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ESHRE guideline for the diagnosis and treatment of endometriosis

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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

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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:

- *Clinical Evidence*: the monthly, updated directory of evidence on the effects of clinical interventions, published by the BMJ Publishing Group (UK).
http://www.clinicalevidence.com.
- NICE Guideline on the assessment and treatment for people with fertility problems, produced by the National Institute for Clinical Evidence.
- http://www.nice.org.uk/Docref.asp?d=106333.
- Green Top Guideline on the investigation and management of endometriosis, produced by the Royal College of Obstetricians and Gynaecologists.

http://www.rcog.org.uk/guidelines.asp?PageID=106& GuidelineID.

- Guideline on the diagnosis and treatment of endometriosis, produced by the Dutch Society of Obstetrics and Gynaecology.
- http://www.nvog.nl/files/endometriose041026.pdf.
- Consensus statement for the management of chronic pelvic pain and endometriosis, produced by a group of US gynaecologists.
- http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve& db=PubMed&list_uids=12413979&dopt=Abstract.

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.

Table I. Hierarchy of evidence

Level	Evidence
1a	Systematic review and meta-analysis of randomized controlled trials (RCT)
1b	At least one RCT
2a	At least one well-designed controlled study without randomization
2b	At least one other type of well-designed quasi-experimental study
3	Well-designed, non-experimental, descriptive studies, such as comparative studies, correlation studies or case studies
4	Expert committee reports or opinions and/or clinical experience of respected authorities

Table II. Strength of evidence corresponding to each level of recommendation

Grade	Strength of evidence
A	Directly based on level 1 evidence
B	Directly based on level 2 evidence or extrapolated recommendation from level 1 evidence
C	Directly based on level 3 evidence or extrapolated recommendation from either level 1 or level 2 evidence
D	Directly based on level 4 evidence or extrapolated recommendation from either level 1, 2 or 3 evidence
GPP	Good practice point based upon the views of the Guideline Development Group

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, 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 dysmenorrhoea; 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).	Evidence level 3

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.	Evidence level 3

Histology

GPP	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 (>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 intrauterine 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, careful consideration 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 neurectomy (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 (Namnoum *et al.*, 1995), provided that all visible endometriotic tissue is removed at the same time (Lefebvre *et al.*, 2002).	

Post-operative treatment

A	Treatment with danazol or a GnRH agonist for 6 months after surgery reduces endometriosis-associated pain and delays recurrence at 12 and 24 months compared with placebo and expectant management. However, post-operative treatment with a COC is not effective (Telimaa *et al.*, 1987; Parazzini *et al.*, 1994; Hornstein *et al.*, 1997; Bianchi *et al.*, 1999; Morgante *et al.*, 1999; Vercellini *et al.*, 1999b; Muzii *et al.*, 2000; Busacca *et al.*, 2001).	Evidence level 1b

Hormone replacement therapy

D	Hormone replacement therapy (HRT) is recommended after bilateral oophorectomy in young women but the ideal regimen is unclear. Adding a progestagen after hysterectomy is unnecessary but should protect against the unopposed action of estrogen on any residual disease. This theoretical benefit must be balanced against the small risk of recurrent disease (Matorras *et al.*, 2002) and the increase in breast cancer risk reported to be associated with both tibolone and combined estrogen and progestagen HRT (Beral and Million Women Study Collaborators, 2003).	Evidence level 4

Treatment of endometriosis-associated infertility in confirmed disease

Treatment of endometriotic lesions

Hormonal treatment

A	Suppression of ovarian function to improve fertility in minimal–mild endometriosis is not effective and should not be offered for this indication alone (Hughes *et al.*, 2004). There is no evidence of its effectiveness in more severe disease.	Evidence level 1a

Surgical treatment

A	Ablation of endometriotic lesions plus adhesiolysis to improve fertility in minimal–mild endometriosis is effective compared to diagnostic laparoscopy alone (Jacobson *et al.*, 2004b).	Evidence level 1a

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.

B	No RCT or meta-analyses are available to answer the question whether surgical excision of moderate–severe endometriosis enhances pregnancy rates. Based upon three studies (Adamson *et al.*, 1993; Guzick *et al.*, 1997; Osuga *et al.*, 2002) 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 (Osuga *et al.*, 2002).	Evidence level 3

A	Laparoscopic cystectomy for ovarian endometriomas >4 cm diameter improves fertility compared to drainage and coagulation (Beretta *et al.*, 1998; Chapron *et al.*, 2002) Coagulation or laser vaporization of endometriomas without excision of the pseudo-capsule is associated with a significantly increased risk of cyst recurrence (Vercellini *et al.*, 2003b).	Evidence level 1b

Post-operative treatment

A	Treatment with danazol or a GnRH agonist after surgery does not improve fertility compared with expectant management (Parazzini *et al.*, 1994; Bianchi *et al.*, 1999; Vercellini *et al.*, 1999b; Busacca *et al.*, 2001).	Evidence level 1b

Assisted reproduction in endometriosis

Intrauterine insemination

A	Treatment with intrauterine insemination (IUI) improves fertility in minimal–mild endometriosis: IUI with ovarian stimulation is effective but the role of unstimulated IUI is uncertain (Tummon *et al.*, 1997).	Evidence level 1b

IVF

B	IVF is appropriate treatment especially if tubal function is compromised, if there is also male factor infertility, and/or other treatments have failed.	Evidence level 2b

A	IVF pregnancy rates are lower in patients with endometriosis than in those with tubal infertility (Barnhart *et al.*, 2002).	Evidence level 1a

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).

GPP	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.	

A	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 (Rickes *et al.*, 2002; Surrey *et al.*, 2002).	Evidence level 1b

Coping with disease

Complementary therapies

D	There is evidence from two systematic reviews suggesting that high frequency transcutaneous electrical nerve stimulation (TENS), acupuncture, vitamin B_1 and magnesium may help to relieve dysmenorrhoea (Proctor and Murphy, 2004; Proctor *et al.*, 2004). Whether such treatments are effective in endometriosis associated dysmenorrhoea is unknown.	Evidence level 4

GPP	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 support groups

GPP	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.

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