ESHRE guideline for the diagnosis and treatment of endometriosis

Stephen Kennedy¹,¹⁰, Agneta Bergqvist², Charles Chapron³, Thomas D’Hooghe⁴, Gerard Dunselman⁵, Robert Greb⁶, Lone Hummelshøj⁷, Andrew Prentice⁸ and Ertan Saridogan⁹ on behalf of the ESHRE Special Interest Group for Endometriosis and Endometrium Guideline Development Group*

¹University of Oxford, Oxford, UK, ²Karolinska Institutet, Stockholm, Sweden, ³Clinique Universitaire Baudelocque, Paris, France, ⁴Leuven University, Leuven, Belgium, ⁵Maastricht University, Maastricht, The Netherlands, ⁶Muenster University Hospital, Muenster, Germany, ⁷Endometriose Foreningen, Denmark, ⁸University of Cambridge, Cambridge, UK and ⁹University College Hospital, London, UK

¹⁰To whom correspondence should be addressed at: Nuffield Department of Obstetrics and Gynaecology, University of Oxford, John Radcliffe Hospital, Oxford OX3 9DU, UK. E-mail: Stephen.kennedy@obs-gyn.ox.ac.uk

The objective was to develop recommendations for the diagnosis and treatment of endometriosis and its associated symptoms. A working group was convened comprised of practising gynaecologists and experts in evidence-based medicine from Europe, as well as an endometriosis self-help group representative. After reviewing existing evidence-based guidelines and systematic reviews, the expert panel met on three occasions for a day during which the guideline was developed and refined. Recommendations based solely on the clinical experience of the panel were avoided as much as possible. The entire ESHRE Special Interest Group for Endometriosis and Endometrium was given the opportunity to comment on the draft guideline, after which it was available for comment on the ESHRE website for 3 months. The working group then ratified the guideline by unanimous or near-unanimous voting; finally, it was approved by the ESHRE Executive Committee. The guideline will be updated regularly, and will be made available at http://www.endometriosis.org/guidelines.html with hyperlinks to the supporting evidence, and the relevant references and abstracts. For women presenting with symptoms suggestive of endometriosis, a definitive diagnosis of most forms of endometriosis requires visual inspection of the pelvis at laparoscopy as the ‘gold standard’ investigation. However, pain symptoms suggestive of the disease can be treated without a definitive diagnosis using a therapeutic trial of a hormonal drug to reduce menstrual flow. In women with laparoscopically confirmed disease, suppression of ovarian function for 6 months reduces endometriosis-associated pain; all hormonal drugs studied are equally effective although their side-effects and cost profiles differ. Ablation of endometriotic lesions reduces endometriosis-associated pain and the smallest effect is seen in patients with minimal disease; there is no evidence that also performing laparoscopic uterine nerve ablation (LUNA) is necessary. In minimal–mild endometriosis, suppression of ovarian function to improve fertility is not effective, but ablation of endometriotic lesions plus adhesiolysis is effective compared to diagnostic laparoscopy alone. There is insufficient evidence available to determine whether surgical excision of moderate–severe endometriosis enhances pregnancy rates. IVF is appropriate treatment especially if there are coexisting causes of infertility and/or other treatments have failed, but IVF pregnancy rates are lower in women with endometriosis than in those with tubal infertility. The management of severe/deeply infiltrating endometriosis is complex and referral to a centre with the necessary expertise is strongly recommended. Patient self-help groups can provide invaluable counselling, support and advice.

Key words: diagnosis/endometriosis/ESHRE guidelines/treatment

*The manuscript was prepared by the first author; all other authors contributed equally and are listed in alphabetical order. Guideline Development Group: Agneta Bergqvist, Karolinska Institutet, Stockholm (Chair), Charles Chapron, Clinique Universitaire Baudelocque, Paris (Working party), Gerard Dunselman, Maastricht University (Working party), Robert Greb, Muenster University Hospital (Working party), Thomas D’Hooghe, Leuven University (Vice-Chair), Lone Hummelshøj, Endometriose Foreningen, Denmark (Working party), Stephen Kennedy, University of Oxford (Report writer), Philippe Koninckx, Leuven University and University of Oxford (Contributor), Roberto Matorras, País Vasco University (Contributor), Michael Mueller, University of Berne (Contributor), Andrew Prentice, University of Cambridge (Working party), Ertan Saridogan, University College Hospital, London (Working party), Juan Garcia-Velasco, Instituto Valenciano de Infertilidad, Madrid (Contributor).
Introduction

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 well-being. Therefore, it is vital to take careful note of the woman’s complaints, and to give her time to express her concerns and anxieties as in other chronic diseases. Some women, however, have no symptoms at all.

Treatment must be individualized, 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. In such circumstances, a multi-disciplinary approach involving a pain clinic and counselling should be considered early in the treatment plan. 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 or refer the woman to a centre with the necessary expertise to offer all available treatments in a multi-disciplinary context, including advanced laparoscopic surgery and laparotomy.

Sources

The guideline was commissioned by the ESHRE Special Interest Group (SIG) on Endometriosis and Endometrium, and developed by a working group. No systematic attempt was made to search the published literature independently of the following sources:

- NICE Guideline on the assessment and treatment for people with fertility problems, produced by the National Institute for Clinical Evidence.
- Green Top Guideline on the investigation and management of endometriosis, produced by the Royal College of Obstetricians and Gynaecologists.
- Consensus statement for the management of chronic pelvic pain and endometriosis, produced by a group of US gynaecologists.

Recommendations

The highest level of available evidence was used to form all the recommendations contained in this guideline. The evidence was graded using standard criteria shown in Table I.

This scale, which was developed to apply to studies about the effectiveness of health-care interventions, is only a guide to the validity and relevance of evidence. Other questions may be more appropriately addressed by different study designs: for example, a question about the predictive power of an investigation is best answered with observational data.

Recommendations were based on, and linked to, the supporting evidence, or, where necessary, the informal consensus of the working group. The strength of evidence corresponding to each level of recommendation is shown in Table II. Regarding diagnostic tests specifically, a recommendation based on the existence of a well-conducted systematic review was assessed as grade A.

Localization and appearance of endometriosis

The most commonly affected sites are the pelvic organs and peritoneum, although other parts of the body such as the 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) and/or extensive fibrosis 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 (ASRM) (1997). 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-purplish, or diffuse cystic 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, polyoid, haemorrhagic, 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 tar; 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 >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 (Koninckx et al., 1991; Porpora et al., 1999; Chapron et al., 2003a).

Symptoms

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 several years between symptom onset and a definitive diagnosis (Hadfield et al., 1996; Arruda et al., 2003; Husby et al., 2003).

The following symptoms can be caused by endometriosis based on clinical and patient experience: severe dysmenorrhea; deep dyspareunia; chronic pelvic pain; ovulation pain; cyclical or perimenstrual symptoms (e.g. bowel or bladder associated) with or without abnormal bleeding; infertility; and chronic fatigue. However, 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.

Clinical signs

Finding pelvic tenderness, a fixed retroverted uterus, tender uterosacral ligaments or enlarged ovaries on examination is suggestive of endometriosis. The diagnosis is more certain if deeply infiltrating nodules are found on the uterosacral ligaments or in the pouch of Douglas, and/or visible lesions are seen in the vagina or on the cervix. The findings may, however, be normal.

| C | Deeply infiltrating nodules are most reliably detected when clinical examination is performed during menstruation (Koninckx et al., 1996). |

Diagnosis

| C | For a definitive diagnosis of endometriosis, visual inspection of the pelvis at laparoscopy is the ‘gold standard’ investigation, unless disease is visible in the vagina or elsewhere. |

Histology

| GPP | Positive histology confirms the diagnosis of endometriosis; negative history 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 (>3 cm in diameter), and in deeply infiltrating disease, histology should be obtained to identify endometriosis and to exclude rare instances of malignancy. |

| GPP | If the patient wants pain symptoms suggestive of endometriosis to be treated without a definitive diagnosis, then a therapeutic trial of a hormonal drug to reduce menstrual flow is appropriate (see ‘Empirical treatment’ section). |

| GPP | The management of severe/deeply infiltrating endometriosis is complex. 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 multi-disciplinary context, including advanced laparoscopic surgery and laparotomy, is strongly recommended. |

Investigations

Ultrasound

| A | Compared to laparoscopy, transvaginal ultrasound (TVS) has no value in diagnosing peritoneal endometriosis, but it is a useful tool both to make and to exclude the diagnosis of an ovarian endometrioma (Moore et al., 2002). TVS may have a role in the diagnosis of disease involving the bladder or rectum. Systematic review of diagnostic tests |

Magnetic resonance imaging

| A | Compared to laparoscopy, magnetic resonance imaging (MRI) has limited value as a diagnostic tool for endometriosis (Ang et al., submitted). Systematic review of diagnostic tests |

Blood tests

| A | Serum CA-125 levels may be elevated in endometriosis. However, compared to laparoscopy, measuring serum CA-125 levels has no value as a diagnostic tool (Mol et al., 1998). Systematic review of diagnostic tests |

Investigations to assess disease extent

| GPP | If there is clinical evidence of deeply infiltrating endometriosis, ureteral, 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 intravesical pressure (IVP) and barium enema studies depending upon the individual circumstances, to map the extent of disease present, which may be multi-focal. |
### Assessment of ovarian cysts

| GPP | Local guidelines for the management of suspected ovarian malignancy should be followed in cases of ovarian endometrioma. Ultrasound scanning ± serum CA-125 testing is usually used to try to identify rare instances of ovarian cancer; however, CA-125 levels can be elevated in the presence of endometriomas. |

### Laparoscopy

| GPP | Good surgical practice is 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. |

| GPP | There is insufficient evidence to justify timing the laparoscopy at a specific time in the menstrual cycle, but it should not be performed during or within 3 months of hormonal treatment so as to avoid under-diagnosis. |

| C | All classification systems for endometriosis are subjective and correlate poorly with pain symptoms, but may be of value in infertility prognosis and management (Chapron et al., 2003b; D’Hooghe et al., 2003). Evidence level 3 |

| C | At laparoscopy, deeply infiltrating endometriosis may have the appearance of minimal disease, resulting in an underestimation of disease severity (Koninckx et al., 1994). Evidence level 3 |

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

| GPP | Empirical treatment for pain symptoms presumed to be due to endometriosis without a definitive diagnosis includes counselling, adequate analgesia, nutritional therapy, progestagens or the combined oral contraceptive (COC). It is unclear whether the COC should be taken conventionally, continuously or in a tricycle regimen. A GnRH agonist may be taken but this class of drug is more expensive, and associated with more side-effects and concerns about bone density. |

### Treatment of endometriosis-associated pain in confirmed disease

#### Non-steroidal anti-inflammatory drugs

| A | Non-steroidal anti-inflammatory drugs (NSAID) may be effective in reducing endometriosis-associated pain (Kauppila et al., 1979; Ylikorkala and Viinikka, 1983; Kauppila and Ronnberg, 1985). Evidence level 1b |

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

#### Hormonal treatment

| A | Suppression of ovarian function for 6 months reduces endometriosis-associated pain. The hormonal drugs investigated—COC, danazol, gestrinone, medroxyprogesterone acetate and GnRH agonists—are equally effective but their side-effects and cost profiles differ (Moore et al., 2004; Prentice et al., 2004a,b; Selak et al., 2004). Evidence level 1a |

The levonorgestrel intruterine system (LNG-IUS) may be effective at reducing endometriosis-associated pain (Vercellini et al., 1999a), but there is insufficient evidence to make recommendations.

#### Duration of GnRH agonist treatment

| A | Treatment for 3 months with a GnRH agonist may be as effective as 6 months in terms of pain relief (Hornstein et al., 1995). Treatment for up to 2 years with combined estrogen progestagen ‘add-back’ appears to be effective and safe in terms of pain relief and bone density protection (Surrey and Hornstein, 2002). However, care should be given to the use of GnRH agonists in women who may not have reached their maximum bone density. Evidence level 1b |

#### Surgical treatment

| GPP | Depending upon the severity of disease found, ideal practice is to diagnose and remove endometriosis surgically at the same time, provided that pre-operative adequate consent has been obtained (Redwine and Wright, 2001; Abbott et al., 2003; Chapron et al., 2003b; Fedele et al., 2004). |

There are no data to justify hormonal treatment prior to surgery to improve the success of surgery (Muzii et al., 1996).

| A | Ablation of endometriotic lesions plus laparoscopic uterine nerve ablation (LUNA) in minimal–moderate disease reduces endometriosis-associated pain at 6 months compared to diagnostic laparoscopy; the smallest effect is seen in patients with minimal disease (Jacobson et al., 2004a). However, there is no evidence that LUNA is a necessary component, as LUNA by itself has no effect on dysmenorrhoea associated with endometriosis (Vercellini et al., 2003a). Evidence level 1b |

There are no data supporting the use of uterine suspension but, in certain cases, there may be a role for pre-sacral neuratomy (Soysal et al., 2003).

| GPP | Endometriosis-associated pain can be reduced by removing the entire lesions in severe and deeply infiltrating disease. If a hysterectomy is performed, bilateral salpingo-oophorectomy should also be considered (Nannoum et al., 1995), provided that all visible endometriotic tissue is removed at the same time (Lefebvre et al., 2002). |
Post-operative treatment

<table>
<thead>
<tr>
<th>Evidence level 1b</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong></td>
</tr>
</tbody>
</table>

Hormone replacement therapy

<table>
<thead>
<tr>
<th>Evidence level 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>D</strong></td>
</tr>
</tbody>
</table>

Treatment of endometriosis-associated infertility in confirmed disease

Treatment of endometriotic lesions

Hormonal treatment

<table>
<thead>
<tr>
<th>Evidence level 1a</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong></td>
</tr>
</tbody>
</table>

Surgical treatment

<table>
<thead>
<tr>
<th>Evidence level 1a</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong></td>
</tr>
</tbody>
</table>

The recommendation above is based upon a systematic review and meta-analysis of two, similar but contradictory RCTs comparing laparoscopic surgery (± adhesiolysis) with diagnostic laparoscopy alone. Nevertheless, some members of the working group questioned the strength of the evidence because: (i) small numbers were treated in one of the studies (Parazzini, 1999); (ii) although in the other, larger study (Marcoux et al., 1997) there was a significantly higher monthly fecundity rate in the treated compared to the control group, patients were apparently not blinded to whether they were treated or not.

Assisted reproduction in endometriosis

Intrauterine insemination

<table>
<thead>
<tr>
<th>Evidence level 1b</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong></td>
</tr>
</tbody>
</table>

IVF

<table>
<thead>
<tr>
<th>Evidence level 2b</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Evidence level 1a</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong></td>
</tr>
</tbody>
</table>

The recommendation above is based on a systematic review but the working group noted that endometriosis does not adversely affect pregnancy rates in some large databases (e.g. SART and HFEA) (Templeton et al., 1996).
Laparoscopic ovarian cystectomy is recommended if an ovarian endometrioma ≥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. The woman should be counselled regarding the risks of reduced ovarian function after surgery and the loss of the ovary. The decision should be reconsidered if she has had previous ovarian surgery.

Prolonged treatment with a GnRH agonist before IVF in moderate–severe endometriosis should be considered and discussed with patients because improved pregnancy rates have been reported (Rickers et al., 2002; Surrey et al., 2002).

Many women with endometriosis report that nutritional and complementary therapies such as reflexology, traditional Chinese medicine, herbal treatments, homeopathy etc., do improve pain symptoms. Whilst there is no evidence from RCTs 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.

Patient self-help groups

Patient self-help groups can provide invaluable counselling, support and advice. The website www.endometriosis.org/support.html provides a comprehensive list of all the self-help groups in the world.

References


Anc, WC, Alvey CM, Marran S, Kennedy SH and Golding S. A systematic review of the accuracy of magnetic resonance imaging (MRI) in the diagnosis of endometriosis. (Submitted for publication.)


Tummon IS, Asher LJ, Martin JS and Tulandi T (1997) Randomized controlled trial of superovulation and insemination for infertility associated with minimal or mild endometriosis. Fertil Steril 68,8–12.


Submitted on April 25, 2005; accepted on April 29, 2005