The ESHRE Guideline on Endometriosis 2008

Notes on this file

This pdf contains the text of the complete ESHRE guideline on Endometriosis. Each section will be presented as the concise guideline followed by the supporting documentation – consequently some text will appear duplicated. This year not every section of the guideline required updating and indeed those updated sections my only have limited changes. Any section which has been updated will appear as highlighted text whilst any ne w section will appear highlighted in this colour. At the end of each of these sections new references will be provided in full. References already quoted in previous versions of the guideline will not appear and those wishing access to them should locate them through the current version of the guideline. We hope that providing the updated guideline in this format will allow the reader to easily identify modified and new sections thus allowing them to focus on changes.

Andrew Prentice September 2008

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 conditions. Some women, however, have no symptoms at all.

Treatment must be individualised, taking the clinical problem in its entirety into account, including the impact of the disease and the effect of its treatment on quality of life.

Pain symptoms may persist despite seemingly adequate medical and/or surgical treatment of the disease. 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 using standard methodology. Thus, the Cochrane

Library and the Cochrane Register of Controlled Trials were searched for relevant RCTs, systematic reviews and meta-analyses as well as MEDLINE and PUBMED (electronic databases) from 1966 - February 2007. In addition, the following sources were used:

- Clinical Evidence - the monthly, updated directory of evidence on the effects of clinical interventions, published by the BMJ Publishing Group (UK).
- NICE Guideline on the assessment and treatment for people with fertility problems, produced by the National Institute for Health and Clinical Excellence.
- Green Top Guideline on the investigation and management of endometriosis, produced by the Royal College of Obstetricians & Gynaecologists.
- Guideline on the diagnosis and treatment of endometriosis, produced by the Dutch Society of Obstetrics and Gynaecology.
- 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 below:

Hierarchy of evidence

Level	Evidence
1a	Systematic review and meta-analysis of randomised controlled trials (RCTs)
1b	At least one RCT
2a	At least one well-designed controlled study without randomisation
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

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 below. Regarding diagnostic tests specifically, a recommendation based on the existence of a well-conducted systematic review was assessed as Grade A.

Some recommendations were extrapolated from strong evidence relating to the management of dysmenorrhoea in women without confirmed endometriosis.

Grades of recommendations

A	Requires at least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation. (Evidence levels 1a, 1b).
B	Requires the availability of well controlled clinical studies but no randomised clinical trials on the topic of recommendations. (Evidence levels 2a, 2b, 3).
C	Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates and absence of directly applicable clinical studies of good quality. (Evidence level 4).
GPP	Recommended best practice based on the clinical experience of the guideline development group.

The only change in this section is that they were transposed in the previous published version of the guideline

Localisation and appearance of endometriosis

Concise

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 puckered lesions, nodules or small cysts containing old haemorrhage surrounded by a variable extent of fibrosis. Atypical or "subtle" lesions are also common, including red implants (petechial, vesicular, polypoid, hemorrhagic, red flame-like) and serous or clear vesicles. Other appearances include white plaques or scarring and yellow-brown peritoneal discoloration of the peritoneum.

Endometriomas usually contain thick fluid like 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 more than 5 mm beneath the peritoneum and may involve the uterosacral ligaments, vagina, bowel, bladder or ureters.

Supporting

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Symptoms and Clinical Signs

Concise

Establishing the diagnosis of endometriosis on the basis of symptoms alone can be difficult because the presentation is so variable and there is considerable overlap with other conditions such as irritable bowel syndrome and pelvic inflammatory disease. As a result there is often a delay of up to 12 years between symptom onset and a definitive diagnosis (Arruda et al., 2003; Hadfield et al., 1996; 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;
- 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 utero-sacral ligaments or enlarged ovaries on examination is suggestive of endometriosis. The diagnosis is more certain if deeply infiltrating nodules are found on the utero-sacral 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.

B	Deeply infiltrating nodules are most reliably detected when clinical examination is performed during menstruation (Koninckx et al., 1996).	Evidence Level 3

Supporting

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 (Arruda et al., 2003; Hadfield et al., 1996; Husby et al., 2003).

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- infertility;
- 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.

A large group of women with endometriosis is completely asymptomatic. In these women endometriosis remains undiagnosed or is diagnosed at laparoscopy for another indication. A subset of women with more advanced disease, ovarian or deep invasive rectovaginal endometriosis, is asymptomatic as well. This makes the development of guidelines for *the* diagnosis and *the* therapy rather cumbersome. Endometriosis should be suspected in women with dysmenorrhoea, deep dyspareunia, acyclic chronic pelvic pain and/or subfertility.

Pain

In adult women, dysmenorrhoea may be especially suggestive of endometriosis if it begins after years of pain-free menses. The dysmenorrhoea often starts before the onset of menstrual bleeding and continues throughout the menstrual period. In adolescents, the pain may be present without an interval of pain-free menses after menarche. The distribution of pain is variable but most often is bilateral. In addition, pain can evolve to become chronic. Depending on the type and localisation of endometriosis, pain can radiate to the upper leg (ovarian), to the perineum (rectum), or the back (uterosacral ligaments). However, deeply infiltrating subperitoneal endometriosis is associated with severe pelvic pain and dyspareunia (Chapron et al., 2003a; Koninckx et al., 1991; Porpora et al., 1999).
The types of pelvic pain are related to the anatomical location of deeply infiltrating endometriotic lesions (Fauconnier et al. 2002).
Possible mechanisms causing pain in patients with endometriosis include local peritoneal inflammation, deep infiltration with tissue damage, adhesion formation, fibrotic thickening, and collection of shed menstrual blood in endometriotic implants, resulting in painful traction with the physiological movement of tissues (Cornillie et al., 1990; Barlow and Glynn, 1993). In rectovaginal endometriotic nodules, a close histological relationship has been observed between nerves and endometriotic foci, and between nerves and the fibrotic component of the nodule (Anaf et al., 2000b).

Chronic disease

For many women, endometriosis becomes a chronic disease affecting quality of life due to incapacitating pain, emotional impact of subfertility, anger about disease recurrence, and uncertainty about the future regarding repeated surgeries or long term medical therapies and their side-effects. Therefore, there is a need to look at endometriosis, at least in a subset of highly symptomatic women, as a chronic disease. Quality of life issues should therefore be addressed (Colwell et al., 1998; Jones et al., 2001).

Subfertility

There is an association between the presence of endometriosis and subfertility. When endometriosis is moderate or severe (ASRM, 1997), it usually involves the ovaries and results in adnexal adhesions that by reducing tubo-ovarian motility impede pick-up function. In this situation, there is likely to be a causal relationship between endometriosis and subfertility. When endometriosis is minimal to mild, a causal relationship is controversial. An increased prevalence of endometriosis in subfertile women when compared to the prevalence in women of proven fertility has been shown (D'Hooghe et al., 2003a). A reduced monthly fecundity rate and cumulative pregnancy rate after donor as well as husband sperm insemination in women with minimal-mild endometriosis when compared to those with a normal pelvis has been shown (Hughes, 1997; Omland et al., 1998; Nuojua-Huttunen et al., 1999). An increased monthly fecundity rate and cumulative pregnancy rate after surgical removal of minimal to mild endometriosis has been shown in a multicentre randomized trial (Marcoux et al., 1997). A negative correlation between the RAFS stage of endometriosis and the cumulative pregnancy rate after surgery has also been found (Adamson et al., 1993; Guzick et al., 1997; Osuga et al., 2002).

Based on controlled prospective studies, there is no evidence that endometriosis is associated with (recurrent) pregnancy loss (Vercammen and D'Hooghe, 2000) or that medical or surgical treatment of endometriosis reduces the spontaneous miscarriage rate (Marcoux et al., 1997; Parazzini, 1999).

Other non-gynaecological symptoms

Rectal bleeding and haematuria during menstruation may occur in women with infiltrating rectosigmoidal and bladder endometriosis, respectively. Women of reproductive age with endometriosis may experience fatigue/exhaustion, abdominal bloating, diarrhoea/painful bowel movements with menstruation, pain during or after sex, heavy or irregular bleeding, nausea/stomach upsets with menstruation, dizziness/headaches with menstruation, low resistance to infection, and some allergies (Sinaii et al., 2002).

Clinical signs

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B	Deeply infiltrating nodules are most reliably detected when clinical examination is performed during menstruation (Koninckx et al., 1996).	Evidence Level 3

Diagnosis

Concise

B	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

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 three months of hormonal treatment so as to avoid under-diagnosis (Evers, 1987).

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 (> 4 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.

Supporting documentation

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Microscopically, endometriotic implants consist of endometrial glands and stoma with or without haemosiderin-laden macrophages. The value of histological confirmation of the laparoscopic view for the diagnosis of endometriosis has to be further evaluated. In some studies the confirmation rate from biopsies of endometriotic lesions with a "typical" appearance has been low (Moen et al., 1992; Walter et al., 2001). This might occur because endometriotic lesions are often either extremely small or consist mainly of fibrotic tissue; because biopsies taken with forceps may miss microscopic endometriotic glands and sparse stroma hidden in fibrosis or other surrounding tissues. Thus, a biopsy might be negative because of the surgeon's limited experience, the size of the biopsy, the experience of the pathologist, the quality of the histological sample

Investigations

Concise

Ultrasound

A	Compared to laparoscopy, trans-vaginal 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

At present, there is insufficient evidence to indicate that magnetic resonance imaging (MRI) is a useful test to diagnose or exclude endometriosis compared to laparoscopy.

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 (trans-rectal and/or trans-vaginal and/or renal), with or without 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 use an instrument such as a grasper, via a secondary port, to mobilise the pelvic organs and to palpate lesions which can help determine their nodularity. It is also important to document in detail the type, location and extent of all lesions and adhesions in the operative notes; ideal practice is to record the findngs 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 three months of hormonal treatment so as to avoid under-diagnosis.

B	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

B	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

Supporting

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	involving the bladder or rectum.	

In a systematic review of the value of TVS as a diagnostic tool in endometriosis, only seven out of the 49 papers identified fulfilled the inclusion criteria (Moore et al., 2002). The positive likelihood ratios ranged from 7.6 - 29.8, and the negative likelihood ratios ranged from 0.12 - 0.4. Confidence intervals were wide. One paper addressed the use of conventional colour Doppler with ultrasound: the positive likelihood ratio was 1.2, with a negative likelihood ratio of 0.4 (Alcázar et al., 1997). One paper assessed the use of colour Doppler energy imaging, and showed a positive likelihood ratio of 33.5, and a negative likelihood ratio of 0.11 (Guerriero et al., 1998). Deep endometriosis in the bladder wall or rectum may be visualised with TVS (Dessole et al., 2003). Trans Rectal Sonography (TRS) may also be useful for diagnosing rectovaginal endometriosis (sensitivity 80-100%, specificity 96-100%) (Fedele et al., 1998). TRS performs better than magnetic resonance imaging (MRI) in the diagnosis of rectal involvement for patients presenting with deeply infiltrating endometriosis. For the diagnosis of rectal involvement, sensitivity, specificity, PPV and NPV for TRS were 97.1%, 89.4%, 86.8% and 97.7% and for MRI they were 76.5%, 97.9%, 96.3% and 85.2% (Chapron et al., 2004).

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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 three months of hormonal treatment so as to avoid under-diagnosis.	

B	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., 2003b).	Evidence Level 3

B	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

Laparoscopy is the gold standard for diagnosing endometriosis, although recognition of endometriosis will vary with the experience of the surgeon, especially for subtle, bowel, bladder, ureteral and diaphragmatic lesions. A meta-analysis of its value against a histological diagnosis showed (assuming a 10% pre-test probability of endometriosis) that a positive laparoscopy increases the likelihood of disease to 32% (95% CI 21 to 46%) and a negative laparoscopy decreases the likelihood to 0.7% (95% CI 0.1 to 5.0%) (Wykes et al., 2004). However, diagnostic laparoscopy is associated with an approximately 3% risk of minor complications (e.g. nausea, shoulder tip pain) and a risk of major complications (e.g. bowel perforation, vascular damage) of between 0.6 to 1.8 per 1000 (Chapron et al., 1998; Harkki-Siren et al., 1999).

At diagnostic laparoscopy, the pelvic and abdominal cavity should be systematically searched for the presence of endometriosis. This must include a complete and systematic inspection and palpation with a blunt probe of the bowel, bladder, uterus, tubes, ovaries, cul-de-sac, broad ligaments and the bottom of peritoneal pockets and hernial sacs. The diagnosis of ovarian endometriosis is facilitated by careful inspection of both ovaries in their entirety, which may be difficult when adhesions are present in more advanced stages of the disease. Endometriosis can be treated during laparoscopy, thus combining diagnosis and therapy.

Because chocolate like fluid may also be found in other types of ovarian cysts, such as haemorrhagic corpus luteal or neoplastic cysts, biopsy and preferably removal of the cyst for histological confirmation is recommended if the cyst is > 3 cms diameter. Ovarian endometriosis as a single finding occurs in < 1% of endometriosis patients, the rest having mostly pelvic and/or intestinal endometriosis as well (Redwine, 1999).

Classification systems

Many classification systems have been proposed, but only one has been generally accepted. This is the revised American Fertility Society (AFS) system (ASRM, 1997). It is based on:

1. the appearance, size, and depth of peritoneal and ovarian implants;
2. the presence, extent and type of lesions: red (red, red-pink, and clear), white (white, yellow-brown, and peritoneal defects) and black (black and blue);
3. the presence, extent, and type of adnexal adhesions and the degree of cul-de-sac obliteration.

Colour photographs are provided by ASRM to assure consistency in describing the appearance. This system reflects the extent of endometriotic disease, but has considerable intra-observer and inter-observer variability (Hornstein et al., 1993; Lin et al., 1998).

Moreover, as the system was developed primarily for the management of infertility, adnexal adhesions contribute disproportionately. Similarly, they do not correlate with the signs and symptoms of the disease, nor with the results of treatment. There are no data to demonstrate that classifying the lesions contributes to any clinical outcome measures.

Treatment of Pain

Concise

Concise section not amended but amendments in supporting documentation

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, progestagens, the combined oral contraceptive (COC) and nutritional therapy. It is unclear whether the COC should be taken conventionally, continuously or in 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	There is inconclusive evidence to show whether NSAIDs (specifically naproxen) are effective in managing pain caused by endometriosis (Allen et al., 2005).	Evidence Level 1a

Hormonal treatment

A	Suppression of ovarian function for 6 months reduces endometriosis associated pain. The hormonal drugs investigated - COCs, danazol, gestrinone, medroxyprogesterone, acetate and GnRH agonists - are equally effective but their side-effect and cost profiles differ (Davis et al., 2007 ; Prentice et al., 1999; Prentice et al., 2000; Selak et al., 2007).	Evidence Level 1a

A	The levonorgestrel intra-uterine system (LNG IUS) reduces endometriosis associated pain.	Evidence Level 1a

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).	Evidence Level 1b

GnRH agonist treatment with 'add-back'

A	Treatment for up to 2 years with combined oestrogen and progestagen 'add-back' appears to be effective and safe in terms of pain relief and bone density protection; progestagen only 'add-back' is not protective (Sagsveen et al., 2003). 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 1a

Hormone replacement therapy

C	Hormone replacement therapy (HRT) is recommended after bilateral oophorectomy in young women given the overall health benefits and small risk of recurrent disease while taking HRT (Matorras et al., 2002). The ideal regimen is unclear: adding a progestagen after hysterectomy is unnecessary but should protect against the unopposed action of oestrogen on any residual disease. However, the theoretical benefit of avoiding disease reactivation and malignant transformation should be balanced against the increase in breast cancer risk reported to be associated with combined oestrogen and progestagen HRT and tibolone (Beral and Million Women Study Collaborators, 2003).	Evidence Level 4

Supporting

Rationale for treatment

In most women with endometriosis, preservation of reproductive function is desirable. The least invasive and least expensive approach that is effective with the least risks in the long run should be chosen. It is important to involve the woman in the decision taken about the treatment options. Symptomatic endometriosis patients can be treated by analgesics, hormones, surgery, assisted reproduction or a combination of these. Many women with endometriosis have pain and subfertility at the same time, which complicates the choice of treatment. Unfortunately, as endometriosis is a chronic disease, elimination of the endometriotic implants by surgical or medical treatment often provides only temporary relief. Therefore, the goal should be to eliminate the endometriotic lesions and, more importantly, to treat the symptoms (pain and subfertility) and prevent recurrence. It has to be kept in mind that endometriosis is a chronic disease and the recurrence rate is high after both hormonal and surgical treatment.

General considerations on medical treatment

Because oestrogen is known to stimulate the growth of endometriosis, hormonal therapy has been designed to suppress oestrogen synthesis, thereby inducing atrophy of ectopic endometrial implants or interrupting the cycle of stimulation and bleeding. Implants of endometriosis react to gonadal steroid hormones in a manner similar but not identical to normally stimulated eutopic endometrium.

Progestagens

Progestagens exert an anti proliferative effect by causing initial decidualisation of endometrial tissue followed by atrophy. They can be considered as a first choice for the treatment of endometriosis because they are as effective in reducing AFS scores and pain as danazol or GnRH analogues and have a lower cost and a lower incidence of side effects than danazol or GnRH analogues (Vercellini et al., 1997). Their use in endometriosis has been the subject of a Cochrane Review (Moore et al., 1997; Prentice et al., 2000). There is no evidence that any single agent or any particular dose is preferable to another. In most studies, the effect of treatment has been evaluated after 3 to 6 months of therapy. Medroxyprogesterone acetate (MPA) has been the most studied agent and is effective in relieving pain starting at a dose of 30 mg/day and increasing the dose based on the clinical response and bleeding patterns (Moghissi and Boyce, 1976; Luciano et al., 1988). Pain was reduced significantly during luteal phase treatment with 60 mg dydrogesterone and this improvement still was evident at 12-month follow-up (Overton et al., 1994). Other progestagens, such as desogestrel, are now being looked at as alternative treatments (Razzi et al., 2006).

Side effects of progestagens include nausea, weight gain, fluid retention, and breakthrough bleeding due to hypo-oestrogenemia. Breakthrough bleeding, although common, is usually corrected by short-term (7-day) administration of oestrogen. Depression and other mood disorders are a significant problem in approximately 1% of women taking these medications. Reports from studies of local progesterone treatment of endometriosis-associated dysmenorrhoea with a levonorgestrel-releasing intrauterine system during 12 months resulted in a significant reduction in dysmenorrhea, pelvic pain and dyspareunia, a high degree of patient satisfaction (Vercellini et al., 1999b; Vercellini et al., 2005; Lockhat et al., 2005; Petta et al., 2005; Varma et al., 2005(Gomes et al. 1231-34)) and a significant reduction in volume of rectovaginal endometriotic nodules (Fedele et al., 2001). Recent data on the use of a depot preparation of Medroxyprogesterone acetate (DMPA-SC 104) demonstrates that pain reduction is as effective as that observed with GnRH analogues (Crosignani et al., 2006). Limited data also exists on the use of another depot preparations (Implanon – Etonogestrel) in the management of endometriosis (Yisa et al., 2004; Yisa et al., 2005).

Combined oral contraceptives - continuous administration

Manipulation of the endogenous hormonal milieu is the basis for the medical management of endometriosis. The treatment of endometriosis with combination of estrogens and progestagens

was originally used to induce "pseudopregnancy" with resultant amenorrhea due to decidualisation of endometrial tissue (Kistner, 1959). The modern equivalent is the continuous use of the combined oral contraceptive pill. Any low-dose combination oral contraceptive pill containing 30-35 mg of ethinyl oestradiol used continuously (to achieve amenorrhea) can be effective in the management of endometriosis (Moghissi, 1999). Symptomatic relief of dysmenorrhoea and pelvic pain is reported in 60-95% of patients. Following a first-year recurrence rate of 17-18%, a 5-10% annual recurrence rate has been observed. Oral contraceptives are less costly than other treatment modalities and may be helpful in the management of endometriosis with potential long-term benefits in some women (Moore et al., 1997).

Combined oral contraceptives - cyclical administration

The cyclical use of combination oral contraceptives may provide prophylaxis against either the development or recurrence of endometriosis. Oestrogens in oral contraceptives potentially may stimulate the proliferation of endometriosis. However, the reduced menstrual bleeding that often occurs in women taking oral contraceptives may be beneficial to women with prolonged, frequent menstrual bleeding, which is a known risk factor for endometriosis (Cramer et al., 1986). Further research is warranted to assess the effect of low-dose oral contraceptives in preventing endometriosis and in treating associated pain. A Cochrane review of the use of the combined oral contraceptive pill identified only one study which demonstrated a reduction in non menstrual symptoms(Davis et al. CD001019). More recently a placebo controlled trial of a combined oral contraceptive (35mcg ethinyl estradiol and 1 mg norethisterone/norethindrone) has shown that combined oral contraceptive usage reduces dysmenorrhoea associated with endometriosis(Harada et al.)

Gestrinone

Gestrinone is a 19-nortestosterone derivative with androgenic, anti-progestagenic, anti-oestrogenic, and anti-gonadotropic properties. It creates a hormonal environment that results in the cellular inactivation and degeneration of endometriotic implants but not their disappearance (Brosens et al., 1987). Amenorrhea occurs in 50-100% of women and is dose-dependent.

The standard dose has been 2.5 mg twice a week, although it has been reported that 1.25 mg twice weekly is equally effective (Hornstein et al., 1990). The clinical side effects are dose-dependent and similar but less intense than those caused by danazol (Fedele et al., 1989). They include nausea, muscle cramps, and androgenic effects such as weight gain, acne, seborrhoea, oily hair/skin, and irreversible voice changes.

Gestrinone is as effective as GnRHa for the treatment of pelvic pain associated with endometriosis (Gestrinone Italian Study Group, 1996). However, gestrinone has fewer side effects. Pregnancy is contraindicated while taking gestrinone because of the risk of masculinisation of the foetus.

Danazol

Danazol suppresses GnRH or gonadotrophin secretion, directly inhibits steroidogenesis, increases metabolic clearance of oestradiol and progesterone, and interacts with endometrial androgen and progesterone receptors. In addition it causes immunologic attenuation of potentially adverse reproductive effects (Barbieri and Ryan, 1981; Hill et al., 1987). The multiple effects of danazol produce a high-androgen, low-oestrogen environment that does not support the growth of endometriosis, and the amenorrhea that is produced prevents new seeding of implants from the uterus into the peritoneal cavity.

Doses of 800 mg/day are frequently used in North America, whereas 600 mg/day is commonly prescribed in Europe and Australia. It appears that the absence of menstruation is a better indicator of response than drug dose. A practical strategy for the use of danazol is to start treatment with 400 mg daily (200 mg twice a day) and increase the dose, if necessary, to achieve amenorrhea and relieve symptoms (Wingfield and Healy, 1993).

The significant adverse side effects of danazol are related to its androgenic and hypo-oestrogenic properties. The most common side effects include weight gain, fluid retention, acne, oily skin, hirsutism, hot flushes, atrophic vaginitis, reduced breast size, reduced libido, fatigue, nausea, muscle cramps, and emotional instability. Deepening of the voice is another potential side effect

that is non reversible. Danazol is contraindicated in patients with liver disease because it is largely metabolized in the liver and may cause hepatocellular damage. Danazol is also contraindicated in patients with hypertension, congestive heart failure, or impaired renal function because it can cause fluid retention. The use of danazol is contraindicated in pregnancy because of its androgenic effects on the foetus. Work has been undertaken to evaluate the effectiveness of low dose danazol administered vaginally to reduce side effects. Initial results suggest this may become a useful therapy(Razzi et al. 789-94)

Gonadotropin-releasing hormone agonists

GnRH agonists bind to pituitary GnRH receptors and initially stimulate LH and FSH synthesis and release. However, prolonged stimulation causes down regulation of gonadotrophic activity. Consequently, ovarian steroid production is suppressed, providing a medically induced and reversible state of pseudo menopause.
Various GnRH agonists have been developed and used in treating endometriosis. These include leuprorelin buserelin, nafarelin, histrelin, goserelin, deslorelin, and triptorelin. These drugs are inactive orally and must be administered intramuscularly, subcutaneously, or intranasally.

The side effects of GnRH agonists are caused by hypo-oestrogenism and include hot flushes, vaginal dryness, reduced libido, and reduction in bone density. Reversibility of bone loss is equivocal and therefore of concern (Barbieri, 1992; Riis et al., 1990), especially because treatment periods of longer than 6 months may be required. Where treatment is restricted to 6 months the effect on bone mineral density virtually resolves by 12 months (Makita et al., 2005). Side effects can be ameliorated by the use of "add-back". The goal of add-back is to effectively treat endometriosis and endometriosis-associated pain, while preventing vasomotor symptoms and bone loss. Add back can be achieved by progestagens only including norethisterone 1.2 mg (Riis et al., 1990), norethindrone acetate 5 mg (Hornstein et al., 1998), but bone loss is not prevented by medrogestone 10 mg/day (Sillem et al., 1999). Add-back can also be achieved by tibolone 2.5 mg/day (Taskin et al., 1997; Lindsay et al., 1996), or by an oestrogen/progestagen combination, i.e. conjugated oestrogens 0.625 mg combined with medroxyprogesterone acetate 2.5 mg (Friedman et al., 1993) or with norethindrone acetate 5 mg (Hornstein et al., 1998), oestradiol 2 mg and norethisterone acetate 1 mg (Franke et al., 2000). However, some concern remains about the long term effects of GnRH analogues on bone loss. In a recent report (Pierce et al., 2000), bone mineral density reduction occurred during long-term GnRH agonist use and was not fully recovered up to 6 years after treatment.

"Draw-back therapy" has been suggested as an alternative in a recent study showing that 6 months intake of 400 microgram nafarelin/day was as effective as "draw-back regimen" consisting of 1 month intake of 400 microgram nafarelin/day followed by 5 months 200 microgram nafarelin/day, with similar oestradiol levels (30 pg/mL) but less loss of bone mineral density (Tahara et al., 2000).

Aromatase inhibitors

Theoretically aromatase inhibitors may have a role to play in the medical management of endometriosis, particularly in postmenopausal women (Attar and Bulun, 2006; Bulun et al., 2000; D'Hooghe, 2003b). Although a number of small studies have confirmed this theoretical promise (Ailawadi et al., 2004; Amsterdam et al., 2005) there is insufficient data to support their widespread use in the management of endometriosis at the present time and particularly in a group of women of predominately reproductive age. It is likely that if aromatase inhibitors do find a role in the management of endometriosis then it will be as part of a combination therapy with other ovarian suppressant drugs (Attar and Bulun, 2006). Combination therapy of Letrozole with norethisterone or desogestrel has been shown to be effective but did not result in disease resolution and symptoms rapidly returned on cessation of therapy. In combination with desogestrel ovaraian cyst production was an issue. (Remorgida et al. 222-25;Remorgida et al. 724-26)

Anti-angiogenic therapies, progesterone anatagonists and Selective Progesterone Receptor Modulators (SERMs)

There are some interesting preliminary results from the laboratory and in animal models of the possible use of angiostatic drugs and anti-vascular endothelial growth factor but no clinical trials

have yet been performed in humans (Ferrero et al., 2006).
Antiprogestagens, such as mifepristone, have been suggested as potential treatments for endometriosis but limited data is available to advocate wider use (Spitz, 2006; Tang and Ho, 2006; Chabbert-Buffet et al., 2005).
There is also little data to support the use of selective progesterone receptor modulators although their potential use has been advocated (Chabbert-Buffet et al., 2005; Chwalisz et al., 2005).

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, progestagens, the combined oral contraceptive (COC) and nutritional therapy. It is unclear whether the COC should be taken conventionally, continuously or in 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.

With no overwhelming medical evidence to support particular treatments over others, it is important to recognise that the decisions involved in any treatment plan are individual, and that the woman is able to make these based on an informed choice and a good understanding of what is happening in her body.
The resentment and frustration, which many with chronic diseases develop over time, more often than not result from a mismatch between clinical management and the woman's expectations - a mismatch that leaves her unprepared for the possibility of side effects or recurrence.

Appropriate counselling before, during, and after treatment, either by the treating physician and/or a counsellor/psychologist, is therefore an imperative part of the treatment process in endometriosis. The pros and cons of each potential treatment must be comprehensively communicated prior to its commencement, as must the setting of realistic expectations for outcome and potential follow-on treatment.
It is common practice to treat women suffering from dysmenorrhoea with analgesics, in fact many women treat themselves with oral analgesics purchased over-the-counter (without a prescription). A systematic review by Zhang and co-workers (1998) found that paracetamol was not more effective than placebo in reducing pain, whilst co-proxamol (paracetamol 650 mg and dextropropoxyphene 65 mg) reduced pain compared with placebo. However, these analyses were based on two relatively small randomised controlled trials comparing paracetamol and co-proxamol with placebo respectively (Evidence Level 1a). Additionally, the dosage of paracetamol was 500 mg four times daily and this may have been somewhat suboptimal. When paracetamol 1000 mg three times daily dosage was compared with either ibuprofen or naproxen no significant differences were found (Proctor and Farquar, 2006a). A recent small RCT again demonstrated that paracetamol (acetaminophen)1000 mg four times daily was superior to placebo for the treatment of primary dysmenorrhoea (Dawood and Khan-Dawood 2007).

A recent systematic review evaluated the use of non-steroidal anti-inflammatory drugs (NSAIDs) for dysmenorrhoea (Marjoribanks et al., 2003). This Cochrane review included the trials evaluating the effectiveness of NSAIDs for primary dysmenorrhoea. Primary dysmenorrhoea was described as menstrual pain without organic pathology; however, exclusion of pelvic pathology was based on physical examination. Hence, it is quite likely that the trials evaluated in this review included patients with endometriosis given that some women with so called 'primary dysmenorrhoea' probably have endometriosis. It is well known that some women who have so called 'primary dysmenorrhoea' have endometriosis. Marjoribanks and co-workers (2003) concluded that NSAIDs, except niflumic acid, were more effective than placebo for pain relief and that there was insufficient evidence to suggest whether any individual NSAID was more effective than others (Evidence Level 1a). Another review concluded that selective cyclo-oxygenase-2 inhibitors rofecoxib, lumiracoxib and etoricoxib were as effective as naproxen and more effective than placebo for the treatment of primary dysmenorrhoea (Proctor and Farquar, 2006a). However, concerns have been raised about the safety of these medications and its manufacturers have recently withdrawn rofecoxib from the market in many countries (Evidence Level 1b).

Combined oral contraceptives (COCs) are also used commonly for the management of patients with dysmenorrhoea, which in some cases may be due to endometriosis. However, there is a paucity of information for the use of modern COCs for primary dysmenorrhoea. A Cochrane review by Proctor et al (2001) suggested that 1st and 2nd generation COCs with 50 mcg or more oestrogen may be more effective than placebo treatment for dysmenorrhoea, however it concluded that the RCTs included for analysis were of poor quality and heterogeneous so that no recommendation could be made regarding the efficacy of modern, lower dose COCs (Evidence Level 1a). A recent RCT comparing a low dose oral contraceptive containing 20 µg ethinyl estradiol and 100 µg levonorgestrel with placebo showed better pain relief in adolescent girls with dysmenorrhoea (Davis et al., 2005). Additionally there is some evidence in general populations that combined oral contraceptives can effectively treat dysmenorrhoea (Proctor and Farquhar 2006a). The COCs have the advantage of long term safety; hence they can be used indefinitely in low risk women. In clinical practice, when they are used for menstrual pain, they may be taken tricyclically or continuously to reduce the number of periods or to avoid them altogether (Evidence Level 4). However, there is no direct comparison of these options with the conventional approach.

Some authors advocate use of empirical medical therapy, as they see laparoscopy as an unnecessary, fruitless and hazardous procedure (Lindheim 1999). Similarly, a recent consensus statement from the 'Chronic Pelvic Pain/Endometriosis Working Group' suggested use of danazol, progestagens and GnRH agonists as 'second line' treatment without laparoscopic confirmation, when endometriosis was suspected as the cause of chronic pelvic pain (Gambone et al., 2002). Their recommendation is to continue with the 'advanced' or 'second line' treatment for six months and then to initiate an appropriate 'maintenance' treatment with NSAIDs or COCs. This statement suggests long term treatment with danazol, GnRH agonists or progestagens if symptoms recur upon reversion to maintenance treatment. The document does not provide evidence for the long term efficacy and safety of the approach, nor does it give data regarding compliance and recurrence rates. In the absence of data, there is a clear need for a randomised controlled trial to compare laparoscopic surgery with 'second line' medical treatment when the 'first line' treatment options (NSAIDs and COCs) fail.

Several Cochrane reviews and one Clinical Evidence review suggest that other treatment modalities which may be helpful in primary dysmenorrhoea include thiamine, vitamin E, high frequency transcutaneous nerve stimulation, topical heat and herbal remedy toki-shakuyaku-san. They also suggest that treatment modalities with unknown benefit are vitamin B12, fish oil, magnesium, acupuncture, other herbal remedies and behavioural interventions and that spinal manipulation is unlikely to be beneficial (Proctor and Murphy 2001; Proctor et al., 2006b; Proctor et al., 2002; Proctor and Farquar 2006a).

Hormonal treatment

Suppression of ovarian function for 6 months reduces endometriosis associated pain. The hormonal drugs investigated - COCs, danazol, gestrinone, medroxyprogesterone, acetate and GnRH agonists - are equally effective but their side-effect and cost profiles differ (Davis et al., 2007; Prentice et al., 2000; Prentice et al., 1999; Selak et al., 2007).

Manipulation of the endogenous hormonal milieu is the basis for the medical management of endometriosis. As oestrogen is known to stimulate the growth of endometriosis, hormonal therapy has been designed to suppress oestrogen synthesis, thereby inducing atrophy of ectopic endometrial implants or interrupting the cycle of stimulation and bleeding. Withdrawal of oestrogen stimulation causes cellular inactivation and degeneration of endometriotic implants but not their disappearance.

Most women with symptomatic endometriosis experience pain relief throughout treatment as shown in several prospective, randomized, placebo-controlled, double-blind studies (Davis et al., 2007; Prentice et al., 2000; Prentice et al., 1999; Selak et al., 2007). The effect lasts for a variable time after cessation of therapy. Progestagens, oral contraceptives, danazol, gestrinone and GnRH agonists are equally effective, so the choice of treatment is guided by side effects and cost.

Treatment of endometriosis-associated pain in confirmed disease

Non-steroidal anti-inflammatory drugs

A	There is inconclusive evidence to show whether NSAIDs (specifically naproxen) are effective in managing pain caused by endometriosis (Allen et al., 2005).	Evidence Level 1a

Non-steroidal anti-inflammatory drugs (NSAIDs) may be effective in reducing endometriosis associated pain (Kauppila et al., 1979; Kauppila and Ronnberg, 1985; Ylikorkala and Viinikka, 1983).

As endometriosis is a chronic inflammatory disease, anti-inflammatory drugs would appear attractive for treatment. Non-steroidal, anti-inflammatory drugs (NSAIDs) have become the most widely used therapeutic agents in the treatment of hyperalgesia induced by the inflammatory process. Although NSAIDs have been used extensively and have often been the first line therapy for reduction of endometriosis related pain, the analgesic effect of NSAIDs has not been studied extensively. Only one small, double-blind, placebo-controlled, four-period, cross-over clinical study has been published (Kauppila and Rönnberg, 1985). This study showed complete or substantial pain relief of endometriosis-related dysmenorrhoea in 83% of cases treated with naproxen compared with 41% in cases treated with placebo. Women who received naproxen needed significantly less supplemental analgesics compared to women on placebo. Some NSAIDs may act not only through central inhibition of the prostaglandin synthesis, but also through the activation of endogenous opioids and serotonergic mechanisms, which can explain the efficacy of NSAIDs in chronic pain conditions. In fact, NSAIDs and opiates have a synergistic effect and combined treatment may contribute to reduction or even prevention of morphine tolerance and be opiate sparing (Hanna et al., 2003).
Endometriosis-related pain is nociceptive (Bajaj et al., 2003), but persistent nociceptive input from endometriotic lesions leads to central sensitization manifested by somatic hyperalgesia and increased referred pain areas. The positive clinical experience of NSAIDs for reduction of endometriosis related pain may be explained by both a local anti-nociceptive effect and a reduced central sensitisation besides the anti-inflammatory effect.

It is important to note that NSAIDs have significant side-effects, including gastric ulceration. Prostaglandins are involved in the follicle rupture mechanism at ovulation and this is why NSAIDs should not be taken at ovulation time by women who wish to become pregnant (Duffy and Stouffer, 2002). Other analgesics may be effective as well but there is insufficient evidence to make specific recommendations.

A recent Cochrane review on the use of NSAIDs for pain in endometriosis appears to contradict the recommendation made here by stating that there is inconclusive evidence to show whether NSAIDS are effective (Allen et al., 2005). However, this review highlights the lack of high quality data in this area and the small size of the trials including the trial previously discussed (Kauppila and Ronnberg, 1985). The trend towards benefit demonstrated in this trial justifies the recommendation that NSAIDs may be effective in reducing endometriosis associated pain, especially when it is considered that as a group they have been shown to be effective for relieving the commonest symptom of endometriosis (dysmenorrhoea) in other situations (Marjoribanks et al., 2003).

Hormonal treatment

A	Suppression of ovarian function for 6 months reduces endometriosis associated pain. The hormonal drugs investigated - COCs, danazol, gestrinone, medroxyprogesterone, acetate and GnRH agonists - are equally effective but their side-effect and cost profiles differ (Davis et al., 2007 ; Prentice et al., 1999; Prentice	Evidence Level 1a

	et al., 2000; Selak et al., 2007).	

There are pilot data suggesting that the aromatase inhibitor, letrozole, may be effective although it is associated with significant bone density loss (Ailawadi et al., 2004).

A	The levonorgestrel intra-uterine system (LNG IUS) reduces endometriosis associated pain.	Evidence Level 1a

A systematic review identified two RCTs and three prospective observational studies, all involving small numbers and a heterogeneous group of patients (Varma et al., 2005). Nevertheless, the evidence suggests that the LNG IUS reduces endometriosis associated pain (Petta et al., 2005; Vercellini et al., 1999a) with symptom control maintained over 3 years (Lockhat et al., 2004; Lockhat et al., 2005).

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).	Evidence Level 1b

GnRH agonist treatment with 'add-back'

A	Treatment for up to 2 years with combined oestrogen and progestagen 'add-back' appears to be effective and safe in terms of pain relief and bone density protection; progestagen only 'add-back' is not protective (Sagsveen et al., 2003). 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 1a

Manipulation of the endogenous hormonal milieu is the basis for the medical management of endometriosis. As oestrogen is known to stimulate the growth of endometriosis, hormonal therapy has been designed to suppress oestrogen synthesis, thereby inducing atrophy of ectopic endometrial implants or interrupting the cycle of stimulation and bleeding. Withdrawal of oestrogen stimulation causes cellular inactivation and degeneration of endometriotic implants but not their disappearance.

Most women with symptomatic endometriosis experience pain relief throughout treatment as shown in several prospective, randomized, placebo-controlled, double-blind studies (Davis et al., 2007; Prentice et al., 1999; Prentice et al., 2000; Selak et al., 2007). The effect lasts for a variable time after cessation of therapy. Progestagens, oral contraceptives, danazol, gestrinone and GnRH agonists are equally effective, so the choice of treatment is guided by side effects and cost.

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Treatment Pain Surgical

Concise

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 (Abbott et al., 2003; Chapron et al., 2003b; Fedele et al., 2004a; Redwine and Wright, 2001).

A	Ablation of endometriotic lesions plus laparoscopic uterine nerve ablation (LUNA) in minimal-moderate disease reduces endometriosis associated pain at 6	Evidence Level 1b

	months compared to diagnostic laparoscopy; the smallest effect is seen in patients with minimal disease (Jacobson et al., 2001). However, there is no evidence that LUNA is a necessary component (Sutton et al., 2001), and LUNA by itself has no effect on dysmenorrhoea associated with endometriosis (Vercellini et al., 2003a).	

There are no data supporting the use of uterine suspension but, in certain cases, there may be a role for pre-sacral neurectomy especially in severe dysmenorrhoea (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, all visible endometriotic tissue should be removed at the same time (Lefebvre et al., 2002). Bilateral salpingo-oophorectomy may result in improved pain relief and a reduced chance of future surgery (Namnoum et al., 1995).	

Pre-operative treatment

A	Although hormonal therapy prior to surgery improves rAFS scores, there is insufficient evidence of any effect on outcome measures such as pain relief (Yap et al., 2004).	Evidence Level 1a

Post-operative treatment

A	Compared to surgery alone or surgery plus placebo, post-operative hormonal treatment does not produce a significant reduction in pain recurrence at 12 or 24 months, and has no effect on disease recurrence (Yap et al., 2004).	Evidence Level 1a

The above quoted Cochrane review is based on two studies of 6 months post-operative GnRHa treatment, indicating that more research is obviously needed. As endometriosis is a chronic oestrogen-dependent disease, further hormonal treatment is often needed in many women.

In a small RCT, the LNG IUS, inserted after laparoscopic surgery for endometriosis associated pain, significantly reduced the risk of recurrent moderate-severe dysmenorrhoea at 1 year follow-up (Vercellini et al., 2003c).

Hormone replacement therapy

C	Hormone replacement therapy (HRT) is recommended after bilateral oophorectomy in young women given the overall health benefits and small risk of recurrent disease while taking HRT (Matorras et al., 2002). The ideal regimen is unclear: adding a progestagen after hysterectomy is unnecessary but should protect against the unopposed action of oestrogen on any residual disease. However, the theoretical benefit of avoiding disease reactivation and malignant transformation should be balanced against the increase in breast cancer risk reported to be associated with combined oestrogen and progestagen HRT and tibolone (Beral and Million Women Study Collaborators, 2003).	Evidence Level 4

Supporting

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 (Abbott et al., 2003; Chapron et al., 2003b; Fedele et al., 2004a; Redwine and Wright, 2001).

There are no data to justify hormonal treatment prior to surgery to improve the success of surgery (Muzii et al., 1996; Audebert et al., 1998).

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., 2001). However, there is no evidence that LUNA is a necessary component (Sutton et al., 2001), and 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 especially in severe dysmenorrhoea (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, all visible endometriotic tissue should be removed at the same time (Lefebvre et al., 2002). Bilateral salpingo-oophorectomy may result in improved pain relief and a reduced chance of future surgery (Namnoum et al., 1995).

The goal of surgery is to excise or coagulate all visible endometriotic peritoneal lesions, endometriotic ovarian cysts, deep rectovaginal endometriosis and associated adhesions, and to restore normal anatomy. Laparoscopy can be used in most women, and this technique decreases cost, morbidity, and the risk of adhesions postoperatively. In the absence of deep endometriosis laparoscopy can be performed as day surgery. Laparotomy should be reserved for patients with advanced stage disease in whom laparoscopic surgery is not possible.

Peritoneal endometriosis

Endometriosis lesions can be removed during laparoscopy by excision, coagulation or vaporization by laser (carbon dioxide laser, potassium-titanyl-phosphate laser or argon laser). No controlled evidence is available demonstrating that one laser technique is better than the other. The effectiveness of surgical ablation of peritoneal endometriosis has been convincingly shown in two RCTs where the control group underwent a laparoscopy without surgical ablations of lesions. The treated group had a significant reduction of symptoms that persisted for 12 months (Abbott et al., 2004) and 18 months (Sutton et al., 1997; Sutton et al., 1994).

The effectiveness of laparoscopic uterine nerve ablation (LUNA) in women with symptomatic endometriosis has not been proven (Vercellini et al., 2003a). The effectiveness of surgical treatment by laparotomy has not been investigated by a RCT. The many observational studies that have been published claim a high percentage of success.

Ovarian endometriosis

Superficial ovarian lesions can be coagulated or vaporized. The primary indication for extirpation of an endometrioma is to ensure it is not malignant. Small ovarian endometrioma (< 3 cm diameter) can be aspirated, irrigated, and inspected for intracystic lesions. Their interior wall can be coagulated or vaporized to destroy the mucosal lining. Ovarian endometrioma > 3 cm should be removed completely (Chapron et al., 2002b). In cases where excision is technically difficult without removing a large part of the ovary, a two-step procedure (marsupialisation and rinsing followed by hormonal treatment and surgery 3 months later) should be considered (Donnez et al., 1996). Although as little as one-tenth of an ovary may be enough to preserve function and fertility, at least for a while, there is increasing concern that ovarian cystectomy with concomitant removal or destruction of normal ovarian tissue may reduce ovarian follicle reserve and reduce fertility (Loh et al., 1999). Therefore, it has been proposed to replace cystectomy by fenestration and coagulation of the inner cyst wall (Hemmings et al., 1998) but a case-control study (Saleh and Tulandi, 1999) and a randomized controlled trial (Beretta et al., 1998) have demonstrated that pain and subfertility, related to ovarian endometriomas, were improved more by cystectomy than by fenestration/coagulation. Therefore, based on the current evidence, ovarian cystectomy seems to be the method of choice (Chapron et al., 2002) with a significantly decreased risk of cyst recurrence (Vercellini et al., 2003b).

Adhesiolysis

If the endometriosis-related adhesions are part of an inflammatory fibrosis, they should be removed carefully. So far there is no evidence from randomized controlled trials that routine use of pharmacological or liquid agents prevent postoperative adhesions after fertility surgery (Watson et al., 2000).

Deep rectovaginal and rectosigmoidal endometriosis

Deep endometriosis is usually multifocal and complete surgical excision must be performed in a one step surgical procedure, in order to prevent more than one surgery, provided the woman is fully informed (Chapron et al., 2003a; Chapron et al., 2003b). Because of the fact that management of deeply infiltrating endometriosis is complex, referral to a centre with expertise to offer all available treatments in a multidisciplinary approach is strongly recommended. Surgical management is only for symptomatic deeply infiltrating endometriosis. Asymptomatic patients must not be operated upon. Progression of the disease and appearance of specific symptoms rarely occurred in patients with asymptomatic rectovaginal endometriosis (Fedele et al., 2004b). When surgical treatment is decided the treatment must be radical with excision of all deep lesions. In cases of intestinal endometriosis, segmental resection improves the outcome without affecting the chance of conception (Fedele et al., 2004a).

Preoperatively the patients' agreement must be obtained to perform this difficult and high risk surgical procedure. RCTs are difficult since these severe cases are all very individual and moreover, not all surgeons are familiar with all treatment options. Complete excision might comprise the resection of the uterosacral ligaments, the resection of the upper part of the posterior vaginal wall, discoid or segmental bowel resection followed by end-to-end anastomosis, partial cystectomy and ureterolysis, eventually resection, re-anastomosis and re-implantation, sometimes still preserving the uterus and ovarian tissue.

Segmental recto sigmoid resection can be performed by laparotomy, laparoscopy or by laparoscopically assisted vaginal technique (Redwine et al., 1996). Surgical excision of deep rectovaginal and rectosigmoidal endometriosis is difficult and can be associated with major complications such as bowel perforations with resulting peritonitis (Koninckx et al., 1996). Preoperative laxatives, starch-free diet and full bowel preparation are needed to allow bowel suturing, if needed. Assessment of deep invasive endometriosis by TRS or MRI might be performed. A bowel contrast enema might be performed preoperatively if deep endometriosis is suspected by clinical exam and bowel symptoms. As endometriosis sometimes involves non-gynaecological organs, i.e. the bowel, the urinary tract or pelvic bones, other surgically devoted specialists such as bowel surgeons and urologists sometimes have to be involved. Bowel surgery has to be discussed preoperatively when indicated and planned accordingly. Ureteric catheters may be required before excision of periureteral endometriosis. A multidisciplinary approach involving gynaecological surgeons, bowel surgeons and urologists may be the safest approach; these severe cases should be handled by centres with special expertise. Moreover, as the pattern of pain in endometriosis is complicated and pain does not always respond to treatment, having access to a multidisciplinary team including pain specialists is very important. As the women sometimes have multiple problems close collaboration with other health-care professionals is mandatory.

Oophorectomy and hysterectomy

Radical procedures such as oophorectomy or total hysterectomy are indicted only in severe cases. If a hysterectomy is performed, the cervix should be extirpated as persistent pain in a remaining cervix is common due to endometriosis in the cervix or endometriosis in the utero-sacral ligaments. However, it is important to note that women younger than 30 years at the time of hysterectomy for

endometriosis-associated pain are more likely than older women to have residual symptoms, to report a sense of loss, and to report more disruption from pain in different aspects of their lives. Radical resection is an effective treatment for rectovaginal endometriosis. Hysterectomy and rectal resection were associated with a better response and quality of life (Ford et al., 2004).

Results of surgical treatment

The outcome of surgery in patients with endometriosis and pain is influenced by many psychological factors related to personality, marital and psychosexual issues. It is difficult to evaluate the objective effect of different surgical approaches scientifically as not only the extirpation/destruction of the pathological tissue can impact on the results but also surgery per se, the doctor-patient relationship, complications etc. Diagnostic laparoscopy without complete removal of endometriosis has been found to alleviate pain in 50% of patients (Sutton et al., 1994). There is a significant placebo response to all kind of therapy. Similar results have been reported using oral placebo (Overton et al., 1994). Moreover, the long standing effect of surgery on pain is difficult to evaluate as the follow up time is not long enough, usually just a few months. The risk of recurrences is significantly correlated to the age of the patients. The younger the patients are at the moment of the diagnosis the higher the risk of recurrence. Higher recurrence rates in younger patients seem to justify a more radical treatment in this group (Fedele et al., 2004a).

The major shortcomings of surgical treatment in endometriosis related pain is the lack of prospective, RCTs with a follow up time long enough to draw clear clinical conclusions. In a prospective, controlled, randomized, double-blind study, surgical therapy has been shown to be superior to expectant management six months after treatment of mild and moderate endometriosis (Sutton et al., 1994). Treatment was least effective in women with minimal disease. One year later, symptom relief was still present in 90% of those who initially responded (Sutton et al., 1997).

In a randomised blinded crossover study it was confirmed that laparoscopic excision of endometriosis is more effective than placebo in reducing pain and improving quality of life (Abbott et al., 2004). Surgery resulted in pain relief in 80% of patients with severe disease who did not respond to medical therapy (Sutton and Hill, 1990). All these studies, however, have the drawback of no or very short follow up time.

Pre-operative treatment

A	Although hormonal therapy prior to surgery improves rAFS scores, there is insufficient evidence of any effect on outcome measures such as pain relief (Yap et al., 2004).	Evidence Level 1a

Post-operative treatment

A	Compared to surgery alone or surgery plus placebo, post-operative hormonal treatment does not produce a significant reduction in pain recurrence at 12 or 24 months, and has no effect on disease recurrence (Yap et al., 2004).	Evidence Level 1a

Postoperative hormonal treatment (GnRHa) does not produce a significant reduction in pain recurrence, but has a tendency to delay recurrence. Postoperative GnRHa treatment resulted in reduced pain scores, and in a delay of pain recurrence with more than 12 months, if the agonists were given for 6 months (Hornstein et al., 1997; Vercellini et al., 1999b) but not if they were administered only for 3 months (Parazzini et al., 1994). Similarly, postoperative hormonal treatment with danazol 100 mg/day (low dose) during 12 months after surgery for moderate to severe endometriosis resulted in a significantly lower pain score in the treated group when compared to a placebo group. In contrast, high dose danazol (600 mg/day) for 3 months was not superior to expectant management with respect to pain recurrence in an identical patient population (Bianchi et al., 1999). In a RCT postoperative administration of low-dose cyclic oral contraceptives did not significantly affect the long-term recurrence rate of endometriosis after surgical treatment. A delay in recurrence was evident at life-table analysis (Muzii et al., 2000). In a small RCT, the LNG IUS, inserted after laparoscopic surgery for endometriosis associated pain, significantly reduced the risk of recurrent moderate-severe dysmenorrhoea at 1 year follow-up (Vercellini et al., 2003c).
As endometriosis is a chronic oestrogen-dependent disease, further hormonal treatment may be needed, but the data is insufficient and further studied are needed.

Hormone replacement therapy

C	Hormone replacement therapy (HRT) is recommended after bilateral oophorectomy in young women given the overall health benefits and small risk of recurrent disease while taking HRT (Matorras et al., 2002). The ideal regimen is unclear: adding a progestagen after hysterectomy is unnecessary but should protect against the unopposed action of oestrogen on any residual disease. However, the theoretical benefit of avoiding disease reactivation and malignant transformation should be balanced against the increase in breast cancer risk reported to be associated with combined oestrogen and progestagen HRT and tibolone (Beral and Million Women Study Collaborators, 2003).	Evidence Level 4

Treatment of endometriosis-associated infertility in confirmed disease

Concise

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., 2007). The published evidence does not comment on 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., 2002).	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 as small numbers were treated in one of the studies (Parazzini, 1999), and 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 seemingly not blinded to whether they were treated or not. Furthermore the fecundity rates in the latter study was below that observed in control groups from other studies (Hughes et al., 2007).

B	No RCTs or meta-analyses are available to answer the question whether surgical excision of moderate to severe endometriosis enhances pregnancy rate. 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; Hart et al., 2005).	Evidence Level 1b

Post-operative treatment

A	Compared to surgery alone or surgery plus placebo, post-operative hormonal treatment has no effect on pregnancy rates (Yap et al., 2004).	Evidence Level 1a

Supporting

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 (Abbott et al., 2003; Chapron et al., 2003b; Fedele et al., 2004a; Redwine and Wright, 2001).

There are no data to justify hormonal treatment prior to surgery to improve the success of surgery (Muzii et al., 1996; Audebert et al., 1998).

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., 2001). However, there is no evidence that LUNA is a necessary component (Sutton et al., 2001), and 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 especially in severe dysmenorrhoea (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, all visible endometriotic tissue should be removed at the same time (Lefebvre et al., 2002). Bilateral salpingo-oophorectomy may result in improved pain relief and a reduced chance of future surgery (Namnoum et al., 1995).

The goal of surgery is to excise or coagulate all visible endometriotic peritoneal lesions, endometriotic ovarian cysts, deep rectovaginal endometriosis and associated adhesions, and to

restore normal anatomy. Laparoscopy can be used in most women, and this technique decreases cost, morbidity, and the risk of adhesions postoperatively. In the absence of deep endometriosis laparoscopy can be performed as day surgery. Laparotomy should be reserved for patients with advanced stage disease in whom laparoscopic surgery is not possible.

Peritoneal endometriosis

Endometriosis lesions can be removed during laparoscopy by excision, coagulation or vaporization by laser (carbon dioxide laser, potassium-titanyl-phosphate laser or argon laser). No controlled evidence is available demonstrating that one laser technique is better than the other. The effectiveness of surgical ablation of peritoneal endometriosis has been convincingly shown in two RCTs where the control group underwent a laparoscopy without surgical ablations of lesions. The treated group had a significant reduction of symptoms that persisted for 12 months (Abbott et al., 2004) and 18 months (Sutton et al., 1997; Sutton et al., 1994).

The effectiveness of laparoscopic uterine nerve ablation (LUNA) in women with symptomatic endometriosis has not been proven (Vercellini et al., 2003a). The effectiveness of surgical treatment by laparotomy has not been investigated by a RCT. The many observational studies that have been published claim a high percentage of success.

Ovarian endometriosis

Superficial ovarian lesions can be coagulated or vaporized. The primary indication for extirpation of an endometrioma is to ensure it is not malignant. Small ovarian endometrioma (< 3 cm diameter) can be aspirated, irrigated, and inspected for intracystic lesions. Their interior wall can be coagulated or vaporized to destroy the mucosal lining. Ovarian endometriomas > 3 cm should be removed completely (Chapron et al., 2002b). In cases where excision is technically difficult without removing a large part of the ovary, a two-step procedure (marsupialisation and rinsing followed by hormonal treatment and surgery 3 months later) should be considered (Donnez et al., 1996). Although as little as one-tenth of an ovary may be enough to preserve function and fertility, at least for a while, there is increasing concern that ovarian cystectomy with concomitant removal or destruction of normal ovarian tissue may reduce ovarian follicle reserve and reduce fertility (Loh et al., 1999). Therefore, it has been proposed to replace cystectomy by fenestration and coagulation of the inner cyst wall (Hemmings et al., 1998) but a case-control study (Saleh and Tulandi, 1999) and a randomized controlled trial (Beretta et al., 1998) have demonstrated that pain and subfertility, related to ovarian endometriomas, were improved more by cystectomy than by fenestration/coagulation. Therefore, based on the current evidence, ovarian cystectomy seems to be the method of choice (Chapron et al., 2002) with a significantly decreased risk of cyst recurrence (Vercellini et al., 2003b).

Adhesiolysis

If the endometriosis-related adhesions are part of an inflammatory fibrosis, they should be removed carefully. So far there is no evidence from randomized controlled trials that routine use of pharmacological or liquid agents prevent postoperative adhesions after fertility surgery (Watson et al., 2000).

Deep rectovaginal and rectosigmoidal endometriosis

Deep endometriosis is usually multifocal and complete surgical excision must be performed in a one step surgical procedure, in order to prevent more than one surgery, provided the woman is fully informed (Chapron et al., 2003a; Chapron et al., 2003b). Because of the fact that management of

deeply infiltrating endometriosis is complex, referral to a centre with expertise to offer all available treatments in a multidisciplinary approach is strongly recommended. Surgical management is only for symptomatic deeply infiltrating endometriosis. Asymptomatic patients must not be operated upon. Progression of the disease and appearance of specific symptoms rarely occurred in patients with asymptomatic rectovaginal endometriosis (Fedele et al., 2004b). When surgical treatment is decided the treatment must be radical with excision of all deep lesions. In cases of intestinal endometriosis, segmental resection improves the outcome without affecting the chance of conception (Fedele et al., 2004a).

Preoperatively the patients' agreement must be obtained to perform this difficult and high risk surgical procedure. RCTs are difficult since these severe cases are all very individual and moreover, not all surgeons are familiar with all treatment options. Complete excision might comprise the resection of the uterosacral ligaments, the resection of the upper part of the posterior vaginal wall, discoid or segmental bowel resection followed by end-to-end anastomosis, partial cystectomy and ureterolysis, eventually resection, re-anastomosis and re-implantation, sometimes still preserving the uterus and ovarian tissue.

Segmental recto sigmoid resection can be performed by laparotomy, laparoscopy or by laparoscopically assisted vaginal technique (Redwine et al., 1996). Surgical excision of deep rectovaginal and rectosigmoidal endometriosis is difficult and can be associated with major complications such as bowel perforations with resulting peritonitis (Koninckx et al., 1996). Preoperative laxatives, starch-free diet and full bowel preparation are needed to allow peroperative bowel suturing, if needed. Assessment of deep invasive endometriosis by TRS or MRI might be performed. A bowel contrast enema might be performed preoperatively if deep endometriosis is suspected by clinical exam and bowel symptoms. As endometriosis sometimes involves non-gynaecological organs, i.e. the bowel, the urinary tract or pelvic bones, other surgically devoted specialists such as bowel surgeons and urologists sometimes have to be involved. Bowel surgery has to be discussed preoperatively when indicated and planned accordingly. Ureteric catheters may be required before excision of periureteral endometriosis. A multidisciplinary approach involving gynaecological surgeons, bowel surgeons and urologists may be the safest approach; these severe cases should be handled by centres with special expertise. Moreover, as the pattern of pain in endometriosis is complicated and pain does not always respond to treatment, having access to a multidisciplinary team including pain specialists is very important. As the women sometimes have multiple problems close collaboration with other health-care professionals is mandatory.

Oophorectomy and hysterectomy

Radical procedures such as oophorectomy or total hysterectomy are indicted only in severe cases. If a hysterectomy is performed, the cervix should be extirpated as persistent pain in a remaining cervix is common due to endometriosis in the cervix or endometriosis in the utero-sacral ligaments. However, it is important to note that women younger than 30 years at the time of hysterectomy for endometriosis-associated pain are more likely than older women to have residual symptoms, to report a sense of loss, and to report more disruption from pain in different aspects of their lives. Radical resection is an effective treatment for rectovaginal endometriosis. Hysterectomy and rectal resection were associated with a better response and quality of life (Ford et al., 2004).

Results of surgical treatment

The outcome of surgery in patients with endometriosis and pain is influenced by many psychological factors related to personality, marital and psychosexual issues. It is difficult to evaluate the objective effect of different surgical approaches scientifically as not only the extirpation/destruction of the

pathological tissue can impact on the results but also surgery per se, the doctor-patient relationship, complications etc. Diagnostic laparoscopy without complete removal of endometriosis has been found to alleviate pain in 50% of patients (Sutton et al., 1994). There is a significant placebo response to all kind of therapy. Similar results have been reported using oral placebo (Overton et al., 1994). Moreover, the long standing effect of surgery on pain is difficult to evaluate as the follow up time is not long enough, usually just a few months. The risk of recurrences is significantly correlated to the age of the patients. The younger the patients are at the moment of the diagnosis the higher the risk of recurrence. Higher recurrence rates in younger patients seem to justify a more radical treatment in this group (Fedele et al., 2004a).

The major shortcomings of surgical treatment in endometriosis related pain is the lack of prospective, RCTs with a follow up time long enough to draw clear clinical conclusions. In a prospective, controlled, randomized, double-blind study, surgical therapy has been shown to be superior to expectant management six months after treatment of mild and moderate endometriosis (Sutton et al., 1994). Treatment was least effective in women with minimal disease. One year later, symptom relief was still present in 90% of those who initially responded (Sutton et al., 1997).

In a randomised blinded crossover study it was confirmed that laparoscopic excision of endometriosis is more effective than placebo in reducing pain and improving quality of life (Abbott et al., 2004). Surgery resulted in pain relief in 80% of patients with severe disease who did not respond to medical therapy (Sutton and Hill, 1990). All these studies, however, have the drawback of no or very short follow up time.

Pre-operative treatment

A	Although hormonal therapy prior to surgery improves rAFS scores, there is insufficient evidence of any effect on outcome measures such as pain relief (Yap et al., 2004).	Evidence Level 1a

Post-operative treatment

A	Compared to surgery alone or surgery plus placebo, post-operative hormonal treatment does not produce a significant reduction in pain recurrence at 12 or 24 months, and has no effect on disease recurrence (Yap et al., 2004).	Evidence Level 1a

Postoperative hormonal treatment (GnRHa) does not produce a significant reduction in pain recurrence, but has a tendency to delay recurrence. Postoperative GnRHa treatment resulted in reduced pain scores, and in a delay of pain recurrence with more than 12 months, if the agonists were given for 6 months (Hornstein et al., 1997; Vercellini et al., 1999b) but not if they were administered only for 3 months (Parazzini et al., 1994). Similarly, postoperative hormonal treatment with danazol 100 mg/day (low dose) during 12 months after surgery for moderate to severe endometriosis resulted in a significantly lower pain score in the treated group when compared to a placebo group. In contrast, high dose danazol (600 mg/day) for 3 months was not superior to expectant management with respect to pain recurrence in an identical patient population (Bianchi et

al., 1999). In a RCT postoperative administration of low-dose cyclic oral contraceptives did not significantly affect the long-term recurrence rate of endometriosis after surgical treatment. A delay in recurrence was evident at life-table analysis (Muzii et al., 2000). In a small RCT, the LNG IUS, inserted after laparoscopic surgery for endometriosis associated pain, significantly reduced the risk of recurrent moderate-severe dysmenorrhoea at 1 year follow-up (Vercellini et al., 2003c).
As endometriosis is a chronic oestrogen-dependent disease, further hormonal treatment may be needed, but the data is insufficient and further studied are needed.

Hormone replacement therapy

C	Hormone replacement therapy (HRT) is recommended after bilateral oophorectomy in young women given the overall health benefits and small risk of recurrent disease while taking HRT (Matorras et al., 2002). The ideal regimen is unclear: adding a progestagen after hysterectomy is unnecessary but should protect against the unopposed action of oestrogen on any residual disease. However, the theoretical benefit of avoiding disease reactivation and malignant transformation should be balanced against the increase in breast cancer risk reported to be associated with combined oestrogen and progestagen HRT and tibolone (Beral and Million Women Study Collaborators, 2003).	Evidence Level 4

Treatment of endometriosis-associated infertility in confirmed disease

Concise

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., 2007). The published evidence does not comment on 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., 2002).	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 as small numbers were treated in one of the studies (Parazzini, 1999), and 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 seemingly not blinded to whether they were treated or not. Furthermore the fecundity rates in the latter study were below that observed in control groups from other studies (Hughes et al., 2007).

B	No RCTs or meta-analyses are available to answer the question whether surgical excision of moderate to severe endometriosis enhances pregnancy rate. 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; Hart et al., 2005).	Evidence Level 1b

Post-operative treatment

A	Compared to surgery alone or surgery plus placebo, post-operative hormonal treatment has no effect on pregnancy rates (Yap et al., 2004).	Evidence Level 1a

Supporting

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., 2007). The published evidence does not comment on 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., 2002).	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 as small numbers were treated in one of the studies (Parazzini, 1999), and 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 seemingly not blinded to whether they were treated or not. Furthermore the fecundity rates in the latter study was below that observed in control groups from other studies (Hughes et al., 2007).

B	No RCTs or meta-analyses are available to answer the question whether surgical excision of moderate to severe endometriosis enhances pregnancy rate. 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 endometriosis without excision of the pseudo-capsule is associated with a significantly increased risk of cyst recurrence (Hart et al., 2005; Vercellini et al., 2003b).	Evidence Level 1b

When endometriosis causes mechanical distortion of the pelvis, surgery should be performed if reconstruction of normal pelvic anatomy can be achieved. According to some published studies there seems to be a negative correlation between the stage of endometriosis and the spontaneous cumulative pregnancy rate after surgical removal of endometriosis. However, data from different studies can not easily be compared as the surgical procedures; extent of surgery, skill of the surgeon etc differed and has certainly not been standardised. No randomised controlled trials or meta-analyses are available to answer the question whether surgical excision of moderate to severe endometriosis enhances the pregnancy rate. Most studies present only crude pregnancy rates without detailed information regarding time of follow-up and are therefore not relevant.

Based on the available literature there is no consensus on the treatment of ovarian endometriosis cysts in women with subfertility. The presence of an endometriotic cyst in women undergoing IUI or IVF supposedly has a negative influence on the results of these treatments, although the literature is far from consistent on this point (Olivennes et al., 1995; Arici et al., 1996). The advantage of surgically treating a cyst before IVF or IUI is the acquisition of a histological diagnosis. A disadvantage is the loss of ovarian tissue containing follicles close to the cyst.

Based on the available literature it is difficult to decide which type of surgical treatment would be the most appropriate for ovarian endometriosis: fenestration and drainage, fenestration, drainage and coagulation of the cystic wall, or cystectomy (Fayez et al., 1988; Fayez et al., 1991; Hemmings et al., 1998; Saleh et al., 1999). Fenestration and drainage does not seem to be sufficient, although no randomised study has been performed (Saleh et al., 1999). A prospective randomised trial compared cystectomy with bipolar coagulation of the cyst wall using recurrence and pregnancy figures as endpoints of the study: cystectomy was shown to be the better treatment for both endpoints (Beretta et al., 1998).

Assisted Reproduction

Concise

One added recommendation here

Intra-uterine insemination

A	Treatment with intra-uterine 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

In vitro fertilisation

B	In vitro fertilisation (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).

A	Treatment with a GnRH agonist for 3-6 months before IVF or ICSI should be considered in women with endometriosis as it increases the odds of clinical pregnancy fourfold. However the authors of the Cochrane review stressed that the recommendation is based on only one properly randomised study and called for further research, particularly on the mechanism of action (Sallam et al., 2006).	Evidence Level 1b

B	Controlled ovarian hyperstimulation (COH) for IVF/ICSI is equally effective with both GnRH antagonist and GnRH-a protocols in terms of implantation and clinical pregnancy	Evidence Level 1b

	rates, but COH with GnRH-a may be preferred because of the availability of more MII oocytes and embryos (Pabuccu et al., 2007, Ref 12903).	

B	Risk for recurrence is no reason to withhold IVF therapy after surgery for endometriosis stage III or IV since cumulative endometriosis recurrence rates are not increased after ovarian hyper stimulation for IVF (D´Hooghe et al., 2006).	Evidence Level 2a

A	Laparoscopic ovarian cystectomy in patients with unilateral endometriomas between 3 and 6 cm in diameter before IVF/ICSI can decrease ovarian response without improving cycle outcome (Demirol et al., 2006).	Evidence Level 1b

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.

Supporting

Intra-uterine insemination

A	Treatment with intra-uterine 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

IUI with or without controlled ovarian hyper stimulation (COH) is associated with a higher pregnancy rate than expectant management: the RR was 5.6 (95% CI: 1.8-17.4) when women with minimal-mild

endometriosis were randomised to IUI + COH (127 cycles, 53 couples) compared to no treatment (184 cycles, 50 couples) (Tummon et al., 1997). Another RCT reported a non-significant RR for pregnancy of 1.6 but a significant increase in cycle fecundity (0.148 v 0.045) comparing ovulation induction cycles without IUI with expectant management in 49 patients with minimal-mild endometriosis (Fedele et al., 1992). In another RCT, the effect of IUI + COH with gonadotrophins versus IUI alone was compared by alternating treatment cycles in 119 women without endometriosis and 57 women with the disease (Nulsen et al., 1993). Over 127 treatment cycles in the affected women, IUI +COH significantly increased the probability of pregnancy compared to IUI alone (RR 5.1, CI 1.1-22.5).

IUI is often used as treatment for ovulatory infertility which includes unexplained, male and cervical infertility and endometriosis. Most prospective randomized studies on the effectiveness of IUI combine the data of patients with different types of ovulatory infertility including surgically corrected endometriosis.

A systematic review of the treatment of ovulatory infertility with clomifene citrate (CC) and intrauterine insemination (IUI) identified four randomized trials combining patients with surgically corrected minimal to mild endometriosis and patients with unexplained infertility. Two trials reported significantly improved cycle pregnancy rates comparing CC plus IUI versus no CC (NC) plus timed intercourse (TI), and gonadotrophins plus IUI versus CC plus IUI, respectively. Two trials reported non-significant odds ratios comparing CC plus IUI versus NC plus IUI and CC plus IUI versus CC plus TI (Costello, 2004). Thus, CC and IUI is an effective treatment option resulting in a higher clinical pregnancy rate compared to NC and TI. Treatment with gonadotrophins and IUI results in a higher clinical pregnancy rate compared to CC and IUI.

In patients with unexplained infertility including minimal/mild or surgically treated endometriosis logistic regression analysis of a meta-analysis of 13 trials showed that the likelihood of conception was significantly increased by each of the interventions clomifene treatment, hMG treatment and IUI, independently by ~ 2 fold (The ESHRE Capri Workshop, 1996).

Another logistic regression model of 5214 IUI cycles from twenty-two randomized studies identified significant adjusted odds ratios for the likelihood of conception for the independent variables FSH-stimulation (OR 2.35) and IUI (OR 2.82). However, the presence of endometriosis reduced treatment effectiveness of IUI significantly by approximately half (OR, 0.45) (Hughes, 1997).

Reduced fecundibility associated with the presence of endometriosis (disease severity unclassified) was also shown in prospective cohort studies of donor insemination (Jansen, 1986; Hammond et al., 1986). The negative effect of minimal-mild endometriosis on pregnancy rates after donor insemination was reported to persist after surgical or medical treatment (Toma et al., 1992).

Pregnancy rates following homologous insemination within 6 months of surgical treatment were as high in women with endometriosis as in the control group with unexplained infertility in a case control study (Werbrouck et al., 2006).

In conclusion, a significant improvement of pregnancy rates can be achieved by COH and IUI compared to expectant management, despite the negative impact of endometriosis on treatment effectiveness.

In general, repetitive COH-IUI cycles are characterised by a plateau effect after 3-4 cycles, so the monthly fecundity rate after several unsuccessful cycles could be even lower than that of patients undergoing expectant management (Deaton et al., 1990). Thus, counselling patients to stop

treatment or to switch to other treatment options, such as IVF, is advisable after repetitive treatment failures.

In vitro fertilisation

B	In vitro fertilisation (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

Impaired tubal function and disturbed interaction between the fallopian tubes and the ovary may result in reduced fimbrial efficiency to pick up eggs from the ovarian surface and in impaired tubal transport of eggs, sperm and embryos. IVF treatment appears therefore to be appropriate particularly in patients with advanced disease which is frequently associated with adhesions, ovarian endometriomas and tubal obstruction.

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).

A systematic review indicated that pregnancy rates are lower in women undergoing IVF treatment with endometriosis than in women with tubal infertility (Barnhart et al., 2002). The review included 22 studies, consisting of 2,377 cycles in women with endometriosis and 4,383 in women without the disease. After adjusting for confounding variables, there was a 35% reduction in the chance of achieving pregnancy with IVF in women with endometriosis (OR, 0.63; CI, 0.51-0.77). Other outcome parameters, e.g. fertilization rate, implantation rate, mean number of oocytes retrieved and peak oestradiol concentration were also significantly lower in women with endometriosis compared to those with tubal factor infertility. The data therefore suggest that the presence of endometriosis affects multiple factors determining reproductive success during IVF.

It has to be noted that endometriosis does not adversely affect pregnancy rates in some large databases (e.g. SART and HFEA) (Templeton et al., 1996). However, since the inclusion of confounding factors in the systematic review strengthened the negative association between endometriosis and IVF outcome, this might explain the findings in the large databases which are not controlled for confounders. In an observational study on IVF/ICSI outcome, women with minimal to mild endometriosis had a better live-birth rate than women with moderate to severe endometriosis or women with tubal factor infertility (Kuivassari et al., 2005).

Only one prospective randomized study is available to address the impact of assisted embryo hatching on ART outcome in women with endometriosis. No significant effects on pregnancy rate and implantation rate could be detected. However, the study comprising 90 cycles randomized in a 2:1 ratio favouring the assisted hatching study group was underpowered to detect clinically meaningful differences (Nadir et al., 2005).

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To investigate possible mechanisms for reduced pregnancy rates in endometriosis patients, data from donor egg IVF-programs can be analyzed to dissect out the influence on embryo implantation and pregnancy of ovarian/oocyte and uterine factors, depending on whether endometriosis is present in the donor or recipient. Only retrospective studies are available addressing this issue. Similar implantation and pregnancy rates have been reported in two cohorts of recipients with stage III-IV endometriosis (n=25) and recipients without endometriosis (n=33), who received randomly distributed donor eggs from healthy donors. In contrast, another small retrospective study demonstrated that oocytes donated by women with stage III-IV endometriosis (n=14) to women with a normal pelvis gave rise to embryos with reduced quality, and reduced implantation rates per embryo were also observed (Simon et al., 1994; Garrido et al., 2002). A study analyzing a cohort of 170 oocyte donors reported no significant effects but a trend for reduced pregnancy rates in recipient cycles if the donor had endometriosis and a trend for reduced implantation rates in recipients with endometriosis, suggesting a potential mild effect of endometriosis on both the uterine environment and the quality of the oocyte (Katsoff et al., 2006). In conclusion more studies are needed to provide adequate power to address the question whether endometriosis-associated subfertility is related to reduced oocyte quality or to reduced endometrial receptivity.

A	Treatment with a GnRH agonist for 3-6 months before IVF or ICSI should be considered in women with endometriosis as it increases the odds of clinical pregnancy fourfold. However the authors of the Cochrane review stressed that the recommendation is based on only one properly randomised study and called for further research, particularly on the mechanism of action (Sallam et al., 2006).	Evidence Level 1b

In a prospective randomized study, a significantly higher cumulative pregnancy rate over up to 3 cycles of IVF/ICSI therapy was achieved in patients with stage III-IV endometriosis after ultralong (5-6 months) GnRH-agonist treatment (82%) compared to patients with ovarian stimulation using a long protocol starting the agonist on day 18 of the previous cycle (40%) (Rickes et al., 2002).

A similar, prospective, randomized study showed that 25 patients who received a GnRH agonist for 3 months prior to IVF had a significantly higher ongoing pregnancy rate per cycle initiated compared to 26 patients undergoing the regular mid-luteal start long protocol. The number of oocytes retrieved, fertilisation rates, and implantation rates were not significantly different between the groups. However, randomization was not successful in achieving similar baseline characteristics between the groups: in the ultra long protocol group a significantly higher portion of patients were classified as moderate to severe endometriosis, compared to the long protocol group (Surrey et al., 2002).

B	Controlled ovarian hyperstimulation (COH) for IVF/ICSI is equally effective with both GnRH antagonist and GnRH-a protocols in terms of implantation and clinical pregnancy rates, but COH with GnRH-a may be preferred because of the availability of more MII oocytes and embryos (Pabuccu et al., 2007, Ref 12903).	Evidence Level 1b

A prospective randomized trial designed as a feasibility study estimated outcome differences between controlled ovarian hyper stimulation (COH) for IVF/ICSI with GnRH antagonist or GnRH agonist (GnRH-a) in mild-to-moderate endometriosis and in patients with endometriomas. Three groups of patients were included and analyzed separately: Group I) Stage I-II endometriosis, group II) history of ovarian surgery for endometrioma and group III) women with uni- or bilateral endometrioma and no history of previous ovarian surgery. No significant differences were found in group I. In group II and III treatment with GnRH-a resulted in a higher ovarian response compared with GnRH antagonist, indicated by significantly more metaphase II oocytes and a higher number of available embryos. The clinical pregnancy rate and implantation rate was not significantly different between treatment groups, but the study was not powered to address these parameters (Pabuccu et al., 2007, Ref 12903).

B	Risk for recurrence is no reason to withhold IVF therapy after surgery for endometriosis stage III or IV since cumulative endometriosis recurrence rates are not increased after ovarian hyperstimulation for IVF (D´Hooghe et al., 2006).	Evidence Level 2a

Since endometriosis is an oestrogen-dependant disease, there is concern about the negative impact of supra-physiological oestradiol levels during COH. A retrospective cohort study including 67 infertility patients after surgery for endometriosis stage III or IV showed a significantly lower cumulative endometriosis recurrence rate (CERR) in patients treated with IVF only compared to patients treated with IUI. Moreover, CERR before and after assisted reproductive technology were similar, suggesting that cumulative exposure to high levels of oestradiol during ovarian hyper stimulation is not a risk factor for endometriosis recurrence (D'Hooghe et al., 2006). However, rare case reports have described increased growth and recurrence of endometriotic lesions during COH and the onset of severe symptoms coincided with high levels of plasma oestradiol (Renier et al., 1995; Govaerts et al., 1998; Anaf et al., 2000, Jun and Lathi, 2007, Ref 12316).

A	Laparoscopic ovarian cystectomy in patients with unilateral endometriomas between 3 and 6 cm in diameter before IVF/ICSI can decrease ovarian response without improving cycle outcome (Demirol et al., 2006).	Evidence Level 1b

There is one RCT (Demirol et al., 2006) and two systematic reviews of retrospective studies (Gupta et al., 2006; Somigliana et al., 2006a) on the impact of ovarian endometriomas and their removal on the outcome of assisted reproduction. In the prospective randomized trial 49 patients underwent conservative ovarian surgery before the ICSI cycle and 50 patients underwent the ICSI cycle directly. Ovarian stimulation parameters for those who underwent ovarian endometrioma cystectomy were significantly reduced and fewer mature oocytes were retrieved in the cystectomy group. No difference in implantation and clinical pregnancy rates were detected (Demirol et al., 2006). Studies evaluating the response to ovarian stimulation in patients previously operated for endometriomas have led to controversial results in terms of ovarian response and cycle outcome. In patients with unilateral disease a significantly reduced number of follicles in the operated ovary compared to the intact side were reported in several but not all studies. The authors of one systematic review conclude that overall evidence suggests that surgery does not benefit asymptomatic women preparing to undergo IVF-ICSI who are found to have an endometrioma (Somigliana et al., 2006a).

The other meta analysis indicates that ovarian endometrioma have adverse effects on follicle number and oocytes retrieved but not on embryo quality or pregnancy outcomes. Surgery may decrease the number of retrieved oocytes, but the overall fertility outcome is not affected (Gupta et al., 2006). Most publications do not report the size of endometriomas or only endometriomas > 3 cm were considered for data analysis. Subsequently, in a prospective randomized study in patients undergoing ovarian stimulation for IUI no significant differences in follicular responses were observed between normal ovaries and ovaries with endometriomas previously treated by laparoscopy. No differences in the number of follicles were detected between ovaries randomized in the cystectomy versus fenestration and coagulation group (Alborzi et al, 2007, Ref 12314).

The observation of an impaired ovarian response in women with endometriomas does not clarify whether the damage is consequent to surgery or antecedent to the intervention. An observational study in women with unilateral endometriomas who did not undergo previous ovarian surgery showed a significant mean reduction in follicles in the affected ovaries, suggesting that the presence of ovarian endometriomas is associated with a reduced responsiveness to gonadotrophins (Somigliana et al., 2006b).

GPP	Laparoscopic ovarian cystectomy can be considered if an ovarian endometrioma >3 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.

In summary, since no indication exists that even in experienced hands laparoscopic surgery of endometriomas improves ovarian function or enhances IVF outcome substantially, practical considerations have to be taken into account and patients have to be counselled on an individual basis. Surgical removal of endometriomas gives histological information and can rule out malignancy, can relieve discomfort and pain, may reduce the risk of rupture and adnexal torsion and may facilitate transvaginal access to ovarian follicles. On the other hand, the possibility of ovarian failure due to destruction of normal ovarian tissue during surgery, especially in patients who have already had repetitive surgery for endometriomas, has to be considered.

Extragenital endometriosis

Concise

Endometriosis can be found in almost any tissue in the body apart from the spleen.

Symptoms will depend on the site of the disease. Cyclicity of symptoms is usually present, at least in early stages, and may be the only clue which leads to the diagnosis of endometriosis.

Treatment will again depend on the site. If complete excision is possible, this is the treatment of choice; when this is not possible, long term medical treatment is necessary. The same principles of

medical treatment for pelvic endometriosis will apply for extra genital endometriosis (see section Treatment of Confirmed Disease) (Berqvist 1992; Joseph and Sahn 1996; Jubanyik and Comite 1997; Nisolle et al., 2007).

B	Appendicular endometriosis is usually treated by appendectomy. Surgical treatment of bladder endometriosis is usually in the form of excision of the lesion and primary closure of the bladder wall. Ureteral lesions may be excised after stenting the ureter, however in the presence of intrinsic lesions or significant obstruction segmental excision with end-to-end anastomosis or reimplantation may be necessary Abdominal wall and perineal endometriosis is usually treated by complete excision of the nodule.	Evidence Level 3

Supporting

Endometriosis can be found in almost any tissue in the body apart from the spleen. Symptoms will depend on the site of the disease. Cyclicity of symptoms is usually present, at least in early stages, and may be the only clue which leads to the diagnosis of endometriosis. Treatment will again depend on the site. If complete excision is possible, this is the treatment of choice; when this is not possible, long term medical treatment is necessary. The same principles of medical treatment for pelvic endometriosis will apply for extragenital endometriosis (see section Treatment of Confirmed Disease) (Berqvist 1992; Joseph and Sahn 1996; Jubanyik and Comite1997; Nisolle et al., 2007).

B	Appendicular endometriosis is usually treated by appendectomy. Surgical treatment of bladder endometriosis is usually in the form of excision of the lesion and primary closure of the bladder wall. Ureteral lesions may be excised after stenting the ureter, however in the presence of intrinsic lesions or significant obstruction segmental excision with end-to-end anastomosis or reimplantation may be necessary Abdominal wall and perineal endometriosis is usually treated by complete excision of the nodule.	Evidence Level 3

Our knowledge of extragenital endometriosis mainly comes from case series or reports and there are no comparative studies due to the relative rarity of this condition. The subject has been reviewed by several authors over the last two decades (Berqvist 1992; Joseph and Sahn 1996; Jubanyik and Comite 1997; Nisolle et al., 2007).

Patients with distant site endometriosis may not be diagnosed for several years due to their physicians being unfamiliar with the diagnosis of endometriosis or its symptoms. Symptoms will depend on the site of the disease. Cyclicity of symptoms is usually present, at least in early stages, and may be the only clue which leads to the diagnosis of endometriosis. Diagnosis is usually made by histological confirmation, this is important to exclude other pathology, particularly malignancy.

Additional imaging and endoscopic investigations specific to the location may also be used. Treatment will again depend on the site. In general if complete excision is possible surgery would be the treatment of choice, however when this is not possible long term medical treatment is necessary. The same principles of medical treatment for pelvic endometriosis will apply for extragenital endometriosis (see section Treatment of Confirmed Disease).

Intestinal endometriosis

Bowel endometriosis is reported to be present in 5-40% of patients with pelvic endometriosis. Rectum and sigmoid are the most common sites (up to 95% of cases) and 5-20% of the cases have appendix endometriosis (Jubanyik and Comite 1997). Endometriosis of the small intestine is relatively rare.

Depending on the location, some patients with intestinal endometriosis may have no symptoms, but chronic abdominal pelvic pain, dyschezia (pain during defecation during menstrual period), dysmenorrhoea, dyspareunia, tenesmus, constipation or diarrhoea and rectal bleeding are reported by some patients. Diagnosis is usually made at laparoscopy, additional imaging techniques such as MRI, contrast studies or sigmoidoscopy may be used. Surgical treatment of recto sigmoid endometriosis is discussed in detail in the Surgical Treatment section. Appendicular endometriosis is usually treated by appendicectomy.

Urinary tract endometriosis

Urinary tract endometriosis is found in 1-4% of women with pelvic endometriosis, 80-90% of these are on the bladder and the rest are ureteral endometriosis. Endometriosis of the kidney is extremely rare (Jubanyik and Comite 1997). Ureteral endometriosis is of particular importance as it may cause obstruction and functional loss of a kidney without causing symptoms (i.e. silent kidney). The majority of ureteral endometriosis lesions are extrinsic, lesions within the wall of the ureters are less common.

The symptoms of bladder endometriosis include cyclical suprapubic pain, dysuria, frequency and haematuria. Ureteral endometriosis is mostly asymptomatic but may cause low back pain, haematuria and recurrent urinary tract infections.

Pelvic and abdominal ultrasonography, computerised tomography or MRI, intravenous urography and cystoscopy with biopsy are helpful investigations used for the diagnosis of bladder endometriosis (Jubanyik and Comite 1997). If rectovaginal endometriosis is diagnosed on physical examination MRI, sonography of the kidney or an intravenous pyelography is of use to diagnose or exclude ureteral obstruction. If ureteral obstruction is diagnosed renography is indicated to diagnose loss of kidney function.

Surgical treatment of bladder endometriosis is usually in the form of excision of the lesion and primary closure of the bladder wall. Ureteral lesions may be excised after stenting the ureter, however in the presence of intrinsic lesions or significant obstruction segmental excision with end-to-end anastomosis or reimplantation may be necessary. When surgery is not possible medical treatment options may also be used.

Abdominal wall and perineal endometriosis

This form of endometriosis is usually the easiest to diagnose and treat. Endometriotic lesions at the site of previous surgical scars, umbilicus or inguinal canal have been reported. These lesions are

located within the scar of gynaecological operations, particularly hysterotomy, caesarean sections or episiotomy (Jubanyik and Comite 1997; Nisolle et al., 2007). They appear as dark red-blue or brown, tender nodules. They usually become more painful during menstruation and occasionally there might be cyclical bleeding from these lesions.

Diagnosis is usually by history and clinical examination and treatment is by complete excision of the nodule (Nisolle et al., 2007).

Thoracic endometriosis

Endometriotic lesions of the pleura, lung parenchyma and the diaphragmatic surface may present with pneumothorax, haemothorax, haemoptysis, chest pain and dyspnoea. The symptoms are in general cyclical and tend to start within 24-48 hours after the onset of menstruation (Joseph and Sahn 1996). Women with pleural disease frequently have pelvic endometriosis, it almost always affects the right side (Nisolle et al., 2007), the right to left ratio being 9:1 (Jubanyik and Comite 1997). In contrast, the lung parenchyma is a bilateral disease. This pattern is probably due to pleural/diaphragmatic lesions being secondary to transabdominal and transdiaphragmatic migration while lung lesions being due to lymphovascular embolisation (Nisolle et al., 2007).

Diagnosis may be based on history, chest X-ray, computerised tomography or MRI but additional investigations to confirm diagnosis or exclude other pathology include thoracoscopy, thoracotomy for pleural/diaphragmatic disease and bronchoscopy for pulmonary disease. However, the latter group have limited diagnostic value due to inaccessibility of pulmonary lesions at bronchoscopy or localised nature of pleural lesions.

Medical, surgical or combination treatment options are used. Immediate treatment of pneumothorax or haemothorax is by insertion of a chest tube drain. Hormonal treatment is known to be effective in a significant proportion of the patients. In cases of recurrent pneumothorax or haemothorax chemical pleurodesis, pleural abrasion or pleurectomy may be helpful. Persistent haemoptysis due to parenchymal lesions may be treated by lobectomy, segmentectomy or rarely tracheobronchoscopic laser ablation (Nisolle et al., 2007)

Adolescents

Concise

Symptoms

B	It is hard to predict the presence of endometriosis in adolescents with pelvic pain merely from the presenting symptoms, because similar symptoms occur in patients evaluated laparoscopically for pelvic pain with and without endometriosis (Reese et al., 1996; Laufer et al., 1997).	Evidence Level 3

Laparoscopic evaluation of chronic pelvic pain

B	Laparoscopy should be considered if adolescents with chronic pelvic pain who do not respond to medical treatment (NSAIDs, OCPs) since endometriosis is very common under these circumstances (Goldstein et al., 1980; Vercellini et al., 1989; Reese et al, 1996; Laufer et al., 1997; Emmert et al., 1998; Hassan et al., 1999; Kontoravdis et al., 1999; Shin et al., 2005; Stavroulis et al., 2006).	Evidence Level 3

Extent and appearance of the disease

B	Minimal to mild endometriosis according to the rASRM classification are the most common stages of the disease in adolescents. Gynaecologic surgeons should pay special attention to red, clear or white lesions which were reported to be more prevalent in adolescents as opposed to adults who have endometriosis (Goldstein et al., 1980; Vercellini et al., 1989; Davis et al., 1993; Reese et al, 1996; Laufer et al., 1997; Emmert et al., 1998; Hassan et al., 1999; Bai et al., 2002; Marsh and Laufer, 2005).	Evidence Level 3

Obstructive genital anomalies

B	Menstrual outflow obstructions such as Müllerian anomalies may cause early development of endometriosis in adolescents. Regression of the disease has been observed once surgical correction of the anomaly has been accomplished (Sanfilippo et al., 1986; Ugur et al., 1995; Hur et al., 2007).	Evidence Level 3

Supporting

Symptoms

B	It is hard to predict the presence of endometriosis in adolescents with pelvic pain merely from the presenting symptoms, because similar symptoms occur in patients evaluated laparoscopically for pelvic pain with and	Evidence Level 3

	without endometriosis (Reese et al., 1996; Laufer et al., 1997).	

Endometriosis can be confirmed by laparoscopy in adolescents under evaluation for chronic pelvic pain. The most common presenting symptom in adolescents with endometriosis is cyclic pain. Less commonly acyclic pain, dyspareunia, gastrointestinal symptoms, irregular menses, urinary symptoms and vaginal discharge are described (Goldstein et al., 1980; Bai et al., 2002; Ballweg, 2003). However, similar presenting symptoms occur in adolescent patients evaluated for pelvic pain with and without endometriosis (Reese et al., 1996; Laufer et al., 1997).

Laparoscopic evaluation of chronic pelvic pain

B	Laparoscopy should be considered if adolescents with chronic pelvic pain who do not respond to medical treatment (NSAIDs, OCPs) since endometriosis is very common under these circumstances (Goldstein et al., 1980; Vercellini et al., 1989; Reese et al, 1996; Laufer et al., 1997; Emmert et al., 1998; Hassan et al., 1999; Kontoravdis et al., 1999; Shin et al., 2005; Stavroulis et al., 2006).	Evidence Level 3

Endometriosis lesions can be detected frequently in adolescent patients with chronic pelvic pain. Prevalence rates of endometriosis in adolescent patients undergoing laparoscopy for chronic pelvic pain range from 19% to 73% (Goldstein et al., 1980; Vercellini et al., 1989; Reese et al, 1996; Laufer et al., 1997; Emmert et al., 1998; Hassan et al., 1999; Kontoravdis et al., 1999; Shin et al., 2005). Because dysmenorrhoea is very common in adolescents not all young women with pelvic pain can be subjected to invasive diagnosis by laparoscopy. However, if combination hormone therapy (such as oral contraceptive pills) or non-steroidal anti-inflammatory drugs fail, 35-73% of adolescents do have endometriosis at the time of laparoscopy (Reese et al, 1996; Laufer et al., 1997; Stavroulis et al., 2006).

Extent and appearance of the disease

B	Minimal to mild endometriosis according to the rASRM classification are the most common stages of the disease in adolescents. Gynaecologic surgeons should pay special attention to red, clear or white lesions which were reported to be more prevalent in adolescents as opposed to adults who have endometriosis (Goldstein et al., 1980; Vercellini et al., 1989; Davis et al., 1993; Reese et al, 1996; Laufer et al., 1997; Emmert et al., 1998; Hassan et al., 1999; Bai et al., 2002; Marsh and Laufer, 2005).	Evidence Level 3

Obstructive genital anomalies

B	Menstrual outflow obstructions such as Müllerian anomalies may cause early development of endometriosis in adolescents. Regression of the disease has been observed once surgical correction of the anomaly has been accomplished (Sanfilippo et al., 1986; Ugur et al., 1995; Hur et al., 2007).	Evidence Level 3

Similar prevalence rates of endometriosis were reported in a group of 186 patients with Müllerian anomalies compared to controls without Müllerian anomalies (19.8 % vs. 19.1 %). However, if patients without functioning endometrium were excluded, endometriosis was found significantly more common in patients with outflow obstruction (57.6 %) compared to patients with non-obstructive type of anomaly (17.6 %) (Ugur et al., 1995).

Treatment

GPP	Physicians treating adolescents with endometriosis should adopt a multidimensional approach: Surgery, hormonal manipulation, pain medication, mental health support, complementary and alternative therapies, and education in self management strategies are useful components.

C	Due to concerns of adverse effects on final bone density formation gonadotrophin-releasing hormone agonists are usually only possible for adolescents age 17 years or older, if symptoms persist (Propst and Laufer, 1999; ACOG Committee Opinion, 2005.	Evidence Level 4

Treatment algorithms for management of adolescent endometriosis are based upon pathophysiologic principles and extrapolation of data from adult endometriosis. A small case series of 11 laparoscopically and hormonally treated adolescent patients reported excellent responses even in patients with severe endometriosis (Stavroulis et al., 2006). A literature review on the impact of gonadotrophin-releasing hormone agonists on bone mass in adolescents not responding to conventional therapy could not identify any study specifically studying the adolescent population. Thus, the ideal dosage and long-term effects of add-back therapy remains to be determined (Lubianca et al., 1998).

Coping with Disease

Concise

Complementary therapies

C	There is evidence from two systematic reviews suggesting that high frequency TENS, acupuncture, vitamin B1 and magnesium may help to relieve dysmenorrhoea (Proctor et al., 2002; Proctor and Murphy, 2001). One RCT has shown that vitamin E may relieve primary dysmenorrhoea and reduce blood loss (Ziaei et al., 2005). Whether such treatments are effective for endometriosis associated dysmenorrhoea and heavy bleeding is unknown.	Evidence Level 4

GPP	Many women with endometriosis report that nutritional and complementary therapies such as homeopathy, reflexology, Traditional Chinese Medicine, herbal treatments, 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. Self-management programmes may prove beneficial in providing the woman with tools to enable her to live with a chronic disease.

Supporting

Complementary therapies

C	There is evidence from two systematic reviews suggesting that high frequency TENS, acupuncture, vitamin B1 and magnesium may help to relieve dysmenorrhoea (Proctor et al., 2002; Proctor and Murphy, 2001). One RCT has shown that vitamin E may relieve primary dysmenorrhoea	Evidence Level 4

	and reduce blood loss (Ziaei et al., 2005). Whether such treatments are effective in endometriosis associated dysmenorrhoea and heavy bleeding is unknown.	

Many consumers are now seeking complementary therapies over conventional medicine. In the field of menstrual disorders, there is some support for this approach from a systematic review suggesting that nutritional intake and metabolism may play an important role in the cause and treatment of such problems (Proctor and Murphy, 2001).

In three double-blinded, but small, RCTs it was shown that magnesium was more effective than placebo for pain relief and the need for additional medication was less (Davis, 1988; Fontana-Klaiber and Hogg, 1990; Seifert et al., 1989). The largest of these trials (n=50) also reported that women taking the magnesium therapy had substantially lower levels of PGF2-α in their menstrual blood than those on placebo ($p<0.05$), which mirrored the therapeutic decrease in pain experienced by the participants (Seifert et al., 1989). Overproduction of PGF2 has been shown to be a substantial contributing factor to the painful cramps associated with dysmenorrhoea. This emphasises the potential biological rationale behind magnesium therapy for dysmenorrhoea, as magnesium inhibits the biosynthesis of PGF2-α as well as having a role in muscle relaxation and vasodilation (Altura and Altura, 1985; Reavely, 1998).

Vitamin B1 plays an important role in metabolism and deficiency can result in fatigue, muscle cramps, various pains, and a reduced tolerance to pain, which are all factors that can be associated with dysmenorrhoea (Reavely, 1998). This may be why one large trial (n=556) showed a daily intake of 100mg of vitamin B1 for two months to be an effective treatment for dysmenorrhoea, with none of the women taking placebo experiencing complete pain relief (Gokhale, 1996).

In a randomised controlled trial 278 girls aged 15-17 with primary dysmenorrhoea were given 200 units of vitamin E or placebo twice a day, beginning two days before the expected start of menstruation and continued through the first three days of bleeding over four consecutive menstrual periods. At four months, the vitamin E group had lower pain severity assessed by visual analogue scale (0.5 vs. 6, $p>0.001$), shorter pain duration (1.6 hours vs. 17 hours, $p>0.0001$) and reduced blood loss assessed by pictorial blood loss assessment chart (46 vs. 70, $p>0.0001$). (Ziaei et al., 2001). Another two randomized, double-blinded, placebo controlled trials have demonstrated significant decrease in median pain scores in the groups treated with vitamin E compared to placebo for primary dysmenorrhoea (Butler et al., 1955; Ziaei et al., 2005).

A systematic review concluded that transcutaneous electrical nerve stimulation (TENS) and acupuncture can be effective in the treatment of dysmenorrhoea. Though there was insufficient evidence to determine and assess the treatments accurately, the reviewers concluded that TENS represents a suitable alternative for women, who prefer not to use medication or wish to minimise their intake of NSAIDs (Proctor et al., 2002).

Whether any of these treatments are effective in endometriosis associated dysmenorrhoea has not been shown.

Proctor et al highlight that one small but methodologically sound trial of acupuncture suggests benefits for this modality (Helms, 1987), and in a retrospective study of 47 families with paediatric

pain patients (median age 16, 6 of whom were diagnosed with endometriosis) 70% felt the treatment helped their symptoms (Kemper et al., 2000).

A randomised controlled trial of 90 women with endometriosis compared Shu-Mu acupuncture (n=30), routine needling acupuncture (n=30) and oral Danazol (n=30). The total effective rate was similar in the three groups, however the Shu-Mu point combination group was superior to the other two groups in improvement of dysmenorrhoea and irregular menstruation, and serum CA125 in the Shu-Mu point combination treated group was significantly decreased (Sun and Chen, 2006).

GPP	Many women with endometriosis report that nutritional and complementary therapies such as homeopathy, reflexology, Traditional Chinese Medicine, herbal treatments, etc, do improve pain symptoms. Whilst there is little 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.

Extending the therapeutic network

Given the chronic and stubborn nature of endometriosis, there may be times when it can be beneficial to extend the therapeutic network beyond the medical mainstream; especially when women report that nutritional and complementary therapies, such as homeopathy, reflexology, Traditional Chinese Medicine (TCM), herbal treatments, physiotherapy, etc, improve their pain symptoms.

Whilst there is little evidence from any of the above to support these treatments in endometriosis related symptoms these should not be ruled out if the woman feels that they are beneficial to her overall pain management and/or quality of life.

Nutritional therapy/dietary modification

Nutritional therapy/dietary modification has shown promising effects on dysmenorrhoea in three small RCTs, specifically supplementation with omega-3 fish oil combined with vitamin B12 and a diet high in vegetables and low in animal fats (Harel et al., 1996; Deutch et al., 2000; Barnard et al., 2000; Fjerbaek and Knudsen, 2007).

Parazzini et al found that intake of fruit and green vegetables decreased the risk of endometriosis, whereas ham, beef and other red meat increased the risk (Parazzini et al., 2004), Several studies also link fibre intake to an increased oestrogen excretion (Rose et al., 1997; Kaneda et al., 1997).

A randomized comparative study evaluated conservative surgery plus placebo compared with conservative surgery plus hormonal suppression treatment or dietary therapy (vitamins, minerals, lactic ferments, fish oil). It showed that hormonal suppression therapy and dietary supplementation were equally effective in reducing non-menstrual pelvic pain and improving quality of life compared with placebo in women with endometriosis stage III-IV (Sesti et al, 2007).

An RCT of 80 women with endometriosis demonstrated that two months of high-dose vitamin E and C therapy was associated with significant improvement in endometriosis pain and a reduction in inflammatory markers (Santanam et al., 2003).

Homeopathy

In a very small, non-randomised, study in eight patients diagnosed with endometriosis, five out of seven, who had dysmenorrhoea, reported relief from symptoms (and two had intermittent relief) following individualised homeopathic treatment (Hunton, 1993).

Herbal remedies/Traditional Chinese Medicine

A systematic review of clinical and experimental data on the use of medicinal herbs in the treatment of endometriosis suggest that medical botanicals may have anti-inflammatory and pain-alleviating properties. Medicinal herbs and their active components exhibit cytokine-suppressive, COX-2-inhibiting, antioxidant, sedative and pain-alleviating properties. Each of these mechanisms of action would be predicted to have salutary effects in endometriosis (Wieser et al, 2007).

However, another systematic review (Proctor and Murphy, 2001) concluded that there was insufficient evidence to recommend the use of the herbal remedies considered in the review. One small trial, however, showed that a herbal combination was more effective for pain relief than placebo and that less rescue medication was needed by the treatment group (Kotani et al., 1997).

A randomised controlled trial, which compared Yiweining (YWN) with Gestrinone post-operatively showed a recurrence rate of 5.0% and 5.3% respectively compared with a 30.7% in the placebo group, however, the adverse reaction rate in the YWN was lower (10.0%) than that in the Gestrinone group (31.6%) (Yang et al., 2006). Another randomised controlled trial also compared gestrinone, but this time with Quyu Jiedu Recipe (QJR) and showed a marked improvement of the symptoms of menorrhagia and menstrual disorders, speculating that its mechanism might be related with the lowering of eutopic endometrial VEGF expression (Lian et al, 2007).

Furthermore, Qu et al have demonstrated in endometriosis model rats that the Chinese herb Yiweining (YWN) can prevent the growth of ectopic endometrium by inhibiting the synthesis and secretion of TNF-alpha, IL-6, and IL-8 (Qu et al., 2005), and can reduce the positive expressions of MMP-2 and COX-2 mRNAs (Qu et al., 2006).

Exercise

Whereas physiotherapy, yoga, Pilates, and gentle exercise may assist the body in getting back into shape during/after prolonged periods of pain and/or after surgery to strengthen compromised pelvic/abdominal/back muscles, and whereas reflexology has anecdotally been reported to relieve pain symptoms, there is no evidence published relating to their therapeutic effect on dysmenorrhoea or endometriosis-related symptoms.

Coaching, self management and patient support groups

GPP	Coaching and self-management programmes may prove beneficial in providing the woman with tools to enable her to make informed decisions and learn to live with a chronic disease. 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.

Physical and psychological trauma can contribute to a negative self-image and negative internal dialogue (Stones, 2000). Thus some women with endometriosis may benefit from working with a counsellor/psychologist, in particular a pain psychologist, to develop strategies on how to cope with endometriosis including breaking the pain cycle, dealing with stress and anxiety, and resolve feelings about infertility.

An essential component of high quality clinical care is an informed and engaged patient (Coulter et al, 2007). Coaching can be used in chronic conditions where the clinician and patient work together to reach informed decisions about the plan of care on the basis of the patient's clinical needs, priorities, and values. In menorrhagia, women who have had additional coaching to express their treatment preferences had greater satisfaction and reduced hysterectomy rates, as well as lower service costs (Kennedy et al, 2002).

Self-management (also called the Expert Patients Programme) is a rigorously researched patient led programme developed by Stanford University in the United States. Coventry University has researched self-management in the United Kingdom and their findings support the Stanford research.

The underlying basis of the course is the symptom/pain cycle, showing the interaction between disease, fatigue, depression, anger/fear/frustration, stress/anxiety and tense muscles. The aim of the course is to provide tools to break the cycle at any given point through weekly sessions with tutors, who also have chronic diseases (see: http://www.endometriosis.org/best-practise-falconer.html for more information).

For some women, all they need is to talk to others with the disease - to share mutual experiences, coping techniques, and discuss treatment methods. Patient organisations play an important role in providing women and girls with emotional support, and collaborate closely with physicians and legislators in providing guidance and information about the disease. A list of current global resources for support can be found at: **www.endometriosis.org/support.html**

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Malignancy

Concise

In recent years the issue of whether endometriosis is associated with or indeed causes malignant disease has been raised in the scientific literature. Consequently women now occasionally raise this issue with their physicians.

This section aims to summarise the available literature in a manner that allows clinicians to answer commonly posed questions. The guideline group does not believe that the definitive answer is yet possible but there is enough data on this issue that requires an attempt to address it.

The issues raised by patients can be covered by these four questions:

Are women with endometriosis more likely to develop any cancer?

For women with endometriosis, the overall risk of cancer is estimated to be around 0.7 to 1.0%, suggesting, that endometriosis is not associated with an increased risk of cancer in general. (Heaps et al, 1990)

Does endometriosis turn into cancer?

The transformation of endometriosis to malignancy has been described but is extremely rare.

Is endometriosis associated with the development of specific cancers?

An increased risk of some types of malignancy has been shown for women with endometriosis. The clinical relevance of these associations remains unknown

Is screening for specific cancers indicated?

In the absence of established screening programmes for these conditions specific additional screening cannot be advocated.

Supporting

In recent years the issue of whether endometriosis is associated with or indeed causes malignant disease has been raised in the scientific literature. Consequently women now occasionally raise this issue with their physicians.

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