

CLINICAL REVIEW

Endometriosis

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Endometriosis is a relatively common and potentially debilitating condition affecting women of reproductive age. Prevalence is difficult to determine, firstly because of variability in clinical presentation, and, secondly because the only reliable diagnostic test is laparoscopy, when endometriotic deposits can be visualised and histologically confirmed. Population based studies report a prevalence of around 1.5% compared with 6-15% in hospital based studies.¹ Endometriosis can be asymptomatic, but those with symptoms generally present early in reproductive life and improve after menopause. Symptomatic endometriosis can result in long term adverse effects on personal relationships, quality of life, and work productivity. A European survey of nearly 1000 women indicated that the average annual cost per woman with endometriosis was nearly €1000 (£822, \$1380) with two thirds of the costs from loss of productivity.² The most important predictor of healthcare costs is decreased quality of life, and this is found to be greatest in women with pain, infertility, and persistent disease.³ We have described the clinical evaluation, implications, and management of endometriosis for the primary care provider.

What is endometriosis?

Endometriosis is an oestrogen dependent, benign inflammatory disease characterised by ectopic endometrial glands and stroma, which are often accompanied by fibrosis. These glands and stroma are typically pelvic but are also found in other locations, most commonly the bowel, diaphragm, umbilicus, and pleural cavity. There are three subtypes of endometriosis: superficial peritoneal lesions, deep infiltrating lesions, and cysts (endometriomas) containing blood and endometrium-like tissue. Symptoms vary considerably but typically include painful intercourse (deep dyspareunia) and pain before and/or during menstruation (dysmenorrhoea), bladder and bowel pain, and chronic pelvic pain. Endometriosis is commonly associated with infertility, with many asymptomatic women being diagnosed with endometriosis during investigations for infertility.

What are the causes of endometriosis?

The pathogenesis of endometriosis is unknown, but leading theories include retrograde menstruation, altered immunity, metaplasia of the germinal epithelium, and metastatic spread. Recent studies have also proposed stem cell and genetic origins of the disease.⁵ Consistent evidence from family and twin based studies supports a heritable component to endometriosis, but no specific gene has been identified, and there are currently no genetic tests available. Results of recent genome-wide association studies are consistent with a heritable component in endometriosis.⁶

What is the natural course of endometriosis?

The natural course of symptomatic endometriosis is difficult as almost all adolescent girls report painful periods, and it is not possible to exclude a diagnosis of endometriosis without invasive testing. It is not clear whether endometriosis is a progressive disease and, if so, what factors regulate progression. Observational studies in untreated women with infertility suggest that deposits can spontaneously regress in up to a third and progress is around 50% over 6-12 months.⁷ It is also unknown if early treatment reduces disease progression.

Are any other conditions commonly associated with endometriosis?

Survey data from selected groups such as the Endometriosis Association report an increase in self reported conditions such as autoimmune disease, chronic fatigue, allergies, asthma, and fibromyalgia among their members. Endometriosis is a benign disease, but there is a small but consistently reported association between histologically confirmed endometriosis and clear cell or endometrioid ovarian cancer. A recent meta-analysis has shown that endometriosis about doubles the risk of a diagnosis of ovarian cancer.⁸

Summary points

Medical treatment is not recommended for women with endometriosis who are trying to conceive as it does not improve pregnancy rates and delays fertility

The combined oral contraceptive, oral or depot MPA (medroxyprogesterone acetate), and Mirena (levonorgestrel releasing intrauterine system) are as effective as the GnRH (gonadotrophin releasing hormone) analogues and can be used long term

When surgical treatment is being considered, attempt laparoscopic excision or ablation at the time of diagnostic laparoscopy when possible

The cyst wall of endometriomas should ideally be removed instead of drainage and ablation but treatment can lead to reduced ovarian reserve

In the five years after surgery or medical treatment, 20-50% of women will experience recurrence of symptoms

Long term medical treatment (with or without surgery) might reduce recurrence but more data are needed to define the optimum medical treatment

Sources and selection criteria

We searched Medline and Pubmed, used personal archives of references, and consulted with other experts to inform this manuscript. When available, data from systematic reviews and randomised controlled trials were used. We also used expert guidelines such as the recent European Society of Human Reproduction and Embryology (ESHRE) consensus.⁴

When should a clinician suspect endometriosis?

The clinical presentation of endometriosis is highly variable and relates poorly to the extent of disease (table 1).[↓] The key clinical features that should raise suspicion include pelvic pain, typically starting soon after menarche, and infertility. As many women do not seek treatment for infertility, the clinic history should include time to achieve pregnancy or previous infertility.

Pain

Endometriosis is the most common cause of chronic pelvic pain. Pain might not be confined to the pelvis, is not always cyclical, and is common in the lower back. Typical symptoms include dysmenorrhoea, deep dyspareunia (pain on deep penetration), dyschezia (pelvic pain with defecation), dysuria (pain with micturition), and chronic pelvic pain. A large primary care based case-control study¹ showed that 25% of women with endometriosis reported dysmenorrhoea to their general practitioner in the three years before diagnosis, 24% reported urinary tract symptoms, 11% reported symptoms relating to sexual intercourse, 2% reported rectal bleeding or dyschezia, and 16% reported pelvic pain. A total of 58% of women with endometriosis had abdominopelvic pain. While these symptoms can also be present in women without endometriosis, they occur much less frequently. Compared with women without endometriosis, affected women were 10 times more likely to report dysmenorrhoea, twice as likely to report urinary tract symptoms, seven times more likely to report symptoms related to sexual intercourse, twice as likely to report rectal bleeding or dyschezia, and 13 times more likely to report pelvic pain.¹ A systematic review has shown that associated bladder pain syndrome/interstitial cystitis affects around two thirds of women with endometriosis and chronic pelvic pain.⁹

Deep infiltrating nodules can have more specific pain symptoms, such as deep dyspareunia, because of their location but there does not seem to be any clear association between the severity of pain reported and the extent or type of disease present. The mechanisms by which endometriosis causes pain are poorly understood but potentially include hormonal stimulation of the deposits, stimulation of neural pathways, inflammation, local bleeding, or a combination of these. Sensitisation of the central nervous system to pain can lead to chronic pelvic pain even without ongoing stimulation.

Infertility

An estimated 25-50% of women with infertility have endometriosis and around 30-50% of women with endometriosis have infertility.⁵ The mechanisms linking endometriosis and infertility are poorly understood, and causation is not established. Even mild endometriosis can impair fertility, and severe disease can lead to tubal adhesions, reduced ovarian reserve and oocyte and embryo quality, and poor implantation.⁵ Endometriosis can further impair fertility by disturbing the function of the fallopian tube, embryo transport, and the eutopic endometrium.

What clinical examination is helpful to diagnose endometriosis?

Clinical examination cannot provide a definitive diagnosis of endometriosis but pain on vaginal examination, tender nodules in the posterior fornix, adnexal masses, and immobility of the uterus, particularly fixed retroversion, are diagnostic pointers. A comparative study between clinical examination, transvaginal ultrasonography, and magnetic resonance imaging (MRI) showed that bimanual examination lacked sensitivity and specificity in the diagnosis of endometriosis, with less than 50% accuracy. Transvaginal ultrasonography was superior to MRI in terms of sensitivity (95% v 76%), specificity (98% v 68%), and accuracy (97% v 71%).¹⁰

What is the role of imaging in the diagnosis of endometriosis?**Ultrasonography**

A systematic review has shown that transvaginal ultrasonography can reliably identify endometriomas and can show adhesions or pelvic fluid,¹¹ and ovarian endometriosis has clear and reproducible features on ultrasonography.¹² Ultrasonography cannot reliably detect small (<1 cm) endometriotic deposits or depth of infiltration. Transvaginal ultrasonography with bowel preparation and transrectal ultrasonography can detect deep infiltrating lesions affecting the bowel, bladder, and rectovaginal pouch.¹³ Routine screening for ovarian cancer with transvaginal ultrasonography or blood tests such as CA125 are not indicated.

Magnetic resonance imaging (MRI)

MRI can be used to identify subperitoneal endometriotic deposits, though these might be masked by distorted pelvic

anatomy and endometriomas. Expert opinion suggests that MRI can be valuable in the diagnosis of deep infiltrating endometriosis, with contrast enema helping to detect low colorectal invasion.¹⁴ Comparative studies, however, suggest that MRI is less accurate overall than transvaginal ultrasonography in detecting possible endometriosis.¹⁰

Are biomarkers useful in diagnosing endometriosis?

A non-invasive diagnostic test for endometriosis would be a useful early detection tool in symptomatic women with normal findings on pelvic ultrasonography. Although over 100 putative biomarkers for endometriosis have been proposed, a systematic review found that none have consistently been shown to be clinically useful.¹⁵ Biomarkers such as CA125 lack specificity, and routine testing is not recommended. Similarly, although eutopic endometrium differs in women with endometriosis, there is not yet an endometrial biopsy test to diagnose endometriosis in clinical practice.

What are the indications for laparoscopy?

The experience of period pain does not necessarily indicate underlying pathology, but there is expert consensus that laparoscopy should be considered when symptoms are severe and/or persistent despite medical treatment such as the combined oral contraceptive.¹⁶ Laparoscopy might be indicated for the investigation of infertility in asymptomatic women. Tubal patency can be investigated with outpatient hysterosalpingo-contrast sonography (HyCoSy) or hysterosalpingography, but this is unlikely to show pelvic disease. Women with chronic pelvic pain also report beneficial emotional, social, and employment effects from confirmation of a diagnosis of endometriosis.¹⁷ Diagnosis is made by visualisation at laparoscopy and can be supported by histological confirmation. Endometriotic deposits classically resemble dark “powder burn” lesions, but their presence is often more subtly revealed as clear vesicles, which might be missed by inexperienced surgeons. At laparoscopy the extent of disease can be classified with the American Society for Reproductive Medicine revised system (minimal, mild, moderate, severe). This staging system, however, correlates poorly with clinical symptoms.

How can endometriosis be treated?

Treatment of endometriosis will depend on the severity of symptoms, reproductive plans, patient’s age and medical history, and side effect profiles of both surgical and medical treatments. An overview of 19 Cochrane reviews summarises both medical and surgical treatments.¹⁸

Medical treatments to improve pain by suppression of endometriosis

Ovarian suppression can reduce disease activity and pain. A systematic review has confirmed the efficacy of combined hormonal contraceptives and continuous progestogens, including medroxyprogesterone acetate, norethisterone, cyproterone acetate, or dienogest, for pain associated with endometriosis.¹⁸

Second line medical treatments include GnRH (gonadotrophin releasing hormone) agonists and the levonorgestrel releasing intrauterine device (IUD).¹⁸ Danazol and the antiprogestone gestrinone should not be used as androgenic side effects outweigh benefits. Ovarian suppression with GnRH agonists

improves symptoms but induces vasomotor symptoms in most women, and prolonged use (more than six months) can lead to bone demineralisation. Prospective studies have shown that this bone loss is reversible and that concurrent treatment with a low dose oestrogen and progestogen hormone replacement therapy (HRT) regimen or tibolone (“add back”) can extend use without reducing treatment efficacy.¹⁹ There is limited evidence from randomised trials to show superior efficacy of one ovulation suppression treatment for pain over another,¹⁸ and, in clinical practice, choice of treatment is commonly guided by the tolerability of available treatments. GnRH agonists are sometimes used to “trial” how a patient might respond to surgical menopause, but the predictive value of this approach is not known (table 2).¹⁹

Analgesia for pain associated with endometriosis

Analgesics such as non-steroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed for endometriosis pain, but there is little evidence for their efficacy compared with placebo.¹⁸

Emerging medical treatments for endometriosis

A systematic review has shown that aromatase inhibitors, which prevent conversion of testosterone to oestrogen, effectively reduce the severity of pain associated with endometriosis, but there are insufficient data to determine whether long term administration of aromatase inhibitors is superior to currently available endocrine treatments in terms of improvement of pain, adverse effects, and patient satisfaction.²⁰ Hypoestrogenic side effects of aromatase inhibitors can limit their use. Selective oestrogen (SERM) and progesterone receptor modulators (SPRM) have the potential to target endocrine action of endometriosis and are under development.

Endometriosis is increasingly recognised as a chronic inflammatory condition. Proinflammatory cytokines and oxidative stress activate inflammatory mediators such as NF- κ B (nuclear factor κ light chain enhancer of activated B cells), can drive further inflammation and abnormal angiogenesis, and are potential targets for treatment. Systematic reviews have shown that there is currently insufficient evidence to support the use of anti-TNF- α drugs²¹ or pentoxifylline²² for symptoms of endometriosis.

Surgical treatments for pain associated with endometriosis

Surgical treatment of endometriosis requires appropriate skill and training, particularly when disease affects the bowel and other organs as there might be associated morbidity. Moreover, expert consensus is that women with suspected or diagnosed deep infiltrating endometriosis should be referred to an expert centre that offers all available treatments in a multidisciplinary context, including advanced operative laparoscopy or laparotomy.⁴

Two randomised controlled trials have shown the effectiveness of surgical treatment for pain associated with superficial endometriosis,^{23 24} which can be by excision or ablation of the endometriotic deposits, although there is limited long term follow-up. A large randomised controlled trial has shown that the addition of uterosacral nerve ablation is ineffective in reducing pain²⁵ and should not be performed. Prospective clinical studies confirm that surgery for endometriomas reduces ovarian reserve, particularly in women with bilateral disease, and that this has an adverse effect on fertility.²⁶ This is particularly

relevant for women undergoing IVF treatment as ovarian stimulation might be compromised by a reduction in ovarian reserve.

Prospective observational studies indicate that hysterectomy with bilateral salpingo-oophorectomy is a successful strategy for women who are not pursuing trying to get pregnant but results in surgical menopause. Retrospective data suggest that hysterectomy alone (with ovarian conservation) reduces pain as dysmenorrhoea no longer occurs. Around a third of women, however, will require further surgery for symptoms at five years, compared with 10% of those who undergo hysterectomy with oophorectomy for endometriosis. In younger women (aged 30-39), however, removal of the ovaries did not significantly improve the surgery-free time and is likely to lead to adverse symptomatic and health consequences associated with surgical menopause.²⁷

Oestrogen (as HRT) is advised for young (aged under 45) and/or symptomatic women after oophorectomy for endometriosis, but HRT or tibolone can potentially lead to recurrence. There is, however, no indication to use combined HRT after hysterectomy for endometriosis.

Is there any evidence for complementary therapies in treatment of endometriosis?

The evidence to support complementary therapies for symptoms or infertility associated with endometriosis is limited. Randomised trials of acupuncture and Chinese medicine have had inconsistent results, and a systematic review has concluded that there is currently insufficient evidence to support their use.^{28 29}

What is the treatment for infertility associated with endometriosis?

Treatment focuses on improving fertility by removing or reducing endometrial glands and stroma and restoring normal pelvic anatomy (table 3).[↓] A systematic review has concluded that medical treatment should be avoided in women with endometriosis and subfertility who want to conceive as it has not been shown to improve fertility and delays conception.³⁰ The exception is women with advanced disease undergoing IVF, in whom a systematic review has shown that three months of pretreatment with GnRH agonist³¹ or the combined oral contraceptive³² before IVF improves fertility rates.

Summary of fertility treatment options

Treatment decisions for infertile women with endometriosis should consider pelvic anatomy, extent of disease, ovarian reserve and age, male factors, presence of endometriomas, and duration of infertility. Options can include expectant management, surgical removal of ectopic implants, ovulation induction, or IVF. For women with minimal or mild disease (stage I/II), expert consensus is that the decision to surgically resect endometriotic lesions before other treatments should consider the patient's age and ovarian reserve. In women with endometriomas receiving surgery for infertility or pain, excision of endometrioma capsule increases the rate of spontaneous postoperative pregnancy compared with drainage and electrocoagulation of the endometrioma wall.³³ Surgery to endometriomas, however, can also reduce ovarian reserve and fertility due to removal of normal ovarian tissue, and a Cochrane review based on four randomised controlled trials concluded that surgical treatment to endometriomas before assisted

reproduction treatment (ART) has no benefit over expectant management with regard to clinical pregnancy rate.³⁴ For advanced endometriosis, expert consensus recommends IVF to reduce time to pregnancy, reserving surgery for women who present with larger or symptomatic endometriomas.^{5 16} Controlled ovarian stimulation for IVF does not increase recurrence of endometriosis.⁴

If endometriomas are surgically removed, this should be by cystectomy rather than fenestration/coagulation or laser ablation since a systematic review has shown that this reduces symptom recurrence and improves pregnancy rates.³⁵

Potential future treatments for infertility associated with endometriosis

Novel treatments under development or clinical trials include immunotherapies and aromatase inhibitors. Immunotherapies target aberrantly expressed tissue factor on the endometriotic endothelium to reduce vascularisation. Future treatments could include targeting altered molecular pathways in endometriosis and correcting epigenetic changes such as abnormal methylation or replacing damaged endometrium with stem cell treatments.^{28 29 36}

What happens if endometriosis recurs after treatment and can recurrence be prevented?

Endometriosis is a chronic disease, and prospective data indicate that recurrence after surgery ranges from 10-50% at one year and increases over time.³⁷

Pain from endometriosis might become chronic even when visible disease has been removed. Several medical treatments have been trialled after surgery to maintain the beneficial effects of surgery on symptoms. A systematic review has shown that use of oral contraceptives can reduce pain after surgery and reduce recurrence of endometriomas and is as effective and better tolerated than gestrinone, mifepristone, or GnRH agonists without hypoestrogenic side effects.³⁸ A randomised controlled trial has shown that the efficacy of the levonorgestrel releasing intrauterine system (Mirena) is comparable with GnRH agonists in the relief of chronic pelvic pain after surgery for endometriosis.³⁹ A systematic review has shown that Mirena is effective at preventing recurrence of symptoms after surgery and does not negatively affect bone or metabolic parameters.⁴⁰

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Information resources for patients

Patient.co.uk (www.patient.co.uk/showdoc/23068733/)—provides a useful overview about the symptoms of endometriosis, the difficulties in diagnosis, and the range of medical and surgical treatment options

Besthealth (<http://besthealth.bmj.com/x/topic/392785/essentials.html>)—a site for both patients and doctors, it provides comprehensive and research based information of the symptoms, diagnosis, and treatments of endometriosis. It also provides women with some possible questions that might be helpful to guide discussions with their doctor

Endometriosis UK (www.endo.org.uk/)—a charity that provides support and information for women with endometriosis. There is a joining fee, but this provides access to a newsletter and a social media community

The Endometriosis SHE Trust UK (www.shetrust.org.uk/)—a charity that offers information on symptoms, diagnosis, and treatment of endometriosis

Endometriosis NZ (www.nzendo.co.nz/)—a charity raising funds to support women with endometriosis. It provides information about the possible cause, symptoms, diagnosis, and treatments for endometriosis. It also provides a telephone support line

Tips for non-specialists

Endometriosis should be suspected in women with persistent pelvic pain that interferes with normal life and that has poorly responded to hormonal suppression (combined oral contraceptive), or where there is dyspareunia, pain with bowel opening (not relieved by defecation as in irritable bowel syndrome) or pain on micturition, lower back pain that is not from other conditions such as urinary tract infection or musculoskeletal pain. Pelvic examination might reveal nodules, masses, and tenderness that can be suggestive of endometriosis

Transvaginal ultrasonography can identify ovarian endometriotic cysts

CA 125 levels, magnetic resonance imaging, and computed tomography are not recommended as initial investigations but might be of value as part of investigations before surgery

Patients with suspected endometriosis should be referred to an appropriate specialist clinic if treatment of primary dysmenorrhoea with oral contraceptives and analgesia has failed and if there is persistent pain requiring regular analgesia leading to days off school or work. Infertility associated with pelvic pain and women with recurrence of pain after treatment of their endometriosis need appropriate secondary or tertiary care referral

Unanswered clinical questions

What is the natural course of pain associated with endometriosis?

Which is more effective: medical or surgical treatment?

Does dysmenorrhoea in adolescence increase the risk of endometriosis later?

Does early treatment of disease alter progression?

What mediates the relation between endometriosis and infertility?

What is the relation between endometriosis and adenomyosis?

Does the long term use of the hormonal drugs to suppress endometriosis reduce recurrence?

What is the benefit of laparoscopic surgery for rectovaginal disease?

Should endometriomas be removed before fertility treatment?

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Tables

Table 1 | Common clinical presentations of endometriosis

Symptom	Alternative diagnoses to endometriosis
Chronic painful periods	Adenomyosis, physiological
Painful sex (deep dyspareunia)	Psychosexual problems, vaginal dryness
Painful micturition	Cystitis
Painful defecation (dyschezia)	Constipation, anal fissure
Chronic lower abdominal pain	Irritable bowel syndrome, neuropathic pain, adhesions
Chronic lower back pain	Musculoskeletal strain
Adnexal masses	Benign and malignant ovarian cysts, hydrosalpinges
Infertility	Other causes of infertility

Table 2| Medical treatment for pain associated with endometriosis*

Drug	Mechanism of action	Length of treatment recommended	Adverse events	Notes
Continuous progestogens	Ovarian suppression	Long term	Weight gain, bloating, acne, unscheduled bleeding	Oral or intramuscular (depot)
Danazol	Ovarian suppression	6-9 months	Weight gain, bloating, acne, hirsutism, skin rashes	Adverse effects on lipid profiles
Oral contraceptive	Ovarian suppression	Long term	Nausea, headaches	Can be used to continuously
Gonadotrophin releasing hormone analogue	Ovarian suppression	6 months	Vasomotor symptoms, vaginal dryness, sleep disturbance	By injection or nasal spray
Levonorgestrel intrauterine system	Endometrial suppression and some ovarian suppression	Long term	Unscheduled bleeding	Amenorrhoea common after prolonged use

*Decision about medical treatment will depend on patient choice, available resources, plans for fertility, and symptoms. Side effect profile might influence choice.

Table 3| Treatment options for infertility associated with endometriosis

Option	Suitable for	Fertility rates	Note
Expectant management	Mild-moderate endometriosis	Less than those after laparoscopic surgery (odds ratio 1.64)	Unsuitable for severe disease
Hormonal treatments to suppress ovulation	Nil	Contraceptive during use. No improvement on subsequent fertility	Delay pregnancy with no benefit
Surgical treatment	Mild-severe endometriosis	Insufficient evidence to recommend in severe disease. Improved fecundity in mild disease	Laparoscopic surgery is more cost effective, shorter hospital stay, shorter recovery compared with laparotomy
Surgical treatment	Endometriomas	Endometrioma resection increases spontaneous pregnancy rate in women with infertility	
Preoperative or postoperative ovarian suppression	All disease	Does not improve surgical outcome or fecundity rate	
Superovulation and intrauterine insemination	Mild-moderate endometriosis	Can improve fecundity if anatomy not supported ⁵	Evidence does not support efficacy in severe disease
Assisted reproductive technology (ART)	All disease	Most effective treatment for infertility associated with endometriosis	Removal of endometriomas before ART does not increase pregnancy rate ¹⁸
Prolonged ovarian suppression with GnRH agonist before ART	All disease	More pregnancies after prolonged ovarian suppression	Not effective in women with endometriomas ¹⁸