BMJ Best Practice

Endometriosis

Straight to the point of care

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Summary

Endometriosis is a chronic inflammatory condition defined by endometrial stroma and glands found outside of the uterine cavity. The most common sites affected are the pelvic peritoneum and ovaries.

May present incidentally in asymptomatic women, or more commonly in women of reproductive age who complain of chronic pelvic pain and/or sub-fertility.

Clinical suspicion is generally sufficient to initiate therapy, but the diagnosis can only be confirmed by direct visualisation and focused biopsies during laparoscopy.

Treatment options include non-steroidal anti-inflammatories (NSAIDs), combined oral contraceptive pills, progestin-containing compounds, gonadotrophin-releasing hormone (GnRH) agonists and antagonists, danazol (or related androgens), and surgical destruction or excision of lesions. Controlled ovarian hyper-stimulation and IVF may be considered for women with sub-fertility.

Individualised care for women with pelvic pain should incorporate a multi-disciplinary evaluation and treatment plan that focuses on limiting the risk of recurrence and improving quality of life.

Definition

Endometriosis is defined as the presence of endometrial glands and stroma outside the endometrial cavity and uterine musculature. Surgical appearance varies significantly from superficial blebs to infiltrating fibrosis. While direct visualisation confirmed by histological examination remains the gold standard for diagnosis, surgical confirmation of endometriosis is not required before starting therapy.

Epidemiology

Epidemiological factors have been extrapolated primarily from cohorts of women with pelvic pain and infertility, which complicate the assessment of prevalence. It is generally accepted that up to 10% of reproductive-aged women are affected by endometriosis.[3] [4] [5] Endometriosis is most commonly diagnosed between the ages of 18 and 29 years.[5] Women with a first-degree relative with endometriosis have a 7- to 10-fold increased risk of having it themselves.[6] [7] Genetic predisposition to the disease has been well documented in sibling pair studies.[8] [9]

Documentation of endometriosis requires a more thorough examination than may be performed during procedures with indications other than pelvic pain. A study that assessed pathological specimens from women undergoing vaginal hysterectomy for chronic pelvic pain documented a rate of endometriosis of 8.3%.[10] Higher estimates may be seen in cohorts undergoing laparoscopy for pelvic pain (12% to 70%) or infertility (9% to 50%), especially in adolescent populations who have chronic pain refractory to medical management.[11] [12] [13] Such a large range of estimates may be explained by heterogeneity in study design with more recent studies including diagnostic criteria not previously established.[12] Global trends of disease are even less reliable due to the reliance on surgical findings as confirmation of disease and the inconsistent documentation of pelvic pain in the literature.[14] An epidemiological assessment from the ENDO Study Working Group provided estimates of prevalence based on operative findings as well as magnetic resonance imaging, suggesting that endometriosis may be more prevalent than previously reported, with a strong association with infertility.[15]

Endometriosis typically affects women of reproductive age, but a wide spectrum of age at diagnosis exists.[4] Contrary to previous paradigms, pre-menarcheal girls presenting with chronic pelvic pain should be evaluated for endometriosis as this condition has been reported in this young cohort.[16] Adolescents who complain of moderate-to-severe dysmenorrhoea since menarche and whose complaints progress and become more acyclic may have endometriosis. This group is often overlooked.[1] [17] Furthermore, endometriosis can present in menopausal women.[2]

The prevalence is thought to be higher in white women and in those with a lower body mass index.[11] [18]

Aetiology

Several theories have been proposed to explain the underlying mechanisms that allow for the development and progression of endometriosis, yet no single one holds true for every woman or manifestation.

- Retrograde menstruation: represents a portal for endometrial tissue to gain exposure to peritoneal surfaces.[19] Although logical, this concept fails to explain the low rate of disease compared with such a common event (90% of menstruating women will manifest retrograde flow).[20]
- Deficient cell-mediated immune response: reduced scavenger receptivity by activated, non-adherent macrophages (first-line response to foreign body) is present in women with endometriosis and may represent an ineffective mechanism for clearing menstrual effluent.[21]
- Mullerian rests: differentiation of coelomic epithelium into endometrial glands is a possible mechanism. Endometriosis documented in pre-menarcheal girls is thought to arise from mullerian rests, cells of paramesonephric origin already in the pelvis, which are stimulated by oestrogen production once maturation of the hypothalamic-pituitary-ovarian axis occurs.[22] Deep peritoneal disease with no obvious superficial implants is suggestive of this process, and may explain advanced stages noted in particularly young cohorts.

- Vascular and lymphatic dissemination: suggested by presence of endometriosis pulmonary disease.
- Increased levels of various inflammatory and angiogenic mediators have been consistently documented in peritoneal fluid of women with endometriosis.[23] [24] Products of oxidative stress further contribute to the inflammatory reaction by formation of free radicals and through lower levels of protective antioxidants.[25]
- Post-pubertal girls with mullerian anomalies that obstruct flow of menstrual blood are also at risk for developing endometriosis.[26] This includes transverse vaginal septum, uterine didelphys (double uterus) with obstructed hemivagina, and imperforate hymen (not mullerian).
- An increased prevalence of autoimmune diseases has been noted in women with surgically confirmed endometriosis.[27]
- Genetic predisposition to disease has been well documented in sibling pair studies.[9] [28]
- The composite theory asserts that the underlying mechanism of endometriosis includes both vascular/lymphatic dissemination and the differentiation of coelomic epithelium into endometrial glands.

Pathophysiology

Whereas the association between severe endometriosis and sub-fertility appears logical (distorted anatomy, significant involvement of the tube and/or ovary due to scarring or prostaglandin over-production that can interfere with fertilisation or implantation), the mechanism for lesser stages is not so clear. It has been postulated that an altered immune response, hormonal influences, and production of various cytokines and growth factors affect ovulation, oocyte transport within the tube and embryo implantation in the uterus.[4] None of these have been confirmed.

Pelvic pain is a common complaint for women with endometriosis, yet the degree of involvement noted at surgery does not always correlate with the severity of symptoms. Dysmenorrhoea may be most common in early stage disease since prostaglandin production may be higher within these implants. It has been suggested that chronic pain may be due to the resulting fibrosis that occurs with longstanding inflammation. The resulting deeply infiltrating disease and adhesions distort normal anatomy. What remains unclear is which aetiological processes produce such aggressive features; for example, does early stage progress to late stage, or do mullerian rests invade deep into the pelvic floor from their initial starting point? Noxious stimuli (e.g., cytokines) can provoke pelvic floor nerves and musculature, which can also contribute to chronic symptoms. Furthermore, fibrotic disease and peritoneal disease, which are often associated with ovarian endometrioma, distort normal anatomy and represent the probable aetiology of the pelvic pain.[9] In less common scenarios, patients may present with neuropathic pain due to nerve entrapment from endometriosis, often involving the sacral nerve roots or pudendal nerve. Even when endometriosis has been surgically documented, the physician should remain alert to other potential causes of chronic pain and not always assume a causal relationship. Women with endometriosis may demonstrate a heightened myofascial as well as central nervous system response when provoked, further contributing to the development of associated pain syndromes.[29] [30]

Case history

Case history #1

A 32-year-old nulliparous white female presents with a history of progressively worsening menstrual pain that is now causing her distress for most of the month. She misses 2 to 3 days of work each month. She finds no relief from ibuprofen and can no longer tolerate the headaches associated with her contraceptive

pills. She is currently sexually active with her long-term partner. Her relationship is being affected by associated stress and pain during intercourse. On vaginal examination, her pelvic musculature is moderately tender. Her uterus is of normal size and minimally tender. Rectovaginal examination reveals uterosacral nodularity and exquisite tenderness. Stool is soft, brown, and haeme-negative.

Case history #2

A 41-year-old white female presents to her gynaecologist for a routine healthcare visit. She has no complaints except for some mild lower abdominal bloating. Her past medical and surgical history is unremarkable. Her sister has recently been diagnosed with endometriosis. She and her husband have been trying to conceive for the past 2 years and have been unsuccessful. She is requesting a referral to an infertility consultant. On examination, she is thin and in no distress. Pelvic examination reveals 10 cm bilateral adnexal masses indistinguishable from the uterus. Transvaginal ultrasound performed in the clinic is significant for ovarian masses with homogeneous, low-level internal echoes.

Other presentations

Endometriosis should be considered in adolescent girls and young women who have had primary dysmenorrhoea since menarche and who do not experience clinical improvement after 3 to 6 months of empirical therapy, as well as those with secondary dysmenorrhoea.[1] Endometriosis can present in menopausal women.[2]

Approach

Although no single symptom or finding is diagnostic, clinical suspicion for endometriosis is generally sufficient for presumptive diagnosis.[4]

Clinical evaluation

A history of painful menstrual cramps (dysmenorrhoea), especially if unrelieved by non-steroidal anti-inflammatories (NSAIDs), is fairly suggestive of the diagnosis.[13] Primary dysmenorrhoea (menstrual cramps that occur in the absence of obvious pelvic pathology) is extremely common in younger women.[1] Pain characterised as progressively worsening and continuous, however, is most characteristic for women with endometriosis.

Women may present with a spectrum of symptoms, including various genitourinary (e.g., dysuria, flank pain, haematuria) and gastrointestinal (e.g., dyschezia, haematochezia) complaints.[17] [31] Commonly, women may also describe deep dyspareunia or pain on deep penetration during intercourse.[5]
The diagnosis should also be considered in women presenting with unexplained sub-fertility.[33]
Endometriosis is present in up to 40% of women presenting with unexplained sub-fertility.[33] These women may otherwise be asymptomatic.

Several demographic and anthropometric measures such as white ethnicity, low body mass index, and social behaviours (late first sexual encounters, smoking) have been weakly associated with endometriosis.[11] [18]

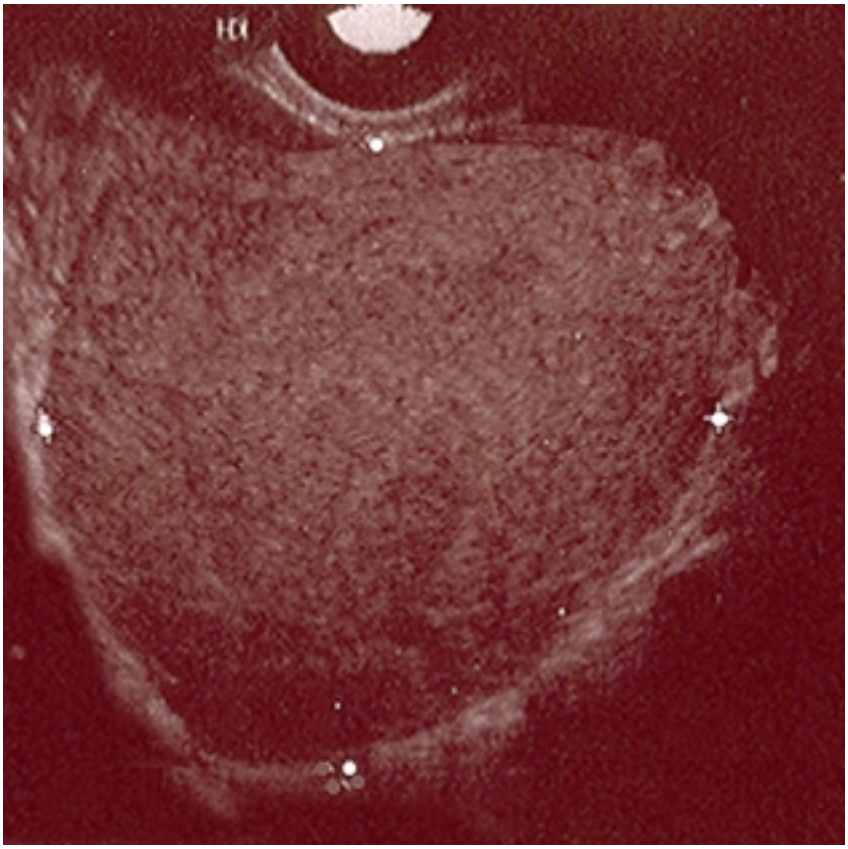
Depression and anxiety appear to be associated with endometriosis, especially if chronic pain is present.[34] [35] Therefore, women presenting with endometriosis should be assessed for comorbid mood or anxiety disorders. A multi-system approach that considers physical and psychological perspectives is required. See Depression in adults and Generalised anxiety disorder .

Enquire about a possible family history of endometriosis, as well as whether the woman misses work or school because of debilitating pain. Having a first-degree relative with a history of endometriosis increases the likelihood of endometriosis.[36] Absenteeism from work or school, along with a positive family history of endometriosis, is strongly correlated with a diagnosis of endometriosis.[37]

A gentle and thorough examination may help distinguish endometriosis from other pelvic pain disorders. Single digit pelvic examination, followed by bi-manual and rectovaginal examinations may reveal pelvic mass (ovarian endometrioma), fixed and retroverted uterus or uterosacral ligament nodularity and tenderness.[17] Inspection and palpation of the abdomen is also recommended.[17] [36] Clinical examination may be normal in women with endometriosis.[17] [36] Physical examination should be decided on a case-by-case basis, and with informed patient consent. The National Institute for Health and Care Excellence (NICE) in the UK recommends that an abdominal examination should still be offered (to exclude abdominal masses) if a pelvic examination is declined or is unsuitable.[36]

Ancillary studies

Transvaginal ultrasound is the imaging modality of choice to assess for the presence of endometriosis.[36] [38] Transvaginal ultrasound may not detect early disease. Sensitivity and specificity for detecting endometriomas is 93% and 96%, respectively.[39]



Ultrasound of ovarian endometrioma

From the collection of Dr Jonathon Solnik; used with permission

Transvaginal ultrasound has high specificity, but limited sensitivity, for diagnosis of vaginal, bladder, parametrium, rectovaginal septum, and uterosacral ligament endometriosis.[40] [41] [42] [43] For the diagnosis of rectosigmoid deep endometriosis, the specificity is 97% and the sensitivity is 89%.[44] Rectal endoscopic ultrasound may be considered in women with suspected deep pelvic endometriosis or involvement of the colon/rectum, as this may help plan surgical resection.[39]

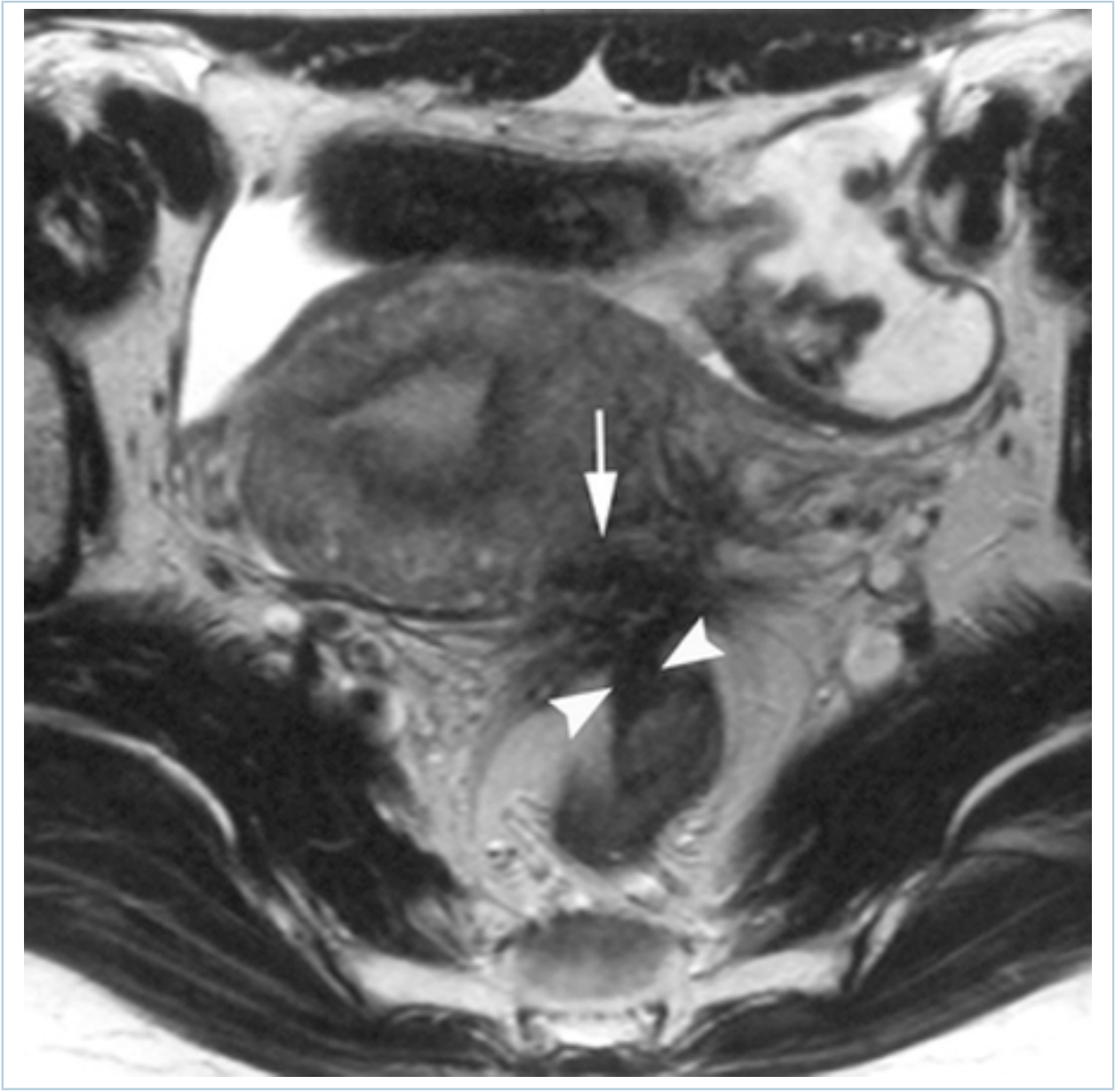
The 'sliding sign' can be used to assess for posterior cul-de-sac obliteration. A negative sliding sign is documented when the rectosigmoid colon does not slide smoothly over the posterior uterus/cervix. A negative sliding sign is both sensitive and specific for deep endometriosis and posterior cul-de-sac obliteration.[45]

In the UK, NICE recommends that additional investigations and referral (if necessary) should be carried out concurrently, and alongside starting initial pharmacological management.[36] This is to reduce delays in diagnosis.[36] They recommend that all patients with suspected endometriosis should be offered a transvaginal ultrasound (organised by the patient's general practice), even if the physical examination is normal.[36] If a transvaginal ultrasound is unsuitable or declined by the patient, NICE recommends that a transabdominal ultrasound of the pelvis should be considered.[36] They noted that although there was much less evidence on the transabdominal approach versus transvaginal, it was still necessary to provide an alternative option for when the latter is declined or unsuitable.[36] The transvaginal ultrasound is used to:[36]

- Identify ovarian endometriomas and deep endometriosis (including that involving the bowel, bladder or ureter)

- Identify or rule out alternative pathologies
- Guide management and enable referral to an appropriate service. Note that a normal ultrasound scan does not exclude endometriosis and referral may still be appropriate.

Magnetic resonance imaging (MRI) may be considered in selected patients.[17] [36] MRI can detect extra-pelvic and rectovaginal implants. MRI (or specialist transvaginal ultrasound) may be used to diagnose and assess the extent of deep endometriosis.[17] [36] NICE advises that these scans should be planned and interpreted by a professional with specialist expertise in gynaecological imaging.[36]



MRI - fibrotic nodules involving the uterosacral ligaments and rectal wall

Bazot M, et al. Radiology. 2004 Aug;232(2):379-89; used with permission

MRI, 3D ultrasonography or hysterosalpingography are ideal for imaging women with mullerian anomalies (e.g., transverse vaginal septum) or for identifying any scarring or tubal blockage causing outflow tract obstruction (e.g., in those with sub-fertility).

MRI or specialist pelvic ultrasound may also be used prior to operative laparoscopy in patients with suspected deep endometriosis.[36]

Normal imaging (e.g., ultrasound, MRI) does not exclude endometriosis.[36]

Serological markers such as CA-125 lack specificity and have not been shown to be useful diagnostic tools, while studies for other biomarkers are ongoing.[46] [47]

NICE recommends referring patients to gynaecology for further investigation and management if they have any of the following:[36]

- symptoms of endometriosis which have a detrimental impact on their daily functioning or which are persistent or recurrent
- pelvic signs of endometriosis (without suspected deep endometriosis)
- suspected or confirmed endometrioma, deep endometriosis, or endometriosis outside the pelvic cavity. These patients should be referred to a specialist endometriosis service.

NICE recommends referring patients aged under 18 with suspected or confirmed endometriosis to a paediatric and adolescent gynaecology service or specialist endometriosis service.[36]

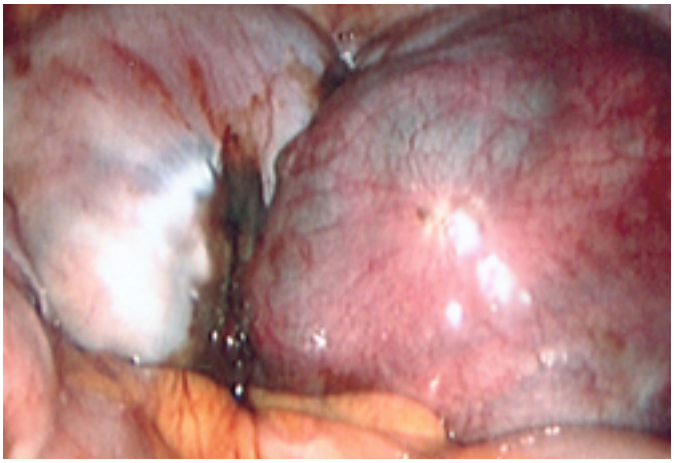
Surgical findings

Surgical inspection with histopathological confirmation remains the definitive test for diagnosis, although a negative histological result does not exclude endometriosis, and up to 50% of peritoneal biopsies obtained during laparoscopy for pelvic pain show no evidence of disease.[36] [48] The use of preoperative imaging is associated with decreased morbidity and mortality and can aid patient decision making, surgical planning, and management.[49] Symptom severity may not correlate with the extent of disease seen on careful surgical inspection. Not all women require surgical investigation. However, some physicians feel that if first line medical treatments (oral contraceptive pills, NSAIDs) fail, or if signs and symptoms are highly suspicious for endometriosis at initial evaluation, proceeding to surgery is an appropriate early measure. Diagnostic laparoscopy may be considered for suspected endometriosis even if other investigations (e.g., imaging) have been normal.[36]

Laparoscopic evaluation is the preferred approach given the shorter recovery time compared with exploratory laparotomy. Surgical treatment can be simultaneously performed (with prior patient consent).[36]

Operative findings widely vary and women should be staged according to the extent and type of lesions; size and depth of peritoneal/ovarian implants; and presence and extent of pelvic adhesions and degree of cul-de-sac obliteration.[50]

- Early stage (minimal to mild) is marked by superficial peritoneal implants that appear vesicle-like (clear or red). These can be isolated or scattered and are more common in adolescents.
- Moderate disease is typically characterised by multiple superficial or deep lesions with a variable degree of adhesions.
- Advanced disease is typified by multiple implants (deep and fibrotic), parametrial or retroperitoneal extension, ovarian endometrioma, an obliterated cul-de-sac, and pelvic adhesions.



Laparoscopic image of ovarian endometrioma

From the collection of Dr Jonathon Solnik; used with permission

History and exam

Key diagnostic factors

presence of risk factors (common)

- Key risk factors include reproductive age, positive family history, non-parous women, and mullerian anomalies.

dysmenorrhoea (common)

- Primary dysmenorrhoea is extremely common in young girls and may be difficult to distinguish from dysmenorrhoea caused by endometriosis.[1]
- Suspect endometriosis if dysmenorrhoea progresses and becomes acyclic.

chronic or cyclic pelvic pain (common)

- The cause of chronic pain is often multi-factorial, but endometriosis must be considered. Pain characterised as progressively worsening and continuous, however, is most characteristic for women with endometriosis.

dyspareunia (common)

- Approximately 30% of women with endometriosis report dyspareunia.[5] Pain during sexual intercourse, particularly with deep penetration, may be caused by distortion of pelvic anatomy and rectovaginal involvement.

sub-fertility (common)

- Endometriosis is present in up to 40% of women presenting with unexplained infertility.[33] These women may otherwise be asymptomatic.
- Due to scarring or prostaglandin over-production that can interfere with fertilisation or implantation.

uterosacral ligament nodularity (common)

- Palpable by rectovaginal examination.
- A "guitar string" texture associated with tenderness is typical when these peritoneal structures are involved. Sensitivity as high as 85%.[51]

pelvic mass (common)

- Ovarian endometriomas (chocolate cysts) may be felt on pelvic examination. Although classified as stage III or IV endometriosis, these women may be asymptomatic.

fixed, retroverted uterus (common)

- Late finding suggestive of peritoneal fibrosis and pelvic adhesions. May be associated with a "frozen pelvis" (posterior cul-de-sac is filled with immobile pelvic organs). Commonly manifests as uterine tenderness.

depression (common)

- Present in 30% to 85% of women with endometriosis.[34] Women with endometriosis are more likely to have depression, compared with healthy controls, but not compared with people with chronic pelvic pain from other causes.[35] Therefore, women presenting with endometriosis, especially if associated with chronic pain, should be assessed for signs and symptoms of depression.

anxiety (common)

- Women with endometriosis are more likely to have anxiety, compared with healthy controls, but not compared with people with chronic pelvic pain from other causes.[35]

unable to attend work or school due to dysmenorrhoea (common)

- Absenteeism from work or school is predictive of a diagnosis of endometriosis.[37]

Other diagnostic factors

dysuria, flank pain, haematuria (uncommon)

- May be present if the bladder or ureters are involved.[17] [31]

dyschezia, haematochezia (uncommon)

- Painful bowel movements (dyschezia), particularly during menstruation, or the passage of fresh blood in the stool (haematochezia) may be indicative of colorectal involvement.[17] [31]

DIAGNOSIS

Risk factors

Strong

reproductive age group

- Endometriosis typically affects women of reproductive age, but a wide spectrum of age at diagnosis exists.[4]

positive family history

- Genetic predisposition to disease has been well documented in sibling pair studies.[9] [28] A first-degree relative with endometriosis imparts a 7- to 10-fold increased risk of diagnosis.[6] [7]

nulliparity

- Nulliparous women are more likely than parous women to be diagnosed with endometriosis.[31]

mullerian anomalies

- Differentiation of coelomic epithelium into endometrial glands is a possible mechanism. Endometriosis documented in pre-menarcheal girls is thought to arise from mullerian rests, cells of paramesonephric origin already in the pelvis, which are stimulated by oestrogen production once maturation of the hypothalamic-pituitary-ovarian axis occurs.[22] Deep peritoneal disease with no obvious superficial implants is suggestive of this process, and may explain advanced stages noted in particularly young cohorts.

Weak

white ethnicity

- The prevalence is thought to be higher in white women.[11] [18]

low body mass index (BMI)

- The prevalence is thought to be higher in those with lower BMIs.[11]

autoimmune disease

- An increased prevalence of autoimmune diseases has been noted in women with surgically confirmed endometriosis.[27]

late first sexual encounter

- Has been weakly associated with endometriosis.[11]

smoking

- Has been weakly associated with endometriosis.[11]

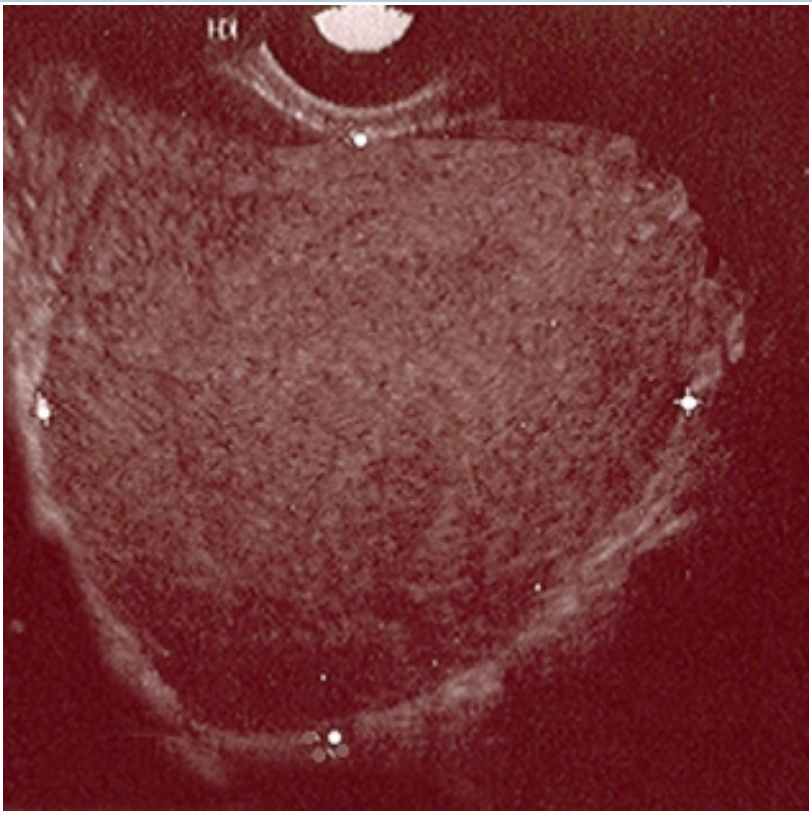
previous caesarean section

- Has been weakly associated with general pelvic endometriosis.[32] Further studies are needed to confirm the association.

Investigations

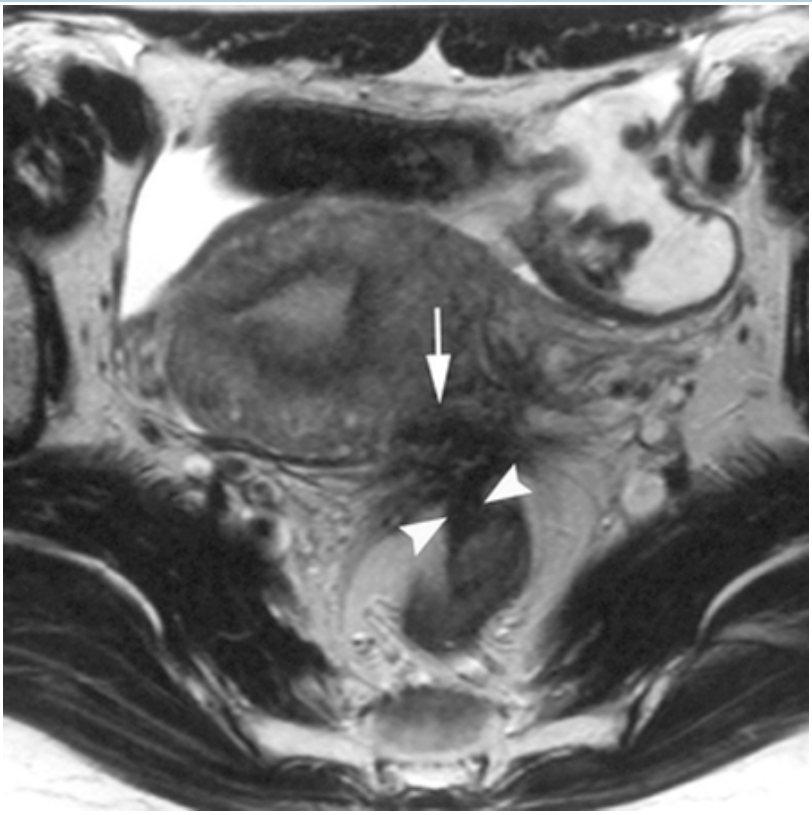
1st test to order

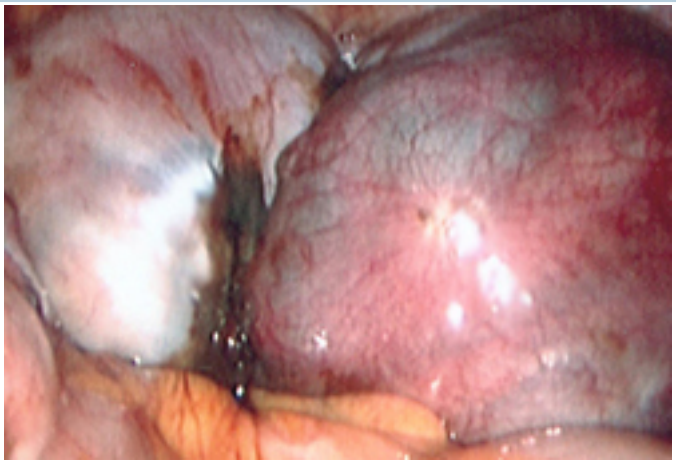
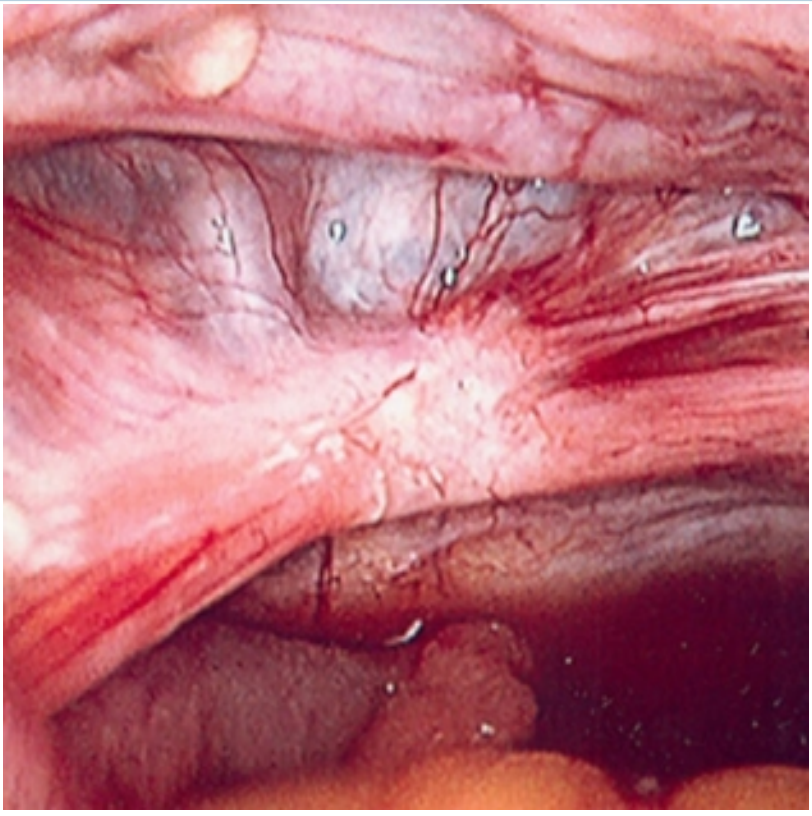
Test	Result
transvaginal ultrasound • Should be offered to all patients with suspected endometriosis.[1] [36] [49] The transvaginal ultrasound is used to: identify ovarian endometriomas and deep endometriosis (including that involving the bowel, bladder or ureter); identify or rule out alternative pathologies; guide management and enable referral to an appropriate service.[36] Note that a normal ultrasound scan does not exclude endometriosis and referral may still be appropriate.[36] • Confirmatory for endometriomas but criteria are less well defined for peritoneal fibrosis.	**may show ovarian endometrioma (homogeneous, low-level echoes) or deep pelvic endometriosis such as uterosacral ligament involvement (hypoechoic linear thickening) or parametrium, bladder, or rectovaginal septum involvement**

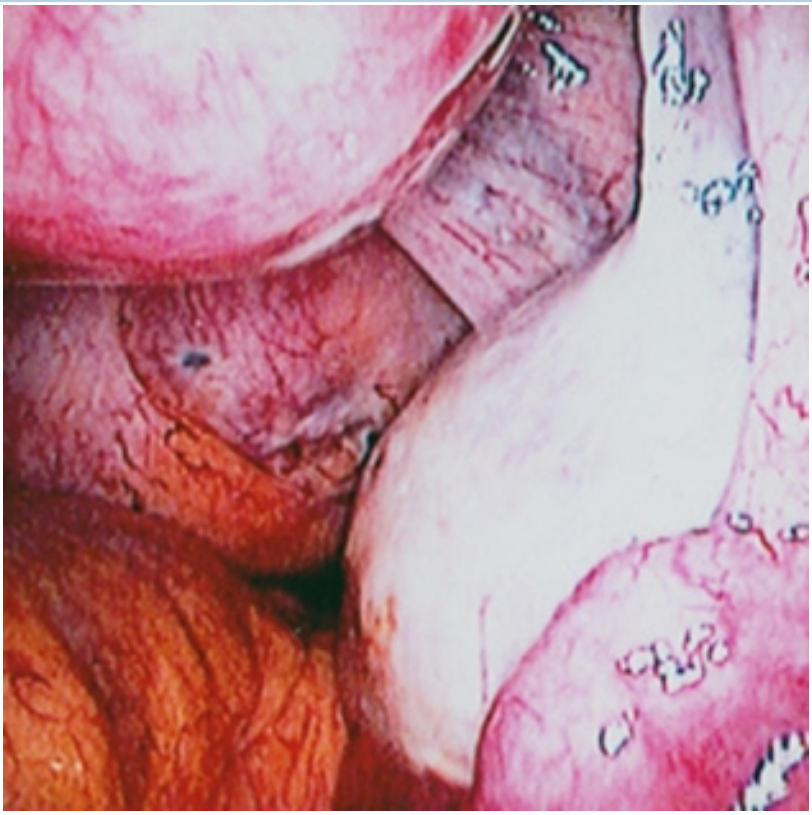
Test	Result
 *Ultrasound of ovarian endometrioma* *From the collection of Dr Jonathon Solnik; used with permission* • Sensitivity and specificity for detecting endometriomas is 93% and 96%, respectively.[39] • Sensitivity is 58%, and specificity 96%, for detecting vaginal endometriosis. Sensitivity is 53% to 65%, and specificity 92% to 93% for detecting uterosacral ligament disease.[40] [43] • Sensitivity 49%, and specificity 98% for detecting rectovaginal septal disease.[40] • Sensitivity is 89%, and specificity 97%, for rectosigmoid deep endometriosis.[44] • Sensitivity is 55%, and specificity 99%, for bladder deep endometriosis.[41] • Sensitivity is 31%, and specificity 98%, for parametrial deep endometriosis.[42] • Ultrasound exam is limited by retroverted uterus. • A negative uterine 'sliding sign' predicts deep infiltrating endometriosis in the rectum.[45] • If a transvaginal ultrasound is unsuitable or declined by the patient, NICE recommends that a transabdominal ultrasound of the pelvis should be considered.[36]	

Other tests to consider

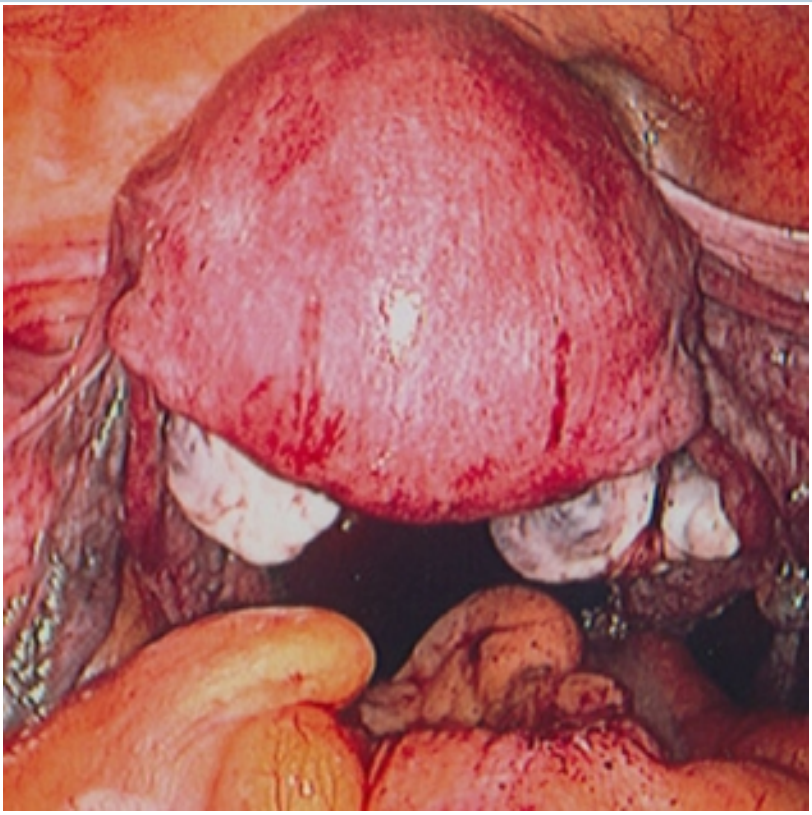
Test	Result
rectal endoscopic ultrasound • Designed to assess for uterosacral, rectovaginal, and intestinal endometriosis. Rectal endoscopic ultrasound may be considered in women with suspected deep pelvic endometriosis or involvement of the colon/rectum, as this may help plan surgical resection.[39] • There is a growing body of literature demonstrating improved detection of deep pelvic disease with endoscopically guided endorectal ultrasound. • Sensitivity and specificity are at least 90% in most studies, but like transvaginal ultrasound, the available data are difficult to interpret.[52]	**hypoechoic nodule or mass**
3D ultrasonography • Less invasive than hysterosalpingography, hysteroscopy, or laparoscopy and more cost-effective than MRI as a test to confirm mullerian anomalies. • Few comparative studies are available; limited to specialised centres.	**Three-dimensional image of the endometrial cavity (varies based on type of anomaly)**
hysterosalpingography • Useful for women thought to have a mullerian anomaly (such as unicornuate uterus or uterine didelphys [double uterus]), which accounts for a small percentage of women with endometriosis. • A useful adjunct for women with sub-fertility. • Also evaluates tubal diameter and patency.	**contrast will delineate the endometrial cavity from surrounding/ internal filling defects (varies based on type of mullerian anomaly)**
MRI pelvis • Useful for imaging the entire abdomen and pelvis. Ovarian disease can be easily seen. MRI can detect extra-pelvic and rectovaginal implants. MRI may be used to diagnose and assess the extent of deep endometriosis.[17] [36]	**hypo-intense, irregular thickening or mass of uterosacral ligament; replacement of fat tissue plane between uterus and rectum/sigmoid with tissue mass**

Test	Result
 *MRI - fibrotic nodules involving the uterosacral ligaments and rectal wall* *Bazot M, et al. Radiology. 2004 Aug;232(2):379-89; used with permission* • Sensitivity and specificity for deep pelvic disease is approximately 90%, but is consistently lower for uterosacral ligament and higher for gastrointestinal disease.[53] • NICE advises that pelvic MRI scans should be planned and interpreted by a professional with specialist expertise in gynaecological imaging.[36]	
diagnostic laparoscopy • Direct visualisation of implants at time of surgery and histopathology do not always correlate since there is no standardised method used by all pathologists and atypical lesions may be difficult to assess without biopsy.	**direct visualisation with biopsy-confirmed endometrial glands or stroma outside of the uterine cavity. Early stage (minimal to mild) is marked by superficial peritoneal implants which appear vesicle-like (clear or red). Moderate disease is typically characterised by multiple superficial or deep lesions with a variable degree of adhesions. Advanced disease is typified by multiple implants (deep and fibrotic), parametrial or retroperitoneal extension, ovarian endometrioma, an**

Test	Result
 *Laparoscopic image of ovarian endometrioma* *From the collection of Dr Jonathon Solnik; used with permission*	**obliterated cul-de-sac and pelvic adhesions.**
 *Laparoscopic image of endometriotic nodule* *From the collection of Dr Jonathon Solnik; used with permission*	

Test	Result
 *Laparoscopic image of peritoneal window* *From the collection of Dr Jonathon Solnik; used with permission*	

Test	Result



Laparoscopic image of retroverted uterus
From the collection of Dr Jonathon Solnik; used with permission

- Surgical experience may increase the sensitivity to 97%.[54]
- Diagnostic laparoscopy may be considered for suspected endometriosis even if other investigations (e.g., imaging) have been normal.[36]

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Adenomyosis	• Symptoms may be identical to those of endometriosis.	• Pre-operative MRI findings may show diffuse or focal widening of the junctional zone (inner myometrium), islands of endometrial tissue or cystic dilation of glands or haemorrhage, linear striations radiating out from the endometrium into the myometrium, mass within the myometrium (adenomyoma). • Laparoscopy may reveal a normal pelvis or concurrent endometriosis. • Histopathological evaluation of the uterus after hysterectomy shows endometrial glands/stroma in the myometrium.
Interstitial cystitis	• Symptoms primarily localised to the bladder, such as urinary frequency and urgency. Women complain of pain with a full bladder that is relieved upon voiding. • Diffuse chronic pain and dyspareunia are common and often indistinguishable from endometriosis.	• Cystoscopy with hydrodistention shows glomerulations (pinpoint mucosal haemorrhages) and Hunner ulcers as distention medium is released. • Potassium chloride sensitivity test: after instilling a dilute solution of potassium chloride into the bladder with a catheter, the woman will note a change in urinary urgency and frequency scores.
Pelvic inflammatory disease (PID)	• Fever, nausea, acute pain along with malodorous vaginal discharge and cervical motion tenderness/ adnexal tenderness is typical for acute PID. • Chronic PID may be indistinguishable from endometriosis.	• Cervical cultures for *Neisseria gonorrhoea* or *Chlamydia trachomatis* may be positive. • Pelvic ultrasonography may show complex adnexal masses as distinguished from homogeneous, low-level echoes typically seen with endometrioma.
Irritable bowel syndrome	• Change in bowel habits (alternating constipation and diarrhoea; bloating) may help differentiate. Dyschezia more typical of endometriosis.	• Diagnosis is usually clinical and based on an absence of ultrasound, MRI or laparoscopic findings of endometriosis.

Condition	Differentiating signs / symptoms	Differentiating tests
Ovarian cyst (benign)	• May be asymptomatic with an incidental pelvic mass or present with acute rather than chronic pain, such as in the case of haemorrhagic cysts.	• Transvaginal ultrasound: enlarged ovary with a simple or complex cystic structure emanating from the ovary as distinguished from homogeneous, low-level echoes typically seen with endometrioma. Ultrasound is ideal for differentiating liquid from solid material.
Ovarian cancer, epithelial	• Typical symptoms represent advanced-stage cancer, and include weight gain despite lack of appetite, increased abdominal girth and altered bowel habits. • Endometriosis may be an uncommon risk factor for developing epithelial ovarian cancer.	• Transvaginal ultrasound: complex adnexal mass (solid and cystic) with multiple loculations or thick septa; ascites. Most women present with advanced-stage disease. • Histopathology: there are many cell types and various stains can be used to verify/ differentiate.
Pelvic floor tension myalgia	• May be unable to differentiate clinically. • Clinically, women have chronic pelvic pain and dyspareunia (or inability to have intercourse due to spasm and pain). • An experienced clinician can elicit focal spasm and tenderness on pelvic and rectovaginal examination.	• No diagnostic test available. Lack of positive findings on other investigations.
Neuropathic pain	• Burning, shock-like pain associated with paraesthesia or dysaesthesia.	• No diagnostic test available. Lack of positive findings on other investigations.
Uterine myoma	• Many are asymptomatic, but often present with heavy and/or irregular menstrual bleeding. • Pelvic examination may show an enlarged, nodular pelvic mass that can vary in size and shape.	• Transvaginal ultrasound: concentric, solid, hypoechoic (dark) mass or masses within the endometrium (sub-mucosal), myometrium (intramural) or external (sub-serosal). Small myoma may be isoechoic, but if calcified, myoma can also appear hyperechoic (bright).

Criteria

The gold standard for diagnosis of endometriosis is histological verification of endometrial glands and stroma from surgically excised tissue specimens. However, surgical confirmation of disease is not required to initiate medical management. The use of preoperative imaging is associated with decreased morbidity and mortality and can aid patient decision making, surgical planning, and management.[49]

Revised American Society for Reproductive Medicine score

The classification of endometriosis is typically based on visual inspection during laparoscopy. A cumulative score yields 4 stages (I to IV, or minimal to severe) and is based on:

- The appearance, size, and depth of peritoneal and ovarian implants
- The presence, extent, and type of lesions (red, red-pink and clear, white, peritoneal defects and black)
- Presence, extent, and type of pelvic adhesions (ovaries and tubes) and the degree of cul-de-sac obliteration.

Stage I (minimal): total score 1 to 5

- Small, superficial peritoneal or adnexal implants (<1 to 3 cm); filmy adhesions.

Stage II (mild): total score 6 to 15

- Larger lesions (>3 cm), some deeply infiltrating.

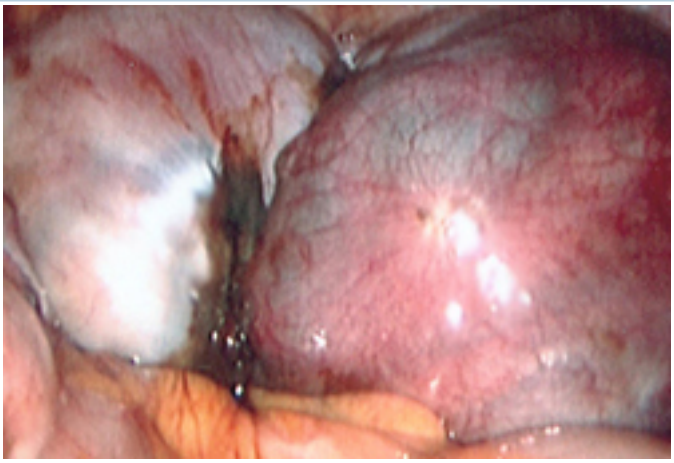
Stage III (moderate): total score 16 to 40

- Larger lesions, more of which are infiltrative, partial cul-de-sac obliteration; dense adhesions involving adnexa.

Stage IV (severe): total score >40

- Deep ovarian lesions (endometrioma) with dense adnexal adhesions; cul-de-sac obliteration.

This method of classification was designed to predict fertility outcomes, but has been criticised for its poor predictive power. Its utility for general practice should be limited to complete and reproducible operative documentation. Rather than computing a score after each case, a thorough dictation with specific implant/adhesion characteristics should be described.



Laparoscopic image of ovarian endometrioma
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Approach

Since women with endometriosis can present with a myriad of complaints, therapy should be individualised.[4] Clinical suspicion should guide therapy in the absence of positive findings for tests ordered during the assessment phase. Surgical diagnosis is not required before the initiation of empirical therapy. The primary objective of management should be to provide safe and effective care while minimising potential risks and addressing the woman's concerns, such as pain or fertility. A multi-disciplinary approach should be undertaken since the list of differential diagnoses is considerable, and often, no single intervention provides effective long-term therapy.

Treatment regimens outlined here do not always provide definitive relief from pain. Therapy should focus on reducing the risk of recurrent symptoms that may occur within a few months after completion of medical or surgical options.[55] [56]

Medical management

- For women without confirmed ovarian endometrioma, or without suspected severe or deep disease, non-steroidal anti-inflammatory drugs (NSAIDs) and hormonal contraceptives (combined oral contraceptive pills [OCPs] and progestogens) are generally regarded as first-line agents.[1] However, there is an increasing debate on the use of OCPs as first-line therapy because of concern over oestrogenic side effects and progression of more advanced stage disease. NSAIDs antagonise prostaglandin-mediated pain and steroid hormone-derived medicines suppress growth and activity of ectopic endometrial implants and induce amenorrhoea via the hypothalamic-pituitary-ovarian axis.
- There appears to be positive feedback between prostaglandin (PG) synthesis, aromatase activity, and oestrogen production, mediated by abnormally high COX-2 activity in the setting of endometriosis.[57] Superficial, often atypical implants (seen more commonly in adolescents) are active PG producers. Since endometriosis is a chronic inflammatory condition, NSAIDs may improve symptoms of PG-associated inflammation and pain by interrupting receptor-mediated signalling pathways. In clinical trials, NSAIDs effectively treat primary dysmenorrhoea and provide adequate analgesia, but their use remains inconclusive for endometriosis-associated pain.[58] [59] NSAIDs may be used alone or in combination with other medical therapies. In the UK, the National Institute for Health and Care Excellence (NICE) recommends paracetamol (alone or in combination with an NSAID) as an alternative first-line analgesic for women with endometriosis-related pain.[36]
- Most hormonal options appear to be equally effective in treating endometriosis-associated pain.[60] [61] [62] [63] [64] [65] Use is generally limited by lack of a response, bothersome side effects, or contraceptive implications for those who want to conceive.
- OCPs are commonly used for cycle control and to suppress ovulation. If pain is strictly related to the menstrual cycle, then continuous use of the OCP can be recommended as women may become amenorrhoeic and will experience less cyclic pain.[66] Women should be made aware that irregular spotting is common with continuous use. Side effects are generally mild and time-limited. Life-threatening cardiovascular adverse events are more likely to occur in women aged over 35 years, who are heavy smokers, have acquired/inherited thrombophilia, or have experienced a prior cardiovascular event. Therefore, OCPs are not recommended for these women. Some reports indicate a reduction in anatomical relapse, and in the frequency and intensity of dysmenorrhoea recurrence with postoperative use of OCPs.[67] [68] [69] Clinical trials lack appropriate controls, and so the decision to prescribe OCPs is based on common practice guidelines rather than scientific evidence.[60]

- OCPs can be prescribed in a cyclical or continuous fashion. While a continuous schedule with no pill-free interval may lead to reduced rates of dysmenorrhoea and postoperative endometrioma recurrence, side effects are more common.[70] [71]
- Progestogens (e.g., medroxyprogesterone, levonorgestrel, and dienogest) and antiprogestins have been shown to be as effective as other hormonal therapies, with varying degrees of tolerability.[61] [72] As a result, there is increasing debate that progestin-only therapies be considered as first-line agents moving forward.[6] [73] The levonorgestrel IUD is an effective treatment modality for long-term use, with improvement noted in staging and pelvic pain at 6 to 12 months of follow-up.[62] [74] It can be used in the setting of advanced disease.[62] [75] Similarly, there is increasing evidence that the etonogestrel-releasing subdermal implant improves endometriosis-related pain symptoms and quality of life.[76] Dienogest is an oral progestin approved for the treatment of endometriosis in Europe, Canada, and Japan, among other countries. It has been shown to reduce endometriotic lesions and provide symptomatic relief equivalent to gonadotrophin-releasing hormone (GnRH) agonists (e.g., leuprolide), while also improving various quality-of-life measures.[77] It is not currently available in the US and some other countries, except in combination with estradiol valerate. However, this combination is sometimes used off-label for endometriosis. Some progestogens may decrease bone mineral density (BMD), especially with prolonged use. This effect may be more marked in adolescents, when the rate of bone mineralisation peaks. The subcutaneous form of medroxyprogesterone acetate, and IUD levonorgestrel, may reduce this risk.[55] [75] Other unwanted side effects include weight gain, irregular uterine bleeding, and mood changes.
- In the UK, NICE recommends that the patient should be referred (if not already) to a gynaecology service for further investigation and management, if initial pharmacological management (e.g., NSAIDs, paracetamol, and first-line hormonal contraceptives) is not effective, not tolerated or is contraindicated.[36]
- GnRH analogues, including both agonists and antagonists, are typically offered if first-line treatments are ineffective, either alone or as an adjunct to surgery for deep endometriosis.[1] [31] [36][78] [79] [80][Evidence B] [Evidence C] Some clinicians administer these agents as first-line therapy.
- Elagolix is an oral GnRH antagonist that suppresses ovarian oestrogen production in a dose-dependent manner.[78] In the US, it is licensed for the treatment of moderate to severe endometriosis-related pain. Two 6-month placebo-controlled phase 3 trials reported significant reductions in dysmenorrhoea and non-menstrual pelvic pain among women with endometriosis-associated pain who were randomised to elagolix.[79] Hypo-oestrogenic adverse effects were similar to those of injectable GnRH agonists, and included hot flushes, increased serum lipids, and decreased BMD.[79] The maximum recommended duration of elagolix use is 6 to 24 months (depending on dose) to reduce the extent of bone loss.
- Relugolix, another GnRH antagonist, is available in combination with estradiol and norethisterone, which are thought to reduce hypo-oestrogenic adverse effects.[80] In the US, it is licensed for the treatment of moderate to severe endometriosis-related pain. In two 6-month phase 3 trials, significantly more women who received relugolix combination therapy experienced improvements in dysmenorrhoea and non-menstrual pelvic pain, compared with those who received placebo.[80] The least squares mean percentage loss in lumbar spine and total hip bone mineral density was less than 1% after 24 weeks. Headache, nasopharyngitis, and hot flushes were the most common adverse effects.[80] The maximum recommended treatment duration for relugolix combination therapy is 24 months due to the risk for continued bone loss.

- GnRH agonists induce a profound hypo-oestrogenic state, and may be administered for up to 12 months.[1] Approximately 85% of women with confirmed endometriosis will experience significant reduction in pain complaints.[82] Empirical use in women with chronic pelvic pain may also be considered, regardless of the diagnosis.[83] NICE advises that 3 months of pre-operative GnRH agonist treatment should be considered as an adjunct to surgery for deep endometriosis involving the bowel, bladder or ureter.[36] 'Add-back' hormonal therapy is indicated to reduce menopausal symptoms and the impact on BMD and should be offered at the beginning of treatment with GnRH agonists.[1][64] [84] [85] Non-hormonal forms of 'add-back' therapy to alleviate vasomotor symptoms include selective serotonin reuptake inhibitors, serotonin-noradrenaline re-uptake inhibitors, and various herbal remedies. GnRH agonists lack some bothersome side effects of progestogens and androgens and may be recommended prior to initiating other hormonal therapies, but they may not be well tolerated. Due to the effects on BMD, GnRH agonists may not be an ideal choice in adolescents. Results of one trial suggest that GnRH agonists have similar efficacy to that of continuous OCPs in treating endometriosis-associated pain.[86]
- Danazol (a synthetic androgen) has been shown to be of subjective and objective benefit, but its use is limited by adverse effects that include darkening facial hair, acne, oily skin, deepening of the voice, and male-pattern hair loss.[63] [87] Furthermore, reports have linked danazol to ovarian cancer.[88]
- There is insufficient evidence supporting the use of pentoxifylline with respect to fertility and pain management in women with endometriosis.[89]

Surgical management with preservation of fertility potential

Surgical management is generally indicated for pain refractory to medical management, advanced disease, endometriomas, and associated sub-fertility. It may also be used to confirm endometriosis before initiating medical therapy; however, surgical diagnosis is not required to initiate medical therapy. Several studies have established a clear relationship between surgical intervention and reduction of pain in women with endometriosis.

Exactly when to offer surgery is debatable and varies among specialists. It is usually determined by the individual clinician and woman. The patient's symptoms, preferences and priorities regarding pain and fertility are elements that should be considered.[36] Side effects of hormonal therapy may influence the decision (e.g., in adolescents, it may not be ideal to initiate GnRH agonist or progestogen therapy because of potential impact on BMD at such a critical point in development). The ultimate goal is to minimise the number of surgeries for endometriosis. Therefore, empirical medical management is recommended before surgical management. If women are refractory to first-line agents, surgery may be considered because the probability of encountering true disease is higher. In women suspected of deep endometriosis or severe advanced disease based on symptoms and clinical findings, surgery can be considered before medical therapy.[90]

Ovarian endometriomas do not resolve in response to hormonal suppression and, if symptomatic, should be addressed surgically. There is insufficient evidence to determine whether hormonal suppression, either before or after surgery for endometriomas, is associated with any significant benefit compared with surgery alone.[91] [92] However, there may be some benefit of prolonged hormone therapy because lower rates of dysmenorrhoea and endometrioma recurrence have been reported with continuous OCPs (compared with cyclical OCP) and progestin-only therapy after resection of endometrioma.[70] [91] [93]

Laparoscopically targeted destruction of implants and restoration of pelvic anatomy significantly reduces pain in the majority of women, although recurrence of disease and pain are not uncommon.[94] [95]

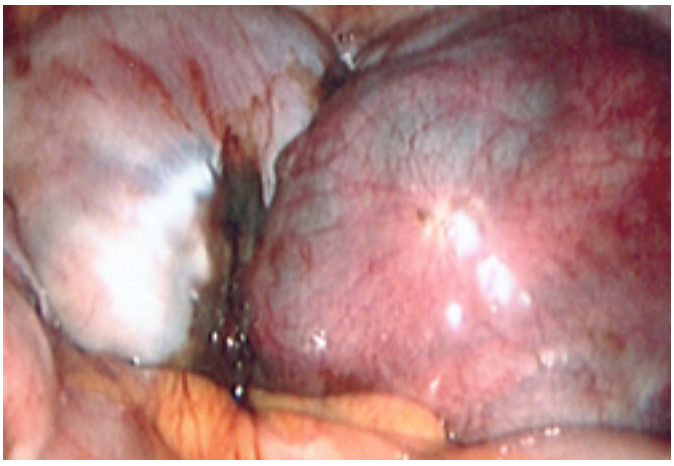
Although laparoscopic findings do not always correlate with the degree of symptoms, pain seems to correlate well with the depth of peritoneal invasion.[96] Ablative therapy with electrosurgery or laser effectively provides relief (for at least 6 months) in women with minimal to moderate disease.[94] Radical excision of affected areas with restoration of normal anatomy is the preferred method of treating symptomatic women with deep peritoneal disease.[96] [97]

Improvement in pain may last up to 5 years after surgery, but the risk of re-intervention approaches 50% in women with moderate to severe disease.[98] Less aggressive surgical measures and younger age are predictive of recurrence.[95] [99] For this reason, prolonged hormonal suppression is recommended after surgery for endometriosis.[6] [100]

Appendectomy may be considered in women undergoing laparoscopic surgery for suspected endometriosis if there is a complaint of right-sided pain and the appendix appears abnormal. Up to 50% of appendiceal specimens will yield abnormal pathology, but the effect on pain and future adverse outcomes is difficult to assess.[101]

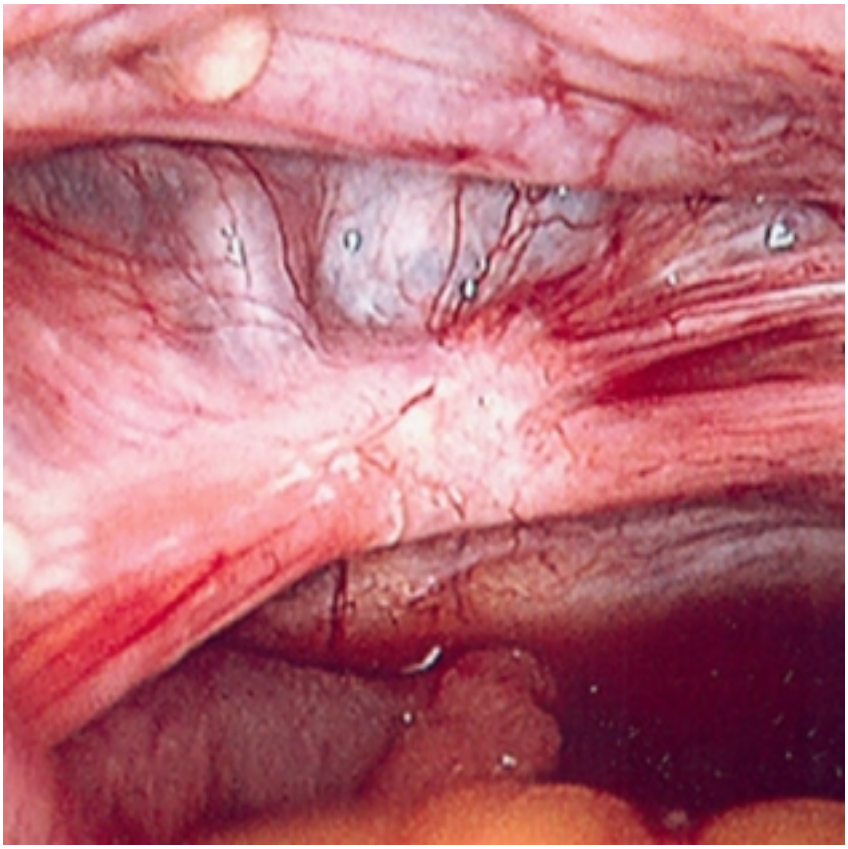
Colorectal resection may be considered in women with intestinal disease and related complaints, although this remains controversial. A moderate-sized series demonstrated significant reduction in pain scores and improvement in quality-of-life assessments, yet major complications such as rectovaginal fistula formation (approximately 10%) occurred.[102] One meta-analysis found that disc excision was less associated with post-operative bowel stenosis, compared with segmental resection.[103] Rectal shaving may be considered for women with endometriosis that infiltrates the rectum, and is associated with fewer post-operative complications than disc excision or segmental resection.[103] [104] [105] Disc excision or segmental resection can be performed by laparoscopy or laparotomy, while preserving the uterus and adnexa for women who wish to have children.

Benefit of surgery must outweigh inherent surgical risks such as bowel perforation and ureteral injury associated with adhesions and distorted anatomy.



Laparoscopic image of ovarian endometrioma

From the collection of Dr Jonathon Solnik; used with permission



Laparoscopic image of endometriotic nodule

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Surgical management if continued fertility is not desired

Definitive surgical options for symptomatic women who have persistent pain despite conservative measures, and no longer desire childbearing potential, include hysterectomy with or without adnexectomy. For the best chance of cure, hysterectomy with bilateral salpingo-oophorectomy and excision of visible peritoneal disease should be offered, focusing on excising deep infiltrating lesions.[106] The principle is based on removal of common areas of implantation along with the primary source of endogenous oestrogen production. However, there is little distinction in the literature as to whether this is an effective treatment modality specifically for cyclical pain.[107] Although women with endometriosis may develop non-cyclical pain, a comprehensive pain assessment should be undertaken prior to offering hysterectomy to minimise risk of an unsuccessful surgery. Oestrogen replacement is generally warranted to reduce vasomotor symptoms and risk of bone loss, especially in pre-menopausal and symptomatic post-menopausal women. The risks (e.g., increases in risk of breast cancer, venous thrombosis and stroke in post-menopausal women) versus the benefits of hormone replacement therapy should be discussed with the woman before initiating treatment.

Endometriosis and sub-fertility

Endometriosis-related subfertility should be managed by a multidisciplinary team with input from a fertility specialist.[36] Sub-fertility associated with endometriosis can be treated with medical intervention (controlled ovarian hyper-stimulation), IVF, or surgical ablation of the endometrial implants. A Cochrane review demonstrated a lack of evidence to support ovulation suppression in sub-fertile women with endometriosis before they attempt to conceive naturally.[87] Further, in the UK, the National Institute

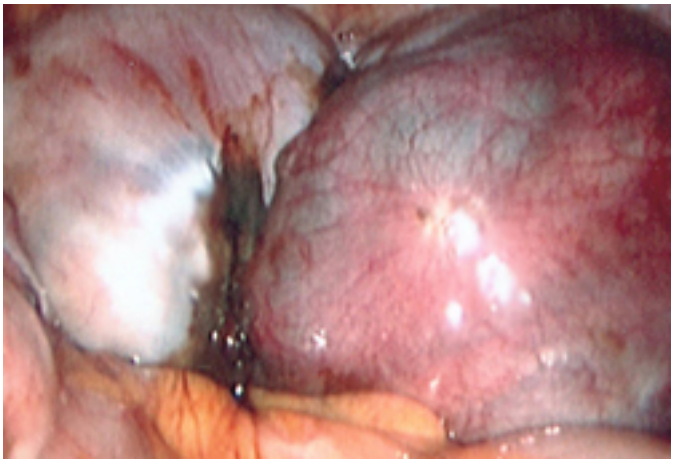
for Health and Care Excellence (NICE) does not recommend the use of hormonal treatment (either alone or in combination with surgical management) for patients with endometriosis who are trying to conceive.[36] They found mixed evidence as to whether combining hormonal treatment with surgery improves pregnancy rates, with some evidence showing no difference.[36] However, there is increasing evidence that GnRH agonist or progestin-only therapy before IVF may improve fertility outcomes.[108] The role of surgery is controversial since advanced reproductive technologies successfully treat infertility despite most disease state considerations. However, if the woman is symptomatic, surgery should be offered regardless of age. For women with or without severe disease who have failed IVF, surgery is probably indicated and endometrial implants should be adequately treated if noted. One meta-analysis of data from cohort studies found that women who had surgery for deep infiltrating endometriosis before IVF were 2.2 times more likely to have a live birth, compared with unoperated women with deep infiltrating endometriosis who underwent IVF.[109]

Controlled ovarian hyper-stimulation may be achieved in these women with ovulation induction medications, including a selective oestrogen receptor modulator (i.e., clomifene), an aromatase inhibitor (e.g., letrozole), highly purified gonadotrophins (also known as menotrophins), or recombinant follicle-stimulating hormone.

Although there is no consensus among experts, there has been a recent shift in the paradigm for those with sub-fertility and endometriosis. Many agree that IVF may be a more viable option for older women and those with multiple contributing factors to sub-fertility (e.g., endometriosis) when compared with surgery. Although IVF is costly it may be the most viable option for women with advanced endometriosis and sub-fertility; however, there are no validating, large randomised trials. Treatment of sub-fertility in the setting of advanced endometriosis is controversial, but it remains a viable option for women with advanced disease who are symptomatic or have failed previous IVF cycles.[110]

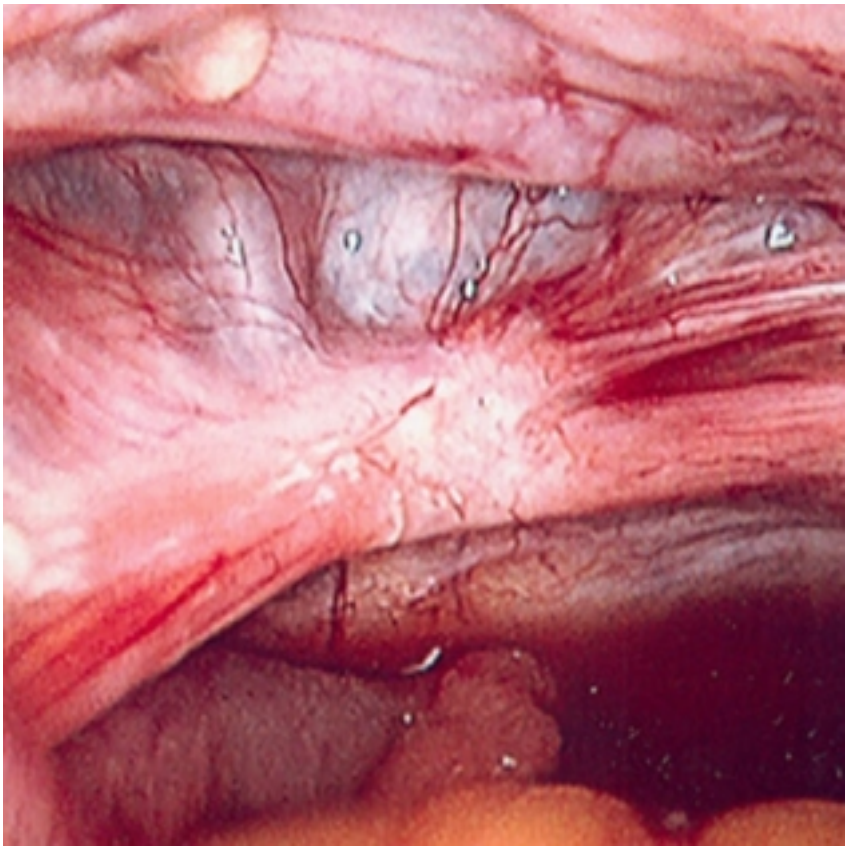
Laparoscopic surgery as the sole treatment of women with minimal to mild endometriosis may improve sub-fertility, but this remains an area of controversy that requires further research.[111] Repeat surgery for recurrent endometriosis may have less impact on the postoperative conception rate compared with that after primary surgery.[112] When counselling women with stage III/IV endometriosis (endometriomas), however, the decision to proceed with conservative surgical management should be based on symptomatology. If there is pain or a mass effect due to the endometrioma surgical excision is warranted. However, if the endometrioma is an incidental finding and the main concern is fertility, treatment may start with assisted reproduction. Excising the cyst wall is most effective in reducing pain and preventing cyst recurrence compared with drainage and ablation of the cyst wall.[113] However, NICE guidelines recommend that either of these techniques can be offered for endometriomas in patients who wish to prioritise fertility, taking into consideration the potential impact on the patient's ovarian reserve (advising that laparoscopic drainage and ablation may preserve ovarian reserve more than cystectomy), and note that there was no evidence of an important difference in pregnancy rates between the two techniques for endometriomas larger than 3 cm.[36]

Risk of ovarian failure (reduced number of primordial follicles) after excising endometriomas is approximately 2.4%.[95] Sub-fertile women with endometrioma may show a diminished response to gonadotrophin stimulation, but the IVF success rates match those who deferred surgery.[114]



Laparoscopic image of ovarian endometrioma

From the collection of Dr Jonathon Solnik; used with permission



Laparoscopic image of endometriotic nodule

From the collection of Dr Jonathon Solnik; used with permission

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Ongoing (summary)		
immediate fertility not desired: pain without endometrioma or suspected severe/deep disease		
	1st	analgesia
	1st	combined oral contraceptive pill (OCP)
	adjunct	analgesia
	1st	progestogen
	adjunct	analgesia
	2nd	gonadotrophin-releasing hormone (GnRH) antagonist
	adjunct	analgesia
	adjunct	laparoscopy
	2nd	gonadotrophin-releasing hormone (GnRH) agonist
	adjunct	analgesia
	adjunct	laparoscopy
	3rd	androgen
	adjunct	analgesia
	adjunct	laparoscopy
	4th	hysterectomy
	adjunct	bilateral salpingo-oophorectomy and excision of visible peritoneal disease
	adjunct	hormone replacement therapy (HRT)
immediate fertility not desired: pain with endometrioma or suspected severe/deep disease		
	1st	surgery
	adjunct	post-surgery hormonal therapy
immediate fertility desired		
	1st	controlled ovarian hyper-stimulation
	adjunct	analgesia
	adjunct	therapeutic laparoscopy

Ongoing		(summary)
	2nd	IVF
	adjunct	analgesia
	adjunct	therapeutic laparoscopy

Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Ongoing

immediate fertility not desired: pain without endometrioma or suspected severe/deep disease

1st **analgesia**

Primary options

» ibuprofen: 400 mg orally every 4-6 hours when required, maximum 2400 mg/day

OR

» naproxen: 250-500 mg orally twice daily when required, maximum 1250 mg/day

OR

» celecoxib: 200 mg orally once or twice daily

OR

» paracetamol: 500-1000 mg orally every 4-6 hours when required, maximum 4000 mg/day

Secondary options

» ketorolac: consult specialist for guidance on dose

» In clinical trials, non-steroidal anti-inflammatory drug (NSAIDs) effectively treat primary dysmenorrhoea and provide adequate analgesia, but their use remains inconclusive for endometriosis-associated pain.[58] [59]

» There appears to be positive feedback between prostaglandin (PG) synthesis, aromatase activity, and oestrogen production, mediated by abnormally high COX-2 activity in the setting of endometriosis.[57] Superficial, often atypical implants (seen more commonly in adolescents) are active PG producers.

» Since endometriosis is a chronic inflammatory condition, NSAIDs may improve symptoms of PG-associated inflammation and pain by interrupting receptor-mediated signalling pathways.

Ongoing

» Variable responses may be seen with different medicines in each woman.

» Ketorolac is only indicated for acute, moderate to severe pain or during the postoperative period; do not use for chronic conditions.

» If dysmenorrhoea is the primary complaint, pre-emptively administer oral NSAIDs prior to onset of menses.

» In the UK, the National Institute for Health and Care Excellence recommends paracetamol (alone or in combination with an NSAID) as an alternative first-line analgesic for women with endometriosis-related pain.[36]

1st **combined oral contraceptive pill (OCP)**

» OCPs suppress the hypothalamic-pituitary-ovarian axis and subsequent oestrogen/progesterone secretion, thereby inducing atrophy of ectopic implants.

» If pain is strictly related to the menstrual cycle, then continuous use of the OCP can be recommended as women may become amenorrhoeic and will experience less cyclic pain.[66] Women should be made aware that irregular spotting is common with continuous use.

» Side effects are generally mild and time-limited. Life-threatening cardiovascular adverse events are more likely to occur in women aged over 35 years, who are heavy smokers, have acquired/inherited thrombophilia, or have experienced a prior cardiovascular event. Therefore, OCPs are not recommended for these women.

» There is an increasing debate on the use of OCPs as first-line therapy because of concern over oestrogenic side effects and progression of more advanced stage disease.

» Consult product literature for guidance on dosage for individual preparations.

adjunct **analgesia**

Treatment recommended for SOME patients in selected patient group

Primary options

» ibuprofen: 400 mg orally every 4-6 hours when required, maximum 2400 mg/day

OR

MANAGEMENT

Ongoing

» naproxen: 250-500 mg orally twice daily when required, maximum 1250 mg/day

OR

» celecoxib: 200 mg orally once or twice daily

OR

» paracetamol: 500-1000 mg orally every 4-6 hours when required, maximum 4000 mg/day

Secondary options

» ketorolac: consult specialist for guidance on dose

» May be used in combination with an oral contraceptive pill.

» In clinical trials, non-steroidal anti-inflammatory drug (NSAIDs) effectively treat primary dysmenorrhoea and provide adequate analgesia, but their use remains inconclusive for endometriosis-associated pain.[58] [59]

» There appears to be positive feedback between prostaglandin (PG) synthesis, aromatase activity, and oestrogen production, mediated by abnormally high COX-2 activity in the setting of endometriosis.[57] Superficial, often atypical implants (seen more commonly in adolescents) are active PG producers.

» Since endometriosis is a chronic inflammatory condition, NSAIDs may improve symptoms of PG-associated inflammation and pain by interrupting receptor-mediated signalling pathways.

» Variable responses may be seen with different medicines in each woman.

» Ketorolac is only indicated for acute, moderate to severe pain or during the postoperative period; do not use for chronic conditions.

» If dysmenorrhoea is the primary complaint, pre-emptively administer oral NSAIDs prior to onset of menses.

» In the UK, the National Institute for Health and Care Excellence recommends paracetamol (alone or in combination with an NSAID) as an alternative first-line analgesic for women with endometriosis-related pain.[36]

Ongoing

1st **progestogen**

Primary options

» medroxyprogesterone: 150 mg intramuscularly every 3 months; 104 mg subcutaneously every 3 months

OR

» levonorgestrel intrauterine device: 52 mg/unit every 5 years

OR

» etonogestrel subdermal implant: 68 mg/unit every 3 years

OR

» estradiol valerate/dienogest: 1 tablet once daily according to product literature

OR

» dienogest: 2 mg orally once daily

» Progesterone induces decidualisation and eventual atrophy of implants. Certain formulations also suppress the hypothalamic-pituitary-ovarian axis, resulting in decreased steroid hormone stimulation of implants. Many such women will become amenorrhoeic.[61] Continuous administration significantly reduces pain, whereas prescribing a luteal phase-only regimen is ineffective.

» The levonorgestrel IUD is approved for long-term use, with individual devices approved for up to 5 to 6 years of use prior to exchange. The levonorgestrel IUD significantly reduces pelvic pain (up to 6 months of therapy) and the recurrence of painful periods after surgery. This effect is more dramatic in women with advanced-stage disease.[62] Serum progestin levels remain low, allowing the device to provide effective therapy without promoting a hypo-oestrogenic state. The etonogestrel-releasing subdermal implant can also be considered for long-term therapy because it lasts for 3 years.[76]

» Dienogest, an oral progestin, reduces endometriotic implants while providing similar symptomatic relief to gonadotrophin-releasing hormone (GnRH) agonists, with better quality-of-

Ongoing

life scores.[77] Three to 4 months of treatment may be required to see the full effect. It is not currently available in the US and some other countries, except in combination with estradiol valerate. However, this combination is sometimes used off-label for endometriosis.

» Serious adverse events that occur with progestogens include decreased bone mineral density, especially with prolonged use. This effect may be more marked in adolescents, when the rate of bone mineralisation peaks. The subcutaneous form of medroxyprogesterone acetate and IUD levonorgestrel may reduce this risk.[55] [75] IUD levonorgestrel should be placed during the early proliferative phase of the menstrual cycle. Other bothersome side effects include weight gain, irregular uterine bleeding, and mood changes.

» Use caution with medroxyprogesterone. Doses of subcutaneous and intramuscular formulations are different.

adjunct **analgesia**

Treatment recommended for SOME patients in selected patient group

Primary options

» ibuprofen: 400 mg orally every 4-6 hours when required, maximum 2400 mg/day

OR

» naproxen: 250-500 mg orally twice daily when required, maximum 1250 mg/day

OR

» celecoxib: 200 mg orally once or twice daily

OR

» paracetamol: 500-1000 mg orally every 4-6 hours when required, maximum 4000 mg/day

Secondary options

» ketorolac: consult specialist for guidance on dose

» In clinical trials, non-steroidal anti-inflammatory drug (NSAIDs) effectively treat primary dysmenorrhoea and provide adequate analgesia, but their use remains inconclusive for endometriosis-associated pain.[58] [59]

Ongoing

» There appears to be positive feedback between prostaglandin (PG) synthesis, aromatase activity, and oestrogen production, mediated by abnormally high COX-2 activity in the setting of endometriosis.[57] Superficial, often atypical implants (seen more commonly in adolescents) are active PG producers.

» Since endometriosis is a chronic inflammatory condition, NSAIDs may improve symptoms of PG-associated inflammation and pain by interrupting receptor-mediated signalling pathways.

» Variable responses may be seen with different medicines in each woman.

» Ketorolac is only indicated for acute, moderate to severe pain or during the postoperative period; do not use for chronic conditions.

» If dysmenorrhoea is the primary complaint, pre-emptively administer oral NSAIDs prior to onset of menses.

» In the UK, the National Institute for Health and Care Excellence recommends paracetamol (alone or in combination with an NSAID) as an alternative first-line analgesic for women with endometriosis-related pain.[36]

2nd **gonadotrophin-releasing hormone (GnRH) antagonist**

Primary options

» elagolix: 150 mg orally once daily for up to 24 months; women with dyspareunia: consider initiating treatment at the higher dose of 200 mg twice daily for up to 6 months; moderate hepatic impairment: 150 mg once daily for up to 6 months

OR

» relugolix/estradiol/norethisterone acetate: 40 mg (relugolix)/1 mg (estradiol)/0.5 mg (norethisterone) orally once daily for up to 24 months

» Elagolix is an oral GnRH antagonist that suppresses ovarian oestrogen production in a dose-dependent manner.[78] In the US, it is licensed for the treatment of moderate to severe endometriosis-related pain.

» Two 6-month placebo-controlled phase 3 trials reported significant reductions in dysmenorrhoea and non-menstrual pelvic pain among women

Ongoing

with endometriosis-associated pain who were randomised to elagolix.[79]

» Hypo-oestrogenic adverse effects were similar to those of injectable GnRH agonists, and included hot flushes, increased serum lipids, and decreased bone mineral density.[79]

» The maximum recommended duration of elagolix use is 6 to 24 months (depending on dose) to reduce the extent of bone loss.

» A lower initial dose and longer treatment course (up to 24 months) is recommended in women without coexisting dyspareunia. A higher initial dose can be considered in women with coexisting dyspareunia; however, women on the higher dose should receive a shorter treatment course (up to 6 months). The dose should be adjusted to the lowest effective dose guided by the severity of symptoms.

» Elagolix is contraindicated in women with severe hepatic impairment. Women with moderate hepatic impairment should only be prescribed the lower dose for up to 6 months. Women with mild impairment do not require any modifications to the recommended dose regimen.

» Relugolix, another GnRH antagonist, is available in combination with estradiol and norethisterone, which are thought to reduce hypo-oestrogenic adverse effects.[80] In the US, it is approved for the management of moderate to severe endometriosis-related pain.

» In two 6-month phase 3 trials, significantly more women who received relugolix combination therapy experienced improvements in dysmenorrhoea and non-menstrual pelvic pain compared with those who received placebo.[80] The least squares mean percentage loss in lumbar spine and total hip bone mineral density was less than 1% after 24 weeks. Headache, nasopharyngitis, and hot flushes were the most common adverse effects.[80]

» The maximum recommended treatment duration for relugolix combination therapy is 24 months due to the risk for continued bone loss.

» Relugolix/estradiol/norethisterone is contraindicated in patients with hepatic impairment of any severity.

adjunct **analgesia**

Ongoing

Treatment recommended for SOME patients in selected patient group

Primary options

» ibuprofen: 400 mg orally every 4-6 hours when required, maximum 2400 mg/day

OR

» naproxen: 250-500 mg orally twice daily when required, maximum 1250 mg/day

OR

» celecoxib: 200 mg orally once or twice daily

OR

» paracetamol: 500-1000 mg orally every 4-6 hours when required, maximum 4000 mg/day

Secondary options

» ketorolac: consult specialist for guidance on dose

» In clinical trials, non-steroidal anti-inflammatory drug (NSAIDs) effectively treat primary dysmenorrhoea and provide adequate analgesia, but their use remains inconclusive for endometriosis-associated pain.[58] [59]

» There appears to be positive feedback between prostaglandin (PG) synthesis, aromatase activity, and oestrogen production, mediated by abnormally high COX-2 activity in the setting of endometriosis.[57] Superficial, often atypical implants (seen more commonly in adolescents) are active PG producers.

» Since endometriosis is a chronic inflammatory condition, NSAIDs may improve symptoms of PG-associated inflammation and pain by interrupting receptor-mediated signalling pathways.

» Variable responses may be seen with different medicines in each woman.

» Ketorolac is only indicated for acute, moderate to severe pain or during the postoperative period; do not use for chronic conditions.

» If dysmenorrhoea is the primary complaint, pre-emptively administer oral NSAIDs prior to onset of menses.

Ongoing

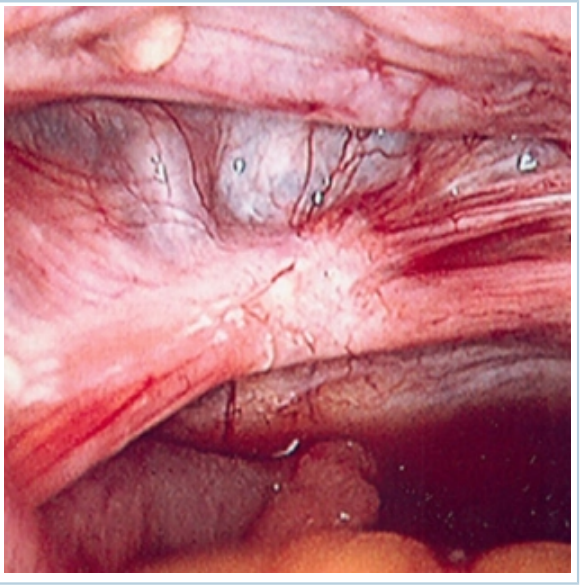
» In the UK, the National Institute for Health and Care Excellence recommends paracetamol (alone or in combination with an NSAID) as an alternative first-line analgesic for women with endometriosis-related pain.[36]

adjunct **laparoscopy**

Treatment recommended for SOME patients in selected patient group

» When to offer surgery is debatable and varies among specialists. It is usually determined by the individual clinician and woman. The patient's symptoms, preferences and priorities regarding pain and fertility are elements that should be considered.[36] The side effects of hormonal therapy may influence the decision to proceed to surgery. For example, gonadotrophin-releasing hormone agonists and progestogens are not ideal options in adolescents due to the potential impact on bone mineral density at such a critical point in development. Therefore, laparoscopy may be preferred. Furthermore, both progestogens and androgens have bothersome side effects that may result in a preference for surgery.

» Conservative surgical management with laparoscopic excision or ablation of visible implants provides effective treatment of pain-related complaints.



Laparoscopic image of endometriotic nodule
From the collection of Dr Jonathon Solnik; used with permission

Diagnostic laparoscopy alone may impart a therapeutic response in up to 30% of women.[98] Several studies have established a clear relationship between surgical

Ongoing

intervention and reduction of pain in women with endometriosis.

» Rectal, bladder, and ureteral injury may occur because of the alterations in normal anatomy. These risks should be discussed prior to surgery. Bowel preparation facilitates these difficult procedures and should be administered to any woman undergoing operative laparoscopy.

» Appendectomy should be considered in women undergoing laparoscopic surgery for suspected endometriosis if there is a complaint of right-sided pain and the appendix appears abnormal. Up to 50% of appendiceal specimens will yield abnormal pathology, but the effect on pain and future adverse outcomes is difficult to assess.[101]

2nd **gonadotrophin-releasing hormone (GnRH) agonist**

Primary options

» leuprorelin: 3.75 mg intramuscularly once monthly; or 11.25 mg intramuscularly every 3 months
-or-
» nafarelin: 200 micrograms (1 spray) in one nostril in the morning and 200 micrograms (1 spray) in the other nostril in the evening; start between days 2-4 of menstrual cycle
-or-
» goserelin: 3.6 mg subcutaneously every 28 days

--AND--

» norethisterone: 5 mg orally once daily
-or-
» oestrogens, conjugated/medroxyprogesterone: 0.3 mg/1.5 mg orally once daily initially, increase according to response

» Rapidly induce a hypo-oestrogenic state by down-regulating the hypothalamic-pituitary-ovarian axis. An initial rise in gonadotrophins and oestrogen (flare) occurs after administration, but chronic exposure provides the desired response.

» Approximately 85% of women with confirmed endometriosis will experience significant reduction in pain complaints.[82] Empirical use in women with chronic pelvic pain may also be considered, regardless of the diagnosis.[83] One systematic review found no difference in the positive therapeutic effect of GnRH agonists when compared with other hormonal regimens.[64] However results of one trial

Ongoing

suggest that GnRH agonists have similar efficacy to that of continuous oral contraceptive pills in treating endometriosis-associated pain.[86]

» Prolonged exposure (>6 months) can lead to an irreversible decrease in bone mineral density (BMD).[115] GnRH agonists may not be an ideal choice in adolescents because of the potential impact on BMD at such a critical point in development. To reduce menopausal symptoms and the effect on BMD without reducing the efficacy of pain relief, GnRH agonists should be administered with hormonal add-back therapy (e.g., norethisterone or conjugated oestrogens plus medroxyprogesterone), which should be offered from the beginning of treatment. Non-hormonal forms of add-back therapy to alleviate vasomotor symptoms include selective serotonin reuptake inhibitors, serotonin-noradrenaline (norepinephrine) reuptake inhibitors, and various herbal remedies.

» GnRH agonists lack the bothersome side effects of progestogens (weight gain, irregular uterine bleeding, mood changes) and androgens (darkening facial hair, acne, oily skin, deepening of the voice, and male-pattern hair loss) and are therefore usually recommended prior to initiating these other hormonal therapies. However, they are typically less well tolerated than progestogens.

adjunct **analgesia**

Treatment recommended for SOME patients in selected patient group

Primary options

» ibuprofen: 400 mg orally every 4-6 hours when required, maximum 2400 mg/day

OR

» naproxen: 250-500 mg orally twice daily when required, maximum 1250 mg/day

OR

» celecoxib: 200 mg orally once or twice daily

OR

» paracetamol: 500-1000 mg orally every 4-6 hours when required, maximum 4000 mg/day

Secondary options

Ongoing

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» Since endometriosis is a chronic inflammatory condition, NSAIDs may improve symptoms of PG-associated inflammation and pain by interrupting receptor-mediated signalling pathways.

» Variable responses may be seen with different medicines in each woman.

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» If dysmenorrhoea is the primary complaint, pre-emptively administer oral NSAIDs prior to onset of menses.

» In the UK, the National Institute for Health and Care Excellence recommends paracetamol (alone or in combination with an NSAID) as an alternative first-line analgesic for women with endometriosis-related pain.[36]

adjunct **laparoscopy**

Treatment recommended for SOME patients in selected patient group

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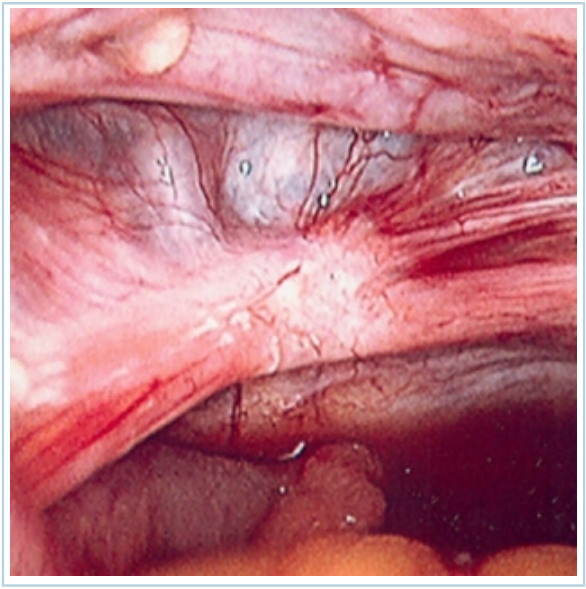
Ongoing

bothersome side effects which may result in a preference for surgery.

» Conservative surgical management with laparoscopic excision or ablation of visible implants provides effective treatment of pain-related complaints.



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3rd **androgen**

Primary options

» danazol: 200-800 mg/day orally given in 2 divided doses

Ongoing

» Produce a hypo-oestrogenic state by directly suppressing the hypothalamic-pituitary-ovarian axis. Onset of amenorrhoea seems to correlate with therapeutic effect.

» Clinical trials have shown that androgens (e.g., danazol) effectively reduce pain related to endometriosis when compared with placebo.[63] They may also be effective post-surgical adjuncts. Improved revised American Society for Reproductive Medicine scores were noted at laparoscopy.[63] However, their use is limited by adverse effects that include darkening facial hair, acne, oily skin, deepening of the voice, and male-pattern hair loss.[63] [87] Furthermore, reports have linked danazol to ovarian cancer.[88]

» Initial dosing schedule depends on severity of disease. Maintenance dose is achieved when women experience amenorrhoea or a reduction in pain.

adjunct **analgesia**

Treatment recommended for SOME patients in selected patient group

Primary options

» ibuprofen: 400 mg orally every 4-6 hours when required, maximum 2400 mg/day

OR

» naproxen: 250-500 mg orally twice daily when required, maximum 1250 mg/day

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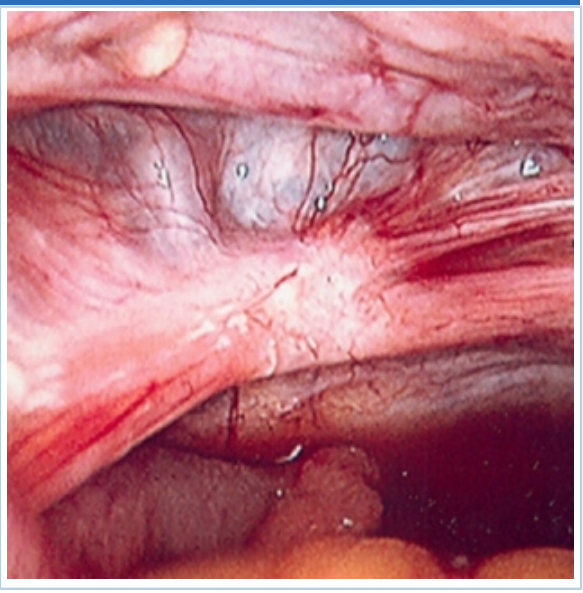
Ongoing



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4th **hysterectomy**

» Considered the definitive treatment for symptomatic women who have persistent pain despite conservative measures, and no longer desire childbearing potential.

adjunct **bilateral salpingo-oophorectomy and excision of visible peritoneal disease**

Treatment recommended for SOME patients in selected patient group

MANAGEMENT

Ongoing

» For the best chance of cure, hysterectomy with bilateral salpingo-oophorectomy and excision of visible peritoneal disease should be offered, focusing on excising deep infiltrating lesions.[106] The principle is based on removal of common areas of implantation along with the primary source of endogenous oestrogen production, and with a focus on excising deep infiltrating lesions. However, there is little distinction in the literature as to whether this is an effective treatment modality specifically for cyclical pain.[107]

adjunct **hormone replacement therapy (HRT)**

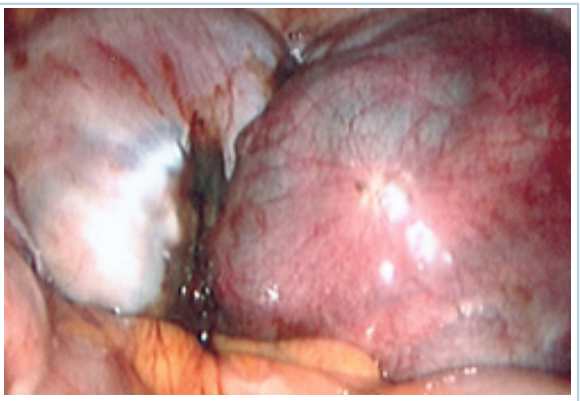
Treatment recommended for SOME patients in selected patient group

» Oestrogen replacement is generally warranted after hysterectomy with bilateral salpingo-oophorectomy to reduce vasomotor symptoms and risk of bone loss, especially in pre-menopausal and symptomatic post-menopausal women. HRT reduces the incidence of fracture and the risk of coronary artery disease in pre-menopausal women who undergo surgical menopause. However, there are increases in risk of breast cancer, venous thrombosis, and stroke in post-menopausal women. Therefore, risks versus benefits of HRT should be discussed with the woman before initiating treatment.

immediate fertility not desired: pain with endometrioma or suspected severe/deep disease

1st **surgery**

» Ovarian endometriomas do not resolve in response to hormonal suppression and, if symptomatic, should be addressed surgically.



Laparoscopic image of ovarian endometrioma
From the collection of Dr Jonathon Solnik; used with permission

Ongoing

» Radical excision of affected areas with restoration of normal anatomy is the preferred method of treating symptomatic women with deep peritoneal disease.[96] [97]

» NICE advises that 3 months of pre-operative gonadotrophin-releasing hormone (GnRH) agonist treatment should be considered as an adjunct to surgery for deep endometriosis involving the bowel, bladder or ureter.[36]

» Improvement in pain may last up to 5 years after surgery, but the risk of re-intervention approaches 50% in women with moderate to severe disease.[98] Less aggressive surgical measures and younger age are predictive of recurrence.[95] [99]

» For this reason, prolonged hormonal suppression is recommended after surgery for endometriosis.[6]

adjunct **post-surgery hormonal therapy**

Treatment recommended for SOME patients in selected patient group

» If surgery does not result in complete removal of implants, postoperative medical therapy using a gonadotrophin-releasing hormone agonist, progestogen, or androgen may be indicated to increase the duration of pain relief and delay recurrence of symptoms. Some reports indicate a reduction in anatomical relapse, and in the frequency and intensity of dysmenorrhoea recurrence with postoperative use of oral contraceptive pills.[67] [68] [69] There is insufficient evidence to determine whether hormonal suppression, either before or after surgery, is associated with any significant benefit compared with surgery alone.[91] [92] [93]

immediate fertility desired

1st **controlled ovarian hyper-stimulation**

Primary options

» clomifene: 50-200 mg orally once daily for 5 days

OR

» letrozole: 5 to 7.5mg orally once daily for 5 days, starting on day 3 of cycle

Secondary options

» menotrophin: consult product literature for guidance on dose

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OR

» follitropin alfa: 75-225 international units subcutaneously once daily

» May be achieved with ovulation induction medications including a selective oestrogen receptor modulator (i.e., clomifene), an aromatase inhibitor (e.g., letrozole), highly purified gonadotrophins (also known as menotrophin), or recombinant follicle-stimulating hormone (FSH).

» Clomifene (a competitive antagonist of estradiol) disrupts negative feedback and augments gonadotrophin-releasing hormone production.

» Letrozole (a competitive reversible inhibitor of testosterone aromatisation) decreases circulating oestrogen, affects the hypothalamic feedback, and induces greater levels of FSH.

» A typical starting dose of any gonadotrophin is dependent on the woman's age, diagnosis, and prior stimulation history. The length of the stimulation is dependent on the response to medications.

» These medications should only be utilised by experienced infertility practitioners because of the high risk of ovarian hyper-stimulation syndrome and higher-order multiple gestations.

adjunct **analgesia**

Treatment recommended for SOME patients in selected patient group

Primary options

» ibuprofen: 400 mg orally every 4-6 hours when required, maximum 2400 mg/day

OR

» naproxen: 250-500 mg orally twice daily when required, maximum 1250 mg/day

OR

» celecoxib: 200 mg orally once or twice daily

OR

» paracetamol: 500-1000 mg orally every 4-6 hours when required, maximum 4000 mg/day

Ongoing

Secondary options

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» Since endometriosis is a chronic inflammatory condition, NSAIDs may improve symptoms of PG-associated inflammation and pain by interrupting receptor-mediated signalling pathways.

» Variable responses may be seen with different medicines in each woman.

» Ketorolac is only indicated for acute, moderate to severe pain or during the postoperative period; do not use for chronic conditions.

» If dysmenorrhoea is the primary complaint, pre-emptively administer oral NSAIDs prior to onset of menses.

» In the UK, the National Institute for Health and Care Excellence recommends paracetamol (alone or in combination with an NSAID) as an alternative first-line analgesic for women with endometriosis-related pain.[36]

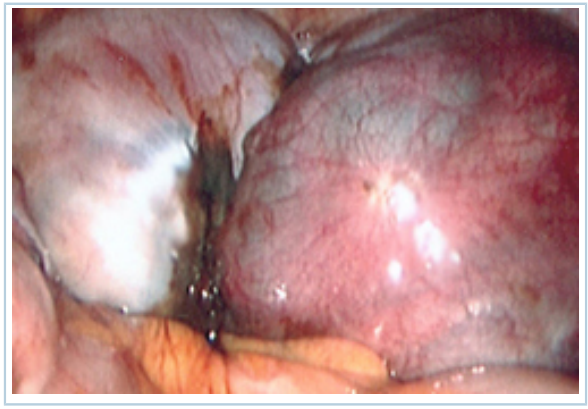
adjunct **therapeutic laparoscopy**

Treatment recommended for SOME patients in selected patient group

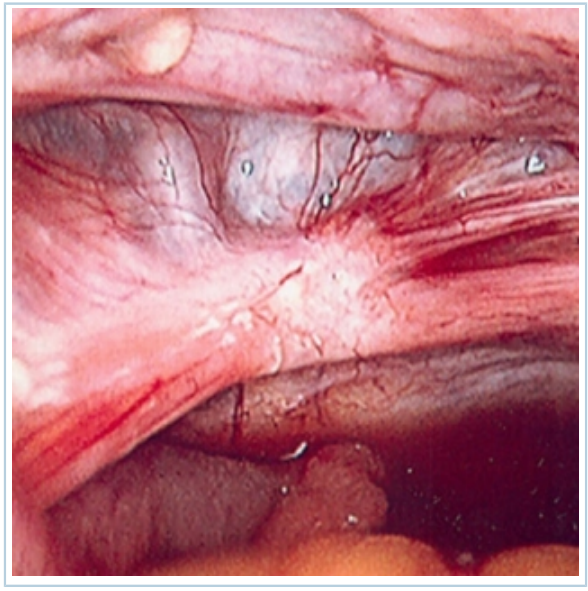
» The role of surgery is controversial since advanced reproductive technologies successfully treat infertility despite most disease state considerations. However, if symptomatic women without endometrioma or severe deep disease desire fertility, surgery should be offered regardless of age. Women with endometrioma or severe deep disease usually require surgery if pain or large endometrioma (>3 cm) present. Women who fail fertility treatment can be offered surgery, and there is some evidence in support of fertility treatments soon after

Ongoing

corrective surgery. One meta-analysis of data from cohort studies found that women who had surgery for deep infiltrating endometriosis before IVF were 2.2 times more likely to have a live birth, compared with unoperated women with deep infiltrating endometriosis who underwent IVF.[109]



Laparoscopic image of ovarian endometrioma
From the collection of Dr Jonathon Solnik; used with permission



Laparoscopic image of endometriotic nodule
From the collection of Dr Jonathon Solnik; used with permission

» Risk of ovarian failure (reduced number of primordial follicles) after excising endometriomas is approximately 2.4%.[95]

2nd **IVF**

» Although there is no consensus among experts, there has been a recent shift in the paradigm for those with sub-fertility and endometriosis. Many agree that IVF may be a more viable option for older women and

Ongoing

those with multiple contributing factors (such as endometriosis) when compared with surgery. Although IVF is costly it may be the most viable option for women with advanced endometriosis and sub-fertility; however, there are no validating, large randomised trials. Sub-fertility in the setting of advanced endometriosis is controversial, but it remains a viable option for women with advanced disease who are symptomatic or have failed previous IVF cycles.[110]

» Sub-fertile women with endometrioma may show a diminished response to gonadotrophin stimulation, but the IVF success rates match those who defer surgery.[114]

adjunct **analgesia**

Treatment recommended for SOME patients in selected patient group

Primary options

» ibuprofen: 400 mg orally every 4-6 hours when required, maximum 2400 mg/day

OR

» naproxen: 250-500 mg orally twice daily when required, maximum 1250 mg/day

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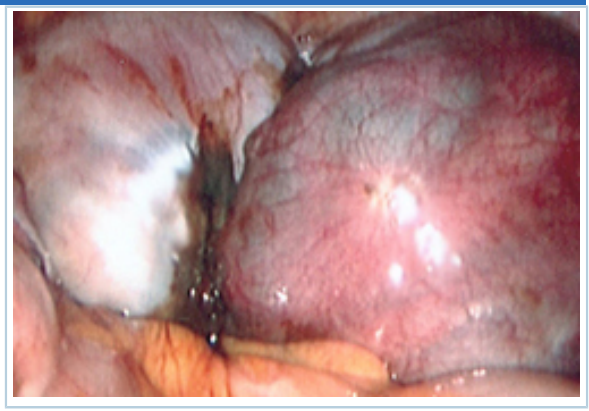
Ongoing



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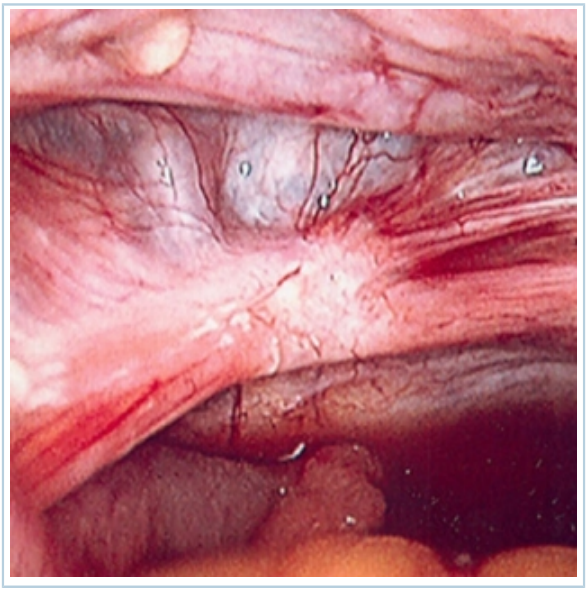

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Emerging

Antiprogestins

Gestrinone is a 19-nortestosterone (androgen) derivative with anti-progestagenic properties. It is a long-acting drug that also possesses anti-oestrogenic and anti-gonadotrophic properties.[61] [116] Side effects are primarily androgen-excess-related (oily skin, irreversible voice changes, acne). It is not currently available in the US. Mifepristone may improve symptoms of dysmenorrhoea and dyspareunia, although further research is required to determine safety profiles and optimal dosage.[117]

Selective progesterone receptor modulators (SPRMs)

In early clinical trials, SPRMs effectively treated endometriosis-associated pain when compared with controls.[72] [118] [119] The mechanism of action is thought to be the anti-proliferative actions on the endometrium without suppressing oestrogen production (avoiding vasomotor symptoms and loss in bone mineral density). Progesterone blockade may result in endometrial hyperplasia.

Anti-tumour necrosis factor alpha

Currently, there is insufficient evidence to recommend the use of anti-tumour necrosis factor alpha agents for the relief of pelvic pain in women with endometriosis.[120]

Adjunctive surgical procedures

Adjunctive surgeries that interrupt nerve pathways have been extensively studied in the gynaecological literature. These include laparoscopic uterosacral nerve ablation or LUNA (interrupt bundles that attach to the cervix/uterus) and pre-sacral neurectomy or PSN (interrupt larger, general pathways to the pelvis). Despite the potential benefit seen in small groups of specific cohorts, LUNA and PSN remain investigational procedures.[121] [122] There are, however, more recent data that support the use of PSN for central pelvic pain.[123]

Complementary medicines

Side-effect profiles and lack of efficacy of various medicines used to treat endometriosis have motivated women to seek complementary and alternative medicines. One 2016 Cochrane review found limited evidence for the use of vitamin B1 and fish oil, among other supplements, in treating primary dysmenorrhoea, but these findings are limited by a lack of studies, small sample sizes, low quality evidence, and no standardised dosing regimen. Given the studies available for review, there is insufficient evidence to recommend these supplements.[124] Another Cochrane review found that Chinese herbal medication was beneficial in alleviating endometriosis-related pain post-laparoscopy when compared with hormonal therapy. However, further research into the role of complementary medicines is required before they may be considered for use as standard therapy.[124] [123]

Patient discussions

Women should be advised to try to maintain a positive outlook and return to normal activities. If being evaluated for sub-fertility, they should be advised to seek counselling and/or treatment with a reproductive endocrinologist/infertility consultant before or shortly after being treated. Additional support from a psychologist or endometriosis support group can help some women when trying to cope with debilitating symptoms. [endometriosis.org] (http://www.endometriosis.org) Depression and anxiety appear to be associated with endometriosis, especially if chronic pain is present.[34] [35]

FOLLOW UP

Monitoring

Monitoring

No specific monitoring guidelines have been proposed, and follow-up should be on an individual basis and based on the primary complaint. Women with functional pain (i.e., no identifiable source) should be managed with a team approach and require response-led follow-up. Multi-disciplinary teams may include a combination of an endometriosis specialist, pelvic floor physiotherapy, chronic pain services, and psychological support for mindfulness-based approaches to pain management.[131]

An exception would be women with an ovarian mass. If suspicious for an endometrioma and the woman is asymptomatic, imaging can be repeated at 3- to 6-month intervals. If the woman becomes symptomatic or the parameters of the cyst become more suspicious for a malignancy, then surgery is indicated. The risk of malignancy index, along with appropriate tumour marker studies, can help stratify risk and referral practices.[132] There is evidence that women with endometriosis may have up to a twofold increased relative risk of epithelial ovarian cancers (clear cell and endometrioid type epithelial ovarian carcinoma).[130] However, this amounts to a very small proportion of women with endometriosis and no standardised screening regimen exists.

Complications

Complications	Timeframe	Likelihood
ovarian failure post-surgical intervention	**short term**	**low**
Ovarian failure infrequently occurs after excision of ovarian endometrioma. This is probably due to a lowered number of ovarian follicles that produce oestrogen. The benefit of reduced symptom recurrence must be balanced with the risk of ovarian failure (2.4%).[129] Pre-operative counselling is critical.		
epithelial cell ovarian cancer	**long term**	**low**
There is evidence that women with endometriosis may have up to a twofold increased relative risk of epithelial ovarian cancers (clear cell and endometrioid type epithelial ovarian carcinoma).[130] However, this amounts to a very small proportion of women with endometriosis, and no standardised screening regimen exists. Patients often present with vague, non-specific symptoms such as abdominal bloating, early satiety, and dyspepsia (suggestive of upper abdominal disease). Other symptoms are more suggestive of pelvic disease, such as pelvic pain, abdominal or pelvic pressure, low back pain, and urinary urgency. Women with a suspicious pelvic mass should be referred to a gynaecological oncologist for further evaluation.		
adhesion formation	**variable**	**medium**
Adhesions probably result from the inflammatory disruption of peritoneal surfaces and are potentiated by surgical trauma. The risk of this occurrence is not well known, and may occur at any point. Sequelae may include pain (although this has yet to be established) and bowel obstruction. Adhesiolysis predisposes to unrecognised bowel injuries, which may result in postoperative complications such as peritonitis or obstruction.		

Prognosis

Endometriosis-associated pain can be managed by medical and surgical means, with a varying degree of recurrence and progression.

Delays in diagnosis are common and result in untreated pain. Data from the Endometriosis Association revealed a mean of 10 years from onset of symptoms to therapeutic intervention.[125] Woman and physician awareness can improve this deficiency in care, especially for younger groups of women who are more prone to such delays.

Treatment failures are likely to occur when other causes of pain are not appropriately addressed (e.g., pelvic floor tension myalgia). Women may undergo repeated surgical procedures, which not only increase the risk of peri-operative complications, but have no lasting effect on pain relief.

Long-term studies are difficult and expensive to maintain. In the absence of such data, it is difficult to provide generalised prognoses. Younger women and those with severe disease, however, are more likely to experience recurrent symptoms.

Studies from 2020 and 2016 have also postulated a link between endometriosis and later development of cardiovascular disease.[126] [127] However, this may be associated with ovarian suppression, earlier surgical menopause, or other confounders in women with endometriosis, and thus more research is required in this area.

Endometriosis and sub-fertility

The prognosis for sub-fertile women with endometriosis varies and is dependent on multiple factors such as age, anovulation, tubal function, and male factor. National US data are available regarding success of IVF by diagnosis. [Society for Assisted Reproductive Technology] (http://www.sart.org) One population-based study from the UK of almost 15,000 women, followed for more than 30 years, compared women with surgically documented endometriosis with those with no known disease. Investigators found a statistically significant relationship with a positive history and first and third trimester obstetrical complications.[128]

Diagnostic guidelines

United Kingdom

Endometriosis: diagnosis and management (https://www.nice.org.uk/guidance/ng73)

Published by: National Institute for Health and Care Excellence **Last published:** 2024

Europe

Endometriosis guideline of the European Society of Human Reproduction and Embryology (https://www.eshre.eu/Guidelines-and-Legal/Guidelines.aspx)

Published by: European Society of Human Reproduction and Embryology **Last published:** 2022

North America

ACR appropriateness criteria: endometriosis (https://www.acr.org/Clinical-Resources/Clinical-Tools-and-Reference/Appropriateness-Criteria)

Published by: American College of Radiology **Last published:** 2024

Treatment of pelvic pain associated with endometriosis: a committee opinion (https://www.asrm.org/news-and-publications/practice-committee-documents)

Published by: American Society for Reproductive Medicine **Last published:** 2014

Endometriosis: diagnosis and management (https://www.jogc.com/article/S1701-2163(16)34589-3/fulltext)

Published by: Society of Obstetricians and Gynaecologists of Canada **Last published:** 2010

Asia

Guideline for the diagnosis and treatment of endometriosis (https://pubmed.ncbi.nlm.nih.gov/34954958)

Published by: Chinese Obstetricians and Gynecologists Association; Cooperative Group of Endometriosis, Chinese Society of Obstetrics and Gynecology, Chinese Medical Association **Last published:** 2021

Oceania

Endometriosis clinical practice guideline (http://ranzcog.edu.au/resources/statements-and-guidelines-directory)

Published by: Royal Australian and New Zealand College of Obstetricians and Gynaecologists **Last published:** 2021

Treatment guidelines

United Kingdom

Endometriosis: diagnosis and management (https://www.nice.org.uk/guidance/ng73)

Published by: National Institute for Health and Care Excellence **Last published:** 2024

Fertility problems: assessment and treatment (https://www.nice.org.uk/guidance/cg156)

Published by: National Institute for Health and Care Excellence **Last published:** 2017

Europe

Endometriosis guideline of the European Society of Human Reproduction and Embryology (https://www.eshre.eu/Guidelines-and-Legal/Guidelines.aspx)

Published by: European Society of Human Reproduction and Embryology **Last published:** 2022

North America

Endometriosis and infertility: a committee opinion (https://www.asrm.org/news-and-publications/practice-committee-documents)

Published by: American Society of Reproductive Medicine **Last published:** 2012

Management of endometriosis (https://www.acog.org/clinical/clinical-guidance/practice-bulletin)

Published by: American College of Obstetricians and Gynecologists **Last published:** 2010 (reaffirmed 2022)

Endometriosis diagnosis and management (https://www.jogc.com/article/S1701-2163(16)34589-3/fulltext)

Published by: Society of Obstetricians and Gynaecologists of Canada **Last published:** 2010

Asia

Guideline for the diagnosis and treatment of endometriosis (https://pubmed.ncbi.nlm.nih.gov/34954958)

Published by: Chinese Obstetricians and Gynecologists Association; Cooperative Group of Endometriosis, Chinese Society of Obstetrics and Gynecology, Chinese Medical Association **Last published:** 2021

Oceania

Endometriosis clinical practice guideline (http://ranzcog.edu.au/resources/statements-and-guidelines-directory)

Published by: Royal Australian and New Zealand College of Obstetricians and Gynaecologists

Last published: 2021

Online resources

1. Society for Assisted Reproductive Technology (http://www.sart.org) *(external link)*

2. endometriosis.org (http://www.endometriosis.org) *(external link)*

Evidence tables

What are the effects of gonadotrophin-releasing hormone (GnRH) agonists compared with other active treatments in women with endometriosis?[81]

This table is a summary of the analysis reported in a guideline (underpinned by a systematic review) that focuses on the above important clinical question.

View the full source guideline (https://www.nice.org.uk/guidance/ng73/evidence)

Evidence B *	Confidence in the evidence is moderate or low to moderate where GRADE has been performed and there may be no difference in effectiveness between the intervention and comparison for key outcomes.

Population: Women with endometriosis
Intervention: GnRH agonists
Comparison: Other active treatments

Outcome	Effectiveness (BMJ rating)†	Confidence in evidence (GRADE)‡
GnRH agonist versus danazol		
Pelvic tenderness at 6 months (assessed with Total Symptom Severity Score [TSSS], scale not defined)	No statistically significant difference	Moderate
Pelvic induration at 6 months (assessed with TSSS, scale not defined)	No statistically significant difference	Moderate
Patients requiring surgery due to reappearance of symptoms and positive findings at pelvic examination at >12 months post treatment	No statistically significant difference	Moderate
Quality of life (assessed with Psychological General Well-Being Index [PGWB] plus a modification of Part II of the Nottingham Health Profile)	No statistically significant difference	Low
GnRH agonist versus levonorgestrel-releasing intrauterine system		

Outcome	Effectiveness (BMJ rating)†	Confidence in evidence (GRADE)‡
Quality of life at 6 months (assessed with PGWB scale 0–110)	No statistically significant difference	Moderate
GnRH agonist versus depot medroxyprogesterone acetate (subcutaneous injections)		
Effect on daily activities (assessed by mean number of hours of productivity lost at employment at 18 months)	No statistically significant difference	High
Effect on daily activities (assessed by mean number of hours of productivity lost at housework at 18 months)	No statistically significant difference	Moderate
GnRH agonist plus placebo versus progestin plus placebo		
Paid working life (follow up: 6 months [at the end of treatment] and 12 months [6 months after the end of the treatment] assessed with Nottingham Health Profile)	No statistically significant difference	Very low
Household work (follow up: 6 months [at the end of treatment] and 12 months [6 months after the end of the treatment] assessed with Nottingham Health Profile)	No statistically significant difference	Very low
Vacation life (follow up: 6 months [at the end of treatment] and 12 months [6 months after the end of the treatment] assessed with Nottingham Health Profile)	No statistically significant difference	Very low
Leisure (follow up: 6 months [at the end of treatment] and 12 months [6 months after the end of the treatment] assessed with Nottingham Health Profile)	No statistically significant difference	Very low

Outcome	Effectiveness (BMJ rating)†	Confidence in evidence (GRADE)‡
Sexual life (follow up: 6 months [at the end of treatment] and 12 months [6 months after the end of the treatment] assessed with Nottingham Health Profile)	No statistically significant difference	Very low
Disturbed sleep (follow up: 6 months [at the end of treatment] and 12 months [6 months after the end of the treatment] assessed with Goldberg's General Health Questionnaire)	No statistically significant difference	Very low
Anxiety/depression (follow up: 6 months [at the end of treatment] and 12 months [6 months after the end of the treatment] assessed with Goldberg's General Health Questionnaire)	No statistically significant difference	Very low
Motivation (follow up: 6 months [at the end of treatment] and 12 months [6 months after the end of the treatment] assessed with Coping Wheel, Inventory of Social Support and Interaction [ISSI] & demands, control & support questionnaire)	No statistically significant difference	Very low
Emotional balance (follow up: 6 months [at the end of treatment] and 12 months [6 months after the end of the treatment] assessed with Coping Wheel, ISSI & demands, control & support questionnaire)	No statistically significant difference	Very low
Structure (follow up: 6 months [at the end of treatment] and 12 months [6 months after the end of the treatment] assessed with Coping Wheel, ISSI &	No statistically significant difference	Very low

Outcome	Effectiveness (BMJ rating)†	Confidence in evidence (GRADE)‡
demands, control & support questionnarie)		
Coping (follow up: 6 months [at the end of treatment] and 12 months [6 months after the end of the treatment] assessed with Coping Wheel, ISSI & demands, control & support questionnaire)	No statistically significant difference	Very low
Psychological work demands (follow up: 6 months [at the end of treatment] and 12 months [6 months after the end of the treatment] assessed with Coping Wheel, ISSI & demands, control & support questionnaire)	No statistically significant difference	Very low
Intellectual discretion at work (follow up: 6 months [at the end of treatment] and 12 months [6 months after the end of the treatment] assessed with Coping Wheel, ISSI & demands, control & support questionnaire)	No statistically significant difference	Very low
Authority over decisions at work (follow up: 6 months [at the end of treatment] and 12 months [6 months after the end of the treatment] assessed with Coping Wheel, ISSI & demands, control & support questionnaire)	No statistically significant difference	Very low
Social support at work (follow up: 6 months [at the end of treatment] and 12 months [6 months after the end of the treatment] assessed with Coping Wheel, ISSI &	No statistically significant difference	Very low

Outcome	Effectiveness (BMJ rating)†	Confidence in evidence (GRADE)‡
demands, control & support questionnaire)		
GnRH agonist plus placebo versus danazol plus placebo		
Relief of painful symptoms: pelvic tenderness (follow up: 6 months measured with 4-point numerical scale)	No statistically significant difference	Very low
Relief of painful symptoms: pelvic induration (follow up: 6 months measured with 4-point numerical scale)	No statistically significant difference	Very low
Relief of painful symptoms: pelvic tenderness (follow up: 12 months)	No statistically significant difference	Very low
Relief of painful symptoms: pelvic induration (follow up: 12 months)	No statistically significant difference	Very low
GnRH agonist plus ethinylestradiol pill versus ethinylestradiol pill		
Pain at the end of treatment period (12 months): dysmenorrhoea (10-point Visual Analogue Scale [VAS])	Favours intervention	Moderate
Pain at the end of treatment period (12 months): non-menstrual pain (10-point VAS)	Favours comparison	Low
GnRH agonist versus combined oral contraceptive pill		
Pain at the end of treatment period (6 months): dyspareunia (10-point VAS)	Favours intervention	Low
Pain at the end of treatment period (6 months): non-menstrual pain (10-point VAS)	No statistically significant difference	Low
Pain at 6 months after treatment period: dysmenorrhoea (10-point VAS)	No statistically significant difference	Very low

Outcome	Effectiveness (BMJ rating)†	Confidence in evidence (GRADE)‡
Pain at 6 months after treatment period: dyspareunia (10-point VAS)	No statistically significant difference	Low
Pain at 6 months after treatment period: non-menstrual pain (10-point VAS)	No statistically significant difference	Low

Recommendations as stated in the source guideline

Offer hormonal treatment (eg., combined oral contraceptive pill or a progestogen) to women with suspected, confirmed, or recurrent endometriosis.

Note

- The results in this table are based on pairwise analyses. The guideline committee noted that these results were broadly consistent with network meta-analysis results reported in the guideline, which support the use of hormonal therapy for pain relief in women with endometriosis, and which were used by the guideline committee for most decision-making.
- The guideline committee also stated that adverse events were varied across different types of hormonal treatment, but were consistent within drug classes; they noted that the benefit and harms of hormonal therapy should be discussed with women.
- The committee noted that the network meta-analysis found a higher risk of withdrawal due to adverse events and more serious adverse events (e.g., bone density changes) with GnRH agonists. They added that use of GnRH agonists requires guidance from a specialist.
- The guideline committee also noted that it should be explained to women with suspected or confirmed endometriosis that hormonal treatment can reduce pain and has no permanent negative effect on subsequent fertility.
- If hormonal treatment does not work, the guideline stated women should be referred to a gynaecology, specialist endometriosis, or paediatric and adolescent gynaecology service for investigation and treatment options.

What are the effects of hormonal treatment before or after surgery for the treatment of endometriosis?[81]

This table is a summary of the analysis reported in a guideline (underpinned by a systematic review) that focuses on the above important clinical question.

View the full source guideline (https://www.nice.org.uk/guidance/ng73/evidence)

Evidence C *	Confidence in the evidence is very low or low where GRADE has been performed and the intervention may be more effective/beneficial than the comparison for key outcomes. However, this is uncertain and new evidence could change this in the future.

Population: Women with endometriosis
Intervention: Pharmacological therapy before or after surgery
Comparison: Placebo or no pharmacological therapy

Outcome	Effectiveness (BMJ rating)†	Confidence in evidence (GRADE)‡
Pain recurrence (visual analogue scale [VAS]): pelvic pain (follow up: 12 months)	Favours intervention	Moderate
Pain recurrence (VAS): dysmenorrhoea (follow up: 12 months)	Favours intervention	Low
Pain recurrence (VAS): deep dyspareunia (follow up: 12 months)	Favours intervention	Very low
Pain recurrence (questionnaire based): abdominal pain at 12 months post-treatment completion	No statistically significant difference	Low
Pain recurrence (questionnaire based): dysmenorrhoea at 12 months post-treatment completion	No statistically significant difference	Very low
Pain recurrence (questionnaire based): dyspareunia at 12 months post-treatment completion	Favours intervention	Low

Outcome	Effectiveness (BMJ rating)†	Confidence in evidence (GRADE)‡
Pain recurrence (Andersch and Milsom): pelvic pain (follow up: 12 months)	No statistically significant difference	Low
Dysmenorrhoea (follow up: 12 months)	Favours intervention	Moderate
Re-operation (women with endometriosis)	No statistically significant difference	Very low
Endometriosis recurrence (dichotomous): disease recurrence at 5-6 months (follow up: 5-6 months)	No statistically significant difference	Very low
Endometriosis recurrence (dichotomous) (follow up: 12 months)	No statistically significant difference	Very low
Endometriosis recurrence (dichotomous) (follow up: 24 months)	No statistically significant difference	Very low
Endometrioma recurrence (dichotomous): recurrence at 13-36 months	Favours intervention	Low
Endometrioma recurrence (dichotomous) (follow up: 60 months)	No statistically significant difference	Low
Patient satisfaction	No statistically significant difference	Low

Recommendations as stated in the source guideline

After laparoscopic excision or ablation of endometriosis, consider hormonal treatment (e.g., the combined oral contraceptive pill) to prolong the benefits of surgery and manage symptoms.

Note

- The results in this table are based on pairwise analyses.
- The included studies only cover pharmacological therapy after surgery versus surgery alone. There was no available evidence covering pharmacological therapy before surgery.
- The guideline committee prioritised pain relief, health-related QoL, and adverse events as critical outcomes. Many of the studies include gonadotrophin-releasing hormone (GnRH) agonists. They comment that the use of GnRH agonists requires guidance from a specialist due to risk of serious adverse effects.

- The guideline committee concluded that the combined oral contraceptive pill or long-acting reversible progestogen contraceptives were the preferable treatments, although not appropriate for women trying to conceive.
- The recommendation (above) was made based on the results of a separate network meta-analysis, which found that the addition of hormonal treatment after surgery (laparoscopic excision or ablation) reduced the risk of recurrence and symptoms.

* Evidence levels

The Evidence level is an internal rating applied by BMJ Best Practice. See the EBM Toolkit (https://bestpractice.bmj.com/info/evidence-tables/) for details.

Confidence in evidence

A - High or moderate to high

B - Moderate or low to moderate

C - Very low or low

† Effectiveness (BMJ rating)

Based on statistical significance, which demonstrates that the results are unlikely to be due to chance, but which does not necessarily translate to a clinical significance.

‡ Grade certainty ratings

High	The authors are very confident that the true effect is similar to the estimated effect.
Moderate	The authors are moderately confident that the true effect is likely to be close to the estimated effect.
Low	The authors have limited confidence in the effect estimate and the true effect may be substantially different.
Very Low	The authors have very little confidence in the effect estimate and the true effect is likely to be substantially different.

BMJ Best Practice EBM Toolkit: What is GRADE? (https://bestpractice.bmj.com/info/toolkit/learn-ebm/what-is-grade/)

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Images

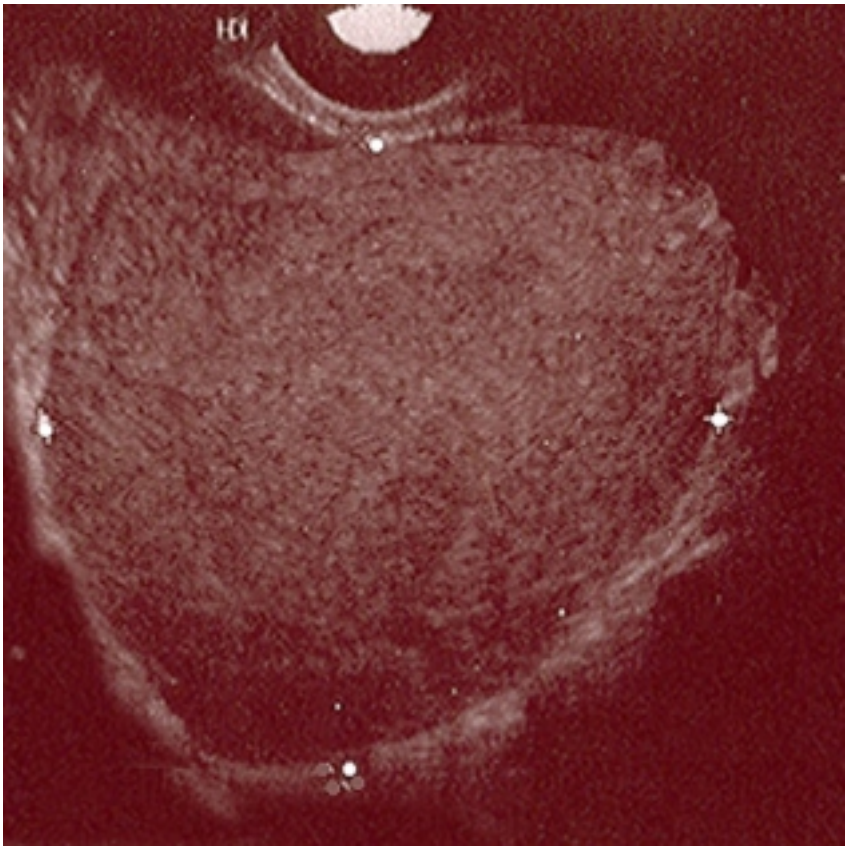

Figure 1: Ultrasound of ovarian endometrioma

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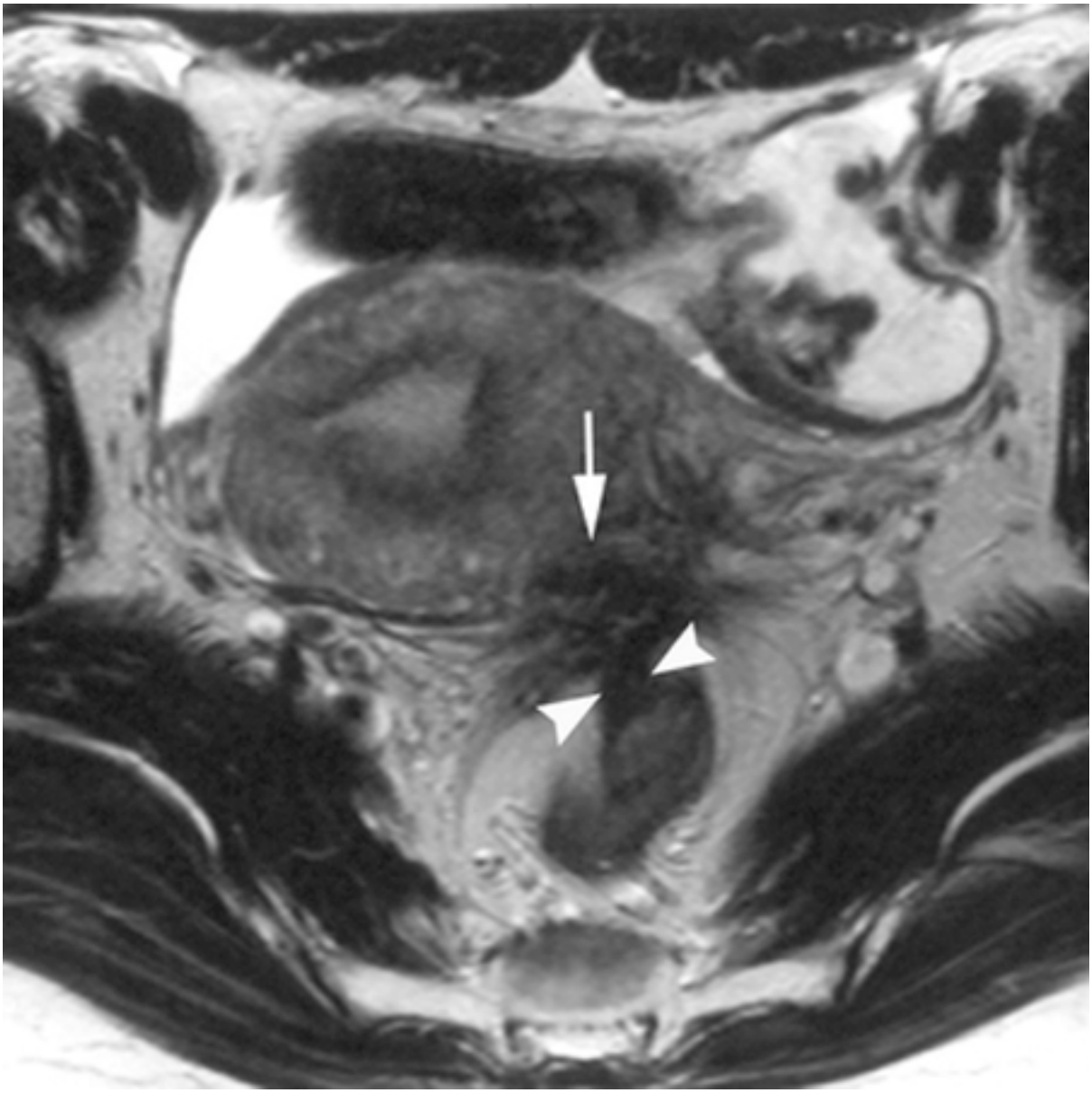

Figure 2: MRI - fibrotic nodules involving the uterosacral ligaments and rectal wall

Bazot M, et al. Radiology. 2004 Aug;232(2):379-89; used with permission

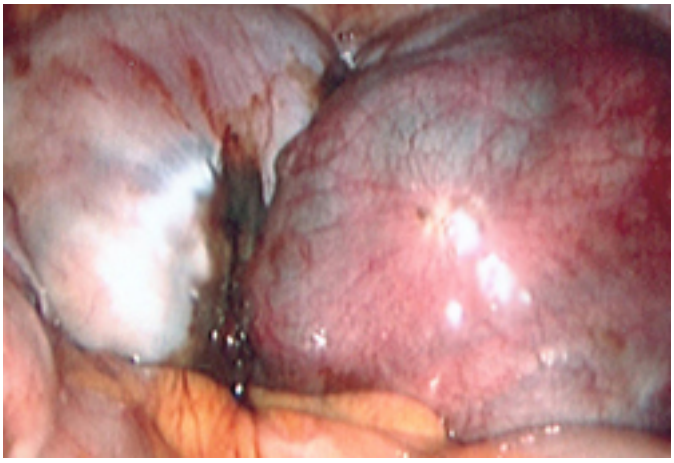

Figure 3: Laparoscopic image of ovarian endometrioma

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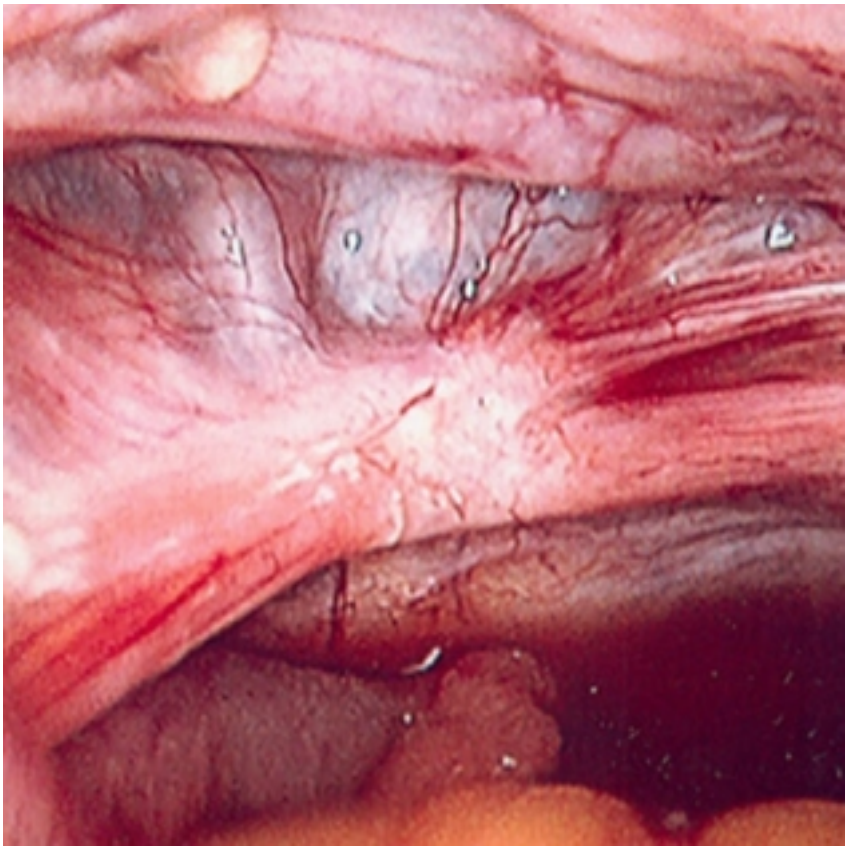

Figure 4: Laparoscopic image of endometriotic nodule

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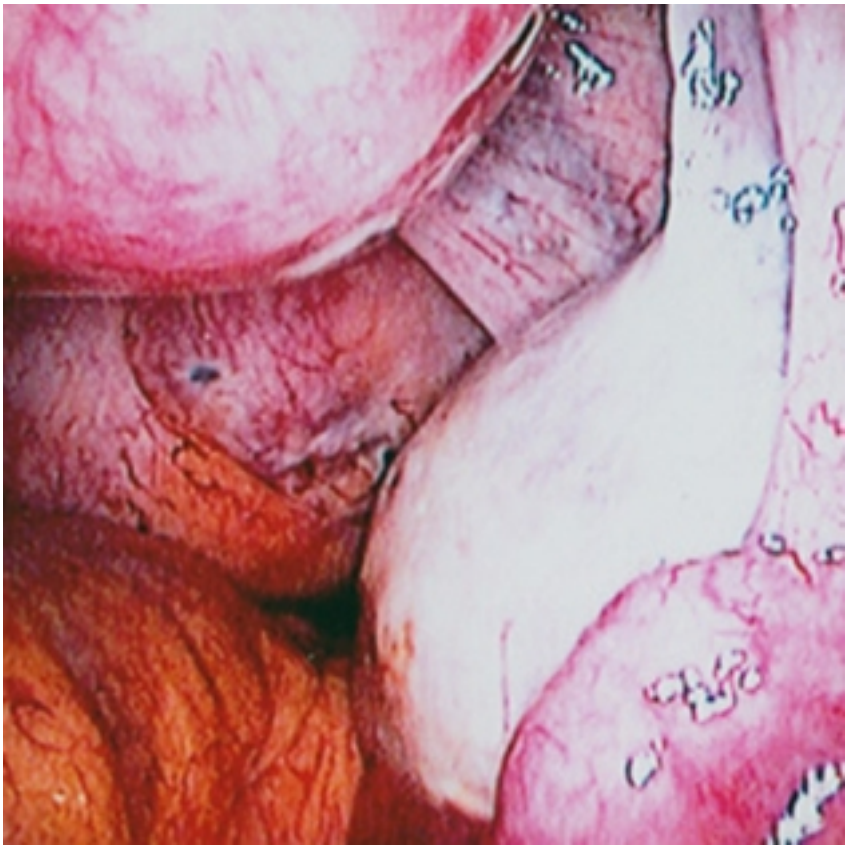

Figure 5: Laparoscopic image of peritoneal window

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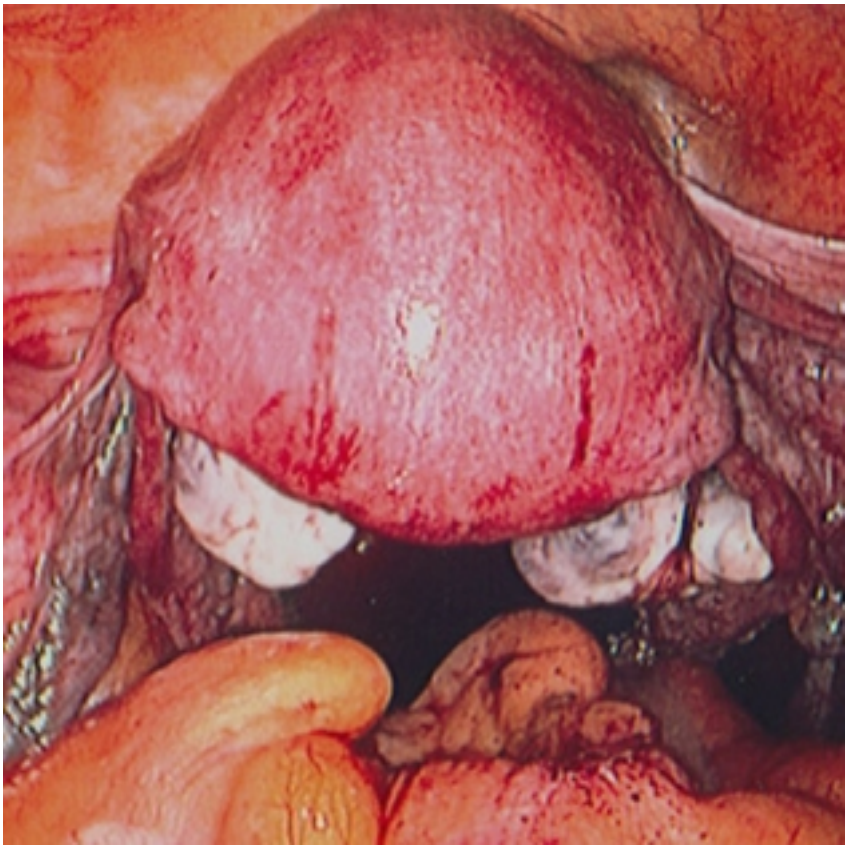

Figure 6: Laparoscopic image of retroverted uterus

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NICE Summary

The recommendations in this Best Practice topic are based on authoritative international guidelines, supplemented by recent practice-changing evidence and expert opinion. For your added benefit, we summarise below the key recommendations from relevant NICE guidelines.

Key NICE recommendations on diagnosis

Suspect endometriosis in women (including those aged under 18 years) presenting with 1 or more of the following:

- Chronic pelvic pain (i.e., pelvic pain lasting for 6 months or more)
- Dysmenorrhoea affecting functioning and quality of life
- Deep pain associated with sexual intercourse
- Period-related or cyclical gastrointestinal symptoms, in particular, painful bowel movements
- Period-related or cyclical urinary symptoms, in particular, blood in the urine or pain passing urine
- Infertility in association with 1 or more of the above.

Ask if any first-degree relatives have a history of endometriosis, as this increases the likelihood of endometriosis.

Discuss keeping a pain and symptom diary.

- Consider that the person's experience of pain is unique to them and may be expressed in different ways, both verbally and non-verbally (and in particular, may vary with cultural background, beliefs, socioeconomic status and neurodiversity).

Offer an abdominal and pelvic (internal vaginal) examination to women and people with suspected endometriosis to identify abdominal masses and pelvic signs (e.g., reduced organ mobility and enlargement, tender nodularity in the posterior vaginal fornix, and visible vaginal endometriotic lesions).

- If a pelvic examination is declined or unsuitable, offer an abdominal examination to exclude abdominal masses.

A normal physical examination **does not** exclude endometriosis.

Carry out additional investigations (e.g., ultrasound) and referral (if necessary, see below) in parallel with each other, **and in conjunction with** initial pharmacological treatment (see *Key NICE recommendations on management*).

Offer a transvaginal ultrasound scan (organised by the person's general practice) to all women or people with suspected endometriosis, even if physical examination is normal, to:

- Identify ovarian endometriomas and deep endometriosis (including that involving the bowel, bladder or ureter)
- Identify or rule out other pathology which may be causing symptoms
- Guide management options and enable referral to an appropriate service, depending on the ultrasound findings.

Consider a transabdominal pelvic ultrasound if transvaginal ultrasound is declined or unsuitable.

Normal ultrasound **does not** exclude endometriosis. Recognise that referral may still be necessary even with a normal scan.

Refer women or people with symptoms of (or confirmed) endometriosis to a gynaecology service for further investigation and management if they have:

- Symptoms of endometriosis which have a detrimental impact on daily activities, **or**
- Persistent or recurrent symptoms of endometriosis, **or**
- Pelvic signs of endometriosis (but deep endometriosis is not suspected).

Refer women or people to a specialist endometriosis service if they have suspected or confirmed:

- Endometrioma, **or**
- Deep endometriosis (including that involving the bowel, bladder or ureter), **or**
- Endometriosis outside the pelvic cavity.

Refer young women or people under 18 years with suspected or confirmed endometriosis to a paediatric and adolescent gynaecology service or specialist endometriosis service for further investigation and management.

Specialist transvaginal ultrasound scan or pelvic MRI (planned and interpreted by a professional with specialist expertise in gynaecological imaging) should be considered to diagnose (and assess the extent of) deep endometriosis.

Do not use serum CA125 to diagnose endometriosis.

Definitive diagnosis can only be made by specialist laparoscopic visualisation of the pelvis.

- Diagnostic laparoscopy should be considered for diagnosis of suspected endometriosis, even if imaging is normal.
- During diagnostic laparoscopy, a biopsy of suspected endometriosis may be taken:
  - To confirm the diagnosis (though normal histology **does not** exclude endometriosis)
  - To exclude malignancy if an endometrioma is treated but not excised.
- See further laparoscopy recommendations in *Surgical management* below.

Link to NICE guidance

Endometriosis: diagnosis and management (NG73) November 2024. https://www.nice.org.uk/guidance/ng73 https://www.nice.org.uk/guidance/ng73

Key NICE recommendations on management

Please be aware that some of the following indications for medications may not be licensed by the manufacturer (i.e., the use of the medication is 'off-label'). Refer to the full NICE guideline and your local drug formulary for further information when prescribing.

Offer endometriosis treatment according to the woman's symptoms, preferences and priorities, rather than the stage of the endometriosis.

Explain that available evidence does not support the use of traditional Chinese medicine or other Chinese herbal medicines or supplements in the treatment of endometriosis.

Women or people with endometriosis-related subfertility who wish to prioritise fertility should be managed by a multidisciplinary team with input from a fertility specialist. See the NICE guideline section *Management if fertility is a priority* for further information.

- Management should include the recommended diagnostic fertility or preoperative tests, as well as other recommended fertility treatments (e.g., assisted reproduction) that are included in the NICE guideline *Fertility problems: assessment and treatment (CG156)*.
- **Do not** offer hormonal treatment (alone or in combination with surgery) to women or people with endometriosis who are trying to conceive, because it does not improve spontaneous pregnancy rates.

Initial pharmacological treatment for suspected or confirmed endometriosis

Consider a short trial (e.g., 3 months) of paracetamol or a non-steroidal anti-inflammatory drug alone or in combination, as first-line management for endometriosis-related pain.

- If a trial does not provide adequate pain relief, consider referring for further assessment and offering other forms of pain management.

Offer hormonal treatment (e.g., combined oral contraceptive pill or a progestogen) to women or people with suspected, confirmed or recurrent endometriosis who are **not** trying to conceive.

- Explain that it can reduce pain and has no permanent negative effect on subsequent fertility.

Neuromodulators and other neuropathic pain treatments may be considered to treat neuropathic pain, in line with the NICE guideline *Neuropathic pain in adults: pharmacological management in non-specialist settings (CG173)*.

Refer to an appropriate gynaecology service for further investigation and management if initial treatment is not effective, not tolerated or is contraindicated.

Surgical management

Surgical management may be considered, depending on the woman's symptoms, preferences and priorities with respect to pain and fertility.

- Surgery for endometriosis is performed laparoscopically unless there are contraindications.
- Surgical treatment may take place (with prior patient consent) during a diagnostic laparoscopy if any uncomplicated endometriosis is found.
- If deep endometriosis is suspected, a specialist pelvic ultrasound or MRI should be considered before an operative laparoscopy.
- Excision rather than ablation should be considered to treat endometriomas, taking into account the woman's desire for fertility and her ovarian reserve (e.g., if fertility is a priority, excision **or** ablation and drainage should be considered, as the latter may preserve ovarian reserve more than cystectomy).
- If hysterectomy is indicated (e.g., the woman has adenomyosis or heavy menstrual bleeding that has not responded to other treatments), all visible endometriotic lesions should be excised at the time of the hysterectomy.

Hormonal treatment may be used alongside surgical management, except in women or people who are trying to conceive.

- A 3-month treatment with gonadotrophin-releasing hormone agonists should be considered as an adjunct before surgery for deep endometriosis involving the bowel, bladder or ureter.
- Post-operative hormonal treatment (e.g., combined oral contraceptive pill) should be considered after laparoscopic excision or ablation, to prolong the benefits of surgery and manage symptoms.

Monitoring

Women with confirmed endometriosis (particularly those who decline surgery) should be considered for outpatient follow-up if they have:

- Deep endometriosis involving the bowel, bladder or ureter, **or**

- 1 or more endometrioma that is larger than 3 cm.

Link to NICE guidance

Endometriosis: diagnosis and management (NG73) November 2024. https://www.nice.org.uk/guidance/ng73
https://www.nice.org.uk/guidance/ng73

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This approach is in line with the guidance of the International Bureau of Weights and Measures Service.

Figure 1 – BMJ Best Practice Numeral Style

5-digit numerals: 10,000

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