Endometriosis

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Neil Johnson and Cynthia M. Farquhar

ABSTRACT

INTRODUCTION: Ectopic endometrial tissue is found in up to 20% of asymptomatic women, up to 60% of those with dysmenorrhoea, and up to 30% of women with subfertility, with a peak incidence at around 40 years of age. However, symptoms may not correlate with laparoscopic findings. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of hormonal treatments given at diagnosis of endometriosis? What are the effects of hormonal treatments before surgery for endometriosis? What are the effects of non-hormonal medical treatments for endometriosis? What are the effects of surgical treatments for endometriosis? What are the effects of hormonal treatment after conservative surgery for endometriosis? What are the effects of hormonal treatment after oophorectomy (with or without hysterectomy) for endometriosis? What are the effects of treatments for ovarian endometrioma? We searched: Medline, Embase, The Cochrane Library and other important databases up to April 2006 (BMJ Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 32 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: combined oral contraceptives; danazol; dydrogesterone; gestrinone; gonadorelin analogues; hormonal treatment before surgery; hormonal treatment; laparoscopic cystectomy; laparoscopic removal of endometriotic deposits (alone or with uterine nerve ablation); laparoscopic removal plus presacral neurectomy; laparoscopic uterine nerve ablation; non-steroidal anti-inflammatory drugs; presacral neurectomy alone; and progestogens other than dydrogesterone.

QUESTIONS

What are the effects of hormonal treatments given at diagnosis of endometriosis? . . . 3

What are the effects of hormonal treatments before surgery for endometriosis? . . . 8

What are the effects of non-hormonal medical treatments for endometriosis? . . . 9

What are the effects of surgical treatments for endometriosis? . . . 10

What are the effects of hormonal treatment after conservative surgery for endometriosis? . . . 13

What are the effects of hormonal treatment after oophorectomy (with or without hysterectomy) for endometriosis? . . . 16

What are the effects of treatments for ovarian endometrioma? . . . 17

INTERVENTIONS

HORMONES AT DIAGNOSIS

Beneficial

Combined oral contraceptives at diagnosis . . . 3

Progestogens (other than dydrogesterone) at diagnosis . . . 7

Trade off between benefits and harms

Danazol, gestrinone, or gonadorelin analogues at diagnosis . . . 4

Unknown effectiveness

Dydrogesterone at diagnosis . . . 8

PREOPERATIVE HORMONES

Unknown effectiveness

Hormonal treatment before surgery . . . 8

NON-HORMONAL MEDICAL TREATMENTS

Unknown effectiveness

Non-steroidal anti-inflammatory drugs . . . 9

SURGERY

Likely to be beneficial

Laparoscopic removal of endometriotic deposits alone . . . 11

Laparoscopic removal of endometriotic deposits plus uterine nerve ablation . . . 10

Unknown effectiveness

Laparoscopic removal plus presacral neurectomy . . . 12

Laparoscopic uterine nerve ablation alone . . . 13

Presacral neurectomy alone . . . 13

HORMONES AFTER CONSERVATIVE SURGERY

Likely to be beneficial

Hormonal treatment after conservative surgery . . . 13

HORMONES AFTER OOPHORECTOMY

Unknown effectiveness

Hormonal treatment after oophorectomy . . . 16

TREATING OVARIAN ENDOMETRIOMA

Likely to be beneficial

Laparoscopic cystectomy for ovarian endometrioma (reduces pain compared with drainage and cyst wall electrosurgical ablation) . . . 17

Covered elsewhere in Clinical Evidence

Subfertility in women with endometriosis (see female infertility)

Key points

- Ectopic endometrial tissue is found in up to 20% of asymptomatic women, up to 60% of those with dysmenorrhoea, and up to 30% of women with subfertility, with a peak incidence at around 40 years of age. However, symptoms may not correlate with laparoscopic findings.

  Without treatment, endometrial deposits may resolve spontaneously in up to a third of women, deteriorate in nearly half, and remain unchanged in the remainder.

  Oral contraceptives reduce the risk of endometriosis, whereas an early menarche and late menopause increase the risk.

- Hormonal treatments (oral contraceptives, danazol, gestrinone, gonadorelin analogues, and medroxyprogesterone acetate) can reduce the pain attributed to endometriosis when given at diagnosis, but adverse effects are common.

  Combined oral contraceptives may be less effective than gonadorelin analogues, but are less likely to reduce bone mineral density or to cause other adverse effects such as hot flushes and vaginal dryness.

  We do not know whether hormonal treatment given before surgery makes it easier to perform surgery, or reduces subsequent pain.

- Laparoscopic removal of endometrial deposits reduces pain and improves quality of life compared with no removal, but it can be complicated by adhesions and damage to other pelvic structures.

  Combining laparoscopic removal of deposits with uterine nerve ablation may improve pain relief compared with diagnostic laparoscopy alone, but we do not know whether uterine nerve ablation alone is of any benefit in reducing symptoms.

  Laparoscopic excision of endometrial cysts in the ovary may reduce pelvic pain and recurrence of cysts compared with laparoscopic drainage and cyst wall electrosurgical ablation, with similar risks of adverse effects.

- The hormonal treatments danazol, medroxyprogesterone acetate, and gonadorelin analogues may reduce pain and other symptoms when given for 6 months after conservative surgery, although studies of other hormonal treatments have given conflicting results.

- We do not know whether hormone replacement therapy prevents or promotes recurrence of endometriosis in women who have had oophorectomy.

DEFINITION

Endometriosis is characterised by ectopic endometrial tissue, which can cause dysmenorrhoea, dyspareunia, non-cyclical pelvic pain, and subfertility. Diagnosis is made by laparoscopy. Most endometrial deposits are found in the pelvis (ovaries, peritoneum, uterosacral ligaments, pouch of Douglas, and rectovaginal septum). Extrapelvic deposits, including those in the umbilicus and diaphragm, are rare. Severity of endometriosis is defined by the American Fertility Society: this review uses the terms mild (stage I and II), moderate (stage III), and severe (stage IV). [1] Endometriomas are cysts of endometriosis within the ovary. This review assesses dysmenorrhoea, dyspareunia (painful sexual intercourse), dyschezia (painful defecation), and non-cyclical pelvic pain associated with endometriosis. For infertility associated with endometriosis, see review on female infertility.

INCIDENCE/ PREVALENCE

In asymptomatic women, the prevalence of endometriosis is 2–22%. [2] [3] [4] [5] Variations in estimates of prevalence are thought to be mostly because of differences in diagnostic thresholds and criteria between studies, and in variations in childbearing age between populations, rather than underlying genetic differences. In women with dysmenorrhoea, the incidence of endometriosis is 40–60%, and in women with subfertility it is 20–30%. [3] [6] [7] The severity of symptoms and the probability of diagnosis increase with age. [8] Incidence peaks at about 40 years of age. [9] Symptoms and laparoscopic appearance do not always correlate. [10]

AETIOLOGY/ RISK FACTORS

The cause of endometriosis is unknown. Risk factors include early menarche and late menopause. Embryonic cells may give rise to deposits in the umbilicus, whereas retrograde menstruation may deposit endometrial cells in the diaphragm. [11] [12] Use of oral contraceptives reduces the risk of endometriosis, and this protective effect persists for up to 1 year after their discontinuation. [9]

PROGNOSIS

We found two RCTs in which laparoscopy was repeated after treat ment in women given placebo. [13] [14] Over 6–12 months, endometrial deposits resolved spontaneously in up to a third of women, deteriorated in nearly half, and were unchanged in the remainder.

AIMS OF INTERVENTION

To relieve pain (dysmenorrhoea, dyspareunia, and other pelvic pain), with minimal adverse effects.

OUTCOMES American Fertility Society scores for size and number of deposits; [1] recurrence rates; time between stopping treatment and recurrence; rate of adverse effects of treatment. **In women with pain:** Relief of chronic pain, assessed by a visual analogue scale ranging from 0–10, and subjective improvement. The different types of chronic pelvic pain include dysmenorrhoea, non-menstrual pelvic pain (both mid-cycle and non-cyclic pain), dyspareunia, and dyschezia. **In women having surgery:** Ease of surgical intervention (rated by the surgeon as easy, average, difficult, or very difficult). [15]

METHODS *BMJ Clinical Evidence* search and appraisal April 2006. For this review, the following were used for the identification of studies: Medline 1966 to April 2006, Embase 1980 to April 2006, and The Cochrane Library 2006, Issue 1. Additional searches were carried out on the NHS Centre for Reviews and Dissemination (CRD), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA), Turning Research into Practice (TRIP), and the National Institute of Health and Clinical Excellence (NICE) guidance websites. Abstracts of studies retrieved in the search were assessed independently by two information specialists. Predetermined criteria were used to identify relevant studies. Study design criteria included systematic reviews and RCTs, which were at least single blind. We excluded all studies described as "open", "open label" or "non-blinded", unless the interventions could not be "blinded". The minimum number of individuals in each trial was 20. The size of follow up was 80% or more. There was no minimum length of follow up. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 21).

QUESTION What are the effects of hormonal treatments given at diagnosis of endometriosis?

OPTION COMBINED ORAL CONTRACEPTIVES AT DIAGNOSIS

Pain

Compared with progestogens Combined oral contraceptives may be as effective as progestogens at reducing pain (very low-quality evidence).

Compared with gonadorelin analogues Combined oral contraceptives may be less effective at reducing pain compared with gonadorelin analogues (low-quality evidence).

Combined oral contraceptives plus danazol compared with progestogens Combined oral contraceptives plus danazol may be less effective at reducing dysmenorrhoea compared with medroxyprogesterone acetate (very low-quality evidence).

Note

We found no direct information about whether combined oral contraceptives are better than no active treatment in women with endometriosis.

For GRADE evaluation of interventions for endometriosis, see table, p 21 .

Benefits:

Combined oral contraceptives versus placebo:
We found no systematic reviews or RCTs.

Combined oral contraceptives versus progestogens:
We found no systematic reviews or RCTs.

Combined oral contraceptives versus gonadorelin analogues:
We found one systematic review (search date 2003 [16]), one additional RCT, [17] and one subsequent RCT. [18] The review [16] (1 RCT, [19] 57 women with endometriosis confirmed by diagnostic laparoscopy, and moderate or severe pain) found that goserelin (3.6 mg subcutaneous depot formulation monthly for 6 months of treatment) was significantly more effective for relief of dysmenorrhoea than was cyclic low dose monophasic combined oral contraceptive (21/24 [88%] with goserelin *v* 0/25 [0%] with combined oral contraceptive; OR 33.1, 95% CI 10.8 to 101.0). [16] After 6 months of follow up without treatment, all women improved (24/24 [100%] with goserelin *v* 25/25 [100%] with combined oral contraceptive). The review found no significant difference between combined cyclic low dose monophasic oral contraceptives and goserelin in the relief of dyspareunia or non-menstrual pain at the end of 6 months of treatment (OR 0.93, 95% CI 0.25 to 3.53). [16]

One additional RCT (102 women with endometriosis who undergone surgery previously; 81% had previous laparoscopy, 19% had previous laparotomy) compared combined oral contraceptive for 12 months versus combined oral contraceptive for 4 months followed by gonadorelin analogues for 8 months. [17] It found no significant difference in the proportion of women with pain (either menstrual or non-menstrual) at 12 months (menstrual pain: 14/47 [30%] with combined oral contraceptive *v* 16/55 [29%] with combined oral contraceptive followed by gonadorelin analogues; non-

menstrual pain: 15/47 [32%] with combined oral contraceptive *v* 17/55 [31%] with combined oral contraceptive followed by gonadorelin analogues; reported as non-significant, CI not reported).

One subsequent RCT (133 women with persistent endometriosis related pain despite previous endometriosis surgery) found that gonadorelin analogues (with and without addback oestrogen/progestogen) for 12 months significantly reduced dysmenorrhoea, pelvic pain, and dyspareunia compared with combined oral contraceptive for 12 months (133 women, pain measured on visual analogue scale after 6 months' follow up [range not reported]; dysmenorrhoea: 3.1 with leuprolide acetate plus norethindrone *v* 3.4 with leuprolide acetate *v* 4.9 with estroprogestin, P = 0.01; pelvic pain: 3.7 with leuprolide acetate plus norethindrone *v* 3.2 with leuprolide acetate *v* 5.9 with estroprogestin, P = 0.01; dyspareunia: 2.7 with leuprolide acetate plus norethindrone *v* 2.2 with leuprolide acetate *v* 3.9 with estroprogestin, P = 0.01 for leuprolide acetate plus norethindrone *v* estroprogestin). [18]

Combined oral contraceptives plus danazol versus medroxyprogesterone acetate :
See benefits of progestogens at diagnosis., p 7

Harms:

Combined oral contraceptives versus placebo:
We found no systematic reviews or RCTs.

Combined oral contraceptives versus progestogens:
We found no systematic reviews or RCTs.

Combined oral contraceptives versus gonadorelin analogues:
The systematic review found that goserelin significantly increased hot flushes, insomnia, and vaginal dryness compared with combined oral contraceptives (hot flushes, 1 RCT: 1/28 [4%] with combined oral contraceptives *v* 24/29 [83%] with goserelin, OR 0.04, 95% CI 0.02 to 0.12; insomnia, 1 RCT: 0/28 [0%] with combined oral contraceptives *v* 7/29 [24%] with goserelin, OR 0.11, 95% CI 0.02 to 0.53; vaginal dryness: 0/28 [0%] with combined oral contraceptives *v* 5/29 [17%] with goserelin, OR 0.12, 95% CI 0.02 to 0.74). [16] The additional RCT gave no information on adverse effects. [17] The subsequent RCT found that gonadorelin analogues (with and without add-back oestrogen/progestogen) significantly increased bone mineral density loss compared with combined oral contraceptive (P < 0.01 for leuprolide acetate *v* estroprogestin; P < 0.05 for leuprolide acetate plus norethindrone *v* estroprogestin). It found that gonadorelin analogues alone significantly increased bone mineral density loss compared with gonadorelin analogues plus add-back oestrogen/progestogen (P < 0.05 for leuprolide acetate *v* leuprolide acetate plus norethindrone). [18]

Combined oral contraceptives plus danazol versus medroxyprogesterone acetate :
See harms of progestogens at diagnosis., p 7

Comment: The RCTs were mainly small, with no long term follow up.

OPTION DANAZOL, GESTRINONE, OR GONADORELIN ANALOGUES AT DIAGNOSIS

Pain

Danazol compared with placebo Danazol and gonadorelin analogues may reduce severe and moderate pain at 6 months compared with placebo (moderate-quality evidence).

Danazol compared with gestrinone Danazol may be as effective as gestrinone at reducing dysmenorrhoea (moderate-quality evidence).

Danazol compared with progestogens Danazol seems to be as effective as medroxyprogesterone acetate at improving pain (moderate-quality evidence).

Danazol plus combined oral contraceptives compared with progestogens Combined oral contraceptives plus danazol may be less effective at reducing dysmenorrhoea compared with medroxyprogesterone acetate (very low-quality evidence).

Gonadorelin analogues compared with placebo Gonadorelin analogues may reduce severe and moderate pain at 6 months compared with placebo (low-quality evidence).

Gonadorelin analogues compared with combined oral contraceptives Gonadorelin analogues may be more effective than combined oral contraceptives at reducing pain (low-quality evidence).

Gonadorelin analogues compared with danazol Gonadorelin analogues are as effective as danazol at reducing menstrual pain and dyspareunia (high-quality evidence).

Gonadorelin analogues compared with levonorgestrel-releasing intrauterine system Gonadorelin analogues may be as effective as levonorgestrel-releasing intrauterine systems at reducing pain (low-quality evidence).

Gestrinone compared with gonadorelin analogues Gestrinone may reduce menstrual pain compared with gonadorelin analogues, but only after 6 months' treatment (low-quality evidence).

Symptoms of endometriosis
Compared with progesterones Gonadorelin analogues may be as effective as medroxyprogesterone acetate at improving symptoms of endometriosis (low-quality evidence).

Gonadorelin analogues compared with laparoscopic removal Gonadorelin analogues may be less effective than laparoscopic removal of deposits at improving symptoms of endometriosis after 12 months (low-quality evidence).

Adverse effects
Adverse effects of hormonal treatments are common, and include hot flushes and bone loss with gonadorelin analogues or gestrinone, and androgenic adverse effects with danazol. Add-back hormone replacement plus gonadorelin analogues may reduce the risk of reduced bone mineral density loss, hot flushes, insomnia, and vaginal dryness compared with gonadorelin analogues alone. Gonadorelin analogues may have fewer adverse effects than danazol.

For GRADE evaluation of interventions for endometriosis, see table, p 21 .

Benefits:

We found three systematic reviews (search dates 1998, [22] 2000, [23] and 2001, [24]) of 6 months of continuous ovulation suppression (using danazol, gestrinone, gonadorelin analogues, or medroxyprogesterone acetate). The reviews found that all treatments reduced severe and moderate pain at 6 months compared with placebo, and were similarly effective. We found one additional RCT, [25] and one subsequent RCT. [26]

Danazol, gestrinone, or gonadorelin analogues versus placebo or no treatment:
Two RCTs (98 women) identified by the reviews [22] [23] [24] found that danazol and gonadorelin analogues significantly reduced pain at 3–6 months compared with placebo (see table 1, p 20).

Danazol versus gestrinone:
The second review identified one RCT (269 women with endometriosis confirmed by laparoscopy) comparing danazol 200 mg daily versus gestrinone 2.5 mg twice weekly. [27] It found no significant difference in dysmenorrhoea over 6 months of treatment between danazol and gestrinone (reported as non-significant, results presented graphically), although both groups significantly improved from baseline ($P < 0.001$).

Danazol versus gonadorelin analogues:
The first systematic review identified 15 RCTs (1299 women) comparing gonadorelin analogues versus danazol. [22] After 6 months of treatment, the review found no significant difference in menstrual pain (5 RCTs, 386 women; RR 1.09, 95% CI 0.99 to 1.20), dyspareunia (6 RCTs, 476 women; RR 0.98, 95% CI 0.93 to 1.02), or resolution of endometrial deposits (3 RCTs, 426 women; RR 0.84, 95% CI 0.56 to 1.26). [22] A subsequent RCT (59 women with endometriosis confirmed by diagnostic laparoscopy, some of whom had a therapeutic intervention during the procedure) found no significant difference in the improvement of total symptom severity score, which included pelvic pain, dysmenorrhoea, and dyspareunia, after 180 days of treatment for the gonadorelin analogue nafarelin compared with danazol (mean reduction in total symptom severity score [SD]: –4.2 ± 2.4 with nafarelin *v* –4.6 ± 1.7 with danazol, $P = 0.502$). [26]

Gestrinone versus gonadorelin analogues:
One RCT identified by the second systematic review (55 women with endometriosis confirmed by diagnostic laparoscopy, but who had no previous therapeutic surgery for endometriosis) [23] found that gestrinone modestly, but significantly, reduced dyspareunia after 6 months' treatment compared with gonadorelin analogues (measured on a visual analogue scale [range 0–10]: WMD –1.16, 95% CI –2.08 to –0.24). Gonadorelin analogues significantly reduced dysmenorrhoea compared with gestrinone (WMD 0.82, 95% CI 0.15 to 1.49). The RCT found no significant difference in non-menstrual pain between gestrinone and gonadorelin analogues (WMD –0.41, 95% CI –1.76 to + 0.94). After 6 months' follow up, the RCT found that gestrinone significantly reduced dysmenorrhoea, dyspareunia, and non-menstrual pain compared with gonadorelin (dysmenorrhoea: WMD –3.00, 95% CI –4.79 to –1.21; dyspareunia: WMD –2.34, 95% CI –3.60 to –1.02; non-menstrual pain: WMD –2.30, 95% CI –3.70 to –0.90).

Danazol versus medroxyprogesterone acetate:
See benefits of progestogens at diagnosis., p 7

Danazol plus combined oral contraceptives versus medroxyprogesterone acetate:
See benefits of progestogens at diagnosis., p 7

Gonadorelin analogues versus medroxyprogesterone acetate:
See benefits of progestogens at diagnosis., p 7 .

Gonadorelin analogues versus levonorgestrel-releasing intrauterine system:
See benefits of progestogens at diagnosis., p 7

Gonadorelin analogues versus combined oral contraceptives:
See benefits of combined oral contraceptives at diagnosis, p 3 .

Gonadorelin analogues versus laparoscopic removal of deposits:
See benefits of laparoscopic removal alone, p 11 .

Harms:

Danazol, gestrinone, or gonadorelin analogues versus placebo or no treatment:
One review found that gonadorelin analogues significantly increased hot flushes and headaches compared with placebo (hot flushes: about 80% with gonadorelin analogues *v* 30% with placebo, RR 2.7, 95% CI 1.5 to 4.8; headaches: 33% with gonadorelin analogues *v* 10% with placebo, RR 3.6, 95% CI 1.1 to 11.5). [22] Gonadorelin analogues are associated with hypo-oestrogenic symptoms, such as hot flushes and vaginal dryness.

Danazol versus gestrinone:
The second review found that gestrinone significantly increased greasy skin and hirsutism compared with danazol (greasy skin, 2 RCTs: 69/149 [46%] with gestrinone *v* 37/153 [24%] with danazol, OR 2.68, 95% CI 1.67 to 4.31; hirsutism, 2 RCTs: 68/149 [46%] with gestrinone *v* 38/153 [25%] with danazol, OR 2.63, 95% CI 1.62 to 4.28). [23] However, it found that gestrinone significantly reduced muscle cramps, hunger, and breast size reduction compared with danazol (muscle cramps, 2 RCTs: 48/149 [32%] with gestrinone *v* 75/153 [49%] with danazol, OR 0.49, 95% CI 0.31 to 0.78; hunger, 1 RCT: 69/130 [53%] with gestrinone *v* 88/134 [66%] with danazol, OR 0.59, 95% CI 0.36 to 0.97; reduction in breast size, 2 RCTs: 54/149 [36%] with gestrinone *v* 73/153 [48%] with danazol, OR 0.62, 95% CI 0.39 to 0.98). [23]

Gonadorelin analogues versus danazol/gestrinone:
One systematic review found that, after 6 months, danazol/gestrinone increased bone mineral density from baseline at the lumbar spine, whereas gonadorelin analogues decreased bone mineral density, and the difference between treatments was significant (search date 2003, 4 RCTs, 287 people; SMD –1.12, 95% CI –1.38 to –0.86). [28] The review found no significant difference between gonadorelin analogues and danazol/gestrinone in percentage change in bone mineral density at the femoral neck (1 RCT, 70 people; SMD –0.31, 95% CI –0.78 to + 0.16). One RCT identified by the second systematic review found that gestrinone significantly reduced hot flushes compared with gonadorelin analogues (8/27 [30%] with gestrinone *v* 19/28 [68%] with gonadorelin analogues; OR 0.22, 95% CI 0.08 to 0.64). [23] Another subsequent RCT found a more unfavourable lipid profile in women treated with danazol than with the gonadorelin analogue nafarelin after 180 days' treatment, especially the change in levels of protective high density lipoprotein cholesterol (mean + 2.4 [SD 8.2] for nafarelin *v* mean –20.6 [SD 10.4] for danazol). [26]

Gonadorelin analogues versus medroxyprogesterone acetate:
The RCT gave no information on adverse effects. [25]

Gonadorelin analogues versus levonorgestrel-releasing intrauterine system:
See harms of progestogens at diagnosis, p 7 .

Danazol versus medroxyprogesterone acetate:
See harms of progestogens at diagnosis, p 7 .

Gonadorelin analogues plus addback hormone replacement treatment versus gonadorelin analogues alone:
Three RCTs found that adding oestrogen, progestogens, or tibolone significantly relieved hot flushes caused by gonadorelin analogues (reducing symptom scores by greater-than or equal to 50%). [29] [30] [31] One systematic review found a significantly greater percentage reduction in bone mineral density at the lumbar spine with 6 months' gonadorelin analogue alone than with gonadorelin analogue plus addback progestogen at the end of treatment (search date 2003, 1 RCT, 20 people: SMD –1.07, 95% CI –2.03 to –0.12). [28]

Gonadorelin analogues plus addback hormone replacement with high dose progestogen versus gonadorelin analogues plus addback hormone replacement with low dose progestogen:
One subsequent RCT reported a more deleterious effect on lipid profile with higher dose progestogen addback than with low dose progestogen addback after 6 months' treatment (norethindrone 5 mg resulted in mean high density lipoprotein cholesterol/low density lipoprotein cholesterol ratio 0.57, SD 0.05; norethisterone 1 mg resulted in mean high density lipoprotein cholesterol/low density lipoprotein cholesterol ratio 0.44, SD 0.04; P = 0.045). [21]

Gonadorelin analogues versus combined oral contraceptives:
See harms of combined oral contraceptives at diagnosis, p 3 .

Comment: The RCTs were mainly small, with no long term follow up. The RCT addressing quality of life had high withdrawal rates (18/48 [38%]). [25]

OPTION PROGESTOGENS (OTHER THAN DYDROGESTERONE) AT DIAGNOSIS

Pain
Compared with placebo Medroxyprogesterone acetate reduces severe and moderate pain at 6 months compared with placebo (moderate-quality evidence).

Compared with danazol Medroxyprogesterone acetate seems to be as effective as danazol at improving pain (moderate-quality evidence).

Compared with combined oral contraceptives Progestogens may be as effective as combined oral contraceptives at reducing pain (very low-quality evidence).

Compared with combined oral contraceptives plus danazol Medroxyprogesterone acetate may be more effective at reducing dysmenorrhoea compared with combined oral contraceptives plus danazol (very low-quality evidence). Compared with gonadorelin analogues

Levonorgestrel-releasing intrauterine system compared with gonadorelin analogues Levonorgestrel-releasing intrauterine systems may be as effective as gonadorelin analogues at reducing pain (low-quality evidence).

Symptoms of endometriosis
Compared with gonadorelin analogues Medroxyprogesterone acetate may be as effective as gonadorelin analogues at improving symptoms of endometriosis (low-quality evidence).

For GRADE evaluation of interventions for endometriosis, see table, p 21 .

Benefits: We found three systematic reviews (search dates 1998, [22] 2000, [23] 2001, [24]) of 6 months of continuous ovulation suppression (using danazol, gestrinone, gonadorelin analogues, or medroxyprogesterone acetate). The reviews found that all treatments reduced severe and moderate pain at 6 months compared with placebo, and were similarly effective. We found one additional RCT, [25] and one subsequent RCT. [32]

Medroxyprogesterone acetate versus gonadorelin analogues:
We found one RCT (double blind, 48 women with endometriosis confirmed by laparoscopy or laparotomy, treated for 6 months and followed for 1 year after allocation), which compared medroxyprogesterone versus gonadorelin analogues. [25] It found that both treatments significantly improved symptoms attributable to endometriosis, sleep disturbances, and anxiety–depression scores from baseline measurements (P < 0.05 for all outcomes). It found no significant difference between treatments (reported as non-significant, CI not reported).

Levonorgestrel-releasing intrauterine system versus gonadorelin analogues:
One subsequent RCT (82 women with surgically and histologically confirmed endometriosis) found no significant difference between levonorgestrel-releasing intrauterine system and a depot gonadorelin analogue leuprolelin in reduction of VAS for chronic pelvic pain throughout the 6 months' treatment (post-treatment change in VAS scores not specified, P value for the difference in VAS change > 0.600). [32]

Medroxyprogesterone acetate versus danazol:
One RCT identified by the second review [23] (34 women with endometriosis confirmed by diagnostic laparoscopy, 27% of whom had electrocoagulation during the procedure) compared three treatments: medroxyprogesterone acetate, danazol, and placebo. The RCT found no significant difference in pelvic pain and total symptoms between medroxyprogesterone acetate and danazol after 6 months' treatment (34 people, 4 point verbal rating scale; pelvic pain: WMD + 0.10, 95% CI –0.26 to + 0.46;

sum of all symptoms: WMD + 0.50, 95% CI –1.10 to + 2.10). The RCT found that medroxyprogesterone acetate reduced total symptoms compared with danazol, but it found no significant difference in pelvic pain after 6 months' follow up (4 point verbal rating scale; pelvic pain: WMD + 0.23, 95% CI –0.11 to + 0.57; total symptoms: WMD –3.40, 95% CI –4.83 to –1.97). [23]

Progestogens versus combined oral contraceptives:
See benefits of combined oral contraceptives at diagnosis, p 3 .

Harms:

Medroxyprogesterone acetate versus gonadorelin analogues:
The RCT gave no information on adverse effects. [25]

Levonorgestrel-releasing intrauterine system versus gonadorelin analogues:
The RCT found more adverse effects in levonorgestrel-releasing intrauterine system users, with increased breast tenderness (data not reported) and ongoing bleeding (70% of levonorgestrel intrauterine system users *v* 98% of gonadorelin analogue users reported lower bleeding scores during 6 months' treatment; absolute numbers not reported). Differences in other adverse effects, including abdominal distension and peripheral oedema, were not found. [32]

Medroxyprogesterone acetate versus danazol:
The RCT found no significant difference in acne, oedema, muscle cramps, and spotting between medroxyprogesterone acetate and danazol (acne: 6/16 [38%] with medroxyprogesterone acetate *v* 11/18 [61%] with danazol, OR 0.40, 95% CI 0.11 to 1.51; oedema: 11/16 [69%] with medroxyprogesterone acetate *v* 8/18 [44%] with danazol, OR 2.60, 95% CI 0.68 to 9.91; muscle cramps: 3/16 [19%] with medroxyprogesterone acetate *v* 6/18 [33%] with danazol, OR 0.48, 95% CI 0.11 to 2.17; spotting: 6/16 [38%] with medroxyprogesterone acetate *v* 5/18 [28%] with danazol, OR 1.54, 95% CI 0.37 to 6.36). [23]

Progestogens versus combined oral contraceptives:
See harms of combined oral contraceptives at diagnosis, p 3 .

Comment: The RCTs were mainly small, with no long term follow up. The RCT addressing quality of life had high withdrawal rates (18/48 [38%]). [25]

OPTION DYDROGESTERONE AT DIAGNOSIS

Pain
Compared with placebo Dydrogesterone may be no more effective than placebo at reducing pain (low-quality evidence).

For GRADE evaluation of interventions for endometriosis, see table, p 21 .

Benefits: We found one systematic review (search date 2000, [23]) of 6 months of continuous ovulation suppression using progestogens.

Dydrogesterone versus placebo:
One RCT (22 women) identified by the second review [23] found no significant difference between dydrogesterone 40 or 60 mg and placebo in the proportion of women who had pain relief, but it may have been underpowered to detect a clinically important difference (see table 1, p 20).

Harms: The review did not report on harms from dydrogesterone. [23]

Comment: None.

QUESTION What are the effects of hormonal treatments before surgery for endometriosis?

OPTION PREOPERATIVE HORMONAL TREATMENT

Pain
Compared with no hormonal treatment Hormonal treatment before surgery may not reduce pain scores compared with no hormonal treatment (moderate-quality evidence).

Compared with hormonal treatment after surgery Hormonal treatment given only before surgery leads to similar pain scores as hormonal treatment given only after surgery (moderate-quality evidence).

Ease of surgery
Compared with no hormonal treatment Hormonal treatment before surgery does not seem to improve the ease of surgery for endometriosis compared with no hormonal treatment (moderate-quality evidence).

For GRADE evaluation of interventions for endometriosis, see table, p 21 .

Benefits:

Hormonal treatment before surgery versus no hormonal treatment:
We found one systematic review [33] and one additional RCT. [34] The systematic review (search date 2003) found that hormonal treatment before surgery significantly improved American Fertility Society (AFS) scores compared with no pre-surgical hormone treatment (1 RCT, 80 women; WMD –9.60, 95% CI –11.42 to –7.78). However, the RCT did not report on pain outcomes. [33] The additional RCT (48 women with moderate or severe endometriosis) compared 3 months' goserelin treatment before surgery with no preoperative hormonal treatment, and found similar symptoms in both groups at 6 months after surgery. [34] It also found no significant difference in the proportion of women whose surgery was rated as "moderately" or "very" difficult (14/20 [70%] with goserelin before surgery *v* 20/27 [74%] with no treatment before surgery; RR 0.94, 95% CI 0.60 to 1.50).

Hormonal treatment before surgery versus hormonal treatment after surgery:
We found one systematic review, [33] which found one RCT comparing 6 months of nafarelin before surgery versus surgery followed by 6 months of nafarelin. [15] It found that 6 months of nafarelin 200 µg before surgery significantly reduced symptom scores compared with 6 months of nafarelin 200 µg after surgery (75 women with moderate or severe endometriosis; mean AFS score: 0 with nafarelin before surgery *v* 6 with nafarelin after surgery; P = 0.007). [15] It found no significant difference in ease of surgery as assessed by the surgeon (proportion of women judged easy to treat: 14/25 [56%] with nafarelin before surgery *v* 10/28 [36%] with no treatment before surgery; RR 1.60, 95% CI 0.86 to 2.90). [15] It also found no significant difference in pelvic pain between hormonal treatment before and after surgery (RR 1.01, 95% CI 0.49 to 2.07). [33]

Hormonal treatment before and after surgery versus hormonal treatment after surgery:
We found one systematic review, [33] which found one RCT [15] comparing 6 months of intramuscular triptorelin 3.75 mg before and after surgery versus intramuscular triptorelin 3.75 mg after surgery. It found no significant difference in AFS scores between groups (25 women with ovarian endometrioma > 3 cm unilateral/bilateral; total AFS score: WMD + 3.49, 95% CI –5.10 to + 12.08; implant AFS score: WMD –0.37, 95% CI –1.17 to + 0.43; adhesion AFS score: WMD + 0.55, 95% CI –7.16 to + 8.26). However, the RCT did not report on pain outcomes. [33]

Harms:

See also harms of hormonal treatments at diagnosis, p 3 .

Hormonal treatment before surgery versus no hormone treatment:
The RCT identified by the review did not report on adverse effects. [33] In the additional RCT, adverse events were reported frequently, both in women receiving gonadorelin analogues before surgery and in women receiving no treatment (AR for at least 1 adverse event: 18/21 [86%] with gonadorelin analogue *v* 21/27 [78%] with no treatment; RR 1.1, 95% CI 0.8 to 1.4). [34] The most frequently reported adverse effects were hot flushes and headaches, and these happened only in women receiving gonadorelin analogue (hot flushes: 13/21 [62%]; headaches: 6/21 [29%]).

Hormone treatment before surgery versus hormone treatment after surgery:
The RCT identified by the review [33] found that nafarelin was associated with hot flushes (96% with nafarelin before surgery *v* 92% with nafarelin after surgery), vaginal dryness (43% with nafarelin before surgery *v* 32% with nafarelin after surgery), and decreased libido (36% with nafarelin before surgery *v* 36% with nafarelin after surgery). [15]

Hormonal treatment before and after surgery versus hormonal treatment after surgery:
The RCT identified by the review did not report on adverse effects. [33]

Comment:

One RCT identified by the review may have been too small to detect a difference between groups in ease of surgery and pelvic pain. [15] The additional RCT may also have been too small to detect a clinically important effect. [34]

QUESTION What are the effects of non-hormonal medical treatments for endometriosis?

OPTION NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

Pain
Compared with placebo Non-steroidal anti-inflammatory drugs may be no more effective than placebo in women with pain attributed to endometriosis (low-quality evidence).

For GRADE evaluation of interventions for endometriosis, see table, p 21 .

Benefits:

Non-steroidal anti-inflammatory drugs versus placebo:
We found one systematic review (search date 2005 [35]), which included one crossover RCT (24 women with mild to severe endometriosis) comparing non-steroidal anti-inflammatory drugs (naproxen) versus placebo. The RCT found no significant difference in overall pain relief between non-steroidal anti-inflammatory drugs and placebo (OR 3.3, 95% CI 0.6 to 17.7; absolute numbers not reported). [35]

Harms:

Non-steroidal anti-inflammatory drugs versus placebo:
The RCT provided insufficient evidence as to whether non-steroidal anti-inflammatory drugs were associated with more adverse effects compared with placebo (OR 0.46, 95% CI 0.09 to 2.47; absolute numbers not reported). [35]

Comment:

We found one RCT assessing the efficacy of the cyclo-oxygenase 2 inhibitor rofecoxib. [36] However, this RCT has been excluded from this review because rofecoxib has been associated with adverse cardiovascular effects and has been withdrawn from clinical use.

QUESTION What are the effects of surgical treatments for endometriosis?

OPTION LAPAROSCOPIC REMOVAL OF ENDOMETRIOTIC DEPOSITS PLUS UTERINE NERVE ABLATION

Pain
Compared with diagnostic laparoscopy Laparoscopic removal of endometriotic deposits plus laparoscopic uterine nerve ablation reduces pain compared with diagnostic laparoscopy at 6 months (moderate-quality evidence). Pain reduction may persist for up to 5 years in more than half of women.

Compared with laparoscopic removal alone Laparoscopic uterine nerve ablation does not increase pain relief at 6 months to 3 years when performed with laparoscopic ablation of endometrial deposits compared with ablation of deposits alone (high-quality evidence).

Adverse effects
Compared with laparoscopic presacral neurectomy The risk of complications is lower with laparoscopic uterine nerve ablation compared with presacral neurectomy (moderate-quality evidence).

For GRADE evaluation of interventions for endometriosis, see table, p 21 .

Benefits:

Laparoscopic removal plus laparoscopic uterine nerve ablation (LUNA) versus diagnostic laparoscopy:
We found one systematic review (search date 1999), [37] which identified one RCT (63 women with mild to moderate endometriosis, two publications) [38] [39] comparing laparoscopic removal of deposits plus LUNA versus diagnostic laparoscopy. The RCT found that laparoscopic removal plus LUNA significantly reduced pain at 6 months (median decrease in pain score on a 10 cm visual analogue scale: 2.85 cm with laparoscopic removal *v* 0.05 cm with diagnostic laparoscopy; P = 0.01). [37] Follow up of the RCT suggested that 90% of the women who responded continued to have pain improvement at 1 year, [38] and 55% at 5 years. [39]

Laparoscopic removal plus LUNA versus laparoscopic removal alone:
We found one systematic review [40] of laparoscopic removal of endometrial deposits plus LUNA. The review (search date 2004) identified four RCTs (439 women with mild to severe endometriosis; age range 18–40 years) comparing laparoscopic ablation plus LUNA versus laparoscopic removal alone, where data could be pooled in a meta-analysis. [40] The systematic review found no significant difference in dysmenorrhoea pain relief at up to 6, 12, or 36 months for laparoscopic removal of endometriotic deposits plus LUNA compared with laparoscopic removal alone (6 months, 3 RCTs, 190 women: 59/94 [62.8%] with laparoscopic removal plus LUNA *v* 60/96 [62.5%] with laparoscopic removal alone, OR 1.03, 95% CI 0.52 to 2.02; 12 months, 2 RCTs, 217 women: 62/108 [57%] with laparoscopic removal plus LUNA *v* 68/109 [62%] with laparoscopic removal alone, OR 0.77, 95% CI 0.43 to 1.39; 36 months, 1 RCT, 116 women: 38/59 [64%] with laparoscopic removal plus LUNA *v* 39/57 [68%] with laparoscopic removal alone, OR 0.84, 95% CI 0.39 to 1.80). [40] Absence of benefit of adding LUNA was also supported by other data from these RCTs that could not be pooled in the meta-analysis. One RCT (81 women) identified by the review found that satisfaction with treatment was high in both groups (68% with laparoscopic removal plus LUNA *v* 73% with laparoscopic removal alone). Another RCT (67 women with stage I–IV endometriosis, 66 analysed at 3 months, 56 analysed at 1 year) found no significant difference in relief of dysmenorrhoea at 12 months, non-menstrual pelvic pain, deep dyspareunia, or dyschezia for laparoscopic surgery plus LUNA compared with laparoscopic surgery alone (greater-than or equal to 50% reduction in visual analogue scale; dysmenorrhoea: 7/21 [33%] with laparoscopic surgery plus LUNA *v* 11/24 [46%]

with laparoscopic surgery alone, P = 0.58; non-menstrual pelvic pain: 11/22 [50%] with laparoscopic surgery plus LUNA *v* 15/30 [50%] with laparoscopic surgery alone, P = 1.00; deep dyspareunia: 6/10 [60%] with laparoscopic surgery plus LUNA *v* 8/16 with [50%] laparoscopic surgery alone, P = 0.70; dyschezia: 7/14 [50%] with laparoscopic surgery plus LUNA *v* 10/23 [43%] with laparoscopic surgery alone, P = 0.70). [41]

Harms:

Laparoscopic removal plus LUNA versus diagnostic laparoscopy:
The RCT identified by the first review reported that no adverse effects were observed. [37]

Laparoscopic removal plus LUNA versus laparoscopic removal alone:
The RCTs found no adverse effects (specifically changes in bladder or intestinal function, incidence of ureteric injury, or vaginal prolapse) attributable to LUNA. [40]

Laparoscopic removal plus LUNA versus presacral neurectomy:
See comments of Laparoscopic removal plus presacral neurectomy, p 10 .

Comment: None.

OPTION LAPAROSCOPIC REMOVAL OF ENDOMETRIOTIC DEPOSITS ALONE

Pain
Compared with diagnostic laparoscopy or no treatment Laparoscopic removal of endometriotic deposits alone improves pain symptoms and quality of life at 6 months compared with diagnostic laparoscopy (moderate-quality evidence).

Compared with laparoscopic removal plus laparoscopic uterine nerve ablation Laparoscopic ablation of deposits alone is as effective as laparoscopic ablation plus uterine nerve ablation (LUNA) for pain relief at 6 months to 3 years (high-quality evidence).

Symptoms of endometriosis
Laparoscopic removal compared with gonadorelin analogues Laparoscopic removal of deposits may be more effective than gonadorelin analogues at improving symptoms of endometriosis after 12 months (low-quality evidence).

Laparoscopic excision compared with laparoscopic ablation Laparoscopic excision of deposits may be as effective as laparoscopic ablation at improving symptoms of endometriosis (low-quality evidence).

Note
We found no clinically important results about the effects of laser versus electrosurgical removal of endometriotic deposits.

For GRADE evaluation of interventions for endometriosis, see table, p 21 .

Benefits:

Laparoscopic removal alone versus diagnostic laparoscopy or no treatment:
We found a crossover double blinded RCT (39 women with stage I–IV endometriosis, analysed precrossover 6 months after treatment), which compared laparoscopic removal of endometriotic deposits alone (by excisional surgery) versus diagnostic laparoscopy in women with pain attributed to endometriosis. [42] It found that laparoscopic excision significantly improved pain symptoms compared with diagnostic laparoscopy at 6 months (proportion of women reporting improvement in pain symptoms: 16/20 [80%] with laparoscopic excision *v* 6/19 [32%] with diagnostic laparoscopy; P = 0.002). It also found that laparoscopic excision improved EuroQol (EQ-5D) visual analogue scale summary, but found no significant difference in any other quality of life measures between groups at 6 months (mean scores, higher score indicates better quality of life; EQ-5D index summary: 0.77 with laparoscopic excision *v* 0.74 with diagnostic laparoscopy, P = 0.07; EQ-5D visual analogue scale summary: 83.6 with laparoscopic excision *v* 65.9 with diagnostic laparoscopy, P = 0.01; Short Form-12 Item Scale physical component score: 48.2 with laparoscopic excision *v* 45.5 with diagnostic laparoscopy, P = 0.36; Short Form-12 Item Scale mental component score: 47.6 with laparoscopic excision *v* 45.3 with diagnostic laparoscopy, P = 0.55). [42]

Laparoscopic excision versus laparoscopic ablation:
We found one small RCT (24 women with pain attributed to mild endometriosis), which compared laparoscopic excision versus laparoscopic ablation of endometriotic lesions. [43] The RCT found no differences between the two groups, with 67% of women in both treatment groups reporting good symptomatic relief (absolute numbers not reported; significance not assessed). [43]

Laparoscopic removal alone versus laparoscopic removal plus laparoscopic uterine nerve ablation (LUNA):
See benefits of laparoscopic removal plus LUNA, p 10 .

Laser versus diathermy ablation:
We found no RCTs.

Laparoscopic removal versus gonadorelin analogue hormonal treatment:
We found one RCT (35 women with minimal to moderate endometriosis), which assessed primarily treatment costs of laparoscopic ablation or excision with helium thermal coagulator *v* 6 months of treatment with the gonadorelin analogue Zoladex. At 12 months' follow up, more women treated surgically than treated medically were symptom free (symptom free: 9/17 [53%] of women treated surgically *v* 3/18 [17%] of women treated with gonadorelin analogues; significance not reported). [44]

Harms:

Laparoscopic removal alone versus laparoscopic removal plus uterine nerve ablation:
See benefits of laparoscopic removal of endometriotic deposits plus uterine nerve ablation, p 10 .
Potential harms of laparoscopic surgery include adhesions, reduced fertility, and damage to other pelvic structures.

Laparoscopic removal alone versus diagnostic laparoscopy or no treatment:
The crossover RCT reported more complications with laparoscopic excision than with diagnostic laparoscopy (2/20 [10%] with laparoscopic excision *v* 0/19 [0%] with diagnostic laparoscopy; significance not reported). In the laparoscopic excision group, complications were: one woman required a laparotomy for repair of excision site of posterior cervix endometriosis and one woman required a blood transfusion for symptomatic anaemia. [42]

Laparoscopic excision versus laparoscopic ablation:
One small RCT (24 women) reported no difference in morbidity between laparoscopic excision and laparoscopic ablation of endometriosis (significance not assessed). [43]

Laparoscopic removal alone versus laparoscopic removal plus laparoscopic uterine nerve ablation (LUNA):
See harms of laparoscopic removal plus LUNA, p 10 .

Laser versus diathermy ablation:
We found no RCTs.

Laparoscopic removal versus gonadorelin analogue hormonal treatment:
The RCT gave no information on adverse effects. [44]

Comment:

In the crossover RCT, precrossover results are presented, because the effects of precrossover treatment may persist after crossover, reducing the reliability of postcrossover results. However, the power calculation in the RCT was based on postcrossover results, so precrossover results may be underpowered to detect a clinically important difference in outcomes. [42] Further trials are needed. A multicentre RCT of laparoscopic uterine nerve ablation is underway in Birmingham, UK, for women with mild endometriosis, mild adhesions, or no laparoscopically detectable pathology (K Khan, personal communication, 2005).

OPTION LAPAROSCOPIC REMOVAL PLUS PRESACRAL NEURECTOMY

Pain
Compared with laparoscopic removal alone Laparoscopic removal of endometriotic deposits plus laparoscopic presacral neurectomy is more likely to lead to improvement in midline dysmenorrhoea at 6 and 12 months compared with laparoscopic removal alone (high-quality evidence).

Adverse effects
Compared with laparoscopic uterine nerve ablation The risk of complications is higher with presacral neurectomy compared with laparoscopic uterine nerve ablation (moderate-quality evidence).

For GRADE evaluation of interventions for endometriosis, see table, p 21 .

Benefits:

Laparoscopic removal plus presacral neurectomy versus laparoscopic removal alone:
We found one systematic review [40] of laparoscopic removal of endometrial deposits plus presacral neurectomy (PSN). The review (search date 2004) identified three RCTs (245 women with mild to severe endometriosis; age range 18–40 years) comparing laparoscopic ablation plus PSN versus laparoscopic removal alone, where data could be pooled in a meta-analysis. [40] The review provided limited evidence of improvement in midline dysmenorrhoea pain relief at both 6 and 12 months after laparoscopic removal plus PSN compared with laparoscopic removal alone (pain relief at 6 months after treatment, 1 RCT, 126 women: 55/63 [87%] with laparoscopic removal plus PSN *v* 38/63 [60%] with laparoscopic removal alone, OR 4.52, 95% CI 1.84 to 11.09; 12 months after

treatment, 2 RCTs, 197 women: 83/98 [85%] with laparoscopic removal plus PSN *v* 63/99 [64%] with laparoscopic removal alone, OR 3.14, 95% CI 1.59 to 6.21). [40]

Harms: **Laparoscopic removal plus presacral neurectomy versus laparoscopic removal alone:** The systematic review found a significantly higher incidence of adverse effects in women undergoing laparoscopic removal plus presacral neurectomy compared with laparoscopic removal alone (1 RCT, 71 women, 18/35 [51%] with laparoscopic removal plus presacral neurectomy *v* 0/36 [0%] with laparoscopic removal alone, OR 14.6, 95% CI 5.04 to 42.15). Symptoms were typically mild and transient, with constipation being the most commonly reported side effect. [40]

Comment: One RCT found that complication rates were significantly lower for laparoscopic uterine nerve ablation than for laparoscopic PSN (67 women with primary dysmenorrhoea: OR 0.02, 95% CI 0.01 to 0.06). [40]

OPTION LAPAROSCOPIC UTERINE NERVE ABLATION ALONE

We found no clinically important results about the effects of laparoscopic uterine nerve ablation alone in women with pain attributed to endometriosis.

For GRADE evaluation of interventions for endometriosis, see table, p 21 .

Benefits: We found no systematic review or RCTs evaluating laparoscopic uterine nerve ablation alone in women with pain attributed to endometriosis.

Laparoscopic uterine nerve ablation plus laparoscopic removal of endometrial deposits: See benefits of laparoscopic removal of endometrial deposits, p 11 .

Harms: Potential harms of laparoscopic uterine nerve ablation include denervation of pelvic structures and uterine prolapse (see harms of laparoscopic removal of endometrial deposits, p 11).

Comment: None.

OPTION PRESACRAL NEURECTOMY ALONE

We found no clinically important results about the effects of presacral neurectomy alone in women with pain attributed to endometriosis.

For GRADE evaluation of interventions for endometriosis, see table, p 21 .

Benefits: We found no systematic review or RCTs evaluating presacral neurectomy alone in women with pain attributed to endometriosis.

Presacral neurectomy plus laparoscopic removal of endometrial deposits: See benefits of laparoscopic removal of endometrial deposits, p 11 .

Harms: Potential harms of presacral neurectomy include constipation, bladder dysfunction, presacral haematoma, and subsequent painless labour (see harms of laparoscopic removal of endometrial deposits, p 11).

Comment: None.

QUESTION What are the effects of hormonal treatment after conservative surgery for endometriosis?

OPTION HORMONAL TREATMENT AFTER CONSERVATIVE SURGERY

Pain

Danazol compared with placebo Danazol may reduce pain in women who have had surgery for endometriosis compared with placebo (very low-quality evidence).

Gonadorelin analogues compared with placebo Gonadorelin analogues may be no more effective than placebo at reducing pain in women who have had surgery for endometriosis (low-quality evidence).

Medroxyprogesterone acetate compared with placebo Medroxyprogesterone acetate may reduce pain in women who have had surgery for endometriosis compared with placebo (low-quality evidence).

Cyproterone acetate compared with combined oral contraceptives Cyproterone acetate may be as effective as combined oral contraceptives at reducing pain in women who have had surgery for endometriosis (low-quality evidence).

Levonorgestrel intrauterine device compared with no treatment The levonorgestrel intrauterine device reduces pain following surgery for endometriosis compared with surgery alone (moderate-quality evidence).

Danazol compared with gonadorelin analogues Danazol may be as effective as gonadorelin analogues at reducing pain in women who have had surgery for endometriosis (low-quality evidence).

Compared with hormonal treatment before surgery Hormonal treatment given only after surgery leads to similar pain scores as hormonal treatment given only before surgery (moderate-quality evidence).

Recurrence of endometriosis
Combined oral contraceptives compared with placebo Combined oral contraceptives for 6 months may not prevent recurrence of endometriosis compared with placebo (moderate-quality evidence).

For GRADE evaluation of interventions for endometriosis, see table, p 21 .

Benefits:

We found one systematic review, [33] one subsequent [45] and two additional RCTs [46] [47] investigating hormonal treatment after surgery. The review (search date 2003, 8 RCTs, 811 people) found that hormonal treatment after surgery significantly improved American Fertility Society scores compared with surgery alone or surgery plus placebo (search date 2003; WMD –2.30, 95% CI –4.02 to –0.58). [33] The review found no significant difference in pain between groups at 12 or 24 months (12 months, 3 RCTs, 332 people: RR 0.76, 95% CI 0.52 to 1.10; 24 months, 3 RCTs, 312 people: RR 0.70, 95% CI 0.47 to 1.03). The systematic review did not perform separate meta-analyses for different drugs or treatment lengths. Results from the individual RCTs are summarised below under relevant subheadings. Four RCTs found that 6 months of treatment with danazol, medroxyprogesterone acetate, or gonadorelin analogues after laparoscopic conservative surgery reduced pain over 1–2 years compared with placebo or expectant management. [46] [48] [49] [50] However, three RCTs found no significant difference in pain relief if treatment was given for 3 months. [51] [52] [53] One RCT found no significant difference between 6 months of treatment with a monophasic combined oral contraceptive and placebo in pain at 22 months. [54] One RCT found that cyproterone acetate and combined oral contraceptives were similarly effective in women with modest and severe pain. [55] One small RCT found that a levonorgestrel-releasing intrauterine device (Lng-IUD) inserted after surgery significantly reduced dysmenorrhoea compared with surgery alone at 1 year. [47] One subsequent RCT found no significant different in pain control and American Fertility Society score between triptorelin and danazol. [45]

Combined oral contraceptive versus placebo for 6 months:
One RCT identified by the review [33] (70 women treated after laparoscopic conservative surgery) comparing combined oral contraceptives after surgery versus placebo for 6 months found no significant difference in recurrence of endometriosis (mean follow up 22 months; recurrences: 2/33 [6%] with oral contraceptives *v* 1/35 [3%] with no treatment; RR 2.1, 95% CI 0.2 to 22.3). [54] The RCT may have been underpowered to detect a clinically important difference.

Danazol versus placebo or versus expectant management for 6 months:
One additional RCT (28 women with moderate endometriosis, treated with conservative surgery followed by monthly injections of decapeptyl for 6 months) compared danazol 100 mg daily for 6 months versus expectant management. [46] It found that danazol significantly reduced pain at both 12 months ($P < 0.01$) and 24 months ($P < 0.05$). Overall, recurrence at 24 months was 44% with danazol compared with 67% with expectant management ($P < 0.05$). One RCT identified by the review [33] (60 women with mild to severe endometriosis who had had conservative surgery) compared three interventions: danazol 600 mg daily, medroxyprogesterone 100 mg daily, or placebo for 180 days after surgery. It found that danazol significantly reduced pain compared with placebo at 6 months (absolute results presented graphically; $P < 0.05$). [48]

Danazol versus placebo for 3 months:
One RCT identified by the review [33] (77 women with moderate to severe endometriosis, treated after laparoscopic conservative surgery) compared danazol 600 mg daily with placebo for 3 months. [52] It found no significant difference in pain relief 6 months after finishing treatment (moderate to severe pain: 7/31 [23%] with danazol *v* 9/29 [31%] with placebo; RR 0.73, 95% CI 0.31 to 1.70).

Gonadorelin (gonadotrophin releasing hormone) analogues versus placebo or expectant management for 6 months:
One RCT identified by the review [33] (109 women with mild to moderate symptomatic endometriosis treated after laparoscopic conservative surgery) found that nafarelin 200 µg twice daily after surgery

significantly reduced pain after 6 months of treatment compared with placebo (P = 0.001). [49] A second RCT identified by the review (269 women with mild to moderate symptomatic endometriosis who had had laparoscopic conservative surgery) compared 6 months of open label allocation of 3.6 mg of subcutaneous goserelin versus expectant management with 2 years of follow up. [50] It found that goserelin reduced recurrence of pain over 2 years, but the difference was not significant (proportion of women experiencing recurrence of pain symptoms: 19/81 [24%] with goserelin *v* 27/74 [37%] with expectant management; P = 0.082) and delayed the recurrence of pain by more than 12 months. [50]

Gonadorelin analogues versus placebo or expectant management for 3 months:
The review [33] identified three RCTs. [51] [53] [56] One RCT identified by the review (75 women with mild to moderate endometriosis and 1 year of infertility, treated after laparotomy) compared nafarelin after surgery versus placebo for 3 months. [51] It found no significant difference in pain at 12 months (assessed by a visual analogue scale [range 0–10]: 7.0 with nafarelin *v* 6.9 with placebo; reported as non-significant, CI not reported). [51] A second RCT identified by the review (89 women with moderate to severe endometriosis treated after laparoscopic conservative surgery) compared monthly intramuscular leuprolide acetate depot injections after surgery for 3 months versus expectant management with 36 months of follow up. [53] It found no significant difference in pain (moderate to severe pain recurrence during follow up: 10/44 [23%] with leuprolide acetate *v* 11/45 [24%] with expectant management; cumulative pain recurrence rates at 18 months: 23% with leuprolide acetate *v* 29% with expectant management; log rank test not significant). A third RCT identified by the review compared triptorelin for 3 months versus expectant management and it found no significant difference in pelvic pain between groups. It was reported only in abstract form, so we could not reliably review its methods. [56]

Medroxyprogesterone acetate versus placebo for 6 months:
One RCT identified by the review [33] (60 women with mild to severe endometriosis treated after conservative surgery) compared three interventions: medroxyprogesterone 100 mg daily, danazol 600 mg daily, or placebo for 180 days after surgery. It found that medroxyprogesterone significantly reduced pain compared with placebo at 6 months (absolute results presented graphically; P < 0.05). [48]

Cyproterone acetate versus combined oral contraceptive:
We found no systematic reviews or RCTs.

Levonorgestrel intrauterine systems:
We found one small additional RCT (40 women, treated with conservative laparoscopic surgery). [47] After 1 year of follow up, it found that a levonorgestrel Lng-IUD inserted after surgery significantly reduced moderate or severe dysmenorrhoea compared with surgery alone (dysmenorrhoea assessed on 0–100 mm visual analogue scale [0 = no pain, 100 = most severe pain]; AR for score > 51: 2/20 [10%] with Lng-IUD *v* 9/20 [45%] with no Lng-IUD; P = 0.03). It found no significant difference between treatments in the proportion of women who were satisfied with treatment after 1 year (15/20 [75%] with Lng-IUD *v* 10/20 [50%] with no Lng-IUD; P value not reported). The RCT may have been too small to detect a clinically important difference in satisfaction. [47]

Danazol versus gonadorelin analogues:
One subsequent RCT (40 women with moderate to severe endometriosis, 95% had had ovarian cystectomy, 5% had had unilateral oophorectomy) found no significant difference in pain control and American Fertility Society score between triptorelin (intramuscular depot preparation) and oral danazol at 36 weeks (mean pain score [range 0–6, based on the sum of severity of dysmenorrhoea and pelvic pain, graded 0–3 each]: 0.50 with danazol *v* 0.61 with triptorelin, P value reported as non-significant; American Fertility Society score on laparoscopy at end of treatment: 23.6 with danazol *v* 34.8 with triptorelin, P value reported as non-significant). [45]

Hormonal treatment before and after surgery versus hormonal treatment after surgery:
See benefits of preoperative hormone treatment, p 8 .

Hormonal treatment before surgery versus hormonal treatment after surgery:
See benefits of preoperative hormone treatment, p 8 .

Harms:

See also harms of hormonal treatments at diagnosis, p 3 . The systematic review did not perform meta-analyses of adverse effects. [33] Results from individual RCTs are summarised below.

Combined oral contraceptive versus placebo for 6 months:
One RCT identified by the review [33] did not report on adverse effects. [54]

Danazol versus placebo or expectant management for 6 months:
The additional RCT found that danazol 100 mg daily after surgery increased adverse effects after 6 months compared with no treatment (spotting: 12% with danazol *v* 7% with no treatment; bloating: 16% with danazol *v* 9% with no treatment; headache: 21% with danazol *v* 13% with no treatment; weight gain: 22% with danazol *v* 14% with no treatment; significance not reported). [46] One RCT identified by the review [33] found that danazol increased weight gain, breakthrough bleeding, and acne compared with placebo (weight gain: 3.4 kg with danazol *v* 0.4 kg with placebo; breakthrough bleeding: 56% with danazol *v* 6% with placebo; acne: 56% with danazol *v* 6% with placebo; significance not reported). [48]

Danazol versus placebo for 3 months:
One RCT identified by the review [33] found that danazol increased hyperandrogenism and weight gain compared with expectant management (hyperandrogenism: 16.7% with danazol; weight gain greater-than or equal to 3 kg: 8.3% with danazol; no adverse effects reported for expectant management). [52]

Gonadorelin (gonadotrophin releasing hormone) analogues versus placebo or expectant management for 6 months:
Two RCTs identified by the review [33] did not report on adverse effects. [49] [50]

Gonadorelin analogues versus placebo or expectant management for 3 months:
One RCT identified by the review [33] found that most women on leuprolide acetate experienced menopausal symptoms and all became amenorrhoeic (data not reported). [53] A second RCT identified by the review found that nafarelin increased amenorrhoea compared with placebo (36/36 [100%] with nafarelin *v* 0/39 [0%] with placebo; significance not reported). [51] A third RCT identified by the review was reported only in abstract form, and it did not report on adverse effects. [56]

Medroxyprogesterone acetate versus placebo for 6 months:
One RCT identified by the review [33] found that medroxyprogesterone acetate increased breakthrough bleeding compared with placebo (breakthrough bleeding: 65% with medroxyprogesterone acetate *v* 6% with placebo; significance not reported). [48]

Cyproterone acetate versus combined oral contraceptive:
We found no systematic reviews or RCTs.

Levonorgestrel intrauterine systems:
The additional RCT comparing Lng-IUD versus no Lng-IUD reported adverse effects in eight women who had a Lng-IUD inserted. The Lng-IUD was removed in one woman because the system became displaced. [47] Adverse effects among women with Lng-IUD included bloating (6/20 [30%]), weight gain (6/20 [30%]), headache (3/20 [15%]), seborrhoea and acne (2/20 [10%]), breast tenderness (1/20 [5%]), decreased libido (1/20 [5%]), and pelvic pain (1/20 [5%]). The RCT gave no information on adverse effects in the control group.

Danazol versus gonadorelin analogues:
One subsequent RCT found that danazol increased breakthrough bleeding and withdrawals compared with triptorelin (breakthrough bleeding: 2/20 [10%] with danazol *v* 0/19 [0%] with triptorelin; withdrawal: 7/20 [35%] with danazol *v* 1/19 [5%] with triptorelin). [45]

Hormonal treatment before and after surgery versus hormonal treatment after surgery:
See harms of preoperative hormone treatment, p 8 .

Hormonal treatment before surgery versus hormonal treatment after surgery:
See harms of preoperative hormone treatment, p 8 .

Comment: The RCTs were mainly small, with no long term follow up.

QUESTION **What are the effects of hormonal treatment after oophorectomy (with or without hysterectomy) for endometriosis?**

OPTION **HORMONAL TREATMENT AFTER OOPHORECTOMY**

Recurrence of endometriosis
Compared with no treatment Hormone replacement therapy may not prevent recurrence of endometriosis after oophorectomy compared with no treatment (very low-quality evidence).

For GRADE evaluation of interventions for endometriosis, see table, p 21 .

Benefits: We found no systematic review. We found one RCT (172 women who had previously had bilateral salpingo-oophorectomy, 91.8% of whom had total abdominal hysterectomy) comparing hormone replacement therapy (HRT; 115 women) versus no treatment (57 women). [57] HRT consisted of two, weekly 1.5 mg oestradiol patches and 200 mg daily of micronised progesterone given orally during 14 days followed by a 16 day interval free of treatment. HRT was started 4 weeks after the salpingo-oophorectomy. The RCT found no significant difference in recurrence rates at a mean of 45 months (4/115 [4%] with HRT *v* 0/57 [0%] with no HRT; ARI + 3.5%, 95% CI –3.2% to + 8.6%). The risk factors for recurrence were women who had endometriotic peritoneal involvement greater than 3 cm (2.4% with HRT *v* 0.3% with no HRT) and incomplete hysterectomy (22.2% with HRT *v* 1.9% with no HRT).

Harms: The RCT found that surgical reinterventions were more frequent with HRT but this difference was not significant (2.6% with HRT *v* 0% with no HRT; OR 4.5, 95% CI 0.4 to 60.0). [57]

Comment: The RCT had insufficient power to detect clinically important differences. [57]

QUESTION What are the effects of treatments for ovarian endometrioma?

OPTION LAPAROSCOPIC CYSTECTOMY

Pain
Laparoscopic cystectomy compared with laparoscopic ablation Laparoscopic excisional cystectomy reduces pain compared with laparoscopic cyst drainage and cyst wall ablation in women with endometrioma (moderate-quality evidence).

Adverse effects
Complication rates are similar for cyst excision compared with cyst ablation.

For GRADE evaluation of interventions for endometriosis, see table, p 21 .

Benefits: **Laparoscopic cystectomy in women with pain attributed to endometrioma:**
We found one systematic review, which included two RCTs (164 women) comparing excisional surgery (laparoscopic cystectomy) versus ablative surgery (laparoscopic drainage and cyst wall electrosurgical ablation). [58] The systematic review found that excisional surgery, compared with ablative surgery, significantly reduced the recurrence of dysmenorrhoea (9/57 [16%] with laparoscopic cystectomy *v* 26/47 [55%] with ablative surgery, OR 0.15, 95% CI 0.06 to 0.38), dyspareunia (3/15 [20%] with laparoscopic cystectomy *v* 9/12 [75%] with ablative surgery, OR 0.08, 95% CI 0.01 to 0.51), non-menstrual pelvic pain (2/20 [10%] with laparoscopic cystectomy *v* 9/17 [53%] with ablative surgery, OR 0.10, 95% CI 0.02 to 0.56), and endometrioma (11/84 [13%] with laparoscopic cystectomy *v* 21/80 [26%] with ablative surgery, OR 0.41, 95% CI 0.18 to 0.93). The review also found that excisional surgery significantly improved subsequent conception at 12 months compared with ablative surgery (22/41 [54%] with laparoscopic cystectomy *v* 8/47 [17%] with ablative surgery, OR 5.24, 95% CI 1.92 to 14.27). [58]

Harms: The systematic review of RCTs reported no intraoperative or postoperative complications in either group. [58]

Comment: None.

GLOSSARY

Conservative surgery Surgery to conserve the pelvic organs.
Laparoscopic cystectomy During laparoscopy, the cyst wall of the endometrioma is excised or stripped.
Laparoscopic drainage During laparoscopy, the endometrioma contents are drained out.
Laparoscopic removal of endometrial deposits A surgical procedure where a long tube with a fibreoptic telescope (the laparoscope) is inserted into a woman's abdomen to ablate (destroy) or excise (cut out) the endometrial deposits around the ovaries and uterus in order to relieve pain.
Laparoscopic uterine nerve ablation (LUNA) The cutting of nerves in the uterus to stop chronic pain. This is carried out laparoscopically through a small incision in the abdomen, so the outside surface of the uterus and uterine nerves can be seen.
Presacral neurectomy (PSN) The cutting of the presacral nerve (superior hypogastric nerve plexus) that lies in front of the sacrum behind the peritoneum. This can be undertaken laparoscopically or at open surgery.
Severity of endometriosisMild (stage I and II):moderate (stage III):severe (stage IV): Determination of the stage or degree of endometrial involvement is based on the American Fertility Society Scale of weighted point scale of estimations, evaluating the degree of involvement of the peritoneum, ovaries, and fallopian tubes. [1] According to the allocated score, endometriosis is categorised as follows. American Fertility Society score of 1–15 points; American Fertility Society score of 16–40 points; American Fertility Society score of > 40 points.

Total abdominal hysterectomy Open operation through the abdominal wall to remove the uterus. In some situations, this is performed in conjunction with a bilateral salpingo-oophorectomy, the removal of both ovaries and fallopian tubes.
High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.
Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Combined oral contraceptives at diagnosis Two RCTs added. [20] [21] benefits and harms enhanced; categorisations unchanged.
Danazol, gestrinone or gonadorelin analogues at diagnosis One RCT added. [26] benefits and harms enhanced; categorisations unchanged.
Laparoscopic cystectomy: One systematic review added. [58] Benefits and harms enhanced; categorisation unchanged (Likely to be beneficial).
Laparoscopic removal of endometriotic deposits: Two RCTs added. [43] [44] Benefits and harms enhanced; categorisation changed (Unknown effectiveness to Likely to be beneficial).
Progestogens at diagnosis One RCT added. [32] benefits and harms enhanced; categorisation unchanged.

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Neil Johnson
Associate Professor in Obstetrics and Gynaecology
University of Auckland
Auckland
New Zealand

Cynthia Farquhar
School of Medicine
University of Auckland
Auckland
New Zealand

Competing interests: NJ and CF are authors of 2 studies referenced in this review (40 & 41). CF is also the author of reference 33.

Disclaimer

TABLE 1 **RCTs comparing hormonal treatment at diagnosis versus placebo.** [22] [23] [24]

Ref	Comparison	Number of RCTs	Population	Outcome	Results (95% CI)
[22]	Gonadorelin analogues *v* placebo	1	63 women with endometriosis	Symptom severity at 3 months	Mean change in dysmenorrhoea: –2.3 with gonadorelin analogues *v* –0.3 with placebo Mean change in pelvic pain: –1.2 with gonadorelin analogues *v* –0.2 with placebo Mean change in dyspareunia: –0.2 with gonadorelin analogues *v* + 0.1 with placebo
[23]	Dydrogesterone 40 mg or 60 mg *v* placebo	1	62 women with endometriosis diagnosed by laparoscopy	Proportion of women with pain relief at 6 months	4/11 [36%] with dydrogesterone 40 mg *v* 5/11 [45%] with placebo; RR 0.80 (0.29 to 2.21) 7/10 [70%] with dydrogesterone 60 mg *v* 5/11 [45%] with placebo; RR 1.54 (0.72 to 3.31)
[23]	Medroxyprogesterone acetate 100 mg daily *v* placebo*	1	33 with endometriosis diagnosed by laparoscopy, who had had no previous surgical or medical endometriosis treatment	Symptom severity at 6 months	WMD –5.20 (–6.80 to –3.60)
[24]	Danazol *v* placebo*	1	35 women with endometriosis diagnosed by laparoscopy, who had had no previous surgical or medical endometriosis treatment	Symptom severity at 6 months	WMD –5.70 (–7.51 to –3.89)

Ref, reference. *This RCT was a three arm trial: medroxyprogesterone acetate, danazol, and placebo.

TABLE **GRADE evaluation of interventions for endometriosis**

Important outcomes	Endometrial deposits, pain, ease of surgery, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consis-tency**	**Direct-ness**	**Effect size**	**GRADE**	**Comment**
What are the effects of hormonal treatments given at diagnosis of endometriosis?									
2(98) [22] [24]	Pain	Danazol *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
2(98) [22] [24]	Pain	Gonadorelin analogues *v* placebo	4	–2	0	0	0	Low	Quality point deducted for sparse data and incomplete reporting of results
1 (33) [23]	Pain	Medroxyprogestogen *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (22) [23]	Pain	Dydrogesterone *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (90) [20]	Pain	Combined oral contraceptives *v* pro-gestogens	4	–2	0	-1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted as all women had had surgery
3 (292) [19] [17] [18]	Pain	Combined oral contraceptives *v* go-nadorelin analogues	4	–1	–1	0	0	Low	Quality point deducted for incomplete report-ing of results. Consistency point deducted for conflicting results
1 (80) [23]	Pain	Progestogen *v* combined oral contra-ceptives plus danazol	4	–2	–1	0	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Consistency point deducted for conflicting results
1 (269) [27]	Pain	Danazol *v* gestrinone	4	–1	0	0	0	Moderate	Quality point deducted for incomplete report-ing of results
7 (535) [22] [26]	Pain	Gonadorelin analogues *v* danazol	4	0	0	0	0	High	
1 (55) [23]	Pain	Gestrinone *v* gonadorelin analogues	4	–1	–1	0	0	Low	Quality point deducted for sparse data. Con-sistency point deducted for conflicting results at different endpoints
1 (48) [25]	Symptoms of en-dometriosis	Gonadorelin analogues *v* progestogens	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (34) [23]	Pain	Danazol *v* progestogens	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (82) [32]	Pain	Levonorgestrel-releasing intrauterine system *v* gonadorelin analogue	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
What are the effects of hormonal treatments before surgery for endometriosis?									
1 (48) [34]	Pain	Hormone treatment before surgery *v* no hormonal treatment	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
2 (123) [34] [15]	Ease of surgery	Hormone treatment before surgery *v* no hormonal treatment	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (75) [15]	Pain	Hormonal treatment before surgery *v* hormonal treatment after surgery	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
What are the effects of non-hormonal medical treatments for endometriosis?									
1 (24) [35]	Pain	NSAIDs *v* placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
What are the effects of surgical treatments for endometriosis?									

Important outcomes	Endometrial deposits, pain, ease of surgery, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
1 (63) [37]	Pain	Laparoscopic removal plus laparoscopic uterine nerve ablation (LUNA) *v* diagnostic laparoscopy	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
5 (506) [40] [41]	Pain	Laparoscopic ablation plus LUNA *v* laparoscopic removal alone	4	0	0	0	0	High	
1 (39) [42]	Pain	Laparoscopic removal alone *v* diagnostic laparoscopy or no treatment	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (24) [43]	Symptoms of endometriosis	Laparoscopic excision *v* laparoscopic ablation	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (35) [44]	Symptoms of endometriosis	Laparoscopic removal *v* gonadorelin analogue	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
3 (245) [40]	Pain	Laparoscopic removal plus presacral neurectomy *v* laparoscopic removal alone	4	0	0	0	0	High	
1 (67) [40]	Complications of surgery	Laparoscopic uterine nerve ablation *v* laparoscopic presacral neurectomy	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
What are the effects of hormonal treatment after conservative surgery for endometriosis?									
1 (70) [54]	Recurrence of endometriosis	Combined oral contraceptives *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
3 (165) [46] [48] [52]	Pain	Danazol *v* placebo	4	–2	–1	0	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Consistency point deducted for conflicting results
5 (at least 542) [49] [50] [51] [53] [56]	Pain	Gonadorelin analogues *v* placebo	4	0	–1	–1	0	Low	Consistency point deducted for conflicting results. Directness point deducted for inclusion of different interventions and study durations
1 (60) [48]	Pain	Progestogens *v* placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (90) [55]	Pain	Cyproterone acetate *v* combined oral contraceptives	4	–2	0	0	0	Low	Quality points deducted for sparse data and lack of blinding
1 (40) [47]	Pain	Levonorgestrel intrauterine system *v* no hormonal treatment	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (40) [45]	Pain	Danazol *v* gonadorelin analogue	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
What are the effects of hormonal treatment after oophorectomy (with or without hysterectomy) for endometriosis?									
1 (172) [57]	Recurrence of endometriosis	HRT *v* no treatment	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and lack of blinding. Directness point deducted as most women had hysterectomy
What are the effects of treatments for ovarian endometrioma?									

Important outcomes	Endometrial deposits, pain, ease of surgery, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consis-tency**	**Direct-ness**	**Effect size**	**GRADE**	**Comment**
2 (164) [58]	Pain	Laparoscopic excision of cyst *v* laparo-scopic ablation	4	–1	0	0	0	Moderate	Quality point deducted for sparse data

Type of evidence: 4 = RCT; 2 = Observational; 1 = Non-analytical/expert opinion. Consistency: similarity of results across studies.
Directness: generalisability of population or outcomes.
Effect size: based on relative risk or odds ratio.