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ORIGINAL ARTICLE *ESHRE pages*

ESHRE guideline: management of women with endometriosis†

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STUDY QUESTION: What is the optimal management of women with endometriosis based on the best available evidence in the literature?

SUMMARY ANSWER: Using the structured methodology of the *Manual for ESHRE Guideline Development*, 83 recommendations were formulated that answered the 22 key questions on optimal management of women with endometriosis.

WHAT IS KNOWN ALREADY: The European Society of Human Reproduction and Embryology (ESHRE) guideline for the diagnosis and treatment of endometriosis (2005) has been a reference point for best clinical care in endometriosis for years, but this guideline was in need of updating.

STUDY DESIGN, SIZE, DURATION: This guideline was produced by a group of experts in the field using the methodology of the *Manual for ESHRE Guideline Development*, including a thorough systematic search of the literature, quality assessment of the included papers up to January 2012 and consensus within the guideline group on all recommendations. To ensure input from women with endometriosis, a patient representative was part of the guideline development group. In addition, patient and additional clinical input was collected during the scoping and review phase of the guideline.

PARTICIPANTS/MATERIALS, SETTING, METHODS: NA.

MAIN RESULTS AND THE ROLE OF CHANCE: The guideline provides 83 recommendations on diagnosis of endometriosis and on the treatment of endometriosis-associated pain and infertility, on the management of women in whom the disease is found incidentally (without pain or infertility), on prevention of recurrence of disease and/or painful symptoms, on treatment of menopausal symptoms in patients with a history of endometriosis and on the possible association of endometriosis and malignancy.

LIMITATIONS, REASONS FOR CAUTION: We identified several areas in care of women with endometriosis for which robust evidence is lacking. These areas were addressed by formulating good practice points (GPP), based on the expert opinion of the guideline group members.

WIDER IMPLICATIONS OF THE FINDINGS: Since 32 out of the 83 recommendations for the management of women with endometriosis could not be based on high level evidence and therefore were GPP, the guideline group formulated research recommendations to guide future research with the aim of increasing the body of evidence.

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Introduction

Endometriosis is defined as the presence of endometrial-like tissue outside the uterus, which induces a chronic, inflammatory reaction (Kennedy *et al.*, 2005). While some women with endometriosis can experience painful symptoms and/or infertility, others have no symptoms at all. The exact prevalence of endometriosis is unknown but estimates range from 2 to 10% of women of reproductive age, to 50% of infertile women (Eskenazi and Warner, 1997; Meuleman *et al.*, 2009).

Why were these guidelines produced?

The *ESHRE Guideline for the Diagnosis and Treatment of Endometriosis (2005)* has been a reference point for best clinical care in endometriosis for years (Kennedy *et al.*, 2005). Since this European Society of Human Reproduction and Embryology (ESHRE) guideline needed updating, a *Guideline on the Management of Endometriosis* was produced, using the methodology of the *Manual for ESHRE Guideline Development* published in 2009 (http://www.eshre.eu/Guidelines), with the aim of offering best practice advice on the care of women with endometriosis, including diagnosis and treatment for endometriosis-associated pain and infertility. Furthermore, information is provided on asymptomatic endometriosis, on primary and secondary prevention, on menopausal symptoms in women with a history of endometriosis and on endometriosis and malignancy.

What are the similarities and differences with the previous guideline?

The current guideline development was initiated by members of the 2005 guideline development group (GDG), supplemented with advice from additional experts in the field. Key questions were formulated and European and national patient organizations representing women with endometriosis were asked, which were the main problems they faced in the management of the disease. This resulted in key questions that, as could be expected, were not essentially different from the key questions that formed the basis of the former guideline. Interestingly, a substantial part of the recommendations is also similar, indicating on the one hand a lack of recent, high quality studies in some areas and on the other hand similarities in retrieving the evidence from the literature by experts and the formal retrieving process of the evidence by a structured methodology of extensive literature searches.

However, the main difference between the two guidelines is the structured methodology, based on the *Manual for ESHRE Guideline Development*, including objective assessment of the literature and an extensive and transparent review by relevant stakeholders.

Methods

All details on the methodological approach of this guideline can be found in the *Manual for ESHRE Guideline Development* (W.L.D.M. Nelen *et al.*, version 2009).

In short, questioning patients and clinicians resulted in 22 questions on the management of women with endometriosis that were structured in PICO format (Patient, Intervention, Comparison and Outcome). For each question the best available evidence for answering the key questions was searched in PUBMED/MEDLINE and the Cochrane library. The literature searches included studies written in English and published before 1 January 2012 or entered in PUBMED before 1 January 2012. Based on the collected evidence, and after constructing evidence tables and quality assessment, draft recommendations were written by the assigned expert guideline group member. Three 2-day meetings were organized to discuss the evidence and recommendations and to reach consensus on the final formulation of the recommendations.

For each recommendation, a Grade (A–D, where A is the highest quality) was assigned based on the strength of the supporting evidence (scored from

Table I Key to grades of recommendations used in ESHREguideline.

Grade of recommendations	Based on
A	Meta-analysis or multiple randomized trials (of high quality)
B	Meta-analysis or multiple randomized trials (of moderate quality) Single randomized trial, large non-randomised trial(s) or case control/cohort studies (of high quality)
C	Single randomized trial, large non-randomised trial(s) or case control/cohort studies (of moderate quality)
D	Non-analytic studies or case reports / case series (of high or moderate quality)
GPP (Good practice point)	Based on experts' opinion

All studies of low quality were excluded from the guideline

1++ to 4), based on the grading system of the Scottish Intercollegiate Guidelines Network (2010), which was a reference system in 2010 when the guideline development was initiated. In the case of the absence of evidence, the GDG could decide on writing good practice points (GPP), based on clinical expertise (Table I).

After finalization of the guideline draft, stakeholders were invited through the ESHRE newsletter ($n = 6000$) or personal email ($n = 692$) to review the guideline. Four hundred and eighty-four comments from 61 reviewers were processed by the methodological expert (NV) and the chair of the GDG (GD) either by adapting the content of the guideline and/or by replying to the reviewer. The review process was summarized in the review report, published on the ESHRE website.

The guideline will be considered for update 4 years after publication, with an intermediate assessment of the need for updating 2 years after publication.

Key questions and recommendations

Diagnosis

Several studies have reported a long delay in the diagnosis of endometriosis. Recent studies report, specifically for Europe, an overall diagnostic delay of 10 years in Germany and Austria, 8 years in the UK and Spain, 7 years in Norway, 7–10 years in Italy and 4–5 years in Ireland and Belgium (Ballard *et al.*, 2006; Nnoaham *et al.*, 2011; Hudelist *et al.*, 2012).

Which symptoms are associated with or predictive of the diagnosis of endometriosis?

Several studies explored symptoms and signs associated with endometriosis, resulting in a long list of endometriosis-associated symptoms, including dysmenorrhoea, chronic pelvic pain, deep dyspareunia, cyclical intestinal complaints, fatigue/weariness and infertility. However, the included studies all had a retrospective design and did not show a predictive value of these symptoms (Davis *et al.*, 1993; Forman *et al.*, 1993; Lemaire, 2004; Thomassin *et al.*, 2004; Seracchioli *et al.*, 2008; Luscombe *et al.*, 2009; Bellelis *et al.*, 2010).

One large retrospective analysis described symptoms that are predictive of the diagnosis of endometriosis, including severe dysmenorrhoea in infertile women, abdominopelvic pain, dysmenorrheoa, heavy menstrual bleeding, infertility, dyspareunia, postcoital bleeding and/or previous diagnosis of ovarian cyst, irritable bowel syndrome or pelvic inflammatory disease (Ballard *et al.*, 2008).

Based on the included studies and expert opinion, the GDG decided on the following GPP:

The GDG recommends that clinicians should consider the diagnosis of endometriosis: in the presence of gynaecological symptoms such as: dysmenorrhoea, non-cyclical pelvic pain, deep dyspareunia, infertility and fatigue in the presence of any of the above. in women of reproductive age with non-gynaecological cyclical symptoms (dyschezia, dysuria, haematuria and rectal bleeding, shoulder pain).	GPP

What findings during clinical examination are predictive for the presence and localization of pelvic endometriosis?

Clinical examination in women suspected to have endometriosis includes physical examination of the pelvis but also the inspection and palpation of the abdomen. Regarding findings during clinical examination predictive for the presence and localization of pelvic endometriosis, the following recommendations were written:

The GDG recommends that clinicians should perform clinical examination in all women suspected of endometriosis, although vaginal examination may be inappropriate for adolescents and/or women without previous sexual intercourse. In such cases, rectal examination can be helpful for the diagnosis of endometriosis.	GPP
Clinicians may consider the diagnosis of deep endometriosis in women with (painful) induration and/or nodules of the rectovaginal wall found during clinical examination or visible vaginal nodules in the posterior vaginal fornix (Bazot *et al.*, 2009).	C
Clinicians may consider the diagnosis of ovarian endometrioma in women with adnexal masses detected during clinical examination (Ripps and Martin, 1992; Koninckx *et al.*, 1996; Eskenazi *et al.*, 2001; Condous *et al.*, 2007; Bazot *et al.*, 2009).	C
Clinicians may consider the diagnosis of endometriosis in women suspected of the disease even if the clinical examination is normal (Chapron *et al.*, 2002).	C

Can the diagnosis of endometriosis be made by application of specific medical technologies?

The diagnosis of endometriosis is suspected based on the history, the symptoms and signs, is corroborated by physical examination and imaging techniques and is finally proven by histological examination of specimens collected during laparoscopy. The combination of laparoscopy and the histological verification of endometrial glands and/or stroma is considered to be the gold standard for the diagnosis of the disease. In many cases the typical appearances of endometriosis implants in the abdominal cavity are regarded as proof that endometriosis is present.

Instead of establishing the diagnosis of endometriosis by invasive approaches, such as surgery, empirical medical treatment for pain symptoms can be prescribed, as discussed later.

Laparoscopy. A systematic review on the accuracy of laparoscopy to diagnose endometriosis, with biopsy and histology as gold standard, showed that only limited reports of good quality exist assessing the value of visual diagnosis of endometriosis at laparoscopy. As shown in a systematic review, the accuracy of a diagnostic laparoscopy was evaluated in only four studies in a total of 433 women. A negative diagnostic laparoscopy seems to be highly accurate for excluding endometriosis and thereby useful to aid the clinician in decision-making. However, this is under the assumption that the diagnostic laparoscopy is well performed and preceded by appropriate preoperative assessment. A positive laparoscopy is less informative and of limited value when used without taking biopsies to get histological confirmation of the diagnosis (Wykes *et al.*, 2004).

The GDG recommends that clinicians: perform a laparoscopy to diagnose endometriosis, although evidence is lacking that a positive laparoscopy *'without histology'* proves the presence of disease. confirm a positive laparoscopy by histology, since positive histology confirms the diagnosis of endometriosis even though negative histology does not exclude it.	GPP
The GDG recommends that clinicians obtain tissue for histology in women undergoing surgery for ovarian endometrioma and/or deep infiltrating disease, to exclude rare instances of malignancy.	GPP

Ultrasound.

In women with symptoms and signs of rectal endometriosis, transvaginal sonography (TVS) is useful for identifying or ruling out rectal endometriosis (Hudelist *et al.*, 2011).	A

The GDG notes that TVS for the diagnosis of rectal endometriosis is highly operator dependent, and experience is often lacking, hence TVS is not recommended for diagnosis of rectal endometriosis, unless it is performed by clinicians highly experienced in TVS.

Clinicians are recommended to perform TVS to diagnose or to exclude an ovarian endometrioma (Moore *et al.*, 2002).	A
The GDG recommends that clinicians base the diagnosis of ovarian endometrioma in premenopausal women on the following ultrasound characteristics: ground glass echogenicity and one to four compartments and no papillary structures with detectable blood flow (Van Holsbeke *et al.*, 2010).	GPP

Clinicians should be aware that the usefulness of 3D ultrasound to diagnose rectovaginal endometriosis is not well established (Pascual *et al.*, 2010).	D

Magnetic resonance imaging.

Clinicians should be aware that the usefulness of magnetic resonance imaging (MRI) to diagnose peritoneal endometriosis is not well established (Stratton *et al.*, 2003).	D

Biomarkers.

Clinicians are recommended not to use biomarkers in endometrial tissue, menstrual or uterine fluids (May *et al.*, 2011) and/or immunological biomarkers, including CA-125, in plasma, urine or serum, (Mol *et al.*, 1998; May *et al.*, 2010) to diagnose endometriosis.	A

Can the extent of deep endometriosis be established by application of specific medical technologies (Barium enema, transvaginal sonography (TVS), transrectal sonography and MRI)?

The GDG recommends that clinicians should assess ureter, bladder and bowel involvement by additional imaging if there is a suspicion based on history or physical examination of deep endometriosis, in preparation for further management.	GPP

Treatment of endometriosis-associated pain

Empirical treatment of pain

Many women suffering from pelvic pain, while there is a high suspicion of endometriosis, use analgesics and hormonal medication without a prior definitive diagnosis of the disease by laparoscopy. This is partially due to the invasiveness of the laparoscopic procedure, but also to the ease of prescribing hormonal contraceptives, which would be prescribed for prevention of pregnancy anyway. This empirical treatment is especially common in adolescents with pelvic pain and dysmenorrhoea. However, before starting empirical treatment other causes of pelvic pain symptoms should be considered and excluded where possible. It is common practice that if women do not react favourably to empirical treatment a laparoscopy is performed to exclude or diagnose endometriosis. However, the response to hormonal treatment does not always predict the presence or absence of endometriosis (Ling, 1999; Jenkins *et al.*, 2008). Finally, it has been argued that starting hormonal contraceptives in young girls because of primary dysmenorrhoea could be indicative of the diagnosis of deep endometriosis in later life (Chapron *et al.*, 2011). It is clearly a paradox that by recommending empirical treatment in symptomatic (young) women one might induce the above mentioned delay in diagnosing the disease.

The GDG recommends clinicians to counsel women with symptoms presumed to be due to endometriosis thoroughly, and to empirically treat them with adequate analgesia, combined hormonal contraceptives or progestagens.	GPP

Are hormonal therapies effective for painful symptoms associated with endometriosis?

Currently, hormonal contraceptives, progestagens and anti-progestagens, GnRH agonists and antagonists and aromatase inhibitors are in clinical use. With no overwhelming evidence to support particular treatments over others, it is important that the decisions involved in any treatment plan are individual, and that a woman is able to make these based on an informed choice and a good understanding of what is happening to her body.

Clinicians are recommended to prescribe hormonal treatment [hormonal contraceptives (Level B), progestagens (Level A), anti-progestagens (Level A), or GnRH agonists (Level A)] as one of the options, as it reduces endometriosis-associated pain (Vercellini *et al.*, 1993; Brown *et al.*, 2010, 2012).	A–B
The GDG recommends that clinicians take patient preferences, side effects, efficacy, costs and availability into consideration when choosing hormonal treatment for endometriosis-associated pain.	GPP

Hormonal contraceptives. Hormonal contraceptives were shown to be effective in treating pain in women with endometriosis, as discussed in a Cochrane review, which is based on only one small study (Vercellini *et al.*, 1993; Davis *et al.*, 2007). Other studies compared different regimens and routes of administration for hormonal contraceptives (Vercellini *et al.*, 2003, 2010a,b). Despite limited evidence of effectiveness, hormonal contraceptives are widely used as treatment for pain in women with endometriosis, which could be due to some practical

advantages, including contraceptive protection, long-term safety and control of menstrual cycle.

Clinicians can consider prescribing a combined hormonal contraceptive, as it reduces endometriosis-associated dyspareunia, dysmenorrhoea and non-menstrual pain (Vercellini *et al.*, 1993).	B
Clinicians may consider the continuous use of a combined oral contraceptive pill in women suffering from endometriosis-associated dysmenorrhoea (Vercellini *et al.*, 2003).	C
Clinicians may consider the use of a vaginal contraceptive ring or a transdermal (oestrogen/progestin) patch to reduce endometriosis-associated dysmenorrhoea, dyspareunia and chronic pelvic pain (Vercellini *et al.*, 2010a,b).	C

Progestagens and anti-progestagens.

Clinicians are recommended to use progestagens [medroxyprogesterone acetate (oral or depot), dienogest, cyproterone acetate, norethisterone acetate or danazol] or anti-progestagens (gestrinone) as one of the options, to reduce endometriosis-associated pain (Brown *et al.*, 2012).	A
The GDG recommends that clinicians take the different side-effect profiles of progestagens and anti-progestagens into account when prescribing these drugs, especially irreversible side effects (e.g. thrombosis and androgenic side effects).	GPP
Clinicians can consider prescribing a levonorgestrel-releasing intrauterine system (LNG-IUS) as one of the options to reduce endometriosis-associated pain (Petta *et al.*, 2005; Gomes *et al.*, 2007; Ferreira *et al.*, 2010).	B

GnRH agonists. GnRH agonists, with and without add-back therapy, are effective in the relief of endometriosis-associated pain, but can be associated with severe side effects, which should be discussed with the woman when offering treatment. No evidence exists on the effectiveness of GnRH antagonists for endometriosis-associated pain (Brown *et al.*, 2010).

Clinicians are recommended to use GnRH agonists (nafarelin, leuprolide, buserelin, goserelin or triptorelin), as one of the options for reducing endometriosis-associated pain, although evidence is limited regarding dosage or duration of treatment (Brown *et al.*, 2010).	A
Clinicians are recommended to prescribe hormonal add-back therapy to coincide with the start of GnRH agonist therapy, to prevent bone loss and hypoestrogenic symptoms during treatment. This is not known to reduce the effect of treatment on pain relief (Makarainen *et al.*, 1996; Bergqvist *et al.*, 1997; Taskin *et al.*, 1997; Moghissi *et al.*, 1998).	A
The GDG recommends clinicians to give careful consideration to the use of GnRH agonists in young women and adolescents, since these women may not have reached maximum bone density.	GPP

Aromatase inhibitors.

In women with pain from rectovaginal endometriosis, refractory to other medical or surgical treatment, clinicians can consider prescribing aromatase inhibitors in combination with oral contraceptive pills, progestagens or GnRH analogues, as they reduce endometriosis-associated pain (Nawathe *et al.*, 2008; Ferrero *et al.*, 2011).	B

Due to the severe side effects, aromatase inhibitors should only be prescribed to women after all other options for medical or surgical treatment are exhausted.

Are analgesics effective for symptomatic relief of pain associated with endometriosis?

There is virtually no evidence on the use of non-steroidal anti-inflammatory drugs (NSAIDs) for endometriosis, except from one study published in 1985 and one study on the cyclo-oxygenase 2 inhibitor rofecoxib, that has been withdrawn from the market in many countries due to severe side effects (Allen *et al.*, 2009). However, NSAIDs have a favourable effect on primary dysmenorrhoea and are widely used as a first-line treatment of endometriosis-associated pain (Marjoribanks *et al.*, 2010).

The GDG recommends that clinicians should consider NSAIDs or other analgesics to reduce endometriosis-associated pain.	GPP

When prescribing NSAIDs, clinicians should discuss the side effects associated with frequent use, including inhibition of ovulation, risk of gastric ulceration and cardiovascular disease, with the patient.

Is surgery effective for painful symptoms associated with endometriosis?

When endometriosis is identified at laparoscopy, clinicians are recommended to surgically treat endometriosis, as this is effective for reducing endometriosis-associated pain, i.e. 'see and treat' (Jacobson *et al.*, 2009).	A

Laparotomy and laparoscopy are equally effective in the treatment of endometriosis-associated pain, but laparoscopic surgery is usually associated with less pain, shorter hospital stay and quicker recovery as well as better cosmetic outcome, hence it is usually preferred to open surgery.

Clinicians may consider both ablation and excision of peritoneal endometriosis to reduce endometriosis-associated pain (Wright *et al.*, 2005; Healey *et al.*, 2010).	C

Excision of lesions could be preferential with regard to the possibility of retrieving samples for histology. Furthermore, ablative techniques are unlikely to be suitable for advanced forms of endometriosis.

When performing surgery in women with ovarian endometrioma, clinicians should perform cystectomy instead of drainage and coagulation, as cystectomy reduces endometriosis-associated pain (Hart *et al.*, 2008).	A
Clinicians can consider performing cystectomy rather than CO_2 laser vaporization in women with ovarian endometrioma, because of a lower recurrence rate of the endometrioma (Carmona *et al.*, 2011).	B

Surgery for deep endometriosis appears possible and effective but is associated with significant complication rates, particularly when bowel surgery is required. The reported total intraoperative complication rate is 2.1% and total post-operative complication rate is 13.9% (9.5% minor, 4.6% major complications) (Kondo *et al.*, 2011). There is an ongoing debate about the indication for shaving nodules as opposed to

segmental resection (Donnez and Squifflet, 2010; Meuleman *et al.*, 2011a,b).

Clinicians can consider performing surgical removal of deep endometriosis, as it reduces endometriosis-associated pain and improves quality of life (De Cicco *et al.*, 2011; Meuleman *et al.*, 2011a, b).	B
The GDG recommends that clinicians refer women with suspected or diagnosed deep endometriosis to a centre of expertise that offers all available treatments in a multidisciplinary context.	GPP

Hysterectomy.

The GDG recommends that clinicians consider hysterectomy with removal of the ovaries and all visible endometriosis lesions in women who have completed their family and failed to respond to more conservative treatments. Women should be informed that hysterectomy will not necessarily cure the symptoms or the disease.	GPP

Surgical interruption of pelvic nerve pathways.

Clinicians should not perform laparoscopic uterosacral nerve ablation (LUNA) as an additional procedure to conservative surgery to reduce endometriosis-associated pain (Proctor *et al.*, 2005).	A
Clinicians should be aware that presacral neurectomy (PSN) is effective as an additional procedure to conservative surgery to reduce endometriosis-associated midline pain, but it requires a high degree of skill and is a potentially hazardous procedure (Proctor *et al.*, 2005).	A

Adhesion prevention after endometriosis surgery.

Clinicians can use oxidized regenerated cellulose during operative laparoscopy for endometriosis, as it prevents adhesion formation (Ahmad *et al.*, 2008).	B
It is not reasonable for clinicians to use icodextrin after operative laparoscopy for endometriosis to prevent adhesion formation, as no benefit has been shown (Brown *et al.*, 2007; Trew *et al.*, 2011).	B
The GDG recommends that clinicians should be aware that other anti-adhesion agents (polytetrafluoroethylene surgical membrane, hyaluronic acid products) have been studied and proven effective for adhesion prevention in the context of pelvic surgery, although not specifically in women with endometriosis.	GPP

Are preoperative hormonal therapies effective for treatment of pain?

Clinicians should not prescribe preoperative hormonal treatment to improve the outcome of surgery for pain in women with endometriosis (Furness *et al.*, 2004).	A

Are short-term post-operative hormonal therapies effective for treatment of pain?

The GDG recommends that clinicians clearly distinguish adjunctive short-term (<6 months) hormonal treatment after surgery from long-term (>6 months) hormonal treatment; the latter is aimed at secondary prevention.	GPP

Based on the current evidence, the GDG concluded that there is no proven benefit of post-operative hormonal therapy (within 6 months after surgery), if this treatment is prescribed with the sole aim of improving the outcome of surgery (Furness *et al.*, 2004). However, there is also no proven harm of prescribing hormonal therapy after surgery; hence some forms of post-operative hormonal therapy could be prescribed for other indications, as contraception or secondary prevention.

Clinicians should not prescribe adjunctive hormonal treatment in women with endometriosis for endometriosis-associated pain after surgery, as it does not improve the outcome of surgery for pain (Furness *et al.*, 2004).	A

Is there a role for secondary prevention of disease and painful symptoms in women treated for endometriosis?

Secondary prevention is defined as interventions to prevent the recurrence of pain symptoms or the recurrence of disease in the long-term, defined as more than 6 months after surgery.

The GDG states that there is a role for prevention of recurrence of disease and painful symptoms in women surgically treated for endometriosis. The choice of intervention depends on patient preferences, costs, availability and side effects. For many interventions that might be considered here, there are limited data.	GPP
In women operated on for an endometrioma (≥3 cm), clinicians should perform ovarian cystectomy, instead of drainage and electrocoagulation, for the secondary prevention of endometriosis-associated dysmenorrhoea, dyspareunia and non-menstrual pelvic pain (Hart *et al.*, 2008).	A
After cystectomy for ovarian endometrioma in women not immediately seeking conception, clinicians are recommended to prescribe combined hormonal contraceptives for the secondary prevention of endometrioma (Vercellini *et al.*, 2010a, b).	A
In women operated on for endometriosis, clinicians are recommended to prescribe post-operative use of a LNG-IUS or a combined hormonal contraceptive for at least 18–24 months, as one of the options for the secondary prevention of endometriosis-associated dysmenorrhoea, but not for non-menstrual pelvic pain or dyspareunia (Abou-Setta *et al.*, 2006; Seracchioli *et al.*, 2009).	A

Extragenital endometriosis

Extragenital endometriosis can affect different tissues and body parts outside the genital tract. Pain is the most common presenting symptom, although a wide range of symptoms can manifest. The evidence of the results of the different options to treat extragenital endometriosis is limited and mainly published in case reports resulting in Level D recommendations.

Clinicians may consider surgical removal of symptomatic extragenital endometriosis, when possible, to relieve symptoms (Liang *et al.*, 1996; Marinis *et al.*, 2006; Nisolle *et al.*, 2007; Nissotakis *et al.*, 2010; Nezhat *et al.*, 2011; Song *et al.*, 2011).	D

When surgical treatment is difficult or impossible, clinicians may consider medical treatment of extragenital endometriosis to relieve symptoms (Bergqvist, 1992; Joseph and Sahn, 1996; Jubanyik and Comite, 1997). D

What other pain management strategies are effective for symptomatic relief of pain associated with endometriosis?

The GDG has retrieved and evaluated existing evidence on complementary and alternative treatment options for pain in women with endometriosis, and concluded that the effectiveness of high-frequency transcutaneous electrical nerve stimulation, dietary supplements, acupuncture and traditional Chinese medicine are not well established for pain management in endometriosis (Astin *et al.*, 1998; Eisenberg *et al.*, 1998; Proctor *et al.*, 2002; Sesti *et al.*, 2007; Flower *et al.*, 2009; Zhu *et al.*, 2011).

The GPP below should be considered in light of the methodological restriction to papers written in English and of the inherent difference between the holistic Chinese approach and the scientific approach of the Western world.

The GDG does not recommend the use of nutritional supplements, complementary or alternative medicine in the treatment of endometriosis-associated pain, because the potential benefits and/or harms are unclear. However, the GDG acknowledges that some women who seek complementary and alternative medicine may feel benefit from this. GPP

Treatment of endometriosis-associated infertility

Women with endometriosis are often confronted with infertility. For the literature searches, the outcomes included were live birth rate, pregnancy, multiple pregnancy rates, miscarriage rates, ectopic pregnancy, teratogenicity and side effects of treatment. It should be noted that although live birth rate is the most relevant outcome to be assessed, most studies only report on (biochemical or clinical) pregnancy rates. An increase in pregnancy rate could be an indication of, but does not necessarily translate to, an increase in live birth rate.

Are hormonal therapies effective for infertility associated with endometriosis?

Suppression of ovarian function (by means of hormonal contraceptives, progestagens, GnRH analogues or danazol) to improve fertility in minimal to mild endometriosis is not effective and should not be offered for this indication alone. The published evidence does not comment on more severe disease (Hughes *et al.*, 2007).

In infertile women with endometriosis, clinicians should not prescribe hormonal treatment for suppression of ovarian function to improve fertility (Hughes *et al.*, 2007). A

Is surgery effective for infertility associated with endometriosis?

In women with minimal to mild endometriosis, the evidence, summarised in a Cochrane review, shows that operative laparoscopy is more effective than diagnostic laparoscopy in improving ongoing pregnancy rates. The comparative effectiveness of different surgical techniques is less well studied (Nowroozi *et al.*, 1987; Chang *et al.*, 1997; Jacobson *et al.*, 2010).

In infertile women with AFS/ASRM Stage I/II endometriosis, clinicians should perform operative laparoscopy (excision or ablation of the endometriosis lesions) including adhesiolysis, rather than performing diagnostic laparoscopy only, to increase ongoing pregnancy rates (Nowroozi *et al.*, 1987; Jacobson *et al.*, 2010). A

In infertile women with AFS/ASRM Stage I/II endometriosis, clinicians may consider CO_2 laser vaporization of endometriosis, instead of monopolar electrocoagulation, since laser vaporization is associated with higher cumulative spontaneous pregnancy rates (Chang *et al.*, 1997). C

In women with ovarian endometrioma receiving surgery for infertility or pain, excision of endometrioma capsule increases the spontaneous post-operative pregnancy rate when compared with drainage and electrocoagulation of the endometrioma wall (Hart *et al.*, 2008).

In infertile women with ovarian endometrioma undergoing surgery, clinicians should perform excision of the endometrioma capsule, instead of drainage and electrocoagulation of the endometrioma wall, to increase spontaneous pregnancy rates (Hart *et al.*, 2008). A

The GDG recommends that clinicians counsel women with endometrioma regarding the risks of reduced ovarian function after surgery and the possible loss of the ovary. The decision to proceed with surgery should be considered carefully if the woman has had previous ovarian surgery. GPP

In women with moderate to severe endometriosis, there are no controlled studies comparing reproductive outcome after surgery and after expectant management. Two high quality prospective cohort studies showed crude spontaneous pregnancy rates of 57–69% (moderate endometriosis) and 52–68% (severe endometriosis) after laparoscopic surgery, which are much higher than the crude pregnancy rates of 33% (moderate) and 0% (severe) after expectant management, reported in a third prospective cohort study (Olive *et al.*, 1985; Nezhat *et al.*, 1989; Vercellini *et al.*, 2006).

In infertile women with AFS/ASRM Stage III/IV endometriosis, clinicians can consider operative laparoscopy, instead of expectant management, to increase spontaneous pregnancy rates (Nezhat *et al.*, 1989; Vercellini *et al.*, 2006). B

Are hormonal therapies effective as an adjunct to surgical therapy for treatment of infertility?

In infertile women with endometriosis, the GDG recommends clinicians not to prescribe adjunctive hormonal treatment before surgery to improve spontaneous pregnancy rates, as suitable evidence is lacking. GPP

It is important to realize that clinicians should not withhold hormonal treatment for pain from symptomatic women in the waiting period before undergoing surgery or medically assisted reproduction (MAR).

In infertile women with endometriosis, clinicians should not prescribe adjunctive hormonal treatment after surgery to improve spontaneous pregnancy rates (Furness *et al.*, 2004). A

What other management strategies are effective for infertility associated with endometriosis?

No evidence was found showing a beneficial effect of different types of nutritional supplements, complementary and alternative treatments

for improving infertility in women with endometriosis (Gerhard and Postneek, 1992; Harris and Rees, 2000; Xu et al., 2003; Agarwal et al., 2005; Burks-Wicks et al., 2005; Chan, 2008; Wurn et al., 2008; Zhou and Qu, 2009).

The GDG does not recommend the use of nutritional supplements, complementary or alternative medicine in the treatment of endometriosis-associated infertility, because the potential benefits and/or harms are unclear. However, the GDG acknowledges that some women who seek complementary and alternative medicine may feel benefit from this.	GPP

MAR in women with endometriosis

The World Health Organization ICMART (International Committee for Monitoring Assisted Reproductive Technology) definitions are used for the terms MAR and assisted reproduction technology (ART) (Zegers-Hochschild et al., 2009).

Is MAR effective for infertility associated with endometriosis?

Intrauterine insemination. In a RCT, the live birth rate was found to be 5.6 times higher (95% confidence interval (CI) 1.18–17.4) in couples with minimal to mild endometriosis after controlled ovarian stimulation with gonadotrophins and IUIcompared with couples after expectant management (Tummon et al., 1997). A longitudinal study showed a 5.1 times higher pregnancy rate (95% CI 1.1–22.5) in couples receiving Intrauterine insemination (IUI) after controlled ovarian stimulation with gonadotrophins compared with IUI alone. (Nulsen et al., 1993).

In infertile women with AFS/ASRM Stage I/II endometriosis, clinicians may perform IUI with controlled ovarian stimulation,	C
instead of expectant management, as it increases live birth rates (Tummon et al., 1997).	
instead of IUI alone, as it increases pregnancy rates (Nulsen et al., 1993).	
In infertile women with AFS/ASRM Stage I/II endometriosis, clinicians may consider performing IUI with controlled ovarian stimulation within 6 months after surgical treatment, since pregnancy rates are similar to those achieved in unexplained infertility (Werbrouck et al., 2006).	C

ART. The influence of endometriosis on the success rate of IVF/ICSI is not unequivocal. The pregnancy rates after IVF/ICSI were reported to be lower in patients with Stage III and IV endometriosis as compared with those with tubal factor (Barnhart et al., 2002). It has to be noted however, that some large databases show that endometriosis does not adversely affect pregnancy rates [e.g. the Society for Assisted Reproductive Technology (SART) and the Human Fertilisation and Embryology Authority (HFEA)]. GnRH antagonist protocol may be not inferior to GnRH agonist protocol in women with minimal to mild endometriosis and endometrioma (Pabuccu et al., 2007).

The GDG recommends the use of ART for infertility associated with endometriosis, especially if tubal function is compromised or if there is male factor infertility, and/or other treatments have failed.	GPP
In infertile women with endometriosis, clinicians may offer treatment with ART after surgery, since cumulative endometriosis recurrence rates are not increased after controlled ovarian stimulation for IVF/ICSI (D'Hooghe et al., 2006; Benaglia et al., 2010; Coccia et al., 2010; Benaglia et al., 2011).	C
In women with endometriomas, clinicians may use antibiotic prophylaxis at the time of oocyte retrieval, although the risk of ovarian abscess following follicle aspiration is low (Benaglia et al., 2008).	D

Are medical therapies effective as an adjunct to treatment with ART for endometriosis-associated infertility?

In a Cochrane review on the effect of hormonal treatment prior to MAR, the authors conclude that down-regulation for 3–6 months with a GnRH agonist in women with endometriosis increases the odds of clinical pregnancy by >4-fold (Sallam et al., 2006). Potential adverse effects of the intervention (miscarriage rates, multiple pregnancy rates or ectopic pregnancy rates) were not addressed in the included studies.

Clinicians can prescribe GnRH agonists for a period of 3–6 months prior to treatment with ART to improve clinical pregnancy rates in infertile women with endometriosis (Sallam et al., 2006).	B

Should surgery be performed prior to treatment with ART to improve reproductive outcomes?

One retrospective cohort study compared reproductive outcomes in a group of women with minimal to mild endometriosis in whom all visible endometriosis was completely removed using laparoscopy prior to ART to women undergoing diagnostic laparoscopy only and found a significantly higher implantation rate, pregnancy rate and live birth rate in the treated group (Opoien et al., 2011). However, this does not imply that a laparascopy should be performed prior to ART in all women with the only aim to diagnose and subsequently treat peritoneal endometriosis in order to improve the result of the ART treatment.

In infertile women with AFS/ASRM Stage I/II endometriosis undergoing laparoscopy prior to treatment with ART, clinicians may consider the complete surgical removal of endometriosis to improve live birth rate, although the benefit is not well established (Opoien et al., 2011).	C

Several studies have evaluated the usefulness of cystectomy prior to ART to improve reproductive outcome in women with ovarian endometrioma, but there is limited consistency in the interpretation of the results (Donnez et al., 2001; Hart et al., 2008; Benschop et al., 2010). Based on no difference in pregnancy rate, some authors advise cystectomy, whereas others advise caution with surgery because of the possible harmful effect on ovarian reserve.

In infertile women with endometrioma larger than 3 cm there is no evidence that cystectomy prior to treatment with ART improves pregnancy rates (Donnez et al., 2001; Hart et al., 2008; Benschop et al., 2010).	A
In women with endometrioma larger than 3 cm, the GDG recommends clinicians only to consider cystectomy prior to ART to improve endometriosis-associated pain or the accessibility of follicles.	GPP
The GDG recommends that clinicians counsel women with endometrioma regarding the risks of reduced ovarian function after surgery and the possible loss of the ovary. The decision to proceed with surgery should be considered carefully if the woman has had previous ovarian surgery.	GPP

For infertile women with deep endometriosis, we found no evidence to recommend performing surgical excision of deep nodular lesions prior to ART to improve reproductive outcomes (Bianchi et al., 2009; Papaleo

et al., 2011). However, these women often suffer from pain, requesting surgical treatment.

The effectiveness of surgical excision of deep nodular lesions before treatment with ART in women with endometriosis-associated infertility is not well established with regard to reproductive outcome (Bianchi et al., 2009; Papaleo et al., 2011).	C

Menopause in women with endometriosis

How should menopausal symptoms be treated in women with a history of endometriosis?

Although it is not possible to rule out the possibility that hormone replacement therapy could result in pain and/or disease recurrence in women with endometriosis, there is no evidence that supports depriving severely symptomatic women of this treatment to relieve their menopausal symptoms (Al Kadri et al., 2009).

In women with surgically induced menopause because of endometriosis, oestrogen/progestagen therapy or tibolone can be effective for the treatment of menopausal symptoms (Al Kadri et al., 2009).	B
The GDG recommends that in post-menopausal women after hysterectomy and with a history of endometriosis, clinicians should avoid unopposed oestrogen treatment. However, the theoretical benefit of avoiding disease reactivation and malignant transformation of residual disease should be balanced against the increased systemic risks associated with combined oestrogen/progestagen or tibolone.	GPP
The GDG recommends that clinicians continue to treat women with a history of endometriosis after surgical menopause with combined oestrogen/progestagen or tibolone at least up to the age of natural menopause.	GPP

Asymptomatic endometriosis

Asymptomatic endometriosis is defined as the incidental finding of peritoneal, ovarian or deep endometriosis without pelvic pain and/or infertility. The true prevalence of asymptomatic endometriosis is not known but between 3 and 45% of women undergoing laparoscopic sterilization has been diagnosed with endometriosis (Rawson, 1991; Gylfason et al., 2010).

Is surgery beneficial for incidental finding of asymptomatic endometriosis at time of surgery?

No clinical trials have been performed to assess whether surgery is beneficial for an incidental finding at the time of surgery. Furthermore, a follow-up study concluded that there is little risk that asymptomatic, minimal endometriosis found incidentally will become symptomatic (Moen and Stokstad, 2002). Hence, surgical excision or ablation (and its inherent risks of damage to the bowel, bladder, ureter and blood vessels) for an incidental finding of asymptomatic endometriosis cannot be endorsed.

The GDG recommends that clinicians should not routinely perform surgical excision and ablation for an incidental finding of asymptomatic endometriosis at the time of surgery, since the natural course of the disease is not clear.	GPP
The GDG recommends that clinicians fully inform and counsel women about any incidental finding of endometriosis.	GPP

Primary prevention of endometriosis

Is there a role for primary prevention of endometriosis?

Primary prevention is aimed at protecting healthy, asymptomatic women from developing endometriosis. From a broad literature search on endometriosis and primary prevention, but also on factors associated with the occurrence, prevalence and development of endometriosis, we only found evidence on oral contraceptives and physical exercise for primary prevention.

The usefulness of oral contraceptives for the primary prevention of endometriosis is uncertain (Vercellini et al., 2011).	C
The usefulness of physical exercise for the primary prevention of endometriosis is uncertain (Vitonis et al., 2010).	C

Endometriosis and cancer

What information could be provided to women with endometriosis regarding the development of cancer?

The GDG recommends that clinicians inform women with endometriosis requesting information on their risk of developing cancer that: there is no evidence that endometriosis causes cancer, there is no increase in overall incidence of cancer in women with endometriosis, some cancers (ovarian cancer and non-Hodgkin's lymphoma) are slightly more common in women with endometriosis.	GPP
The GDG recommends that clinicians explain the incidence of some cancers in women with endometriosis in absolute numbers.	GPP
The GDG recommends no change in the current overall management of endometriosis in relation to malignancies, since there are no clinical data on how to lower the slightly increased risk of ovarian cancer or non-Hodgkin's lymphoma in women with endometriosis.	GPP

Conclusion

This guideline on the management of women with endometriosis is the first guideline written using the structured methodology as described in the *Manual for ESHRE Guideline Development* (2009), including an objective and systematic assessment of the literature and an extensive and transparent review by relevant stakeholders. A strong point is that the Guideline was refereed by many clinicians and patient organizations. Not less than 484 comments were received of which 255 indeed in some way changed the content of the Guideline. The first and foremost goal of the guideline is to provide guidance to clinicians who care for women with endometriosis. The objective was to improve on the diagnosis and treatment of endometriosis based on the available literature and, if not present, based on the opinion of members of the GDG. Care was taken to involve women with endometriosis by explicitly asking patient organizations to come up with unsolved problems that were felt to be important. One of the most striking experiences in writing this guideline was the notion that so many key questions could either not be answered or that only little or low quality data were available. Indeed, many issues could not be resolved based on the available literature. Of the 83 recommendations, almost half (32) could only be formulated as a GPP due to lack of robust data.

As a consequence, the lack of clear-cut evidence leads to many research questions. We propose that future research on clinical aspects of endometriosis should include at least: (i) The effectiveness of surgical excision of AFS/ASRM Stage III–IV endometriosis in the treatment of infertility in comparison to direct referral to ART, (ii) the diagnostic value of laparoscopy with or without histological verification, (iii) the best way of secondary prevention of endometriosis, (iv) the best management, with respect to both reproductive outcome and pain, of ovarian endometrioma and of deep endometriosis in women with an active child wish, (v) the use of biomarkers for diagnosis and disease monitoring in endometriosis, (vi) the benefit of anti-adhesion agents in surgery for endometriosis-associated pain, (vii) the clinical management of endometriosis in adolescents, (viii) the psychosocial impact of endometriosis and how this should be addressed: patient-centred care, couple-centred interventions, interventions to improve quality of life, (ix) the definition of the prerequisites of centres of expertise in the management of endometriosis, and finally, (x) the achievement of an earlier diagnosis of the disease, by raising the awareness amongst primary care specialists, gastroenterologists and internal medicine specialists.

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Authors' roles

G.D. chaired the GDG and hence fulfilled a leading role in collecting the evidence, writing the manuscript and dealing with reviewer comments. N.V., as methodological expert, performed all literature searches for the guideline, provided methodological support and was overall coordinator of the guideline production. In an earlier stage, A.P. had an important role in scoping the guideline and writing key questions, W.N. had a role as methodological expert and ESHRE Guideline Program coordinator. All other authors, listed in alphabetical order, as guideline group members, contributed equally to the manuscript, by drafting key questions, synthesizing evidence, writing the different parts of the guideline and discussing recommendations until consensus within the group was reached.

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Conflict of interest

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