Endometriosis

Endometriosis is a chronic, inflammatory gynaecological condition.

This article summarises how we approach endometriosis in primary care, using the NICE endometriosis guidelines (NICE 2017, NG73), the European Society of Human Reproduction and Embryology (ESHRE) guidelines on endometriosis (updated in 2022) and a State of the Art Review and Easily Missed article on endometriosis in the BMJ (BMJ, 2022;379:e070750; BMJ,2022;379:e068950).

This article was last reviewed in April 2023.

Why is endometriosis important for primary care?

It is common: affecting around 10% of women of reproductive age.

It is easily missed.

- Although >50% of adults with endometriosis report symptoms from adolescence, the average time from onset of symptoms to diagnosis is 7y.
- Diagnosis can be delayed due to lay and medical perception that pelvic pain and menstrual cramps are normal.
- Symptoms of endometriosis can be non-specific and overlap with other conditions such as IBS or PID.

It is debilitating.

- Endometriosis can have a significant impact on physical, sexual and psychological health, and is associated with reduced quality of life.
- There is no cure, and there is no evidence to suggest that earlier treatment affects disease outcome. However, symptomatic relief aims to improve quality of life and ability to function.
- Women with endometriosis lose around 11 hours of work per week, which is comparable to those affected by chronic diseases such as type 2 diabetes, Crohn's and rheumatoid arthritis.
- The economic burden in the UK is around £12.5 billion due to work loss and healthcare costs.

(BMJ, 2022;379:e070750; BMJ,2022;379:e068950)

What is endometriosis?

Cause

- Endometriosis is an oestrogen-dependent condition of unknown (but likely multifactorial) cause.
- Twin studies suggest there may be a genetic component (positive family history may therefore be relevant), but specific susceptibility genes have not yet been identified.
- It is believed to result from the implantation of endometrial cells disseminated into the pelvis (and sometimes beyond) by retrograde menstruation.
- Underlying mechanisms are unclear, but are likely to involve a complex interplay of genetic, hormonal, vascular and immune-related factors.
- The growth of endometrial-like tissue outside the uterus induces a chronic inflammatory reaction and leads to adhesions, fibrosis and anatomical distortion.

Location

Endometriosis can be found anywhere outside the uterus (e.g. in the pelvis, bowel, bladder, thoracic cavity; it has been found in Caesarian section scars).

Subtypes

There are broadly 3 subtypes:

- Superficial peritoneal endometriosis (accounts for around 80% of disease).
- Ovarian endometriosis (endometrioma or 'chocolate cysts').
- Deep endometriosis (lesions penetrate ≥5mm below peritoneal surface – BMJ,2022;379:e068950).

Clinical course

This is variable: it can be progressive, remain stable or improve with time. Resolution of symptoms may be the result of treatment, age, hormonal state or other unknown pathways.

(BMJ, 2022;379:e070750)

Symptoms of endometriosis

- **The cardinal symptoms of endometriosis are pain and infertility.**
- Severity of symptoms does not always correlate with severity of disease identified on investigations.
- Presentation of endometriosis is quite variable and can be non-specific.

Pain

This may range from mild to debilitating, and includes:

- Cyclical pelvic pain, typically starting a few days before menstruation.
- Dysmenorrhoea.
- Non-cyclical chronic pelvic pain (*30% of patients with endometriosis develop chronic pelvic pain which is unresponsive to conventional treatments, including surgery*).
- Dyspareunia.
- Dyschezia (difficulty having a bowel movement).
- Dysuria.

A patient's pain experience may transition from an episodic, localised pain to a more chronic, generalised and debilitating picture. Associated symptoms can include fatigue and depression.

Infertility

- Women with endometriosis are twice as likely to experience infertility compared with women without endometriosis.
- Around 30–50% of women who undergo assisted reproduction are found to have endometriosis.

Asymptomatic endometriosis

- Endometriosis may be asymptomatic and be identified incidentally during investigations for something else, e.g. on an ultrasound or during a laparoscopy.
- **Asymptomatic endometriosis does not need treatment.**

(BMJ, 2022;379:e070750)

Endometriosis: associations

Endometriosis is associated with other comorbidities and disease entities (see table below). These diagnoses/symptoms may arise as a result of:

- The direct effect of endometrial deposits.
- Similar chronic inflammatory processes.
- Shared genetic or environmental factors.
- Nerve sensitisation and changes in pain perception.
- Gynaecological investigation and treatment (e.g. an ultrasound may identify the presence of fibroids).

Conditions associated with endometriosis
• Fibromyalgia. • Migraine. • Arthritis (osteo-, rheumatoid and psoriatic). • Irritable bowel syndrome. • Chronic back, bladder, bowel pain. • Other benign gynaecological conditions (e.g. uterine fibroids and adenomyosis). • Early menopause. • Cardiovascular disease. • Ovarian cancer (absolute lifetime risk of 2.5% compared with 1.3% in general population).

(BMJ, 2022;379:e070750)

Diagnosis of endometriosis

This table is based on the NICE guideline (NICE 2017, NG73).

Assessment	
History	We should suspect endometriosis if ≥1 of the following symptoms are reported in any girl or woman: • Pelvic pain (can be frequent, chronic and/or severe). • Dysmenorrhoea affecting daily activities and quality of life. • Deep dyspareunia or postcoital pelvic pain. • Cyclical gastrointestinal symptoms, e.g. dyschezia (painful defecation). • Cyclical urinary symptoms, e.g. haematuria/dysuria. • Infertility in association with any of the above. **Suggest keeping a pain or symptom diary to further evaluate symptoms and their impact.**
Examination	Signs suggestive of endometriosis: • Focal pelvic tenderness. • Tender nodularity in the posterior fornix. • Reduced organ mobility and enlargement. • Visible vaginal lesions. **But remember: a normal examination does not exclude endometriosis!**
Investigations	
Imaging	Transvaginal ultrasound (TVS) can detect endometriosis (**but remember: a normal TVS does not exclude it!**). Appearances may include: • Endometriomas (endometriotic ovarian cysts). • Adhesions or pelvic fluid. • Deep infiltrating lesions. Consider abdominal ultrasound if TVS is not appropriate. The following have NO role in the *diagnosis* of endometriosis: • CA125 (may be elevated but is not specific enough). • MRI (but may be used preoperatively to assess extent of deep endometriosis near bowel/ureter/bladder).
Diagnosis	
• Endometriosis may be *suspected* from symptoms, signs and ultrasound. • The ESHRE states that if an ultrasound is normal and the individual is not trying to conceive, we should offer medical management initially (see below for first-line medical management). • If symptoms then improve, endometriosis may be 'presumed' to be possible and no further investigation is needed. **Diagnostic laparoscopy** • A patient may be keen to undergo a laparoscopy to get a diagnosis and explanation of her symptoms, and this may have psychological benefit. • However, laparoscopy is a surgical procedure done under general anaesthetic so is invasive and risky (and relatively expensive). • 40% of laparoscopies done for pelvic pain do not identify any pathology. • Definitive diagnosis may be obtained histologically via biopsy, but negative histology does not (always) exclude endometriosis either! • There is no evidence of superiority over imaging and empirical treatment. • **Diagnostic laparoscopy should be considered only in patients with negative imaging results and unsuccessful empirical management** (see 'when should I refer' box, below). ***Basically, in primary care, we can make a presumptive diagnosis on the basis of our clinical assessment.***	

Management of endometriosis

General principles of management include:

- Great communication, explanation and information about the disease.
- Symptomatic management of pain with analgesia.
- Hormonal therapies to achieve ovarian suppression, with the aim of reducing endometriosis symptoms (provided the woman is not trying to conceive).
- Discussion of contraception and plans for future pregnancy.
- Surgery if appropriate (see below).
- Management of associated subfertility and complications.

This table is based on the NICE guideline (NICE 2017, NG73); recommendations from ESHRE are referenced separately.

Management	
Management options depend on patient preference, symptoms and desire to conceive, so may change with age.	
When should I refer?	
Refer if…	• Managing subfertility is a priority (arrange appropriate investigations and refer to fertility services). • Initial medical management is not effective, not tolerated or is contraindicated. • The patient has severe, persistent or recurrent symptoms of endometriosis. • Pelvic signs of endometriosis (reduced organ mobility, visible/palpable lesions, endometriomas on TVS).
Medical management	
First-line medical management (should be initiated in primary care)	The main goal of all these options is to reduce pain. They should NOT be used to manage infertility. NICE suggests we offer 3m trial of: • Paracetamol and/or a NSAID. • Hormonal treatment to suppress ovarian function, providing the person is NOT wishing to conceive. **Hormonal options** Both ESHRE and NICE recommend that we offer any of the following based on side-effects, suitability and patient preference: • **Combined hormonal contraception** – oral, transdermal or vaginal ring; may be used continuously. • **Progestogen-only injectables** (as Depo-Provera or Sayana Press). • **Oral progestogens,** e.g. medroxyprogesterone acetate 10mg 3 times a day (Provera), norethisterone 5mg 3 times a day, desogestrel POP (other POPs could be tried, although they may not be effective). There is no evidence supporting one oral progestogen over another. • **Levonorgestrel IUS** (the 52mg IUSs are usually used as they contain more levonorgestrel and are supported by evidence, but lower dose IUSs may be tried if a smaller, lower-dose device is preferable). • **Etonogestrel-releasing subdermal implant.** *(There is a link to a patient decision aid on hormonal treatment for endometriosis symptoms in the useful resources at the end of the article).*
Second-line medical options (initiated in secondary care)	• Dienogest 2mg daily (available as Zalkya or Dimetrum) is a nortestosterone-derived progestogen licensed for endometriosis, and has been shown to reduce endometriosis pain. There is some evidence that ovarian suppression associated with usage may reduce bone mineral density (Reprod. Sci.,2021;28:1556). *Due to its cost (approx. £20/month) and being a relatively new agent, initiation should be by secondary care.* • GnRH agonists (e.g. leuprorelin, goserelin) with combined hormonal add-back therapy, *i.e. HRT or CHC for menopausal symptoms and bone protection*. • Oral GnRH antagonists (relugolix, elagolix and linzagolix) – with or without add-back HRT – have been studied as new potential treatments for endometriosis. Preliminary data suggests efficacy, but larger, long-term data is needed, and they are not currently licensed in the UK for endometriosis (Fertility and Sterility, 2022;118(6):1102). • Aromatase inhibitors (e.g. letrozole).
Surgical management	
Aims	• To offer patient definitive diagnosis and surgical treatment via laparoscopy. • To remove/destroy endometriotic deposits and divide adhesions, with restoration of normal anatomy. • To improve pregnancy rates in endometriosis-associated infertility. There is good evidence that post-surgical hormone therapy is more beneficial than surgery alone – presumably by shrinking established lesions and preventing new lesions developing.
Options	• Therapeutic laparoscopy with ablation, excision of lesions or adhesiolysis. • Laparoscopic ovarian cystectomy of endometriomas. • For deep endometriosis affecting bowel, bladder or ureter: pelvic MRI should be undertaken before operative laparoscopy, and 3m GnRH agonist treatment given before surgery. • Hysterectomy is not a treatment for endometriosis alone, but may be done if heavy menstrual bleeding or adenomyosis co-exist. Endometrial deposits should be excised at the same time, and hysterectomy may delay recurrence of the disease, particularly if an oophorectomy is performed at the same time.

Endometriosis and fertility

Endometriosis may impair fertility through a number of mechanisms:

- Peritoneal inflammation and hormonal disruption.
- Ovarian dysfunction and low oocyte yield.
- Anatomical distortion and adhesions.

- Dyspareunia and reduced sexual activity.

The NICE guideline on infertility (CG156, 2013) recommends early referral for women who have a known clinical cause of infertility – such as endometriosis. The ESHRE states that there is evidence that surgical treatment improves the chances of spontaneous pregnancy in women with mild endometriosis. Results are less good for women with moderate to severe disease.

Endometriomas and fertility

In 2017, the RCOG published a scientific impact paper looking at how surgical treatment for endometrioma affects fertility (RCOG SIP 55, September 2017). It found little good-quality evidence to guide practice and concluded that:

- Endometriomas are associated with reduced fertility, but a causal relationship has not been established.
- It is unclear whether removing endometriomas improves fertility, and surgery may damage ovarian tissue, potentially reducing ovarian reserve.
- Management should be individualised and based on the patient's age, symptoms, size of cyst, any suspicious features and patient preference *(this is a secondary care decision)*.
- Young women with regular periods and an incidental finding of an endometrioma without any suspicious features should be encouraged to try to conceive naturally before seeking fertility treatment (*so perhaps we don't need to rush to refer these patients...*).

Endometriosis and menopause

As endometriosis is an oestrogen-dependent condition, it generally resolves in menopause, and there is a *theoretical* risk that HRT may stimulate, and cause, a relapse of endometriotic disease. This has not been demonstrated in the literature so the ESHRE recommends:

- Women with endometriosis who have a surgically-induced menopause may be prescribed combined HRT or tibolone for any menopausal symptoms *(note: those <40y should have HRT for bone and cardiovascular protection as well as for symptoms*).
- Postmenopausal women who have a history of endometriosis and have undergone hysterectomy should avoid unopposed oestrogens because of a theoretical risk of malignant transformation of residual disease. Combined HRT or tibolone should be prescribed if indicated.

Is adenomyosis associated with endometriosis?

No! It is considered a separate entity to endometriosis.

Adenomyosis is characterised by the presence of ectopic endometrial tissues within the smooth muscle cells of the myometrium. It is believed to result from tissue injury and inflammatory repair mechanisms mediated by oestrogen.

Characteristics	**Diagnosis**	**Treatment**
• Commonly diagnosed in women aged 40–50y, but does occur in younger women. • Classically presents with dysmenorrhoea, heavy or abnormal uterine bleeding pain, heavy bleeding and an enlarged uterus. • May be asymptomatic.	• Traditionally a pathological diagnosis post-hysterectomy. • The prevalence of adenomyosis in hysterectomy specimens ranges from 5–70% (Am J Obstet Gynecol 2009;201:107). • It can be identified on TVS or MRI.	Similar to other causes of abnormal uterine bleeding (see article on *Menstrual problems: abnormal uterine bleeding*): • Hormonal suppressive treatments, e.g. combined hormonal contraceptives, high-dose progestogens. • IUS. • Conservative surgical techniques, e.g. adenomyotic muscle excision. If asymptomatic: does not need treating.

(J Minimally Invasive Gynecol 2011;18:428; BMJ, 2022;379:e070750).

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Endometriosis

- Common chronic disease resulting in significant morbidity from pain and infertility.
- Consider the diagnosis when women present with pelvic pain, dysmenorrhoea, dyspareunia, cyclical gastrointestinal or bladder symptoms, or infertility.
- Normal pelvic examination and normal ultrasound do not rule it out.
- Laparoscopy and histological confirmation is the gold standard investigation, BUT a trial of treatment is reasonable before referral UNLESS fertility is a concern.
- If pain is the major concern, offer CHC, progestogens and/or NSAIDs.
- Surgery can improve pain and fertility.
- Off treatment, recurrence of symptoms is common – this is a long-term condition.
- Women with a history of endometriosis who have had a hysterectomy should NOT be given oestrogen-only HRT. Use combined HRT/tibolone to prevent exposure of residual endometriosis to unopposed oestrogen.

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Useful resources for patients:

Websites (all resource are hyperlinked for ease of use in Red Whale Knowledge)

- Endometriosis UK
- Pelvic Pain
- NICE - patient decision aid on hormonal treatment for endometriosis
- RCOG - endometriosis patient information leaflet

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