



Setting standards to improve women's health

## THE INVESTIGATION AND MANAGEMENT OF ENDOMETRIOSIS

This is the second edition of this guideline, which was originally published in July 2000 under the same title.

### 1. Purpose and scope

The aim of this guideline is to provide clinicians with up-to-date information about the diagnosis and treatment of endometriosis, based upon the best available evidence. The treatment options are examined in the light of presenting symptoms and associated infertility.

### 2. Background

Endometriosis is defined as the presence of endometrial-like tissue outside the uterus, which induces a chronic, inflammatory reaction. The condition is predominantly found in women of reproductive age, from all ethnic and social groups. The associated symptoms can impact on general physical, mental and social wellbeing. It is therefore vital to take careful note of the woman's complaints and to give her time to express her concerns and anxieties, as with other chronic diseases. However, women may have no symptoms at all. Finding endometriosis in some women, therefore, may be coincidental.

Treatment must be individualised, taking the clinical problem in its entirety into account, including the impact of the disease and the effect of its treatment on quality of life. Pain symptoms may persist despite seemingly adequate medical and/or surgical treatment of the disease. This may suggest another source of pain, such as the uterus (adenomyosis), bladder (interstitial cystitis) or musculoskeletal causes (pelvic floor muscle spasm). In such circumstances, the appropriate therapy or a multidisciplinary approach involving a pain clinic and counselling should be considered. It is also important to involve the woman in all decisions, to be flexible in diagnostic and therapeutic thinking, to maintain a good relationship with the woman and to seek advice where appropriate from more experienced colleagues.

### 3. Identification and assessment of evidence

This RCOG guideline was developed in accordance with standard methodology for clinical guidelines. The Cochrane Library (including the Cochrane Database of Systematic Reviews, DARE and EMBASE), TRIP, Medline and PubMed (electronic databases) were searched for relevant randomised controlled trials, systematic reviews and meta-analyses. The search was restricted to articles published in English between January 2000 and April 2006. Recent consensus documents were also studied. The databases were searched using the relevant MeSH terms including all sub-headings and this was combined with a keyword search. Main keywords included 'endometriosis', 'endometriosis, diagnosis', 'endometriosis, drug therapy', 'endometriosis, complications', 'endometriomas', 'endometriosis, surgery'.

A guideline, *The Diagnosis and Treatment of Endometriosis*, produced by the European Society for Human Reproduction and Embryology (ESHRE) Special Interest Group for Endometriosis and the Endometrium Guideline Development Group, published in 2005,<sup>1</sup> was consulted in producing this guideline. The ESHRE guideline is updated regularly and made available at [www.endometriosis.org/guidelines.html](http://www.endometriosis.org/guidelines.html) with hyperlinks to the supporting evidence and the relevant references and abstracts. The ESHRE guideline was developed without a systematic search of the published literature; it relied instead on existing review journals, such as *Clinical Evidence*.<sup>2</sup> The definitions of the types of evidence used in this guideline originate from the US Agency for Health Care Policy and Research. Where possible, recommendations are based on, and explicitly linked to, the evidence that supports them. Areas lacking evidence are highlighted and annotated as ‘good practice points’.

#### 4. Localisation and appearance of endometriosis

The most commonly affected sites are the pelvic organs and peritoneum, although other parts of the body such as the bowel or lungs are occasionally affected. The extent of the disease varies from a few, small lesions on otherwise normal pelvic organs to large, ovarian endometriotic cysts (endometriomas). There can be extensive fibrosis in structures such as the uterosacral ligaments and adhesion formation causing marked distortion of pelvic anatomy. Disease severity is assessed by simply describing the findings at surgery or quantitatively, using a classification system such as the one developed by the American Society for Reproductive Medicine.<sup>3</sup> There is no correlation between such systems and the type or severity of pain symptoms.

Endometriosis typically appears as superficial ‘powder-burn’ or ‘gunshot’ lesions on the ovaries, serosal surfaces and peritoneum: black, dark-brown or bluish puckered lesions, nodules or small cysts containing old haemorrhage surrounded by a variable extent of fibrosis. Atypical or ‘subtle’ lesions are also common, including red implants (petechial, vesicular, polypoid, hemorrhagic, red flame-like) and serous or clear vesicles. Other appearances include white plaques or scarring and yellow-brown peritoneal discoloration of the peritoneum.

Endometriomas usually contain thick fluid, like chocolate. Such cysts are often densely adherent to the peritoneum of the ovarian fossa and the surrounding fibrosis may involve the tubes and bowel. Deeply infiltrating endometriotic nodules extend more than 5 mm beneath the peritoneum and may involve the uterosacral ligaments, vagina, bowel, bladder or ureters. The depth of infiltration is related to the type and severity of symptoms.<sup>4-6</sup>

Severe cases of endometriosis should be referred to units with the necessary expertise to offer all available treatments in a multi-disciplinary context, including advanced laparoscopic surgery.



#### 5. Diagnosis

##### 5.1 Which symptoms are typically associated with endometriosis?

Based on clinical and patient experience, endometriosis can cause the following symptoms:

- severe dysmenorrhoea
- deep dyspareunia
- chronic pelvic pain
- ovulation pain
- cyclical or perimenstrual symptoms, such as bowel or bladder, with or without abnormal bleeding or pain
- infertility
- chronic fatigue
- dyschezia (pain on defaecation).



The predictive value of any one symptom or set of symptoms remains uncertain, as each of these symptoms can have other causes and a significant proportion of affected women are asymptomatic. Establishing the diagnosis of endometriosis on the basis of symptoms alone can be difficult because the presentation is so variable and there is considerable overlap with other conditions such as irritable bowel syndrome and pelvic inflammatory disease. As a result, there is often a delay of up to 12 years between symptom onset and a definitive diagnosis.<sup>7-9</sup>

### 5.2 *When in the menstrual cycle is clinical examination most reliable for diagnostic purposes?*

**Deeply infiltrating nodules are most reliably detected when clinical examination is performed during menstruation.**

**B**

Finding pelvic tenderness, a fixed, retroverted uterus, tender uterosacral ligaments or enlarged ovaries on examination is suggestive of endometriosis. The findings may, however, be normal. The diagnosis is more certain if deeply infiltrating nodules are palpated on the uterosacral ligaments or in the pouch of Douglas and/or visible lesions are seen in the vagina or on the cervix. The detection of nodules is improved by performing the clinical examination during menstruation,<sup>10</sup> although patient acceptance may be an issue.

Evidence level III

### 5.3 *What is the 'gold standard' diagnostic test?*

**For a definitive diagnosis of endometriosis, visual inspection of the pelvis at laparoscopy is the gold standard investigation, unless disease is visible in the posterior vaginal fornix or elsewhere.**

**B**

**Good surgical practice is to use an instrument such as a grasper, via a secondary port, to mobilise the pelvic organs and to palpate lesions, which can help determine their nodularity. It is also important to document in detail the type, location and extent of all lesions and adhesions in the operative notes. Ideal practice is to record the findings on video or DVD.**



Laparoscopy is the gold standard diagnostic test in clinical practice. A meta-analysis of its value against a histological diagnosis showed (assuming a 10% pre-test probability of endometriosis) that a positive laparoscopic examination increases the likelihood of detecting the disease to 32% (95% CI 21–46%) and a negative laparoscopy decreases the likelihood to 0.7% (95% CI 0.1–5.0%).<sup>11</sup> However, diagnostic laparoscopy is associated with an approximately 3% risk of minor complications, such as nausea or shoulder tip pain, and a risk of major complications, such as bowel perforation, vascular damage, of between 0.6/1000 and 1.8/1000.<sup>12,13</sup> There is insufficient evidence to justify scheduling the laparoscopy for a specific time in the menstrual cycle but it should not be performed during or within 3 months of hormonal treatment, to avoid under-diagnosis.<sup>14</sup>

Systematic review of diagnostic tests

All classification systems for endometriosis are subjective and correlate poorly with pain symptoms but may be of value in infertility prognosis and management.<sup>15,16</sup> At laparoscopy, deeply infiltrating endometriosis may have the appearance of minimal disease, resulting in an underestimation of disease severity.<sup>17</sup>

Evidence level III

### 5.4 *Is histological confirmation necessary?*

**Positive histology confirms the diagnosis of endometriosis; negative histology does not exclude it. Whether histology should be obtained if peritoneal disease alone is present is controversial.**



**Visual inspection is usually adequate but histological confirmation of at least one lesion is ideal. In cases of ovarian endometrioma (greater than 3 cm in diameter) and in deeply infiltrating disease, histology should be obtained to identify endometriosis and to exclude rare instances of malignancy.**



### 5.5 How reliable is imaging for diagnostic purposes?

**Compared with laparoscopy, transvaginal ultrasound (TVS) has limited value in diagnosing peritoneal endometriosis but it is a useful tool both to make and to exclude the diagnosis of an ovarian endometrioma.**

**A**

A systematic review of the accuracy of ultrasound identified seven relevant studies, all using TVS to diagnose endometriomas.<sup>18</sup> The positive likelihood ratios ranged from 7.6 to 29.8 and the negative likelihood ratios ranged from 0.12 to 0.4. TVS may have a role in the diagnosis of disease involving the bladder or rectum. At present, there is insufficient evidence to indicate that magnetic resonance imaging (MRI) is a useful test to diagnose or exclude endometriosis compared to laparoscopy.

Systematic review of diagnostic tests

### 5.6 How reliable is serum CA125 measurement for diagnostic purposes?

**Serum CA125 levels may be elevated in endometriosis. However, compared with laparoscopy, measuring serum CA125 levels has no value as a diagnostic tool.**

**A**

Elevated serum CA125 levels are usually associated with ovarian malignancy but can be reported in association with endometriosis. The performance of CA125 measurement has been assessed in a meta-analysis: 23 studies have investigated serum CA125 levels in women with surgically confirmed endometriosis.<sup>19</sup> The test's performance in diagnosing all disease stages was limited: the estimated sensitivity was only 28% for a specificity of 90% (corresponding likelihood ratio of a raised level is 2.8). The test's performance for moderate-severe endometriosis was better: for a specificity of 89%, the sensitivity was 47% (corresponding likelihood ratio of a raised level is 4.3).

Systematic review of diagnostic tests

## 6. Empirical treatment of pain symptoms without a definitive diagnosis

**If a woman wants pain symptoms suggestive of endometriosis to be treated without a definitive diagnosis, a therapeutic trial of a hormonal drug to reduce menstrual flow is appropriate.**

✓

Empirical treatment for pain symptoms presumed to be caused by endometriosis without a definitive diagnosis includes counselling, adequate analgesia, progestogens or the combined oral contraceptive. It is unclear whether the combined oral contraceptives should be taken conventionally, continuously or in a tricycle regimen. A gonadotrophin-releasing hormone (GnRH) agonist may be taken but this class of drug is more expensive and associated with more adverse effects and concerns about bone density.

## 7. Medical treatment of endometriosis-associated pain

### 7.1 How effectively do nonsteroidal anti-inflammatory drugs (NSAIDs) treat endometriosis-associated pain?

**There is inconclusive evidence to show whether NSAIDs (specifically naproxen) are effective in managing pain caused by endometriosis.**

**A**

Some women prefer to avoid hormonal therapy and can manage their symptoms effectively with analgesia and/or a complementary medicine approach. Although NSAIDs may be effective in endometriosis-associated pain, there are too few randomised controlled trials to assess their effectiveness. In a recent meta-analysis,<sup>20</sup> only one randomised controlled trial was included: comparing naproxen with placebo, there was no evidence of a positive effect on pain relief (odds ratio 3.27, 95% CI 0.61-17.69) in women with endometriosis.<sup>21</sup> It is also important to

Evidence level Ia

note that NSAIDs have significant adverse effects, including gastric ulceration and an antiovolatory effect when taken at mid-cycle. Other analgesics may be effective but there is insufficient evidence to make recommendations.

Evidence level Ia

### 7.2 How effectively do hormonal drugs treat endometriosis-associated pain?

**Suppression of ovarian function for 6 months reduces endometriosis-associated pain.**

A

**Symptom recurrence is common following medical treatment of endometriosis.**

B

The hormonal drugs investigated (combined oral contraceptives, danazol, gestrinone, medroxyprogesterone acetate and GnRH agonists) are equally effective but their adverse-effect and cost profiles differ.<sup>22-27</sup> Some adverse effects limit their long-term use and often produce poor compliance.

Evidence level Ia

Hormonal manipulation probably does not affect any of the primary biological mechanisms responsible for the disease process. Consequently, medical treatment does not always provide complete pain relief and some women fail to respond at all. Symptom recurrence is common following medical treatment. In a retrospective study following hormonal treatment, the median time to recurrence of pain was 6.1 months for danazol-treated women and 5.2 months for those treated with a GnRH agonist.<sup>28</sup>

Evidence level III

There are pilot data suggesting that the aromatase inhibitor, letrozole, may be effective although it is associated with significant bone density loss.<sup>29</sup>

Evidence level III

### 7.3 Is there a role for the levonorgestrel intrauterine system (LNG-IUS)?

**The LNG-IUS appears to reduce endometriosis-associated pain.**

A

A systematic review identified two randomised controlled trials and three prospective observational studies, all involving small numbers and a heterogeneous group of patients.<sup>30</sup> Nevertheless, the evidence suggests that the LNG-IUS reduces endometriosis-associated pain<sup>31,32</sup> with symptom control maintained over 3 years.<sup>33</sup>

Evidence level Ia

### 7.4 How long should treatment be continued?

**Duration of therapy should be determined by the choice of drug, response to treatment and adverse-effect profile.**



Duration of therapy is limited for some drugs and the adverse-effect profiles differ. These are factors determining which treatment a woman chooses. The combined oral contraceptive and Depo-Provera® can be used long term but the use of danazol and GnRH agonists is usually restricted to 6 months, although one randomised controlled trial suggests that treatment for 3 months with a GnRH agonist may be as effective as 6 months in terms of pain relief.<sup>34</sup> GnRH agonist therapy is limited due to possible loss of up to 6% of bone mineral density in the first 6 months and the loss may not always be entirely reversible. Conversely, danazol produces an increase in bone mineral density.

### 7.5 Can bone mineral density loss while taking a GnRH agonist be prevented using 'add-back' therapy?

**The use of a GnRH agonist with 'add-back' (oestrogen and progestogen) therapy protects against bone mineral density loss at the lumbar spine during treatment and for up to 6 months after treatment.**

A

Add-back therapy involves taking one of the following medications at the same time as a GnRH agonist: a low-dose estrogen, a low-dose progestin or tibolone (a synthetic steroid which mimics the activity of estrogen and progesterone in the body). In a meta-analysis, comparing GnRH agonist treatment with GnRH agonist plus 'add-back' therapy (i.e. estrogen and progestogen or estrogen only) for at least 6 months, bone mineral density was significantly higher in women taking estrogen and progestogen as 'add-back' compared with a GnRH agonist alone (SD -0.49, 95 % CI -0.77 to -0.21).<sup>35</sup> In addition, hypoestrogenic adverse effects were significantly less severe in the women who received 'add-back'. Progestogen only 'add-back' is not protective. There is insufficient evidence regarding calcium-regulating agents.

Evidence level Ia

How long a GnRH agonist plus 'add-back' may safely be continued is unclear, but treatment for up to 2 years with combined estrogen and progestogen 'add-back' appears to be effective and safe in terms of pain relief and bone mineral density protection.<sup>35</sup> However, careful consideration should be given to the use of GnRH agonists in women who may not have reached their maximum bone density.

Evidence level Ia

## 8. Preoperative assessment

### 8.1 What investigations are recommended to assess disease extent?

If there is clinical evidence of deeply infiltrating endometriosis, ureteric, bladder and bowel involvement should be assessed. Consideration should be given to performing MRI or ultrasound (transrectal and/or transvaginal and/or renal), with or without IVP and barium enema studies, to map the extent of disease as it may be multifocal.



### 8.2 How should suspected endometriomas be managed?

A guideline for the management of suspected ovarian malignancy should be followed in cases of ovarian endometrioma.



An example of a guideline on this topic is the Scottish Intercollegiate Network Guideline on epithelial ovarian cancer.<sup>36</sup>

### 8.3 How should suspected severe/deeply infiltrating disease be managed?

The management of severe/deeply infiltrating endometriosis is complex. Surgery is usually required and multiple organs are sometimes involved. Therefore, if disease of such severity is suspected or diagnosed, referral to a centre with the necessary expertise to offer all available treatments in a multidisciplinary context, including advanced laparoscopic surgery and laparotomy, is strongly recommended.



## 9. Surgical treatment of endometriosis-associated pain

### 9.1 When should surgical treatment be considered?

Ideal practice is to diagnose and remove endometriosis surgically.



Depending upon the severity of disease found, ideal practice is to diagnose and remove endometriosis surgically, provided that adequate preoperative consent has been obtained.<sup>15,37-39</sup>

### 9.2 Does surgical treatment relieve pain?

#### **Ablation of endometriotic lesions reduces endometriosis-associated pain compared with diagnostic laparoscopy.**

**A**

Two double-blind studies have addressed the question, although the second is not included in the relevant Cochrane review, as it has not been updated since 2001.<sup>40</sup> The first randomised controlled trial compared the effects of laser ablation of minimal-moderate endometriosis plus uterine nerve ablation with diagnostic laparoscopy alone for pain relief.<sup>41</sup> At 6 months' follow-up, 63% of the treated patients reported improvement or resolution of symptoms compared with 23% in the no-treatment group. Outcome was poorest in women with minimal endometriosis.

Evidence level Ia

In the second randomised controlled trial, women with all disease stages were randomised to either a diagnostic procedure or excisional surgery initially, followed 6 months later by a repeat laparoscopy at which any endometriosis present was treated.<sup>42</sup> Significantly more women (80% versus 32%) reported symptomatic improvement after initial excisional surgery than after placebo, as well as general improvement in quality of life measures. At 12 months' follow-up, women in both groups reported a significant reduction in all the pain parameters, except dyschezia, compared with assessment at 6 months.

Evidence level Ia

Although there are limited data available from randomised controlled trials assessing the effectiveness of surgery in relieving pain, it is clearly effective for many women. However, clinical experience shows that some women fail to respond to surgical treatment either because of incomplete excision or postoperative disease recurrence or because some of their pain was not due to endometriosis in the first place.

Evidence level III

### 9.3 Does nerve ablation provide pain relief?

#### **Laparoscopic uterine nerve ablation by itself does not reduce endometriosis-associated pain.**

**A**

There is no evidence that laparoscopic uterine nerve ablation is necessary when ablating endometriotic lesions<sup>43</sup> and laparoscopic uterine nerve ablation by itself has no effect on dysmenorrhoea associated with endometriosis.<sup>44</sup>

Evidence level Ib

In cases that have failed to respond to conservative laparoscopic surgery, there may be a role for presacral neurectomy, especially in severe dysmenorrhoea, although the evidence is inconclusive.<sup>44</sup>

Evidence level Ib

### 9.4 What is the role of more radical surgery?

#### **Endometriosis associated pain can be reduced by removing the entire lesions in severe and deeply infiltrating disease.**



If a hysterectomy is performed, all visible endometriotic tissue should be removed at the same time.<sup>45</sup> Bilateral salpingo-oophorectomy may result in improved pain relief and a reduced chance of future surgery.<sup>46</sup>

### 9.5 Is there a role for hormonal treatment before or after surgery?

#### **There is insufficient evidence of benefit to justify the use of preoperative or postoperative hormonal treatment.**

**A**

Although hormonal therapy prior to surgery improves the revised American Fertility Society classification system (rAFS) scores, there is insufficient evidence of any effect on outcome measures such as pain relief to justify its usage.<sup>47</sup>

Evidence level Ia

Compared with surgery alone or surgery plus placebo, postoperative hormonal treatment does not produce a significant reduction in pain recurrence at 12 or 24 months and has no effect on disease recurrence.<sup>47</sup>

Evidence level Ia

In a small randomised controlled trial, the LNG-IUS, inserted after laparoscopic surgery for endometriosis associated pain, significantly reduced the risk of recurrent moderate-severe dysmenorrhoea at 1 year follow-up.<sup>48</sup>

Evidence level Ia

### 9.6 What type of hormone replacement treatment (HRT) should be prescribed after bilateral oophorectomy?

**The ideal regimen for HRT after bilateral oophorectomy is unclear and should be discussed on an individual basis.**



HRT is recommended after bilateral oophorectomy in young women, given the overall health benefits and small risk of recurrent disease while taking HRT.<sup>49</sup> The ideal regimen is unclear: adding a progestogen after hysterectomy is unnecessary but may protect against the unopposed action of oestrogen on any residual disease. However, the theoretical benefit of avoiding disease reactivation or malignant transformation should be balanced against the increase in breast cancer risk reported to be associated with combined oestrogen and progestogen HRT and tibolone.<sup>50</sup>

Evidence level IV

## 10. Treatment of endometriosis-associated infertility

### 10.1 Is there a role for hormonal treatment in endometriosis-associated infertility?

**Suppression of ovarian function to improve fertility in minimal-mild endometriosis is not effective and should not be offered for this indication alone. There is no evidence of its effectiveness in more severe disease.**



The value of ovarian suppression with danazol, medroxyprogesterone acetate or gestrinone versus placebo/no treatment has been assessed in a Cochrane review.<sup>51</sup> The odds ratio for pregnancy following ovulation suppression versus placebo or no treatment was 0.74 (95% CI 0.48-1.15). These data were statistically homogeneous, despite the use of a variety of suppression agents. The odds ratio for pregnancy following all agents versus danazol, the most commonly used agent prior to the advent of GnRH agonists, was 1.3 (95% CI 0.97-1.76). Clearly, there is no evidence to support the use of ovarian suppression agents in the treatment of endometriosis-associated infertility. More harm than good may result from treatment, because of adverse effects and the lost opportunity to conceive.

Evidence level Ia

### 10.2 Does surgery for minimal-mild disease improve pregnancy rates?

**Ablation of endometriotic lesions plus adhesiolysis to improve fertility in minimal-mild endometriosis is effective compared with diagnostic laparoscopy alone.**



The recommendation is based upon a systematic review and meta-analysis of two similar, but contradictory, randomised controlled trials comparing laparoscopic surgery ( $\pm$  adhesiolysis) with diagnostic laparoscopy alone.<sup>52</sup> The combined data showed that surgery was beneficial for ongoing pregnancy and live birth rates (OR 1.64, 95% CI 1.05-2.57). Nevertheless, the strength of the evidence is questionable as small numbers were treated in one of the studies, which showed no benefit (pregnancy OR 0.76, 95% CI 0.31-1.88; live birth OR 0.85, 95% CI 0.32-2.28).<sup>53</sup> In the other, larger study<sup>54</sup> there was a significantly higher monthly fecundity rate in the treated compared with the control group, with an increased chance of pregnancy (OR

Evidence level Ia



2.03, 95% CI 1.28–3.24) and ongoing pregnancy rate after 20 weeks (OR 1.95, 95% CI 1.18–3.22). However, only blue-black lesions were ablated, adhesions were lysed if present, and women were seemingly not blinded to whether they were treated or not.

Evidence level Ia

### 10.3 Does surgery for moderate-severe disease improve pregnancy rates?

**The role of surgery in improving pregnancy rates for moderate-severe disease is uncertain.**

**B**

No randomised controlled trials or meta-analyses are available to answer the question. Nevertheless, based upon three studies<sup>55-57</sup> there seems to be a negative correlation between the stage of endometriosis and the spontaneous cumulative pregnancy rate after surgical removal of endometriosis but statistical significance was only reached in one study.<sup>56</sup>

Evidence level III

### 10.4 How should ovarian endometriomas be managed?

**Laparoscopic cystectomy for ovarian endometriomas is better than drainage and coagulation.**

**A**

The recurrence of endometriomas and symptoms are reduced by excisional surgery more so than drainage and ablation. Subsequent spontaneous pregnancy rates in women who were previously subfertile are also improved with this treatment.<sup>58</sup>

Evidence level Ia

### 10.5 Is there a role for hormonal treatment after surgery?

**Postoperative hormonal treatment has no beneficial effect on pregnancy rates after surgery.**

**A**

Compared with surgery alone or surgery plus placebo, postoperative hormonal treatment has no effect on pregnancy rates.<sup>47</sup>

Evidence level Ia

### 10.6 Is there a role for flushing the fallopian tubes?

**Tubal flushing appears to improve pregnancy rates in women with endometriosis-associated infertility.**

**A**

Tubal flushing with oil-soluble media versus no intervention in infertile women is associated with a significant increase in the odds of pregnancy (Peto OR 3.30, 95% CI 2.00–5.43) and live birth (Peto OR 2.98, 95% CI 1.40–6.37). The effect is most pronounced in women with endometriosis: odds of pregnancy (Peto OR 6.76, 95% CI 2.14–21.35) and live birth (Peto OR 5.17, 95% CI 1.55–17.23).<sup>59</sup>

Evidence level Ib

## 11. Assisted reproduction in endometriosis

### 11.1 Does intrauterine insemination (IUI) improve pregnancy rates?

**Treatment with IUI improves fertility in minimal to mild endometriosis.**

**A**

This recommendation is based on the National Collaborating Centre for Women's and Children's Health guidance *Fertility: assessment and treatment for people with fertility problems*, which identified two relevant randomised controlled trials with inconsistent results. The first showed that IUI plus gonadotrophins significantly increased live birth rates compared with no treatment (26% v. 8%; RR 3.3, 95% CI 1.2 to 9.4).<sup>60</sup> The second showed no difference between IUI plus gonadotrophins and expectant management (29% v. 20%; OR 1.5, 95% CI 0.5 to 4.0).<sup>61</sup> The combined RR for live births was 2.3 (95% CI 1.1 to 4.6).

Evidence level Ib

### 11.2 Is in vitro fertilisation (IVF) indicated?

**IVF is appropriate treatment, especially if tubal function is compromised, if there is also male factor infertility, and/or other treatments have failed.**

**B**

A meta-analysis of published studies suggests that IVF pregnancy rates are lower in women with endometriosis than in those with tubal infertility.<sup>62</sup> However, as noted in the ESHRE Guideline,<sup>1</sup> endometriosis does not appear to adversely affect pregnancy rates, as suggested in large databases such as the Society for Assisted Reproductive Technology and the Human Fertilisation and Embryology Association.<sup>63</sup>

Evidence level III

### 11.3 Is there a role for surgical treatment of endometriomas before IVF?

**Laparoscopic ovarian cystectomy is recommended for endometriomas  $\geq 4$  cm in diameter.**

✓

There are no randomised controlled trials comparing laparoscopic excision with no treatment before IVF. However, laparoscopic ovarian cystectomy is recommended if an ovarian endometriomas  $\geq 4$  cm in diameter is present to confirm the diagnosis histologically; reduce the risk of infection; improve access to follicles, and possibly improve ovarian response and prevent endometriosis progression. The woman should be counselled regarding the risks of reduced ovarian function after surgery<sup>64,65</sup> and the loss of the ovary. The decision should be reconsidered if she has had previous ovarian surgery.

### 11.4 Is there a role for hormonal treatment before IVF?

**Treatment with a GnRH agonist for 3–6 months before IVF in women with endometriosis increases the rate of clinical pregnancy.**

**A**

A Cochrane review identified three randomised controlled trials involving women with endometriosis who were treated with a standard protocol or a GnRH agonist for 3–6 months before IVF. The clinical pregnancy rate per woman was significantly higher (OR 4.28, 95% CI 2.00–9.15) in women receiving a GnRH agonist compared with controls.<sup>66</sup> However, the authors of the Cochrane review stressed that the recommendation is based on only one properly randomised study and called for further research, particularly on the mechanism of action.

Evidence level Ia

## 12. Coping with disease

### 12.1 What is the role for complementary therapies?

**The role of complementary therapies in relieving endometriosis-associated pain is unclear.**

✓

There is evidence from two systematic reviews suggesting that high frequency TENS, acupuncture, vitamin B1 and magnesium may help to relieve dysmenorrhoea.<sup>67,68</sup> One randomised controlled trial has shown that vitamin E may relieve primary dysmenorrhoea and reduce blood loss.<sup>69</sup> Whether such treatments are effective in endometriosis-associated dysmenorrhoea is unknown.

**C**

Many women with endometriosis report that nutritional and complementary therapies such as homeopathy, reflexology, traditional Chinese medicine or herbal treatments, do improve pain symptoms. While there is no evidence from randomised controlled trials in endometriosis to support these treatments, they should not be ruled out if the woman feels that they could be beneficial to her overall pain management and/or quality of life, or work in conjunction with more traditional therapies.

## 12.2 What is the role for patient support groups?

Patient self-help groups can provide invaluable counselling, support and advice.



The website [www.endometriosis.org/support.html](http://www.endometriosis.org/support.html) provides a comprehensive list of self-help groups throughout the world.

## 13. Auditable standards

1. Documentation of endometriosis localisation, appearance and severity.
2. Rates of histological confirmation of endometriomas and deeply infiltrating disease.
3. Documentation of counselling on medical treatment options.
4. Documentation of counselling on surgical treatment options.
5. Surgical complication rates.

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## APPENDIX

Clinical guidelines are: 'systematically developed statements which assist clinicians and patients in making decisions about appropriate treatment for specific conditions'. Each guideline is systematically developed using a standardised methodology. Exact details of this process can be found in Clinical Governance Advice No. 1: *Guidance for the Development of RCOG Green-top Guidelines* (available on the RCOG website). These recommendations are not intended to dictate an exclusive course of management or treatment. They must be evaluated with reference to individual patient needs, resources and limitations unique to the institution and variations in local populations. It is hoped that this process of local ownership will help to incorporate these guidelines into routine practice. Attention is drawn to areas of clinical uncertainty where further research may be indicated.

The evidence used in this guideline was graded using the scheme below and the recommendations formulated in a similar fashion with a standardised grading scheme.

Classification of evidence levels	Grades of recommendations
Ia Evidence obtained from meta-analysis of randomised controlled trials.	<b>A</b> Requires at least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation. (Evidence levels Ia, Ib)
Ib Evidence obtained from at least one randomised controlled trial.	<b>B</b> Requires the availability of well controlled clinical studies but no randomised clinical trials on the topic of recommendations. (Evidence levels IIa, IIb, III)
IIa Evidence obtained from at least one well-designed controlled study without randomisation.	<b>C</b> Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality. (Evidence level IV)
IIb Evidence obtained from at least one other type of well-designed quasi-experimental study.	<b>Good practice point</b>
III Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies.	<input checked="" type="checkbox"/> Recommended best practice based on the clinical experience of the guideline development group.
IV Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities.	

### DISCLAIMER

The Royal College of Obstetricians and Gynaecologists produces guidelines as an educational aid to good clinical practice. They present recognised methods and techniques of clinical practice, based on published evidence, for consideration by obstetricians, gynaecologists and other relevant health professionals. The ultimate judgement regarding a particular clinical procedure or treatment plan must be made by the doctor or other attendant in the light of clinical data presented by the patient and the diagnostic and treatment options available.

This means that RCOG Guidelines are unlike protocols or guidelines issued by employers, not being intended to be prescriptive directions defining a single course of management. Departure from the local prescriptive protocols or guidelines should be fully documented in the patient's case notes at the time the relevant decision is taken.

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unless otherwise indicated