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Endometriosis: an overview of Cochrane Reviews (Review)

Brown J, Farquhar C

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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 post-operatively, 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 post-operatively, 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 17β 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 pre-menopausal 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-α drugs

One review (Lu 2013) found low quality evidence that anti-TNF-α 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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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 Triptorelin 3.75mg	No treatment Leuprolide acetate 0.5 to 1.0mg GnRH agonist 3.75mg	Clinical pregnancy Dose of FSH/HMG Duration of FSH Number of oocytes retrieved	Only 3 trials Trials lacked details of allocation concealment No blinding
Brown 2010	27/09/2010	42 RCTs	4935 women	Any GnRHa	No treatment Placebo Danazol Intrauterine progesterone devices Another GnRHa	Pain relief Adverse effects Resolution of endometriosis Quality of life 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 No treatment Other surgical or medical therapy	Clinical pregnancy rate Live birth Adverse events Quality of life Pain Recurrence	No live birth reported in the included trials. Overall trials well conducted but two of the trials did not conduct any blinding

Table 1. Details of reviews *(Continued)*

						Estrodial levels Number of mature oocytes	
Ovarian suppression							
Hughes 2007	19/04/2009 (stable review no longer being updated)	25 RCTs	2600 women	Dienogest Triptorelin MPA Leuprolide acetate Nafarelin Provera Goserelin Danazol Mestronol Gestrinone Buserelin	Triptorelin Expectant management Placebo No treatment Nafarelin Danazol	Live birth Clinical pregnancy	Only 2 trials reported live birth 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)*

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 Satisfaction Withdrawal Side effects 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 Satisfaction 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 Tibolone	Pain 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 Placebo No treatment	Pain AFS score Pregnancy Side effects Symptoms Hormone level 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 Gestrinone 2.5mg Dienogest 2mg Dydrogesterone 40/60 mg	Nafarelin 200 ug IN Danazol 400mg/ 600mg Leuprolide 3.75mg/ 11.25mg IM Buserelin 300ug IN	Pain scores rAFS Side effects Fertility Bone mineral density Lipid profiles Biochemical measures	

Table 1. Details of reviews *(Continued)*

				Cyproterone acetate 12.5mg	Oral contraceptive Placebo	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 allocation concealment, and risk of attrition bias

Table 1. Details of reviews *(Continued)*

Hart 2008	31/08/2009	2 RCTs	Not detailed in review	Excision	Drainage and ablation	Pelvic pain Spontaneous conception Recurrence of endometrioma Requirements for further surgery Conversion to laparotomy Pregnancy rate Ovarian response to stimulation	No reporting of live birth 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 Danazol 600mg Leuprolide acetate 3.5mg	Pre and post-surgical triptorelin No treatment/placebo	Pregnancy	Live birth not reported

Table 1. Details of reviews *(Continued)*

				Triptorelin 3.75mg Nafarelin 400 µg MPA 100mg Goserelin 3.6mg Gestrinone 2.5 mg			
Lu 2012	20/03/2012	4 RCTs	334 women	Laparoscopic surgery + Pentoxifylline	Laparoscopic surgery alone or + Placebo	Reduction in pain Clinical pregnancy Recurrence rates	Live birth not reported 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-α	Placebo No treatment Medical treatment Surgical treatment	Biberoglu and Behrman score Visual analogue pain score 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 Symptomatic relief Dysmenorrhoea score Rectal irritation relief Tenderness of vaginal nodes Adnexal masses, tenderness or shrinkage	No live birth reported. Evidence is based on single trials.

Table 1. Details of reviews *(Continued)*

Zhu 2011	27/7/2010	1 RCT	67 women	Acupuncture	Chinese herbal medicine	"cured" of pain	There was a lack of adequate explanation for randomisation and allocation concealment and there were no details on blinding
Furness 2004	20/09/2010	10 RCTs	1046 women	Post-surgical triptorelin 3.75mg Danazol 600mg Leuprolide acetate 3.5mg Triptorelin 3.75mg Nafarelin 400 µg MPA 100mg Goserelin 3.6mg Gestrinone 2.5 mg	Pre and post-surgical triptorelin 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. 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.
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). 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. 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. 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. 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. 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. 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. Women in the included study had deep endometriosis 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. 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
AMAS1061	Abou-Setta 2013	Levonorgestrel-releasing intrauterine device (LNG-IUD) for symptomatic endometriosis following surgery	#	#	#	#	#	#	#	#	#	#
MCA871	Allen 2009	Non-steroidal anti-inflammatory drugs for pain in women with endometriosis	#	#	#	#	#	#	#	#	x	#
HAK1181	Al-Kadri 2009	Hormone therapy for endometriosis and surgical menopause	#	#	#	#	#	#	#	#	x	#
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	#	#	#	#	#	#	#	#	#	#

Table 3. AMSTAR assessment *(Continued)*

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	#
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	#	#	#	#	#	#	#	#	#	#
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 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-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	#
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 (20.58 lower to 1.58 higher) on a VAS 0-100 scale		39 (1 study)	Low	Very serious imprecision - single small study, wide confidence intervals

Table 5. Pain outcomes *(Continued)*

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 alone group	-	40 (1 study)	Low	Evidence based on a single trial, quality of blinding very uncertain
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

Table 5. Pain outcomes *(Continued)*

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
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-α 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-α plus surgery versus place-	The mean Biberoglu and Behrman	The mean Biberoglu and Behrman score in the intervention groups was	-	21 (1 study)	Low	Evidence based on a single trial and not ITT conducted.

Table 5. Pain outcomes *(Continued)*

bo plus surgery - patient score	score in the control groups was 1.7	0.2 lower (0.68 lower to 0.28 higher)				
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 higher (0.15 to 1.49 higher)	-	55 (1 study)	Moderate	Evidence was based on a single trial
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	-	The mean overall pain score at 4 weeks in the	-	120 (1 study)	Low	Allocation concealment and blinding were inadequately ex-

Table 5. Pain outcomes *(Continued)*

GnRHas versus placebo		intervention group was 2.9 higher (2.11 to 3.69 higher) than in the placebo group				plained and the evidence was based on a single trial
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-α plus surgery versus placebo plus surgery - clinician score	The mean Biberoglu and Behrman score in the control groups was 1.45	The mean Biberoglu and Behrman score in the intervention groups was 0.15 lower (0.45 lower to 0.15 higher)	-	21 (1 study)	Low	Evidence was based on a single trial. No ITT analysis conducted
Lu 2013	The mean Biberoglu and Behrman	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)*

Anti-TNF-α plus surgery versus placebo plus surgery - patient score	score in the control groups was 0.15	0.15 lower (0.51 lower to 0.21 higher)				
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
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	-	The mean recurrence (AFS) score was 3.49 higher (5.1 to 12.08 high-	-	25 (1 study)	Very low	Lacked sufficient detail on randomisation and allocation concealment and there was a lack of precision

Table 5. Pain outcomes *(Continued)*

pre and post-surgical medical therapy with GnRHa		er) in the intervention group				
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 9.5 higher (10.77 lower to 29.77 higher)	-	18 (1 study)	Low	Open label study with no blinding and evidence based on a single 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

Table 5. Pain outcomes *(Continued)*

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 progestagens versus other treatment	The mean change in AFS scores in the control group was 1.31	The mean AFS score in the intervention group was 0.34 higher (0.01 lower to 0.70 higher)	-	302 (1 study)	Moderate	There was an inadequate explanation 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

Table 5. Pain outcomes *(Continued)*

Brown 2010 Gn-RHas (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
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 raw data)	There was a lack of adequate explanation for allocation concealment, 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						

Table 5. Pain outcomes *(Continued)*

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 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 therapy versus pre and post-surgical medical therapy with GnRHa	500/1000	0/1000	RR 0.0 (0 to 0)	25 (1 study)	Very low	Included studies lacked adequate explanation 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 explanation 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

Table 6. Fertility outcomes *(Continued)*

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 didnot adequately describe randomisation methods; one study was at high risk of attrition bias
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

APPENDICES

Appendix 1. Protocols and titles for future inclusion in this review

Protocols and titles for future inclusion in this overview

Protocols

Bignardi 2011: Excisional versus ablative surgery for peritoneal endometriosis

Fu 2012: Progesterone receptor antagonists and progesterone receptor modulators for endometriosis

Titles

Houda unpublished 2013: Gonadotrophin antagonists for endometriosis

Chen unpublished 2013: Selective estrogen receptor modulators (SERMs) for endometriosis

WHAT'S NEW

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