Clinical Expert Series

CME

Comprehensive Review of Endometriosis Care

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Endometriosis is an estrogen-dependent, chronic inflammatory disorder characterized by the presence of endometrium-like tissue outside the uterus, affecting approximately 10% of individuals of reproductive age. It contributes to chronic pelvic pain, dysmenorrhea, and subfertility, resulting in substantial societal economic burdens. Genetic and environmental risk factors have been identified, and recent research suggests that endometriosis functions as a systemic disease affecting nonreproductive systems and increasing susceptibility to other health conditions. Various phenotypes—superficial peritoneal endometriosis, ovarian endometriomas, and deep endometriosis—may develop under different mechanisms, yet the relationship between these presentations remains unclear. Diagnosis relies on clinical evaluation, imaging, and surgical staging, and the advent of advanced ultrasonography and magnetic resonance imaging has helped to enhance accuracy. Although medical management focuses on hormonal modulation to alleviate symptoms, surgical intervention remains a critical tool for refractory symptoms. Postoperative care and patient education are essential to manage recurrence and to improve quality of life. Current research emphasizes the need for comprehensive, interdisciplinary approaches to endometriosis management, incorporating novel diagnostic tools, diverse therapeutic avenues, and patient-centered care models. Addressing disparities in treatment access is essential to improving outcomes. To achieve this, recruiting and analyzing data from racially, socioeconomically, and geographically diverse cohorts will reveal how disease presentation and treatment efficacy vary across populations. Continued efforts in research and health care policy are necessary to develop effective and personalized strategies in managing endometriosis.

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Endometriosis is a prevalent estrogen-dependent, chronic inflammatory condition characterized by endometrium-like tissue outside the uterus. The disease affects approximately 10% of reproductive-aged individuals with a uterus. It is disproportionately found among patients experiencing chronic pelvic pain (60%), dysmenorrhea (80%), and subfertility or infertility (up to 50%).[1] It can have consequences spanning from pregnancy morbidity to increased ovarian cancer risk. Endometriosis is associated with significant patient and societal costs, with an estimated $12,118 of direct costs and $15,737 of indirect costs per patient yearly in the United States.[2]

Risk factors for endometriosis include müllerian anomalies, in utero diethylstilbestrol exposure, low body mass index (BMI), and prolonged endogenous

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Table 1. Theories of Endometriosis Disease Pathogenesis

Theory	Description or Mechanism
Retrograde menstruation[16,17]	Menstrual dissemination into the peritoneal cavity with endometrial cell implantation on peritoneal or ovarian surfaces
Recurrent tissue injury and repair[16]	Heavy menstrual bleeding creates the presence of excess iron in the peritoneal cavity, thereby promoting oxidative stress, chronic inflammation, and local tissue destruction.
Endometrial stem cell recruitment[16,18]	Circulating endometrial progenitor or stem cells may shed into the pelvic cavity after birth or be trapped outside of the uterus.
Müllerian rest induction[16]	Primitive endometrial tissue may displace along the migratory pathway of fetal organogenesis (a process known as müllerianosis) and implant as endometriosis lesions.
Coelomic metaplasia[16]	Metaplasia represents the reversible transformation of 1 differentiated cell type to another differentiated cell type. Thus, cells from the coelom, or nascent body cavity, may differentiate into endometrium-like tissue within the peritoneal cavity.
Lymphatic or hematogenous spread[16]	Entry of endometrial cells into angiolymphatic circulation with extravasation from vessels in ectopic sites
Genetic–epigenetic changes[16]	Regardless of the original cell, a combination of genetic and epigenetic cellular incidents can create a heterogeneous environment of aromatase activity, progesterone resistance, angiogenesis, inflammation, immunologic changes, and bleeding.
Microbiome alteration[16,19]	The microbiome may influence immune-mediated chronic inflammation through bacterial contamination, production of estrogen through bacterial metabolism, epigenetic–genetic changes that promote dysbiosis, and promotion of neuroinflammation through the gut–brain axis.

estrogen exposure with early menarche, shorter menstrual cycle length, and low parity or nulliparity.[1] Endometriosis is increasingly characterized as a systemic disorder and can have effects on nonreproductive organs, hormonal metabolism, autoimmune disorders, and cardiovascular disease.[3–5]

Patients with an affected first-degree relative have a 7% likelihood of having endometriosis disease.[6] Although approximately 51% of the latent variation of endometriosis risk may be attributable to genetic factors,[7] fewer than 10% of underlying genes have been identified, likely because of the polygenic and multifactorial pattern of endometriosis inheritance.[8,9] Genetic studies have been limited by small sample sizes, poor reproducibility, and population differences (Appendix 1, available online at http://links.lww.com/AOG/E218).

PATHOPHYSIOLOGY

Hormonal, Inflammatory, and Neurobiological Mechanisms

Endometriosis is a chronic estrogen-dependent condition. Reduction of estrogen production or action can be effective in disease management. Endometriotic lesions resemble eutopic endometrium histologically, and eutopic dysfunction can disrupt ectopic progesterone and estrogen receptor activity and increase inflammation at ectopic sites. Despite some similarities, ectopic lesions are distinct entities with separate physiologic behaviors. Increased aromatase P450 activity within ectopic endometrial lesions leads to localized estrogen elevation, driving tissue growth, adhesion formation, and immune system imbalance within the pelvic cavity.[10] Ectopic lesions induce proinflammatory mediators (interleukin [IL]-1β, IL-6, IL-8, IL-17, tumor necrosis factor-α, cyclooxygenase-2); this impairs peritoneal macrophage and natural killer cell function, disrupts the inflammasome pathway, and elevates prostaglandin E2 production. This perpetuates inflammation and hinders effective hormonal regulation[11,12] (Fig. 1).

Endometriosis-Associated Pain

Endometriosis-associated pain can manifest in various clinical forms, including dysmenorrhea, cyclic and noncyclic pelvic pain, dyspareunia, dysuria, and dyschezia. Symptoms vary on the basis of disease location and organ involvement. Although some patients may be asymptomatic, others may experience episodic pelvic pain or constant pain across multiple areas. Pain severity has not been found to correlate with disease severity. As with other chronic pain conditions, fatigue, depression, and other comorbid chronic overlapping pain conditions are common, and optimization of each improves overall quality of life (Fig. 2). Rarely, extrapelvic disease may present in the abdominal wall, lymphatic system, sacral nerve roots, lung pleura, pericardium, and brain. Not all pelvic pain is attributable to endometriosis-associated pain, and other pain generators should be identified and treated independently.

Endometriosis-associated pain arises from a complex interplay of inflammation, abnormal nerve signaling, and changes within the peripheral and

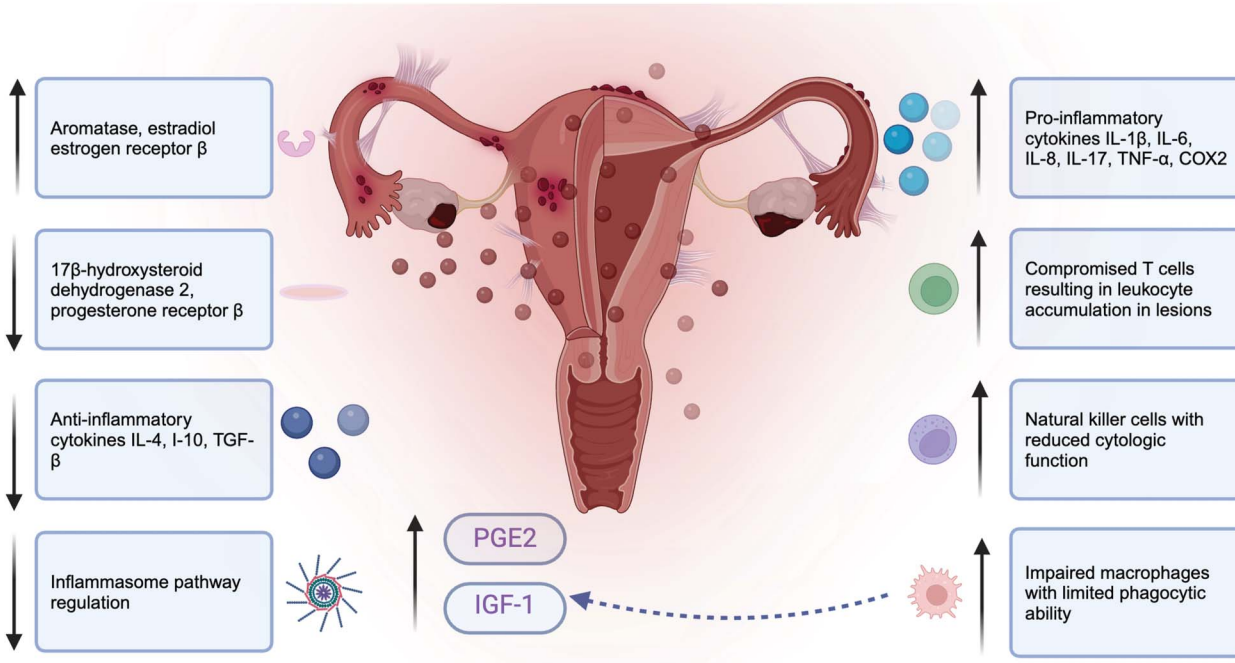

Fig. 1. Ectopic endometrial lesions release inflammatory mediators such as cytokines and prostaglandins that promote lesion survival, growth, and immune evasion while suppressing anti-inflammatory responses. This dysregulation fosters chronic inflammation, driven by impaired macrophages, natural killer cells, and T cells. Estrogen enhances proinflammatory factor secretion, and the dysfunction of the inflammasome pathway and the production of prostaglandin E2 (PGE2) further perpetuate inflammation, complicating hormonal regulation and disease progression. IL, interleukin; TNF-α, tumor necrosis factor-α; COX2, cyclooxygenase-2; TGF-β, transforming growth factor-β; IGF-1, insulin-like growth factor 1. Created in BioRenderhttps://BioRender.com/v76v855.
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central nervous systems. Endometriosis lesions initiate an inflammatory response that sensitizes adjacent nerves, resulting in altered pain perception. Elevated levels of insulin-like growth factor 1 produced by macrophages within endometriosis lesions act as a neurotrophic factor, enhancing nerve responsiveness and contributing to pain expression.[13] Patients may experience both somatic and visceral pain, with an increased likelihood of developing peripheral and central sensitization. Viscero-viscero and viscero-somatic convergence in sensory pathways contributes significantly to the onset of both acute and chronic visceral pain syndromes in endometriosis, increasing nociceptive neuron sensitivity and resulting in abnormal pain perception[14] (Fig. 3).

Endometriosis-Associated Infertility

The association between endometriosis and infertility is well known, although the exact cause–effect mechanism remains uncertain. Natural fecundity can decrease to 2–10% in couples with endometriosis.[15] Hypotheses proposed to explain endometriosis-associated infertility include distorted pelvic anatomy, cytokine-influenced sperm DNA damage and dysmotility, diminished ovarian reserve, and dysregulated ovulation, fertilization, and embryo implantation.[15]

DISEASE COURSE

Endometriosis Pathogenesis Across Phenotypes

Endometriosis is differentiated into three phenotypes: superficial peritoneal endometriosis, ovarian endometrioma disease, and deep endometriosis. Endometriosis phenotypes may change throughout an individual's lifespan; however, there is no strong evidence to confirm whether this is caused by disease progression, incomplete lesion excision, or disease recurrence.

Current theories of endometriosis pathogenesis include retrograde menstruation, recurrent tissue injury and repair, endometrial stem cell recruitment, müllerian rest induction, coelomic metaplasia, lymphatic or hematogenous spread, genetic or epigenetic changes, and microbiome alteration[16–19] (Table 1).

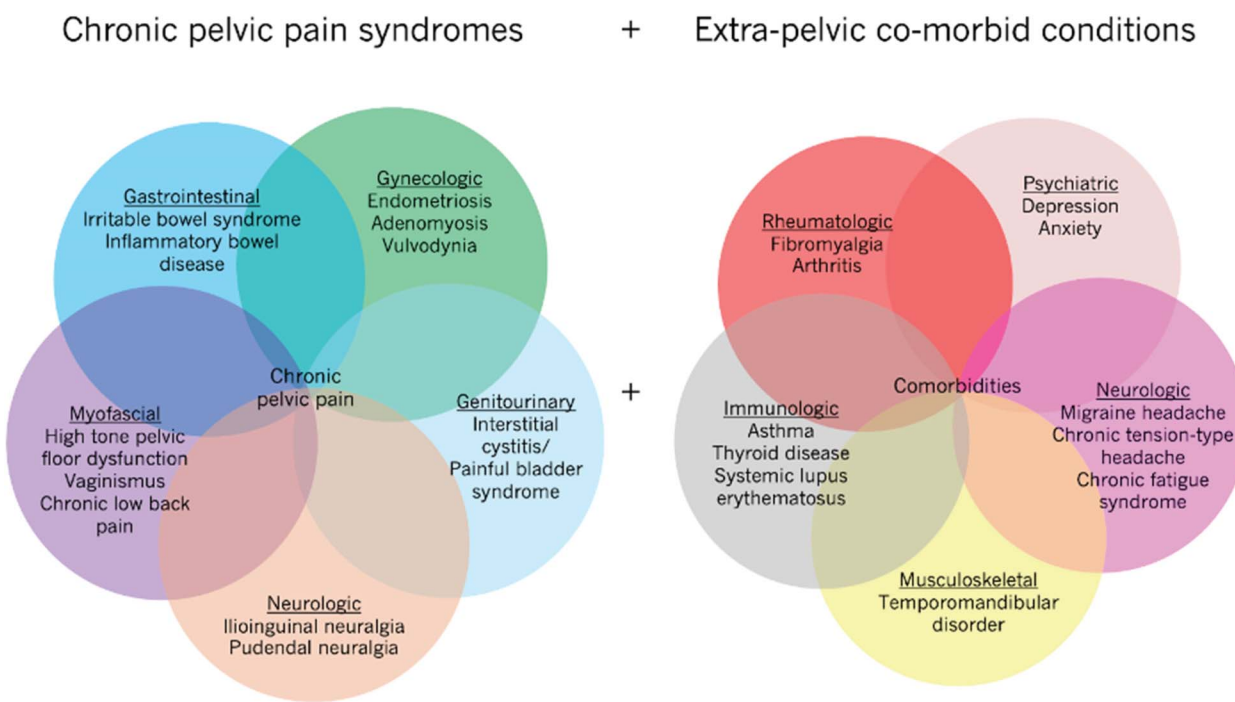

Fig. 2. Endometriosis and common comorbid overlapping conditions.
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The retrograde menstruation theory, originating from the Sampson[17] hypothesis, suggests that endometriosis results from peritoneal dissemination of menstrual effluent. However, this theory cannot account for the retroperitoneal smooth muscle hyperplasia commonly found with deep endometriosis. The endometrial stem cell recruitment theory may explain the pathogenesis of deep endometriosis and the origin of adolescent endometriosis, whereas müllerian rest induction may account for the presence of ectopic endometrial tissue along common sites of deep endometriosis.[18] Genetic–epigenetic theory can explain the variable phenotypic expressions of superficial peritoneal endometriosis, ovarian endometrioma, and deep endometriosis diseases; the heritability of endometriosis; and the clonality of ovarian endometrioma and deep endometriosis disease. It is likely that endometriosis pathogenesis involves multiple integrated models, with theories that are yet to be explored.[16]

Phenotypes

It remains unclear whether each of the 3 endometriosis phenotypes develops through different mechanisms or is a part of a continuous spectrum of disease presentation. Arguments favoring a progressive phenotype include the high correlation of all phenotypes together and the similar role that estrogen and progesterone receptors play in each.[20,21] However, progression from superficial peritoneal endometriosis to ovarian endometrioma or deep endometriosis disease has never been observed or demonstrated.

Deep endometriosis is defined as lesion invasion of more than 5-mm peritoneal depth. It is distinctly characterized by fibromuscular tissue invasion, oxidative stress, neuroangiogenesis, hormone-regulated bleeding, and smooth muscle metaplasia. Deep endometriosis is typically found in sites associated with the müllerian ducts during uterine embryogenesis, including the rectovaginal septum and the fibromuscular uterine ligaments.

Ovarian endometrioma disease shares some features with superficial peritoneal endometriosis. Endometrioma cells appear to implant superficially on the outside of the ovary rather than as a deep nidus of disease. Tissue along the inside of an endometrioma is also morphologically and functionally similar to superficial endometrium, with similar extracellular matrix enzymes and vascularization patterns.[18]

Microbiome Influence

The microbiome encompasses all the genetic material from microbes within the human body. It is believed to influence immune-mediated chronic inflammation through multiple mechanisms.[22] Microbial

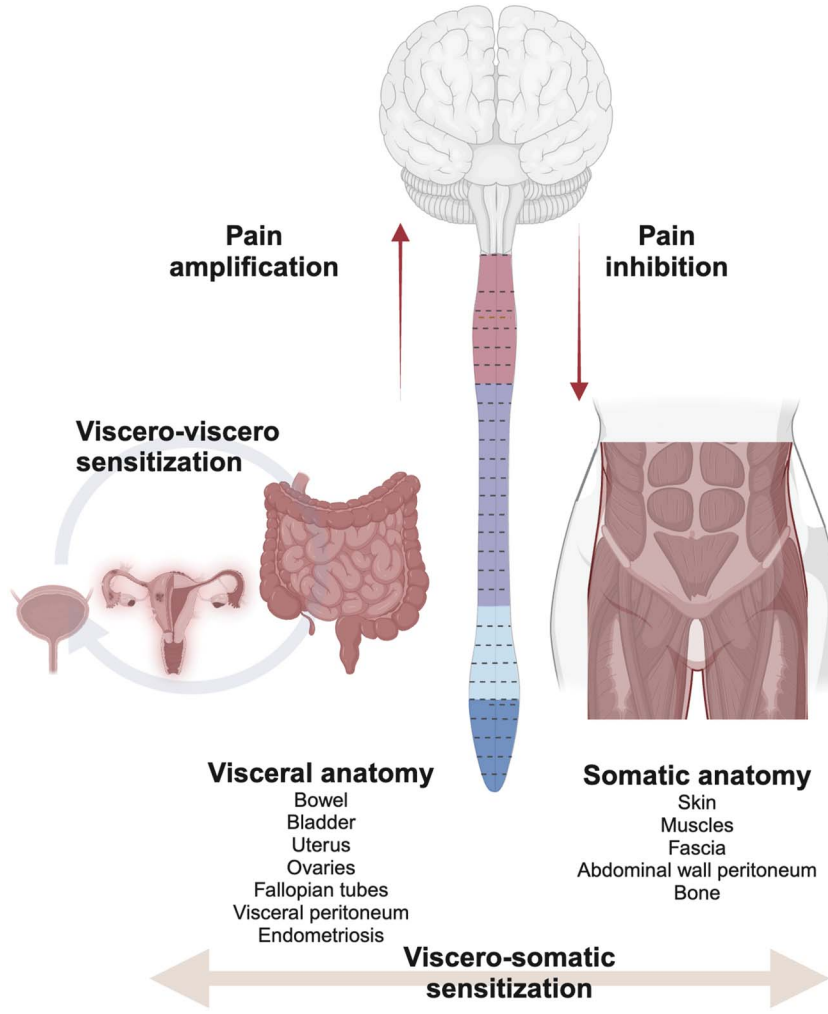

Fig. 3. *Viscero-viscero* refers to a reflex action in which a stimulus from one internal organ triggers a response in another, leading to pain or discomfort in one organ as a result of issues in an adjacent organ. Conversely, *viscero-somatic* describes a reflex whereby stimulation of an internal organ causes pain in the musculoskeletal system, suggesting that discomfort from an organ can be referred to specific areas of the body such as the peritoneum, muscles, or skin. Created in BioRenderhttps://BioRender.com/a35q975.
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contamination of menstrual effluent may introduce bacterial endotoxin or lipopolysaccharide into the peritoneal cavity.[23] This may explain the higher Escherichia coli colony counts of patients with endometriosis[24] and the threefold greater risk of endometriosis among patients with a history of pelvic inflammatory disease.[25] Endometriosis microbiome research, however, remains limited by geographic and ethnic variation, control definition, and multiple confounders.

DIAGNOSIS

History and Examination

A comprehensive history and clinical examination remain key diagnostic tools for patients with suspected endometriosis. An abdominal examination identifies tenderness, abdominopelvic masses, and prior surgical incisions. A pelvic examination with single-digit palpation of the levator ani and obturator internus muscles can identify high-tone pelvic floor dysfunction or tender points, indicating a need for targeted pelvic floor myofascial therapy. A bimanual examination assesses the size, shape, flexion, and mobility of the uterus and identifies adnexal masses. A speculum examination may reveal vaginal endometriosis lesions, and a rectovaginal examination aids in assessing the rectovaginal septum and uterosacral ligaments.

Surgical Staging

Traditional disease staging is performed at the time of surgery. Twenty-two endometriosis staging classifications have been described since 1973.[26] The revised American Society of Reproductive Medicine staging system is widely used, assigning scores to differentiate minimal-to-mild disease (stage I and II) from moderate-to-severe disease (stage III–IV).[27] Limitations of the revised American Society of Reproductive Medicine staging include an emphasis on

adnexal disease and an inability to predict quality-of-life indicators. Endometriosis Fertility Index staging is useful for predicting fertility outcomes from surgical findings,[28] whereas Enzian classification provides information on deep disease.[29] The AAGL classification system enhances the description of surgical complexity but does not predict fertility outcomes.[30] Although disease stage does not correlate with symptom severity, it can inform fertility outcomes through the Endometriosis Fertility Index and describe disease severity through the Enzian and AAGL systems. Nonetheless, an ideal classification that encompasses surgical complexity, pain, fertility outcomes, and the presence of adenomyosis and extrapelvic disease remains to be developed.[26]

Imaging

Imaging has a critical role in disease identification. Although a recent Cochrane review concluded that no imaging modality could replace the diagnostic role of surgery,[31] imaging has been increasingly relied on for diagnosis, preoperative planning, and deep endometriosis disease characterization.

Pelvic ultrasonography remains the preferred imaging modality for patients with clinically suspected endometriosis because of its availability, low cost, and ability to identify other causes of pain. Although ultrasonography has the highest sensitivity and specificity for identifying ovarian endometrioma disease, detection of superficial peritoneal endometriosis and deep endometriosis can be challenging and requires time, expertise, and a dedicated team. Without an explicit endometriosis protocol, ultrasonography results can be cursory and misleading. The International Deep Endometriosis Analysis consensus outlines steps needed for advanced ultrasonography to investigate endometriosis, with good sensitivity and high specificity for localizing deep endometriosis.[32]

The uterine sliding sign is a maneuver to aid ultrasound evaluation of deep endometriosis. Pressure from a transvaginal ultrasound probe is applied to the cervix to assess whether the anterior rectum can easily move across the adjacent vagina. This augmented ultrasonography requires no specialized expertise, adds approximately 5 minutes to routine ultrasonography, and generates additional information about the presence of deep endometriosis disease and rectovaginal adhesions.[33]

Magnetic resonance imaging (MRI) is invaluable for evaluating disease phenotype, burden, and anatomic distribution, particularly when ultrasound results are ambiguous. It is also beneficial in assessing extrapelvic endometriosis. Proper patient preparation and a dedicated imaging protocol are key; techniques such as partial bladder distension, vaginal distension with ultrasound gel, and use of antiperistaltic agents such as glucagon or hyoscine butylbromide can aid disease detection.[34] Although the use of positron emission tomography with ^{18}F-fluoroestradiol tracers has been explored, it currently cannot reliably detect endometriosis lesions.

High-volume endometriosis centers have demonstrated similar diagnostic accuracy of ultrasonography and MRI.[35] The performance of any imaging technique for endometriosis is operator dependent, with accuracy improving along with increased training, exposure, and patient volume.

Endometriosis Biomarkers

For an endometriosis biomarker to replace surgery as the gold standard diagnostic tool, it must achieve at least a 94% sensitivity and 79% specificity.[36] Despite extensive research on blood and serum, salivary, and endometrial sites, no current biomarker reliably meets these diagnostic criteria[36] (Appendix 2, available online at http://links.lww.com/AOG/E218). Although some biomarkers have been brought to market, validation remains a key step before commercialization, a milestone many fail to reach. Clinicians should take care to balance commercial and patient pressures with the uncertain outcomes of currently available tests to limit inappropriate clinical conclusions and to prevent unnecessary cost and resource strain.

MEDICAL TREATMENT

Empiric treatment for suspected endometriosis-associated pain remains the primary recommendation among experts worldwide, although a patient's response or lack of response to medical therapy does not definitively confirm or refute a diagnosis of endometriosis.

Hormonal Medical Treatment

When tolerated, hormonal medical therapy is highly effective in pain management for all subtypes of endometriotic disease. Hormonal medical therapy cannot, however, be used for patients actively seeking fertility. In the United States, the U.S. Food and Drug Administration has approved several therapies for managing endometriosis-associated pain[37] (Table 2).

Combined hormonal contraceptives (CHCs) are first-line treatment to achieve ovulation suppression in patients with suspected endometriosis, given their high tolerability and low risk profile.[38] Approximately 30% of patients, however, report no improvement in

Table 2. Hormone Modulation of Endometriosis

Drug Class	Mode of Administration	Dose	Length of Treatment	Mechanism of Action	Side Effects	Monitoring Required
CHC	Oral, patch, vaginal ring	Cyclic or continuous	Long term	Ovarian suppression, endometrial decidualization or atrophy of lesions	Breakthrough bleeding, breast tenderness, headaches, nausea, mood changes	None
Progestins	Oral SC or IM injection IUS Implant	Norethindrone acetate: 5–15 mg orally daily* Drospirenone: 4 mg orally daily Dienogest: 2 mg orally daily† MPA: 30 mg orally for 6 mo, then 100 mg IM every 22 wk for 2 mo, then 200 mg IM monthly for 4 mo DMPA: 104 mg SC every 3 mo* Levonorgestrel-releasing IUS: every 5 y (approximately 20–micrograms/d release, decreasing over time; may require earlier replacement) Etonogestrel-releasing implant: every 3 y	Long term	Endometrial decidualization or atrophy of lesions, some ovarian suppression (systemic), angiogenesis inhibition	Acne, breakthrough bleeding, breast tenderness, headaches, nausea, mood changes, weight gain, lipid abnormalities, loss of bone density (especially with higher doses and longer durations, particularly with MPA)	Lipid levels (higher doses and longer durations), bone density (long-term use of MPA)
GnRH agonists	SC or IM injection Intranasal	Leuprolide depot: 3.75 mg IM every 1 mo or 11.25 mg IM every 3 mo* Goserelin: 3.6 mg SC every month or 10.8 mg IM every 3 mo* Nafarelin: 200 micrograms intranasally twice daily*	6 mo or less (with add-back, longer durations possible)	Ovarian suppression	Mood changes, vasomotor symptoms, decreased libido, vaginal dryness, loss of bone density. Add-back therapy (eg, norethindrone acetate) can mitigate some side effects	Bone density with prolonged use

(*continued*)

Table 2. Hormone Modulation of Endometriosis (*continued*)

Drug Class	Mode of Administration	Dose	Length of Treatment	Mechanism of Action	Side Effects	Monitoring Required
GnRH antagonists	Oral	Elagolix: 150 mg orally daily or 200 mg orally twice daily* Relugolix: 40 mg/ estradiol 1 mg/ norethindrone acetate 0.5 mg daily*	24 mo or less 6 mo or less 24 mo or less	Ovarian suppression	Mood changes, vasomotor symptoms, decreased libido, lipid abnormalities, loss of bone density, sleep disturbance	None specified (monitor for general health and hypoestrogenic changes)
Aromatase inhibitors	Oral	Letrozole: 2.5 mg orally daily Anastrozole: 1 mg orally daily	6 mo or less (with add-back, longer durations possible)	Block aromatase, limiting androgen conversion to estrogen	Mood changes, vasomotor symptoms, vaginal dryness, headaches, loss of bone density, may require CHC or progestin use to prevent follicular ovarian cysts formation	Bone density with prolonged use
Androgens	Oral Vaginal	Danazol: 100–400 mg orally twice daily or 100 mg vaginally daily*	6 mo or less	Ovarian suppression, decrease in estrogenic steroids	Undesirable androgenic side effects (acne, hirsutism, hair loss, weight gain, mood changes, voice changes, lipid abnormalities), often limiting use	None specified
Antiandrogens	Oral	Cyproterone acetate: 12.5 mg orally daily†	Varies	Competitively inhibits the androgen receptor	Hair loss, breast tenderness, weight gain, meningioma (prolonged use)	None specified
Selective progesterone receptor modulators	Oral	Mifepristone: 50 mg orally daily† Ulipristal acetate: 15 mg orally every other day†	6 mo or less 3 mo or less	Ovarian suppression, agonistic and antagonistic effect at receptor (drug dependent)	Breakthrough bleeding, dizziness, headaches, nausea, liver toxicity	Liver function tests

CHC, combined hormonal contraceptive; SC, subcutaneous; IM, intramuscular; IUS, intrauterine system; MPA, medroxyprogesterone acetate; DMPA, depot medroxyprogesterone acetate; GnRH, gonadotropin-releasing hormone.
* U.S. Food and Drug Administration–approved.[37]
† Available as monotherapy outside the United States.

pelvic pain with CHC use.[39] No route of administration (oral, transdermal, vaginal) has proved more effective.[38] Patients additionally seeking menstrual suppression may use CHCs continuously rather than cyclically.[38,39] Breakthrough bleeding is common but often manageable by temporarily pausing treatment, typically resuming use within 7 days.

Progesterone analog use is preferred for patients older than 35 years of age with tobacco use or risk factors for myocardial infarction, stroke, or venous

thromboembolism (VTE). Although progestins have historically been considered safer for patients at risk for VTE, much of this information derives from early studies on lower-dose progestins used for contraception. Lower-dose progestins (levonorgestrel intrauterine system, norethindrone, etonogestrel subcutaneous contraceptive implant, oral micronized progesterone) do not increase VTE risk, whereas higher-dose systemic progestins (medroxyprogesterone acetate, norethindrone acetate, and depot medroxyprogesterone acetate) can triple the odds of VTE.[40] Progestin monotherapy is considered first-line medical treatment among some endometriosis experts because progestins inhibit cell proliferation, inflammation, neovascularization, and neurogenesis. Disruptions in progesterone receptor expression, however, can lead to "progesterone resistance" at ectopic sites and varied progestin effectiveness.[41] Limited comparative data have not demonstrated any clear superiority among progestins.[42] The levonorgestrel-releasing intrauterine system is effective for endometriosis-associated pain, but the 20–micrograms/d release decreases over time and may require earlier replacement for symptom control.[43] Breakthrough bleeding is common with systemic medications and may resolve with the intermittent addition of oral estrogen for 7–14 days.

Gonadotropin-releasing hormone (GnRH) is physiologically released in an estrogen-dependent pulsatile fashion. The GnRH agonists cause continuous GnRH release, suppressing luteinizing hormone and follicle-stimulating hormone and inducing hypoestrogenism. The GnRH agonists are not considered first-line treatments because of their higher cost and considerable side effects. The addition of add-back hormone therapy (HT; eg, with norethindrone acetate 5 mg daily) has been found to limit bone mineral density loss without compromising endometriosis treatment efficacy. The GnRH agonists improve endometriosis-associated pain by 50–90% regardless of add-back HT, although the duration of use remains limited to no more than 6 months given the risk of irreversible bone mineral density loss. The GnRH antagonists partially suppress estradiol, lessening hypoestrogenic side effects while achieving an efficacy similar to that of GnRH agonists.[44] Regardless of hormonal add-back therapy, use is limited to up to 24 months.

Aromatase inhibitors target aromatase, a key enzyme in estrogen biosynthesis within endometriosis lesions. Although data suggest symptom improvement with aromatase inhibitor use, current guidelines recommend use only for refractory endometriosis along with other medications because of its side-effect profile.[45]

Two systematic reviews compared medical treatments for endometriosis-associated pain. The first noted that dysmenorrhea was best relieved at 3 months with GnRH agonists alone (likely because of induced amenorrhea); at 6 months, GnRH agonists plus CHCs were most effective.[46] Dyspareunia was best treated by CHCs alone at 3 months, but adding aromatase inhibitors improved 6-month outcomes. For overall pelvic pain, CHCs worked best at 3 months, and progestins plus aromatase inhibitors worked best at 6 months.[46] The second systematic review and meta-analysis noted that CHCs and progestins are equally effective for endometriosis symptom management, including pain and psychological well-being.[47]

Phenotype-directed medical therapy focuses management on the specific disease phenotype. A systematic review and meta-analysis indicated that dienogest, CHCs, or norethindrone acetate with aromatase inhibitor use can lead to ovarian endometrioma size reduction at 24 weeks.[48] Conservative medical treatment of colorectal deep endometriosis can provide symptom relief provided that there is no significant luminal narrowing.[49] Hormonal suppression of deep endometriosis can reduce the risk of disease progression.[49]

Nonhormonal Medical Treatment

Patient education is central to managing endometriosis-associated pain. Endometriosis often coexists with anxiety, depression, and sexual dysfunction; thus, partnership with mental health professionals is necessary to enhance quality-of-life outcomes. A 2023 systematic review found that psychologic interventions, including cognitive–behavioral therapy, mindfulness, and yoga, improved pain levels and overall well-being.[50] Acupuncture and related therapies are generally safe and well tolerated and reduce dysmenorrhea symptoms. As with other endometriosis therapies, benefits are not sustained beyond the active treatment period.

Physical activity and regular exercise are mainstays of chronic disease management. Although a systematic review and meta-analysis of the effect of physical activity and exercise on endometriosis-associated symptoms was inconclusive,[51] physical therapy has been shown to improve pain intensity and overall physical function for patients with endometriosis.

Natural therapies for endometriosis, including herbal extracts, plant-based compounds, and traditional Chinese medicine, have shown promise in preclinical studies because of their antiproliferative,

anti-inflammatory, and antioxidant effects. Low-fat, high-fiber diets have been associated with reduced circulating estrogen.[52] Dietary interventions tend to have positive effects on endometriosis symptoms,[53] although specific diets such as gluten-free or low fermentable oligosaccharides, disaccharides, monosaccharides, and polyols lack evidence for endometriosis benefit alone. The combined use of vitamin C and vitamin E can reduce endometriosis-associated pain, and N-acetylcysteine, a potent antioxidant, has been shown to reduce endometrioma size and to provide analgesia. These therapies are safe to use in patients trying to conceive.

SURGICAL TREATMENT

Surgery for endometriosis-associated pain may be effective, although the necessity and benefit can vary according to a patient's age, symptoms, fertility goals, ovarian reserve, and surgical history.[54] Surgery can be considered for patients who have not responded to or are intolerant of medical therapies.[55] However, decision making is complex for those seeking to optimize fertility or for whom infertility is the sole symptom.

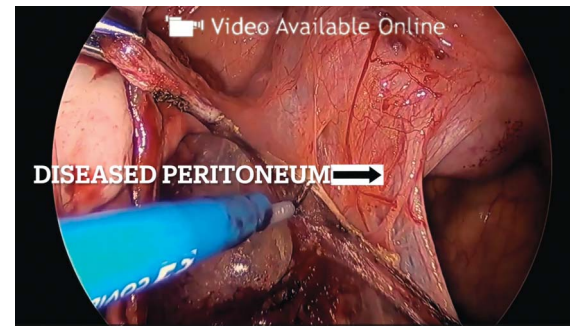
Identification of disease at time of surgery is critical and heavily dependent on surgeon experience. Newer operative modalities, including near-infrared imaging combined with indocyanine green dye, have shown minimal improvement in disease detection.[56]

A minimally invasive approach with either traditional or robot-assisted laparoscopy is now standard of care.[57] Although robotics offers superior visual optics over conventional laparoscopy, superior outcomes have not been demonstrated.[58,59] Surgeon training, experience, and patient preference should dictate the ultimate route of surgery.

Fertility preservation options should be discussed preoperatively, particularly in the setting of risk factors for ovarian insufficiency, including large or bilateral ovarian disease, advanced age, and low ovarian reserve. Techniques for preservation include oocyte, embryo, and ovarian tissue freezing, although additional data are needed to understand cost-effectiveness and optimal patient selection.

Superficial Peritoneal Endometriosis

Superficial peritoneal endometriosis can be treated through electrosurgical ablation or excision with peritonectomy (Video 1). Although no significant differences in outcomes have been noted between methods, larger studies are needed.[60] Ablation near vital structures should be avoided because of injury risk. Excision may improve pain outcomes, but its effects on fertility are complex. A 2014 Cochrane review found that although pregnancy rates increased after surgery for stage I–II disease, the high number needed to treat favored fertility treatments over initial surgical management.[61]



Video 1. Approach to minimal stage endometriosis. Pelvic peritoneal stripping demonstrated for excision of diseased peritoneum in a case of stage I endometriosis. Video created by Dr. Zaraq Khan. Used with permission.

Scan this image to view Video 1 on your smartphone.

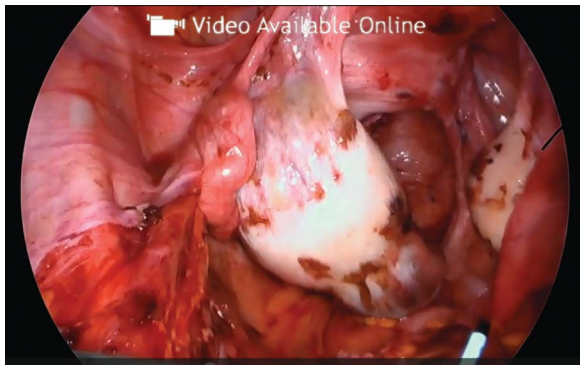
Ovarian Endometrioma

Decision making for ovarian endometrioma surgery is multifaceted, influenced by patients' fertility goals, age, ovarian reserve, endometrioma size and number, and fertility and surgical history. Surgery can be considered before fertility treatments to alleviate pain or to improve access to follicles for oocyte retrieval.

However, preoperative discussion is essential because ovarian surgery is linked to lower serum anti-müllerian hormone levels, although recovery can occur long term. Ovarian cortical tissue preservation and the use of hemostatic agents and suturing rather than electrosurgery is ideal.

Ovarian endometrioma can be surgically treated through 1) cyst excision, 2) drainage and ablation, or 3) sclerotherapy. Cyst excision reduces pain and lowers recurrence risk, with only 3–16% of patients requiring further surgery compared with 32% after drainage and ablation. Ovarian endometrioma excision does not, however, significantly change the rate of spontaneous pregnancy in the first year after surgery (Video 2). Although cyst ablation causes less

damage to ovarian reserve, this is offset by higher recurrence rates and minimal pain relief. Ultrasound-guided ovarian endometrioma sclerotherapy shows minimal effect on ovarian reserve, but more data are needed to support routine use.



Video 2. Approach to ovarian endometrioma with cystectomy. The video demonstrates ovarian cystectomy technique for an endometrioma. Correlation between magnetic resonance imaging and intraoperative disease findings are highlighted. Video created by Dr. Zaraq Khan. Used with permission.

Scan this image to view Video 2 on your smartphone.

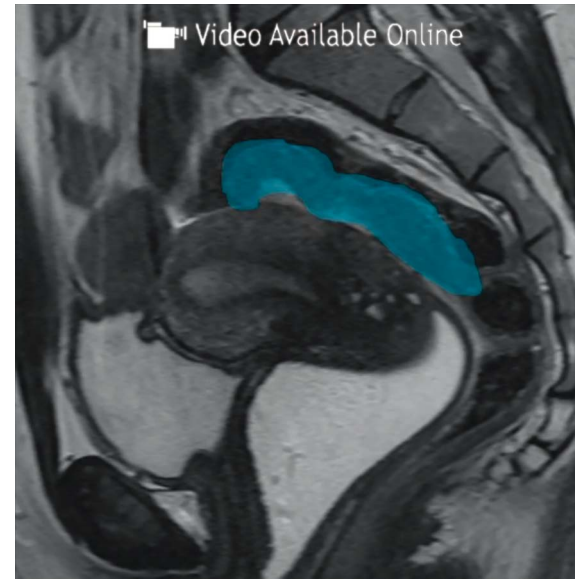
Deep Endometriosis

Patients with deep endometriosis often present with pain and fertility concerns, making surgical management challenging and requiring specialized expertise. Although surgical excision of deep endometriosis may be effective for pain,[54] the reproductive benefits remain unclear.[55]

Colorectal Disease

Up to 12% of patients with endometriosis have colorectal disease. Rectal and sigmoid colon endometriosis are most common, although disease can also involve the appendix, cecum, ileocecal valve, and small bowel. Symptoms include dyschezia, constipation, bloating, and diarrhea.[62] Because of the vague nature of these symptoms, advanced imaging can aid diagnosis. Colorectal endometriosis rarely invades the bowel mucosa, making endoscopic imaging (colonoscopy or sigmoidoscopy) largely unhelpful.

Limited data support colorectal disease resection for patients who seek only fertility optimization. Surgical excision of colonic disease is achieved by rectal shaving, discoid resection, and segmental resection (Video 3). Segmental resection is reserved for lesions 3 cm or larger, skip lesions, or more than 40% bowel circumference involvement. Notable perioperative risks include anastomotic leak, fistula, and long-term bowel dysfunction, with frequency increasing with the invasiveness of the excision. Although the involvement of a colorectal surgeon is at the discretion of the endometriosis specialist, it should be considered in advanced cases requiring bowel resection.



Video 3. Approach to bowel endometriosis. The video highlights a segmental excision with primary end-to-end anastomosis for deep endometriosis of the rectosigmoid. Video created by Dr. Zaraq Khan. Used with permission.

Scan this image to view Video 3 on your smartphone.

Urinary Tract Disease

Urinary tract endometriosis occurs in 1–6% of patients. It affects primarily the bladder (70–85%),

ureters (9–23%), and kidneys (4%).[63] Detailed imaging is necessary for accurate diagnosis. Symptoms vary by location: bladder disease may cause urgency, frequency, and pain; ureteric disease is often asymptomatic but can present with flank pain and hydronephrosis. Hematuria is rare with bladder and ureteral disease but may be the only symptom in renal disease. Treatment may be required to prevent obstructive uropathy and permanent renal injury. Although surgery can reduce pain, its effect on fertility remains unclear.

Tubal Disease

Endometriosis disease often affects the fallopian tubes, causing fibrotic fimbriae, tubal blockage, and hydrosalpinx formation. The presence of a hydrosalpinx is associated with lower embryo implantation and pregnancy rates, and current guidelines recommend hydrosalpinx treatment for patients seeking fertility.[64] Although a salpingostomy may be considered for a mild hydrosalpinx in a patient desiring to become pregnant naturally, ectopic rates can reach 10%.[64] Salpingectomy is preferred for optimal disease excision and assisted reproductive technology outcomes.

Extrapelvic Endometriosis

Extrapelvic disease, although rare, can be frequently encountered in high-volume centers. Surgical excision of extrapelvic deep endometriosis can provide symptom relief, with uncertain effects on fertility (Appendix 3, available online at http://links.lww.com/AOG/E218).

Role of Oophorectomy and Hysterectomy

The roles of oophorectomy and hysterectomy in endometriosis management are often misunderstood. Bilateral oophorectomy is nearly curative for endometriosis but can have significant long-term health consequences in premenopausal women. Removal of ovaries before 45 years of age should occur only after other options have failed,[65] and HT should be considered after bilateral oophorectomy.

Although hysterectomy is not a cure, it may lead to long-term pain improvement. It can be considered for patients with adenomyosis, those who have significant dysmenorrhea, and those with breakthrough bleeding despite medical suppression. A total hysterectomy with removal of the cervix is preferred over a supracervical hysterectomy because of a lower risk of persistent pain.[55] Although hysterectomy with bilateral salpingo-oophorectomy lowers reoperation rates (5% vs 13%), persistent pain rates are similar, indicating that ovarian status does not affect long-term endometriosis-associated pain.[66] In addition, hysterectomy alone with ovarian conservation is still associated with increased risks of cardiovascular events, some cancers, additional surgeries, premature ovarian failure or menopause, depression, and other adverse outcomes, particularly for those younger than 35 years of age.[67]

POSTOPERATIVE CONSIDERATIONS

Recurrence Prevention and Hormonal Suppression

Medical and surgical interventions aim to suppress disease, treat symptoms, and prolong symptom-free intervals. Surgery can alleviate symptoms, restore normal anatomy, and enhance fertility outcomes.[54,55] However, postsurgery recurrence rates are significant, with reoperation rates for ovarian-sparing surgeries ranging up to 58%.[68,69] For patients not seeking immediate conception, postoperative HT may reduce recurrence and repeat surgeries.[70] A recent trial found a 40% reduction in pain 3 years after conservative surgery with long-acting progestins or CHCs, with those on long-acting progestins 33% less likely to experience treatment failure.[71] Most experts advocate for long-term postoperative hormonal suppression.

Postsurgical Fertility Care

Spontaneous pregnancy rates can reach 22% after complete disease resection.[72] However, patients with advanced disease often require fertility assistance. Those who are older or have low ovarian reserve, low Endometriosis Fertility Index, compromised tubal function, or significant male factor infertility should be referred to fertility specialists for assisted reproductive technology.

Endometriosis-Related Antepartum and Postpartum Complications

Although some endometriosis lesions regress during pregnancy,[73] endometriosis-associated obstetric complications stem from defective decidualization and placentation, abnormal progesterone signaling, and spiral arteriole remodeling.[74] Patients with endometriosis face a higher risk of pregnancy loss because of immunologic dysregulation and impaired endometrial decidualization,[75] as well as increased rates of ectopic pregnancy linked to altered tubal motility and adhesions.[76] They are also at heightened risk of hypertensive disorders, abnormal placentation, preterm premature rupture of membranes, preterm labor, cesarean delivery, and thromboembolic events.[73–75] These findings challenge the notion that pregnancy

suppresses endometriosis and highlights counseling needs during pregnancy and postpartum.

SPECIAL POPULATIONS

Adolescent Disease

Adolescents with endometriosis typically present with cyclic pain and school absenteeism, along with common symptoms such as dysmenorrhea, dyspareunia, dyschezia, and nausea-associated chronic pelvic pain. A detailed history should include a family history and any obstructive genital malformations. Imaging with transabdominal or transperineal ultrasonography or MRI is preferred over examinations. First-line treatment for pain is medical suppression of ovarian function with CHCs or progestins. Laparoscopy may be considered for those unresponsive to medical treatment, with biopsies obtained. Postoperative use of hormonal suppression is crucial because symptom recurrence is high without ongoing suppression. There is no evidence that early surgical intervention prevents disease progression or improves future fertility outcomes.

Postmenopausal Disease

Women with endometriosis are at risk of early menopause.[77] Use of HT in early menopause reduces cardiovascular disease risk and promotes bone health.[78]

Postmenopausal recurrence can be as high as 5%, likely as a result of adipose tissue estrogen production and local lesion aromatase activity,[79] and is associated with peritoneal involvement more than 3 cm and uterine conservation.[80] Limited data on postmenopausal pain and disease recurrence should not deter clinicians from prescribing HT.

A key question is whether to prescribe combination or estrogen-only HT to patients who have undergone hysterectomy. Retrospective studies indicate that estrogen-only HT may have similar or higher disease recurrence risk compared with combined HT.[81] Among postmenopausal patients with endometriosis who experienced malignant transformation, approximately 75% of HT users were using estrogen-only HT. Consensus statements by the European Society of Human Reproduction and Embryology and the European Menopause and Andropause Society recommend combined HT for menopausal symptom management, yet no high-quality evidence shows that the addition of progesterone to HT decreases the risks of disease recurrence or malignant transformation.[55,82]

Malignant Transformation

Endometriosis is classified as a benign condition, yet patients with endometriosis face a significantly increased risk of ovarian cancer, particularly ovarian clear cell and endometrioid carcinomas.[83] Risk factors for endometriosis-associated ovarian cancer include genetic predispositions, high-estrogen states, and environmental influences.[83] Endometriosis-associated ovarian cancers may arise from endometriosis caused by somatic mutations in cancer-promoting genes linked to the phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin pathway, although the mechanism of progression to ovarian cancer remains unclear.[84]

A large population-based study found that women with endometriosis had a 4.20 times greater likelihood of developing ovarian cancer. The risk varied by endometriosis subtype, with deep endometriosis or ovarian endometrioma disease carrying a 9.66-fold increased risk and superficial peritoneal endometriosis disease a 2.82-fold increased risk of all ovarian cancers.[85] There are no established guidelines for ovarian cancer screening in patients with active endometriosis or history of disease, and risk reduction interventions remain unexplored. Clarifying research is needed to understand the link between endometriosis and cancer and to improve screening and prevention strategies for this higher-risk population.

ADDRESSING DISPARITIES AND BARRIERS IN CARE

Racial disparities affect the entire spectrum of endometriosis care. A 2019 meta-analysis found that Black women were less likely, Asian women were more likely, and Hispanic women were similarly likely to be diagnosed with endometriosis compared with White women. Asian women may also present with more severe disease.[86] The average diagnosis of endometriosis is delayed by 7–12 years from symptom onset, heavily influenced by access to surgical care and clinician bias. There are no reliable data on any racial differences in endometriosis incidence, suggesting that disparities in diagnosis are attributable to bias and confounding factors.[87] Significant differences in treatments between White and Black patients have further been demonstrated. Non-White women also have higher odds of perioperative complications and open surgical approaches, with Black women three times more likely to have an oophorectomy in their 20s.[87] Socioeconomic and insurance disparities deeply affect endometriosis care, with more educated patients having higher diagnosis rates. Scant research exists on the experiences of transgender men with endometriosis. Transgender men may have a higher prevalence of endometriosis disease than cis-gender women despite testosterone use, highlighting the need for ongoing

research.[88] Systemic changes in endometriosis health care policy, education, and programming are needed to address these disparities.

FUTURE DIRECTIONS

Electronic medical records are emerging as valuable longitudinal data sources for endometriosis phenotyping and prediction. Artificial intelligence models have shown strong capabilities in diagnosis, and machine learning model platforms have been developed to predict disease using patient-reported symptoms or comorbidities.[89–91] Telehealth offers valuable support for patients and clinicians by promoting access to care and facilitating interdisciplinary consultations, especially for geographically remote and financially insecure patients.[92]

Immunomodulator use (including anti–tumor necrosis factor-α agents, kinase inhibitors, and cytokine therapies) has been explored; however, current use is limited by side effects and insufficient data.[93] Novel hormonal agents continue to be developed, including new GnRH antagonists.[94] Dopamine agonists, selective estrogen receptor modulators, and selective progesterone receptor modulators all represent therapeutic targets.[95]

Patient perceptions of medical care influence quality of life, treatment compliance, and coping ability.[96] Only 55% of patients with endometriosis report satisfaction with their medical support.[97] Patient-centered care is essential for effective communication and physician integration into treatment. The goal should be to prioritize patient autonomy, validate diverse experiences, and provide education to enhance patient satisfaction and outcomes.[98] Centers-of-excellence models have the potential to act as a home for complex patient-centered care by enhancing access to specialists, interdisciplinary partnerships, surgical expertise, and research initiatives, thereby offering patients an essential access point for long-term and high-quality endometriosis care.[99] In complex clinical scenarios, trained endometriosis experts are crucial to ensure accurate diagnosis, personalized treatment planning, and comprehensive management.[99] In addition, care teams may include pelvic floor physical therapists, nurse navigators, psychologists, radiologists, colorectal surgeons, infertility specialists, and menopause experts to provide comprehensive, multidisciplinary management based on individual needs.

CONCLUSIONS

Endometriosis is a complex condition for patients and clinicians alike. Optimal treatment depends on each patient's unique clinical factors and care goals. Endometriosis is increasingly viewed as a systemic disease requiring more than surgical invention, with the 2017 National Institute for Health and Care Excellence guidelines encouraging empiric medical management before surgery.[100] However, both medical and surgical treatments often provide limited benefits along with side effects and morbidity. Progress has been slow because of limited funding and research support, with only three new drugs approved for endometriosis use since 1990, compared with more than 100 drugs for cancer.[101] Patients urgently need effective medication options throughout their reproductive lifespan. Improved imaging techniques and biomarker identification could enhance diagnosis and counseling without surgery. Implementing a center-of-excellence model for endometriosis care may strengthen patient confidence and adherence to treatment strategies.[102]

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