

Clinical Management of Endometriosis

Tommaso Falcone, MD, and Rebecca Flyckt, MD

Endometriosis is a common and challenging condition of reproductive-aged women that carries a high individual and societal cost. The many molecular dissimilarities between endometriosis lesions and eutopic endometrium create difficulties in the development of new drug therapies and treatments. Surgery remains the gold standard for definitive diagnosis, but it must be weighed against the risks of surgical morbidity and potential decreases in ovarian reserve, especially in the case of endometriomas. Safe and effective surgical techniques are discussed within this article for various presentations of endometriosis. Medical therapy is suppressive rather than curative, and regimens that are long-term and affordable with minimal side effects are recommended. Recurrences are common and often rapid when medical therapy is discontinued. Endometriosis in the setting of infertility is reviewed and appropriate management is discussed, including when and whether surgery is warranted in this at-risk population. In patients with chronic pain, central sensitization and myofascial pain are integral components of a multidisciplinary approach. Endometriosis is associated with an increased risk of epithelial ovarian cancer; however, the risk is low and currently no preventive screening is recommended. Hormone therapy for symptomatic women with postsurgical menopause should not be delayed as a result of concerns for malignancy or recurrence of endometriosis.

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Endometriosis is diagnosed by the presence of viable, estrogen-sensitive endometrial-like glands and stroma outside the uterus. Although no clinical symptoms are required, in many patients, endometriosis is a chronic inflammatory disorder that significantly decreases quality of life. The societal burden of endometriosis is estimated to be more than \$49 billion in the United States with patients undergoing surgery estimated to incur higher direct and indirect costs and productivity losses per woman that are twice as high

as health care costs.¹ The most common clinical presentations are adnexal masses, infertility, and dysmenorrhea. Although the presence of ectopic endometrial tissue is the key pathologic feature, there are many molecular differences that make endometriosis lesions distinct from eutopic endometrium. These molecular dissimilarities make the development of new drug therapies and treatments challenging.

INCIDENCE AND EPIDEMIOLOGIC FACTORS

This enigmatic disease is influenced by multiple genetic, environmental, and epidemiologic factors. It affects 6–10% of reproductive-aged women and has been found in premenarchal and postmenopausal women. The average age at diagnosis is approximately 28 years. Several conditions show greater concordance with endometriosis. For example, endometriosis is present in 21–47% of women presenting with subfertility² and 71–87% of those with chronic pelvic pain.³ Early menarche, short menstrual cycle length, heavy menstrual periods, and nulliparity are associated with increased risk. Other factors associated with increased prevalence are low body mass index and alcohol use, as well as certain phenotypes such as freckles and nevi. Exercise appears to be

From the Obstetrics, Gynecology, and Women's Health Institute, Cleveland Clinic, Cleveland, Ohio.

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Corresponding author: Tommaso Falcone, MD, Obstetrics, Gynecology, and Women's Health Institute, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; email: falcont@ccf.org.

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protective. Oral contraceptive use is associated with decreased prevalence of endometriosis and possibly lower prevalence of endometrioma at first laparoscopy.⁴

Endometriosis has a strong familial component; a first-degree relative with endometriosis increases risk 7- to 10-fold. A meta-analysis of genome-wide association studies has shown common genetic variants in seven risk loci.⁵ The genetic burden appears to increase along with the severity of disease.

The long interval between presentation of symptoms and the definitive diagnosis of endometriosis is 7–8 years. This is attributed in part to the overlap between symptoms associated with endometriosis and other pain-associated syndromes (Table 1). Clinical diagnosis can be confirmed surgically with direct inspection and tissue biopsy of visible lesions. Endometriosis most likely does not have a single unifying explanation that accounts entirely for the varied clinical manifestations of the disease.

PATHOPHYSIOLOGY

An endometriotic lesion has the same histologic appearance as the endometrium with distinct endometrial glands and stroma. The etiology of endometriosis is still described in terms of implantation of eutopic endometrium from retrograde menstruation or metaplasia of coelomic pluripotential mesothelial cells lining the peritoneum into endometrial tissue at ectopic sites (Appendix 1, available online at <http://links.lww.com/AOG/B60>). Why only a minority of women develop endometriosis from a common phenomenon of retrograde menstruation is attributed in part to an inherent dysfunction of the peritoneal immune system. A third theory proposed to better describe endometriosis infiltrating into the cul de sac and uterosacral ligaments is the theory of müllerianosis, which pro-

poses that at the time of fetal organogenesis, misplaced endometrial tissue such as what is observed in the cul de sac develops into endometriosis (Appendix 1, available online at <http://links.lww.com/AOG/B60>). Distant metastases and implantation of cells through hematogenous or lymphatic embolization can explain endometriosis observed in nontraditional locations. None of these theories is mutually exclusive. Furthermore, all phenotypes of the disease can manifest within the same patient. The challenge of implantation theories is the fact that although ectopic endometriosis lesions resemble eutopic endometrium histologically, they do not function physiologically in a similar manner. The implication of this observation is that the response of endometriosis lesions to medical therapy will probably be unlike that of eutopic endometrium.

The multitude of abnormal molecular events in the eutopic endometrium results in altered hormone response and altered receptivity as well as enhanced cellular survival and inflammation at ectopic sites. Cross-talk between the ectopic lesions and the eutopic endometrium can influence gene expression in the endometrium. In endometriotic lesions it is postulated that defective methylation occurs in critical genes, which influence downstream progesterone and estrogen receptor expression. This, in combination with increased aromatase expression in the ectopic endometrium, results in a higher concentration of local, more metabolically active estradiol. These observed changes are summarized as progesterone resistance (Appendix 2, available online at <http://links.lww.com/AOG/B60>). Relative progesterone resistance in the endometrium can explain in part the dysregulated genes critical for implantation.⁶ In addition to epigenetic modification of select genes, altered microRNA expression may influence gene transcription and posttranslational events associated with proliferation or regulation of cell survival.⁷

Table 1. Symptoms of Endometriosis

Symptom	Disorders With Similar Clinical Presentation
Dysmenorrhea	Adenomyosis; primary dysmenorrhea; in adolescents—obstructed müllerian anomalies
Nonmenstrual pelvic–abdominal pain	Irritable bowel syndrome; neuropathic pain; adhesions; abdominal wall nerve entrapment syndromes
Dyspareunia	Psychosocial issues; pelvic floor disorders
Bowel symptoms (diarrhea, cramping, constipation)	Hemorrhoids; constipation; irritable bowel syndrome
Defecation pain (dyschezia)	Anal fissures; pelvic floor disorders
Infertility	Unexplained subfertility
Ovarian mass or tumor	Benign ovarian cyst
Painful bladder symptoms and dysuria	Painful bladder syndrome; interstitial cystitis; pelvic floor disorders



The resultant lesions are associated with chronic inflammation and immune dysregulation (Appendix 2, available online at <http://links.lww.com/AOG/B60>). Excision of endometriosis has been shown to decrease proinflammatory cytokines.

MECHANISM OF OVARIAN CYST DEVELOPMENT (ENDOMETRIOMA)

Endometriomas are cysts within the ovary containing “chocolate” fluid (Appendix 3, available online at <http://links.lww.com/AOG/B60>). Endometriosis cysts are thought to arise from the surface, with superficial ovarian implants commonly observed at laparoscopy. Promoted by adhesions from the ovary to the sidewall, implants of endometrial glands and stroma invaginate or become entrapped within the cortex to progressively form cystic lesions.

Another hypothesis of endometrioma formation is that the peritoneal mesothelium covering of the ovary can differentiate into endometrioid epithelium and subsequently forms an invaginating cyst in a similar manner (metaplasia theory). Still another hypothesis suggests that müllerian epithelium from the tube or endometrium can implant on the surface of the ovary and lead to cyst formation. This latter concept is similar to most surface epithelial tumors and is supported by the recent association of ovarian cancer with tubal tissue. The process of endometrioma formation is closely linked to ovulation because prevention of ovulation with cyclic oral contraceptives reduces the risk of endometrioma recurrence. There may be seeding of endometriosis tissue into a hemorrhagic corpus luteum with progression from a hemorrhagic corpus luteum to an endometrioma.

The inner surface of an endometrioma is lined by endometriosis with variable penetration into the surrounding fibrosis. The mean cyst wall thickness is 1.2–1.6 mm. Endometriotic tissue covers approximately 60% of the inner surface of the cyst with a depth of penetration of 1.5 mm.⁸ This observation is important if energy forms are used to ablate the endometriotic cysts rather than excisional strategies. The unique features of endometriomas are intense fibrosis and inflammation. Contrary to other cysts, endometriomas are firmly adherent to the cortex as well as the underlying stroma (Appendix 3, available online at <http://links.lww.com/AOG/B60>). This dissimilarity can explain some differences in clinical manifestation from epithelial tumors such as the presence of pain as well as the surgical observation that excision is difficult and can result in the inadvertent removal of normal ovarian tissue.

MECHANISM OF PAIN

The chronic inflammation of endometriosis is characterized by increased systemic and local proinflammatory cytokines and growth factors that are closely related to pain sensation including dyspareunia (ie, nerve growth factor, prostaglandin E₂). Long-term exposure to these proinflammatory substances can lead to peripheral sensitization characterized by a hyperalgesic state, central sensitization, and myofascial pain.⁹ The concept of central sensitization is critical to understanding chronic pain and will help in avoiding repetitive surgery. It is postulated that repetitive and persistent noxious stimulation, chronic inflammation, and nerve injury will alter pain processing, resulting in central sensitization. It is important to treat pain symptoms quickly to avert this condition. Surgical intervention may actually increase central sensitization and these patients often report worsening of symptoms after surgery. The recent observation of altered brain chemistry in women with endometriosis is positively correlated with pain intensity.¹⁰

MECHANISM OF SUBFERTILITY

The severe adhesive disease associated with advanced endometriosis is an obvious impairment to fertility. However, it is not obvious how a small lesion seen at laparoscopy can cause infertility. There is strong debate whether minimal endometriosis can cause infertility different from idiopathic infertility.

The peritoneal environment of women with endometriosis may lead to increased sperm DNA damage as well as an abnormal oocyte cytoskeleton.¹¹ Monthly fecundity rates are lower in women with mild endometriosis undergoing therapeutic donor insemination (azoospermic partners) compared with women without endometriosis.¹² However, implantation and clinical pregnancy rates were similar between women with and without disease in a donor egg program with the use of sibling oocytes in women with advanced endometriosis and those without disease. In another study with a similar methodology, using sibling oocytes from the same donor in recipients with and without endometriosis resulted in lower implantation and pregnancy rates in patients with endometriosis.¹³ The authors suggested an endometrial defect as the explanation. This observation is supported by numerous studies showing decreased expression for several biomarkers of implantation. It is difficult to ascertain whether lower implantation rates may also be explained by coexisting undiagnosed adenomyosis.

Kitajima et al¹⁴ opine that women with endometriomas experience accelerated depletion of follicles



from enhanced activation of granulosa cells leading to dyssynchronous oocyte maturation and oocyte apoptosis. Women with endometriomas have lower baseline antimüllerian hormone levels than their unaffected counterparts; presurgical antimüllerian hormone levels in women with endometriomas were 45% lower than in patients with no endometriosis and 36% lower than in patients found to have only pelvic endometriosis.¹⁵ Other studies have shown a similar effect on ovarian reserve, especially with bilateral endometriomas. It is not clear whether deeply infiltrating endometriosis is independently associated with infertility.

NATURAL COURSE OF ENDOMETRIOSIS

Endometriosis should not be assumed to be progressive. The short-term natural course of the disease has been demonstrated in randomized studies, which include a placebo control group completing baseline diagnostic laparoscopy. In the pooled placebo group, 162 patients reveal a disease in flux with nearly equal distribution among deterioration (31%), no change (31%), and improvement (38%).¹⁶ It is unclear which lesions recur and whether recurrence is associated with symptoms. Some recurrences are persistent disease that was not completely treated surgically. The natural course of recurrent symptoms may not necessarily reflect the recurrence of endometriosis lesions. Given the high rate of recurrent symptoms and reoperation in women treated without suppressive postoperative medical therapy, more women will likely have their endometriosis track toward disease progression rather than resolution. The mechanisms responsible for ongoing symptom expression are likely complex and multifactorial.

CLINICAL PRESENTATION AND DIAGNOSIS

Most women with endometriosis will present with a collection of symptoms, including dysmenorrhea, deep dyspareunia, dyschezia, and chronic abdominopelvic pain as well as subfertility. Each of these symptoms can significantly impair a woman's physical, mental, and socioemotional well-being. History-taking should include a family history of endometriosis as well as past surgeries known to increase the risk of local endometriosis such as cesarean delivery and myomectomy. When considering endometriosis-associated pelvic pain, the clinician should bear in mind the extensive differential diagnosis and potential contributors to the pain syndrome. These include pelvic inflammatory disease, adhesions, abdominal wall pain, irritable bowel syndrome, interstitial cysti-

tis, myofascial pain and pelvic floor disorders, depression, and a history of sexual abuse.

Pain levels should be documented using a visual analog scale (usually 0–10). Although there is a poor correlation between level of pain and disease severity, deeply infiltrating endometriosis is associated with increased severity of pain. Implants do not localize well to subjective pain locations with the exception of deeply infiltrating endometriosis. In patients with endometriomas, severe pain is often associated with the presence of deeply infiltrating disease rather than the size of the cyst.¹⁷ Therefore, surgical treatment of an endometrioma requires concomitant treatment of deeply infiltrating endometriosis if present to obtain optimal pain relief.

The physical examination should be detailed, looking for multiple causes of pain such as nerve entrapment, myofascial pain, and pelvic floor disorders. On pelvic examination, signs of advanced disease are tenderness or nodules of the cul de sac or uterosacral ligaments, tenderness of the adnexa, rectovaginal septum induration, and the presence of a fixed retroverted uterus.

Three phenotypes of endometriosis can be discerned at surgery: endometriomas (ovarian cysts), superficial endometriotic implants (primarily on the peritoneum), and deeply infiltrating endometriosis, which is defined as a nodule extending more than 5 mm beneath the peritoneum (Fig. 1). When these lesions occur near the uterine ligaments or the bowel, proliferation of the indigenous smooth muscle of these structures creates a mass-like effect and fibrosis that fill the rectovaginal space. Ovarian disease can occur superficially on the cortex but is still associated with inflammation and fibrosis.

Imaging is often used in the investigation of chronic pelvic pain and can also be informative in the preoperative assessment of patients preparing for endometriosis surgery. Imaging sensitivity varies depending on the particular phenotype of lesion (ie, endometrioma, peritoneal disease, or deeply infiltrating endometriosis). For chronic pelvic pain, pelvic ultrasonography remains the modality of choice because it can detect other causes of pelvic pain such as adenomyosis. Transvaginal ultrasonography has the highest sensitivity and specificity in identifying ovarian endometriomas. Classic ultrasonographic features are a unilocular cyst with homogeneous low-level echogenicity of the fluid (ground glass appearance) and poor or mild vascular flow (Fig. 2). If small papilla are present, there should be no flow noted within this area.

Pelvic ultrasonography for deeply infiltrating endometriosis is more challenging. Accurate



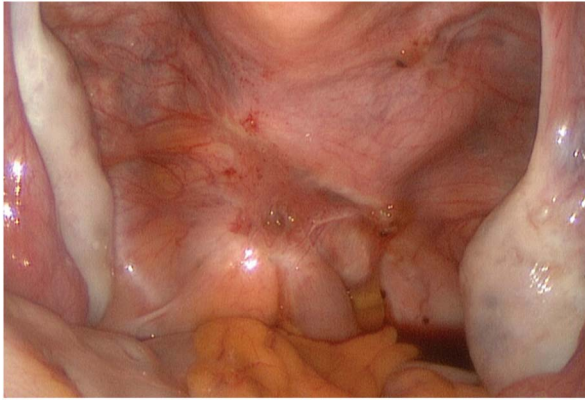


Fig. 1. Deeply infiltrating endometriosis. In this image, the lesion infiltrates the rectum and the rectovaginal space at the level of the cervix.

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preoperative mapping of deeply infiltrating endometriosis will allow more thorough counseling of surgical risks as well as the potential need for bowel or bladder resection; preoperative detection of deeply infiltrating endometriosis will also allow the surgeon to refer a patient to a center skilled in managing advanced disease if necessary. Ultrasonography performed for deeply infiltrating endometriosis should be a dynamic process; dense adhesions and cul de sac obliteration can be detected while moving the ovaries, uterus, or bowel during the examination. A recent consensus report on ultrasonographic terminology for deeply infiltrating endometriosis has been proposed to properly communicate the extent of disease.¹⁸ There are currently no data to establish that preoperative imag-



Fig. 2. Endometrioma. The typical ultrasonographic appearance is shown of a unilocular cyst with homogeneous low-level echogenicity and minimal vascular flow.

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ing results in improved patient outcomes for endometriosis surgery.

In this report there are four ultrasonographic steps to the evaluation of the pelvis with suspected endometriosis. The first step is the 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. In step two, the 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. Step three evaluates 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. The final step is 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. Fluid contrast in the vagina or rectum can improve visualization of bowel or bladder involvement.

The predictive value of this ultrasound approach depends on the experience of the center performing the ultrasonography and is very highly operator-dependent. In experienced centers, the sensitivity and specificity of finding disease at the rectocervical or rectosigmoid levels is higher than 95%.¹⁹ The sensitivity for deeply infiltrating endometriosis overall and the uterosacral ligaments in particular is less (80% and 75%, respectively).²⁰ Magnetic resonance imaging has also been found to have high diagnostic accuracy with similar sensitivity and specificity to ultrasonography in the diagnosis of deep endometriosis of the uterosacral ligaments (85% and 88%), vaginal endometriosis (77% and 70%), and colorectal endometriosis (88% and 92%).²¹ Magnetic resonance imaging with an enema compared with rectal water contrast transvaginal ultrasonography in the diagnosis of rectosigmoid endometriosis has shown similar sensitivity and specificity, reported at higher than 90%. 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.

There are no diagnostic markers with adequate reliability for clinical use. Research has focused on molecular markers in the eutopic endometrium as



well as noncoding RNA in tissue and blood.^{7,22} A 2016 Cochrane review concluded that none of the published biomarkers could be evaluated in a meaningful way and that laparoscopy remains the gold standard.²³ The CA 125 test has poor diagnostic accuracy and has minimal value in the investigation of a patient with chronic pelvic pain. It is often mildly elevated in women with endometrioma. Although a noninvasive diagnostic test for endometriosis is desirable and could help avoid the need for surgery in establishing a definitive diagnosis, there is currently no such test available.

SURGICAL DIAGNOSIS

Surgery remains a fundamental tool in the diagnosis and treatment of endometriosis and allows direct visual identification of disease. Excision and confirmation by histology is highly recommended as a result of the low reliability of visual inspection alone. The typical histologic appearance of endometriosis consists of endometrial glands, stroma, and hemosiderin-laden macrophages.

Staging of endometriosis follows the American Society for Reproductive Medicine system, which assigns a score to designate minimal and mild disease (stage I and II) and moderate and severe disease (stage III and IV).²⁴ The model is not without limitations in clinical utility because there is poor correlation with quality-of-life indicators. Although initially developed for the assessment of fertility, the American Society for Reproductive Medicine staging score is commonly used to quantify disease burden and facilitate uniformity in both research and patient care. Other surgical taxonomies exist such as the Enzian classification, which reports the depth of deep infiltrating endometriosis, and the Endometriosis Fertility Index, which predicts fertility outcomes based on surgical findings.

The most common sites for endometriosis are the ovaries, pelvic peritoneum (the broad ligament and cul de sac), and uterosacral ligaments. A systematic approach to the pelvis will ensure no lesions are missed during surgery.²⁵ Photographing each area will assist in communication with the patient and other physicians.

MEDICAL MANAGEMENT

Medical Therapies for Endometriosis Pain

Accurate clinical diagnosis is important, because many societies including the American College of Obstetricians and Gynecologists and the American Society for Reproductive Medicine endorse empiric therapy before definitive surgical diagnosis.^{24,26}

Response to empiric therapy does not confirm the diagnosis of endometriosis.

There are numerous current medical treatments for the management of endometriosis symptoms. All of these treatments should be considered suppressive rather than curative. Medical therapy will not increase fecundity or resolve endometriomas or deeply infiltrating disease. Because the effectiveness of medical options for reducing symptoms is comparable, selection of an optimal regimen is based on multiple factors including patient age, patient preference, reproductive plans, pain severity, and degree of disease. Additional factors include treatment cost and intended duration as well as treatment risks, side effect profiles, and accessibility. The main objective of medical management is to prevent recurrence and reduce symptoms, thereby eliminating the need for repeat surgery or prolonging the time between surgeries.

Endometriosis is a chronic disease requiring sustained treatment; this key educational point must be reinforced in discussions with patients both before and after surgery. Although patients may desire a single operative procedure to permanently remove endometriosis lesions and provide enduring pain relief, ongoing hormonal suppression after endometriosis surgery is necessary. It is clear that without hormonal suppression, pain symptoms will recur and they often recur rapidly with a recurrence risk of 50% at 5 years.²⁷ Because hormonal management is by necessity long-term, the ideal regimen should be cost-effective, well-tolerated, and without significant risk to the patient. Medical therapies for endometriosis are summarized in Table 2.

For decades, the mainstays of conventional endometriosis treatment have been nonsteroidal antiinflammatory drugs and combined oral contraceptives followed closely by gonadotropin-releasing hormone (GnRH) agonists and oral progestins. This strategy has been endorsed by several professional societies.^{24,26} Despite their widespread use, nonsteroidal antiinflammatory drugs alone are probably of minimal effectiveness in patients with endometriosis. A placebo-controlled, double-blind, randomized trial confirms improvement of dysmenorrhea and reduction in the size of endometriomas greater than 3 cm in women with endometriosis taking combined oral contraceptives compared with placebo.²⁸ The goal of hormonal treatments is to induce a local hypoestrogenic state by suppressing ovulation. Furthermore, the resulting amenorrhea or hypomenorrhea reduces the conversion of arachidonic acid to prostaglandins with menses and subsequently lessens dysmenorrhea and pelvic pain. Continuous rather



Table 2. Medical Therapies for Endometriosis

Class	Mechanism of Pain Relief	Drug	Dose	Side Effects
Estrogen–progestin combinations	<ul style="list-style-type: none"> • Ovulation inhibition • Decidualization or atrophy of lesions 	<ul style="list-style-type: none"> • Monophasic estrogen–progestin* 	Continuous orally daily	Breakthrough bleeding, breast tenderness, nausea, headaches, mood changes
Progestins	<ul style="list-style-type: none"> • Decidualization or atrophy of lesions • Inhibition of angiogenesis • Suppression of matrix metalloproteinase-facilitated growth and implantation of ectopic endometrium 	<ul style="list-style-type: none"> • Depo Provera* • Etonogestrel-releasing implant • Norethindrone acetate* • Levonorgestrel-releasing IUS • Medroxyprogesterone acetate • Dienogest[†] • Leuprolide depot** • Goserelin** • Nafarelin** 	<ul style="list-style-type: none"> • 104 mg SC every 3 mo • 1 for 3 y • 5 mg daily • 1 for 5 y • 30 mg orally for 6 mo, then 100 mg IM every 22 wk for 2 mo, then 200 mg IM monthly for 4 mo • 2 mg daily 	Acne, weight gain, mood changes, headache, breakthrough bleeding, breast tenderness, lipid abnormalities (norethindrone)
GnRH agonists	Inhibition of gonadotropin secretion and subsequent downregulation of ovarian steroidogenesis	<ul style="list-style-type: none"> • Danazol* 	<ul style="list-style-type: none"> • 3.75 mg IM monthly (11.25 mg IM every 3 mo) • 3.6 mg SC monthly (10.8 mg IM every 3 mo) • 200 micrograms intranasally twice daily 	Decreased bone density, atrophic vaginitis, hot flashes, headache, joint pain
Androgenic steroids	<ul style="list-style-type: none"> • Inhibition of pituitary gonadotropin secretion • Local growth inhibitor • Inhibition of estrogenic enzymes 	<ul style="list-style-type: none"> • Danazol* 	<ul style="list-style-type: none"> • 100–400 mg orally twice daily • 100 mg vaginally daily 	Hair loss, weight gain, acne, hirsutism
Antiandrogens	Competitively inhibition of the androgen receptor	<ul style="list-style-type: none"> • Cyproterone acetate[†] 	12.5 mg orally daily	Hair loss, breast tenderness, weight gain
GnRH antagonists	Inhibition of gonadotropin secretion and subsequent downregulation of ovarian steroidogenesis	<ul style="list-style-type: none"> • Elagolix 	150 mg orally daily	Hot flushes, lipid abnormalities, decreased bone density
Aromatase inhibitors	Local blockade of enzymatic (aromatase) conversion of androgens to estrogens	<ul style="list-style-type: none"> • Letrozole • Anastrozole 	<ul style="list-style-type: none"> • 2.5 mg orally daily • 1 mg orally daily 	Hot flushes, headaches, decreased bone density
Selective progesterone receptor modulators	Inhibition of ovulation, agonist or antagonist at progesterone receptor	<ul style="list-style-type: none"> • Mifepristone • Ulipristal acetate 	<ul style="list-style-type: none"> • 50 mg orally daily • 15 mg orally every other day 	Spotting, cramping, dizziness, headache, nausea

SC, subcutaneously; IUS, intrauterine system; IM, intramuscularly; GnRH, gonadotropin-releasing hormone.

* U.S. Food and Drug Administration–approved for endometriosis.

[†] Used as monotherapy outside the United States.

[‡] With add-back, that is, 5 mg norethindrone acetate daily plus 800 international units vitamin D daily plus 1.25 g calcium daily.



than cyclic administration appears to be more effective in reducing the recurrence of dysmenorrhea but not noncyclic pelvic pain or dyspareunia.²⁹ No single route of administration (oral, transdermal, or transvaginal) has been shown to provide superior pain relief. Breakthrough bleeding can typically be managed by a brief interruption in treatment with regimens resuming within 7 days.

Progestin monotherapy has historically been favored in women who fail combined hormone therapy, smokers older than 35 years, and women with predisposing risk factors for myocardial infarction, stroke, or thrombotic events. However, some authors suggest that progestin-only methods such as the 19-nortestosterone derivatives norethindrone acetate and dienogest may be superior to combined oral contraceptives and can be considered first-line, especially in women with rectovaginal and extrapelvic endometriosis.³⁰ The argument for progestin monotherapy is based on a similar combination of ovulation inhibition and amenorrhea but with potentially fewer unfavorable estrogenic effects and equivalent improvements in dysmenorrhea and pelvic pain symptoms when compared with combined oral contraceptives and GnRH agonists. Dienogest has shown benefit in controlling endometriosis pain; however, like cyproterone acetate, it is not currently available as a single agent in the United States. In contrast, norethindrone acetate has a lower cost and is approved for the treatment of endometriosis in the United States by the U.S. Food and Drug Administration (FDA). Furthermore, comparative clinical trials comparing norethindrone acetate with dienogest have not shown superior results for either agent.³¹ The dose of norethindrone acetate can be increased as needed from 5 to 15 mg daily as needed. Lipid profiles should be serially monitored while on higher doses and longer durations of norethindrone acetate.

Progestin-only methods can be administered by 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. The levonorgestrel-releasing intrauterine device, although not FDA-approved for this purpose, has also been shown to be effective in decreasing endometriosis-related pain. Depot medroxyprogesterone acetate is an FDA-approved treatment for endometriosis and has been shown to be as effective as GnRH agonist in a multicenter randomized comparison³²; however, bone density loss is a concern with long-term use.

Gonadotropin-releasing hormone agonists have been considered second or even third line as a result of higher cost, limited accessibility, patient preference

for nonparenteral administration, and presence of hypoestrogenic side effects. They are effective in inhibiting ovarian steroidogenesis through central suppression of gonadotropin release. A Cochrane review from 2010 examined 41 studies and demonstrated that GnRH agonist treatment is superior to placebo and as effective as other combined and progestin-only regimens.³³ Furthermore, a randomized comparison of combined oral contraceptives compared with GnRH agonist therapy demonstrated that although both treatments were effective in reducing pain, the GnRH agonist group reported more significant improvements in dyspareunia.³⁴ Gonadotropin-releasing hormone agonist treatment alone has also been shown to be as effective as surgical management or combined treatment in a prospective randomized trial; however, recurrence risk was lower with combined management.³⁵ Reductions in pain symptoms expected with GnRH agonist therapy range from 50% to 90% and GnRH is considered to be a particularly good agent for suppression of deeply infiltrating endometriosis and extrapelvic endometriosis.

Long-term GnRH agonist use leads to loss of bone density as well as increasingly bothersome hot flashes, vaginal dryness, headaches, and mood changes; GnRH agonist monotherapy should not extend beyond 6 months' duration. Adverse effects can be mitigated by add-back therapy such as 5 mg norethindrone acetate daily or combined hormone treatment with estrogen and progestin, and this can allow longer treatment courses. Despite this, GnRH agonist use is not practical as a long-term strategy for the management of endometriosis. Calcium and vitamin D may also provide some bone protection. Add-back therapy can be initiated concomitantly with GnRH agonist treatment; there is no documented benefit in pain relief with a delayed start.

The ideal method is one that can be used long-term. Therefore, we recommend initial selection of continuous combined oral contraceptives or progestin-only methods such as norethindrone acetate or the levonorgestrel-releasing intrauterine device for medical management of endometriosis symptoms.

Alternative Therapeutic Agents

Danazol is an established and effective endometriosis treatment; however, it is seldom used as a result of undesirable androgenic side effects. Aromatase inhibitors are successfully used in refractory cases to decrease endometriosis-associated pain. Aromatase inhibitors induce hypoestrogenemia by decreasing local enzymatic conversion of androgens to estrogens. Although the target is largely ovarian, aromatase inhibitors block aromatase activity within adipocytes as well as ectopic



aromatase that provides self-sustaining estradiol within endometriotic lesions. Aromatase inhibitors are not FDA-approved, may induce bone loss, and must be combined with combined oral contraceptives, progestins, or GnRH agonists to avoid unwanted ovarian cyst development.

Given the limitations of currently available treatments, new therapeutic options for endometriosis are desirable. Oral GnRH antagonists and selective progesterone receptor modulators have shown potential in investigational settings. The efficacy of oral daily GnRH antagonist therapy for endometriosis pain was established with a multicenter, double-blind, randomized, placebo-controlled phase 3 clinical trial; however, hypoestrogenic side effects were noted.³⁶ Improvements were most notable for dysmenorrhea rather than nonmenstrual pain or dyspareunia.

Selective progesterone receptor modulators have been prospectively studied, but randomized placebo-controlled studies are lacking. Further opportunities for development include immunomodulators and antiangiogenic agents; however, these agents remain highly experimental in the setting of endometriosis treatment.

SURGICAL MANAGEMENT

Surgical management of endometriosis for the management of infertility, chronic pain, or ovarian cysts is effective but has several controversial features. Surgical management is indicated after failure of empiric therapy, failure, or intolerance of medical management or for purposes of diagnosis and immediate treatment. It is also indicated for diagnosis and treatment of an adnexal mass and treatment of infertility in some patients.

The surgical approach can be conservative with treatment of endometriosis or definitive with hysterectomy with or without removal of the ovaries. The management of peritoneal disease can involve ablation of the lesion with an energy form or excision. A recent systematic review of three randomized trials reported no clear statistical difference in pain scores, although there was a trend that favored excision.³⁷ Ablation should not be attempted when endometriosis is located near critical structures such as the ureter, bowel, or bladder because lateral spread of an energy form can damage underlying structures. Furthermore, it is difficult with any energy form to ablate deeply infiltrating disease because the risk of injury to underlying structures is high without proper dissection. Therefore, excision is usually required for the most effective and complete surgical management of endometriosis.

Surgical Outcome in Women With Chronic Pelvic Pain

A recent Cochrane review reported that laparoscopic surgery for endometriosis clearly decreased overall pain at 6 and 12 months compared with diagnostic laparoscopy alone (odds ratio [OR] 10.00, CI 3.21–31.17).³⁸ Furthermore, laparoscopic surgery was superior to diagnostic laparoscopy followed by medical therapy with a GnRH agonist. The recurrence of symptoms is estimated to be approximately 10% at 1 year to as high as 40–50% at 5–7 years.³⁹ Many surgical trials have not consistently used long-term postoperative medical suppressive therapy. The use of immediate postoperative long-term hormonal suppressive medical therapy can reduce the recurrence of symptoms and repeat surgery, an approach that is favored by society guidelines.^{24,26} The ideal duration of suppression is a minimum of 6–24 months.

There have been several suggested approaches to improve surgical outcome. The first concept is to improve visualization of endometriosis at surgery, for example with the use of indocyanine green, a fluorescent dye. There are no high-quality studies to support the use of this product in the surgical management of endometriosis. Although robotic surgery adds another dimension to the visualization and treatment of endometriosis, a recent randomized multicenter clinical trial comparing robotic surgery with conventional laparoscopy showed no advantage in short-term postoperative parameters or improvement in pain scores or other quality-of-life indicators.⁴⁰ Second, uterine denervation or nerve transection procedures have also been performed to improve surgical outcome. Numerous studies have shown that none has improved outcomes with the exception of presacral neurectomy. The presacral neurectomy can help reduce midline pain such as dysmenorrhea, but it is associated with the possible consequences of bowel and bladder denervation with reported increased frequency of constipation and bladder dysfunction.

Management of Endometriomas

Clinical management of an endometrioma requires a clear understanding of the goals of surgery because surgical intervention can clearly cause ovarian damage and decrease ovarian reserve. If surgery is meant to obtain a tissue diagnosis and relieve symptoms, complete excision will accomplish this task most effectively with decreased recurrence. As summarized in a Cochrane review that included two randomized clinical trials, excision of a cyst is associated with a reduced rate of recurrence, reduced symptom recurrence, and increased spontaneous pregnancy



rates (OR 5.1, CI 2.04–13.29) compared with ablative surgery.⁴¹

Despite these favorable observations, there have also been many recent reports of decreased ovarian reserve from cystectomy. Numerous studies have shown a decrease in ovarian reserve with the excisional technique with up to a 30% decrease in antimüllerian hormone after unilateral cystectomy and a 44% decrease after bilateral cystectomy.¹⁵ This ovarian damage can occur at several steps during the excision process including removing normal cortex containing follicles during the dissection and damage incurred while obtaining hemostasis. The excessive use of electrocautery for hemostasis can cause injury, either directly to the follicles or indirectly to the blood vessels. It is possible that newer energy forms such as plasma energy could cause less ovarian damage than excision. In patients with low potential for spontaneous pregnancy as a result of extensive adhesions, for example, those who will need assisted reproductive technology, ablation rather than excision may be more advantageous to maintain ovarian reserve.

Repetitive surgery for recurrent endometriomas is associated with increased harm as evaluated by antral follicle count and ovarian volume. Prospective randomized trials have shown long-term cyclic and continuous oral contraceptives can reduce recurrence of endometriomas. Although the levonorgestrel-releasing intrauterine device is effective for decreasing recurrence of dysmenorrhea, it has not been shown effective in reducing endometrioma recurrence.

Cystectomy Technique

Preoperative imaging is important to determine whether the cyst is bilateral. Dissection of the adherent ovarian cyst complex from the pelvic side wall requires knowledge of the course of the ureter and the ovarian blood supply. As shown in (Appendix 3 available online at <http://links.lww.com/AOG/B60>), the ovarian blood supply has two primary sources: the ovarian vessels that course through the suspensory ligament and the vessels that course through the uteroovarian ligament.

There are several critical steps during surgery. Peritoneal washings should be obtained at the time of the diagnostic laparoscopy if there is any suspicion of malignancy. After this, adhesions are lysed to restore normal anatomy. Endometriomas can then be excised or ablated. Bipolar electrocautery is the most common energy form used for cyst ablation; however, depth of penetration can be up to 12 mm so careful technique is advised. If cystectomy (excision) is performed, dilute vasopressin can be injected to decrease bleeding and an

incision must be made to identify a cleavage plane, although this drug is not approved for this indication. Traction–countertraction is applied to carefully peel the cyst wall from the ovarian cortex. Excessive traction risks the removal of normal tissue. In difficult dissections, extra caution should be taken at the hilum where bleeding commonly occurs. Precise bipolar electrocautery, suturing, or the use of hemostatic sealant agents can be considered in this event. If the cleavage plane cannot be identified, a small portion of tissue can be obtained for histology and the remaining cyst wall can be ablated.

Management of Deeply Invasive and Extrapelvic Endometriosis

Deeply infiltrating endometriosis often involves nongynecologic organs. It can involve the urinary tract, ureter and bladder, bowel, uterosacral ligaments, and rectovaginal septum. Excision of deeply infiltrating endometriosis requires detailed knowledge of the retroperitoneal space.⁴² Simple ablation will not effectively treat deep lesions because they typically involve the anatomic area of the ureter, bladder, or rectal area behind the cervix. Although suppressive medical therapy improves pain in women with deeply infiltrating endometriosis, it has not been shown to improve fertility outcomes.⁴³

Colorectal Endometriosis

Symptoms suggesting bowel involvement of endometriosis overlap with mild or deeply infiltrating endometriosis found in nonbowel sites. Cyclic defecation pain or cyclic constipation is reported in the majority of women with rectal endometriosis (between 55% and 65%), but is also found in between 25% and 40% of women with minimal endometriosis or deeply infiltrating disease at nonbowel sites. In patients with rectal disease, most patients report more frequent and severe symptoms of bloating, constipation, diarrhea, cramping, and defecation pain, but they are not uniquely associated with bowel endometriosis.

The most common site of gastrointestinal tract endometriosis is the rectosigmoid (85%) followed by the appendix, distal ileum, and cecum. Endometriosis involving the bowel usually occurs at the level of the rectocervix rather than the rectovaginal septum. In most cases the septum is spared and dissection under the lesion can be achieved. Pelvic ultrasonography can identify the presence of rectal nodules, although the ability to reliably predict bowel penetration is still unclear.²¹ Accurate determination of this clinical feature is important for surgical management.

Excision of disease of the peritoneum overlying the rectum is straightforward and is not considered



within the context of deeply infiltrating endometriosis. There are three approaches to removing deeply infiltrating endometriosis of the rectum: rectal shaving (refers to excision of disease from the bowel without entering the lumen); discoid excision of the disease with primary closure of the rectal opening; and segmental resection. The choice of surgical approach is not clearly defined, but expert opinions have been published.⁴⁴ Generally, in severely symptomatic women with multiple deeply infiltrating skip lesions, deeply infiltrating lesions more than 3 cm, more than 40% of the circumference of the bowel involved, or depth of invasion into the inner muscularis layer, segmental bowel resection is recommended. In patients with a less than 3-cm nodule and no other criteria listed, a nodule resection only can be performed. In patients with a greater than 3-cm nodule and no other criteria listed, a shaving technique can be used. After resection, pain symptoms have been reported to improve by at least 70% with rate of pain symptoms recurrence ranging from 0% to 34%.⁴⁵ The complications of bowel resection for endometriosis occur in the short term, and these include anastomosis leak, pelvic abscess and fistula as well as bladder and bowel dysfunction and stricture. Long-term complications include a higher frequency of new bowel symptoms such as incomplete bowel movements or unreliable sensations of bowel urgency, but not a higher frequency of worse constipation or fecal incontinence.

Improvements in pain after rectal nodule excision, shaving, and segmental bowel resection appear similar. Consideration should be given to routine removal of a normal-appearing appendix during planned laparoscopic surgery for pelvic endometriosis. Pregnancy rates after excision (shaving technique) have been reported to be 65% at 3 years; 59% conceived spontaneously.⁴⁶ Most authors report similar pain, fertility, and quality-of-life outcomes of the shaving technique with segmental and discoid resection of the lesions; however, some authors report higher rates of symptom recurrence and reintervention with the shaving technique.

Urinary Tract Endometriosis

Like with gastrointestinal symptoms, urinary symptoms can occur even without direct bladder involvement. Clinical symptoms associated with urinary tract involvement are voiding dysfunction, dysuria, urgency, pain with a full bladder, and hematuria. Urodynamic testing demonstrates neurogenic dysfunction. Patients with direct bladder endometriosis more frequently report urinary symptoms, especially painful bladder filling and voiding dysfunction such as dysuria and frequency. Hematuria is infrequent.

Ureter involvement does not typically present with unique symptoms but is considered part of the pain syndrome. Rarely ureteral endometriosis can present with flank pain and hematuria. Most endometriosis of the urinary tract involves solely the peritoneum overlying the bladder or ureter in the pelvis. Deeply infiltrating endometriosis of the bladder involves the muscularis and rarely the submucosa and mucosa and can be diagnosed by transvaginal ultrasonography with variable sensitivity and specificity depending on the technique and experience of the ultrasonographer.

Deeply infiltrating endometriosis of the pelvic ureter can be diagnosed by pelvic or abdominal ultrasonography, which demonstrates a nodular lesion or dilated ureter. Medical treatment of bladder endometriosis can be attempted using combined oral contraceptives or GnRH agonist therapy. Surgical removal is indicated if symptoms persist despite treatment. Ureter involvement with endometriosis is typically from extrinsic compression with marked fibrosis of the muscularis of the ureter. Because of the severe fibrosis, which encases the ureter, medical treatment is unsuccessful and surgery will be necessary in these instances.

Hysterectomy

Hysterectomy is effective in treating women with severe pain associated with endometriosis.³⁹ Long-term follow-up reported a reoperation-free rate at 2, 5, and 7 years of 96%, 92%, and 92% in women with hysterectomy bilateral oophorectomy, respectively, and 96%, 87%, and 77% in women with hysterectomy alone, respectively. The risk of reoperation is 2.44 times higher with conservation of the ovaries. However, in a subgroup analysis of women younger than 40 years of age who underwent hysterectomy with excision of endometriosis but retention of normal ovaries, the risk of reoperation at 7 years was the same as in those patients with removal of normal ovaries. We recommend conservation of normal ovaries in women younger than 40 years of age. Ultimately the patient must choose between an increased risk of recurrence compared with surgical menopause.

ENDOMETRIOSIS IN THE INFERTILE PATIENT Surgical Considerations

Once regarded as a fundamental step in the evaluation and management of the infertile patient, diagnostic laparoscopy for possible endometriosis is now a more restricted procedure. In patients with stage I–II disease, four randomized controlled trials (RCTs) have shed light on the utility of this intervention.



Combined data from the two largest trials demonstrate an increased clinical pregnancy rate after excision or ablation of stage I–II endometriosis; however, the number needed to treat is approximately 40 if an endometriosis prevalence of 30% at the time of laparoscopy is assumed.⁴⁷ There are no RCTs to determine whether clinical pregnancy rates are improved after surgery in patients with stage III–IV disease. Observational studies indicate that surgical intervention results in a 30% pregnancy rate in women with an obliterated cul de sac and a 50–60% pregnancy rate in women after endometrioma excision.⁴⁸ Given these data, women with advanced disease can be counseled toward surgery to optimize fertility if they are young or have significant pain symptoms, large endometriomas, or constriction of the ureter or bowel. Potential benefits of surgery, especially endometrioma excision, must be considered against reductions in ovarian reserve as well as potential surgical risks. Multiple surgeries to improve fertility should not be attempted. Patients with advanced maternal age, low ovarian reserve, male factor, or a combination of these should consider immediate in vitro fertilization (IVF) rather than surgical intervention.

Fertility Treatments and Assisted Reproductive Technology

Women with known endometriosis are often prescribed a combination of oral or injectable fertility agents and intrauterine insemination. The utility of intrauterine insemination in patients with endometriosis is not documented and there is a single RCT to support its use.⁴⁹ Intrauterine insemination may not ameliorate the impairments in follicular development, oocyte competency, endometrial receptivity, and tubal function theorized to play a role in the subfertility of endometriosis. Treatment with intrauterine insemination may actually expose women with stage III–IV disease to a greater recurrence risk than those treated with IVF.

It is unclear whether treatment with GnRH agonists or excision of endometriomas and deeply infiltrating endometriosis improves clinical outcomes with assisted reproductive technology. Although a meta-analysis of three RCTs did demonstrate a positive OR of 4.28 (95% CI 2.00–9.15) for clinical pregnancy after 2–6 months of GnRH agonist pretreatment, more recent data have not shown a significant difference (Rodriguez-Tarrega E, Monzo A, Quiroga R, Romeu M, Polo P, Garcia-Gimeno T, et al. Randomized controlled trial to evaluate the usefulness of GnRH agonist versus placebo on the out-

come of IVF in infertile patients with endometriosis [abstract P-322]. *Hum Reprod* 2016;31(suppl 1)).

Endometrioma excision is similarly controversial. For small endometriomas, there is no evidence that excision is indicated because a small endometrioma will not compromise access to the ovary and spillage risk is minimal. Data from meta-analyses, including randomized controlled studies, suggest no difference in clinical pregnancy or livebirth rates when an endometrioma was excised before initiating an IVF cycle.⁵⁰

Although a prospective study reported higher implantation and pregnancy rates after laparoscopic excision of deeply infiltrating endometriosis, there are no RCTs comparing fertility outcomes after surgical excision of deeply infiltrating endometriosis with IVF. In patients with untreated colorectal endometriosis undergoing IVF, the cumulative pregnancy rates after one, two, and three cycles were 29%, 52%, and 68%, respectively.⁵¹ There is evidence that the presence of deeply infiltrating endometriosis has a negative effect on IVF outcome and excising the disease may improve outcome. However, excision must be balanced with the risks of surgery associated with excision of advanced endometriosis. There is a general consensus that IVF rather than surgery should be the first approach in women who are solely interested in fertility.⁴⁴

Fertility Preservation in Patients With Endometriosis

As awareness and methods for early detection of endometriosis improve, women with endometriosis may be increasingly identified as candidates for fertility preservation. Suggested techniques include oocyte and embryo cryopreservation as well as ovarian tissue freezing. Women who have the greatest potential risk are those who pursue recurrent surgical interventions and women with bilateral endometriomas. Despite growing interest in fertility preservation in this population, there are little data available regarding the cost-effectiveness or feasibility of such an approach.

CHRONIC PELVIC PAIN APPROACH

Not all pelvic pain is endometriosis, even if the disease is found at the time of laparoscopy. Patients may have chronic pain syndromes in the absence of endometriosis and, conversely, patients with endometriosis of all stages may or may not develop chronic pain.

Medical and surgical management is often incomplete in addressing the multiple contributors to



endometriosis symptoms. Endometriosis is recognized as a syndrome of chronic abdominopelvic pain (ie, pain lasting more than 6 months), and the necessity of a chronic care approach for optimal results is clear. Specialized centers with multidisciplinary care can combine medical and surgical interventions with pelvic physical therapy, pain management, biofeedback, nutrition, and psychologic support. Understanding central sensitization (ie, heightened activation of pain pathways within the central nervous system) and myofascial pain is integral to the chronic pain approach (Appendix 4, available online at <http://links.lww.com/AOG/B60>).¹⁰ The hallmarks of central sensitization are allodynia, hyperalgesia, and referred pain. When pain remains after maximizing medical and surgical treatments, it should prompt evaluation for central sensitization and myofascial pain.

Central sensitization follows peripheral nervous system activation. The mechanism of pain is thought to be inflammatory, neuropathic, and nociceptive. Although peripheral nociceptive input may remit with treatment, sensory nerve fibers from established lesions synapse in the sacral spine with central afferent neurons; their repetitive and protracted activation can propagate central sensitization that persists long beyond the initial stimulus.¹⁰ Structural and functional alterations to spinal cord neurons underlie tonic activation and also confer an exaggerated response to peripheral stimuli.

Myofascial pain, characterized by the presence of myofascial trigger points, can both arise from and further sustain centralized pain. Pelvic trigger points are tender, palpable contracted nodules in the musculoskeletal tissues of the pelvis. Typical symptoms are dyspareunia, dyschezia, and dysuria. A complete history, systematic pelvic examination, and detailed neuromuscular evaluation will identify the problem. Trigger points are amenable to pelvic physical therapy and trigger point injection, either with a dry needle or with injection of local anesthetic or botulinum toxin.¹⁰ Physical therapists specifically trained in the management of pelvic floor disorders are an integral part of the team. Opioids should not be prescribed because they are not feasible for long-term pain management and may in fact augment the central phenomenon. Instead, medical therapy that targets the central nervous system is preferred. Pain psychologists can also be useful in the long-term management of chronic endometriosis pain.

ASSOCIATIONS WITH MALIGNANCY

Although endometriosis is a benign disease, it bears many similarities to cancer. Even in nonmalignant

lesions, exome-wide sequencing reveals somatic mutations in cancer-promoting genes.⁵² Malignant transformation of endometriosis lesions is possible and there is consistent evidence that women with endometriosis have an increased risk of epithelial ovarian malignancy, mainly clear cell and endometrioid carcinomas. Furthermore, atypical endometriosis may represent a precursor lesion with characteristic features. Although women with endometriosis may have as high as a fourfold increased risk of developing epithelial ovarian cancer, this remains a tiny fraction of women with endometriosis.⁵³ Preventive screening is not currently recommended. It is uncertain whether ovarian cancer risk reduction is achieved with extended use of combined oral contraceptives, as is reported in the general population. Possible associations between endometriosis and endometrial and breast cancers are of uncertain validity.

MANAGEMENT OF THE POSTMENOPAUSAL WOMAN WITH ENDOMETRIOSIS

The main concerns in managing symptomatic menopausal women with a history of endometriosis are malignant transformation of endometriotic lesions and reactivation of the disease. The available data do not support delaying treatment with hormone replacement therapy in symptomatic women. Recurrence is low at 2.3%.⁵⁴ If a patient enters menopause spontaneously with her uterus in situ, she can be managed similar to other women with combined estrogen and progesterone treatment to prevent endometrial cancer. The same concepts apply to a patient with surgical menopause and an intact uterus; however, the duration of treatment may be longer if this occurs at a young age.

A controversial area is the management of the posthysterectomy young menopausal patient. Whether the menopause is spontaneous or surgical, these patients may require a longer duration of hormone therapy. The challenge is balancing the risk of malignant transformation of endometriotic residual foci with estrogen alone and the known association of increased risk of breast cancer with the use of long-term use of progestins. Although the risk of malignant transformation appears low, no high-quality data exist to advise patients with any degree of accuracy.⁵⁴ There are currently only 25 cases in the entire world literature in postmenopausal women with a history of endometriosis on hormone replacement. Discussion of therapy must take into account individualized breast cancer risk and family history.



DISCUSSION

Managing patients with endometriosis is a complex endeavor. Assembled here are the most up-to-date, evidence-based strategies for treating patients with pain, pelvic dysfunction, and subfertility related to their disease. As our appreciation of the molecular underpinnings of endometriosis deepens, we may better select noninvasive diagnostic strategies and new therapeutic targets and therefore avoid surgical morbidity and diminished ovarian reserve, which occurs with ovarian surgery. A key element in counseling patients is the necessity of prolonged suppressive therapy to avert undesirable recurrences and additional surgery. Special consideration should be given to the patient with chronic pain with increased recognition of the role of central sensitization, myofascial pain, and a multidisciplinary chronic pain approach. Despite a known increased small risk of epithelial ovarian cancer in patients with endometriosis, hormone therapy for symptomatic reproductive-aged women with postsurgical menopause is recommended.

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