NHS Evidence – women’s health
Endometriosis
Annual Evidence Update
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1. Introduction

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This is the fourth Endometriosis Annual Evidence Update.

The purpose of the last Evidence Update in March 2009 was to summarise and update the information contained in the guidelines produced by the Royal College of Obstetricians & Gynaecologists in 2006 and the European Society for Human Reproduction & Embryology (ESHRE) in 2005.

We have continued the same approach in the 2010 update. We provide a summary of the ESHRE guideline (updated in 2008) to the investigation and management of endometriosis, alongside our own search of data from high quality studies published in the last year. References relating to new, clinically relevant studies are provided in the text.

We hope that, in time, this site will become the single portal for all health care professionals and women with endometriosis who require high quality information as an aid to clinical decision-making. We also hope that the information provided will improve standards of care throughout the UK.

Lastly, it is important to mention that endometriosis was chosen as one of the first topics for the Database of Uncertainties about the Effects of Treatments (DUETS). This on-line resource gives priority to identifying and publishing unanswered questions about the effects of treatments which have been asked by patients and clinicians, whilst noting therapeutic uncertainties identified through systematic reviews, clinical guidelines, and other formal mechanisms. Uncertainties that we have identified during our 2010 evidence update can be found listed in the DUETs page of this AEU.
2. Search methodology

The aim of the literature search for the 2010 annual evidence update was to update the search carried out in 2009. Search strategies from the RCOG guideline and the ESHRE guideline were again replicated and the databases searched included the Cochrane Database of Systematic Reviews, Pubmed, OVID Embase and EBSCOHost CINAHL. Systematic reviews, meta-analyses and randomised controlled trials (RCTs) were specifically targeted, using a combination of the Pubmed Systematic Review 2 or more terms minimum difference filter, Pubmed RCT CRD/Cochrane Highly Sensitive filter, Embase OVID Systematic Review SIGN Filter, Embase OVID RCT SIGN Filter, CINAHL Systematic Review SIGN Filter and the CINAHL RCT SIGN Filter. The search terms used included endometriosis; endometriomas; endometriosis/diagnosis; endometriosis/drug therapy; endometriosis/complications; endometriosis/surgery and these were combined with the limits ‘English in language’ and restricted to March 2009 until January/February 2010.

The abstracts of the identified papers were manually inspected to determine their relevance and appropriateness for inclusion in this document. Articles included were good systematic reviews and RCTs, and less robust studies where they were considered to illustrate a point of controversy or indicate a possible future direction for the management of the condition. When a paper was to be included, or where doubt existed over the appropriateness of the data, the full-text was obtained.

The following summary document is based on the existing guidelines, which have been updated where new evidence has become available. These data are cited. Readers are referred to the RCOG guideline for the citation details of the older studies.
3. Epidemiology and aetiology of endometriosis

It is difficult to define the epidemiology of endometriosis precisely because a surgical procedure is required to make the diagnosis definitively. However, the following are best estimates:

- Endometriosis affects 10-15% of all women in the reproductive years.
- The incidence is 40-60% in women with dysmenorrhoea and 20-30% in those with subfertility.
- Risk factors include a heavy menstrual load (due to short cycle length and long duration of flow).
- Current/recent use of the combined oral contraceptive (COC), smoking and exercise may be protective.
- The sisters and daughters of affected women are 6-9 times more likely to develop endometriosis than women in the general population. A recent systematic review has analysed the potential genetic associations with endometriosis. However, no firm conclusions could be drawn. A large number of studies have considered putative genetic markers, and these may be of future benefit in assessing the risk of disease development, or in understanding disease pathogenesis (Montgomery et al., 2008).
- Endometriosis is a considerable burden in terms of both direct and indirect healthcare costs, and its affect on quality of life (Gao et. al., 2006).

A number of hypotheses have been proposed to explain the aetiology of endometriosis. The most dominant theory is retrograde menstruation (the passage of viable endometrial cells along the fallopian tubes into the pelvis at the time of menstruation).

- However, retrograde menstruation occurs commonly in all women. A systematic review found evidence supporting the retrograde menstruation theory. A significantly higher prevalence of endometriotic lesions was found in the right subphrenic area. The authors explain this by the fact that peritoneal fluid, which is transported clockwise, is trapped in the right hypochondrium by the falciform ligament (Vercellini et al., 2007).
- It is likely that aberrant function in related pathophysiological systems (e.g. immunity, cell clearance, angiogenesis) is responsible for the implantation and subsequent growth of endometrial cells in the peritoneal cavity.
- The disease causes chronic inflammation, fibrosis, adhesions and ovarian cyst formation.
- Endometriosis has been associated in the past with various malignancies (e.g. ovarian cancer, breast cancer, melanoma and non-Hodgkin’s lymphoma). However, the data are inconclusive and the risks, if they exist, may not be clinically relevant (Somigliana et al., 2006). Another recent systematic review, however, looked at causality versus bias for interpreting data demonstrating an association between endometriosis and ovarian cancer. The authors
concluded that a causal relationship exists but the frequency of malignant transformation of endometriotic lesions into ovarian cancer is similar to that of eutopic endometrium (Vigano et al., 2007).

- A systematic review of the effect of food intake on endometriosis and dysmenorrhoea revealed that there are no clear data supporting dietary recommendations. Some studies suggested that fish oil (n-3 oils) may reduce pain symptoms in endometriosis. The authors suggested further studies on this issue (Fjerbaek and Knudsen, 2007).

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4. The pathological characteristics of endometriosis

Endometriosis is defined as the presence of endometrial-like tissue in sites outside the uterine cavity, in so far as the lesions have many cellular and molecular characteristics in common with eutopic endometrium.

The types of lesions seen are:

- Superficial deposits on the peritoneal or ovarian surface with a typically blue-black ‘powder-burn’ appearance, but more ‘subtle’ lesions are also recognised (e.g. petechial, vesicular, polypoid, haemorrhagic or flame-like implants).

- Small cysts on the peritoneal or ovarian surface containing old haemorrhage surrounded by varying degrees of fibrosis.

- Endometriomas (ovarian cysts), which contain thick, ‘chocolate-like’ fluid; these are usually stuck to the underlying peritoneal surface (ovarian fossa) and other structures (e.g. fallopian tube, bowel, uterus).

- Deep nodules infiltrating more than 5 mm below the peritoneal surface that may penetrate or adhere to other structures (e.g. bowel, bladder, ureters, vagina).

Recent work has identified nerve fibres within the endometrium of women with endometriosis, which may lead to a better understanding of the disease process. The densities of nerve fibres, staining positive for PGP9.5 (a neuronal marker), neuropeptide Y and vasoactive intestinal polypeptide, were greater in the functional layer of women with endometriosis than women without the disease. Preliminary results suggest nerve fibre density is reduced in women taking hormonal therapy, as compared with those on no treatment, and the type of nerve fibres may also change (Medina and Lebovic, 2009).

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5. The clinical features and diagnosis of endometriosis

The following symptoms have been associated with endometriosis:

- Severe dysmenorrhoea (painful periods)
- Deep dyspareunia (pain on intercourse)
- Chronic non-menstrual pain
- Pain at the time of ovulation
- Dyschezia (pain on defaecation, especially at the time of menstruation)
- Cyclical or perimenstrual symptoms, affecting the bowel or bladder, with or without abnormal bleeding or pain
- Subfertility (difficulty conceiving for more 12 months)
- Chronic fatigue.

However, the predictive value of any one symptom or set of symptoms is uncertain because of the overlap with other conditions, such as irritable bowel syndrome, interstitial cystitis, pelvic inflammatory disease, fibromyalgia and musculoskeletal disorders (ASRM Practice Committee - Pain, 2006.). The difficulties inherent in interpreting such symptoms contribute to the well-recognised delay of up to 10 years between the onset of symptoms and a surgical diagnosis.

Endometriosis should be suspected in women of reproductive age who present with such symptoms, especially if there is a cyclical component. A history and pelvic examination should be performed. There is evidence to suggest that performing the examination during menstruation helps to make the diagnosis, although many women are reluctant to be examined at that time.

The pelvic examination may be entirely normal, but features suggestive of endometriosis include:

- Generalised pelvic tenderness
- Fixed, retroverted uterus (due to adhesions and/or deeply infiltrating disease)
- Tender uterosacral ligaments (nodules may also be palpable)
- Enlarged ovaries
- Seeing lesions/nodules in the vagina or on the cervix.

The diagnosis may be suspected on clinical grounds but it can only be confirmed on visual inspection of the peritoneal cavity at laparoscopy. Diagnostic laparoscopy remains the gold standard for the diagnosis of endometriosis. A recent review considering the value of diagnostic laparoscopy for a variety of conditions concluded that 78-84% of women undergoing
laparoscopy for suspected endometriosis had the disease confirmed at surgery (Richardson, 2009).

Histological confirmation of at least one lesion represents ideal practice, although if an endometrioma is greater than 4cms in diameter or deeply infiltrating disease is present, histology should be obtained to exclude rare instances of malignancy.

Disease severity should be assessed by documenting in detail the type, location and extent of all lesions and adhesions found at surgery. Ideal practice is to record the findings on video or DVD as well. Disease severity can be assessed quantitatively using a classification system such as the one developed by the American Society for Reproductive Medicine (ASRM). However, there is no correlation between such systems and the type or severity of pain symptoms.

Diagnostic laparoscopy is associated with an approximately 3% risk of minor complications, such as nausea or shoulder-tip pain, and a risk of major complications, such as bowel perforation, of between 0.6 to 1.8 per 1,000 procedures. Therefore, a non-invasive test would be clinically useful.

The following tests have been used with varying degrees of success:

• Serum CA-125 (a test for ovarian cancer) – levels may be elevated in endometriosis but the test has little diagnostic value and is not recommended.

• Trans-vaginal ultrasound – a useful tool to make and exclude the diagnosis of an ovarian endometrioma, but it has limited value in diagnosing peritoneal disease. Two studies have proposed different ways of performing ultrasound to detect deeply infiltrating endometriosis: transvaginal ‘tenderness guided’ ultrasound with 91% sensitivity and 89% specificity for vaginal disease, and 74% sensitivity and 88% specificity for rectovaginal disease (Guerriero et. al., 2008), and transrectal ultrasound in rectovaginal disease with a positive post-test prevalence probability of 93% (Griffiths et. al., 2008). The authors advocating the use of transrectal ultrasound concluded that pre-operative scanning for rectovaginal endometriosis strongly predicts the need for extensive laparoscopic dissection and potential bowel resection.

• Magnetic resonance imaging (MRI) – there is insufficient evidence at present regarding its diagnostic potential; however, MRI and other imaging modalities (e.g. transrectal ultrasound, IVP, barium enema) may have a role in defining disease extent in deeply infiltrating endometriosis.

The identification of nerve fibres may hold potential as a diagnostic test for endometriosis in the future. One study has shown 100% sensitivity and specificity to detect endometriosis by tissue biopsy (reviewed in Medina and Lebovic, 2009).

If a woman with symptoms suggestive of endometriosis wants treatment without a definitive diagnosis, the options include counselling, analgesia and hormonal medication to reduce menstrual flow (e.g. progestagens or COC). It is unclear whether the COC should be taken conventionally, continuously or in a tricycle regimen in such circumstances.
A gonadotrophin-releasing hormone (GnRH) agonist may be taken, although this is an expensive option and concerns exist about the effects on bone mineral density (BMD). It is also argued that establishing the correct diagnosis at laparoscopy before initiating therapy with significant short- and long-term side effects is the preferred approach (ASRM Practice Committee - Pain, 2006).

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6. Non-surgical management of endometriosis-associated pain

Endometriosis can be a chronic and debilitating disease, and few treatment options are entirely satisfactory. A cure may be achievable but for many women the medical and surgical treatments currently available have their limitations and symptoms often return after treatment.

Some women prefer not to take hormonal medication and are able to control their symptoms with analgesics. Although non-steroidal inflammatory drugs (NSAIDs) may relieve endometriosis-associated pain, there is too little evidence to assess their effectiveness. NSAIDs have significant side-effects (e.g. gastric ulceration and an anti-ovulatory effect when taken at mid-cycle). Other analgesics may be effective but there is insufficient evidence to make recommendations. A Cochrane review found no significant difference between naproxen sodium and placebo in providing adequate pain relief for endometriosis. However, the authors highlight the paucity of evidence in this area, as only one trial was identified that could be included in this review (Allen, 2009).

There is some evidence that high frequency TENS, acupuncture, vitamin B1 and magnesium may help to relieve dysmenorrhoea, but there is limited evidence on such treatments in managing endometriosis-associated pain. The role of Japanese acupuncture in managing such pain appears to be limited. A 2008 study saw women randomly allocated to acupuncture or sham treatment for an eight week treatment protocol. At four weeks, women in the acupuncture group had a significantly greater decrease in pain scores compared with the sham group. However, this difference was not sustained at eight weeks. Although both groups had a reduction in pain score from baseline, the difference between sham and treatment groups was not significant (Wayne et al., 2008).

A Cochrane review considered the effectiveness and safety of Chinese Herbal Medicine (CHM) in alleviating endometriosis-related pain. After laparoscopic surgery for endometriosis, combined oral and enema administration of CHM has a comparable benefit to gestrinone but with fewer observed side effects. Oral plus enema administration of CHM showed a greater reduction in average pain scores than danazol and in the size of adnexal masses with fewer adverse effects (Flower et al, 2009).

A systematic review of clinical and experimental data on the use of medicinal herbs in the treatment of endometriosis illustrated the lack of evidence from clinical studies (Wieser et al., 2007). However, the review highlighted the anti-inflammatory and pain-alleviating mechanisms of action of many herbal remedies and predicted that they might have a beneficial effect in endometriosis symptoms, if tested in an appropriate manner.

The options for hormonal treatment include the COC, progestagens, androgenic drugs and GnRH agonists; at appropriate doses, all suppress ovarian activity and menstruation. The levonorgestrel intra-uterine system (LNG-IUS) also reduces endometriosis-associated pain (ESHRE 2007).
The principal hormonal drugs studied – COCs, danazol, gestrinone, medroxyprogesterone acetate (MPA) and GnRH agonists – are equally effective at relieving endometriosis-associated pain when prescribed for 6 months but their side-effect and cost profiles differ. When used to manage endometriosis-associated pain, intramuscular depot medroxyprogesterone acetate 150mg can be given every three months. An RCT randomised one group of women to receive monthly injections for 6 months, followed by 3 monthly injections, whilst the second group had 3 monthly injections throughout the treatment period. This trial found no statistically significant difference in patient satisfaction between two different dosing schedules at various follow-up periods (Cheewadhanaraks et al., 2009).

Implanon® may also be an effective treatment for endometriosis related pain. Compared with depot MPA, it demonstrated an equivalent improvement in pain scores over a 12 month study period (Walch et al, 2009).

An RCT in women with endometriosis found dienogest (DNG) to be comparable with buserelin acetate (BA) in reducing symptoms. DNG also resulted in less bone mineral density loss compared with BA (Harada et al, 2009).

Maintaining women symptom free after successful treatment with GnRH agonists has also been considered. Danazol and mid- or low-dose oral contraceptives were shown to maintain women symptom free effectively for 12 months of treatment and prevent the recurrence of disease (Kitawaki et al, 2008).

The use of aromatase inhibitors and their effect on pain in endometriosis was considered in a systematic review. Seven studies (case reports and case series) all tended to show improvement in pain scores, lesion size and quality of life in women using aromatase inhibitors. One RCT also showed that aromastase inhibitors in conjunction with GnRH agonists improved pain scores, as compared to GnRH agonists alone (Patwardhan et al, 2008).

Promising conclusions were found in a literature review regarding medical treatment for rectovaginal disease, which was shown to have a beneficial effect on pain relief and lesion size, as well as patient satisfaction and quality of life. Different forms of medical treatment appeared effective, including GnRH analogues, danazol, the LNG-IUS and aromatase inhibitors (Vercellini et al, 2009).

It is also important to bear in mind that:

- medical treatment does not always provide complete pain relief and some patients fail to respond at all.
- symptom recurrence is common following medical treatment.
- some side-effects limit long-term use and may produce poor compliance, e.g. androgenic side-effects associated with danazol (Selak et al., 2007). GnRH agonist therapy may result in up to 6% BMD loss in the first 6 months and the loss may not always be entirely reversible.
However, the concomitant use of ‘add-back’ (oestrogen and progestagen) therapy protects against BMD loss at the lumbar spine during treatment and for up to 6 months after treatment.

- the COC and Depo-Provera can be used long term, but danazol and GnRH agonists are usually restricted to 6 months; however, one study suggests 3 months with a GnRH agonist may be as effective as 6 months in terms of pain relief.

- although the COC and GnRH agonist therapy appear to be equally effective, the published studies are all small and no other treatments have been assessed as comparators (Davis et al., 2007). Therefore, there is a clear need to evaluate fully the role of the COC in managing symptoms associated with endometriosis.

A small double-blind, randomised, placebo-controlled trial has shown benefit in using a low dose combined oral contraceptive pill (COCP) in reducing endometriosis-associated dysmenorrhea (Harada et al., 2008). The study is helpful because of the uncertainty that exists about the effectiveness of the COCP in the treatment of endometriosis-associated pain (DUETS).

Another small double-blind, randomised, placebo-controlled trial found no benefit from using Infliximab, an anti-TNF-alpha monoclonal antibody, to treat pain associated with deeply infiltrating disease (Koninckx et al., 2008).

It is unclear whether hormonal treatment causes atrophy of endometriotic lesions, especially as the natural history of the untreated disease is unknown. The available data suggest that MPA and luteal phase dydrogesterone are ineffective, whereas gestrinone may be effective. The effects of danazol and the GnRH agonist, triptorelin, are inconclusive.

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7. Surgical management of endometriosis-associated pain

A Cochrane review has shown that laparoscopic surgery gives greater improvement of endometriosis-associated pelvic pain at 6 and 12 months after surgery, than diagnostic laparoscopy alone. However, this finding should be applied with caution to women with severe endometriosis as few women with severe disease were included in this review. No conclusions regarding which specific laparoscopic surgical intervention is most effective could be drawn (Jacobson et al, 2009).

Similarly, a systematic review considering laparoscopic management of endometriosis demonstrated that laparoscopy is beneficial in treating endometriosis related pain at all stages of the disease, although the best way to remove lesions (excision or ablation) is unknown. Although laparoscopic uterosacral nerve ablation was not found to be a useful adjunct in the treatment of endometriosis related pain, presacral neurectomy was found to be of benefit in some patients (Yeung et al, 2009).

There has been continuing uncertainty about the best surgical treatment of ovarian endometriomas to prevent cyst and symptom recurrence (DUETs), as well as its overall effect on quality of life (DUETs).

A Cochrane review update is therefore helpful as it concluded that excisional surgery for endometriomas provides a more favourable outcome than drainage and ablation with regard to cyst recurrence and recurrence of pain symptoms (Hart et al., 2008). Laparoscopic excision of the cyst wall was associated with a reduced recurrence rate of dysmenorrhea (OR 0.15 CI 0.06-0.38), dyspareunia (OR 0.08 CI 0.01-0.51) and non-menstrual pelvic pain (OR 0.10 CI 0.02-0.56), a reduced cyst recurrence rate (OR 0.41 CI 0.18-0.93) and a reduced requirement for further surgery (OR 0.21 CI 0.05-0.79) than surgery to ablate the endometrioma.

In a recent trial, women were randomised to undergo immediate laparoscopic ovarian cystectomy or a three step protocol, which involved endometrioma drainage, 3 months of subsequent GnRH agonist therapy and a second laparoscopy for laser coagulation of the cyst wall. Women who underwent the three step procedure showed a greater increase in anti-Müllerian hormone level (an indicator of ovarian reserve) and a more significant increase in antral follicle count than women undergoing the single step procedure. This may indicate that ovarian function is better preserved following a three step surgical procedure, rather than the traditional single step approach (Tsolakidis, 2009).

Another paper compared the use of bipolar diathermy with suturing to achieve haemostasis after laparoscopic ovarian cystectomy. This found that suturing was associated with fewer post-operative adhesions than diathermy at a “second-look” laparoscopy 60-90 days after initial surgery (Pellicano et al, 2008).
Other techniques of interest are the potential benefit of using mesna (a chemical mucolytic), which appears to reduce operating time and perceived difficulty of operating, and a circular excision technique for endometriotic cysts, which also seemed to improve ease of operating. Finally, three trials have shown a benefit from the use of an adhesion barrier (Interceed, Adept or Oxiplex) during surgery for endometriosis (Yeung et al, 2009).

The use of intra-operative, multi-modal analgesia (diclofenac sodium PR and repivacaine in portal sites and sub-diaphragmatically) was found to reduce post-operative total hospital opioid requirements significantly in women undergoing laparoscopic excision of endometriosis. No difference in post-operative pain intensity between the two groups was demonstrated. A reduction in post-operative opioid use with multi-modal intra-operative analgesia did not translate into a reduction in post-op sedation, nausea and vomiting or hospital stay (Costello et al, 2009).

The use of medical treatment in combination with surgery was also addressed in one review (Yeung et al, 2009). The benefits of pre- and post-operative medical therapy are currently unclear. Two trials compared pre- and post-operative medical therapy (GnRH agonists), and found no difference in pain scores, although a reduction in r-ASRM scores in those women who had pre-operative treatment. One trial also considered the use of the LNG-IUS post-operatively, and found that it significantly improved pain scores compared to expectant management.

The recurrence of endometriosis after treatment is of great concern to patients and gynaecologists alike. A recent review has attempted to quantify this risk, estimated to be 19% over a 2 year period. However, the authors acknowledge that the studies use very different definitions of recurrence, which makes it difficult to compare results. Several have attempted to define risk factors for recurrence, with conflicting results (Guo, 2009).

In one RCT, women who had undergone laparoscopic excision of endometriomas were assigned to no treatment or continuous/cyclical monophasic oral contraceptive pills (OCP) for 24 months. Those women randomised to an OCP had reduced endometrioma recurrence rates compared to those on no treatment (Seracchioli et al, 2008).

An additional study by the same authors, with similar methodology but greater sample size, demonstrated that dysmenorrhoea scores were lowest for the continuous OCP users throughout the 24 months. Although the reduction in dysmenorrhoea scores was not as great in cyclical OCP users, they still had lower scores than untreated women by 18 and 24 months (Seracchioli, 2009a).

In women who had undergone conservative surgery for endometriosis, short term OCP use (6-9.5 months) after surgery does not affect recurrence rates. However, use for 24-36 months does appear to reduce the recurrence of endometriomas. One study indicated 6 months’ treatment was sufficient to reduce dysmenorrhoea and chronic pelvic pain, although a second study did not confirm this. Studies assessing long-term therapy showed a significant reduction in dysmenorrhoea at 6 months for the continuous OCP group, and by 18 months for the cyclical...
OCP group. A second study also showed that 2 years continuous pill taking significantly reduced dysmenorrhoea scores (Seracchioli, 2009b).

An RCT with five year follow-up concluded that adjuvant treatment with a GnRH agonist (for 3 months), following conservative surgery for Stage III-IV endometriosis, is not superior to expectant management in terms of preventing symptom or cyst recurrence (Loverro et al, 2008).

Raloxifene (a selective estrogen receptor modulator) use for 6 months post-operatively was studied in women with pelvic pain and biopsy-confirmed endometriosis. However, there was no evidence of treatment benefit. Furthermore, when compared with those taking placebo, the raloxifene group had return of pain significantly earlier and underwent second surgery more quickly (Stratton et al, 2008).

A small RCT also found that the use of pentoxifylline after conservative surgery for endometriosis improved pain scores at 2 and 3 months follow-up compared to conservative surgery only. The authors suggested prolonged use of pentoxifylline after conservative surgery may improve long-term outcomes after surgical treatment (Kamencic et al, 2008).

The possible benefits of dietary intervention and medical treatments on the recurrence rates of endometriomas after surgery were considered in one study. However, 6 months’ treatment with GnRH agonists, OCP or dietary intervention (vitamins, minerals, salts, lactic ferments and fish oil) did not affect the recurrence rate of endometriomas at 18 months’ follow-up (Sesti, 2009).

Uncertainty has always existed in the minds of clinicians and patients regarding the use of hormone replacement therapy (HRT) following bilateral oophorectomy with or without a hysterectomy for endometriosis. Unfortunately, the results of a recent Cochrane review add little to the evidence base as only two small RCTs were identified, which suggested that HRT can result in pain and disease recurrence (Al Kadri et al, 2009). However, the authors concluded that the evidence is not strong enough to advocate depriving severely symptomatic patients of HRT and there is a need for more RCTs.

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8. Management of endometriosis-associated subfertility

A review article concluded that women with stage I-II endometriosis-associated infertility benefit from laparoscopic treatment. Two studies demonstrated an increased pregnancy rate amongst those who underwent surgical treatment compared with diagnostic laparoscopy alone (Yeung et al., 2009).

Whether endometriosis adversely affects pregnancy rates in assisted reproduction has always been controversial. Interestingly, therefore, a meta-analysis has shown that pregnancy rates following controlled ovarian stimulation and intrauterine insemination (IUI) are significantly lower in women with endometriosis compared to controls, but there are no significant differences in women treated with IVF/ICSI (Kunz et al., 2008).

There has been continuing uncertainty about the best surgical treatment of ovarian endometriomas to improve IVF outcomes (DUETs) and avoid damaging ovarian function (DUETs) in infertile women.

A Cochrane review update concluded that excisional surgery for endometriomas provides a more favourable outcome than drainage and ablation for spontaneous pregnancy (Hart et al., 2008), but there is still insufficient evidence to determine the best treatment before IVF. However, a systematic review and meta-analysis of 20 studies concluded that the available data show surgical management of endometriomas has no effect on IVF pregnancy rates and ovarian response to stimulation compared to no treatment (Tsoumpou et al., 2008).

The optimum technique for cyst removal has also been considered. A review article determined that cyst excision compared with drainage had greater effects on pain and pregnancy outcomes. However, one study showed no difference in pregnancy rates following controlled ovarian stimulation in women undergoing cystectomy rather than drainage (reviewed in Yeung et al., 2009).

There has also been uncertainty about the role of prolonged GnRH agonist treatment before IVF (DUETs). A small RCT has added little to the evidence base by showing that 2 months treatment before IVF produced a ‘trend’ towards an increase in the implantation rate in women with Stage III-IV disease (Ma et al., 2008).

An RCT with five year follow-up concluded that adjuvant treatment with a GnRH agonist, following conservative surgery for Stage III-IV endometriosis had no effect on pregnancy rates (Loverro et al., 2008) and a small RCT suggested that combined laparoscopic surgery and pentoxifylline therapy for endometriosis-associated infertility might improve pregnancy rates at 6 months follow-up (Creus et al, 2008). However, a systematic review concluded that there is overall no evidence to support the use of pentoxifylline as a treatment for subfertility in women with endometriosis, with no evidence of increased clinical pregnancy rates in women treated with pentoxifylline compared with placebo (Lv, 2009).
The potential benefit of second line surgery for women with recurrent endometriosis and a desire for pregnancy has been assessed. Conception rates following second line surgery varied from 12 to 47%. Studies comparing primary surgery with repeat surgery found a reduced pregnancy rate in women undergoing second line surgery. Overall, studies comparing only IVF or second line surgery prior to IVF found no difference in pregnancy rates between each procedure (Vercellini et al., 2009).

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9. Resources

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