# Endometriosis: an overview of Cochrane Reviews (Review)

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[Overview of Reviews]

# Endometriosis: an overview of Cochrane Reviews

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## ABSTRACT

### Background

This overview reports on interventions for pain relief and for subfertility in pre-menopausal women with clinically diagnosed endometriosis.

### Objectives

The objective of this overview was to summarise the evidence from Cochrane systematic reviews on treatment options for women with pain or subfertility associated with endometriosis.

### Methods

Published Cochrane systematic reviews reporting pain or fertility outcomes in women with clinically diagnosed endometriosis were eligible for inclusion in the overview. We also identified Cochrane reviews in preparation (protocols and titles) for future inclusion. The reviews, protocols and titles were identified by searching the Cochrane Database of Systematic Reviews and Archie (the Cochrane information management system) in March 2014.

Pain-related outcomes of the overview were pain relief, clinical improvement or resolution and pain recurrence. Fertility-related outcomes were live birth, clinical pregnancy, ongoing pregnancy, miscarriage and adverse events.

Selection of systematic reviews, data extraction and quality assessment were undertaken in duplicate. Review quality was assessed using the AMSTAR tool. The quality of the evidence for each outcome was assessed using GRADE methods. Review findings were summarised in the text and the data for each outcome were reported in 'Additional tables'.

### Main results

Seventeen systematic reviews published in *The Cochrane Library* were included. All the reviews were high quality. The quality of the evidence for specific comparisons ranged from very low to moderate. Limitations in the evidence included risk of bias in the primary studies, inconsistency between the studies, and imprecision in effect estimates.

**Pain relief (14 reviews)**

*Gonadotrophin-releasing hormone (GnRH) analogues*

One systematic review reported low quality evidence of an overall benefit for GnRH analogues compared with placebo or no treatment.

*Ovulation suppression*

Five systematic reviews reported on medical treatment using ovulation suppression. There was moderate quality evidence that the levonorgestrel-releasing intrauterine system (LNG-IUD) was more effective than expectant management, and very low quality evidence that danazol was more effective than placebo. There was no consistent evidence of a difference in effectiveness between oral contraceptives and goserelin, estrogen plus progestogen and placebo, or progestogens and placebo, though in all cases the relevant evidence was of low or very low quality.

*Non-steroidal anti-inflammatory drugs (NSAIDS)*

A review of NSAIDs reported inconclusive evidence of a benefit in symptom relief compared with placebo.

*Surgical interventions*

There were two reviews of surgical interventions. One reported moderate quality evidence of a benefit in pain relief following laparoscopic surgery compared to diagnostic laparoscopy only. The other reported very low quality evidence that recurrence rates of endometriomata were lower after excisional surgery than after ablative surgery.

*Post-surgical medical interventions*

Two reviews reported on post-surgical medical interventions. Neither found evidence of an effect on pain outcomes, though in both cases the evidence was of low or very low quality.

*Alternative medicine*

There were two systematic reviews of alternative medicine. One reported evidence of a benefit from auricular acupuncture compared to Chinese herbal medicine, and the other reported no evidence of a difference between Chinese herbal medicine and danazol. In both cases the evidence was of low or very low quality.

*Anti-TNF-α drugs*

One review found no evidence of a difference in effectiveness between anti-TNF-α drugs and placebo. However, the evidence was of low quality.

**Reviews reporting fertility outcomes (8 reviews)**

*Medical interventions*

Four reviews reported on medical interventions for improving fertility in women with endometriosis. One compared three months of GnRH agonists with a control in women undergoing assisted reproduction and found very low quality evidence of an increase in clinical pregnancies in the treatment group. There was no evidence of a difference in effectiveness between the interventions in the other three reviews, which compared GnRH agonists versus antagonists, ovulation suppression versus placebo or no treatment, and pre-surgical medical therapy versus surgery alone. In all cases the evidence was of low or very low quality.

*Surgical interventions*

Three reviews reported on surgical interventions. There was moderate quality evidence that both live births or ongoing pregnancy rates and clinical pregnancy rates were higher after laparoscopic surgery than after diagnostic laparoscopy alone. There was low quality evidence of no difference in effectiveness between surgery and expectant management for endometrioma. One review found low quality evidence that excisional surgery resulted in higher clinical pregnancy rates than drainage or ablation of endometriomata.

*Post-surgical interventions*

Two reviews reported on post-surgical medical interventions. They found no evidence of an effect on clinical pregnancy rates. The evidence was of low or very low quality.

*Alternative medicine*

*A* review of Chinese herbal medicine in comparison with gestrinone found no evidence of a difference between the groups in clinical pregnancy rates. However, the evidence was of low quality.

**Adverse events**

Reviews of GnRH analogues and of danazol reported that the interventions were associated with higher rates of adverse effects than placebo; and depot progestagens were associated with higher rates of adverse events than other treatments. Chinese herbal medicine was associated with fewer side effects than gestrinone or danazol.

Three reviews reported miscarriage as an outcome. No difference was found between surgical and diagnostic laparoscopy, between GnRH agonists and antagonists, or between aspiration of endometrioma and expectant management. However, in all cases the quality of the evidence was of low quality.

**Authors' conclusions**

For women with pain and endometriosis, suppression of menstrual cycles with gonadotrophin-releasing hormone (GnRH) analogues, the levonorgestrel-releasing intrauterine system (LNG-IUD) and danazol were beneficial interventions. Laparoscopic treatment of endometriosis and excision of endometriomata were also associated with improvements in pain. The evidence on NSAIDs was inconclusive. There was no evidence of benefit with post-surgical medical treatment.

In women with endometriosis undergoing assisted reproduction, three months of treatment with GnRH agonist improved pregnancy rates. Excisional surgery improved spontaneous pregnancy rates in the nine to 12 months after surgery compared to ablative surgery. Laparoscopic surgery improved live birth and pregnancy rates compared to diagnostic laparoscopy alone. There was no evidence that medical treatment improved clinical pregnancy rates.

Evidence on harms was scanty, but GnRH analogues, danazol and depot progestagens were associated with higher rates than other interventions.

## PLAIN LANGUAGE SUMMARY

**Endometriosis: an overview of Cochrane Reviews**

**Background**

Cochrane review authors examined the evidence on endometriosis from Cochrane systematic reviews published in *The Cochrane Library*. We aimed to summarise the evidence on treatment options that are available to women with pain or subfertility, or both, associated with clinically diagnosed endometriosis.

**Study characteristics**

We included 17 Cochrane systematic reviews. Fourteen reported measures of pain relief and eight reported fertility outcomes. All the reviews were high quality. The quality of the evidence for specific comparisons and outcomes ranged from very low to moderate, due to limitations in the primary studies, inconsistency between the studies and imprecision in the findings.

**Key results**

A number of interventions appeared effective in alleviating pain in women with endometriosis. These were gonadotrophin-releasing hormone (GnRH) analogues when compared with placebo, the levonorgestrel-releasing intrauterine system (LNG-IUD) compared with expectant management, danazol compared with placebo, and progestagens and anti-progestagens compared with placebo. Laparoscopic surgical interventions also appeared to be effective for pain.

In women with endometriosis undergoing assisted reproduction, three months of treatment with GnRH agonist improved pregnancy rates. Excisional surgery improved spontaneous pregnancy rates in the nine to 12 months after surgery compared to ablative surgery. Laparoscopic surgery improved live birth and pregnancy rates compared to diagnostic laparoscopy alone. There was no evidence that medical treatment improved clinical pregnancy rates.

Evidence on harms was scanty but GnRH analogues and danazol were associated with higher rates of adverse effects than placebo, and depot progestagens were associated with higher rates than other treatments.

# BACKGROUND

This overview examines the interventions available for pain relief and for subfertility in pre-menopausal women with clinically diagnosed endometriosis.

## Description of the condition

Endometriosis is characterised by the presence of endometrial tissue in sites other than the uterine cavity. It is a common gynaecological condition affecting women in their reproductive years and is generally believed to be an estrogen-dependent disorder. The many observations that support this view include amelioration of pre-existing endometriosis after surgical or natural menopause (Kitawaki 2002) and the growth of endometrial tissue in animals on estrogen therapy (Bruner-Tran 2002).

Estimates of prevalence in the general population are up to 10% (Ozkan 2008). For women with subfertility the prevalence rate ranges from 25% to 40% (Ozkan 2008). These values are potentially underestimates as visualisation of the disease is required for a diagnosis.

Whilst endometriosis is associated with infertility (occasionally as the cause) (Prentice 1996), it frequently presents with the symptom of pain (Barlow 1993). This pain may take the form of dysmenorrhoea (cyclical pain associated with menstruation), dyspareunia (pain with or following sexual intercourse) and pelvic or abdominal pain. The woman may also present with cyclical symptoms related to endometriosis at extra-pelvic sites.

A major challenge for women with endometriosis is the risk of recurrence. Symptomatic recurrence rates of endometriosis have been reported to range from 21.5% at two years to 50% at five years after treatment (Guo 2009).

The precise pathogenesis (mode of development) of endometriosis remains unclear but it is evident that endometriosis arises from the dissemination of endometrium to ectopic sites and the subsequent establishment of deposits of ectopic endometrium (Haney 1991; McLaren 1996). It has been postulated that the presence of these ectopic deposits gives rise to the symptoms associated with the condition.

## Description of the interventions

There are a number of potential interventions for endometriosis, dependent on whether the primary problem is pain or subfertility. The primary aims of the interventions are the reduction or removal of ectopic endometrial implants, restoration of normal anatomy, reduction of disease progression and symptom relief (Ozkan 2008).

### Pain

In the case of pain the treatments include the following.

**1. Medical therapy**

- Combined oral contraceptive pill (COCP)
- Non-steroidal anti-inflammatory drugs (NSAIDS)
- Gonadotrophin releasing hormone analogues (GnRHa)
- Progestins, including oral and intrauterine
- Androgens (danazol)
- Aromatase inhibitors
- Estrogen ± progesterone
- Anti-TNF (tumour necrosis factor)
- Selective estrogen receptor modulators (SERMS)
- Other treatments such as Chinese herbal medicine and oral supplements

Medical therapy could be independently administered or be used pre or post-surgery.

**2. Surgical intervention**

- Laparoscopic surgery
- Surgical interruption of the nerve pathways
- Excisional versus ablative surgery
- Post-surgical barrier agents to prevent adhesions
- Laparoscopic helium plasma coagulation

### Subfertility

**1. Medical therapy prior to assisted reproductive technologies (ART)**

- GnRHa
- Controlled ovarian hyperstimulation

**2. Medical therapy**

- Ovulation suppression
- Other treatments such as Chinese herbal medicine and oral supplements

**3. Pre or post-operative medical therapy**

- GnRHa
- COCP
- Androgens

**4. Surgical intervention**

- Laparoscopic surgery
- Excisional versus ablative surgery for endometriomata

## How the intervention might work

Surgical removal of endometrial deposits or medical suppression of hormones may decrease endometrial deposits, which may assist in the relief of pain. Removal of endometrial deposits and medical therapy to shrink the size of deposits may increase the chances of conception.

## Why it is important to do this overview

There are now numerous intervention reviews available for the medical and surgical treatment of endometriosis for pain relief and for subfertility. For the first time, this overview brings these together into one coherent document that can be used by clinicians and policy makers in making decisions about optimal treatment based on the available evidence on benefits and harms. It also provides a useful resource to guide consumers and clinicians to the original reviews for further information.

# OBJECTIVES

The objective of this overview was to summarise the evidence from Cochrane systematic reviews on treatment options for women with pain or subfertility associated with endometriosis.

# METHODS

## Criteria for considering reviews for inclusion

Only Cochrane reviews were considered for inclusion in this overview. Cochrane protocols and titles were identified for future inclusion.

### Participants

Eligible participants were pre-menopausal women with a clinical diagnosis of endometriosis who had sought medical attention for pain or subfertility, or both. Women with endometriomata who had sought medical attention for pain or subfertility, or both, were also included.

### Interventions

#### *Interventions for pain relief*

Medical treatments, complementary therapies or surgical interventions (including excisional and ablative surgery for endometriomata) were considered. Medical and complementary therapies could be used as single interventions or administered pre or postoperatively, or both.

#### *Interventions for subfertility*

Medical treatments, complementary therapies or surgical interventions (including excisional and ablative surgery for endometriomata) were considered. Medical and complementary therapies could be used as a single intervention or administered pre or postoperatively, or both.

### Outcomes of interest

#### *Outcomes for pain relief*

Primary outcome measure: self reported pain relief for dysmenorrhoea
Secondary outcome measures: clinical improvement or resolution of endometriosis-related pain; pain recurrence, adverse events

#### *Outcomes for subfertility*

Primary outcome measures: live birth, clinical pregnancy, ongoing pregnancy, miscarriage, adverse events

## Search methods for identification of reviews

The Cochrane Database of Systematic Reviews and Archie (the Cochrane information management system) were searched on 6th March 2014 using the keyword 'endometriosis'. The term was restricted to title, abstract, or keywords. No other databases were searched.

## Data collection and analysis

### Selection of reviews

Reviews addressing treatment of pain associated with endometriosis and reviews addressing treatment of subfertility associated with

endometriosis were identified by one overview author and confirmed for inclusion by the second overview author. Any disagreement was resolved by discussion with a third party.

### Data extraction and management

Data were extracted independently by the two overview authors (CF, JB) using an Excel spreadsheet. Disagreements were resolved by discussion. Where data were missing, the original review authors were contacted for assistance. Information was extracted on the following.

- The population demographics: a summary of the participant characteristics was made.
- Review characteristics: the number of included trials, the number of participants in each review, the date that the review was assessed as up to date, interventions and comparisons, all outcomes, and limitations of the review.
- Statistical summary: the summary effects from relevant comparisons and outcomes.

### Assessment of methodological quality of included reviews

#### Quality of included reviews

The quality of the included reviews was assessed using the AMSTAR tool (Shea 2007). We also noted in each case whether the literature search had been conducted or updated within the past three years (to March 2014).

#### Quality of evidence from primary studies in included reviews

We used the GRADEPro 'Summary of findings' tables from each review (or if necessary we constructed such a table) to indicate the quality of the evidence for the main comparisons. The following criteria were taken into account: study limitations (that is risk of bias), consistency of effect, imprecision, indirectness and publication bias.

### Data synthesis

We combined the reviews in a narrative summary, organised by outcomes.

## RESULTS

Seventeen systematic reviews published in *The Cochrane Library* were included in this overview. See Table 1 for a summary of the characteristics of these reviews (review ID, when the review was last assessed as up to date, how many randomised controlled trials and participants were included, the interventions, comparisons, outcomes, and main limitations of each review). See Table 2 for a description of the populations in the included reviews.

An additional protocol and two titles were identified, which will be added to the overview when they are published as full reviews and the overview is updated. For details see Appendix 1.

### Description of included reviews

#### Pain

Fourteen reviews were identified that reported on pain outcomes in pre-menopausal women with a diagnosis of endometriosis (Abou-Setta 2013; Al-Kadri 2009; Allen 2009; Brown 2010; Brown 2012; Davis 2007; Duffy 2014; Farquhar 2007; Flower 2012; Furness 2004; Hart 2008; Lu 2012; Lu 2013; Zhu 2011).

#### Subfertility

Eight systematic reviews were identified that reported on fertility outcomes in pre-menopausal women with a diagnosis of endometriosis (Benschop 2010; Duffy 2014; Flower 2012; Furness 2004; Hart 2008; Hughes 2007; Lu 2012; Sallam 2006). Sallam 2006 and Benschop 2010 reported ART-related outcomes whilst the other reviews reported spontaneous pregnancy.

### Methodological quality of included reviews

#### 1. Quality of systematic reviews

The quality of the 17 included reviews was rated using the AMSTAR tool (Shea 2007).

- All reviews pre-specified their clinical question and inclusion criteria.
- All reviews conducted study selection and data extraction in duplicate.
- All reviews conducted a comprehensive literature search.
- All reviews included searches of grey literature.
- All reviews listed included and excluded studies.
- All reviews described the characteristics of the included studies.
- All reviews assessed study quality.
- All reviews combined the studies using appropriate methods.
- Eleven of the 17 reviews formally addressed the risk of reporting bias, using a statistical test where appropriate.
- All reviews addressed the potential for conflict of interest.

Eight of the 17 reviews had conducted a literature search within the past three years (to March 2014), or have been deemed stable

(meaning that they will not be updated with a full literature search unless new evidence emerges).
See Table 3 and Table 4 for details.

#### 2. Quality of evidence from primary studies in included reviews

The quality of the evidence reported by the primary studies in the included reviews was rated using GRADE methods and ranged from very low to moderate for individual comparisons. The main reasons for reviews being downgraded for quality were inadequate reporting of allocation concealment and randomisation methods, lack of blinding and imprecision. The evidence frequently comprised a single small trial.
Details of the quality of the evidence for each outcome are reported in Table 5 and Table 6.

## Effect of interventions

#### 1. Pain outcomes

See Table 5

#### 1.1 Gonadotrophin-releasing hormone agonist or antagonist (GnRHa)

Brown 2010 concluded that women receiving GnRHas were more likely to achieve symptom relief than those having no treatment (risk ratio (RR) 3.93, 95% confidence interval (CI) 1.37 to 11.28). There was no statistically significant difference between GnRHas and danazol for the rate of relief of dysmenorrhoea (RR 0.98, 95% CI 0.92 to 1.04). More adverse events were reported in the GnRHa group. There was a benefit in overall pain resolution for GnRHas (RR 1.10, 95% CI 1.01 to 1.21) compared with danazol. There was no statistically significant difference in overall pain scores between the GnRHas and levonorgestrel groups (standardised mean difference (SMD) -0.25, 95% CI -0.60 to 0.10). Evidence was limited on optimal dosage or duration of treatment for GnRHas. No one route of administration appeared superior to another.

#### 1.2 Ovulation suppression

Davis 2007 provided evidence from a single trial of 57 women that found no difference between the oral contraceptive pill and goserelin (a GnRH analogue) for relieving pain associated with endometriosis (odds ratio (OR) 0.76, 95% CI 0.17 to 3.29, 44 participants, 1 trial).
Farquhar 2007 found that treatment with danazol (including its use as an adjunct to surgery) was effective in relieving pain associated with endometriosis when compared with placebo (mean difference (MD) -3.4, 95% CI -4.8 to -1.8, 60 participants, 1 trial). There was also an improvement in laparoscopic scores, although women who received danazol as treatment were more likely to experience side effects than women receiving placebo.
Al-Kadri 2009 found no difference between the groups in pain or recurrence of disease in a randomised trial comparing sequential administration of estrogen and progesterone with placebo. There was also no difference between the groups in pain in a trial comparing non-stop transdermal 17$\beta$ estradiol combined with cyclic medroxyprogesterone acetate compared with tibolone (OR 6.67, 95% CI 0.6 to 74.51, 21 participants, 1 trial).
Abou-Setta 2013 reported on a review of three randomised trials. There was evidence of a significant decrease in recurrence of painful menstruation in the levonorgestrel hormone-releasing intrauterine device (LNG-IUD) group compared with the expectant management group (RR 0.22, 95% CI 0.08 to 0.60, two trials, 95 women). In the third trial (n = 40) there was no evidence of a significant difference in visual analogue scale (VAS) pain scores between the LNG-IUD group and women who received GnRHas.
Brown 2012 conducted a review of progestagens and anti-progestagens for pain associated with endometriosis.There was no evidence of a difference in the American Fertility Society (AFS) scores between the prostagens (medroxyprogesterone) group and the placebo group (mean difference (MD) 0.58, 95% CI -1.41 to 0.25). Progestagens were associated with more adverse events (acne and oedema) than placebo. There was no evidence of a benefit for subjective or objective outcomes for dydrogesterone compared with placebo. When depot progestagens were compared with other treatments, symptoms were improved in the depot group. However there were also more adverse events in the depot group. There was no evidence of a difference in pain outcomes when oral progestagens were compared with other treatments. The evidence for anti-progestagens was mixed, with one study indicating a benefit for anti-progestagens compared to other treatment at 12 months follow-up, and another study finding no evidence of a difference between groups.

#### 1.3 Analgesics

##### *Non-steroidal anti-inflammatory drugs (NSAIDS)*

Allen 2009 reported inconclusive evidence on the effectiveness of NSAIDS (naproxen) when compared with placebo based on the management of pain associated with endometriosis (OR inverse variance 0.33, 95% CI 0.61 to 17.69, 20 participants, 1 trial).

#### 1.4 Surgical interventions

Hart 2008 reported that laparoscopic excision of the cyst wall of the endometrioma was associated with a reduced recurrence

rate of the symptoms of dysmenorrhoea compared to laparoscopic ablation.

Duffy 2014 reported that there was no significant difference between laparoscopic surgery and diagnostic laparoscopy for relief of dysmenorrhoea at 6 or 12 months. However, only one small study reported this outcome and there was very serious imprecision in the result (MD on VAS 0 to 100 scale 2.40, 95% CI -6.18 to 10.98; MD -9.50, 95% CI -20.58 to 1.58, respectively). Laparoscopic surgery was associated with decreased overall pain (measured as 'pain better or improved') compared with diagnostic laparoscopy, both at 6 months (OR 6.58, 95% CI 3.31 to 13.10) and at 12 months (OR 10.00, 95% CI 3.21 to 31.17). When laparoscopic ablation was compared with diagnostic laparoscopy plus medical therapy (GNRHa with add back therapy), more women in the ablation group were pain free at 12 months (OR 5.63, 95% CI 1.18 to 26.85). The difference between laparoscopic ablation and laparoscopic excision in the proportion of women reporting overall pain relief at 12 months on a VAS 0 to 10 pain scale was 0 (95% CI to 1.22 to 1.22). There was insufficient evidence on adverse events to allow any conclusions to be drawn regarding safety.

### 1.5 Post-surgical interventions

Lu 2012 found no evidence of a benefit from pentoxifylline when compared with no treatment on the reduction of pain associated with endometriosis after laparoscopic surgery in one randomised trial; and neither was there evidence of a difference between pentoxifylline and placebo after surgery on recurrence of disease, as reported in the single randomised trial. The mean reduction in pain at three months was 5.53 in the control group. In the intervention group the mean pain reduction was 1.6 lower (range 3.32 lower to 0.12 higher, 34 participants, 1 trial).

Furness 2004 found no evidence of a benefit from pre-surgical medical therapy compared to surgery alone for the symptomatic relief of endometriosis, or for post-surgical hormone suppression compared with surgery alone for the pain and disease recurrence outcomes. There was also no evidence that pre-surgical hormone suppression was different to post-surgical hormone suppression for the outcome of pain, and there were no differences in AFS scores in a comparison of post-surgical medical therapy and pre and post-surgery therapy.

### 1.6 Other medical intervention

#### *Anti-tumour necrosis factor-α (anti-TNF-α)*

Lu 2013 found no evidence to support the use of anti-TNF-α drugs for the alleviation of pain associated with endometriosis. The evidence was based on a single trial. The patient Biberoglu and Behrman score was a mean of 1.7 in the control group and 0.2 lower in the intervention group (range 0.68 lower to 0.28 higher).

### 1.7 Other interventions

Zhu 2011 reported on one trial of 67 women. The trial found that auricular acupuncture was significantly more effective at reducing pain associated with endometriosis than Chinese herbal medicine (RR 3.04, 95% CI 1.65 to 5.62, 67 participants, 1 trial).

Flower 2012 reported on two post-surgical interventions using Chinese herbal medicine. The authors concluded that Chinese herbal medicine may have comparable benefits to conventional medicine (gestrinone and danazol) but with fewer side effects. Chinese herbal medicine appeared to have some superiority over danazol in the relief of symptoms. The review was based on only two randomised trials.

## 2. Fertility outcomes

### 2.1 GnRH agonist

Sallam 2006 reported evidence of significantly more pregnancies among women undergoing ART who received ultra-long GnRH agonist down-regulation than among those who did not receive the agonist (OR 4.28, 95% CI 2.0 to 9.15, 165 participants, 3 trials).

Benschop 2010 found no evidence of a difference in clinical pregnancy rates between GnRH agonists and GnRH antagonists administered for endometrioma prior to ART (OR 0.81, 95% CI 0.26 to 2.54, 67 participants, 1 trial).

### 2.2 Ovulation suppression

Hughes 2007 reported that there was no difference in clinical pregnancy rates between a group receiving ovulation suppression and a group receiving placebo or no treatment (OR 1.02, 95% CI 0.70 to 1.52, 557 participants,11 trials) despite the use of a variety of suppression agents. The review concluded that there was no evidence of a benefit in the use of ovulation suppression in subfertile women with endometriosis who wished to conceive.

### 2.3 Pre-surgical interventions

Furness 2004 reported insufficient evidence to determine whether there was a difference in clinical pregnancy rates when pre-surgical medical therapy was compared with surgery alone (RR 0.46, 95% CI 0.15 to 1.45, 25 participants, 1 trial).

### 2.4 Surgical interventions

Duffy 2014 reported that laparoscopic surgery was associated with a higher live birth or ongoing pregnancy rate than diagnostic laparoscopy (OR 1.94, 95% CI 1.20 to 3.16). The clinical pregnancy rate was also higher (OR 1.89, 95% CI 1.25 to 2.86). There

was insufficient evidence on adverse events to allow any conclusions to be drawn regarding safety.

Hart 2008 reported that two randomised controlled trials suggested a benefit of excisional surgery over drainage or ablation of endometriomata for achieving pregnancy in previously subfertile women (OR 5.24, 95% CI 1.92 to 14.27, 88 participants, 2 trials).

Benschop 2010 found no evidence of a difference in clinical pregnancy rates between surgery (aspiration or cystectomy) for endometrioma prior to ART and expectant management (aspiration OR 1.29, 95% CI 0.45 to 3.64. 81 participants, 1 trial; cystectomy OR 1.15, 95% CI 0.52 to 2.55, 109, 1 trial).

### 2.5 Post-surgical interventions

Lu 2012 reported no evidence of a significant difference in clinical pregnancy rates between the group receiving pentoxifylline and the placebo group in three randomised trials (OR 1.54, 95% CI 0.89 to 266, 285 participants). There was insufficient evidence to recommend the use of pentoxifylline in the management of premenopausal women with endometriosis-associated subfertility.

Furness 2004 found no evidence to support the use of post-surgical medical therapy for increasing pregnancy rates (RR 0.84, 95% CI 0.59 to 1.18, 420 participants, 8 studies).

### 2.6 Other interventions

Flower 2012 found no significant difference between the pregnancy rates in the Chinese herbal medicine group and the gestrinone group in a single randomised trial (RR 1.18, 95% CI 0.87 to 1.59, 45 participants, 1 trial).

## DISCUSSION

### Summary of main results

#### Pain relief (14 reviews)

#### Gonadotrophin-releasing hormone (GnRH) analogues

One systematic review reported low quality evidence of an overall benefit for GnRH analogues compared with placebo or no treatment (Brown 2010).

#### Ovulation suppression

Five systematic reviews reported on medical treatment using ovulation suppression. There was moderate quality evidence that the levonorgestrel-releasing intrauterine system (LNG-IUD) was more effective than expectant management (Abou-Setta 2013), and very low quality evidence that danazol was more effective than placebo (Farquhar 2007). There was no consistent evidence of a difference in effectiveness between oral contraceptives and goserelin (Davis 2007), estrogen plus progestogen (Al-Kadri 2009) and placebo, or progestogens and placebo (Brown 2012), though the relevant evidence was of low or very low quality.

#### Non-steroidal anti-inflammatory drugs (NSAIDS)

A review of NSAIDs reported inconclusive evidence on a benefit in symptom relief compared with placebo (Allen 2009).

#### Surgical interventions

There were two reviews of surgical interventions. One reported moderate quality evidence of a benefit in pain relief following laparoscopic surgery compared to diagnostic laparoscopy. The other review reported very low quality evidence that recurrence rates of endometriomata were lower after excisional surgery than after ablative surgery (Hart 2008; Duffy 2014).

#### Post-surgical medical interventions

Two reviews reported on post-surgical medical interventions. Neither found evidence of an effect on pain outcomes (Furness 2004; Lu 2012); the evidence was of low or very low quality.

#### Alternative medicine

There were two systematic reviews of alternative medicine. One reported evidence of a benefit of auricular acupuncture compared to Chinese herbal medicine (Zhu 2011). The other review reported no evidence of a difference between Chinese herbal medicine and danazol (Flower 2012). In both cases the evidence was of low or very low quality.

#### Anti-TNF-$\alpha$ drugs

One review (Lu 2013) found low quality evidence that anti-TNF-$\alpha$ drugs were no more effective than placebo.

#### Fertility outcomes (eight reviews)

#### Medical interventions

Four reviews reported on medical interventions for improving fertility in women with endometriosis (Benschop 2010; Furness 2004; Hughes 2007; Sallam 2006). One compared three months

of GnRH agonists with a control intervention in women undergoing ART and found very low quality evidence of an increase in clinical pregnancies in the treatment group (Sallam 2006). There was no evidence of a difference in effectiveness between the interventions in the other three reviews, which compared GnRH agonists versus antagonists (Benschop 2010), ovulation suppression versus placebo or no treatment (Hughes 2007), and pre-surgical medical therapy versus surgery alone (Furness 2004). In all cases the evidence was of low or very low quality.

#### Surgical interventions

Three reviews reported on surgical interventions. There was moderate quality evidence of a benefit from laparoscopic surgery compared to diagnostic laparoscopy, with higher live birth or ongoing pregnancy rates and also higher clinical pregnancy rates (Duffy 2014). There was no evidence of a difference in effectiveness between surgery and expectant management for endometrioma (Benschop 2010). One review (Hart 2008) found that excisional surgery resulted in higher clinical pregnancy rates than drainage or ablation of endometrioma. In the latter two cases the evidence was of low quality. However, there are concerns about reducing ovarian reserve in women who have ovarian surgery that should be considered in further studies.

#### Post-surgical interventions

Two reviews reported on post-surgical medical interventions. They found no evidence of an effect on the clinical pregnancy rate ( Furness 2004; Lu 2012). The evidence was of low or very low quality.

#### Alternative medicine

*A* review of Chinese herbal medicine in comparison with gestrinone found no evidence of a difference between the groups in clinical pregnancy rates (Flower 2012). However, the evidence was of low quality.

#### Other outcomes

Reviews of GnRH analogues and of danazol reported that the interventions were associated with higher rates of adverse effects than placebo, and depot progestagens were associated with higher rates of adverse events than other treatments. Chinese herbal medicine was associated with fewer side effects than gestrinone or danazol. Two reviews reported miscarriage as an outcome. For this outcome no difference was found between surgical and diagnostic laparoscopy (Duffy 2014), between GnRH agonists and antagonists (Benschop 2010), or between aspiration of endometrioma and expectant management (Benschop 2010). The quality of the evidence was moderate (Duffy 2014) or low (Benschop 2010).

### Overall completeness and applicability of evidence

All women in the included reviews had confirmed endometriosis. For many interventions there were too few data to reach a firm conclusion.

Nearly all the studies in the reviews of treatment for subfertility associated with endometriosis failed to report live birth rates.

### Quality of the evidence

The included systematic reviews were prepared according to the guidelines of The Cochrane Collaboration and were of high quality in most respects, though only eight of the 17 had had a literature search within the past three years.

The quality of the evidence reported by the primary studies in the included reviews was rated using GRADE methods and ranged from very low to moderate. The main reasons for the quality of the evidence being downgraded were bias in the primary studies (inadequate reporting of allocation concealment and randomisation methods, lack of blinding) and imprecision. The evidence was frequently restricted to a single small trial.

### Potential biases in the overview process

No biases were identified during the overview process.

### Agreements and disagreements with other studies or reviews

No other overviews were identified.

## AUTHORS' CONCLUSIONS

### Implications for practice

For women with pain and endometriosis, suppression of menstrual cycles with GnRH analogues, LNG-IUD and danazol was beneficial. Laparoscopic treatment of endometriosis and excision of endometriomata were associated with pain improvements and therefore surgical approaches can be considered.

There are no medical treatments that are recommended to improve natural fertility in women with endometriosis. Women who are undergoing ART and who have known endometriosis could be treated with three months of a GnRH agonist, as this may improve pregnancy outcomes. Laparoscopic surgery improved fertility outcomes compared to diagnostic laparoscopy. There is insufficient

evidence about the surgical treatment of endometriosis in women undergoing ART interventions.

### Implications for research

Head to head trials of medical and surgical treatments for women with painful symptoms of endometriosis may be useful.

Further trials are required considering the role of surgery in women undergoing ART cycles. In addition, there are concerns about reducing ovarian reserve in women who have ovarian surgery.

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* *Indicates the major publication for the study*

## ADDITIONAL TABLES

**Table 1. Details of reviews**

| Review ID | Date assessed as up to date | Number of included trials | Number of participants | Intervention | Control or comparison intervention | Outcomes for which data assessed | Review limitations |
|---|---|---|---|---|---|---|---|
| GnRH agonist/antagonist | | | | | | | |
| Sallam 2006 | 17/10/2008 | 3 RCTs | 165 women | Leuprolide acetate 3.75mg<br><br>Triptorelin 3.75mg | No treatment<br><br>Leuprolide acetate 0.5 to 1.0mg<br><br>GnRH agonist 3.75mg | Clinical pregnancy<br><br>Dose of FSH/HMG<br><br>Duration of FSH<br><br>Number of oocytes | Only 3 trials<br><br>Trials lacked details of allocation concealment<br><br>No blinding |

**Table 1. Details of reviews** (*Continued*)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | retrieved | |
| Brown 2010 | 27/09/2010 | 42 RCTs | 4935 women | Any GnRHa | No treatment<br>Placebo<br>Danazol<br>Intrauterine progesterone devices<br>Another GnRHa | Pain relief<br>Adverse effects<br>Resolution of endometriosis<br>Quality of life<br>Additional use of analgesia | The trials were limited by lack of adequate information on randomisation, allocation concealment and blinding |
| Benschop 2010 | 04/10/2010 | 4 RCTs | 312 women | Surgical or medical therapy prior to treatment | Placebo<br>No treatment<br>Other surgical or medical therapy | Clinical pregnancy rate<br>Live birth<br>Adverse events<br>Quality of life<br>Pain<br>Recurrence<br>Estrodial levels<br>Number of mature oocytes | No live birth reported in the included trials. Overall trials well conducted but two of the trials did not conduct any blinding |
| Ovarian suppression | | | | | | | |
| Hughes 2007 | 19/04/2009 (stable review no longer being updated) | 25 RCTs | 2600 women | Dienogest<br>Triptorelin<br>MPA<br>Leuprolide acetate<br>Nafarelin<br>Provera<br>Goserelin<br>Danazol<br>Mestronol<br>Gestrinone | Triptorelin<br>Expectant management<br>Placebo<br>No treatment<br>Nafarelin<br>Danazol | Live birth<br>Clinical pregnancy | Only 2 trials reported live birth<br>The majority of the trials included in the review lacked details on randomisation and allocation concealment and there was limited blinding of allocation |

**Table 1. Details of reviews** (*Continued*)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | Buserelin | | | |
| Davis 2007 | 17/05/2007 | 1 RCT | 57 women | Low dose oral contraceptive (0.02mg ethinyl estradiol with 0.15mg desogestrel taken cyclically) | Monthly goserelin 3.6mg subcutaneous | Pain<br>Satisfaction<br>Withdrawal<br>Side effects<br>Economic evaluation | The trial included in the review lacked details on randomisation and allocation concealment, there was no blinding and evidence was based on a single trial |
| Abou-Setta 2013 | 13/6/2012 | 3 RCTs | 135 women | LNG-IUD | Expectant management | Pain<br>Satisfaction<br>Dropout rates | There was no evidence of blinding in two of the trials |
| Al-Kadri 2009 | 10/07/2008 | 2 RCTs | 193 women | Estrogen, with or without progesterone | Placebo<br>Tibolone | Pain<br>Disease recurrence | There was no evidence of blinding and the trials lacked precision |
| Farquhar 2007 | 15/06/2007 (stable review, no longer being updated) | 5 RCTs | 370 women | Danazol 600 mg daily | MPA 100mg<br>Placebo<br>No treatment | Pain<br>AFS score<br>Pregnancy<br>Side effects<br>Symptoms<br>Hormone level<br>Biochemical markers | There was a lack of evidence for randomisation and allocation concealment in many of the included trials and four of the trials were open label |
| Brown 2012 | 17/01/2011 | 13 RCTs | 1511 women | Medroxyprogesterone PO/ depot/sc<br>Gestrinone 2.5mg<br>Dienogest 2mg | Nafarelin 200 ug IN<br>Danazol 400mg/ 600mg<br>Leuprolide 3.75mg/ 11. | Pain scores<br>rAFS<br>Side effects<br>Fertility<br>Bone mineral density<br>Lipid profiles | |

**Table 1. Details of reviews** (*Continued*)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | Dydrogesterone 40/60 mg Cyproterone acetate 12.5mg | 25mg IM Buserelin 300ug IN Oral contraceptive Placebo | Biochemical measures Quality of life | |
| Analgesics | | | | | | | |
| Allen 2009 | 23/04/2008 | 2 RCTs | 48 women | Indomethecin 25mg Acetylsalictyic acid 500mg Tolfenamic acid 200mg Naproxen 275mg | Placebo | Pain Side effects Effects on activities of daily living Additional medication use | Trials lacked detail on allocation concealment and randomisation methods and one of the trials lacked details on blinding |
| Surgical | | | | | | | |
| Benschop 2010 | 04/10/2010 | 4 RCTs | 312 women | Surgery (aspiration or cystectomy) | Expectant management | Clinical pregnancy rate Live birth Adverse events Quality of life Pain Recurrence Estrodial levels Number of mature oocytes | No live birth reported in the included trials. Overall trials well conducted but two of the trials did not conduct any blinding |
| Duffy 2014 | 31.7.13 | 10 RCTs | 973 women | Laparoscopic surgery | Any other laparoscopic or robotic intervention, holistic or medical treatment or diagnostic laparoscopy only | Overall pain Live birth Specific types of pain Clinical pregnancy Adverse events | Common limitations in the primary studies included lack of clearly-described blinding, failure to fully describe methods of randomisation and al- |

**Table 1. Details of reviews** (*Continued*)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | | location concealment, and risk of attrition bias |
| Hart 2008 | 31/08/2009 | 2 RCTs | Not detailed in review | Excision | Drainage and ablation | Pelvic pain<br><br>Spontaneous conception<br>Recurrence of endometrioma<br><br>Requirements for further surgery<br><br>Conversion to laparotomy<br><br>Pregnancy rate<br><br>Ovarian response to stimulation | No reporting of live birth<br><br>Studies lacked details on blinding but otherwise methodologically sound |
| Pre or post-surgical medical therapy | | | | | | | |
| Furness 2004 | 20/09/2010 | 9 RCTS | 769 women | Post-surgical triptorelin 3.75mg<br>Danazol 600mg<br>Leuprolide acetate 3.5mg<br>Triptorelin 3.75mg<br>Nafarelin 400 µg<br>MPA 100mg<br>Goserelin 3.6mg<br>Gestrinone 2.5 mg | Pre and post-surgical triptorelin<br>No treatment/ placebo | Pregnancy | Live birth not reported |

**Table 1. Details of reviews** (*Continued*)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Lu 2012 | 20/03/2012 | 4 RCTs | 334 women | Laparoscopic surgery + Pentoxifylline | Laparoscopic surgery alone or + Placebo | Reduction in pain<br><br>Clinical pregnancy<br><br>Recurrence rates | Live birth not reported<br><br>Only two trials adequately reported allocation concealment. Only one trial reported blinding. All of the trials lacked adequate information on addressing incomplete outcome data |
| Other | | | | | | | |
| Lu 2013 | 3/9/12 | 1 RCT | 21 women | Anti-TNF-$\alpha$ | Placebo<br>No treatment<br>Medical treatment<br>Surgical treatment | Biberoglu and Behrman score<br>Visual analogue pain score<br>Use of analgesics | Did not conduct ITT analysis |
| Flower 2012 | 31/10/2011 | 2 RCTs | 158 women | Chinese herbal medicine | Gestrinone or Danazol or other Chinese herbal medicine | Pregnancy rate<br>Symptomatic relief<br>Dysmenorrhoea score<br>Rectal irritation relief<br>Tenderness of vaginal nodes<br>Adnexal masses, tenderness or shrinkage | No live birth reported. Evidence is based on single trials. |
| Zhu 2011 | 27/7/2010 | 1 RCT | 67 women | Acupuncture | Chinese herbal medicine | "cured" of pain | There was a lack of adequate explanation for ran- |

**Table 1. Details of reviews** (*Continued*)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | | domisation and allocation concealment and there were no details on blinding |
| Furness 2004 | 20/09/2010 | 10 RCTs | 1046 women | Post-surgical triptorelin 3.75mg<br>Danazol 600mg<br>Leuprolide acetate 3.5mg<br>Triptorelin 3.75mg<br>Nafarelin 400 µg<br>MPA 100mg<br>Goserelin 3.6mg<br>Gestrinone 2.5 mg | Pre and post-surgical triptorelin<br>No treatment/ placebo | Pain, recurrence | Most of the included trials lacked adequate methodological detail and there was a lack of blinding |

**Table 2. Description of populations in included reviews**

| Review author | Age (years) | Stage of disease |
|---|---|---|
| Abou-Setta 2013 | No details in review | Eligible participants were women with any stage of endometriosis who had undergone any type of surgical treatment for endometriosis that preserved their uterus, with surgery no more than three months prior to randomisation<br>One trial included women with moderate to severe endometriosis and one trial included only women with severe endometriosis. The third trial included women with moderate to severe endometriosis-related pain who were scheduled for laparoscopic surgery |
| Allen 2009 | Mean age 33 years | Eligible participants were women with any stage or severity of endometriosis. Endometriosis was diagnosed by visualisation (for example laparoscopy or laparotomy) or was a suspected diagnosis based on the history and pelvic examination and other tests such as ultrasound, MRI, and the CA-125 blood test |

**Table 2. Description of populations in included reviews** (*Continued*)

| | | |
|---|---|---|
| Al-Kadri 2009 | No details in review | Eligible participants were women with ectopic endometrial tissue that potentially could lead to distressing and debilitating symptoms regardless of the size and site of the deposits |
| Benschop 2010 | Women with age ranging from 25 to 36 years | Eligible participants were women with endometriomata who underwent surgical, medical or combination treatment or expectant management prior to ART. The endometriomata were diagnosed by laparoscopy or imaging tests such as ultrasound and magnetic resonance imaging (MRI)<br>The women in the included studies had endometriomata ranging in size from ≥ 1.28cm to < 6 cm |
| Brown 2010 | All participants were pre-menopausal | Eligible participants were pre-menopausal women with symptoms ascribed to endometriosis. The clinical diagnosis of endometriosis had to be made by direct visualisation (laparoscopy). Studies were included irrespective of the duration of symptoms<br>There were no details on stage of disease for 26 trials. Twelve trials reported including stages I to IV |
| Brown 2012 | Women with age ranging from 18 to 49 | Eligible participants were women of reproductive years with painful symptoms and a laparoscopic diagnosis of endometriosis |
| Davis 2007 | No details in review | Eligible participants were women of reproductive age who complained of symptoms ascribed to the diagnosis of endometriosis. The diagnosis must have been established during a surgical procedure performed prior to the start of treatment |
| Duffy 2014 | No details in review | Eligible participants were women with endometriosis confirmed with a visual diagnosis at diagnostic or operative laparoscopy |
| Farquhar 2007 | Four trials reported mean ages which ranged from 28.2 to 32.5 years, one trial reported women were aged <41 years | Eligible participants were women of reproductive age with the diagnosis of endometriosis made by direct visualisation (laparoscopy or laparotomy). This included women who were asymptomatic and where endometriosis was an incidental finding<br>Four trials recruited women who mainly had a diagnosis of stage I to II disease, one trial recruited women with moderate to severe disease. Two trials appeared to have recruited women post-surgically |
| Flower 2012 | No details in review | Eligible participants were women of reproductive age with a laparoscopically confirmed diagnosis of endometriosis |

**Table 2. Description of populations in included reviews** (*Continued*)

| | | |
|---|---|---|
| | | No further details in review |
| Furness 2004 | Women of reproductive age or <40 years were included | Eligible participants were women of reproductive age who were undergoing surgery for endometriosis. The diagnosis of endometriosis could have been made provisionally by clinical examination and confirmed during the surgery, or could have been confirmed endometriosis where women were undergoing second or subsequent surgery. They would have further medical treatment either before or after surgery<br>Two trials did not report on inclusion criteria for stage of disease but the remaining trials included women with AFS III to IV |
| Hart 2008 | No details in review | Eligible participants were women with ovarian endometriomata who were undergoing surgery for the indication of pain or infertility. Endometriomata were defined as cysts of endometriosis within the ovary |
| Hughes 2007 | Range 18 to 45 | Eligible participants were women with visually diagnosed endometriosis, either by laparoscopy or laparotomy, who had failed to conceive after 12 or more months of unprotected intercourse. Trials where medical treatment was administered after surgical treatment for endometriosis were included<br>The majority of included trials reported laparoscopically diagnosed endometriosis. Five trials reported including women with any stage of disease and eight trials reported including women with Stage III to IV endometriosis. Three trials included women with mild to moderate disease and the remaining trials did not report on this measure |
| Lu 2012 | Mean ages in the intervention group ranged from 29.7±8.1 to 33.1±3.6; for the control group mean age ranged from 28.31±4.19 to 32.9±6.5 years | Eligible participants were premenopausal, subfertile women with visually diagnosed endometriosis, either by laparoscopy or on the basis of international guidelines used to diagnose endometriosis. Trials where medical treatment was administered after surgical treatment for endometriosis were included<br>Three of the included studies recruited women with AFS I-II and one trial recruited women with Stage I-IV disease |
| Lu 2013 | Women aged 20 to 45 years | Eligible participants were pre-menopausal, subfertile women with visually diagnosed endometriosis, either by laparoscopy or on the basis of international guidelines used to diagnose endometriosis. Trials where medical treatment was administered after surgical treatment for endometriosis were included<br>Women in the included study had deep endometriosis |

**Table 2. Description of populations in included reviews** (*Continued*)

| | | |
|---|---|---|
| | | nodule of at least 1 cm in diameter and severe pain |
| Sallam 2006 | No details in review | Eligible participants were infertile women diagnosed with endometriosis and treated with IVF or ICSI. The diagnosis of endometriosis must have been based on laparoscopy or laparotomy |
| Zhu 2011 | Age range of participants 22 to 47 years | Eligible participants were women of reproductive age with a diagnosis of endometriosis confirmed laparoscopically. Participant exclusion criteria included primary dysmenorrhoea (the absence of an identifiable pathological condition) or asymptomatic endometriosis<br>Women in the included study had all stages of disease from mild to severe |

**Table 3. AMSTAR assessment**

| Review no | First author | REVIEW TITLE | AMSTAR CRITERIA | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Prespecified question and inclusion criteria | Duplicate study selection and data extraction | Comprehensive lit search | Grey lit included | Lists included and excluded studies | Describes characteristics of included studies | Study quality assessed | Studies combined using appropriate methods | Likelihood of publication bias considered/tested | Potential for conflict of interest addressed |
| AMAS10 | Abou-Setta 2013 | Levonorgestrel releasing intrauterine device (LNG-IUD) for symptomatic endometriosis following surgery | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |

**Table 3. AMSTAR assessment** (*Continued*)

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| MCA871 | Allen 2009 | Non-steroidal anti-inflammatory drugs for pain in women with endometriosis | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | x | ✓ |
| HAK118 | Al-Kadri 2009 | Hormone therapy for endometriosis and surgical menopau | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | x | ✓ |
| SG1241 | Benschop 2010 | Interventions for women with endometrioma prior to assisted reproductive technology | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| APO62 | Brown 2010 | Gonadotropl releasing hormone analogues for pain associated | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |

**Table 3. AMSTAR assessment** (*Continued*)

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | with endometriosis | | | | | | | | | | |
| AP061 | Brown 2012 | Progestagens and antiprogestagens for pain associated with endometriosis | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| SK141 | Davis 2007 | Oral contraceptives for pain associated with endometriosis | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | x | ✓ |
| JD1830 | Duffy 2014 | Laparoscopic surgery for endometriosis. | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| VS081 | Farquhar 2007 | Danazol for pelvic pain associated with endometriosis | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | x | ✓ |

**Table 3. AMSTAR assessment** (*Continued*)

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| AF801 | Flower 2012 | Chinese herbal medicine for endometriosis | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| CY571 | Furness 2004 | Pre and post-operative medical therapy for endometriosis surgery | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | x | ✓ |
| RJH961 | Hart 2008 | Excisional surgery versus ablative surgery for ovarian endometriomata | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| EJ254 | Hughes 2007 | Ovulation suppression for endometriosis for women with subfertility | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| DL1540 | Lu 2012 | Pentoxifylline for endometriosis | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |

**Table 3. AMSTAR assessment** (*Continued*)

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| DD1570 | Lu 2013 | Anti-TNF-α treatment for pelvic pain associated with endometriosis | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| HNS881 | Sallam 2006 | Long term pituitary down-regulation before in vitro fertilisation (IVF) for women with endometriosis | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | x | ✓ |
| KRF1291 | Zhu 2011 | Acupuncture for pain in endometriosis | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | x | ✓ |

**Table 4. Search date assessment**

| Review no | Review reference | REVIEW TITLE | <3 yrs since last search (to March 6 2014) |
|---|---|---|---|
| AMAS1061 | Abou-Setta 2013 | Levonorgestrel-releasing intrauterine device (LNG-IUD) for symptomatic | ✓ |

**Table 4. Search date assessment** (*Continued*)

| | | | |
|---|---|---|---|
| | | endometriosis following surgery | |
| MCA871 | Allen 2009 | Non-steroidal anti-inflammatory drugs for pain in women with endometriosis | ✖ |
| HAK1181 | Al-Kadri 2009 | Hormone therapy for endometriosis and surgical menopause | ✖ |
| SG1241 | Benschop 2010 | Interventions for women with endometrioma prior to assisted reproductive technology | ✖ |
| APO62 | Brown 2010 | Gonadotrophin-releasing hormone analogues for pain associated with endometriosis | ✖ |
| AP061 | Brown 2012 | Progestagens and anti-progestagens for pain associated with endometriosis | ✓ |
| SK141 | Davis 2007 | Oral contraceptives for pain associated with endometriosis | ✖ |
| JD1830 | Duffy 2014 | Laparoscopic surgery for endometriosis | ✓ |
| VS081 | Farquhar 2007 | Danazol for pelvic pain associated with endometriosis | Stable |
| AF801 | Flower 2012 | Chinese herbal medicine for endometriosis | ✓ |
| CY571 | Furness 2004 | Pre and post-operative medical therapy for endometriosis surgery | ✖ |
| RJH961 | Hart 2008 | Excisional surgery versus ablative surgery for ovarian endometriomata | ✖ |
| EJ254 | Hughes 2007 | Ovulation suppression for endometriosis for women with subfertility | Stable |
| DL1540 | Lu 2012 | Pentoxifylline for endometriosis | ✓ |
| DD1570 | Lu 2013 | Anti-TNF-$\alpha$ treatment for pelvic pain associated with endometriosis | ✓ |
| HNS881 | Sallam 2006 | Long term pituitary down-regulation before in vitro fertilisation (IVF) for women with endometriosis | ✖ |
| KRF1291 | Zhu 2011 | Acupuncture for pain in endometriosis | ✖ |

**Table 5. Pain outcomes**

| Outcome Intervention and comparison intervention | Illustrative comparative risks (95% CI) | | Relative effect (95% CI) | Number of participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk with comparator | Corresponding risk with intervention | | | | |
| **Reduction in pain at 3 months** | | | | | | |
| Lu 2012 Laparoscopic surgery plus pentoxifylline versus laparoscopic surgery plus placebo | The mean reduction in pain at 3 months in the laparoscopic surgery plus placebo groups was 5.53 (VAS score) | The mean reduction in pain at 3 months in the laparoscopic surgery plus pentoxifylline groups was 1.6 lower (3.32 lower to 0.12 higher) (VAS score) | - | 34 ( 1 study) | Very low | Lacked methodological detail, and lack of precision. Evidence based on a single study |
| **Dysmenorrhoea** | | | | | | |
| Duffy 2014 Laparoscopic excision versus diagnostic laparoscopy | | At 6 months, the mean dysmenorrhoea pain score in the excision group was 2.4 higher than in the diagnostic laparoscopy group (6.18 lower to 10.98 higher) on a VAS 0-100 scale | | 39 (1 study) | Low | Very serious imprecision - single small study, wide confidence intervals |
| Duffy 2014 Laparoscopic excision versus diagnostic laparoscopy | | At 12 months, the mean dysmenorrhoea pain score in the excision group was 9.5 lower than in the diagnostic laparoscopy group | | 39 (1 study) | Low | Very serious imprecision - single small study, wide confidence intervals |

**Table 5. Pain outcomes** (*Continued*)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | (20.58 lower to 1.58 higher) on a VAS 0-100 scale | | | | |
| Furness 2004 Post-surgical medical therapy versus placebo | | - | The mean pain score (VAS) in the intervention group was 0.58 standard deviations lower than in the placebo group (0.87 to 0.28 lower) | - | 187 (1 study) | Low | Lacked sufficient details on allocation concealment and blinding |
| Flower 2012 Chinese herbal medicine Nei Yi pills versus danazol | | - | The mean dysmenorrhoea score in the Chinese herbal medicine Nei Yi pills group was 1.01 lower (3.11 lower to 1.09 higher) than in the danazol group | - | 34 ( 1 study) | Low | Evidence based on a single trial, quality of blinding very uncertain |
| Flower 2012 Chinese herbal medicine Nei Yi pills + Nei Yi enema versus danazol | | - | The mean dysmenorrhoea score in the Chinese herbal medicine Nei Yi pills group was 2.9 lower (4.55 lower to 1.25 higher) than in the danazol group | | 42 (1 study) | Low | Evidence based on a single trial, quality of blinding very uncertain |
| Flower 2012 Chinese herbal medicine Nei Yi pills + Nei Yi enema versus Nei Yi pills | | | The mean dysmenorrhoea score in the Chinese herbal medicine Nei Yi pills + enema group was 1.89 lower (3.89 lower to 0.11 higher) than in the Nei Yi pills | - | 40 (1 study) | Low | Evidence based on a single trial, quality of blinding very uncertain |

**Table 5. Pain outcomes** (*Continued*)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | alone group | | | | |
| Brown 2010 GnRHas versus no treatment | | 188/1000 achieved pain relief | 737/1000 achieved pain relief | RR 3.93 (1.37 to 11.28) | 35 (1 study) | Low | No blinding and evidence based on a single trial |
| Brown 2010 GnRHas versus danazol | | 825/1000 achieved pain relief | 809/1000 achieved pain relief | RR 0.98 (0.92 to 1.04) | 666 (7 studies) | Very low | Randomisation and allocation concealment was inadequately reported in most of the trials. Blinding was unclear in two trials and there was no blinding in two trials. $I^2$ was 44% which suggests some heterogeneity |
| Brown 2010 GnRHas (3 month versus 6 month) | | - | The mean dysmenorrhoea score in the three month group was 0.02 standard deviations lower (0.31 lower to 0.27 higher) than in the six month group | - | 179 (1 study) | Moderate | Evidence was based on a single trial |
| Brown 2010 GnRHas (intranasal versus intramuscular depot) | | 828/1000 achieved pain relief | 778/1000 achieved pain relief | RR 0.94 (0.82 to 1.08) | 192 (1 study) | Low | Lack of adequate explanation of allocation concealment and evidence based on a single trial |
| Brown 2010 GnRHas (intranasal versus subcutaneous) | | 800/1000 achieved pain relief | 976/1000 achieved pain relief | RR 1.22 (0.73 to 2.06) | 10 (1 study) | Low | Open label trial with evidence based on a single trial |

**Table 5. Pain outcomes** (*Continued*)

| | | | | | | |
|---|---|---|---|---|---|---|
| Furness 2004 Pre-surgical medical therapy versus post-surgical medical therapy | See Comment | See Comment | RR 0.0 (0 to 0) | 53 (1 study) | Low | There were no events reported in either the intervention or the control group. There were insufficient methodological details for allocation concealment or randomisation |
| Davis 2007 Oral contraceptive versus goserelin | The mean dysmenorrhoea pain score in the control groups was 7.5 | The mean dysmenorrhoea pain score in the intervention groups was 0.10 lower (1.28 lower to 1.08 higher) | - | 50 (1 study) | Very low | There was a lack of adequate explanation for allocation concealment, and randomisation. There was no blinding. The evidence was based on a single trial |
| Lu 2013 Anti-TNF-$\alpha$ plus surgery versus placebo plus surgery - clinician score | The mean dysmenorrhoea Biberoglu and Behrman score in the control groups was 2.3 | The mean Biberoglu and Behrman score in the intervention groups was 0.2 higher (0.05 lower to 0.45 higher) | - | 21 (1 study) | Low | Evidence based on a single trial and not ITT conducted. |
| Lu 2013 Anti-TNF-$\alpha$ plus surgery versus placebo plus surgery - patient score | The mean Biberoglu and Behrman score in the control groups was 1.7 | The mean Biberoglu and Behrman score in the intervention groups was 0.2 lower (0.68 lower to 0.28 higher) | - | 21 (1 study) | Low | Evidence based on a single trial and not ITT conducted. |
| Brown 2012 Anti-progestagen versus other treatment (end of treatment) | The mean patient assessed efficacy at end of treatment in the control groups was 0.05 | The mean patient assessed efficacy at end of treatment in the intervention groups was 0.82 | - | 55 (1 study) | Moderate | Evidence was based on a single trial |

**Table 5. Pain outcomes** (*Continued*)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | higher (0.15 to 1.49 higher) | | | | |
| Brown 2012 Anti-progestagen versus other treatment (12 months) | | The mean patient assessed efficacy at 12 months follow-up in the control groups was 4.76 | The mean patient assessed efficacy at 12 months follow-up in the intervention groups was 3 lower (4.79 to 1.21 lower) | - | 55 (1 study) | Moderate | Evidence was based on a single trial |
| Brown 2012 Depot progestagen versus other treatment (6 months) | | 978/1000 achieved pain relief | 895/1000 achieved pain relief | OR 0.19 (0.05 to 0.69) | 274 (1 study) | Moderate | Evidence was based on a single trial |
| Brown 2012 Depot progestagen versus other treatment (12 months) | | 768/1000 achieved pain relief | 676/1000 achieved pain relief | OR 0.63 (0.37 to 1.08) | 274 (1 study) | Moderate | Evidence was based on a single trial |
| Brown 2012 Anti-progestagen versus other treatment | | 667/1000 achieved pain relief | 673/1000 achieved pain relief | OR 1.03 (0.55 to 1.93) | 176 (2 studies) | Moderate | Trials lacked details on randomisation. One trial appeared to have inadequate allocation concealment and no blinding |
| **Pain score** | | | | | | | |
| Brown 2010 GnRHas versus placebo | | - | The mean overall pain score at 4 weeks in the intervention group was 2.9 higher (2.11 to 3.69 higher) than in the placebo group | - | 120 (1 study) | Low | Allocation concealment and blinding were inadequately explained and the evidence was based on a single trial |

**Table 5. Pain outcomes** (*Continued*)

| | | | | | | |
|---|---|---|---|---|---|---|
| Abou-Setta 2013 LNG-IUD versus GnRHa | The mean VAS score for painful symptoms in the control groups was 3.63 | The mean VAS score for painful symptoms in the intervention groups was 0.16 lower (2.02 to 1. 7 higher) | - | 40 (1 study) | Very low | No evidence of blinding in the included trial and evidence was based on a single trial. There was also imprecision in the summary statistic |
| Farquhar 2007 Danazol versus placebo (no surgery) | The mean pelvic pain score in the control groups was 1.85 | The mean pelvic pain score in the intervention groups was 1.4 lower (1.33 to 0.77 lower) | | 35 (1 study) | Low | There was a lack of adequate explanation for allocation concealment and randomisation and evidence was based on a single trial |
| Farquhar 2007 Danazol versus placebo (post-surgery) - pelvic pain 6 months | The mean pelvic pain score in the control groups was 1.55 | The mean pelvic pain score in the intervention groups was 1.1 lower (1.38 to 0.82 lower) | | 34 (1 study) | Low | There was a lack of adequate explanation for allocation concealment and randomisation and evidence was based on a single trial |
| Farquhar 2007 Danazol versus placebo (post-surgery) - pelvic pain 6 months | 310/1000 had moderate or severe pelvic pain at 6 months | 226/1000 had moderate or severe pelvic pain at 6 months | OR 0.65 (0.2 to 2.05) | 60 (1 study) | Low | There was a lack of adequate explanation for allocation concealment and randomisation and evidence was based on a single trial |
| Lu 2013 Anti-TNF-$\alpha$ plus surgery versus placebo plus surgery - | The mean Biberoglu and Behrman score in the control groups was | The mean Biberoglu and Behrman score in the intervention groups was | - | 21 (1 study) | Low | Evidence was based on a single trial. No ITT analysis conducted |

**Table 5. Pain outcomes** (*Continued*)

| | | | | | | |
|---|---|---|---|---|---|---|
| clinician score | 1.45 | 0.15 lower (0.45 lower to 0.15 higher) | | | | |
| Lu 2013 Anti-TNF-α plus surgery versus placebo plus surgery - patient score | The mean Biberoglu and Behrman score in the control groups was 0.15 | The mean Biberoglu and Behrman score in the intervention groups was 0.15 lower (0.51 lower to 0.21 higher) | - | 21 (1 study) | Low | Evidence was based on a single trial. No ITT analysis conducted |
| Brown 2012 Oral progestagens versus other treatment (6 months) | The mean self-reported pain in the control group was 41.8 | The mean self-reported pain in the intervention group was 1.6 lower (0.01 lower to 0.57 higher) | - | 252 (1 study) | Low | Open label study with evidence based on a single trial |
| **Supplementary analgesia use** | | | | | | |
| Lu 2013 Anti-TNF-α plus surgery versus placebo plus surgery | The mean use of analgesia in the control group was 0.28 | The mean use of analgesia in the intervention group was 0.1 (0.6 lower to 0.4 higher) | - | 30 (1 study) | Low | Evidence was based on a single trial. No ITT analysis conducted |
| Allen 2009 NSAIDS versus placebo | - | - | OR (inverse variance) 0.12 (0.01 to 12.9) | 20 (1 study) | Unable to conduct GRADE analysis as inverse variance used (no raw data) | There was a lack of adequate explanation for allocation concealment, and randomisation. The evidence was based on a single trial |
| **Disease recurrence/ rAFS** | | | | | | |
| Hart 2008 Excisional versus ablative surgery for endometriomata | 262/1000 | 128/1000 | OR 0.41 (0.18 to 0.93) | 164 (2 studies) | Very low | Included studies lacked blinding |

**Table 5. Pain outcomes** (*Continued*)

| | | | | | | |
|---|---|---|---|---|---|---|
| Furness 2004 Pre-surgical medical therapy versus no medical therapy | - | The mean recurrence (AFS) score was 9.6 lower (11.42 to 7.78 lower) in the intervention group | - | 80 (1 study) | Low | No blinding and trial lacked details on allocation concealment |
| Furness 2004 Post-surgical medical therapy versus pre and post-surgical medical therapy with GnRHa | - | The mean recurrence (AFS) score was 3.49 higher (5.1 to 12.08 higher) in the intervention group | - | 25 (1 study) | Very low | Lacked sufficient detail on randomisation and allocation concealment and there was a lack of precision |
| Furness 2004 Post-surgical medical therapy versus placebo | - | The mean recurrence (AFS) score was 2.29 lower (4.69 lower to 0.11 higher) in the intervention group | - | 43 (1 study) | Low | Lacked sufficient detail on randomisation and allocation concealment |
| Brown 2010 GnRHas versus danazol | - | The mean rAFS in the intervention groups was 0.01 standard deviations lower (0.13 to 0.12) | - | 1012 (10 studies) | Low | There was a lack of adequate explanation for randomisation and allocation concealment and blinding |
| Brown 2010 GnRHas (400 mcg versus 800 mcg) | 200/1000 | 82/1000 | RR 0.41 (0.17 to 1.01) | 143 (1 study) | Low | Lack of adequate explanation for randomisation, allocation concealment and blinding. Evidence was based on a single trial |
| Brown 2010 GnRHas versus intrauterine progestagen device | - | The mean rAFS score in the intervention groups was | - | 18 (1 study) | Low | Open label study with no blinding and evidence based on a single |

**Table 5. Pain outcomes** (*Continued*)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | 9.5 higher (10. 77 lower to 29. 77 higher) | | | | trial |
| Brown 2010 GnRHas (intranasal versus subcutaneous) | | - | The mean rAFS score in the intervention groups was 9 higher (5.93 lower to 23.93 higher) | - | 19 (1 study) | Very low | Lacked an adequate explanation of allocation concealment and randomisation and blinding. Evidence based on a single trial |
| Al-Kadri 2009 Estrogen, with or without progesterone versus placebo | | 0/1000 | 0/1000 | OR 2.53 (0.12 to 53.64) | 172 (1 study) | Very low | There was no evidence of blinding , there was imprecision and the evidence was based on a single trial |
| Farquhar 2007 Danazol versus placebo (no surgery) | | The mean change in total AFS scores in the control group was 0.2 | The mean change in total AFS scores in the intervention group was 1.9 lower (4.16 lower to 0.36 higher) | - | 31 (1 study) | Very low | Lacked an adequate explanation of randomisation and allocation concealment and the evidence was based on a single trial |
| Farquhar 2007 Danazol versus placebo (post-surgery) | | The mean change in total AFS scores in the control group was -4.5 | The mean change in total AFS scores in the intervention group was 0.9 lower (3.02 lower to 1.22 higher) | - | 27 (1 study) | Very low | Lacked an adequate explanation of randomisation and allocation concealment and the evidence was based on a single trial |
| Brown 2012 Anti-progestagen versus other treatment | | The mean AFS score in the control group was 11.8 | The mean AFS score in the intervention group was 1.4 higher (6.76 lower to 9. 56 higher) | - | 16 (1 study) | Very low | The single trial was open label and appeared to have inadequate allocation concealment |
| Brown 2012 Oral progesta- | | The mean change in AFS | The mean AFS score in the in- | - | 302 (1 study) | Moderate | There was an inadequate expla- |

**Table 5. Pain outcomes** (*Continued*)

| | | | | | | |
|---|---|---|---|---|---|---|
| gens versus other treatment | scores in the control group was 1.31 | tervention group was 0.34 higher (0.01 lower to 0.70 higher) | | | | nation of allocation concealment, randomisation and blinding |
| Brown 2012 Progestagen versus placebo | Mean AFS score in the control group was 1.76 | Mean AFS score in the intervention group was 0.58 lower (1.41 lower to 0.25 higher) | - | 33 (1 study) | Low | This single trial provided inadequate detail on allocation concealment and blinding |
| **Resolution of pain** | | | | | | |
| Zhu 2011 Acupuncture versus Chinese herbal medicine | 267/1000 | 811/1000 | RR 3.04 (1.65 to 5.62) | 67 (1 study) | Very low | Lack of methodological detail. No blinding and evidence based on single study |
| Brown 2010 GnRHas versus danazol | 596/1000 | 655/1000 | RR 1.1 (1.01 to 1.21) | 1046 (9 studies) | Low | There was a lack of adequate detail for randomisation and allocation concealment and blinding. Two trials had no blinding |
| Brown 2010 GnRHas versus intrauterine progestagen device (LNG-IUD) | - | The mean relief of painful symptoms in the intervention group was 0.25 standard deviations lower (0.6 lower to 0.1 higher) | - | 129 (3 studies) | Moderate | There was a lack of blinding and inadequate explanation of allocation concealment |
| Brown 2010 GnRHas (400mcg versus 800mcg) | 356/1000 | 334/1000 | RR 0.94 (0.53 to 1.66) | 90 (1 study) | Moderate | Evidence based on a single trial |

**Table 5. Pain outcomes** (*Continued*)

| | | | | | | |
|---|---|---|---|---|---|---|
| Davis 2007 Oral contraceptive versus goserelin | 818/1000 | 774/1000 | OR 0.76 (0.17 to 3.29) | 44 (1 study) | Very low | There was a lack of adequate explanation for allocation concealment, and randomisation. There was no blinding. The evidence was based on a single trial |
| Duffy 2014 Laparoscopic ablation or excision | 321 per 1000 improved or better at 6 months | 756 per 1000 improved or better at 6 months (610 to 861) | OR 6.58 (3.31 to 13.10) | 171 (3 studies) | Moderate | None of studies blinded participants, only one fully described methods of randomisation and allocation concealment |
| Duffy 2014 Laparoscopic ablation or excision | 214 per 1000 improved or better at 12 months | 732 per 1000 improved or better at 12 months (467 to 895) | OR 10.00 (3.21 to 31.17) | 69 (1 study) | Low | Only conference abstract available: randomisation methods not fully described, high risk of attrition bias, unclear whether blinded; single small study |
| Duffy 2014 Laparoscopic surgery versus laparoscopic surgery plus medical therapy | 167 per 1000 pain free at 12 months | 530 per 1000 pain free at 12 months (191 to 843) | OR 5.63 (1.18 to 26.85 | 35 (1 study) | Low | Only conference abstract available: randomisation methods not fully described, unclear whether blinded; single small study |
| Allen 2009 NSAID versus placebo | - | - | OR (inverse variance) 0.327 (0.61 to 17.69) | 20 (1 study) | Unable to conduct GRADE analysis as inverse variance used (no | There was a lack of adequate explanation for allocation concealment, |

**Table 5. Pain outcomes** (*Continued*)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | raw data) | and randomisation. The evidence was based on a single trial |
| Brown 2012 Anti-progestagen versus other treatment | | 667/1000 | 673/1000 | OR 1.03 (0.55 to 1.93) | 176 (2 studies) | Low | Two trials lacked details on randomisation. One of the trials appeared to have inadequate allocation concealment and no blinding |
| **Pain recurrence up to 1 year** | | | | | | | |
| Furness 2004 Post-surgical medical therapy versus placebo | | 273/1000 | 207/1000 | RR 0.76 (0.52 to 1.1) | 332 (3 studies) | Low | Lacked sufficient evidence for allocation concealment or attrition and there was no blinding |
| Abou-Setta 2013 LNG-IUD versus expectant management | | 383/1000 | 84/1000 | RR 0.22 (0.08 to 0.6) | 95 (2 studies) | Moderate | Only one of the two studies had blinded outcome assessment |
| Al-Kadri 2009 Estrogen with or without progesterone versus placebo | | 0/1000 | 0/1000 | OR 4.64 (0.25 to 87.71) | 172 (1 study) | Very low | There was no evidence of blinding , there was imprecision and the evidence was based on a single trial |
| Al-Kadri 2009 Estrogen with or without progesterone versus tibolone | | 91/1000 | 400/1000 | OR 6.67 (0.6 to 74.51) | 21 (1 study) | Very low | There was no blinding and there was a lack of adequate detail on allocation concealment. Evidence |

**Table 5. Pain outcomes** (*Continued*)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | | was based on a single trial |

**Table 6. Fertility outcomes**

| Outcome Intervention and comparison intervention | Illustrative comparative risks (95% CI) | | Relative effect (95% CI) | Number of participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk with comparator | Corresponding risk with intervention | | | | |
| **Clinical pregnancy** | | | | | | |
| Hughes 2007 Ovulation suppression versus placebo (for subfertile couples) | 270/1000 | 274/1000 | OR 1.02 (0.69 to 1.5) | 557 (11 studies) | Low | Included studies lacked adequate explanations for allocation concealment and blinding |
| Sallam 2006 Ultralong GnRHa agonist down-regulation versus no agonist | 325/1000 | 673/1000 | OR 4.28 (2.0 to 9,15) | 165 (3 studies) | Very low | Included studies lacked blinding and explanations for allocation concealment. There was some imprecision |
| Hart 2008 Excisional versus ablative surgery for endometriomata | 170/1000 | 518/1000 | OR 5.24 (1.92 to 14.27) | 88 (2 studies) | Low | Included studies lacked blinding and there was some imprecision |
| Flower 2012 Chinese herbal medicine versus gestrinone | 592/1000 | 699/1000 | RR 1.18 (0.87 to 1.59) | 45 (1 study) | Low | Evidence based on a single study |
| Furness 2004 Post-surgical medical ther- | 500/1000 | 0/1000 | RR 0.0 (0 to 0) | 25 (1 study) | Very low | Included studies lacked adequate ex- |

**Table 6. Fertility outcomes** (*Continued*)

| | | | | | | |
|---|---|---|---|---|---|---|
| apy versus pre and post-surgical medical therapy with GnRHa | | | | | | planation of randomisation, allocation concealment and there was no blinding |
| Furness 2004 Post-surgical medical therapy versus placebo/ no treatment | 246/1000 | 207/1000 | RR 0.84 (0.59 to 1.18) | 420 (8 studies) | Low | Included studies lack ed adequate explana- tion of randomisation and blinding |
| Lu 2012 Laparoscopic surgery plus pentoxifylline versus laparoscopic surgery plus placebo | 196/1000 | 273/1000 | OR 1.54 (0.89 to 2.66) | 285 (3 studies) | Very low | Lacked methodological detail, and lack of precision. No trial reported on live birth |
| Benschop 2010 Aspiration of endometrioma versus expectant management | 200/1000 | 244/1000 | OR 1.29 (0.45 to 3.64) | 81 (1 study) | Low | There was no blinding and evidence was based on a single trial |
| Benschop 2010 Cystectomy of endometrioma versus expectant management | 317/1000 | 348/1000 | OR 1.15 (0.52 to 2.55) | 109 (1 study) | Low | There was no blinding and evidence was based on a single trial |
| Benschop 2010 GnRH agonist versus GnRH antagonist for endometrioma | 242/1000 | 206/1000 | OR 0.814 (0.26 to 2.54) | 67 (1 study) | Low | Evidence based on a single trial |
| Duffy 2014 Laparoscopic ablation or excision versus diagnostic laparoscopy | 186 per 1000 | 302 per 1000 (223 to 396) | OR 1.89 (1.25 to 2.86) | 528 (3 studies) | Moderate | Two studies did- not adequately describe randomisation methods; one study was at high risk of attrition bias |

**Table 6. Fertility outcomes** (*Continued*)

| | | | | | | |
|---|---|---|---|---|---|---|
| **Ongoing pregnancy (20 weeks) or live birth** | | | | | | |
| Duffy 2014 Laparoscopic ablation or excision versus diagnostic laparoscopy | 179 per 1000 | 297 per 1000 (207 to 408) | OR 1.94 (1.20 to 3.16) | 382 (2 studies) | Moderate | One study did not describe methods in detail, as it is only published as an abstract. Most of the data apply to ongoing pregnancy: of 92 events in this comparison, only 12 were live birth |
| **Fetal loss or miscarriage** | | | | | | |
| Duffy 2014 Laparoscopic surgery versus diagnostic laparoscopy | 190/1000 | 181/1000 | OR 0.94 (0.35 to 2.54) | 112 (2 studies) | Moderate | One study did not describe methods in detail, as was only available as an abstract. The larger study (n= 100 pregnancies) did not include fetal losses after 20 weeks |
| Benschop 2010 GnRH agonist versus GnRH antagonist for endometrioma prior to ART | 30/1000 | 29/1000 | OR 0.97 (0.06 to 15.85) | 67 (1 study) | Low | Evidence based on a single trial and wide confidence intervals are indicative of some imprecision |
| Benschop 2010 Aspiration of endometrioma versus expectant management | 100/1000 | 97/1000 | OR 0.97 (0.23 to 4.15) | 81 (1 study) | Low | There was no blinding and the evidence is based on a single trial |

## WHAT'S NEW

Last assessed as up-to-date: 6 March 2014.

| Date | Event | Description |
|---|---|---|
| 16 June 2014 | Amended | Minor typographical errors corrected |

## CONTRIBUTIONS OF AUTHORS

Julie Brown and Cindy Farquhar were responsible for the writing of the protocol and overview.

## DECLARATIONS OF INTEREST

None

## SOURCES OF SUPPORT


### Internal sources

- Department of Obstetrics and Gynaecology, University of Auckland, New Zealand.

### External sources

- Auckland District Health Board Charitable Trust, New Zealand.


## INDEX TERMS

### Medical Subject Headings (MeSH)

*Review Literature as Topic; Acupuncture, Ear; Anti-Inflammatory Agents, Non-Steroidal [therapeutic use]; Drugs, Chinese Herbal [therapeutic use]; Endometriosis [complications; *therapy]; Gonadotropin-Releasing Hormone [analogs & derivatives]; Infertility, Female [etiology; *therapy]; NM23 Nucleoside Diphosphate Kinases [antagonists & inhibitors]; Ovulation Inhibition; Pelvic Pain [etiology; *therapy]

### MeSH check words

Female; Humans