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Endometriosis
A Review

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IMPORTANCE Endometriosis is a chronic, estrogen-dependent, inflammatory disease defined by endometrial-like tissue (lesions) outside the uterine lining. It affects up to 10% of women worldwide, and 9 million women in the US, during reproductive years.

OBSERVATIONS Endometriosis has varying clinical presentations; however, 90% of people with endometriosis report pelvic pain, including dysmenorrhea, nonmenstrual pelvic pain, and dyspareunia, and 26% report infertility. Risk factors for endometriosis include younger age at menarche, shorter menstrual cycle length, lower body mass index, nulliparity, and congenital obstructive müllerian anomalies such as obstructed hemivagina. Although definitive diagnosis requires surgical visualization of lesions, a suspected clinical diagnosis can be made based on symptoms, supported by physical examination findings and imaging with transvaginal ultrasound and/or pelvic magnetic resonance imaging; normal physical examination and imaging do not exclude the diagnosis. The diagnosis is often delayed, averaging 5 to 12 years after onset of symptoms, with most women consulting 3 or more clinicians prior to diagnosis. Hormonal medications, such as combined oral contraceptives and progestin-only options, are first-line treatment and should be offered to symptomatic premenopausal women who do not currently desire pregnancy. In a network meta-analysis (n = 1680, 15 clinical trials), hormonal treatments including combined oral contraceptives, progestins, and gonadotropin-releasing hormone (GnRH) agonists led to clinically significant pain reduction compared with placebo, with mean differences ranging between 13.15 and 17.6 points (0-100 visual analog scale) with little difference in effectiveness among options. However, 11% to 19% of individuals with endometriosis have no pain reduction with hormonal medications and 25% to 34% experience recurrent pelvic pain within 12 months of discontinuing hormonal treatment. Surgical removal of lesions, usually with laparoscopy, should be considered if first-line hormonal therapies are ineffective or contraindicated. Second-line hormone therapies include GnRH agonists and antagonists, and third-line treatments include aromatase inhibitors. Hysterectomy with surgical removal of lesions may be considered when initial treatments are ineffective. However, approximately 25% of patients who undergo hysterectomy for endometriosis experience recurrent pelvic pain and 10% undergo additional surgery, such as lysis of adhesions, to treat pain.

CONCLUSIONS AND RELEVANCE Endometriosis is a common cause of pelvic pain affecting approximately 10% of reproductive-age women. Hormonal suppression with combined estrogen-progestin contraceptives or progestins is first-line treatment for women who are not seeking immediate pregnancy. Surgical removal of endometriosis lesions may be performed if hormonal therapies are ineffective or contraindicated, and hysterectomy may be considered if medical treatments and surgical removal of lesions do not relieve symptoms.

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Endometriosis is a chronic, estrogen-dependent disease defined by the presence of endometrial-like epithelial and/or stroma cells outside of the endometrium and myometrium, usually with an associated inflammatory process, referred to as *endometriosis lesions*.[1] Approximately 10% of reproductive-age women worldwide have endometriosis, including nearly 9 million in the US.[2] To date, there is no medical or surgical cure.

Approximately 90% of women diagnosed with endometriosis have pelvic pain,[3] 50% report moderate to severe fatigue,[4] and 26% experience infertility.[3] Endometriosis is associated with decreased quality of life[5] and accounts for approximately $78 billion in annual health care costs in the US including treatment and missed work.[6] The diagnosis of endometriosis is often delayed, with a systematic review of 17 observational studies (n = 28 389) reporting 5 to 12 years from symptom onset to diagnosis.[7] Most women are evaluated by at least 3 clinicians before receiving a diagnosis of endometriosis,[8,9] with 0.3 to 8.6 years from first consultation to diagnosis.[7]

This review summarizes the epidemiology, pathophysiology, diagnosis, and treatment of endometriosis. We use the term *women* to refer to people born with a uterus.

Methods

A PubMed search was performed for English-language articles using the MeSH term *endometriosis* to identify systematic reviews, meta-analyses, clinical trials, observational studies, and practice guidelines published between January 1, 1999, and December 30, 2024. The search yielded 1656 articles. Additional narrative reviews were selected by the authors based on their knowledge of the literature. A total of 99 studies were included, consisting of 37 systematic reviews or meta-analyses, 4 clinical trials, 31 observational studies, 9 practice guidelines or consensus statements, and 18 narrative reviews.

Epidemiology

Endometriosis is typically diagnosed in individuals in their early 30s,[3] despite average symptom onset in adolescence to the early 20s.[3,10] Although a 10% prevalence of endometriosis among reproductive-age women in the general population is often stated,[2] a systematic review of 69 observational studies reported that prevalence varies widely, depending on geographic location, setting (general or specialist clinic, hospital data and insurance claims), symptoms, age, and diagnosis method (symptoms, ultrasound, surgery).[2] Endometriosis is observed (primarily via laparoscopy) in 28.1% (95% CI, 26.9%-29.4%), as reported in a meta-analysis of 11 observational studies, of women presenting with chronic pelvic pain and 24.8% (95% CI, 23.9%-25.8%), as reported in a meta-analysis of 17 observational studies, of women presenting with infertility.[2] In a systematic review of 27 cross-sectional, case-control, and cohort studies from the US and Europe, women with endometriosis-associated pelvic pain reported significantly reduced health-related quality of life, and impaired mental health, sexual function, and work productivity compared with women without endometriosis.[5]

Risk factors for endometriosis include obstructive müllerian anomaly (uterine anomaly causing blockage of menstrual outflow), which is associated with a 47% prevalence of endometriosis (95% CI, 36%-58%).[11] Other risk factors, based on prospective cohort studies and meta-analyses of cohort and case-control studies, include onset of menarche before age 12 years,[12] menstrual cycle intervals fewer than 28 days,[13] lower body mass index,[14] and nulliparity.[15] Twin studies estimate heritability of endometriosis at approximately 50%,[16,17] but no single genes have been associated with most familial cases. A family history of endometriosis is also a risk factor (for sisters, relative risk, 5.2; 95% CI, 3.4-7.2),[18] which is partially attributable to genetic heritability as well as increased awareness and access to care.

Endometriosis Subtypes

Endometriosis is categorized into 4 subtypes: superficial peritoneal, deep, ovarian (endometriomas), and extrapelvic endometriosis (**Figure 1**). Subtypes may occur alone or in combination and are important to distinguish because they may affect the diagnostic and treatment approach. *Superficial peritoneal endometriosis* lesions occur on the peritoneal surface of serosa of abdominal or pelvic viscera. *Deep endometriosis* lesions penetrate the pelvic peritoneal surface (eg, uterosacral ligaments) or infiltrate the muscularis propria of pelvic visceral organs such as the bowel or urinary tract (bladder or ureter). *Ovarian endometriomas* are cysts within the ovary lined by endometrial glands and stroma. *Extrapelvic endometriosis* refers to lesions outside of the pelvis, which have been reported in nearly every organ system, including the diaphragm, thoracic cavity, abdominal wall, and brain.[20] The prevalence of endometriosis subtypes in the general population is unknown. Available data are from series of surgical cases and vary widely depending on factors such as age, clinical setting (eg, community hospital vs endometriosis referral center), and presurgical symptoms.

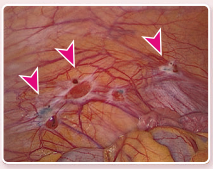
Pathophysiology

The pathogenesis of endometriosis involves sex-steroid and inflammatory processes. Retrograde efflux of endometrial cells through the fallopian tubes into the pelvis during menstruation is widely accepted as a contributor to the origin of lesions within the abdominal-pelvic cavity. Lymphatic or vascular metastasis have also been proposed and cannot be excluded as a cause of extrapelvic lesions.[21-23] Endometriosis lesions are dependent on estradiol-mediated mechanisms that promote cellular proliferation and adhesion, localized fibrosis and inflammation, immune dysregulation, and coordinated nerve and blood vessel ingrowth.[21-23] However, pathophysiological changes extend beyond the lesions and include altered immune and progesterone responsiveness of the uterine endometrium and increased inflammation and angiogenesis in the mesothelial cells of the pelvic peritoneum (**Figure 2**).

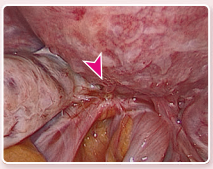
The mechanisms by which endometriosis causes pelvic pain and/or infertility are multifactorial and not fully understood. Pain due to endometriosis can be caused by a combination of nociceptive, neuropathic, and nociplastic mechanisms (Figure 2).[27] *Nociceptive* pain is caused by direct activation of peripheral nociceptors (sensory receptors for noxious stimuli) and is likely due to localized inflammation surrounding lesions. *Neuropathic* pain may be due to peripheral sensitization and/or direct nerve fiber invasion by lesions, which may increase with surgical injury. *Nociplastic* pain (pain from altered pain perception in the central nervous system) manifests as widespread body pain, fatigue, memory difficulties, and poor sleep and is associated with systemic inflammation from immunoreactive white blood cells.[28] Endometriosis may affect fertility through multiple pathways, including impaired ovarian function, adhesions causing tubal blockage, and dysfunction of uterine endometrium.[23]

Figure 1. Characteristic of Endometriosis and Common Conditions With Overlapping Symptoms

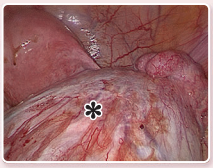
A Characteristics of endometriosis subtypes



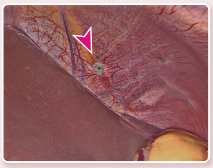
1 Superficial peritoneal endometriosis
- Lesions on peritoneal surface or serosa of abdominal wall or pelvic viscera
- Variable in appearance and any combination of colors such as blue, brown, red, white, or clear



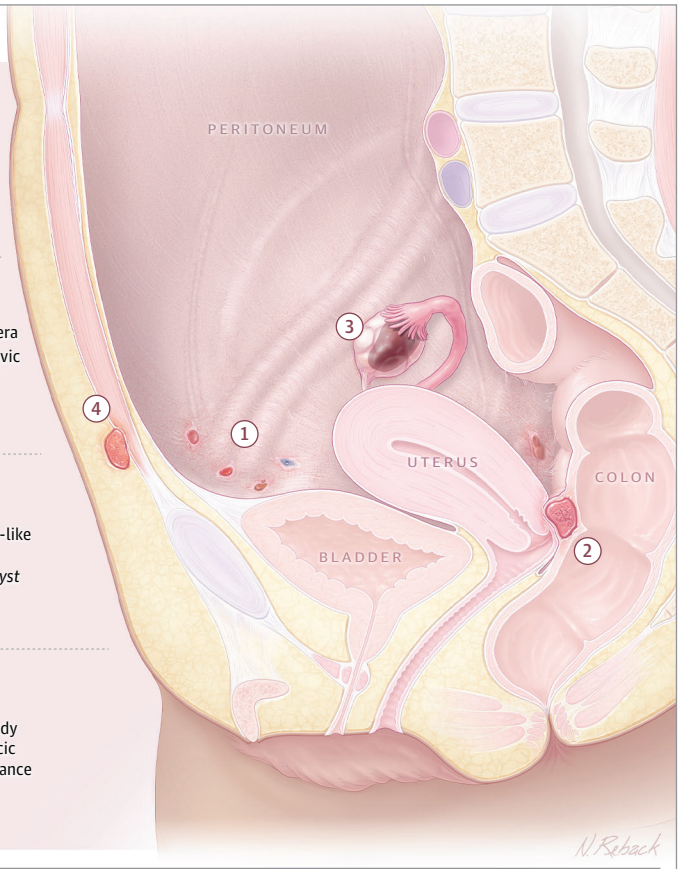
2 Deep endometriosis
- Extends under peritoneal surface or serosa of abdominal wall or pelvic viscera
- May infiltrate muscularis propria of pelvic organs (bowel, bladder, and ureters)
- Nodular appearance and may include fibrosis and adesions



3 Endometrioma
- Ovarian cysts that contain endometrial-like tissue and dark, blood-stained fluid
- Sometimes referred to as a *chocolate cyst*



4 Extrapelvic endometriosis
- Lesions may occur in any part of the body (eg, abdominal wall, diaphragm, thoracic cavity, liver) and are variable in appearance



B Gynecologic and nongynecologic conditions with symptoms that overlap with endometriosis

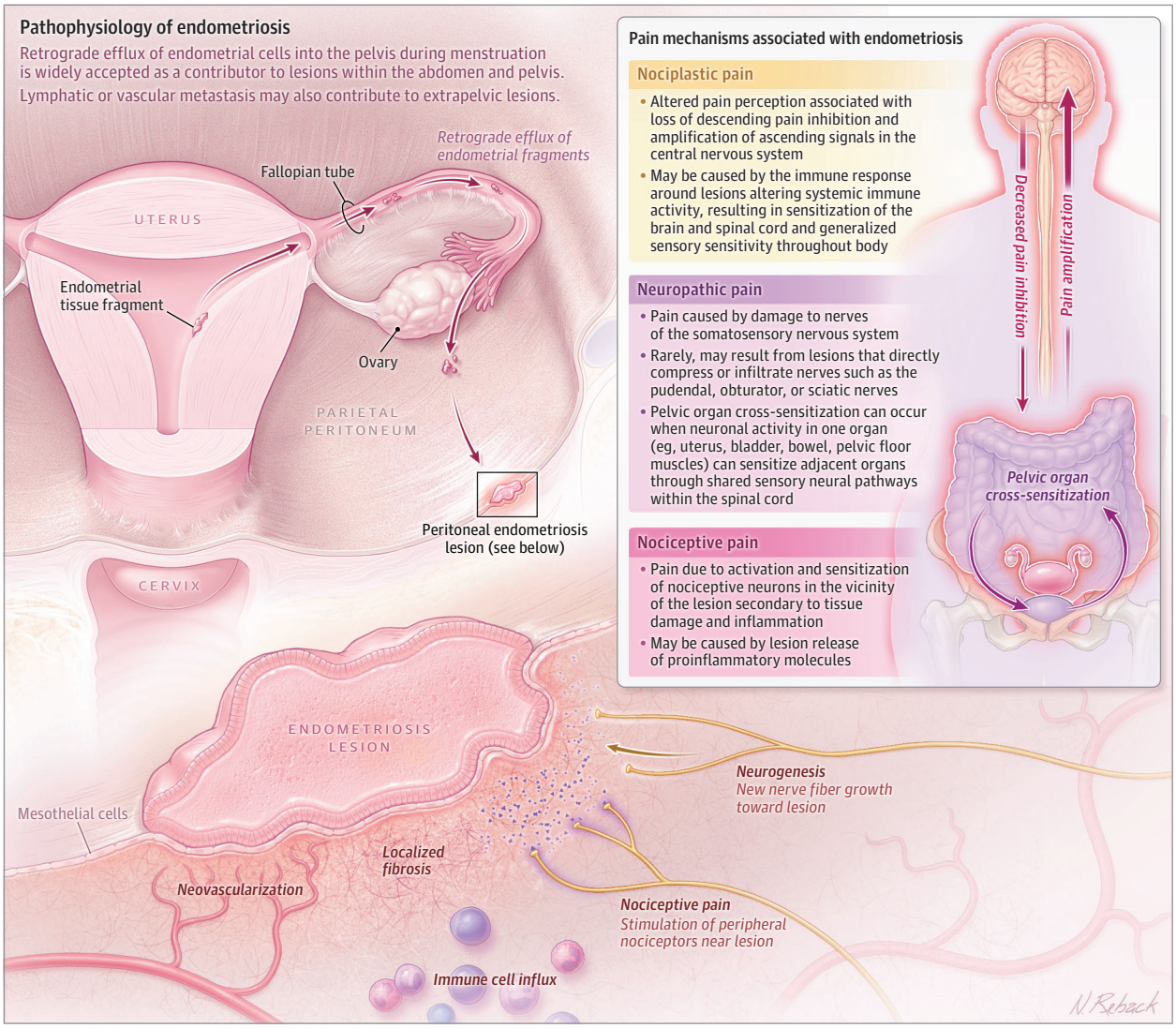
	Alternative conditions	Common symptoms of endometriosis: Dysmenorrhea	Nonmenstrual pelvic pain	Deep dyspareunia	Clinical features of alternative conditions
Gynecologic cause	Adenomyosis	✓	✓	✓	Heavy menstrual bleeding; tender uterus (which is sometimes enlarged); commonly co-occurs with deep endometriosis
	Uterine fibroids	✓	✓	✓	Heavy menstrual bleeding; enlarged or irregular uterus
	Primary dysmenorrhea	✓			Often short duration (<72 h) and responsive to nonsteroidal anti-inflammatory drugs
	Cervical stenosis	✓	✓		Absence of menstrual period (amenorrhea) or decreased menstrual flow; history of cervical surgery or ablation of uterine lining
	Müllerian anomaly with obstruction of genital tract	✓	✓		Amenorrhea with cyclic pain often diagnosed in adolescence
Nongynecologic cause	Pelvic floor myofascial pain	✓	✓	✓	Pain worse with activity and/or at end of day; tender abdominal wall or pelvic floor muscles; can be associated with painful bowel movements (dyschezia), constipation, urinary frequency
	Irritable bowel syndrome		✓		Changes in bowel frequency and stool quality with associated abdominal pain; symptoms may be worse during menses
	Bladder pain syndrome/ interstitial cystitis		✓	✓	Urinary urgency, urinary frequency, and/or nocturia with normal urinalysis; symptoms may be worse during menses
	Pelvic venous disorder		✓	✓	Pelvic heaviness that is worse when standing and at end of the day

Surgical images are provided by authors As-Sanie and Horne. Panel B is adapted from Allaire et al.[19] The asterisk in the third image points to the ovarian endometrioma. In the first image, the red arrowheads point to superficial peritoneal endometriosis lesions; in the second, deep endometriosis lesion of the rectosigmoid and uteroscral ligament; and in the fourth, diaphragmatic endometriosis lesion.

Clinical Presentation and Clinical Course

The most common presenting symptom is pelvic pain, including dysmenorrhea (painful menses), nonmenstrual pelvic pain, and deep dyspareunia (pain with deep vaginal penetration; **Box**). In a cross-sectional study of self-reported survey data from 940 women with surgically confirmed endometriosis, 89.3% reported at least 1 pelvic

Figure 2. Pathophysiology and Pain Mechanisms in Endometriosis-Associated Pelvic Pain



Pelvic pain in patients with endometriosis is multifactorial and can be due to any combination of nociceptive, neuropathic, and nociplastic pain mechanisms. Release of proinflammatory cytokines and pain mediators from endometriosis lesions, in addition to recruitment of immune cells, all may serve both to stimulate and augment nociceptive pain. Neuropathic pain may occur due to direct infiltration of nerves and/or sensitization of second-order neurons innervating adjacent structures and can cause cross-organ sensitization. Nociplastic pain, which manifests as widespread pain, fatigue, memory difficulties, and poor sleep, is due to augmentation of pain perception through central sensitization. The dysregulated immune environment around the lesion leads to changes in systemic immune activity, reflected in circulating monocytes and other white blood cells. These processes contribute to nociplastic pain through sensitization of the spinal cord and brain, resulting in amplification of pain signals, loss of pain inhibition, and development of generalized sensory sensitivity (heightened sensitivity both to internal and external painful and nonpainful stimuli). These pathophysiological processes interact, with compromised function of the hypothalamic-pituitary and sympathetic-adrenal medullary axes leading to further immune dysregulation and amplification of pain-generating signals. Nociplastic pain is highly likely in patients who present with additional pain conditions. This may explain why lesion number and subtype is only weakly associated with the pain severity, why treatments aimed at the lesion (eg, surgery and hormone suppression) do not alleviate pain in all patients, and why pain can recur without evidence of recurrent lesions.

pain symptom, including 78.7% with dysmenorrhea, 69.4% with nonmenstrual pelvic pain, and 44.9% with deep dyspareunia.[3] This study also reported dyschezia (painful bowel movements) in 27.0%, infertility in 26.2%, ovarian cysts in 19.5%, and dysuria in 9.9%; 2% were asymptomatic.[3] In less than 1% of patients, deep endometriosis can cause bowel obstruction, hydroureter, hematochezia, and/or hematuria; these signs and symptoms should raise the suspicion for deep endometriosis.[29,30] The intensity of pelvic pain in patients with endometriosis varies, does not correlate with number, location, or subtype of lesions (except deep disease in the posterior cul-de-sac correlates with dyspareunia) but typically increases during menses.[31,32] Similar to patients with other chronic pain conditions,[28] patients with endometriosis are more likely than women without endometriosis to report moderate to severe fatigue in the absence of anemia (50.7% vs 22.4%),[4] sleep disturbances (29.2% vs 12.5%), and mood disorders (67% vs 51.2% cumulative incidence over 12.5 years).[33]

Symptoms of extrapelvic endometriosis reflect the location of the lesions and, similar to other endometriosis subtypes,

Box. Commonly Asked Questions About Endometriosis

What are the most common symptoms of endometriosis?
Pelvic pain, which can include dysmenorrhea (painful menstrual periods), nonmenstrual pelvic pain, and dyspareunia (pain with vaginal intercourse), is the most common symptom of endometriosis. However, endometriosis lesions do not always cause pain, and patients with endometriosis may also have other conditions that cause pelvic pain, such as adenomyosis, uterine fibroids, pelvic floor myalgia, irritable bowel syndrome, and bladder pain syndrome or interstitial cystitis.

What are first-line therapies for endometriosis?
For patients with endometriosis and pelvic pain who are not currently seeking pregnancy, first-line therapy is hormonal suppression with either combined estrogen-progestin contraception or progestin-only medications. Patients may also be offered nonsteroidal anti-inflammatory drugs (NSAIDs), although their efficacy in treating endometriosis-associated pelvic pain has not been demonstrated. For patients with symptoms of endometriosis who are trying to achieve pregnancy, NSAIDs can be considered for pain management, and hormonal therapy is contraindicated.

When should patients with clinically suspected or confirmed endometriosis be referred to a gynecologist?
Referral to a gynecologist is recommended for patients with endometriosis who decline or are not candidates for first-line hormonal suppression therapy (eg, desire pregnancy or have contraindication), for those with persistent pain after at least 3 months of first-line therapy, and for those with clinical symptoms, physical examination, or pelvic ultrasound or magnetic resonance imaging findings suggestive of an ovarian endometrioma or deep endometriosis.

typically worsen during menses.[20] For example, thoracic endometriosis can cause catamenial (symptoms that recur during menses) pneumothorax, hemoptysis, and/or shoulder pain during menses. Abdominal wall endometriosis is associated with cyclic pain in a palpable subcutaneous nodule. Umbilical skin lesions can bleed during menses.

After menopause, patients with endometriosis typically have resolution of symptoms due to decline in estrogen levels. However, symptoms of endometriosis can persist or present for the first time in menopause, particularly among women who use hormone replacement therapy, although the frequency of incident and prevalent symptoms in menopause is unknown.[34]

Assessment and Diagnosis

Physical Examination

The World Endometriosis Research Foundation[24] and Society of Obstetricians and Gynecologists of Canada[25] provide recommendations on the physical examination of patients with suspected endometriosis using a trauma-informed framework, which minimizes distress, supports autonomy, and builds trust (**Figure 3**). Although a pelvic examination cannot identify superficial peritoneal lesions, it may identify ovarian endometriomas and signs of deep endometriosis and can evaluate for other causes of pelvic pain such as pelvic floor myalgia (tenderness with vaginal palpation of pelvic floor muscles). Several pelvic examination findings suggest deep endometriosis or ovarian endometriomas. In patients with surgically confirmed deep endometriosis, 67% to 95% had palpable thickening, nodularity, or tenderness of the posterior cul-de-sac and/or decreased uterine mobility, and 75% to 90% had a palpable ovarian mass on pelvic examination prior to surgery.[35] Patients with suspected lesions in the vagina, umbilicus, or within abdominal surgical scars should be referred to a gynecologist for possible biopsy of these lesions (Figure 1 and Box).

Imaging

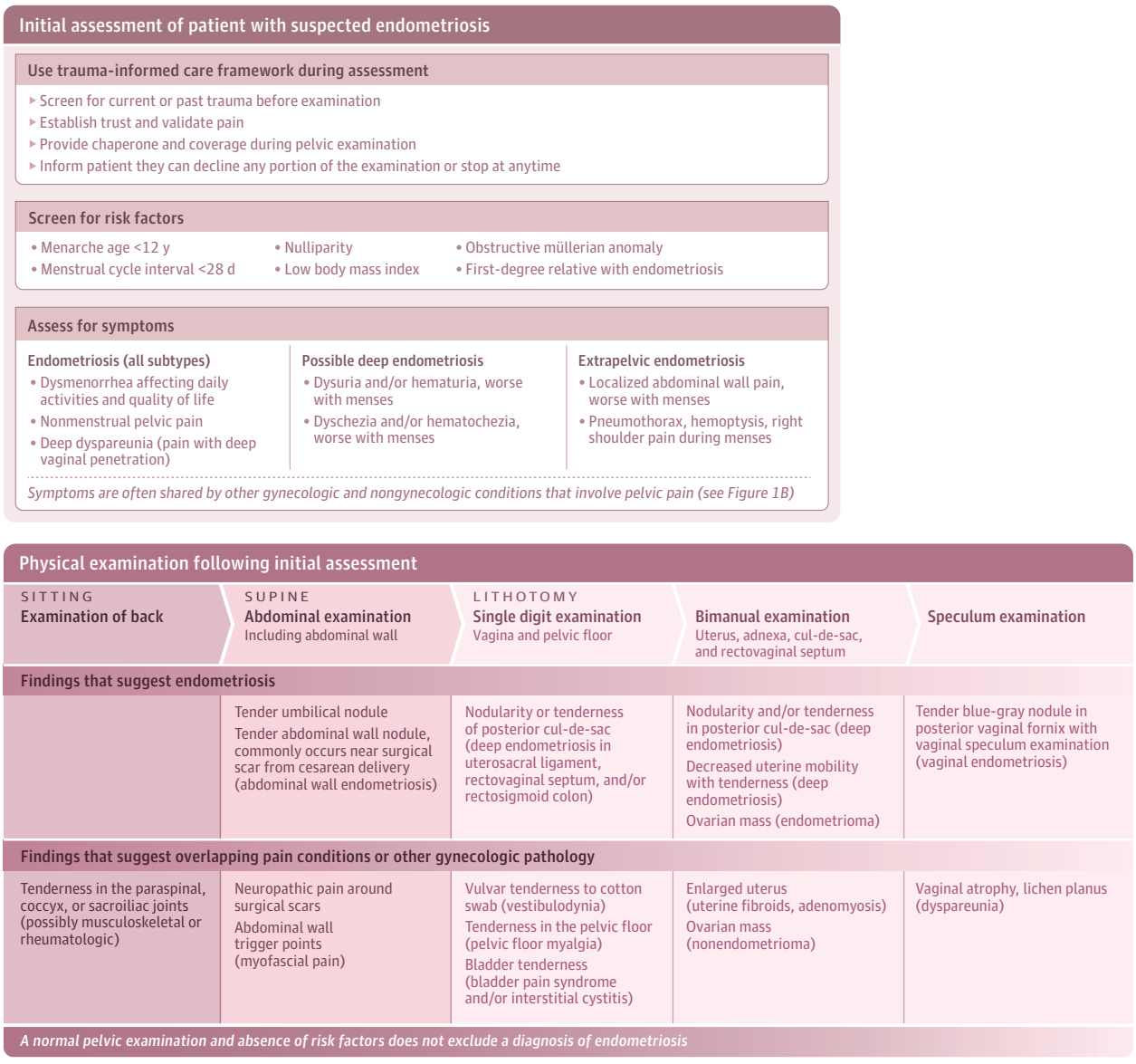
Multiple international guidelines[25,36-39] recommend transvaginal pelvic ultrasound as the initial diagnostic test for patients with pelvic pain and/or suspected endometriosis. A 2016 Cochrane review reported that, compared with surgical visualization, transvaginal ultrasound had high sensitivity (93%, 95% CI, 87%-99%) and specificity (96%, 95% CI, 92%-99%) for ovarian endometriomas (8 studies, n = 765), moderate sensitivity for deep endometriosis (79%, 95% CI, 69%-89%, 9 studies, n = 934), but low sensitivity for superficial peritoneal lesions (65%, 95% CI, 27%-100%).[40] In 2024, the Society of Radiologists in Ultrasound published a consensus on augmented pelvic ultrasound to improve the diagnosis of deep endometriosis.[41] This technique—supported by the European Society of Human Reproduction and Embryology,[39] the Society of Obstetricians and Gynecologists of Canada,[25] and the National Institute for Health and Care Excellence guidelines[38]—is not widely used in the US. Unlike routine transvaginal ultrasound, augmented pelvic ultrasound includes evaluation of the relative position of the ovaries (eg, "kissing ovaries" suggests deep endometriosis) and dynamic uterine sliding (absence of uterine slide against the rectosigmoid suggests adhesions and deep endometriosis). In a prospective observational study of 273 patients undergoing laparoscopic surgery, augmented pelvic ultrasound had a sensitivity of 88.4% (95% CI, 83.2%-92.4%) and specificity of 78.8% (95% CI, 67.0%-87.9%) for detecting deep endometriosis.[42]

Magnetic resonance imaging (MRI) enables evaluation of other pelvic organs, features of ovarian malignancy when ultrasound is inconclusive, and it can diagnose extrapelvic endometriosis.[43] A systematic review (14 observational studies, n = 1577) reported that MRI using an endometriosis-specific protocol interpreted by experienced radiologists had a sensitivity of 91% to 93.5% and a specificity of 86% to 87.5% for deep and ovarian endometriosis compared with laparoscopy or other forms of imaging.[44] Because no imaging modality has 100% sensitivity, absence of findings on imaging does not exclude the diagnosis of endometriosis.

Clinically Suspected vs Surgically Confirmed Diagnosis

Histological confirmation is considered the criterion standard for diagnosing endometriosis, which requires visualization (usually by laparoscopy) to biopsy lesions in the abdomen and pelvis. However, multiple society guidelines[25,36-39] recommend making a presumed diagnosis based on symptoms, supported by physical examination findings and pelvic imaging with ultrasound and/or MRI (Figures 3 and **4**), although no validated diagnostic criteria exist. Additionally, no diagnostic blood or molecular markers for endometriosis have been validated in clinical populations.[45] This shift in diagnostic approach reflects awareness that requiring surgery for diagnosis may delay treatment. Moreover, surgery is not always accessible, and empirical hormonal treatment offers comparable overall efficacy to surgical removal of lesions.

Figure 3. Physical Examination of Patient With Clinical Symptoms of Endometriosis-Associated Pelvic Pain



Treatment

Endometriosis is a chronic condition without medical or surgical cure. Current treatments include nonopioid analgesics, hormonal medications, surgery, and adjunct therapies, such as pelvic floor physical therapy. Treatment focuses on managing pain and reducing recurrence, using individualized strategies based on patient preference and fertility goals, which may change over time.

Hormonal treatment should be offered to symptomatic women with clinically suspected endometriosis who do not wish to conceive immediately. Multiple guidelines[25,38,39] advise that clinicians should not prescribe medical treatments or surgically remove lesions in asymptomatic individuals but should inform patients about the incidental findings. Exceptions include asymptomatic patients with large ovarian endometriomas or deep lesions causing hydronephrosis (see below).

Pharmacological Treatment

Analgesics

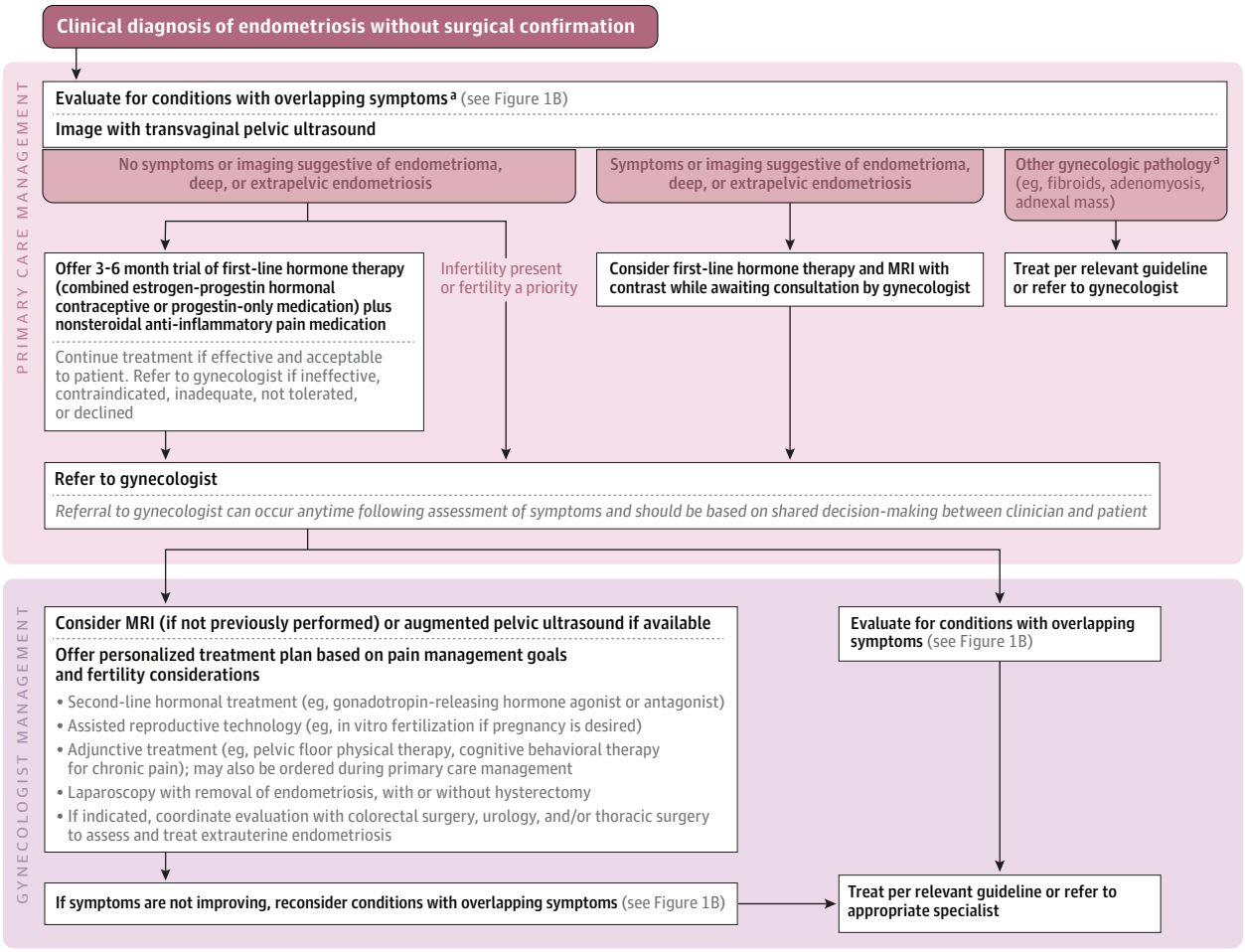
Guidelines state that patients may be offered nonsteroidal anti-inflammatory drugs (NSAIDs) for endometriosis-associated pain; NSAIDs can be used alone or in combination with hormonal treatments.[36-39,46] However, a 2017 Cochrane review found insufficient evidence that NSAIDs reduce pain in endometriosis, with only 1 low-quality trial of 24 participants.[47]

Randomized trials have not evaluated the efficacy of opioid analgesics for treating endometriosis-associated pelvic pain. Due to risk of dependency, opioids are not recommended.

Hormonal Treatment

Hormonal treatment, which can be initiated in the primary care setting, is first-line treatment recommended by international

Figure 4. Diagnostic Algorithm and First-Line Treatment of Endometriosis



[a]Other gynecologic pathology and overlapping pain conditions commonly coexist with endometriosis and have similar symptoms. Health care clinicians should treat both endometriosis and coexisiting gynecologic pathology and pain conditions.

MRI indicates magnetic resonance imaging.

guidelines.[36-39,46] All hormonal treatments target sex steroid-dependent pathophysiology of endometriosis by suppressing ovarian activity and creating a hypoestrogenic environment, which can lead to regression of endometriosis lesions.[48] First-line hormonal treatment includes combined estrogen-progestin contraceptives or progestogens, second-line hormonal treatment includes gonadotropin-releasing hormone (GnRH) agonists and antagonists, and third-line hormonal treatment includes aromatase inhibitors (**Table**). Approximately 25% to 34% of women with endometriosis experience recurrent pelvic pain within 12 months of discontinuing hormonal therapy,[54] and incidence of pain recurrence is likely higher with longer duration of time off hormonal therapy. Despite similar efficacy of hormonal medications, individual responses vary, often necessitating trials of different medications within and across classes to achieve optimal symptom control and minimize adverse effects such as breakthrough bleeding.

Guidelines recommend combined estrogen-progestin contraceptives (typically containing 20 µg-30 µg ethinyl estradiol) and progestin-only medications such as norethindrone acetate as first-line treatment due to their low cost and few adverse effects. A network meta-analysis of 1680 women from 15 RCTs reported that all hormonal treatments led to a similar clinically significant pain reduction measured using a 0 to 100 visual analog scale (minimum clinically important difference, 10 points).[38] Compared with placebo, combined oral contraceptives reduced pelvic pain by a mean difference of 15.1 (95% CI, −20.8 to −9.3); oral progestogens, 12.6 (95% CI, −15.3 to −9.8); progestogens delivered via intrauterine device (52 mg levonorgestrel system), 17.7 (95% CI, −25.5 to −9.8); intramuscular progestogens, 13.2 (95% CI, −16.2 to −10.1); and intramuscular GnRH agonists (leuprolide acetate), 15.7 (95% CI, −21.3 to −10.1). However, a systematic review of 58 studies (38 RCTs, 16 prospective, 4 retrospective cohort studies) with 11 881 participants reported that 11% to 19% of women experienced no pain reduction with hormonal therapy and 5% to 59% still had some pain at the end of the study period despite hormone use.[54]

Guidelines recommend continuous use of a combined estrogen-progestin contraceptive (omitting the hormone-free interval) over cyclic use with the goal of achieving amenorrhea.[39] In a prospective cohort study of 293 women with endometriosis, continuous hormonal suppression was associated with lower frequency of

Table. Pharmacological Treatment Options for Endometriosis-Associated Pelvic Pain

Treatment category	Medication and dose	Mechanism of action	Efficacy at primary end point from randomized trials	Select adverse effects[a]	Additional considerations
First-line treatment					
Combined hormonal contraceptive	Oral pill (1/d) usually containing a progestin and 20-30 µg ethinyl estradiol Vaginal ring changed every 3 wk Transdermal combined estrogen-progestin patch changed once a wk	Suppression of ovarian hormone secretion and inhibition of ovulation via negative feedback loop, leading to hypoestrogenic state, decidualization and atrophy of endometrium and endometriosis lesions	Network meta-analysis[b] Clinically significant reduction in pelvic pain on 0-100 VAS compared with placebo (MD, −15.1; 95% CI, −20.8 to −9.3)[38]	Headache (≤10%), mood changes (≤10%), breast tenderness (≤10%), decreased libido (≤1%), nausea (≤10%, usually subsides)	Contraindications include history of or increased risk of thromboembolism, migraine with aura, hepatic disease Continuous use (eg, skip placebo in pill packet) to achieve amenorrhea likely superior to cyclical use with no difference in safety profiles,[49] which can be achieved with monophasic formulation[c] Multiple formulations of pill available, recommend lowest dose of ethinyl estradiol to achieve amenorrhea, but breakthrough bleeding more common with lower-dose (<20 µg) estradiol formulations
NSAIDs	Oral naproxen, 500 mg, for 1 dose, then 250 mg every 6-8 h as required Oral ibuprofen, 400 mg, for a maximum of 3/d	NSAIDs relieve pain by inhibiting COX enzymes, which reduce the production of prostaglandins involved in inflammation and pain signaling	Insufficient evidence that NSAIDs reduce pain in endometriosis[47]	Gastrointestinal irritation or ulceration, hypersensitivity reaction (eg, asthma exacerbation), kidney impairment (frequencies unavailable)	Use with caution in patients with a history of cardiac disease, kidney disease, uncontrolled hypertension, peptic ulcer disease, or NSAID-exacerbated respiratory disease
Progestins					
Oral progestin	Daily oral norethindrone acetate, 2.5-15 mg (start at 2.5-5 mg and titrate up until amenorrhea) Daily oral medroxyprogesterone acetate, 15-30 mg Daily oral drospirenone, 4 mg Daily oral dienogest, 2 mg	Induce decidualization and atrophy of endometrial tissue, decrease estrogen-induced mitosis, suppress cell proliferation, inhibit inflammatory pathways, angiogenesis and neurogenesis	Network meta-analysis[b] Clinically significant reduction in pelvic pain on 0-100 VAS vs placebo (MD, −12.6; 95% CI, −15.3 to −9.8)[38]	Breakthrough bleeding (>10%), weight gain (≤10%), mood changes (≤10%)	Similar to combined hormonal contraceptive, goal is to achieve amenorrhea Norethindrone acetate typically starts at 5 mg and titrate up by 2.5 mg every 2-4 wk until achieve amenorrhea Drospirenone monotherapy is off label for endometriosis Dienogest not available in the US as a monotherapy
Intramuscular injection	Medroxyprogesterone acetate, 150 mg IM every 3 mo		Network meta-analysis[b] Clinically significant reduction in pelvic pain on 0-100 VAS vs placebo (MD, −13.2; 95% CI, −16.2 to −10.1)[38]	Headache (>10%), weight changes (>10%), gastrointestinal upset (>10%), depression (≤10%), decreased libido (≤10%), breakthrough bleeding (≤1%)	Delay in return of fertility (contraceptive effect and cycle irregularity can persist for up to 12 mo) Bone mineral density loss with prolonged use, particularly in adolescents
Subdermal implant	Etonogestrel, 68 mg, implant, every 3 y		No studies compared with placebo	Breakthrough bleeding (>10%), weight gain (>10%), headache (>10%), acne (>10%), mood changes (≤10%)	10% Discontinue treatment due to unfavorable changes in their bleeding pattern

(continued)

Table. Pharmacological Treatment Options for Endometriosis-Associated Pelvic Pain (continued)

Treatment category	Medication and dose	Mechanism of action	Efficacy at primary end point from randomized trials	Select adverse effects[a]	Additional considerations
Intrauterine system	Levonorgestrel available in 52 mg/device (19.5 mg/device and 13.5 mg/device also available but not studied in endometriosis)	Reduces the expression of estrogen and progesterone receptors in eutopic (endometrium within the uterine lining) and ectopic endometrial tissues, causing glandular atrophy and decidualization of the stroma	Network meta-analysis[b] Clinically significant reduction in pelvic pain on 0-100 VAS compared with placebo (MD, −17.7; 95% CI, −25.5 to −9.8)[38]	Breakthrough bleeding (>10%), headache (<10%), weight gain (<10%), spontaneous expulsion of intrauterine system (<10%), uterine perforation (<1%)	Does not consistently suppress ovulation, therefore, not recommended for management of ovarian endometriomas Also approved for treatment of heavy menstrual bleeding (amenorrhea 20% at 12 mo, 40% at 24 mo) Unlike systemic progestins, no negative effect on lipid profiles
Second-line treatment					
GnRH agonists					
Intramuscular injection	Leuprolide acetate, 3.75 mg IM 1/mo or 11.25 mg IM every 3 mo	Downregulation of GnRH receptors in pituitary gland, inhibiting gonadotropin release and ovarian hormone secretion, leading to hypoestrogenic state	Network meta-analysis[b] Clinically significant reduction in pelvic pain on 0-100 VAS compared with placebo (MD, −15.7; 95% CI, −21.3 to −10.1)[38]	Hot flush (>10%), headache (>10%), difficulty sleeping (>10%), vaginal dryness (≤10%), depressed mood (≤10%)	Bone mineral density loss, may be irreversible if used >6 mo without add-back hormone replacement therapy (low doses of estrogen with or without progestin) Addition of add-back hormone replacement therapy is recommended and reduces menopause-like adverse effects and prevents bone mineral density loss[39]
Intranasal	Nafarelin acetate 1 nasal spray, 200 µg, 2/d		Network meta-analysis[b] Clinically significant reduction in pelvic pain on 0-100 VAS vs placebo (MD, −15.8; 95% CI, −21.4 to −10.1)[38]		
GnRH antagonists					
Oral without add-back hormone replacement therapy	Daily oral elagolix, 150 mg (low dose)	Nonpeptide antagonist of GnRH receptors in pituitary gland, block pituitary gonadotropin secretion within hours, leading to ovulation suppression and hypoestrogenic state	Two parallel phase 3 RCTs of women with moderate to severe endometriosis-associated pain[50] At 6 mo, 42.1% in EM-I, 46.2% in EM-II, 23.1%, and 25.4% in placebo were dysmenorrhea responders[d] At 6 mo, 45.7% in EM-I, 51.6% in EM-II, and 34.9% and 40.6 % in placebo were nonmenstrual pelvic pain responders[d]	Hot flush (24%), headache (17%), nausea (11%), insomnia (6%), mood swings (6%), depressed mood (3%), anxiety (3%), arthralgia (3%)	Dose-dependent bone mineral density loss. Low dose approved for 24 mo, high dose approved for 6 mo use Immediate return of menses upon discontinuation Contraindications include osteoporosis, significant hepatic disease (eg, cirrhosis)
	Daily oral elagolix, 200 mg, 2/d (high dose)		At 6 mo, 75.3% in EM-I, 76.9% in EM-II, and 23.1% and 25.4% in placebo were dysmenorrhea responders[d] At 6 mo, 62.1% in EM-I, 62.2% in EM-II, and 34.9% and 40.6% in placebo were nonmenstrual pelvic pain responders[d]	Hot flush (46%), headache (20%), nausea (16%), insomnia (9%), mood swings (6%), depressed mood (6%), anxiety (5%), arthralgia (5%)	

(continued)

Table. Pharmacological Treatment Options for Endometriosis-Associated Pelvic Pain (continued)

Treatment category	Medication and dose	Mechanism of action	Efficacy at primary end point from randomized trials	Select adverse effects[a]	Additional considerations
Oral with add-back hormone replacement therapy	Relugolix combination therapy (40 mg, estradiol 1 mg, norethindrone acetate 0.5 mg) 1 tablet/d	Add-back therapy included in single pill to mitigate bone mineral density loss and vasomotor symptoms	Two parallel phase 3 RCTs of 638 participants in SPIRIT 1 and 623 in SPIRIT 2 with moderate to severe endometriosis-associated pain[51] At 6 mo, 75% in both SPIRIT groups were dysmenorrhea responders vs 27% in the placebo groups of SPIRIT 1 and 30% in SPIRIT 2[e] At 6 mo, 59% in SPIRIT 1 and 66% in SPIRIT 2 were nonmenstrual pelvic pain responders vs 40% in the placebo groups in SPIRIT 1 and 43% in SPIRIT 2[e] Efficacy was sustained at year 2 in an open-label extension study[52]	Headache (33%), vasomotor symptoms (13.2%), mood disorders (9.1%), abnormal uterine bleeding (6.7%), nausea (6.0%), toothache (5.5%), back pain (4.8%), decreased sexual desire (4.3%), arthralgia (3.6%), fatigue (3.1%), dizziness (3.1%)	Immediate return of menses upon discontinuation Approved for 24 mo use in US and without limitation on duration of use in European Union Contraindications include history of or increased risk of thromboembolism, osteoporosis, migraine with aura, significant hepatic disease (eg, cirrhosis)
Third-line treatment					
Aromatase inhibitors	Daily oral letrozole, 2.5 mg Daily oral anastrazole, 1 mg	Suppress estrogen production in all tissue, including within lesions, by blocking aromatase P450 enzyme	A systematic review of 5 systematic reviews reported low-quality evidence for the use of aromatase inhibitors for endometriosis[53]	Hot flush (50%), night sweats (15%), nausea (9%-17%), myalgia or arthralgia (4%-10%), weight gain (13%)	Off-label use If using in premenopausal women, recommended in combination with a combined estrogen-progestin contraceptive, norethindrone acetate or GnRH agonist to prevent ovarian stimulation and mitigate menopausal symptoms[39] Consider use in postmenopausal women with symptomatic endometriosis since mechanism of action does not depend on suppression of ovarian estrogen production and estradiol inhibition occurs within endometriosis lesions

Abbreviations: COX, cyclooxygenase; EM, endometriosis; GnRH, gonadotropin-releasing hormone; IM, intramuscular; MD, mean difference; NSAIDs, nonsteroidal anti-inflammatory drugs; RCT, randomized clinical trial; VAS, visual analog scale.

[a] Frequencies are included when available, derived from product labeling unless cited otherwise.

[b] Defined as same dose of estrogen and progestin in each pill, vaginal ring, or transdermal patch.

[c] Responder in the EM-I and EM-II RCTs was defined as experiencing a clinically meaningful reduction in the pain score (range, 0 [no pain] to 3 [severe pain]) and a decreased or stable use of rescue analgesic agents. A clinically meaningful threshold for the mean change from baseline compared with placebo was −0.81 for dysmenorrhea and −0.36 for nonmenstrual pelvic pain in EM-I and −0.85 for dysmenorrhea and −0.43 for nonmenstrual pelvic pain in EM-II. The EM-I study randomized 872 women and EM-II randomized 817.

[d] Responder defined by meaningful change thresholds of −2.8 points for dysmenorrhea and −2.1 points for nonmenstrual pelvic pain on the numeric rating scale (0, no pain; 10, pain as bad as you can imagine), excluding those with increased use in analgesics.

[e] Network meta-analysis of 1680 patients with endometriosis treated with hormone therapy.

dysmenorrhea (9.4% vs 20.9%, P = .02) and nonmenstrual pelvic pain (9.4% vs 23.9%, P = .006) when compared with cyclic use.[49] Improvement in pelvic pain should be assessed approximately 3 months after starting oral contraceptives. When hormonal suppression is initiated by primary care clinicians, referral to a gynecologist should be considered if pain persists or adverse effects such as breakthrough bleeding or mood changes are intolerable.

GnRH agonists and antagonists, such as leuprolide and elagolix, are second-line therapy due to their high cost and adverse effects of decreased bone mineral density and vasomotor symptoms, which limit their long-term use.[38,39,46] GnRH agonists and antagonists are typically prescribed by gynecologists, usually after surgical confirmation of endometriosis and removal of lesions, particularly in adolescents.[10,39] To counteract adverse menopausal effects of GnRH medications, current guidelines[25,36,38,39] recommend coadministration of hormonal replacement therapy with combined estrogen-progestin or norethindrone acetate, known as add-back therapy. A meta-analysis (13 RCTs, 945 participants) reported that add-back therapy led to a clinically meaningful reduction in loss of bone mineral density in the lumbar spine compared with GnRH monotherapy (weighted mean difference, −0.03 g/cm^2; 95% CI, −0.05 to −0.02) without reduced efficacy in treating pelvic pain.[55]

In contrast to injectable GnRH agonists, GnRH antagonists are oral medications, have rapid onset of action, and quick return of menses once discontinued (eg, median time to resumption of menses is 31 days for relugolix combination therapy[51]). There are 2 US Food and Drug Administration (FDA)–approved medications: elagolix (low dose, 150 mg once daily; high dose, 200 mg twice daily) and relugolix combination therapy (Table). In replicate randomized clinical trials, 872 and 817 women were randomized in each study, and 653 and 632 completed the trial. At 6 months for both studies, those taking elagolix were more likely than those taking placebo to have a clinically significant reduction in dysmenorrhea: 42.1% and 46.2% in the low-dose groups; 75.3% and 76.9% in the high-dose groups; and 23.1% and 25.4% in the placebo groups and similarly have a clinically significant reduction in and nonmenstrual pelvic pain: 45.7% and 51.6% in the low-dose groups; 62.1% and 62.2% in the high-dose groups; and 34.9% and 40.6% in the placebo groups (P < .001 for all comparisons).[50] Similarly, in replicate clinical trials assessing relugolix, 638 and 623 women were randomized. In both studies 75% in the relugolix group had clinically significant improvement in dysmenorrhea vs 27% and 30% in the placebo groups, respectively; 59% in the first study and 66% in the second study had significant improvement in nonmenstrual pelvic pain vs 40% and 43% in the placebo groups, respectively (P < .001 for all comparisons),[51] with sustained efficacy and tolerability at 2 years.[52]

Aromatase inhibitors are not currently FDA-approved for endometriosis treatment but can be considered as third-line hormonal therapy for patients who do not improve with first-line and second-line hormonal treatments, based on low-quality evidence.[53]

Surgical Treatment of Endometriosis Lesions

International guidelines recommend offering surgery as an option for endometriosis-associated pain if medical treatment is contraindicated, ineffective, or has unacceptable adverse effects.[36-39,46] Surgery should be considered for patients with ovarian endometriomas of any size that have features concerning for malignancy or are large (>5 cm), due to low likelihood of resolution with hormone treatment and risk of ovarian torsion. Based on expert opinion, surgical removal of endometriosis lesions should be performed for deep endometriosis causing hematuria, hematochezia, or obstructive conditions of the urinary or intestinal tract. Evidence supporting the effectiveness of surgery is limited to observational and small randomized studies with follow-up periods of 1 year, often not including or differentiating between endometriosis subtypes.[23,56] In a systematic review of studies of women who underwent surgical removal of endometriosis lesions without postoperative hormone treatment (9 RCTs, 9 prospective, 7 retrospective cohort studies, n = 2652), persistent pain and adverse events such as hemorrhage or fever were reported in 25.0% and 8.1% of women, respectively, at a median follow-up of 24 months.[57]

Surgical efficacy in improving pain varies by endometriosis subtype. Evidence supporting efficacy of laparoscopic surgical removal of superficial peritoneal lesions for pain relief is limited.[58] High-quality evidence comparing efficacy of excision vs ablation (eg, via CO_2 laser) of superficial endometrial lesions is lacking; practice reflects surgeon preference.[59]

For ovarian endometriomas, RCTs have not been performed comparing surgery with no treatment for pain relief. A 2024 Cochrane review of 9 RCTs (n = 578) reported that ovarian cystectomy was associated with reduced dysmenorrhea and cyst recurrence compared with cyst drainage and ablation (dysmenorrhea, 19.5% vs 49.3%; n = 140; P < .001; cyst recurrence, 9.1% vs 36.9%; n = 264; P < .001).[60] However, ovarian cystectomy may harm fertility, as shown by a 38% reduction in postoperative anti-Müllerian hormone levels, a biomarker of ovarian reserve (meta-analysis of 8 studies, n = 237; weighted average preoperative hormone levels, 3.0 ng/mL).[61]

For deep endometriosis, surgical removal may reduce endometriosis-associated pain and improve quality of life.[39] Endometriosis lesions can be excised from most locations. However, resection near or involving the ureter, bowel, or thorax carries increased risk, warranting interdisciplinary care with colorectal, urological, and/or thoracic surgeons. A multicenter prospective cohort study (n = 4721) reported that laparoscopic excision of deep rectovaginal endometriosis was associated with a reduction in menstrual pain 24 months postoperatively.[62] Menstrual pain, measured using a 0 to 10 numeric scale, decreased from a preoperative median of 9 (95% CI, 9-9) to a postoperative score of 5 (95% CI, 4-6), noncyclical pelvic pain from 6 (95% CI, 6-6) to 3 (95% CI, 2-3), deep dyspareunia from 6 (95% CI, 5-6) to 2 (95% CI, 1-2), and cyclical dyschezia from 6 (95% CI, 6-6) to 2 (95% CI, 1-3; P < .001 for all comparisons; minimum clinically important difference, 4).[63] Complications occurred in 7%, with hemorrhage and conversion to laparotomy occurring in less than 1% of patients,[62] supporting the recommendation that experienced surgeons perform deep endometriosis removal.[37-39,64]

Postsurgical Recurrence and Hormone Suppression

A systematic review of 25 studies (9 RCTs, 8 prospective cohort studies, 7 retrospective studies, and 1 longitudinal unmatched study; n = 2652; median follow-up, 24 months) of surgical outcomes without postoperative hormone treatment reported recurrent pain in 15.8% of patients following surgical removal of lesions.[57] A meta-analysis of 11 RCTs and 3 prospective cohort studies (n = 1766) reported postoperative hormonal suppression was associated with reduced endometriosis recurrence at a median follow-up of 18 months based on symptoms or imaging (10.7% vs 26.4%, relative

risk, 0.41; 95% CI, 0.26 to 0.65).[65] Based on a meta-analysis of 6 RCTs and 1 prospective cohort study (n = 652), postoperative hormonal suppression was associated with lower pain scores (standard mean difference, −0.49 [small effect], 95% CI, −0.91 to −0.07) compared with no treatment or placebo.[65]

Hysterectomy

Guidelines recommend offering hysterectomy to women with endometriosis who are not interested in pursuing pregnancy and have treatment-resistant pain, ie, pain despite hormonal suppression and surgical removal of lesions.[36-39,46] However, the quality of evidence for hysterectomy for pain management is low given a lack of randomized trials, short follow-up, and inconsistent outcome definitions.[66,67] A Canadian retrospective cohort study of 4489 individuals who underwent hysterectomy for endometriosis reported a 10.5% reoperation rate (most commonly, oophorectomy and adhesiolysis) within 10 years.[67]

Although not specifically studied in endometriosis, there is evidence that hysterectomy with and without oophorectomy is associated with increased incidence of cardiovascular, metabolic, and mental health disorders, which should be discussed with patients prior to surgery.[68-70] Thus, guidelines recommend offering hysterectomy with excision of endometriosis lesions only to women with persistent pain that reduces quality of life, who do not desire future fertility, and have not responded to other treatments.[36-39,46] Given the risks of surgical menopause and insufficient evidence for pain improvement, ovarian conservation is preferred if the ovaries are normal and there is no known genetic risk of ovarian cancer (eg, *BRCA1*).[71,72]

Adjunct Therapies

Guidelines advise that clinicians discuss nonmedical therapies that may enhance quality of life,[39] such as pelvic floor physical therapy,[73] pain-focused psychological interventions,[74-76] pain education,[77] exercise,[78] dietary modification such as antioxidant use,[79] and acupuncture.[80] Patient education is recommended to help women understand their condition and make informed decisions about treatment.[77,81] However, guidelines do not provide recommendations about specific adjunct treatments due to limited evidence in patients with endometriosis.

Treatment of Endometriosis-Associated Infertility

Hormonal Treatment

Guidelines advise against prescribing hormonal suppression, such as with combined hormonal contraceptives, progestins, or GnRH agonists or antagonists, for women with endometriosis for the sole purpose of enhancing future fertility, including for those planning pregnancy after endometriosis surgery because there is no evidence supporting their efficacy in either situation.[39]

Surgical Treatment

Moderate-quality evidence from a meta-analysis of 3 RCTs with 528 participants suggests laparoscopic treatment (ablation or excision) of superficial peritoneal endometriosis increases viable intrauterine pregnancy rates compared with diagnostic laparoscopy alone (302 vs 186 viable pregnancies per 1000 persons, odds ratio, 1.89; 95% CI, 1.25-2.86).[58] However, data on live birth rates are lacking. No RCTs have been published assessing fertility outcomes after surgery for ovarian or deep endometriosis.

Assisted Reproductive Technology

Guidelines, based on meta-analyses of observational studies,[39] state that assisted reproductive technology such as in vitro fertilization can be used for endometriosis-associated infertility.[26,82] Surgery to remove endometriosis lesions for the sole purpose of improving fertility prior to assisted reproductive technology is not recommended because the potential benefits are unclear.[26]

Practical Considerations and Applications of Evidence

Care of patients may be challenging due to the nonspecific and varying symptoms associated with endometriosis. Pain severity does not correlate with subtype of endometriosis lesions,[31,32] and hormone response does not confirm the diagnosis because pelvic pain of other etiologies, such as primary dysmenorrhea and adenomyosis, also improves with hormone treatment.[83] Furthermore, medications and surgery for endometriosis lesions do not consistently alleviate pain and nearly 50% of patients with a history of endometriosis who undergo a hysterectomy for recurrent pelvic pain do not have evidence of recurrent endometriosis lesions.[84]

Untreated neuropathic and nociplastic pain likely contribute to pain associated with endometriosis, and patients with endometriosis commonly have other painful conditions. For example, 25% of women with endometriosis have at least 1 coexisting pain disorder such as migraine headache, irritable bowel syndrome, interstitial cystitis, or fibromyalgia.[85-87] Although no clinical trials have assessed treating nociplastic pain in patients with endometriosis, those with higher levels of nociplastic pain report greater pain intensity[88] and are less likely to report pain improvement when undergoing hysterectomy[89] or surgical removal of lesions.[90] Therefore, interdisciplinary care including a gynecologist, physiotherapist, and psychologist should be encouraged.[91] Repeated surgeries should be avoided whenever possible because there are no high-quality studies that demonstrate benefit.

Comorbidities

Patients with endometriosis have an increased lifetime risk of ovarian cancer compared with an incidence of approximately 1.1% among all women.[92] A meta-analysis of 24 studies (7 case-control, 14 retrospective, and 3 prospective cohort studies) reported a 93% greater risk of a diagnosis of any type of ovarian cancer among patients with endometriosis.[93] Five meta-analyzed studies confirmed a 3.4-fold and a 2.3-fold greater risk of clear cell and endometrioid cancer subtypes, respectively, among patients with endometriosis compared with those without endometriosis.[93] A recent study reported risk ranging from 4-fold to 19-fold by cancer subtypes among women with endometriosis.[94] However, when accounting for detection bias, the risk estimate corrected to 1.71, consistent with the 24 study meta-analysis.[95] Prophylactic bilateral salpingo-oophorectomy to reduce ovarian cancer risk in patients with normal-appearing ovaries is not recommended by guidelines,[39] given the low absolute rate of ovarian cancer and evidence of adverse consequences of surgical menopause.[72] Individuals with endometriosis are also at increased risk of autoimmune conditions (eg, systemic lupus erythematosus and rheumatoid arthritis[96]), cerebrovascular conditions including myocardial infarction[97] and stroke,[98] and long COVID.[99]

Limitations

This review has several limitations. First, some guideline recommendations are based on low-quality studies. Second, there is

heterogeneity in endometriosis subtypes that most studies do not assess. Third, some studies may have been missed.

Conclusions

Endometriosis is a common cause of pelvic pain affecting approximately 10% of reproductive-age women. Hormonal suppression including combined estrogen-progestin contraceptives or progestins is the first-line treatment in women who are not seeking immediate pregnancy. Surgical removal of endometriosis lesions may be performed if hormonal therapies are ineffective or contraindicated, and hysterectomy may be considered if medical treatments and surgical removal of lesions do not relieve symptoms. Treatment should be based on patient preference, symptom severity, and fertility goals, which may change over the life course.

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