CME

Recognizing and treating endometriosis

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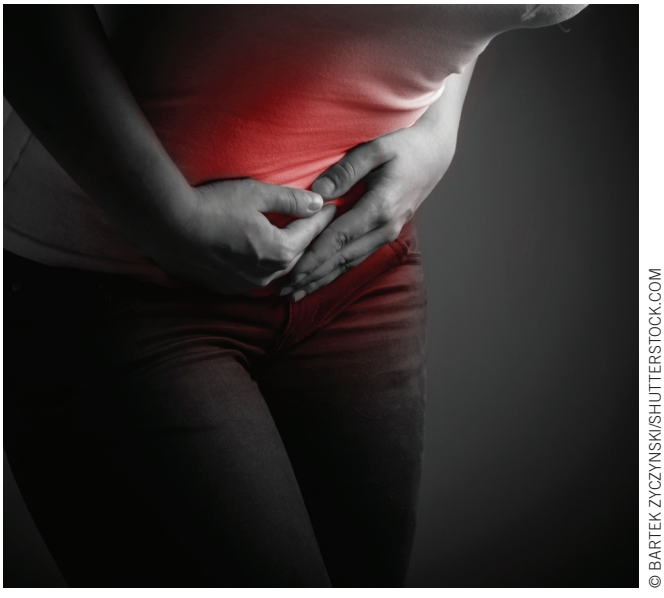
ABSTRACT

Endometriosis, defined as endometrium-like tissue located outside the uterine cavity, is a chronic and frequently painful disease that affects about 10% of reproductive-aged women worldwide. The ectopic endometrial tissue, which is still hormonally responsive, generates a chronic inflammatory state resulting in an array of sometimes debilitating symptoms as well as subfertility. Despite its prevalence and significant effect on a woman's health and quality of life, receiving a diagnosis of endometriosis often takes years. This article reviews the epidemiology, pathophysiology, clinical presentation, and treatment options for managing endometriosis in women who do not desire pregnancy and in those who do, and includes information on the newest treatment option, the oral gonadotropin-releasing hormone (GnRH) antagonist elagolix.

Keywords: endometriosis, infertility, dyschezia, dyspareunia, pelvic pain, GnRH agonist, GnRH antagonist



Learning objectives

- Recognize the variable symptoms and signs of endometriosis.
- List the differential diagnosis for endometriosis and outline an approach to making the diagnosis.
- Describe the pharmacologic and surgical treatment for endometriosis.

A 28-year-old woman presented to her primary care clinic with complaints of progressively worsening pelvic and lower abdominal pain over the past few years. She reported regular menses, with bleeding typically lasting more than a week. Her menses are associated with significant cramping that occasionally kept her home from work. She also reported pain with bowel movements, especially during her menses, and stated that she was diagnosed with irritable bowel syndrome by previous healthcare providers. She has been trying to become pregnant for the past year with no success. On further questioning, she disclosed that intercourse frequently is uncomfortable. A review of systems was positive for fatigue. Her physical examination, including pelvic examination, was unremarkable. How should this patient be further evaluated and managed?

Endometriosis, defined by endometrium-like tissue implanted in locations outside the uterine cavity, is a common chronic inflammatory gynecologic condition affecting up to 10% of reproductive-aged women worldwide.[1] Between 20% and 50% of women with infertility and 71% to 87% of women with chronic pelvic pain have endometriosis.[2] Endometriosis may have significant psychosocial implications in patients due to effects on sexual intimacy, lost productivity at work or home, and healthcare costs. On average, women with endometriosis report losing about 6 hours of workplace productivity and 5 hours of household productivity per week.[3] About 50% of women with endometriosis report spending entire days in bed due to their endometriosis-related symptoms, and on average these women report spending 17 to 18 days in bed per year.[4] Claims data show that the average annual medical and prescription healthcare costs are more than three times

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Key points

- Endometriosis is a common disease with variable symptoms and severity; consider the diagnosis in women with dysmenorrhea, chronic pelvic or lower abdominal pain, dyspareunia, infertility, or cyclic bladder or bowel symptoms.
- Transvaginal ultrasound is the imaging modality of choice for initial evaluation of possible endometriosis; laparoscopy remains the cornerstone for a definitive diagnosis of endometriosis.
- NSAIDs and cyclic or continuous combined hormonal contraception are the first-line treatment for endometriosis-related pelvic pain.
- Surgery is used in patients with pain refractory to medical therapy and sometimes is helpful in promoting conception.

higher for women with endometriosis than for those without endometriosis.[3]

Endometriosis poses significant medical and psychosocial implications, yet one study documented that more than 50% of general practitioners could not identify three main symptoms of endometriosis, and more than 60% were uncomfortable with diagnosing and managing the condition.[5] On average, 7 to 12 years elapse between the onset of symptoms to a surgical diagnosis of endometriosis.[3] Experts postulate that the difficulty in diagnosing endometriosis is likely multifaceted: The symptoms are nonspecific and may be readily attributed to other conditions, the symptoms of dysmenorrhea or dyspareunia may be normalized or stigmatized by clinicians, and both the general public and clinicians lack awareness of the condition. Finally, no specific biomarkers exist for endometriosis and a definitive diagnosis requires an invasive procedure.[6]

PATHOPHYSIOLOGY

The pathogenesis and pathophysiology of endometriosis is not completely understood and involves complex interactions between the endocrine, immune, vascular, and neurologic systems. As well, some genetic predisposition has been documented, with a seven- to 10-fold increased risk of endometriosis in women with an affected first-degree relative.[2] Commonly cited risk factors for endometriosis include early age at menarche (under age 11 years), shortened menstrual cycles (fewer than 28 days), prolonged menses (greater than 5 days), heavy menses, and nulliparity.[4] However, whether these are true risk factors or findings associated with the disease itself remains unclear. Low body mass index and high alcohol or caffeine consumption are associated with an increased risk of endometriosis; regular exercise may reduce the risk.[4]

The most commonly proposed models of pathogenesis include retrograde menstruation, coelomic metaplasia, and lymphatic and vascular metastasis.[3,6] (Coelomic metaplasia refers to the transformation of peritoneal lining into endometrial tissue; this transformation may occur if the lining retains some multipotential cells.) The ovaries are the most common site for endometriosis. Other sites include the posterior cul-de-sac (aka pouch of Douglas), the ovarian and uterine ligaments (especially the uterosacral ligaments), the fallopian tubes, the rectosigmoid colon, and the bladder or distal ureters. Very rarely, endometriotic lesions may occur in extrapelvic locations such as the thoracic cavity. This ectopic endometrial tissue is still hormonally active and responds to cyclic hormonal fluctuations similarly to the intrauterine endometrium. The result is internal bleeding that initiates an inflammatory response, leading to neovascularization, fibrosis, and adhesions. The altered inflammatory response includes an increase in cyclooxygenase-2 (COX-2) activity resulting in the overproduction of local prostaglandins and an increase in aromatase activity, resulting in the overproduction of local estrogen.[2] Peritoneal fluid from affected women has increased concentrations of activated macrophages and proinflammatory cytokines.[6]

Although adhesions from endometriosis may lead to mechanical distortions of female pelvic anatomy and thus impair fertility, the chronic inflammation also contributes to subfertility.[6] Inflammatory mediators can impair sperm mobilization and alter sperm-oocyte binding or fusion. Additionally, the increase in proinflammatory cytokines in endometrial tissue implanted adjacent to ovarian follicles is associated with reduced ovarian function.[7] Finally, the inflammatory milieu appears to result in an eutopic (intrauterine) endometrium that is more progesterone-resistant and less hospitable for embryonic implantation.[6]

The endometrium and endometriotic lesions contain nerve fibers that are stimulated in this inflammatory milieu. The increased nociception appears to change brain chemistry, leading to heightened responsiveness to afferent input. This phenomenon is known as *central sensitization* and contributes to the transition from dysmenorrhea to chronic pelvic pain.[6] **Figure 1** illustrates key features in the pathophysiology of endometriosis, as well as common sites of ectopic endometrial tissue.

Ectopic endometrial tissue location and extent, as well as depth of invasion of the endometriotic lesions and the development of adhesions, all contribute to the symptoms of the disease. Endometriomas are cyst-like masses of ectopic endometrial tissue on the ovaries and may also be referred to as *chocolate cysts*. These lesions are found in 17% to 44% of patients with endometriosis and account for about one-third of all benign ovarian cysts.[8] They may contribute to pain and increase the risk of ovarian torsion as they enlarge. The term *deeply infiltrating endometriosis* (DIE) is defined as the presence of one or more endometrial lesions extending 5 mm or more into the retroperitoneal space (especially the uterosacral ligaments and rectovaginal septum) or pelvic-organ walls (such as the vagina, ureters, bladder, or rectum). DIE likely occurs in a minor-

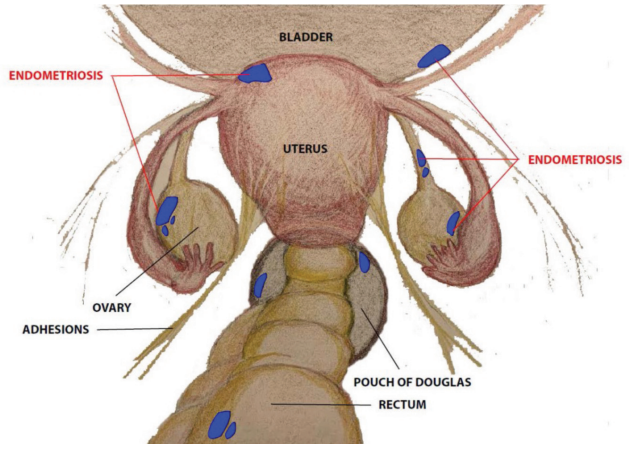

FIGURE 1. Endometriosis pathophysiology[4,6]

Increased local prostaglandins, local estradiol, interleukin-1 beta, 6, and 8; tumor necrosis factor alpha; and nerve sensitization contribute to inflammation and pain. Common sites of endometriosis are the ovaries (55%), anterior cul-de-sac (35%), pouch of Douglas (34%), and uterosacral ligaments (28%). Many patients have multiple foci of endometriosis.

ity of patients with endometriosis, but may be present in up to 40% of women referred to tertiary-care centers and can be more challenging to treat.[9]

CLINICAL PRESENTATION

The clinical presentation of endometriosis is highly variable and ranges from no symptoms to debilitating pelvic pain. The classic symptoms are dysmenorrhea, dyspareunia, chronic pelvic pain, and subfertility. Endometriosis can also cause an array of other symptoms including inguinal area pain, low back pain, dyschezia (pain with defecation), and urinary frequency and hematuria, all of which may be worse with menses. However, the severity of the patient's pain does not necessarily correlate to the extent of the disease on laparoscopy.[6] Dysmenorrhea may be described as a constant dull ache, or as a crampy pain that often starts a few days before menstruation and may continue for days after bleeding ends. Women often have a shortened cycle length and prolonged menstrual flow.[6] Note that endometriosis can be a cause of chronic pelvic pain even in premenarcheal girls. This phenomenon supports the coelomic metaplasia model of endometriosis pathogenesis.

Physical examination findings associated with endometriosis frequently are limited and nonspecific. Findings can include small bluish lesions noted on vaginal speculum examination of the posterior fornix. The bimanual examination may reveal diffuse pelvic tenderness; a tender, fixed adnexal mass; or palpable nodularity of the posterior fornix or the uterosacral ligaments. The uterus is retroverted and fixed in some women with endometrial adhesions. Of note, pelvic examinations are limited in terms of estimating disease extent, and a normal pelvic examination does not rule out endometriosis.[4]

DIAGNOSIS

The diagnosis initially is considered based on patient history and sometimes by pelvic examination findings. Transvaginal ultrasound (TVUS) is the initial imaging modality of choice for evaluating possible endometriosis; the classic findings on TVUS are diffuse homogenous hypoechoic cystic masses. Studies have found TVUS to be particularly helpful in diagnosing ovarian endometriomas and bladder endometriosis.[2,10] Although it may cause the patient more discomfort, TVUS ideally should be performed during menses when the endometriotic lesions enlarge and are easier to detect.[10] TVUS has a sensitivity of 88% in differentiating endometriomas from other ovarian masses and a specificity equivalent to that of an MRI at 90%.[10] Of note, a normal TVUS does not exclude endometriosis and further evaluation should be performed if the diagnosis is strongly suspected.

MRI also may be used in the diagnostic evaluation of possible endometriosis but is second-line to TVUS, in part due to increased cost and decreased availability.[10] MRI is more sensitive for detecting deeply infiltrating endometriosis with lesions appearing as nodules with regular, irregular, or stellate borders.[10] MRI findings may include nodules with high signaling intensity on T1-weighted images and low signaling intensity on T2-weighted images, distorted pelvic anatomy, or a pocket fluid collection.[10] MRI may be considered before laparoscopy to help plan the procedure and make sure all lesions are addressed.

No biomarkers are helpful for diagnosing endometriosis.[6] Although serum CA-125 levels may be elevated in patients with endometriosis, the test is not specific. The American College of Obstetricians and Gynecologists (ACOG) does not endorse using CA-125 to diagnose or monitor endometriosis.[11]

A definitive diagnosis of endometriosis can only be made by histologically confirming the presence of extrauterine endometrial tissue on surgical examination, most often via laparoscopy.[6] However, because laparoscopy is invasive, a presumptive diagnosis of endometriosis can be made on history, physical examination, and imaging results. A clinical diagnosis of endometriosis justifies initiation of lower risk, more easily tolerated treatments (such as NSAIDs or hormonal contraceptives) in women who are not trying to conceive. A definitive histologic diagnosis is prudent before initiating second-line treatments that may have more worrisome adverse reactions and a higher cost. Other pathologies on the differential diagnosis (**Table 1**) should be considered and ideally excluded through appropriate testing.

MANAGEMENT

No cure exists for endometriosis. Treatment options are aimed at managing pain, preserving fertility, and preventing progression. Management strategies vary depending on whether the patient's main concern is pain or infertility.

Table 1. Differential diagnosis of endometriosis[2-4,11]

Alternative diagnosis	Considerations and diagnostic testing
Sexually transmitted infections, pelvic inflammatory disease (PID)	Physical findings, CBC count, and STI testing
Primary (physiologic) dysmenorrhea	History, response to treatment
Other causes of secondary dysmenorrhea, such as uterine fibroids or adenomyosis	Physical findings, abdominal or transvaginal ultrasound
Polycystic ovary syndrome (PCOS) or functional ovarian cysts	Physical findings, history of oligomenorrhea, abdominal or transvaginal ultrasound, androgen levels
Intrauterine or ectopic pregnancy	B-hCG and transvaginal ultrasound
Ovarian torsion	Ultrasound with color doppler
UTI or interstitial cystitis	Urinalysis and culture, consider cystoscopy
Irritable bowel syndrome	History, Rome IV criteria
Other causes of infertility, such as anovulation; cervical, uterine, or tubal structural distortion from nonendometriosis conditions; male factor infertility	History and more detailed infertility evaluation with TSH, hysterosalpingogram, semen analysis, etc.

Medical therapy The first step in treatment typically is medical therapy, particularly for women not desiring conception. Patients should be counseled and prepared for ongoing, long-term treatment, because pain typically recurs if therapy is discontinued. Initial treatment frequently is started with agents that are commonly used for primary dysmenorrhea, such as NSAIDs, combination estrogen/progestin contraceptives, or progestin-only contraceptives.[4] Patients whose endometriosis does not respond adequately to first-line medical treatments benefit from being referred to a women's health specialist for possible laparoscopic confirmation of the diagnosis. The women's health specialist also can talk to the patient about second-line pharmacologic treatments, which are more costly and have more adverse reactions.

Second-line agents include gonadotropin-releasing hormone (GnRH) agonists. These medications are modified forms of GnRH with a longer half-life that bind to receptors in the pituitary. Continuous—as opposed to the normal pulsatile—stimulation of these receptors results in desensitization of GnRH receptors and the downregulation of the pituitary-ovarian axis.[12] The marked suppression of estradiol elicits a pseudo-menopause, with estradiol levels equivalent to that of women who have undergone bilateral oophorectomy. This profound hypoestrogenic state explains the efficacy of these drugs in promoting regression of endometrial implants, and also explains their limited tolerability. Hot flashes, vaginal dryness, bone mineral density loss, and mood swings are recognized adverse reactions.[12] "Add-back" therapy with low-dose estrogen and progestin or progestin alone can be helpful in mitigating these adverse reactions.[6] Leuprolide typically is administered as a monthly IM injection; goserelin is typically administered as a monthly subcutaneous implant.

Elagolix, the newest medication for endometriosis, was approved in July 2018 for moderate to severe endometriosis pain. Elagolix is a GnRH antagonist and represents a new class of medications; these drugs competitively inhibit GnRH receptors in the pituitary, leading to a dose-dependent reduction in the secretion of follicle-stimulating hormone and luteinizing hormone and consequently the suppression of estradiol and progesterone.[13,14] In contrast to the GnRH agonists, elagolix is an oral medication and comes in two dosage strengths. Adverse reactions are similar to GnRH agonists and include hot flashes, headache, insomnia, and mood disturbances. Because elagolix does not reliably suppress ovulation, women should use nonhormonal contraception (such as condoms) while taking elagolix.[14] Clinical trials of elagolix have compared the drug with placebo and leuprolide; comparison with leuprolide caused similar reductions in pain. Elagolix has not been directly compared with combined oral contraceptives or progestins.[14]

Both GnRH agonists and elagolix are expensive drugs, costing several thousand dollars per year. In addition, duration of therapy is limited. Typical use for leuprolide is 6 months but may be extended if add-back therapy is used. The higher dose of elagolix is restricted to 6 months duration, but the FDA has approved the lower dose for use up to 24 months. **Table 2** summarizes medical management options for endometriosis.

Surgical treatment Surgery for endometriosis typically is reserved for women who have persistent significant pain despite trials of medical treatments.[6] A Cochrane meta-analysis that compared diagnostic laparoscopy alone with laparoscopic treatment of visible disease found that pain was significantly improved in the treatment group.[12] Therefore, ablation or excision of visible endometrial lesions may be reasonably done at the time of diagnostic laparoscopy. The optimal surgical technique for treating endometriosis has not been established, but the skill of the surgeon plays a role in achieving complete destruction or removal of endometriotic tissue and adhesions, which may have variable appearance.[6] Surgical treatment for endometrio-

TABLE 2. Medical management options[1,12,14,18-20]

	Advantages and pearls	Disadvantages and caveats
Treatments that can be managed by a primary care provider		
NSAIDs	• Most commonly used first-line agents • Available over the counter or by prescription • No evidence supporting efficacy of one NSAID over another • Start a few days prior to menses and continue through bleeding to diminish phosphodiesterase 2 production and pain	• Adverse reactions: GI upset, peptic ulcer disease, renal effects • NSAIDs may not be as effective for endometriosis-associated pain as they are for primary dysmenorrhea (note that endometriosis is the most common cause of secondary dysmenorrhea)
Combined hormonal contraceptives	• Available as pills, patches, or vaginal rings • Widely available, easily administered, and less costly than second-line agents • May be used for extended periods of time • The dose of ethinyl estradiol (20 versus 35 mcg) does not affect efficacy against pain • May be administered in cyclic or continuous fashion; although data are limited, continuous administration may result in better control of pain and dysmenorrhea • Patient preferences should be explored given multiple options of administration	• Adverse reactions: Breakthrough bleeding, increased thromboembolism risk • Long-term protective effects do not persist when treatment is discontinued; patients should be educated that because endometriosis is a chronic condition, they should continue hormonal suppression unless they are trying to become pregnant • Ineffective in improving immediate spontaneous pregnancy rates after discontinuation
Progesterone-only contraceptives	• Available as pills, IM injections, IUDs, and implants • Can be used for extended periods of time • May produce amenorrhea • Depot medroxyprogesterone acetate (DMPA) may be as effective as GnRH agonists • One study found a levonorgestrel-releasing IUD as effective as a GnRH agonist in pain relief • May be used for women with contraindications to estrogen use, such as high VTE risk or migraine with aura	• Adverse reactions: Menstrual irregularities, weight gain, breast tenderness, acne • Risk of bone mineral density loss with DMPA, but often returns to baseline within 12 months of ceasing treatment • May have prolonged delay in the return of ovulation after ceasing therapy • IUDs and implants have higher upfront costs
Treatments typically managed by a women's health specialist		
GnRH agonists	• Lead to profound hypoestrogenism and amenorrhea • These medications are predominately delivered by IM or subcutaneous injection; no oral formulations available • To counter adverse reactions, women frequently are prescribed add-back therapy with low-dose estrogen and progesterone or progesterone alone • Add-back therapy does not adversely affect the extent of pain relief	• Adverse reactions: Hot flashes, vaginal dryness, insomnia, and bone demineralization • May be a flare of symptoms on initiation • Takes 6-12 weeks for ovarian function to return to baseline following discontinuation • Limited to 6 months of monotherapy; may extend use to 1 year with add-back therapy • Expensive
GnRH antagonist (elagolix)	• Newest medication indicated for moderate to severe endometriosis pain • Available in two oral dosages	• Adverse reactions: similar to GnRH agonists, possibly less severe; no initial flare of symptoms • Does not reliably suppress ovulation, so a barrier method of contraception is recommended during use • Limited to 6 months at higher dosage and 24 months at lower dosage • Less clinical experience given newness • Expensive

sis followed by medical therapy offers longer symptom relief than surgery alone.[12] Postoperative medical therapy should be encouraged if the patient does not desire immediate pregnancy. Note that surgical excision of large endometriomas carries the risk of ovarian damage and diminished ovarian reserve. Patients should avoid multiple surgeries, because surgery carries inherent risks of creating adhesions.[12]

Semiconservative surgical treatment involves a hysterectomy and reduction of endometrial lesions while conserving the woman's ovaries. This procedure is ideal for women who have completed childbearing, continue to have pain despite medical therapy, but are too young or do not want to undergo surgical menopause. Radical surgical treatment involves a total abdominal hysterectomy and bilateral salpingo-oophorectomy and is considered the definitive treatment for endometriosis.[2,12] This procedure may be appropriate for women who have significant pain despite trying more conservative treatments and have completed childbearing.

Management of infertility According to ACOG, in women facing endometriosis-related infertility and desiring pregnancy in the near future, medical pretreatments such as oral contraceptives and GnRH agonists are ineffective in improving spontaneous pregnancy rates.[2] However, conservative surgical treatment may marginally improve spontaneous pregnancy rates. If conservative surgical treatment is not successful in improving fertility, the next step is in vitro fertilization; repetitive surgeries can impair in vitro fertilization outcomes.[2] In general, women with established or strongly suspected endometriosis who desire pregnancy should be promptly referred to infertility specialists. Note that the signs and symptoms of endometriosis typically improve temporarily with pregnancy and breastfeeding.

Associated complications in pregnancy Studies have shown that women with preexisting endometriosis have greater risks of ectopic pregnancy, spontaneous abortion, and a greater risk of stillbirth.[15] Another study found that women with endometriosis before pregnancy have an increased risk of severe preeclampsia, placental complications, and preterm birth.[16] The increased risk of these adverse health outcomes may warrant increased monitoring during pregnancy and childbirth.[16]

Final considerations The natural history of endometriosis is variable. Although endometriosis often is progressive, some studies have shown spontaneous regression of disease in about 40% of women, suggesting that endometriosis may be a stable or progressive disease with possible periods of regression.[6] Most women have improvement or resolution of endometrial symptoms with menopause. Postmenopausal hormone therapy appears to promote recurrence in some women, further warranting a thorough risk/benefit discussion before therapy is prescribed.[17]

Clinicians should recognize the potential need for counseling or support groups to help patients with the psychosocial implications of this diagnosis. Online resources include the Endometriosis Foundation of America (www.endofound.org), Endometriosis Association (www.endometriosisassn.org), and Endometriosis.org.

CONCLUSION

Endometriosis is a common chronic condition of reproductive-age women that can result in significant morbidity. Clinicians should be familiar with the variable signs and symptoms of endometriosis. After diagnosis, a stepwise approach to management is prudent. First-line medications include NSAIDs and hormonal contraceptives; second-line agents include GnRH agonists and a new GnRH antagonist. Surgical therapy is reserved for patients whose symptoms do not adequately respond to medications and also may be helpful in women with subfertility. Because endometriosis has no cure, empathetic and committed support is needed when treating patients with this challenging disease. **JAAPA**

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