Title: Endometriosis: A Review

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Abstract

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, non-menstrual 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. While definitive diagnosis requires surgical visualization of lesions, a suspected clinical diagnosis can be made based on symptoms, supported by physical exam findings and imaging with transvaginal ultrasound and/or pelvic MRI; normal exam and imaging do not exclude the diagnosis. The diagnosis is often delayed, averaging 5-12 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 pre-menopausal women who do not currently desire pregnancy. In a network meta-analysis (n=1,680, 15 clinical trials), hormonal treatments including combined oral contraceptives, progestins, and gonadotropin releasing hormone (GnRH) agonists, led to clinically significant greater pain reduction compared with placebo, with mean difference ranging between 13.15 to 17.6 points (0-100 visual analogue scale) with little difference in effectiveness among options. However, 11-19% of individuals with endometriosis have no pain reduction with hormonal medications and 25-34% 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 other 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 & Relevance: 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 first-line treatment in women who are not seeking immediate pregnancy. Surgical excision 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.

Introduction

Endometriosis is a chronic, estrogen-dependent disease defined by the presence of endometrium-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 healthcare 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 5-12 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 0.3-8.6 years from first consultation to diagnosis.[7]

This review summarizes the epidemiology, pathophysiology, diagnosis, and treatment of endometriosis. We use "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/meta-analyses, 4 clinical trials, 31 observational studies, 9 practice guidelines/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] While a 10% prevalence of endometriosis among reproductive-aged 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/specialist clinic, hospital data/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; meta-analysis of 11 observational studies) of women presenting with chronic pelvic pain and 24.8% (95% CI=23.9-25.8; 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 to 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,[12] menstrual cycle intervals <28 days,[13] lower body mass index (per each 5 kg/m^2),[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, RR=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 as they may affect the diagnostic and treatment approach. Superficial peritoneal endometriosis lesions occur on the peritoneal surface or serosa of abdominal or pelvic viscera. Deep endometriosis lesions penetrate the pelvic peritoneal surface (e.g., uterosacral ligaments) or infiltrate the muscularis propria of pelvic visceral organs such as the bowel or urinary tract (bladder/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.[19] 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 (e.g., community hospital vs. endometriosis referral center), and pre-surgical 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 to contribute 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 extra-pelvic lesions.[20-22] 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.[20-22] However, pathophysiologic 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 any combination of nociceptive, neuropathic, and nociplastic mechanisms (Figure 2).[23] 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.[24] Endometriosis may affect fertility through multiple pathways, including impaired ovarian function, adhesions causing tubal blockage, and dysfunction of uterine endometrium.[22]

Clinical Presentation and Clinical Course

The most common presenting symptom is pelvic pain, including dysmenorrhea (painful menses), non-menstrual pelvic pain, and deep dyspareunia (pain with deep vaginal penetration). In a cross-sectional study of self-reported survey data from 940 women with surgically confirmed endometriosis, 89.3% reported at least one pelvic pain symptom, including 78.7% with dysmenorrhea, 69.4% with non-menstrual 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%, 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.[25, 26] 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 culdesac correlates with dyspareunia), but typically increases during menses.[27,28] Similar to patients with other chronic pain conditions,[24] 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).[29]

Symptoms of extrapelvic endometriosis reflect the location of the lesions and, similar to other endometriosis subtypes, typically worsen during menses.[19] 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.[30]

Assessment and Diagnosis

Physical examination

The World Endometriosis Research Foundation[31] and Society of Obstetricians and Gynecologists of Canada[32] provide recommendations on the physical exam of patients with suspected endometriosis using a trauma-informed framework, which minimizes distress, supports autonomy, and builds trust (Figure 3). While a pelvic exam cannot identify superficial peritoneal lesions, it may identify ovarian endometriomas, signs of deep endometriosis, and can evaluate for other causes of pelvic pain such as pelvic floor myalgia (diagnosed as tenderness with vaginal palpation of pelvic floor muscles). Several pelvic exam findings suggest deep endometriosis or ovarian endometriomas. In patients with surgically-confirmed deep endometriosis, 67-95% had palpable thickening, nodularity, or tenderness of the posterior cul-de-sac and/or decreased uterine mobility, and 75-90% had a palpable ovarian mass on pelvic examination prior to surgery.[33] Patients with suspected lesions outside of the pelvis, e.g. vagina (Figure 1), umbilicus, abdominal surgical scars, should be referred to a gynecologist for possible biopsy of these lesions..

Imaging

Multiple international guidelines[32,34-37] 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%, CI=92-99%) for ovarian endometriomas (8 studies, n=765), moderate sensitivity for deep endometriosis (79%, CI=69%-89%, 9 studies, n=934), but low sensitivity for superficial peritoneal lesions (65%, CI=27%-100%).[38] In 2024, the Society of Radiologists in Ultrasound published a consensus on 'augmented pelvic ultrasound' to improve the diagnosis of deep endometriosis.[39] This technique, supported by The European Society of Human Reproduction and Embryology,[37] the Society of Obstetricians and Gynecologists of Canada,[32] and The National Institute of Health and Care Excellence guidelines,[36] is not widely used in the US. Unlike routine transvaginal ultrasound, augmented pelvic ultrasound includes evaluation of the relative position of the ovaries (e.g. "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.[40]

Magnetic resonance imaging (MRI) enables evaluation of other pelvic organs, features of ovarian malignancy when ultrasound is inconclusive, and can diagnose extrapelvic endometriosis.[41] A systematic review (14 observational studies, n=1577) reported that MRI using an endometriosis-specific protocol interpreted by experienced radiologists had a sensitivity of 91-93.5% and a specificity of 86-87.5% for deep and ovarian endometriosis compared with laparoscopy or other forms of imaging.[42] Because no imaging modality has 100% sensitivity, absence of findings on imaging does not exclude the diagnosis of endometriosis.

Clinically-suspected versus surgically confirmed diagnosis

Histologic 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[32,34-37] recommend making a presumed diagnosis based on symptoms, supported by physical exam findings and pelvic imaging with ultrasound and/or MRI (Figures 3-4), although no validated diagnostic criteria exist. Additionally, no diagnostic blood or molecular markers for endometriosis have been validated in clinical populations.[43] This shift in diagnostic approach reflects awareness that requiring surgery for diagnosis may delay treatment. Moreover, surgery is not always accessible, and empiric hormonal treatment offers comparable overall efficacy to surgical removal of lesions (see below).

Treatment

Endometriosis is a chronic condition without medical or surgical cure. Current treatments include non-opioid 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[32, 36, 37] 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).

Pharmacologic treatment

<u>Analgesics</u>

Guidelines state that patients may be offered non-steroidal anti-inflammatory drugs (NSAIDs) for endometriosis-associated pain; NSAIDs can be used alone or in combination with hormonal treatments.[34-37,44] However, a 2017 Cochrane review found insufficient evidence that NSAIDs reduce pain in endometriosis, with only 1 low-quality trial of 24 participants.[45]

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 guidelines.[34-37,44] 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.[46] 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 1). Approximately 25-34% of women with endometriosis experience recurrent pelvic pain within 12 months of discontinuing hormonal therapy,[47] 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 20–30μg ethinyl estradiol) and progestin-only medications such as norethindrone acetate as first-line due to their low cost and few adverse effects. A network meta-analysis of 1,680 women from 15 RCTs reported that all hormonal treatments led to a similar clinically significant pain reduction measured using a 0–100 visual analogue scale (minimum clinically important difference=10 points).[36] Compared with placebo, combined oral contraceptives reduced pelvic pain by 15.1 points (mean difference 95%

CI -20.8, -9.3), oral progestogens by 12.6 points (95% CI -15.3, -9.8), progestogens delivered via intrauterine device (IUD, 52mg levonorgestrel system) by 17.7 points (95% CI -25.5, -9.8), intramuscular progestogens by 13.2 points (95% CI -16.2, -10.1) and intramuscular GnRH agonists (leuprolide acetate) by 15.7 points (95% CI -21.3, -10.1). However, a systematic review of 58 studies (38 RCTs, 14 prospective, 4 retrospective cohort studies) with 11,881 participants reported that 11–19% of women experienced no pain reduction with hormonal therapy and 5-59% still had some pain at the end of the study period despite hormone use.[47]

Guidelines recommend continuous use of a combined estrogen-progestin contraceptive (omitting the hormone-free interval) over cyclic use with the goal of achieving amenorrhea.[37] In a prospective cohort study of 293 women with endometriosis, continuous hormonal suppression was associated with lower frequency of dysmenorrhea (9.4% vs. 20.9%, p=0.02) and non-menstrual pelvic pain (9.4% vs. 20.9%, p<0.05) when compared with cyclic use.[48] Improvement in pelvic pain should be assessed in approximately 3 months. If 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.

Gonadotropin-releasing hormone (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.[36,37,44] GnRH agonists and antagonists are typically prescribed by gynecologists and usually not without surgical confirmation of endometriosis and removal of lesions, particularly in adolescents.[10,37] To counteract menopausal side-effects of GnRH medications, current guidelines[32,34,36,37] recommend co-administration 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, -0.02) without reduced efficacy in treating pelvic pain.[49]

In contrast to injectable GnRH agonists, GnRH antagonists are oral medications, have rapid onset of action, and quick return of menses once discontinued (e.g, median time to resumption of menses is 31 days for relugolix combination therapy[50]). There are 2 FDA-approved medications: elagolix (low dose=150mg once daily; high dose=200mg twice daily) and relugolix combination therapy (Table 1). In replicate randomized clinical trials (n=872 and n=817), elagolix-treated women were more likely to have a clinically significant reduction in dysmenorrhea (low dose=42.1-46.2%, high dose=75.3-76.9%, placebo= 34.9-40.6%) and non-menstrual pelvic pain (low dose=45.7-51.6%; high dose=62.1-62.2%; placebo=34.9-40.6%) at 6 months compared with placebo (*P*<.001 for all comparisons).[51] Similarly, in replicate randomized clinical trials (n=638 and n=623), 75% and 59-66% of women randomized to relugolix combination therapy had clinically significant improvement in dysmenorrhea and non-menstrual pelvic pain respectively, compared with 27-30% and 40–43% with placebo (*P*<.0001 for all comparisons),[50] 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.[34-37,44] Surgery should be considered in 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 ≤1year, often not including or differentiating between endometriosis subtypes.[22,54] 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.[55]

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.[56] High-quality evidence comparing efficacy of excision versus ablation (e.g., via CO2 laser) of superficial endometrial lesions is lacking; practice reflects surgeon preference.[57]

For ovarian endometriomas, RCTs have not been performed comparing surgery to no treatment for pain relief. A 2024 Cochrane review of 9 RCTs (n=578) reported ovarian cystectomy was associated with reduced dysmenorrhoea and cyst recurrence, compared with cyst drainage and ablation (dysmenorrhoea 19.5% vs. 49.3% (n=140, *P<.001)*; cyst recurrence 9.1% vs 36.9% (n=264, *P<.001*).[58] However, ovarian cystectomy may harm fertility, as shown by a 38% reduction in post-operative anti-Müllerian hormone levels, a biomarker of ovarian reserve (meta-analysis 8 studies, n=237, weighted average pre-operative hormone levels 3.0 ng/ml).[59]

For deep endometriosis, surgical removal may reduce endometriosis-associated pain and improve quality of life.[37] 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, urologic, and/or thoracic surgeons. A multi-center prospective cohort study (n=4721) reported that laparoscopic excision of deep rectovaginal endometriosis was associated with a reduction in menstrual pain 24 months postoperatively.[60] Menstrual pain, measured using a 0-10 numeric scale, decreased from a pre-operative median of 9 (95%CI=9-9) to a post-operative median

of 5 (95%CI=4-6), non-cyclical 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).[61] Complications occurred in 7%, with hemorrhage and conversion to laparotomy occurred in less than 1% of patients,[60] supporting the recommendation that experienced surgeons perform deep endometriosis removal.[35-37,62]

Postsurgical Recurrence and Hormone Suppression

A systematic review (25 studies [9 RCTs, 8 prospective cohort studies, 7 retrospective studies,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.[55] A meta-analysis of 11 RCTs and 3 prospective cohort studies (n=1766) reported post-operative hormonal suppression was associated with reduced endometriosis recurrence at a median follow-up 18 months based on symptoms or imaging (10.7% vs. 26.4%, RR 0.41, 95% CI=0.26–0.65).[63] Based on meta-analysis of 6 RCTs and 1 prospective cohort study (n=652), post-operative hormonal suppression was associated with lower pain scores (SMD -0.49 [small effect], 95% CI=-0.91–-0.07) compared with no treatment or placebo.[63]

Hysterectomy

Guidelines recommend offering hysterectomy to women with endometriosis who are not interested in pursuing pregnancy and have treatment-resistant pain, i.e. pain despite hormonal suppression and surgical removal of lesions.[34-37,44] However, the quality of evidence for hysterectomy for pain management is low given lack of randomized trials, short follow-up, and inconsistent outcome definitions.[64, 65] A Canadian retrospective cohort study of 4489 individuals who underwent hysterectomy for endometriosis reported a 10.5% re-operation rate, such as adhesiolysis, within 10 years.[65]

While 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.[66-68] 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.[34-37,44] Given 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 (e.g. BRCA1).[69,70]

Adjunct Therapies

Guidelines advise clinicians discuss non-medical therapies that may enhance quality of life,[37] such as pelvic floor physical therapy,[71] pain-focused psychological interventions,[72-74] pain education,[75] exercise,[76] dietary modification such as antioxidant use,[77] and acupuncture.[78] Patient education is recommended to help women understand their condition and make informed decisions about treatment.[75,79] However, guidelines do not provide recommendations about specific adjunct treatments due to limited evidence in patients with endometriosis.

Treatment of endometriosis-associated infertility

<u>Hormonal Treatment</u>

Guidelines advise against prescribing hormonal suppression, such as with combined hormonal contraceptives, progestins, or GnRH agonists/antagonists, for women with endometriosis for the sole purpose of enhancing future fertility, including for those planning pregnancy after endometriosis surgery, as there is no evidence supporting their efficacy in either situation.[37]

<u>Surgical Treatment</u>

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 versus 186 viable pregnancies per 1000 persons, OR 1.89, 95% CI=1.25–2.86).[56] 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,[37] state that assisted reproductive technology such as in vitro fertilization can be used for endometriosis-associated infertility.[80,81] Surgery to remove endometriosis lesions for the sole purpose of improving fertility prior to assisted reproductive technology is not recommended, as the potential benefits are unclear.[81]

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,[27,28] and hormone response does not confirm diagnosis because pelvic pain of other etiologies, such as primary dysmenorrhea and adenomyosis, also improves with hormone treatment.[82] 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.[83]

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 co-existing pain disorder such as migraine headache, irritable bowel syndrome, interstitial cystitis, or fibromyalgia.[84-86] While no clinical trials have assessed treating nociplastic pain in patients with endometriosis, those with higher levels of nociplastic pain report greater pain intensity[87] and are less likely to report pain improvement when undergoing hysterectomy[88] or surgical removal of lesions.[89] Therefore, interdisciplinary care including a gynecologist, physiotherapist, and psychologist should be encouraged.[90] Repeated

surgeries should be avoided whenever possible, as there are no high quality studies to 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.[91] A meta-analysis (24 studies: 7 case-control, 14 retrospective, 3 prospective cohort studies) reported a 93% greater risk for diagnosis of any type of ovarian cancer among patients with endometriosis.[92] 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 to those without endometriosis.[92] A recent study reported risk ranging from 4-fold to 19-fold by cancer subtypes among women with endometriosis.[93] However, when accounting for detection bias, the risk estimate corrected to 1.71- consistent with the 24 study meta-analysis.[94] Prophylactic bilateral salpingo-oophorectomy to reduce ovarian cancer risk in patients with normal-appearing ovaries is not recommended by guidelines[37] given the low absolute rate of ovarian cancer and evidence of adverse consequences of surgical menopause.[70] Individuals with endometriosis are also at increased risk for auto-immune conditions (e.g. systemic lupus erythematosus and rheumatoid arthritis[95]), cerebrovascular conditions including myocardial infarction[96] and stroke[97], and long COVID.[98]

Limitations

This review has several limitations. First, some guideline recommendations are based on low-quality studies. Second, there is heterogeneity in endometriosis subtypes and most studies do not assess these differences. 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

447 is first-line treatment in women who are not seeking immediate pregnancy. Surgical excision of
448 endometriosis lesions may be performed if hormonal therapies are ineffective or contraindicated,
449 and hysterectomy may be considered if medical treatments and surgical removal of lesions do not
450 relieve symptoms. Treatment should be based on patient preference, symptom severity, and fertility
451 goals, which may change over the life-course.

References

1. International Working Group of AAGL E, ESHRE and WES. , Tomassetti C, Johnson NP, et al. An international terminology for endometriosis, 2021. *Hum Reprod Open*. 2021;(4):hoab029. doi:10.1093/hropen/hoab029
2. Ghiasi M, Kulkarni MT, Missmer SA. Is Endometriosis More Common and More Severe Than It Was 30 Years Ago? *J Minim Invasive Gynecol*. Feb 2020;27(2):452-461. doi:10.1016/j.jmig.2019.11.018
3. Sinaii N, Plumb K, Cotton L, et al. Differences in characteristics among 1,000 women with endometriosis based on extent of disease. *Fertil Steril*. Mar 2008;89(3):538-45. doi:10.1016/j.fertnstert.2007.03.069
4. Ramin-Wright A, Schwartz ASK, Geraedts K, et al. Fatigue - a symptom in endometriosis. *Hum Reprod*. Aug 1 2018;33(8):1459-1465. doi:10.1093/humrep/dey115
5. As-Sanie S, Shafrir AL, Halvorson L, Chawla R, Hughes R, Merz M. The Burden of Pelvic Pain Associated With Endometriosis Among Women in Selected European Countries and the United States: A Restricted Systematic Review. *J Minim Invasive Gynecol*. Aug 2024;31(8):653-666 e5. doi:10.1016/j.jmig.2024.05.002
6. Soliman AM, Yang H, Du EX, Kelley C, Winkel C. The direct and indirect costs associated with endometriosis: a systematic literature review. *Hum Reprod*. Apr 2016;31(4):712-22. doi:10.1093/humrep/dev335
7. De Corte P, Klinghardt M, von Stockum S, Heinemann K. Time to Diagnose Endometriosis: Current Status, Challenges and Regional Characteristics-A Systematic Literature Review. *BJOG*. Jan 2025;132(2):118-130. doi:10.1111/1471-0528.17973
8. Nnoaham KE, Hummelshoj L, Webster P, et al. Impact of endometriosis on quality of life and work productivity: a multicenter study across ten countries. *Fertil Steril*. Aug 2011;96(2):366-373.e8. doi:10.1016/j.fertnstert.2011.05.090
9. Soliman AM, Fuldeore M, Snabes MC. Factors Associated with Time to Endometriosis Diagnosis in the United States. *J Womens Health (Larchmt)*. Jul 2017;26(7):788-797. doi:10.1089/jwh.2016.6003
10. Shim JY, Laufer MR, King CR, Lee TTM, Einarsson JI, Tyson N. Evaluation and Management of Endometriosis in the Adolescent. *Obstet Gynecol*. Jan 1 2024;143(1):44-51. doi:10.1097/AOG.0000000000005448
11. Vercellini P, Salmeri N, Somigliana E, et al. Mullerian anomalies and endometriosis as potential explanatory models for the retrograde menstruation/implantation and the embryonic remnants/celomic metaplasia pathogenic theories: a systematic review and meta-analysis. *Hum Reprod*. May 10 2024;doi:10.1093/humrep/deae086
12. Lu MY, Niu JL, Liu B. The risk of endometriosis by early menarche is recently increased: a meta-analysis of literature published from 2000 to 2020. *Arch Gynecol Obstet*. Jan 2023;307(1):59-69. doi:10.1007/s00404-022-06541-0
13. Wei M, Cheng Y, Bu H, Zhao Y, Zhao W. Length of Menstrual Cycle and Risk of Endometriosis: A Meta-Analysis of 11 Case-Control Studies. *Medicine (Baltimore)*. Mar 2016;95(9):e2922. doi:10.1097/MD.0000000000002922
14. Liu Y, Zhang W. Association between body mass index and endometriosis risk: a meta-analysis. *Oncotarget*. Jul 18 2017;8(29):46928-46936. doi:10.18632/oncotarget.14916
15. Missmer SA, Hankinson SE, Spiegelman D, et al. Reproductive history and endometriosis among premenopausal women. *Obstet Gynecol*. Nov 2004;104(5 Pt 1):965-74. doi:10.1097/01.AOG.0000142714.54857.f8
16. Saha R, Pettersson HJ, Svedberg P, et al. Heritability of endometriosis. *Fertil Steril*. Oct 2015;104(4):947-52. doi:10.1016/j.fertnstert.2015.06.035
17. Treloar SA, O'Connor DT, O'Connor VM, Martin NG. Genetic influences of endometriosis in an Australian twin sample. *FertilSteril*. 1999;71(4):701-710. IN FILE.

18. Stefansson H, Geirsson RT, Steinthorsdottir V, et al. Genetic factors contribute to the risk of developing endometriosis. *Hum Reprod*. Mar 2002;17(3):555-9. doi:10.1093/humrep/17.3.555
19. Andres MP, Arcoverde FVL, Souza CCC, Fernandes LFC, Abrao MS, Kho RM. Extrapelvic Endometriosis: A Systematic Review. *J Minim Invasive Gynecol*. Feb 2020;27(2):373-389. doi:10.1016/j.jmig.2019.10.004
20. Saunders PTK, Horne AW. Endometriosis: Etiology, pathobiology, and therapeutic prospects. *Cell*. May 27 2021;184(11):2807-2824. doi:10.1016/j.cell.2021.04.041
21. Zondervan KT, Becker CM, Missmer SA. Endometriosis. *N Engl J Med*. Mar 26 2020;382(13):1244-1256. doi:10.1056/NEJMra1810764
22. Horne AW, Missmer SA. Pathophysiology, diagnosis, and management of endometriosis. *Bmj*. Nov 14 2022;379:e070750. doi:10.1136/bmj-2022-070750
23. Coxon L, Demetriou L, Vincent K. Current developments in endometriosis-associated pain. *Cell Rep Med*. Oct 15 2024;5(10):101769. doi:10.1016/j.xcrm.2024.101769
24. Kaplan CM, Kelleher E, Irani A, Schrepf A, Clauw DJ, Harte SE. Deciphering Nociplastic Pain: Clinical Features, Risk Factors and Potential Mechanisms. Jun 2024;20(6):347-363. doi:10.1038/s41582-024-00966-8
25. Musat F, Paduraru DN, Bolocan A, Constantinescu A, Ion D, Andronic O. Endometriosis as an Uncommon Cause of Intestinal Obstruction-A Comprehensive Literature Review. *J Clin Med*. Oct 6 2023;12(19)doi:10.3390/jcm12196376
26. Leone Roberti Maggiore U, Ferrero S, Candiani M, Somigliana E, Vigano P, Vercellini P. Bladder Endometriosis: A Systematic Review of Pathogenesis, Diagnosis, Treatment, Impact on Fertility, and Risk of Malignant Transformation. *Eur Urol*. May 2017;71(5):790-807. doi:10.1016/j.eururo.2016.12.015
27. Pashkunova D, Darici E, Senft B, et al. Lesion size and location in deep infiltrating bowel endometriosis: Correlation with gastrointestinal dysfunction and pain. *Acta Obstet Gynecol Scand*. Sep 2024;103(9):1764-1770. doi:10.1111/aogs.14921
28. Vercellini P, Fedele L, Aimi G, Pietropaolo G, Consonni D, Crosignani PG. Association between endometriosis stage, lesion type, patient characteristics and severity of pelvic pain symptoms: a multivariate analysis of over 1000 patients. *Hum Reprod*. Jan 2007;22(1):266-71. doi:10.1093/humrep/del339
29. Thiel PS, Bougie O, Pudwell J, Shellenberger J, Velez MP, Murji A. Endometriosis and mental health: a population-based cohort study. *Am J Obstet Gynecol*. Feb 1 2024;doi:10.1016/j.ajog.2024.01.023
30. Gemmell LC, Webster KE, Kirtley S, Vincent K, Zondervan KT, Becker CM. The management of menopause in women with a history of endometriosis: a systematic review. *Hum Reprod Update*. Jul 1 2017;23(4):481-500. doi:10.1093/humupd/dmx011
31. Lin T, Allaire C, As-Sanie S, et al. World Endometriosis Research Foundation Endometriosis Phenome and Biobanking Harmonization Project: V. physical examination standards in endometriosis research. *Fertil Steril*. Mar 18 2024;doi:10.1016/j.fertnstert.2024.03.007
32. Singh SS, Allaire C, Al-Nourhji O, et al. Guideline No. 449: Diagnosis and Impact of Endometriosis - A Canadian Guideline. *J Obstet Gynaecol Can*. Mar 28 2024:102450. doi:10.1016/j.jogc.2024.102450
33. Taylor HS, Adamson GD, Diamond MP, et al. An evidence-based approach to assessing surgical versus clinical diagnosis of symptomatic endometriosis. *Int J Gynaecol Obstet*. Aug 2018;142(2):131-142. doi:10.1002/ijgo.12521
34. Practice bulletin no. 114: management of endometriosis. *Obstet Gynecol*. Jul 2010;116(1):223-236. doi:10.1097/AOG.0b013e3181e8b073
35. Australian clinical practice guideline for the diagnosis and management of endometriosis (2021). RANZCOG, Melbourne, Australia. . https://ranzcog.edu.au/wp-content/uploads/2022/02/Endometriosis-clinical-practice-guideline.pdf

36. National Institute for Health and Care Excellence. Endometriosis: diagnosis and management (NICE Guideline 37). Published 6 September 2017, Last updated 16 April 2024. Accessed January 13, 2025, https://www.nice.org.uk/guidance/ng73; https://www.nice.org.uk/guidance/ng73/evidence/full-guideline-pdf-4550371315
37. Becker CM, Bokor A, Heikinheimo O, et al. ESHRE guideline: endometriosis. *Hum Reprod Open*. 2022;2022(2):hoac009. doi:10.1093/hropen/hoac009
38. Nisenblat V, Bossuyt PM, Farquhar C, Johnson N, Hull ML. Imaging modalities for the non-invasive diagnosis of endometriosis. *Cochrane Database Syst Rev*. Feb 26 2016;2(2):Cd009591. doi:10.1002/14651858.CD009591.pub2
39. Young SW, Jha P, Chamie L, et al. Society of Radiologists in Ultrasound Consensus on Routine Pelvic US for Endometriosis. *Radiology*. Apr 2024;311(1):e232191. doi:10.1148/radiol.232191
40. Leonardi M, Uzuner C, Mestdagh W, et al. Diagnostic accuracy of transvaginal ultrasound for detection of endometriosis using International Deep Endometriosis Analysis (IDEA) approach: prospective international pilot study. *Ultrasound Obstet Gynecol*. Sep 2022;60(3):404-413. doi:10.1002/uog.24936
41. VanBuren W, Feldman M, Shenoy-Bhangle AS, et al. Radiology State-of-the-art Review: Endometriosis Imaging Interpretation and Reporting. *Radiology*. Sep 2024;312(3):e233482. doi:10.1148/radiol.233482
42. Avery JC, Knox S, Deslandes A, et al. Noninvasive diagnostic imaging for endometriosis part 2: a systematic review of recent developments in magnetic resonance imaging, nuclear medicine and computed tomography. *Fertil Steril*. Feb 2024;121(2):189-211. doi:10.1016/j.fertnstert.2023.12.017
43. Gibbons T, Rahmioglu N, Zondervan KT, Becker CM. Crimson clues: advancing endometriosis detection and management with novel blood biomarkers. *Fertil Steril*. Feb 2024;121(2):145-163. doi:10.1016/j.fertnstert.2023.12.018
44. Leyland N, Casper R, Laberge P, Singh SS, Canada SoOaGo. Endometriosis: diagnosis and management. *J Obstet Gynaecol Can*. Jul 2010;32(7 Suppl 2):S1-32.
45. Brown J, Crawford TJ, Allen C, Hopewell S, Prentice A. Nonsteroidal anti-inflammatory drugs for pain in women with endometriosis. *Cochrane Database Syst Rev*. Jan 23 2017;1(1):Cd004753. doi:10.1002/14651858.CD004753.pub4
46. Alonso A, Gunther K, Maheux-Lacroix S, Abbott J. Medical management of endometriosis. *Curr Opin Obstet Gynecol*. Oct 1 2024;36(5):353-361. doi:10.1097/GCO.0000000000000983
47. Becker CM, Gattrell WT, Gude K, Singh SS. Reevaluating response and failure of medical treatment of endometriosis: a systematic review. *Fertil Steril*. Jul 2017;108(1):125-136. doi:10.1016/j.fertnstert.2017.05.004
48. Vlahos N, Vlachos A, Triantafyllidou O, Vitoratos N, Creatsas G. Continuous versus cyclic use of oral contraceptives after surgery for symptomatic endometriosis: a prospective cohort study. *Fertil Steril*. Nov 2013;100(5):1337-42. doi:10.1016/j.fertnstert.2013.07.008
49. Wu D, Hu M, Hong L, et al. Clinical efficacy of add-back therapy in treatment of endometriosis: a meta-analysis. *Arch Gynecol Obstet*. Sep 2014;290(3):513-23. doi:10.1007/s00404-014-3230-8
50. Giudice LC, As-Sanie S, Arjona Ferreira JC, et al. Once daily oral relugolix combination therapy versus placebo in patients with endometriosis-associated pain: two replicate phase 3, randomised, double-blind, studies (SPIRIT 1 and 2). *Lancet*. Jun 18 2022;399(10343):2267-2279. doi:10.1016/s0140-6736(22)00622-5
51. Taylor HS, Giudice LC, Lessey BA, et al. Treatment of Endometriosis-Associated Pain with Elagolix, an Oral GnRH Antagonist. *N Engl J Med*. Jul 6 2017;377(1):28-40. doi:10.1056/NEJMoa1700089
52. Becker CM, Johnson NP, As-Sanie S, et al. Two-year efficacy and safety of relugolix combination therapy in women with endometriosis-associated pain: SPIRIT open-label extension study. *Hum Reprod*. Mar 1 2024;39(3):526-537. doi:10.1093/humrep/dead263

603 53. Peitsidis P, Tsikouras P, Laganà AS, Laios A, Gkegkes ID, Iavazzo C. A Systematic Review of
604 Systematic Reviews on the Use of Aromatase Inhibitors for the Treatment of Endometriosis: The
605 Evidence to Date. *Drug Des Devel Ther*. 2023;17:1329-1346. doi:10.2147/dddt.S315726
606 54. Leonardi M, Gibbons T, Armour M, et al. When to Do Surgery and When Not to Do Surgery
607 for Endometriosis: A Systematic Review and Meta-analysis. *J Minim Invasive Gynecol*. Feb
608 2020;27(2):390-407.e3. doi:10.1016/j.jmig.2019.10.014
609 55. Singh SS, Gude K, Perdeaux E, Gattrell WT, Becker CM. Surgical Outcomes in Patients With
610 Endometriosis: A Systematic Review. *J Obstet Gynaecol Can*. Jul 2020;42(7):881-888.e11.
611 doi:10.1016/j.jogc.2019.08.004
612 56. Bafort C, Beebeejaun Y, Tomassetti C, Bosteels J, Duffy JM. Laparoscopic surgery for
613 endometriosis. *Cochrane Database Syst Rev*. Oct 23 2020;10(10):Cd011031.
614 doi:10.1002/14651858.CD011031.pub3
615 57. Burks C, Lee M, DeSarno M, Findley J, Flyckt R. Excision versus Ablation for Management of
616 Minimal to Mild Endometriosis: A Systematic Review and Meta-analysis. *J Minim Invasive Gynecol*.
617 Mar 2021;28(3):587-597. doi:10.1016/j.jmig.2020.11.028
618 58. Kalra R, McDonnell R, Stewart F, Hart RJ, Hickey M, Farquhar C. Excisional surgery versus
619 ablative surgery for ovarian endometrioma. *Cochrane Database Syst Rev*. Nov 26
620 2024;11(11):CD004992. doi:10.1002/14651858.CD004992.pub4
621 59. Raffi F, Metwally M, Amer S. The impact of excision of ovarian endometrioma on ovarian
622 reserve: a systematic review and meta-analysis. *J Clin Endocrinol Metab*. Sep 2012;97(9):3146-54.
623 doi:10.1210/jc.2012-1558
624 60. Byrne D, Curnow T, Smith P, Cutner A, Saridogan E, Clark TJ. Laparoscopic excision of deep
625 rectovaginal endometriosis in BSGE endometriosis centres: a multicentre prospective cohort study.
626 *BMJ Open*. Apr 9 2018;8(4):e018924. doi:10.1136/bmjopen-2017-018924
627 61. Wickstrom K, Edelstam G. Minimal clinically important difference for pain on the VAS scale
628 and the relation to quality of life in women with endometriosis. *Sex Reprod Healthc*. Oct 2017;13:35-
629 40. doi:10.1016/j.srhc.2017.05.004
630 62. Ceccaroni M, Bounous VE, Clarizia R, Mautone D, Mabrouk M. Recurrent endometriosis: a
631 battle against an unknown enemy. *Eur J Contracept Reprod Health Care*. Dec 2019;24(6):464-474.
632 doi:10.1080/13625187.2019.1662391
633 63. Zakhari A, Delpero E, McKeown S, Tomlinson G, Bougie O, Murji A. Endometriosis recurrence
634 following post-operative hormonal suppression: a systematic review and meta-analysis. *Hum Reprod*
635 *Update*. Jan 4 2021;27(1):96-107. doi:10.1093/humupd/dmaa033
636 64. Lewin J, Vashisht A, Hirsch M, Al-Wattar BH, Saridogan E. Comparing the treatment of
637 endometriosis-related pain by excision of endometriosis or hysterectomy: A multicentre prospective
638 cohort study. *BJOG*. Jul 15 2024;doi:10.1111/1471-0528.17910
639 65. Long AJ, Kaur P, Lukey A, et al. Reoperation and pain-related outcomes after hysterectomy for
640 endometriosis by oophorectomy status. *Am J Obstet Gynecol*. Jan 2023;228(1):57.e1-57.e18.
641 doi:10.1016/j.ajog.2022.08.044
642 66. Honigberg MC, Zekavat SM, Aragam K, et al. Association of Premature Natural and Surgical
643 Menopause With Incident Cardiovascular Disease. *JAMA*. Dec 24 2019;322(24):2411-2421.
644 doi:10.1001/jama.2019.19191
645 67. Laughlin-Tommaso SK, Khan Z, Weaver AL, Smith CY, Rocca WA, Stewart EA. Cardiovascular
646 and metabolic morbidity after hysterectomy with ovarian conservation: a cohort study. *Menopause*.
647 May 2018;25(5):483-492. doi:10.1097/GME.0000000000001043
648 68. Laughlin-Tommaso SK, Satish A, Khan Z, Smith CY, Rocca WA, Stewart EA. Long-term risk of
649 de novo mental health conditions after hysterectomy with ovarian conservation: a cohort study.
650 *Menopause*. Jan 2020;27(1):33-42. doi:10.1097/GME.0000000000001415
651 69. Kvaskoff M, Horne AW, Missmer SA. Informing women with endometriosis about ovarian
652 cancer risk. *Lancet*. Dec 2 2017;390(10111):2433-2434. doi:10.1016/S0140-6736(17)33049-0

70. Stewart EA, Missmer SA, Rocca WA. Moving Beyond Reflexive and Prophylactic Gynecologic Surgery. *Mayo Clin Proc*. Feb 2021;96(2):291-294. doi:10.1016/j.mayocp.2020.05.012
71. Abril-Coello R, Correyero-León M, Ceballos-Laita L, Jiménez-Barrio S. Benefits of physical therapy in improving quality of life and pain associated with endometriosis: A systematic review and meta-analysis. *Int J Gynaecol Obstet*. Jul 2023;162(1):233-243. doi:10.1002/ijgo.14645
72. Till SR, As-Sanie S, Schrepf A. Psychology of Chronic Pelvic Pain: Prevalence, Neurobiological Vulnerabilities, and Treatment. *Clin Obstet Gynecol*. Mar 2019;62(1):22-36. doi:10.1097/grf.0000000000000412
73. Hansen KE, Brandsborg B, Kesmodel US, et al. Psychological interventions improve quality of life despite persistent pain in endometriosis: results of a 3-armed randomized controlled trial. *Qual Life Res*. Jun 2023;32(6):1727-1744. doi:10.1007/s11136-023-03346-9
74. Samami E, Shahhosseini Z, Khani S, Elyasi F. Pain-focused psychological interventions in women with endometriosis: A systematic review. *Neuropsychopharmacol Rep*. Sep 2023;43(3):310-319. doi:10.1002/npr2.12348
75. Mardon AK, Leake HB, Szeto K, Moseley GL, Chalmers KJ. Recommendations for patient education in the management of persistent pelvic pain: a systematic review of clinical practice guidelines. *Pain*. Dec 19 2023;doi:10.1097/j.pain.0000000000003137
76. Tennfjord MK, Gabrielsen R, Tellum T. Effect of physical activity and exercise on endometriosis-associated symptoms: a systematic review. *BMC Womens Health*. Oct 9 2021;21(1):355. doi:10.1186/s12905-021-01500-4
77. Meneghetti JK, Pedrotti MT, Coimbra IM, da Cunha-Filho JSL. Effect of Dietary Interventions on Endometriosis: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Reprod Sci*. Dec 2024;31(12):3613-3623. doi:10.1007/s43032-024-01701-w
78. Giese N, Kwon KK, Armour M. Acupuncture for endometriosis: A systematic review and meta-analysis. *Integr Med Res*. Dec 2023;12(4):101003. doi:10.1016/j.imr.2023.101003
79. Mardon AK, Leake HB, Hayles C, et al. The Efficacy of Self-Management Strategies for Females with Endometriosis: a Systematic Review. *Reprod Sci*. Feb 2023;30(2):390-407. doi:10.1007/s43032-022-00952-9
80. Harb HM, Gallos ID, Chu J, Harb M, Coomarasamy A. The effect of endometriosis on in vitro fertilisation outcome: a systematic review and meta-analysis. *BJOG*. Oct 2013;120(11):1308-20. doi:10.1111/1471-0528.12366
81. Hamdan M, Omar SZ, Dunselman G, Cheong Y. Influence of endometriosis on assisted reproductive technology outcomes: a systematic review and meta-analysis. *Obstet Gynecol*. Jan 2015;125(1):79-88. doi:10.1097/AOG.0000000000000592
82. Lamvu G, Carrillo J, Ouyang C, Rapkin A. Chronic Pelvic Pain in Women: A Review. *JAMA*. Jun 15 2021;325(23):2381-2391. doi:10.1001/jama.2021.2631
83. Mowers EL, Lim CS, Skinner B, et al. Prevalence of Endometriosis During Abdominal or Laparoscopic Hysterectomy for Chronic Pelvic Pain. *Obstet Gynecol*. Jun 2016;127(6):1045-1053. doi:10.1097/AOG.0000000000001422
84. Schrepf A, Phan V, Clemens JQ, Maixner W, Hanauer D, Williams DA. ICD-10 Codes for the Study of Chronic Overlapping Pain Conditions in Administrative Databases. *J Pain*. Jan-Feb 2020;21(1-2):59-70. doi:10.1016/j.jpain.2019.05.007
85. Smorgick N, Marsh CA, As-Sanie S, Smith YR, Quint EH. Prevalence of pain syndromes, mood conditions, and asthma in adolescents and young women with endometriosis. *J Pediatr Adolesc Gynecol*. Jun 2013;26(3):171-5. doi:10.1016/j.jpag.2012.12.006
86. Sasamoto N, Shafrir AL, Wallace BM, et al. Trends in pelvic pain symptoms over 2 years of follow-up among adolescents and young adults with and without endometriosis. *Pain*. Mar 1 2023;164(3):613-624. doi:10.1097/j.pain.0000000000002747
87. Till SR, Schrepf A, Clauw DJ, Harte SE, Williams DA, As-Sanie S. Association Between Nociplastic Pain and Pain Severity and Impact in Women With Chronic Pelvic Pain. *J Pain*. Aug 2023;24(8):1406-1414. doi:10.1016/j.jpain.2023.03.004

88. As-Sanie S, Till SR, Schrepf AD, et al. Incidence and predictors of persistent pelvic pain following hysterectomy in women with chronic pelvic pain. *Am J Obstet Gynecol*. Nov 2021;225(5):568.e1-568.e11. doi:10.1016/j.ajog.2021.08.038
89. Orr NL, Huang AJ, Liu YD, et al. Association of Central Sensitization Inventory Scores With Pain Outcomes After Endometriosis Surgery. *JAMA Netw Open*. Feb 1 2023;6(2):e230780. doi:10.1001/jamanetworkopen.2023.0780
90. Fang QY, Campbell N, Mooney SS, Holdsworth-Carson SJ, Tyson K. Evidence for the role of multidisciplinary team care in people with pelvic pain and endometriosis: A systematic review. *Aust N Z J Obstet Gynaecol*. Sep 27 2023;doi:10.1111/ajo.13755
91. Key Statistics for Ovarian Cancer. Accessed 02/04/2025, https://www.cancer.org/cancer/types/ovarian-cancer/about/key-statistics.html
92. Kvaskoff M, Mahamat-Saleh Y, Farland LV, et al. Endometriosis and cancer: a systematic review and meta-analysis. *Hum Reprod Update*. Feb 19 2021;27(2):393-420. doi:10.1093/humupd/dmaa045
93. Barnard ME, Farland LV, Yan B, et al. Endometriosis Typology and Ovarian Cancer Risk. *JAMA*. Aug 13 2024;332(6):482-489. doi:10.1001/jama.2024.9210
94. Terry KL, Harris HR, Missmer SA. Endometriosis and Ovarian Cancer. *JAMA*. Dec 2 2024;doi:10.1001/jama.2024.21905
95. Shigesi N, Kvaskoff M, Kirtley S, et al. The association between endometriosis and autoimmune diseases: a systematic review and meta-analysis. *Hum Reprod Update*. Jul 1 2019;25(4):486-503. doi:10.1093/humupd/dmz014
96. Mu F, Rich-Edwards J, Rimm EB, Spiegelman D, Missmer SA. Endometriosis and Risk of Coronary Heart Disease. *Circ Cardiovasc Qual Outcomes*. May 2016;9(3):257-64. doi:10.1161/CIRCOUTCOMES.115.002224
97. Farland LV, Degnan WJ, 3rd, Bell ML, et al. Laparoscopically Confirmed Endometriosis and Risk of Incident Stroke: A Prospective Cohort Study. *Stroke*. Oct 2022;53(10):3116-3122. doi:10.1161/STROKEAHA.122.039250
98. Wang S, Farland LV, Gaskins AJ, et al. Association of laparoscopically-confirmed endometriosis with long COVID-19: a prospective cohort study. *Am J Obstet Gynecol*. Jun 2023;228(6):714 e1-714 e13. doi:10.1016/j.ajog.2023.03.030
99. Allaire C, Bedaiwy MA, Yong P. Diagnosis and management of endometriosis. *Canadian Medical Association Journal*. 2023;195(10):E363-E371. doi:10.1503/cmaj.220637

BOX. Commonly asked questions

1.	**What are the most common symptoms of endometriosis?** Pelvic pain, which can include dysmenorrhea (painful menstrual periods), non-menstrual 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. Conditions that cause similar symptoms and commonly co-occur with endometriosis include adenomyosis, uterine fibroids, pelvic floor myalgia, irritable bowel syndrome, and bladder pain syndrome/interstitial cystitis.
2.	**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 a non-steroidal anti-inflammatory drug, 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.
3.	**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 (e.g. 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 exam, or pelvic ultrasound or MRI findings suggestive of an ovarian endometrioma or deep endometriosis.

743 **Table 1. 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*	Additional considerations
First line					
Combined hormonal contraceptive	Oral pill (one tablet daily usually containing a progestin and 20-30ug ethinyl estradiol Vaginal ring changed every 3 weeks Transdermal combined estrogen-progestin patch changed weekly	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 of (n=1,680) of patients with endometriosis treated with hormone therapy. Clinically significant reduction in pelvic pain on 0-100 VAS compared with placebo: MD -15.1 (95% CI-20.8 to -9.3)[36]	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 (e.g. skip placebo in pill packet) to achieve amenorrhea likely superior to cyclical use with no difference in safety profiles[48]- which can be achieved with monophasic formulation (defined as same dose of estrogen and progestin in each pill, vaginal ring, or transdermal patch) • Multiple formulations of pill available, recommend lowest dose of ethinyl estradiol to achieve amenorrhea, but breakthrough bleeding more common with lower dose (<20ug) estradiol formulations
NSAIDs	Naproxen PO 500 mg for 1 dose, then 250 mg PO every 6–8 hours as required Ibuprofen PO 400mg max TID	NSAIDs relieve pain by inhibiting cyclooxygenase (COX) enzymes, which reduces the production of prostaglandins involved in inflammation and pain signaling	Insufficient evidence that NSAIDs reduce pain in endometriosis.[45]	Gastrointestinal irritation or ulceration, hypersensitivity reaction (e.g. asthma exacerbation), renal 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	Norethindrone acetate 2.5–15mg po QD (start at 2.5 to 5mg daily, and titrate up until amenorrhea) Medroxyprogesterone acetate 15-30mg po QD Drosperinone 4mg po QD Dienogest 2mg po QD	Induce decidualization and atrophy of endometrial tissue, decrease estrogen-induced mitosis, suppress cell proliferation, inhibit inflammatory pathways, angiogenesis and neurogenesis	Network meta-analysis of (n=1,680) of patients with endometriosis treated with hormone therapy. Clinically significant reduction in pelvic pain on 0-100 VAS compared with placebo: MD -12.6 (95% CI -15.3 to -9.8)[36]	Breakthrough bleeding (>10%), weight gain (≤10%), mood changes (≤10%),	• Similar to combined hormonal contraceptive, goal is to achieve amenorrhea • Norethindrone acetate typically start at 5mg and titrate up by 2.5mg every 2-4 weeks until achieve amenorrhea • Drosperinone monotherapy is off label for endometriosis • Dienogest not available in the US as monotherapy
Intramuscular injection	Medroxyprogesterone acetate 150mg IM Q 3 months		Network meta-analysis of (n=1,680) patients with endometriosis treated with hormone therapy. Clinically significant reduction in pelvic pain on 0-100 VAS	Headache (>10%), weight changes (>10%) , gastrointestinal upset (>10%), depression (≤10%), decreased libido (≤10%),	• Delay in return of fertility (contraceptive effect and cycle irregularity can persist for up to 12 months) • Bone mineral density loss with prolonged use,

			compared with placebo: MD -13.2 (95% CI-16.2 to -10.1)[36]	breakthrough bleeding (≤1%)	particularly in adolescents
Subdermal implant	Etonorgestrel 68 mg, implant, Q3 years		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
Intrauterine system	Levonorgestrel available in 52 mg/device (19.5mg/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 of (n=1,680) patients with endometriosis treated with hormone therapy. Clinically significant reduction in pelvic pain on 0-100 VAS compared with placebo: MD -17.7 (95% CI -25.5 to -9.8)[36]	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 months, 40% at 24 months) • Unlike systemic progestins, no negative effect on lipid profiles
Second line					
GnRH agonists					
Intramuscular injection	Leuprolide acetate 3.75 mg IM q month or 11.25 mg IM q3months	Downregulation of GnRH receptors in pituitary, inhibiting gonadotropin release and ovarian hormone secretion, leading to hypoestrogenic state	Network meta-analysis (n=1,680) of patients with endometriosis. Clinically significant reduction in pelvic pain on 0-100 VAS compared with placebo (MD -15.7 (95% CI -21.3 to -10.1)[36]	Hot flush (>10%), headache (>10%), difficulty sleeping (>10%), vaginal dryness (≤10%), depressed mood (≤10%),	• Bone mineral density loss, may be irreversible if used >6 months 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 side effects and prevents bone mineral density loss[37]
Intranasal	Nafarelin acetate 1 nasal spray (200 µg) BID		Network meta-analysis (n=1,680) of patients with endometriosis. Clinically significant reduction in pelvic pain on 0-100 VAS compared to placebo (MD -15.8 (95% CI -21.4 to -10.1)[36]		
GnRH antagonists					
Oral without add-back hormone replacement therapy	Elagolix 150 mg po once daily (low dose)	Non-peptide antagonist of gonadotropin-releasing hormone 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 (Elaris I (EM-I, n=872) and Elaris II (EM-II, n=817)). At 6 months, 42.1-46.2% were dysmenorrhea responders [1] (23.1-25.4% in placebo group) and 45.7-51.6% were non-menstrual pelvic pain responders [1] (34.9-40.6 % in placebo group).[51]	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 months, high dose approved for 6 months use • Immediate return of menses upon discontinuation • Contraindications include osteoporosis, significant hepatic disease (e.g. cirrhosis)

	Elagolix 200 mg po twice daily (high dose)		Two parallel phase 3 RCTs of women with moderate to severe endometriosis-associated pain (Elaris I (EM-I, n=872) and Elaris II (EM-II, n=817)). At 6 months, 75.3-76.9% were dysmenorrhea responders [1] (19.6–22.7% in placebo group) and 62.1-62.2% were non-menstrual pelvic pain responders [1] (34.9-40.6% in placebo group).[51]	Hot flush (46%), headache (20%), nausea (16%), insomnia (9%), mood swings (6%), depressed mood (6%), anxiety (5%), arthralgia (5%)	
Oral with add-back hormone replacement therapy	Relugolix combination therapy (40mg, estradiol 1mg, norethindrone acetate 0.5mg) 1 tablet po QD	Add-back therapy included in single pill to mitigate bone mineral density loss and vasomotor symptoms	Two parallel phase 3 RCTs (SPIRIT 1, n=638) and SPIRIT 2 (n=623)) of participants with moderate to severe endometriosis associated pain. 6 months: Dysmenorrhea responder[2] 75% (placebo responder[2] 27–30%); non-menstrual pelvic pain responder[2] 59-66% (placebo responder[2] 40–43%).[50] Efficacy sustained at 2 years 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 months use in U.S. 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 (e.g. cirrhosis)
Third line					
Aromatase inhibitors	Letrozole 2.5mg po QD Anastrazole 1 mg po QD	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 flushes (50%), night sweats (15%), nausea (9-17%), myalgia/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[37] • 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

744 Abbreviations: MD, mean difference; VAS, visual analog scale; IM, intramuscular, CI, confidence interval.
745 *Frequencies are included when available, derived from product labelling unless cited otherwise.
746 1. Responder defined as clinically meaningful reduction in the pain score (on a scale ranging from 0 [no pain] to 3 [severe pain]) and a decreased or stable
747 use of rescue analgesic agents. A clinically meaningful threshold for the mean change from baseline, as compared with placebo, was −0.81 for
748 dysmenorrhea and −0.36 for non-menstrual pelvic pain in Elaris EM-I and −0.85 for dysmenorrhea and −0.43 for non-menstrual pelvic pain in Elaris EM-II.
749 2. Responder defined by meaningful change thresholds of –2·8 points for dysmenorrhea and –2·1 points for non-menstrual pelvic pain on NRS (0=no pain;
750 10=pain as bad as you can imagine), excluding those with increased use in analgesics.

Figure 1. Characteristics endometriosis and common conditions with overlapping symptoms.

Surgical images are provided by authors S.A. and A.H. Vaginal endometriosis lesions (seen on vaginal speculum exam) are provided courtesy of Sukhbir S. Singh, MD (University of Ottawa).

Figure 2. Pathophysiology and pain mechanisms in endometriosis-associated pelvic pain.

Pelvic pain in patients with endometriosis is multifactor and can be due to any combination of nociceptive, neuropathic and nociplastic pain mechanisms. Release of pro-inflammatory cytokines and pain mediators from endometriosis lesions, in addition to recruitment of immune cells, all may serve to both 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 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 to both internal and external painful and non-painful 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 (e.g. surgery and hormone suppression) do not alleviate pain in all patients, and pain can recur without evidence of recurrent lesions.

References: this figure was created by S.A., A.S., A.H. based on review of literature, outlined in the manuscript in the section describing pain mechanisms in endometriosis.[31, 32, 82]
Explanation of how this illustration adds to published literature: this is a conceptual model of the various mechanisms that can lead to the experience of chronic pelvic pain in women with endometriosis. I am not aware of a similar illustration in the literature. This drawing is a schematic and will work with illustrator to align organs into anatomically correct locations.

Figure 3. Physical exam of patient with clinical symptoms of endometriosis-associated pelvic pain.

References: [31, 32, 82]
Explanation of how this illustration adds to published literature: this figure provides overview of the steps of the physical exam for a patient presenting with clinical symptoms of endometriosis-associated pain and the specific goals/evaluation of each step. I am not aware of a similar illustration in the literature.

Figure 4. Diagnostic algorithm and first-line treatment of endometriosis.

References: substantially modified/expanded from Allaire et al. 2023[99]
Explanation of how this illustration adds to published literature: This figure provides a diagnostic algorithm on the diagnostic strategy and first line treatment of endometriosis and when to refer to a gynecologist.

Figure 1 (Panel A). Characteristics and visual appearance of endometriosis subtypes

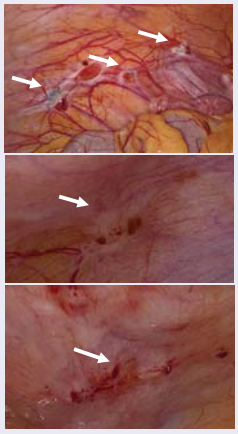
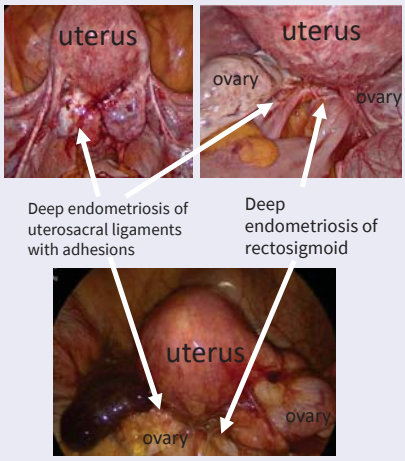
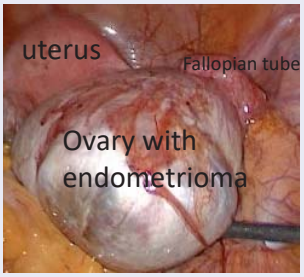
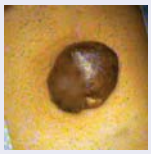
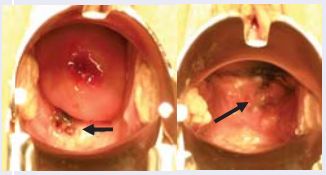
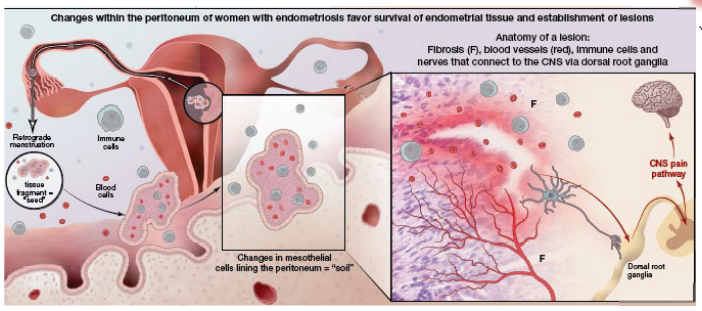
	Superficial peritoneal endometriosis	Deep endometriosis	Endometrioma	Extrapelvic endometriosis
Characteristics	Lesions on the peritoneal surface or serosa of abdominal or pelvic viscera. Lesions can have different appearances and color such as clear, black, brown, blue, white, red.	Lesions that extend under the peritoneal surface or serosa of abdominal or pelvic viscera or infiltrate muscularis propria of pelvic organs (bowel, bladder, ureters). Lesions are nodular, often associated with fibrosis, adhesions, and distortion of normal anatomy.	Ovarian cysts that contain endometrium-like tissue and dark blood-stained fluid. The color and consistency of this fluid within the cyst gives rise to the name “chocolate cysts”.	Lesions located outside of the pelvis.
Images from surgery				Umbilical endometriosis  Vaginal endometriosis 

Figure 1 (Panel B). Gynecologic and non-gynecologic conditions with symptoms that overlap with the most common symptoms of endometriosis.

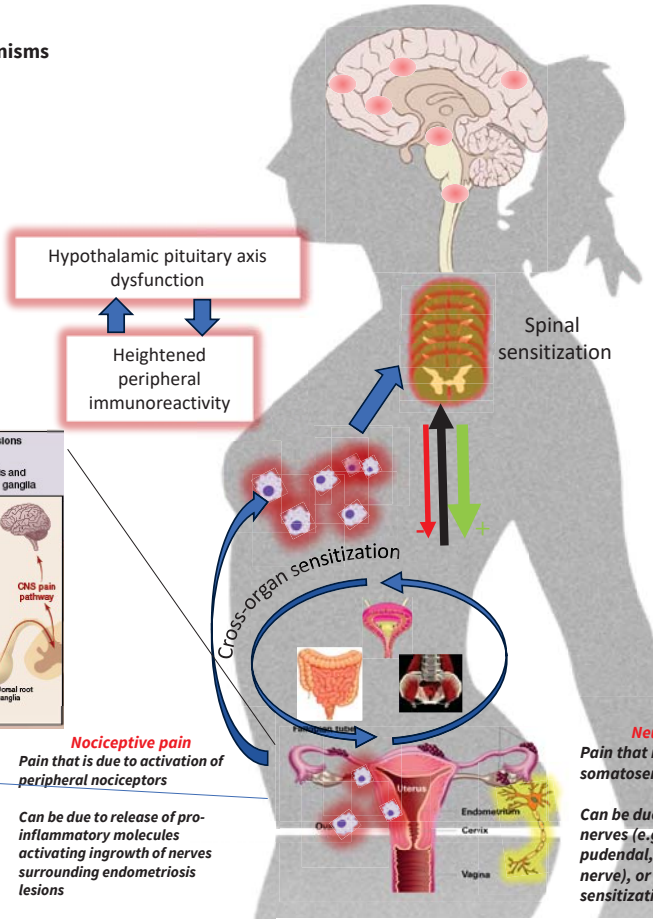
	Most common symptoms of endometriosis			
	Dysmenorrhea	Non-menstrual pelvic pain	Deep dyspareunia	
Conditions with overlapping symptoms				**Common clinical features**
Gynecologic causes				
Adenomyosis	✓	✓	✓	Heavy menstrual bleeding, tender uterus, which is sometimes enlarged, commonly co-occurs with deep endometriosis
Uterine fibroids	✓	✓	✓	Heavy menstrual bleeding, enlarged/irregular uterus
Primary dysmenorrhea	✓			Often short-duration (<72 hours), responsive to non-steroidal anti-inflammatory drugs
Cervical stenosis	✓	✓		Amenorrhea or decreased menstrual flow, history of cervical surgery or ablation of uterine lining
Mullerian anomaly with obstruction of genital tract	✓			Usually diagnosed in adolescence, amenorrhea with cyclic pain
Non-gynecologic causes				
Pelvic floor myofascial pain	✓	✓	✓	Pain worse with activity, worse at end of day, tender abdominal wall or pelvic floor muscles, often associated with dyschezia (painful bowel movements), urinary frequency
Irritable bowel syndrome		✓		Alterations of bowel frequency and stool quality, associated with abdominal pain. Symptoms sometimes worse during menses
Bladder pain syndrome		✓	✓	Urinary urgency, frequency, and/or nocturia with normal urinalysis. Symptoms sometimes worse during menses
Pelvic venous disorder		✓	✓	Pelvic heaviness, worse with standing, worse at end of day

[table modified from: Allaire et al. 2023 [99]]

Figure 2. Conceptual model of endometriosis lesions and pain mechanisms



*This insert image is from Horne H, Saunders P. Snapshot: Endometriosis. Cell, Volume 179, Issue 7, 1677-177.e1. If manuscript is accepted, we will work with illustrator to modify this image.



Nociplastic pain
Pain due to altered pain perception in the central nervous system, associated with loss of descending pain inhibition, amplification of ascending pain signals, and generalized sensory sensitivity.

Clinical presentation characterized by widespread pain, fatigue, poor sleep

Nociceptive pain
Pain that is due to activation of peripheral nociceptors

Can be due to release of pro-inflammatory molecules activating ingrowth of nerves surrounding endometriosis lesions

Neuropathic pain
Pain that is due damage of the somatosensory nervous system

Can be due to direct invasion of nerves (e.g. such as the pudendal, obturator, sciatic nerve), or due to peripheral sensitization

Figure 3. Physical exam of patient with pelvic pain and/or clinical symptoms of endometriosis

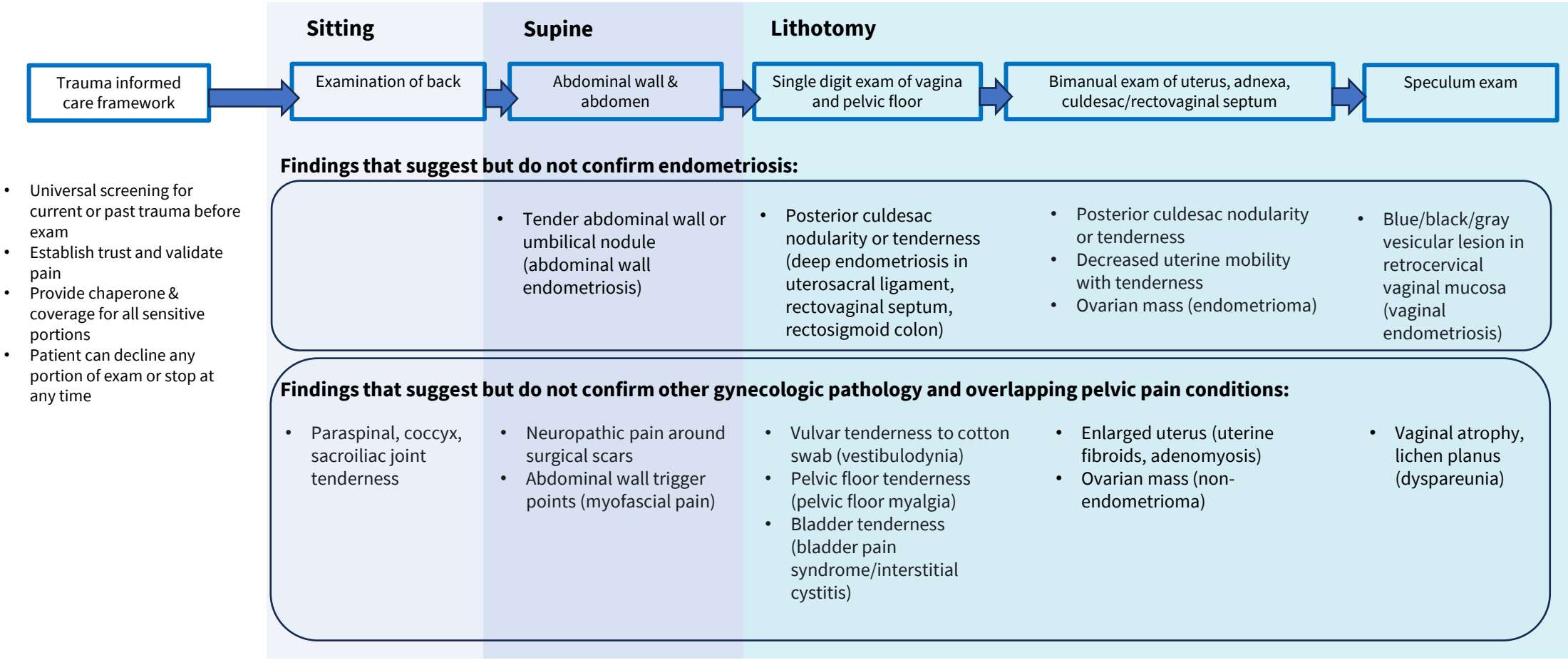
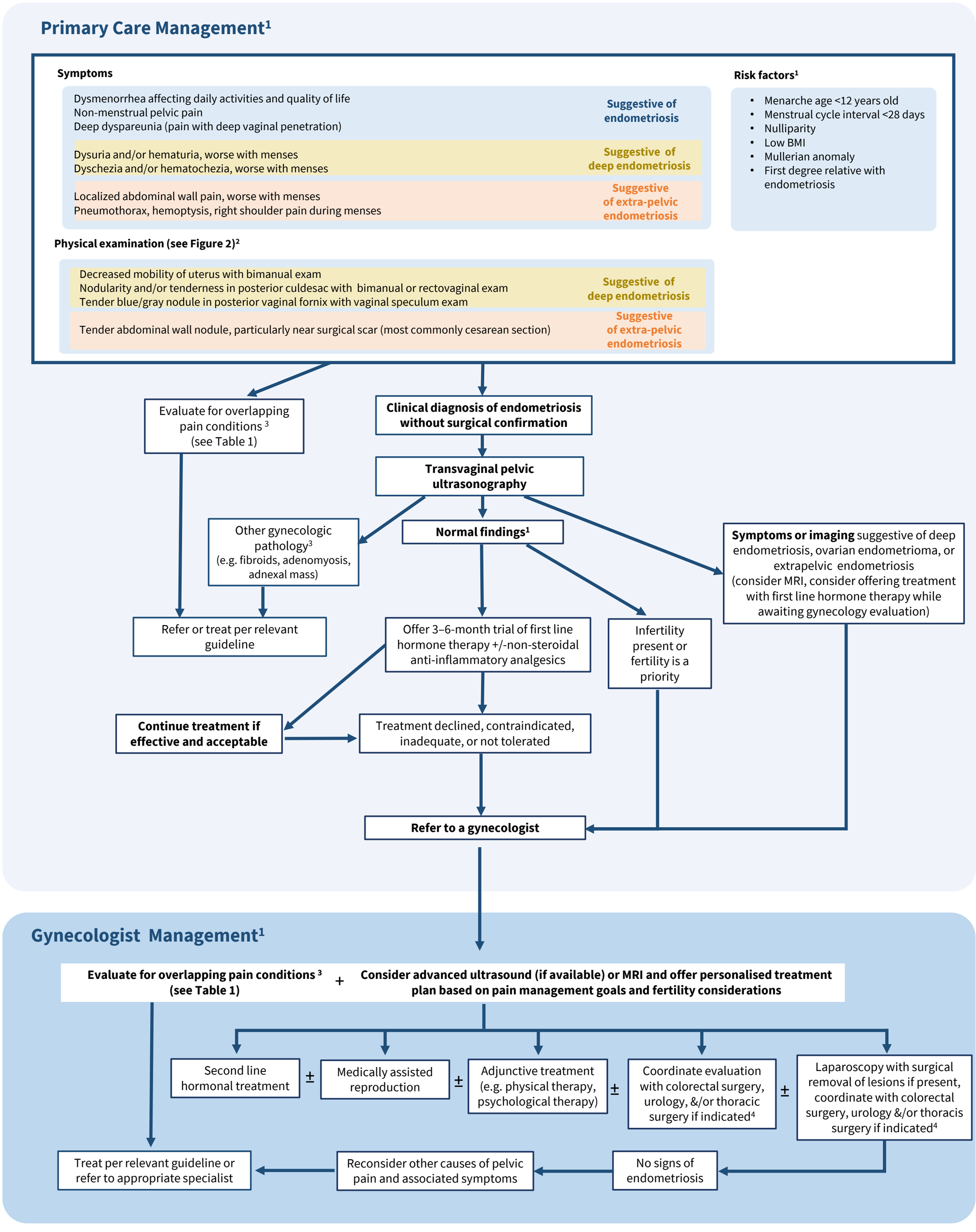


Figure 4. Algorithm for the diagnosis and management of endometriosis



[1] The decision on when to refer to a gynecologist should be based on shared-decision making between primary care provider and patient and can occur at anytime following assessment of symptoms.
[2] Normal pelvic exam, normal pelvic imaging, and absence of risk factor does not exclude a diagnosis of endometriosis.
[3] Other gynecologic pathology and presence of overlapping pain conditions commonly co-exist with endometriosis and have overlapping symptoms.
[4] Interdisciplinary evaluation and treatment of patients with symptoms or imaging suggestive of deep endometriosis involving urinary tract, bowel, or thorax. This may include endoscopic evaluation (e.g. cystoscopy, colonoscopy).