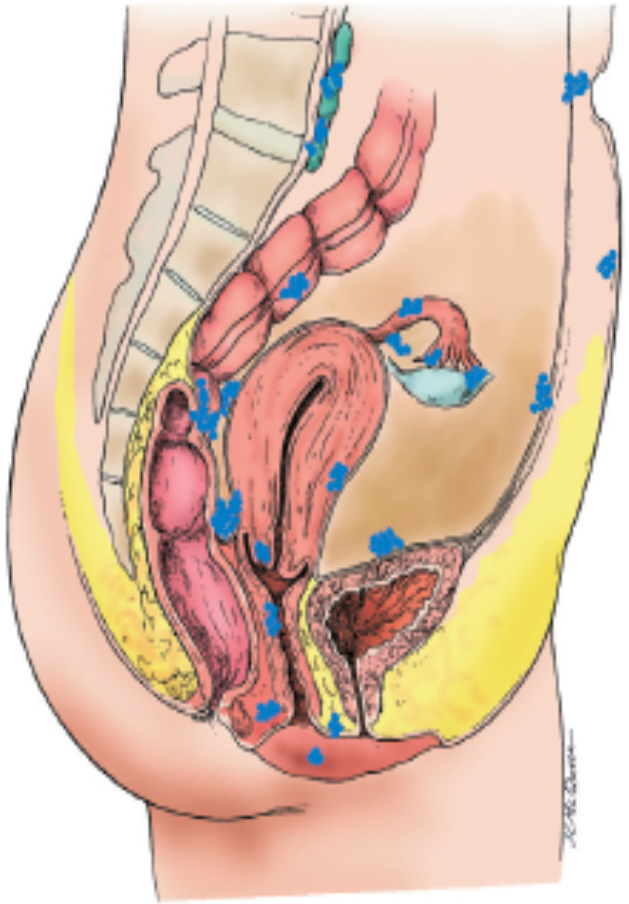
Definition

- 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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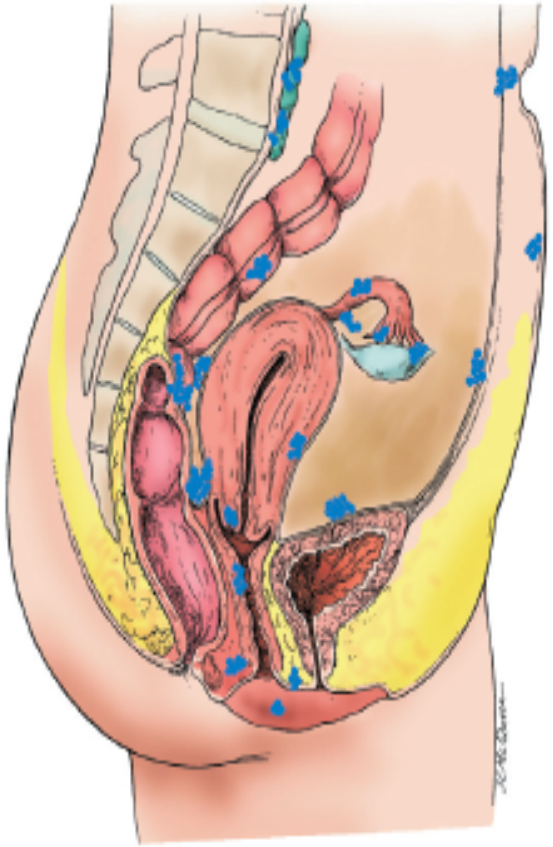
Pathology

- Mostly seen in dependent portions of female pelvis
- **Ovaries**: most common site
- **Deeply infiltrating endometriosis** (**DIE**), penetrations of greater than 5 mm, represent a more progressive form of the disease.
- **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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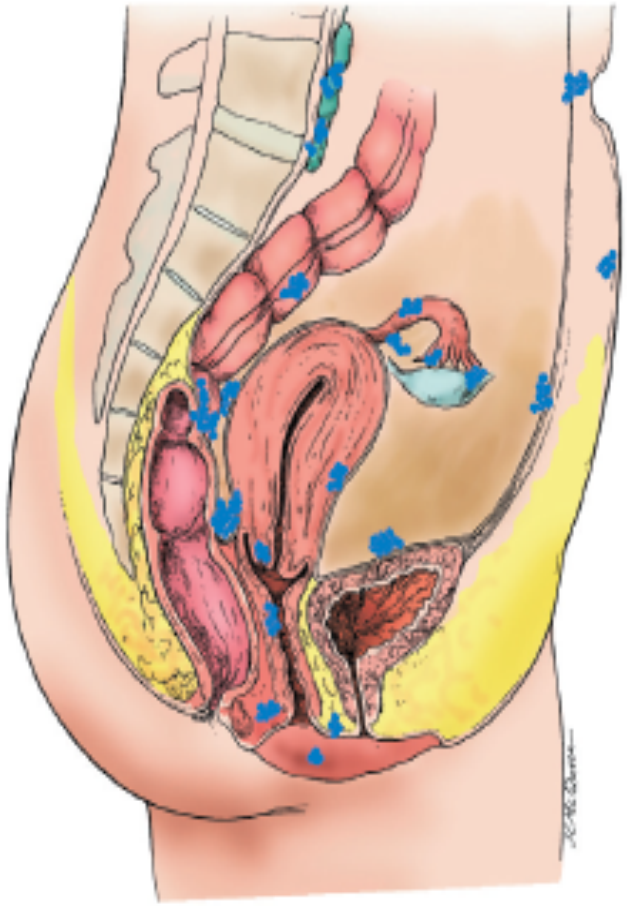
Clinical diagnosis: 1) Symptoms

- 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: 1) Symptoms

- 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: 1) Symptoms

- 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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Clinical diagnosis: 2) Signs

- The classic pelvic finding of endometriosis is a **fixed retroverted uterus**, with scarring and tenderness posterior to the uterus.
- The characteristic nodularity of the uterosacral ligaments and cul-de-sac may be palpated on rectovaginal examination in women with this distribution of the disease.
- The ovaries may be enlarged and tender and are often fixed to the broad ligament or lateral pelvic sidewall.
- In women with unilateral endometriomas, 63% were found in the left ovary.

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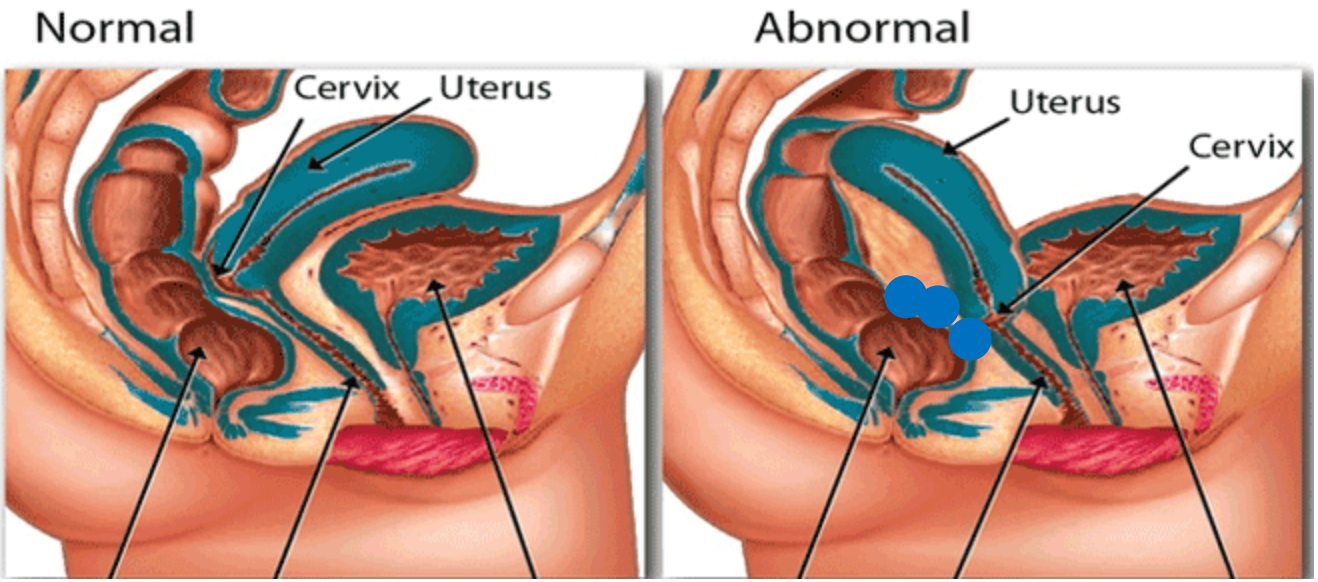
Clinical diagnosis: 2) Signs

Retroverted uterus



Fixed retroverted uterus, nodular culdesac

Clinical diagnosis

- may instruct the patient to return for a pelvic examination during the first or second day of her menstrual flow when the diagnosis of endometriosis is in doubt.→ 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 with its associated scarring and adhesion formation. In many patients it is discovered for the first time during an infertility investigation. Biopsy of selected implants confirms the diagnosis. (GOLD STANDARD: DIRECT VISUALIZATION + BIOPSY)

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Clinical diagnosis

- **Magnetic resonance imaging (MRI)** provides the best diagnostic tool for endometriosis but is not always a practical modality for its diagnosis.
- CA-125 levels are elevated in most patients with endometriosis and increases incrementally with advanced stages

  → non specific! → ELEVATED also in leiomyomas, acute pelvic inflammatory disease, and the first trimester of pregnancy.

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Clinical diagnosis

- Glycodelin → previously known as placental protein 14, has been shown to be elevated in endometriosis and is produced in endometriotic lesions

→ **variable results , that's why not recommended as yet**

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Differential Diagnosis

- Endometriosis exhibits characteristics of both malignancy and sterile inflammation. Therefore, the common considerations in the differential diagnosis include:

1. chronic pelvic inflammatory disease
2. ovarian malignancy
3. degeneration of myomas
4. hemorrhage or torsion of ovarian cysts
5. Adenomyosis
6. primary dysmenorrhea
7. functional bowel disease

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Endometriosis and Ovarian cancer

- risk of developing ovarian cancer may **increase fourfold** in women with endometriosis → Loss of heterozygosity and mutations in suppressor genes, e.g., **p53**, may explain this association.

- These findings warrant caution in the long-term follow-up of women who have extensive disease and ovarian endometriomas.

Endometriosis and Menopause

- Endometriosis is dependent on ovarian hormones (estrogen) to stimulate growth.
- Natural menopause → there is a gradual relief of symptoms.
- Surgical menopause → areas of endometriosis rapidly disappear.
- However, 5% of symptomatic cases of endometriosis present after menopause → The majority of cases in women in their late 50s or early 60s are related to the use of exogenous estrogen.

Etiology

Theories:

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

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:

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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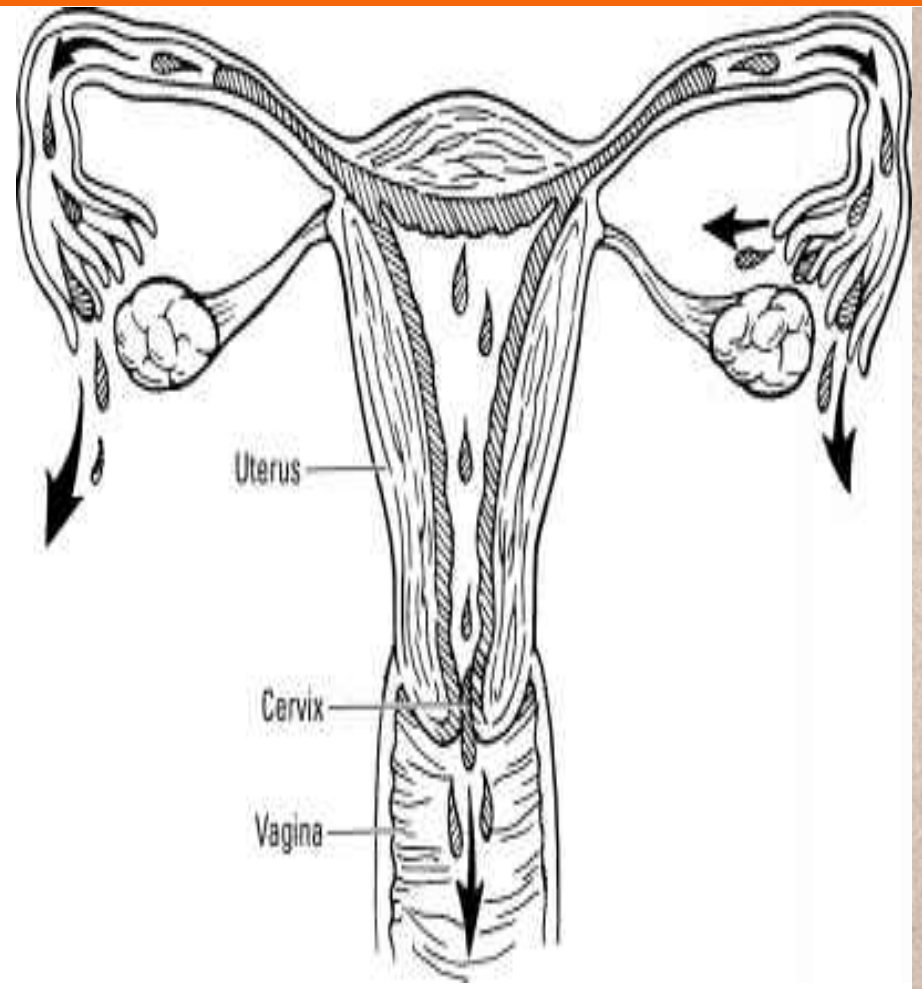
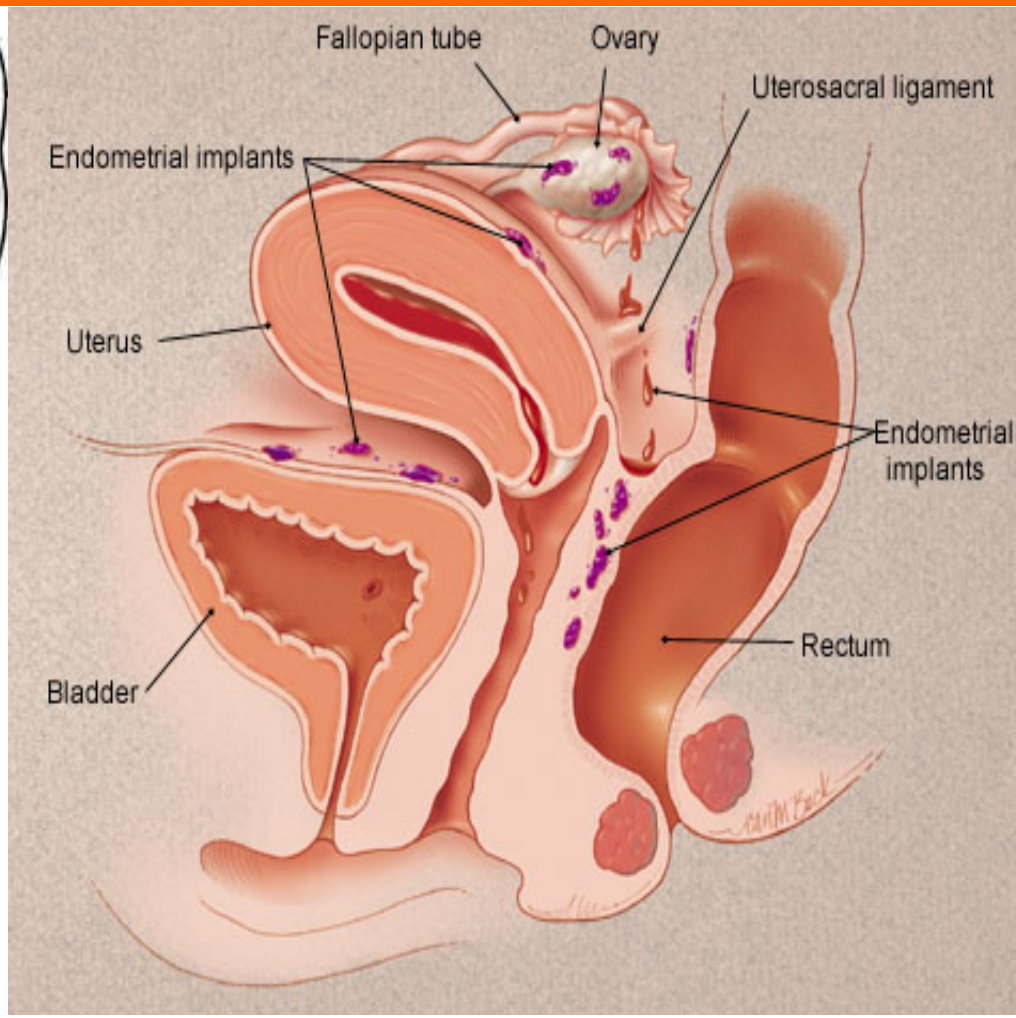
Retrograde menstruation





Retrograde menstruation

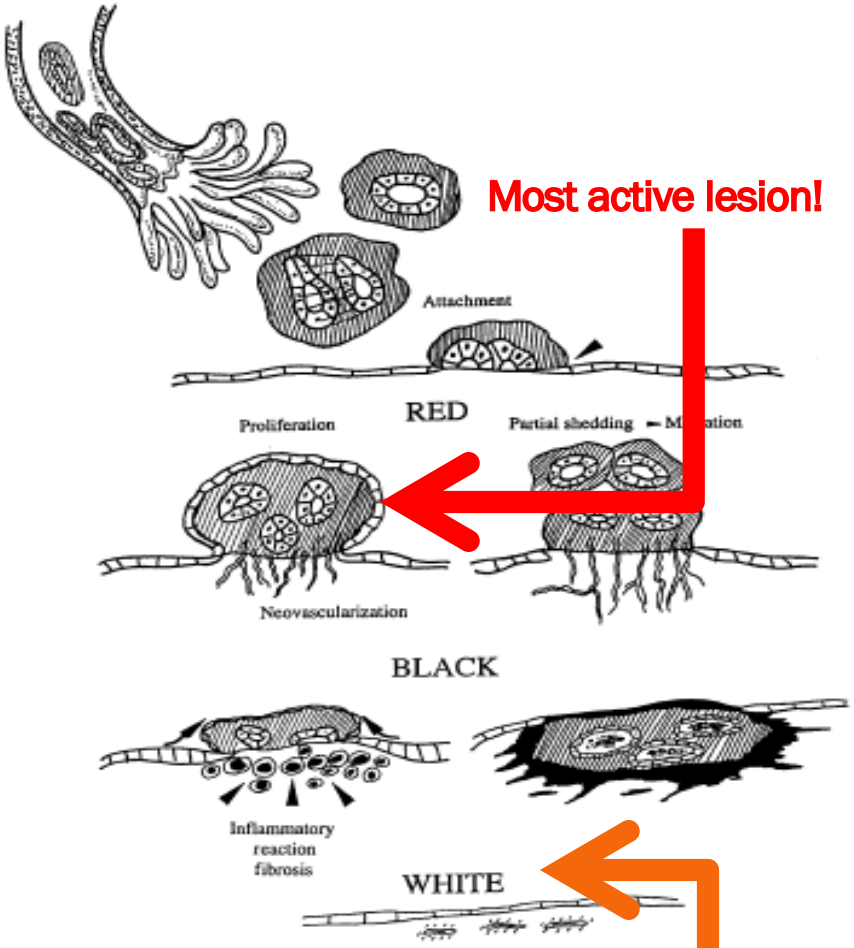
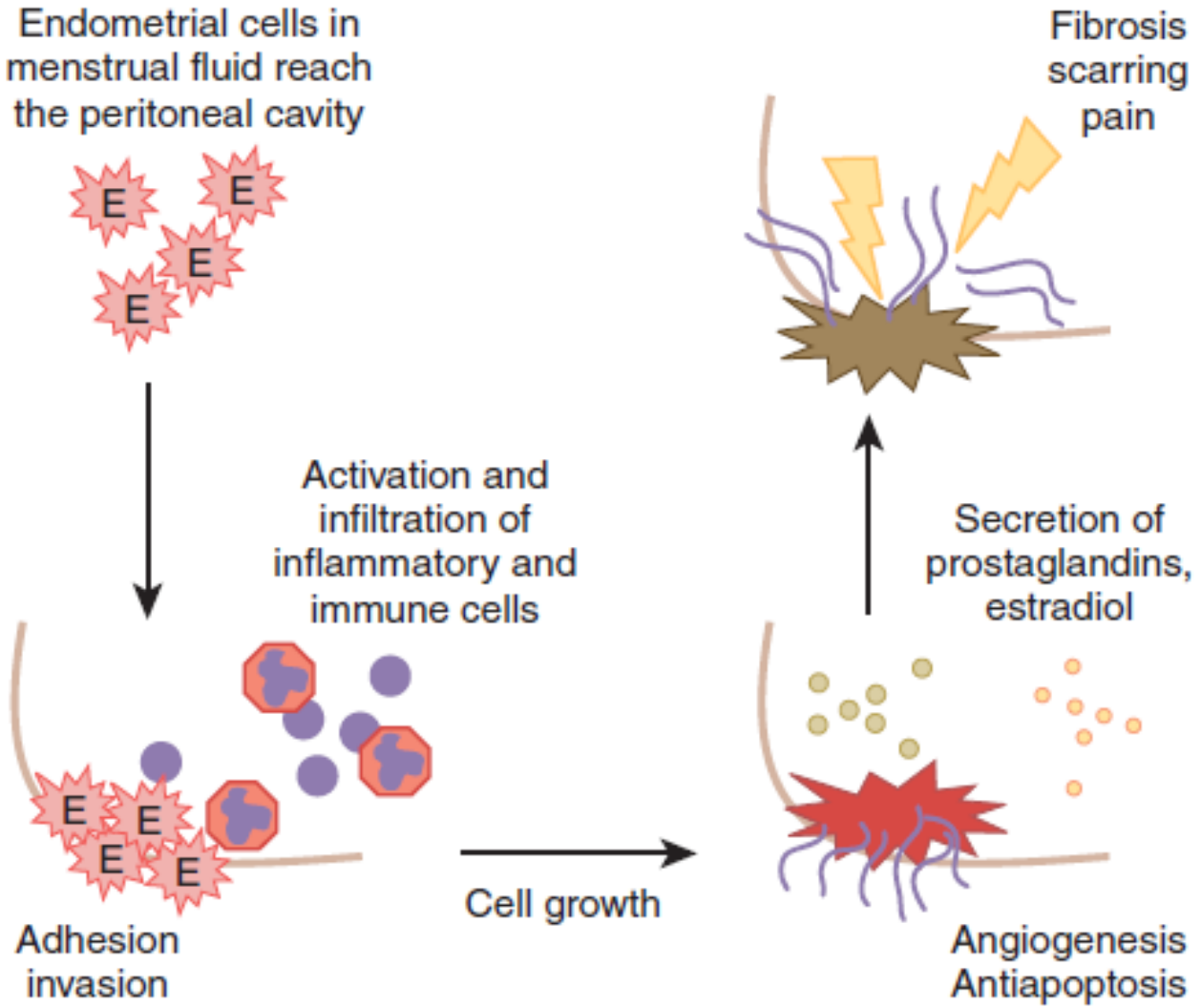


Figure 19-9 Proposed establishment of peritoneal endometriotic implants via retrograde menstruation and the like. (From Strauss JF, Barbieri R: Yen & Jaffe's Reproductive Endocrinology, 5 Philadelphia Saunders, 2004, pp 692-693.)

- Endometriotic lesions:
  1. Red
  2. Black
  3. White
- 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, degree of edema, and the amount of inspissated material

Most likely to provide histologic confrmation

1. Retrograde menstruation



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2. Coelomic metaplasia

- metaplasia of the coelomic epithelium or proliferation of embryonic rests.
- The metaplasia hypothesis postulates that the coelomic epithelium retains the ability for multipotential development
- Examples: Endometriosis has been discovered:

1. in prepubertal girls,
2. women with congenital absence of the uterus, and
3. very rarely in men.

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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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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
- primary immunologic change involves an alteration in the function of the **peritoneal macrophages** prevalent in the peritoneal fluid of patients with endometriosis.
- women who do not develop endometriosis have monocytic-type macrophages in their peritoneal fluid that have a short life span and limited function.
- Conversely, 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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5. Immunologic changes

- **NK cells** have decreased cytotoxicity against endometrial and hematopoietic cells in women with endometriosis.
- **Endo 1** → This chemoattractant protein-enhanced local production of interleukin-6 (IL-6) self-perpetuates lesion/cytokine interactions.
- Further compounding the proliferative activity of endometriosis lesions are angiogenic factors that are increased in lesions.
- Here the expression of basic fibroblast factor, IL-6, IL-8, platelet-derived growth factor (PDGF), and vascular endothelial growth factor (VEGF) are all increased

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5. Immunologic changes

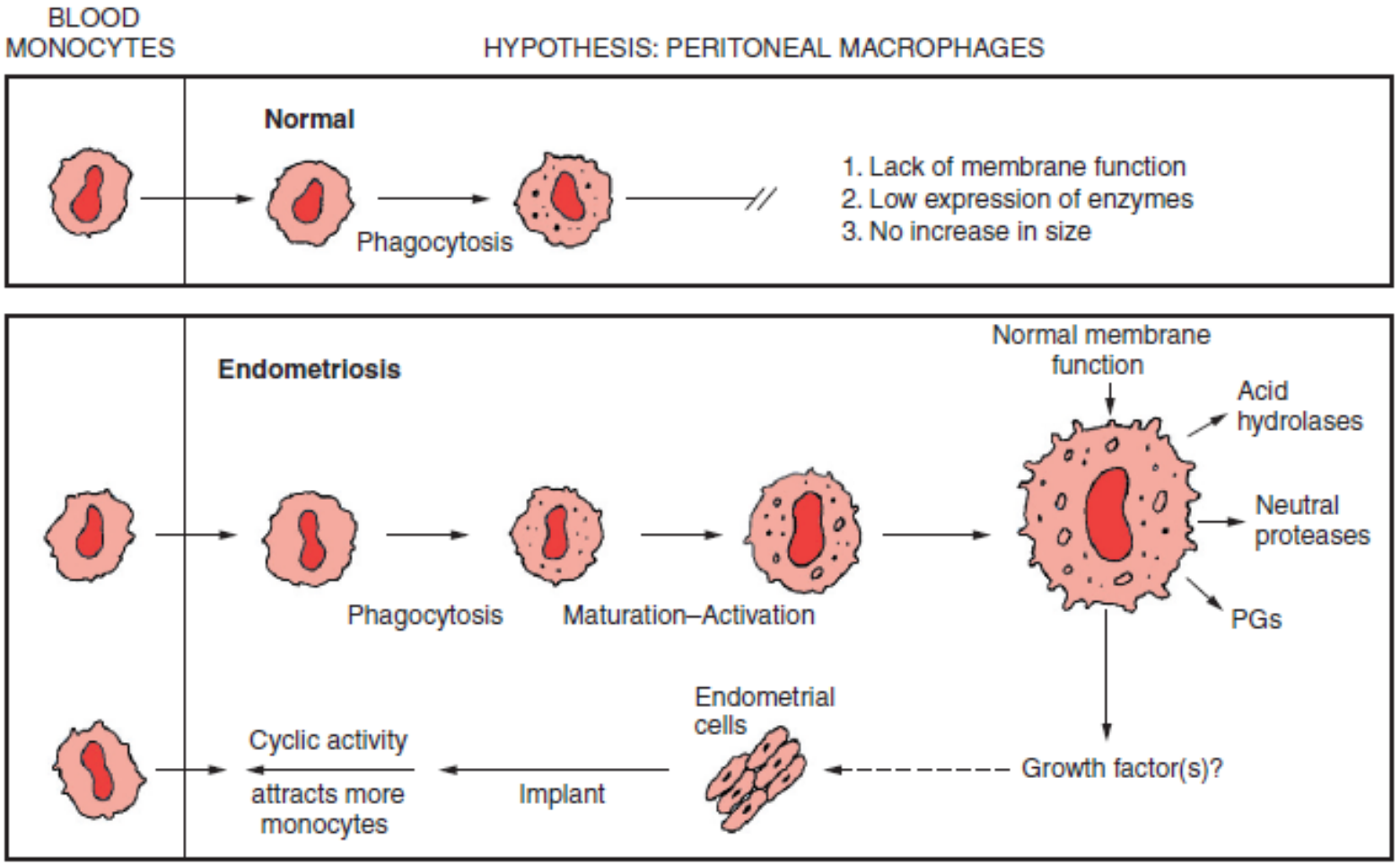

Figure 19-4 Hypothesis regarding pathophysiologic characteristics of human peritoneal macrophages in endometriosis. PG, prostaglandins. (Redrawn from Halme J, Becker S, Haskill S, et al: Altered maturation and function of peritoneal macrophages: Possible role in pathogenesis of endometriosis. Am J Obstet Gynecol 156:787, 1987.)

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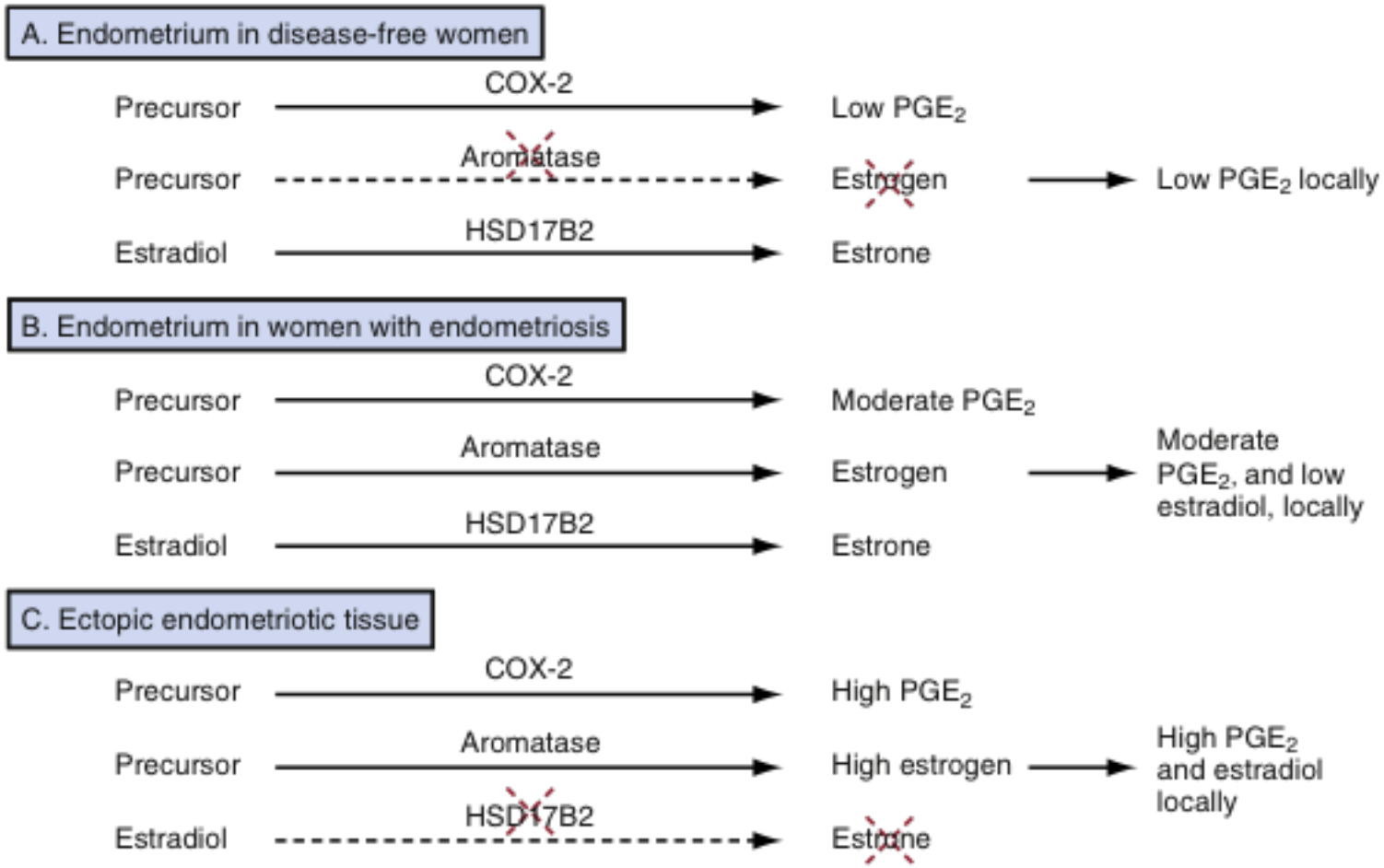
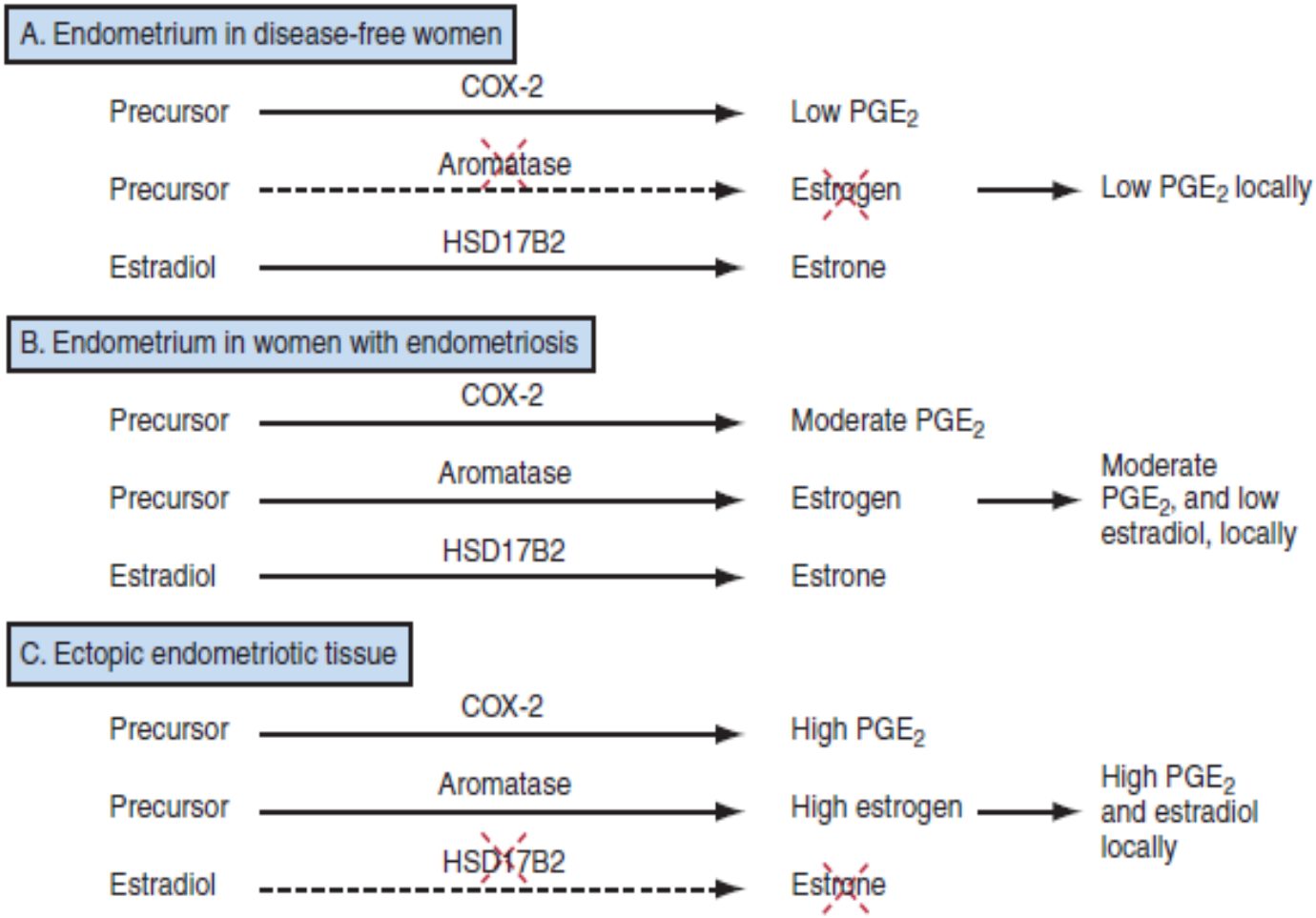
5. Immunologic changes



5. Immunologic changes



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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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Pathophysiology

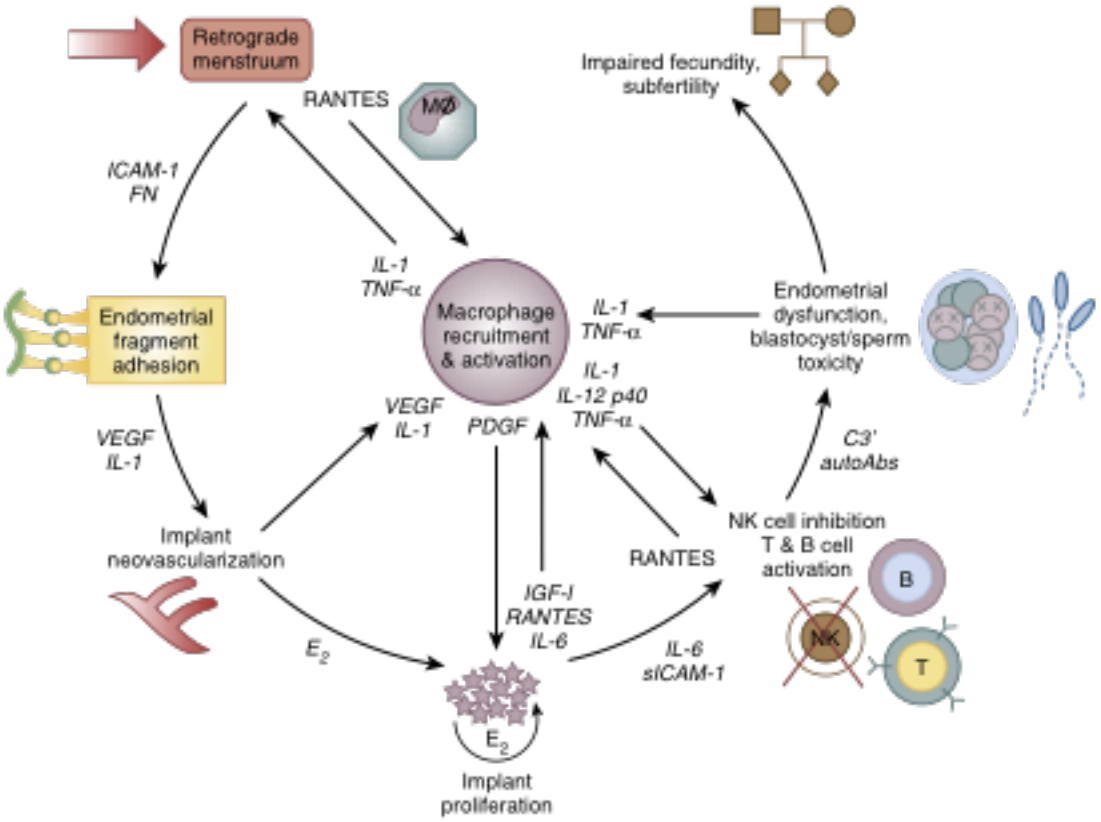
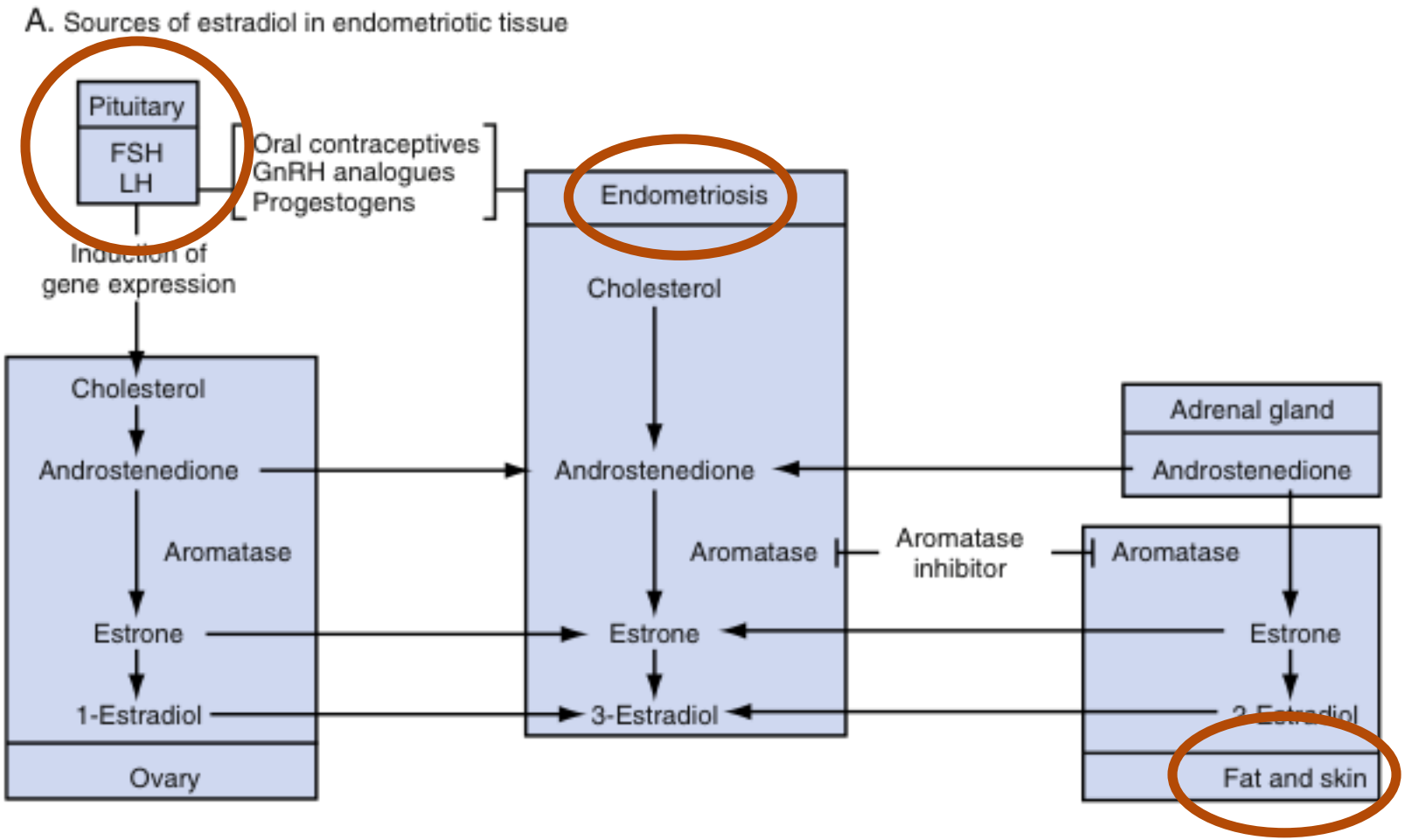
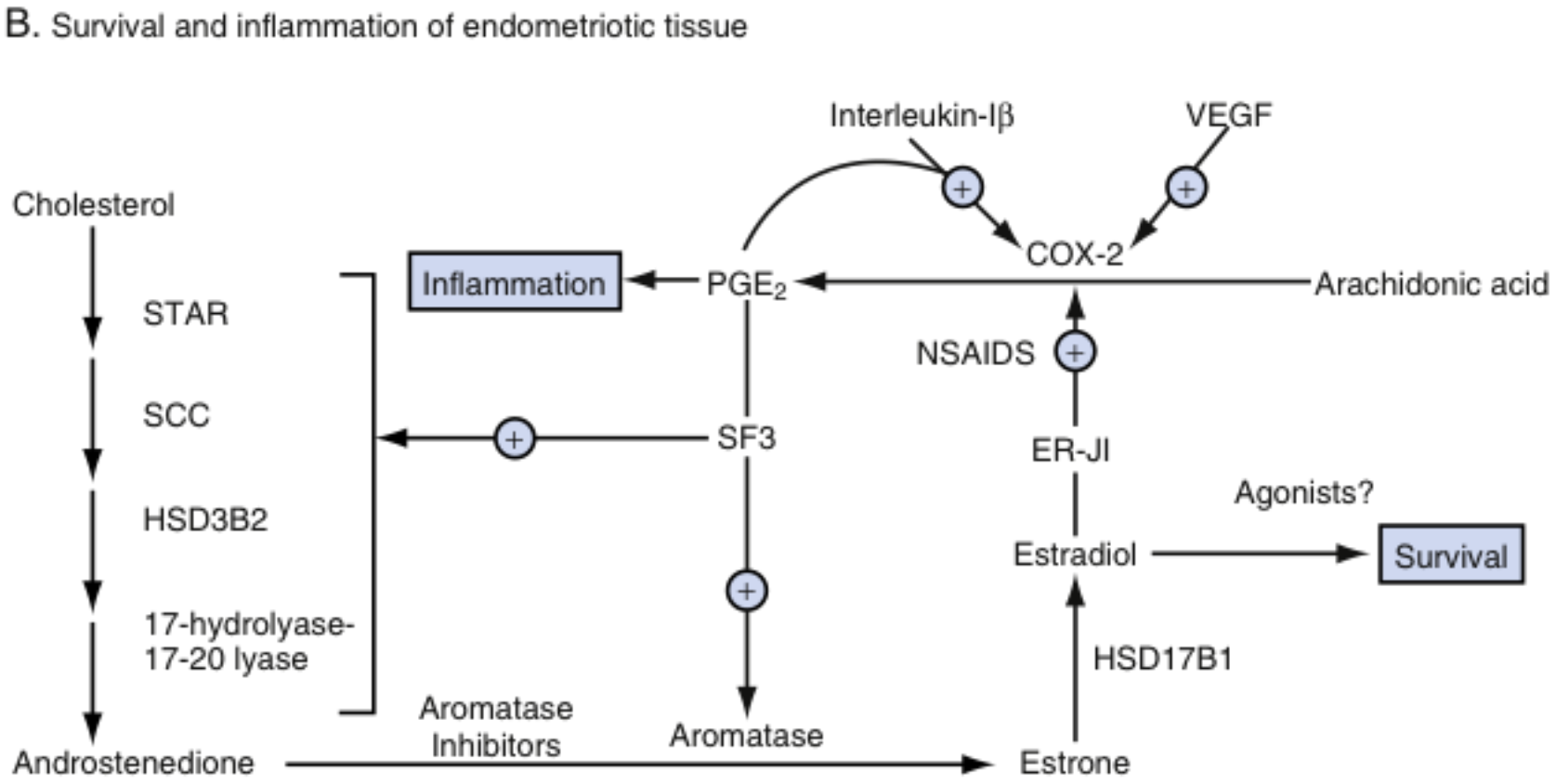


Figure 19.7 Schematogram depicting the network of chemokines, cytokines, and growth factors in the pathophysiology of endometriosis. *autoAbs*, Autoantibodies; *C3*; complement 3; E_2, estradiol; *FN*, fibronectin; *sICAM*, soluble intercellular adhesion molecule; *IGF-1*, insulin-like growth factor-1; *IL*, interleukin; *MØ*, macrophage; *NK cell*, natural killer cell; *PDGF*, platelet-derived growth factor; *RANTES*, regulated on activation, normal IT cell expressed and secreted; *TNF*, tumor necrosis factor; *VEGF*, vascular endothelial growth factor.

Pathophysiology



Pathophysiology



Pathophysiology

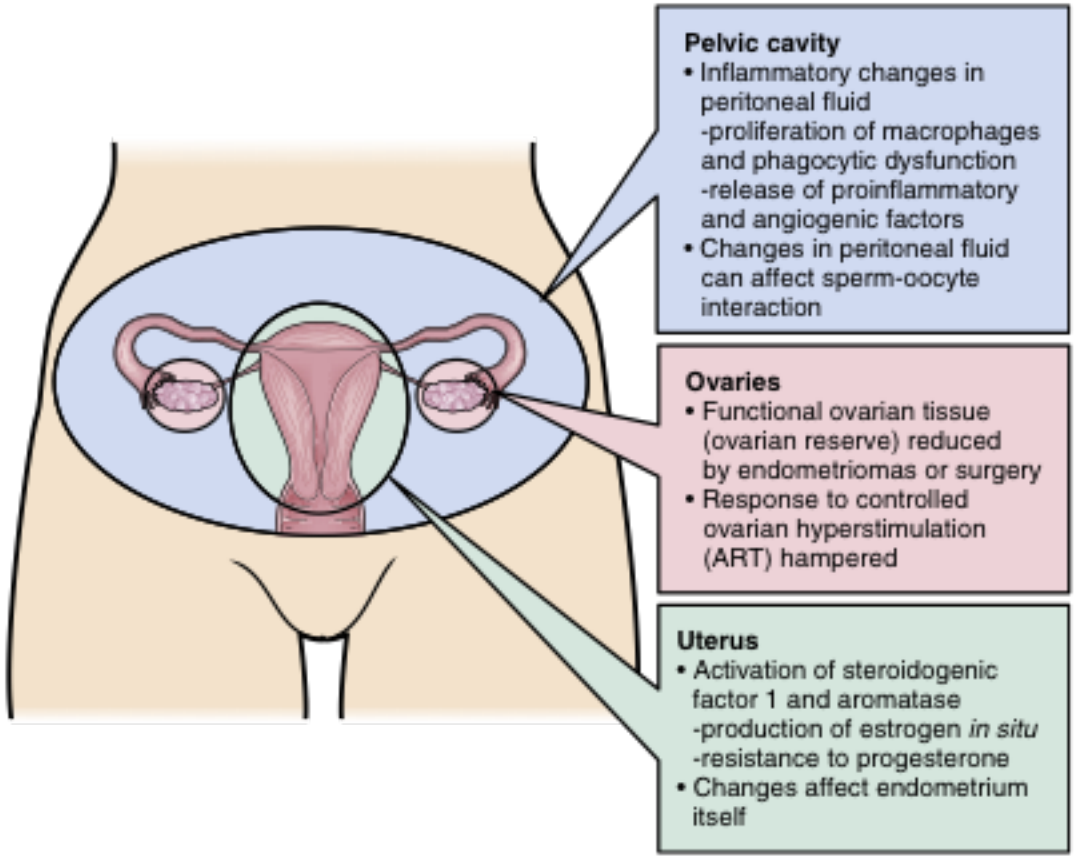


Figure 19.17 Mechanisms of endometriosis associated infertility. *ART,* Assisted reproductive technologies. (Modified from de Ziegler, Borghese B, Chapron C. Endometriosis and infertility: pathophysiology and management. *Lancet.* 2010;376[9742]:730-738. Data from Strauss J, Barbieri R. *Yen and Jaffe's Reproductive Endocrinology.* 7th ed. Philadelphia: Elsevier; 2014.)

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 a combination of both.

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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 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: Medical

- **Aim**: suppression of lesions and associated symptoms, particularly pain.
- Best achieved by menstrual suppression, ideally without inducing hypoestrogenism.
- Unfortunately, once suppressive therapy is stopped, symptoms tend to recur at variable rates.
- The choice of medical therapy should be individualized, weighing in potential adverse effects, side effects, cost of therapy, and expected patient compliance.

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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.

- Although there are several medical therapies for endometriosis, the US Food and Drug Administration (FDA) has approved only **danazol** and **gonadotropin-releasing hormone (GnRH) agonists.**

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TREATMENT: DANAZOL

- Attenuated androgen that is active when given orally.
- Produces a hypoestrogenic and hyperandrogenic effect on steroid-sensitive end organs.
- Mildly androgenic and anabolic. Many of danazol's side effects are directly related to these two properties, which 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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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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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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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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TREATMENT: GnRH agonists

- The primary advantage of GnRH agonists over danazol is better patient compliance.
- Currently, many clinicians "add back" hormone replacement therapy with dosages similar to menopausal therapy.
- The clinical hypothesis is that the add-back medication will reduce or eliminate the vasomotor symptoms and vaginal atrophy and also diminish or overcome the demineralization of bone.

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TREATMENT: GnRH agonists

- E_2 levels of **30 pg/mL** : enough to suppress endometriosis but not too low to cause bone demineralization

- Add-back regimens not only reduce or eliminate adverse clinical and metabolic side effects associated with hypoestrogenism but also facilitate safe and effective prolongation of GnRH agonist therapy for up to 12 months

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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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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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TREATMENT: Oral contraceptives

- Most common side effects:

  weight gain and breast tenderness.

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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: Progestogens

- For women who cannot tolerate the high dosage of estrogen in an oral contraceptive or who have a contraindication to estrogen

- 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.

   → The medication is most appropriate for the older woman who has completed childbearing.

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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: Surgery

- has been the foundation of treatment for women with moderate or severe endometriosis, especially those with adhesions and when the disease involves nonreproductive organs.
- Preferably **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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5. Endometriosis and ovarian cancer
6. Endometriosis and menopause
7. Etiologies/theories
8. Treatment

Adenomyosis

Adenomyosis: Outline

1. Definition
2. Etiology
3. Pathology
4. Clinical diagnosis
5. Diagnostics
6. Management

Adenomyosis

- Adenomyosis is the growth of endometrial glands and stroma into the uterine myometrium to a depth of at least 2.5 mm from the basalis layer of the endometrium.

- Adenomyosis is sometimes termed **"internal endometriosis"** or **"endometriosis interna"**

- This term is misleading because endometriosis and adenomyosis are discovered in the same patient in less than **20%** of women, and are clinically different diseases.

- The only common feature is the **presence of ectopic endometrial glands and stroma**. However, unlike endometriosis, these ectopic glands do not undergo the proliferative and secretory changes that are associated with cyclic ovarian hormone production.

Adenomyosis: etiopathogenesis

- The disease is associated with increased parity, uterine surgeries and traumas.

- The pathogenesis of adenomyosis is unknown but is theorized to be associated with **disruption of the barrier** between the endometrium and myometrium as an initiating step.

Adenomyosis: pathology

- There are two distinct pathologic presentations of adenomyosis:

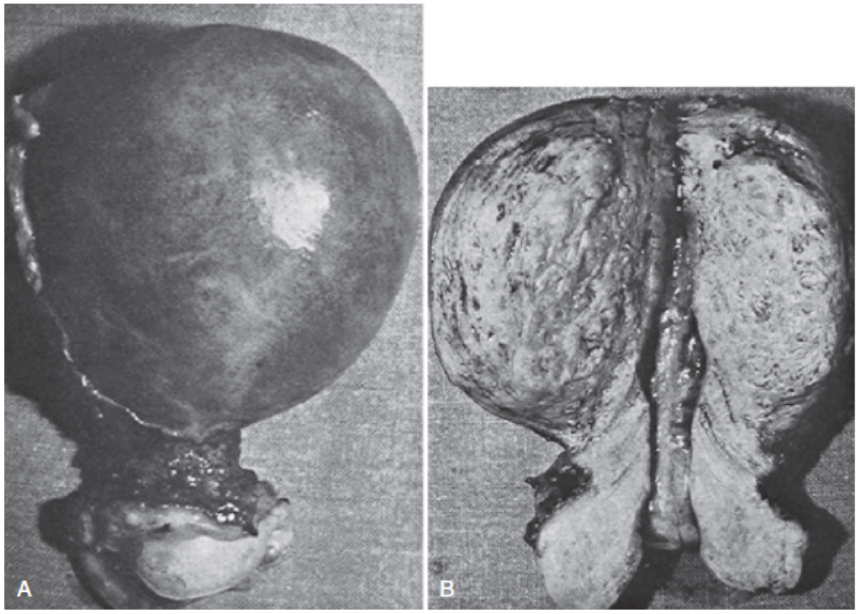
- The most common is a **diffuse** involvement of both anterior and posterior walls of the uterus. The posterior wall is usually involved more than the anterior wall.
- Diffuse adenomyosis is found in two thirds of cases.

- The second presentation is a **focal** area or **adenomyoma.** This results in an asymmetrical uterus, and this special area of adenomyosis may have a pseudocapsule.

Adenomyosis: clinical diagnosis

- The classic symptoms of adenomyosis are **secondary dysmenorrhea** and **menorrhagia/heavy menstrual bleeding**

- On pelvic examination the uterus is **diffusely enlarged** or **globular**, usually two to three times normal size (usually up to 14 weeks size)



Adenomyosis: diagnostics

- Ultrasound and MRI are both useful to help differentiate between adenomyosis and uterine myomas

- Findings of **poorly defined junctional zone** markings in the endometrial-myometrial interface help confirm the diagnosis.

Adenomyosis: Management

- There is **no satisfactory proven medical treatment** for adenomyosis.
- **Hysterectomy is the definitive treatment** for women with failed medical treatment and with completed family size
- However, patients with adenomyosis who **do not want to undergo surgery**, have been **medically treated** with GnRH agonists, progestogens, and progesterone-containing IUDs, cyclic hormones, or prostaglandin synthetase inhibitors for their **abnormal bleeding and pain**.

Adenomyosis: Summary

1. Definition
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Thank you!

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