UNDERSTANDING ENDOMETRIOSIS TO IMPROVE PATIENT CARE

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DISCLOSURES

OBJECTIVES

- Explain the most common causes of pelvic pain
- Understand the endometriosis disease process
- Recognize signs and symptoms suggestive of endometriosis
- Take a detailed patient history that can help when diagnosing endometriosis
- Engage an appropriate multidisciplinary care team to manage endometriosis

HOUSEKEEPING

- Complete the pre-test questions now.
- There is a space to record your answers for the case study.
- Complete the post-test at the end of the session.
- Complete the evaluation form and claim your credit.
- Return the form to a staff member or at the registration desk.

ETIOLOGY AND IMPACT

What is Endometriosis?

- A chronic condition in which tissue similar to the uterine lining grows outside of the uterus, inflaming and promoting scar tissue development in the pelvic region.[1]
- Patients often experience severe pelvic pain that can impact menstrual periods, sexual intercourse, bowel movements, and/or urination.
- Endometriosis can impact fertility and is often associated with abdominal bloating, nausea, fatigue, and psychologic sequelae such as depression and anxiety.[2]
- Endometriosis is idiopathic and may onset at menarche and continue until menopause. It cannot be prevented, and at present, there is no marker to predict who will be affected.

Sources: [1]Soliman AM, et.al. *Adv Ther* 2018;35:408-23; [2]World Health Organization. https://www.who.int/news-room/fact-sheets/detail/endometriosis; 2023.

The Endometriosis Process

- When endometrial tissue grows ectopically, it behaves as it does when lining the uterus--it thickens, breaks down, and bleeds with each menstrual cycle.[5]
- Because the deposited ectopic tissue has no means to exit the body, it aggregates to create various multicellular lesions, including scar tissue, cysts, and fibrous adhesions between organs.
- These lesions are complex, vascularized structures whose regulation is linked to hormones and other steroids, immune cells, and pain pathways.
- Lesions can grow superficially on pelvic organs or within the ovaries (producing cysts known as endometriomas) or deeply infiltrate pelvic structures such as the bowel, bladder, or ligaments (called deeply infiltrating endometriosis [DIE]).
- Lesions may distort tubal anatomy and affect fertility.[6]

Sources: [1]Mayo Clinic. https://www.mayoclinic.org/diseases-conditions/endometriosis/symptoms-causes/syc-20354656; 2023; [2]Mounsey AL, et.al. *Am Fam Physician* 2006;74:594-600.

What Causes Endometriosis

Causes of endometriosis are unknown but may include:[1-3]

- Retrograde menstruation
- Favorable endocrine or metabolic environment
- Cellular metaplasia (epithelial-to-mesenchymal transition)
- Stem cells
- Altered immunity and inflammatory responses in potentially genetically susceptible women

Sources: [1]WHO. https://www.who.int/news-room/fact-sheets/detail/endometriosis; 2023; [2]Mayo Clinic. https://www.mayoclinic.org/diseases-conditions/endometriosis/symptoms-causes/syc-20354656; 2023; [3]Saunders PTK, Horne AW. *Cell* 2021;184:2807-24.

Hormones and Endometriosis

- Local overproduction of prostaglandins from increased COX-2 activity and of estrogen from increased aromatase activity are key components of lesion development.[1]
- Many steroid hormones (e.g., estrogens, androgens, progestins, and glucocorticoids) and their receptors regulate cells in eutopic and ectopic endometrium.
- Lesions exhibit altered steroid tissue microenvironments relative to eutopic endometrium.[2]
- Estrogen level is associated with increased endometriosis inflammation, lesion growth, and pain.[3]

Sources: [1]ACOG. *Obstet Gynecol* 2010;116:223-36; [2]Saunders PTK, Horne AW. *Cell* 2021;184:2807-24; [3]WHO. https://www.who.int/news-room/fact-sheets/detail/endometriosis; 2023.

Impact

- Affects 10% of women of childbearing age globally[1]
- In addition to its impact on daily life, endometriosis exerts a formidable economic impact in terms of direct and indirect costs.[2,3]
- Direct costs for managing endometriosis range from $1,459 to $20,239 per patient per year, while indirect costs from lost productivity range from $4,572 to $14,079.[3]
- A five-year delay in diagnosis adds a minimum direct cost of $20,000 per patient.[3]

Sources: [1]World Health Organization. https://www.who.int/news-room/fact-sheets/detail/endometriosis; 2023; [2]Soliman AM, et.al. *Hum Reprod* 2016;31:712-22; [3]Darba J, Marsa A. *Pharmacoeconomics* 2022;40:1143-58.

Non-Genetic Risk Factors

- Nulliparity[1,2]
- Early age at menarche
- Older menopause onset
- Short menstrual cycles (< 27 days)
- Heavy periods longer than seven days
- Low BMI
- High estrogen levels or exposure
- Conditions that prevent blood from exiting body during periods

Sources: [1]Mayo Clinic. 2023; [2]Shafrir AL, et al. *Best Pract Res Clin Obstet Gynaecol* 2018;51:1-15

Other Risk Factors

Studies of twins have estimated the heritability of endometriosis at approximately 50%.[1]

- Environmental factors such as diet, hormonal/diethylstilbestrol exposure in utero, and exposure to environmental contaminants could possibly account for the balance.[1]
- Variances in study design and methodology have yielded inconsistent association with physical activity, alcohol use, caffeine intake, and lactation, although greater parity has been associated with lower risk for endometriosis.[2]

Sources: [1]Saha R, et al. *Fertil Steril* 2015;104:947-52; [2]Shafrir AL, et al. *Best Pract Res Clin Obstet Gynaecol* 2018;51:1-15.

DIAGNOISING ENDOMETRIOSIS IN PRIMARY CARE

The Primary Symptom of Endometriosis

Pelvic pain, often associated with or exacerbated during menstruation, is the PRIMARY SYMPTOM of endometriosis.

Source: Mayo Clinic. https://www.mayoclinic.org/diseases-conditions/endometriosis/symptoms-causes/syc-20354656; 2023.

Other Endometriosis Symptoms

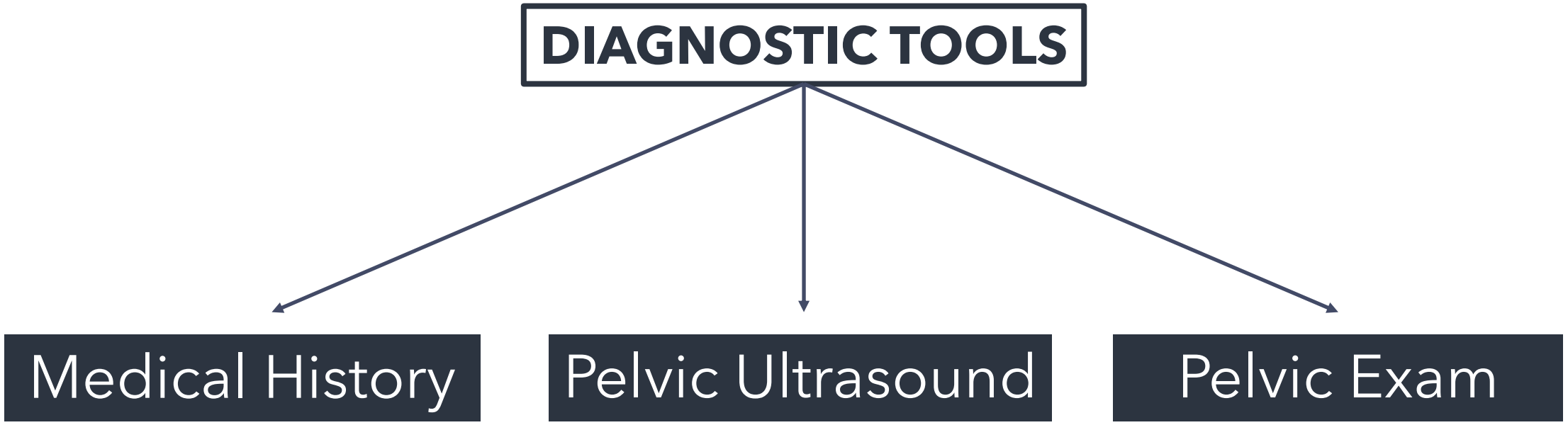
- Dysmenorrhea
- Excessive bleeding, either during menstruation or between periods
- Lower back and abdominal pain
- Painful intercourse, bowel movements, or urination
- Fatigue, diarrhea, constipation, bloating, and nausea, especially during menstrual periods
- Infertility

Source: Mayo Clinic. https://www.mayoclinic.org/diseases-conditions/endometriosis/symptoms-causes/syc-20354656; 2023.

Diagnosing Endometriosis

- Early diagnosis and prompt management can minimize potential disability, inform life planning, and improve quality of life.
- The definitive method of diagnosis is visualization through laparoscopy or other surgery, followed by histologic confirmation.
- In most cases, a reasonably confident diagnosis is possible without surgery.
- Histologic or laparoscopic confirmation of lesions is not always necessary to commence treatment.

Other Endometriosis Symptoms



Medical History

The medical history should assess the SEVERITY OF THE PAIN and potential complications, emphasizing UNDERSTANDING THE RELATIONSHIP BETWEEN REPORTED SYMPTOMS AND THE PATIENT'S MENSTRUAL CYCLE.

What to Ask a Patient with Symptoms of Endometriosis

- Pain symptoms—anatomic location, when and how the patient noted their presence, how they change over time
- Limitations on the patient's activities
- Other symptoms that could indicate endometriosis
- Sexual history, including pain
- Other medical conditions (depression/anxiety)
- Family history of endometriosis or its symptoms
- Medication history
- Diet and activity
- Relevant cancer screenings

Establishing the Patient's Pain Pattern

Endometriosis cannot be managed fully in a single visit.

- Expect two to three months to establish the pattern of pain that will inform optimal management.
- During this time, undertake other investigations as warranted (e.g., ultrasound, vaginal or urine cultures, and referrals to gastroenterology or urology).
- Have the patient record the fluctuation of pain during their menstrual cycle.
- Conceptualize the menstrual period as a "vital sign" of sorts that can inform other areas of inquiry.

Pelvic Ultrasound

- May be performed trans-abdominally or trans-vaginally
- Enables rapid visualization of pelvic organs and structures (e.g., uterus, cervix, vagina, fallopian tubes, and ovaries)[1]
- Is a safe, low-cost tool that can identify abnormalities such as endometriomas or signs of deeply infiltrating endometrial tissue
- Informs on the size, shape, and position of the uterus and ovaries; the presence of fluids; thick, dense masses in the endometrium, myometrium, fallopian tubes, or bladder; cervical length and thickness; and blood flow through pelvic organs
- Will ***not*** indicate small satellites of endometriosis tissue that may be present[2]

Sources: [1]Johns Hopkins Medicine; 2023; [2]Cleveland Clinic; 2023.

Pelvic Ultrasound

- Can rule out significant pelvic pathology
- Can eliminate other anatomic sources of pain, such as fibroids or non-endometrioma ovarian cysts or masses
- Lack of findings on ultrasound does not rule out the condition
- If negative, does not impede endometriosis management

All patients with pelvic pain should receive pelvic ultrasound if feasible.

Pelvic Exam

- Provides an opportunity for the clinician to feel for palpable cysts or scars.
- Small endometriosis lesions may not be detectable from the exam.
- A fixed, retroverted uterus may indicate obliteration of the cul de sac, and point tenderness or uterosacral nodularity, although not commonly appreciated, are clinical signs of endometriosis.

Other Conditions Associated with Pelvic Pain

- Pelvic Inflammatory Disease
- Ovarian Cysts
- Polycystic Ovary Syndrome (PCOS)
- Inflammatory Bowel Disease
- Cancer

DISCUSSING ENDOMETROSIS WITH YOUR PATIENT

Setting the Stage for Effective Management

- Reassure the patient (and their parent or guardian if appropriate) that period-related pain is real.
- Acknowledge the impact that it can have on daily life.
- Frame early conversations to empower the patient to participate in their treatment.
- Foster the patient's sense of control and responsibility.

Setting the Stage for Effective Management

- Factor the patient's concerns into the management plan.
- Recognize that concerns may evolve over time.
- Have the patient write down their questions before coming to the office.
- Ask the patient to express their biggest concern (e.g., fertility issues, missing work or school, participating in sports, cancer risks) to help frame subsequent discussions.

Talking About Endometriosis

- Remind the patient that they are not at fault.
- Stress that many effective options can help to manage endometriosis.
- Discuss medication side effects and onset of efficacy.
- Discourage the use of non-evidence-based practices and agents.
- Stress that managing endometriosis is a journey.

Talking About Endometriosis

- Reiterate that, with proper management, the patient can continue to live a meaningful life with endometriosis.
- Initiate a conversation about how the patient can favorably affect endometriosis through lifestyle changes.
- Discuss reproductive issues and family planning in the context of endometriosis management with appropriate patients.
- Discuss the patient's role in adherence and changes to treatment plans.
- Encourage the patient to use the practice's patient portal to ask quick questions.

Endometriosis and Infertility

- 25%-50% of infertile women have endometriosis.[1]
- May be related to pelvic anatomic distortion, endocrine and ovulatory abnormalities, or altered hormonal and cell-mediated functions in the endometrium.
- Management decisions for an infertile patient should consider the patient's age, desire for fertility, pelvic pain, stage of endometriosis, among other considerations.[1]
- Oral contraceptives and GnRH agonists are ineffective for endometriosis-associated infertility
- Surgical management of endometriosis-related infertility improves pregnancy rates, although the magnitude of improvement is unclear.[2]
- Clinicians should expect to address fertility concerns in the context of endometriosis and to refer patients as appropriate.

Sources: [1]Bulletti C, et.al. *J Assist Reprod Genet* 2010;27:441-47; [2]ACOG. *Obstet Gynecol* 2010;116:223-36.

MANAGING ENDOMETROSIS IN PRIMARY CARE

The Role of the Primary Care Clinician

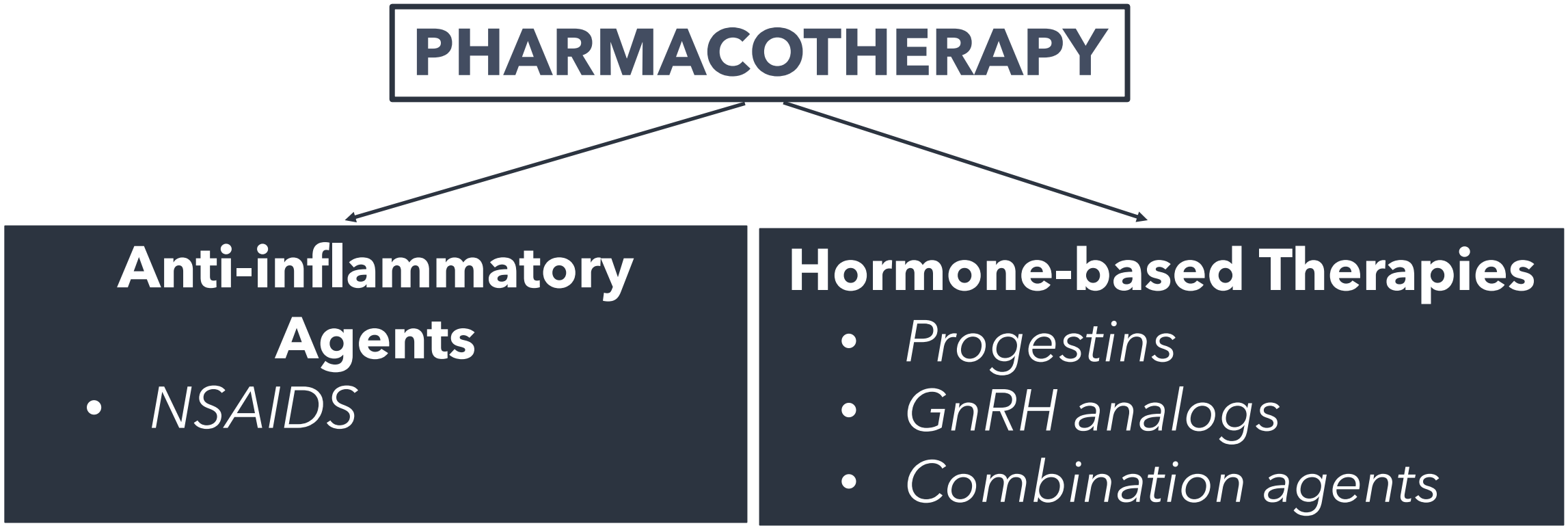
- Identify patients who have endometriosis and differentiate the condition from other causes of pelvic pain
- Assess and determine referral needs
- Discuss management options
- Understand patient preferences for treatment
- Coordinate efforts with a care team (e.g., ob/gyn, therapist) as needed
- Keep the patient actively engaged in disease management

Primary care clinicians play critical roles in identifying patients who have endometriosis and ensuring that they receive prompt and effective care.

Central Concepts of Management

- **Clinicians should be prepared to try combinations of approaches that avoid opioid use or repeated surgical treatment.**
- **Because of the progressive nature of the condition, patients should be monitored regularly.**
- **Optimal management incorporates a holistic approach that combines medical, social, and emotional support.**

Pharmacotherapy Overview



Source: Mayo Clinic. https://www.mayoclinic.org/diseases-conditions/endometriosis/diagnosis-treatment/drc-20354661; 2023.

Pharmacotherapy – **A DISCLAIMER**

Many commonly used and efficacious agents, including anti-inflammatory agents and certain contraceptives, are not specifically indicated for endometriosis by the US FDA. These uses, which are discussed in subsequent slides, are considered “off-label.”

Pharmacotherapy: NSAIDS

- The American College of Obstetricians and Gynecologists (ACOG) notes that various pharmacotherapies, including NSAIDs, GnRH agonists, progestins, and combined oral contraceptives, can be considered as initial treatments to reduce pain in women with suspected endometriosis.[1]
- Over-the-counter (OTC) pain relievers are a logical starting point, assuming no contraindications.
- For patients whose pain does not remit despite maximum OTC dose, consider prescription ibuprofen (400-600 mg), mefenamic acid, or naproxen as appropriate.
- Patients should initiate pain relievers one to two days prior to menstruation, preceding the onset of the pain cycle.

Source: [1]ACOG. *Obstet Gynecol* 2010;116:223-36.

Pharmacotherapy: Gonadotropin-Releasing Hormone (GnRH) Analogs

- Can shrink endometrial tissue by lowering estrogen levels and suppressing ovulation.[1]
- Side effects typically mimic symptoms associated with menopause (e.g., hot flashes, vaginal dryness, decreased libido, headache, fatigue).
- Cause an immediate decrease in bone mineral density (BMD).[2]
- While BMD usually recovers upon cessation after short-term use, GnRH analog use >24 months may promote irreversible bone mineral loss.[2]

Sources: [1]Mayo Clinic. https://www.mayoclinic.org/diseases-conditions/endometriosis/diagnosis-treatment/drc-20354661; 2023; [2]Sauerbrun-Cutler M-T, Alvero R. *Fertil Steril* 2019;112:799-803.

Pharmacotherapy: Gonadotropin-Releasing Hormone (GnRH) Analogs

- GnRH-based therapy is usually supplemented with a low dose of estrogen or progestin (an approach traditionally referred to as "add-back" therapy) to decrease side effects while maintaining bone density.[1]
- Based on efficacy and reduced potential for side effects, ACOG recommends GnRH agonist treatment only in combination with add-back agents; the use of a GnRH agonist alone is not recommended as a primary treatment approach.[2]
- Add-back therapy may be in the form of norethindrone 5 mg, an estradiol patch, or birth control pills.
- Menstruation (and endometriosis-related symptoms) will return upon cessation of treatment with GnRH analogs.

Sources [1]Quaas AM, et.al. *Fertil Steril* 2015;103:612-25; [2]ACOG. *Obstet Gynecol* 2010;116:223-36.

Pharmacotherapy: Progestins

- Synthetic form of progesterone that suppresses hypothalamic GnRH secretion and luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretion by the pituitary gland
- Suppresses ovulation and the growth of endometrial implants
- Widely prescribed birth control agents; available as intrauterine devices, implants, injections, or pills (e.g., the progestin-only "minipill" or in combination with estrogen).
- Side effects include decreased bone density, menstrual irregularities, amenorrhea, weight gain, and acne.

Source: Quaas AM, et.al. *Fertil Steril* 2015;103:612-25.

Pharmacotherapy: Combination Agents

- **The FDA recently approved two combination therapies that include:**
  - ✓a GnRH antagonist (relugolix or elagolix),
  - ✓an estrogen (estradiol), and
  - ✓a progestin (norethindrone acetate).

- These combinations incorporate the "add-back" approach traditionally used with GnRH-based therapies.

Sources: [1]Giudice LC, et.al. *Lancet* 2022;399:2267-79; [2]Schlaff WD, et al. *N Engl J Med* 2020;382:328-40; [3]Simon JA, et al. *Obstet Gynecol* 2020;135:1313-26.

Pharmacotherapy: Combination Agents

- These combinations have a box warning that states: **Estrogen and progestin combinations increase the risk of thrombotic or thromboembolic disorders including pulmonary embolism, deep vein thrombosis, stroke and myocardial infarction, especially in women at increased risk for these events.**

- Contraindicated in women with current/history of thrombotic or thromboembolic disorders and in women at increased risk for these events, including women over age 35 who smoke and women with uncontrolled hypertension.

- Limit use to 24 months because of the risk of potentially irreversible bone loss.

- Discontinue hormonal contraceptives before initiating these agents.

Pharmacotherapy: Combination Agents

Side effects may include:

- Hot flashes
- Headache
- Fatigue
- Nausea
- Decreased libido
- Metrorrhagia

Dietary Interventions

- Nutrient intake can affect inflammation and estrogen and prostaglandin metabolism, diet is a modifiable risk factor that may influence endometriosis severity and progression.[1]
- "DASH" or "Mediterranean" diets are rich in whole foods (e.g., fruits, vegetables, fish, nuts, beans, olive oil) and low in processed foods and saturated fats.[2]
- Can lower blood pressure, protect against chronic conditions, reduce inflammation, and support weight loss regimens.
- Part of a healthy lifestyle that may positively impact endometriosis.

Sources: [1]Piecuch M, et.al. *Nutrients* 2022;14:5283; [2]Harvard Medical School. https://www.health.harvard.edu/blog/a-practical-guide-to-the-mediterranean-diet-201903211619 4; 2023.

Dietary Suggestions for Endometriosis

Recommended	Contraindicated
• Fruits and vegetables • Herbs and spices • White and green tea • Dairy products • Fish • Vegetable oils, nuts, and seeds	• Processed and unprocessed red meat • Animal fats (e.g., butter, lard) • Coffee (> 300 mg caffeine/day) • Highly processed products (e.g., fast food, sweets, instant foods)

Source: Piecuch M, et.al. Nutrients 2022;14:5283

Physical Activity

- Regular activity can reduce estrogen levels and increase levels of cytokines with anti-inflammatory and antioxidant properties.[1]
- The paucity of large-scale RCTs limits conclusions about the effect of specific regimens as treatments for endometriosis symptoms.[2]
- Physical activity provides numerous impactful health benefits (e.g., cardiovascular fitness, muscle strength, improved insulin sensitivity, improved sleep, increased mobility in overweight persons) that can improve quality of life.[3]
- Stretches and physical therapy to strengthen pelvic floor muscles can be useful.
- Body-awareness practices (e.g., Hatha yoga, the Jacobson method, progressive muscle relaxation techniques) have shown benefit in small studies.[4]

Sources: [1]Bonocher CM, et.al. *Reprod Biol Endocrinol* 2014;12:4; [2]Tennfjord MK, et.al. *BMC Womens Health* 2021;21:355; [3]Colberg SR, et al. *Diabetes Care* 2010;33:e147-e167; [4]Tourny C, et al. *Int J Gynaecol Obstet* 2023;Jun 22:Online ahead of print.

Timing of Follow-up Visits

- Although treatment may commence on the initial visit, expect needing 2-3 months to establish the pain pattern.
- Consider 2-3 visits (telehealth or in-person) within 6-8-weeks following the initial consult, with a telehealth follow-up 2 weeks after the initial visit.
- Close contact during the initial phase promotes adherence, allows the patient to ask questions and provide feedback on efficacy, and enables assessment of treatment.

Establishing a dialog and a set schedule will empower patients to take an early, active role in management.

When to Refer

Most patients will be able to manage endometriosis symptoms through continued partnership with a primary care clinician.

Situations that warrant referral include:

- Patients whose condition cannot be managed with pharmacotherapy and lifestyle interventions and for whom surgery may be warranted
- Patients who seek fertility treatment or consultation
- Patients who present with symptoms of cancer
- Patients who have multiple organs involved
- Patients who have high markers of systemic inflammation
- Patients with chronic pain that cannot be managed in the context of previously discussed recommendations

Endometriosis Resources for Clinicians and Patients

Organization	Site
The American College of Obstetricians and Gynecologists (ACOG)	acog.org
American Academy of Family Physicians	aafp.org
National Institute of Child Health and Human Development (NICHD)	nichd.nih.gov
Mayo Clinic	mayoclinic.org
Centers for Disease Control and Prevention	cdc.gov

Conclusion and Clinical Pearls

- Endometriosis is characterized by ectopic growth of the endometrium that usually causes pelvic pain associated with menstruation.
- Endometriosis can often be managed in primary care.
- A thorough medical history, pelvic exam, and pelvic ultrasound are critical for differential diagnosis.
- Management should aim to relieve or reduce pain symptoms, shrink or slow lesion growth, preserve or restore fertility, and prevent/delay recurrence.
- Various anti-inflammatory and hormone-based agents and lifestyle modifications can manage endometriosis and relieve symptoms.
- Proactive management enhances quality of life and prevents tissue damage, and clinicians and patients must partner in decision-making.