Endometriosis

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ABSTRACT

INTRODUCTION: Ectopic endometrial tissue is found in 1.5% to 6.2% of women of reproductive age, in up to 60% of those with dysmenorrhoea, and in 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 December 2009 (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 40 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, aromatase inhibitors, 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

INTERVENTIONS

TREATING OVARIAN ENDOMETRIOMA

Likely to be beneficial

Covered elsewhere in Clinical Evidence

Subfertility in women with endometriosis (see review on female infertility)

Key points

- Ectopic endometrial tissue is found in 1.5% to 6.2% of women of reproductive age, in 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 one 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 (such as combined oral contraceptives, progestogens, and danazol, gestrinone, and gonadorelin analogues) can reduce the pain attributed to endometriosis when given at diagnosis. However, adverse effects are common, particularly with danazol, gestrinone, and gonadorelin analogues.

  Combined oral contraceptives may be less effective than gonadorelin analogues, but they 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 giving the progestogen dydrogesterone at diagnosis is effective in the treatment of endometriosis, or 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 don't know whether uterine nerve ablation alone is of any benefit in reducing symptoms.

- The hormonal treatments danazol, medroxyprogesterone acetate, gonadorelin analogues, and aromatase inhibitors 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 don't know whether hormone replacement therapy prevents or promotes recurrence of endometriosis in women who have had oophorectomy.

- 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.

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

The diagnosis of endometriosis is based on surgical visualisation of the disease; therefore, the true prevalence of the disease in the general population is unknown. 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.The estimated prevalence of endometriosis in the general population is 1.5% to 6.2%. [2] [3] [4] [5] In women with dysmenorrhoea, the incidence of endometriosis is 40% to 60%, and in women with subfertility it is 20% to 30%. [6] [7] [8] The severity of symptoms and the probability of diagnosis increase with age. [9] Incidence peaks at about 40 years of age. [10] Symptoms and laparoscopic appearance do not always correlate. [11]

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. [12] [13] Use of oral contraceptives reduces the risk of endometriosis, and this protective effect persists for up to 1 year after their discontinuation. [10]

PROGNOSIS We found two RCTs in which laparoscopy was repeated after treatment in women given placebo.[14] [15] Over 6 to 12 months, endometrial deposits resolved spontaneously in up to one 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 **Symptoms of endometriosis**: including relief of chronic pain (assessed by a visual analogue scale ranging from 0 to 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; **endometrial deposits**: American Fertility Society scores for size and number of deposits;[1] **recurrence rate**: time between stopping treatment and recurrence; *in women having surgery*: **ease of surgical intervention**: rated by the surgeon as easy, average, difficult, or very difficult;[16] **adverse effects of treatment**.

METHODS *Clinical Evidence* search and appraisal December 2009. For this review, the following were used for the identification of studies: Medline 1966 to December 2009, Embase 1980 to December 2009, and The Cochrane Library 2009, Issue 4. 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 for 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. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 25). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the *Clinical Evidence* population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

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

OPTION COMBINED ORAL CONTRACEPTIVES AT DIAGNOSIS

Symptoms of endometriosis

Combined oral contraceptive compared with placebo Combined oral contraceptive may be more effective at reducing dysmenorrhoea but may be no more effective at reducing non-menstrual pelvic pain (low-quality evidence).

Combined oral contraceptive compared with progestogens We don't know how combined oral contraceptives and progestogens compare at reducing pain associated with dysmenorrhoea, non menstrual pelvic pain, deep dyspareunia, and dyschezia (very low-quality evidence).

Combined oral contraceptive compared with gonadorelin analogues Combined oral contraceptives may be less effective at reducing dyspareunia or non-menstrual pain at 6 months (low-quality evidence).

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

For GRADE evaluation of interventions for endometriosis, see table, p 25 .

Benefits: **Combined oral contraceptives versus placebo:**
We found one RCT (100 women with endometriosis, 91 of whom had endometrioma) comparing combined oral contraceptive versus placebo.[17] It found that combined oral contraceptives significantly reduced dysmenorrhoea severity (measured on a verbal rating scale) compared with placebo at 4 months (change in pain score: –2.0 with combined oral contraceptives *v* –0.6 with placebo; P less than 0.001). The RCT found no significant difference in non-menstrual pain (measured on a visual analogue scale) between groups at 4 months (19.1 with combined oral contraceptives *v* 21.0 with placebo; P = 0.26).[17]

Combined oral contraceptives versus progestogens:
We found one systematic review [18] and one additional RCT. [19]

The review (search date 2009) included one RCT (90 women with rectovaginal endometriosis and persistent pain after conservative surgery) comparing ethinylestradiol (0.01 mg/day) plus cyproterone acetate (3 mg/day) versus norethindrone acetate (2.5 mg/day) for 12 months. It found a similar reduction in visual analogue scale (VAS) pain scores with ethinylestradiol plus cyproterone acetate compared with norethindrone acetate in dysmenorrhoea, non-menstrual pelvic pain, deep dyspareunia, and dyschezia at 12 months (mean reduction of VAS pain scores; dysmenorrhoea: 63.7 with ethinylestradiol plus cyproterone acetate *v* 72.8 with norethindrone acetate; non-menstrual pelvic pain: 27.5 with ethinylestradiol plus cyproterone acetate *v* 43.0 with norethindrone acetate; deep dyspareunia: 35.6 with ethinylestradiol plus cyproterone acetate *v* 37.6 with norethindrone acetate; dyschezia: 42.9 with ethinylestradiol plus cyproterone acetate *v* 45.7 with norethindrone acetate; significance not reported) at 12 months. [18]

The additional RCT (40 women with a surgical diagnosis of mild endometriosis) compared combined oral contraceptive (ethinylestradiol 20 micrograms plus desogestrel 150 micrograms) versus desogestrel (75 micrograms/day continuously). [19] It found that pain scores (assessed on a VAS) were reduced with both treatments from baseline to 6 months; the significance of the difference between groups was not assessed (VAS scores at 6 months: 2.3 with combined oral contraceptive *v* 2.5 with desogestrel; significance not assessed). [19]

Combined oral contraceptives versus gonadorelin analogues:
We found one systematic review (search date 2007), [20] one additional RCT, [21] and one subsequent RCT. [22] The review [20] (1 RCT, [23] 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 compared with 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). [23] [20] 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). [20]

One additional RCT (102 women with endometriosis who had had 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. [21] 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 not 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 VAS 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). [22]

Combined oral contraceptives plus danazol versus medroxyprogesterone acetate:
See benefits of progestogens at diagnosis., p 8

Harms:

Combined oral contraceptives versus placebo:
The RCT found that combined oral contraceptive increased irregular uterine bleeding and nausea compared with placebo (irregular uterine bleeding: 60% with combined oral contraceptives *v* 26% with placebo; nausea: 24% with combined oral contraceptives *v* 0% with placebo; significance not assessed). [17]

Combined oral contraceptives versus progestogens:
The RCT included in the systematic review found that adverse effects were less common with combined oral contraceptive compared with norethisterone, but that the difference was not significant (16/41 [39%] with combined oral contraceptive *v* 21/42 [50%] with norethisterone acetate; P = 0.43). [18] The additional RCT found that 3/20 (15%) women reported an increase in body weight with

combined oral contraceptive, and that 4/20 (20%) women reported breakthrough bleeding with desogestrel. [19]

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). [20] The additional RCT gave no information on adverse effects. [21] The subsequent RCT found that gonadorelin analogues (with and without addback oestrogen/progestogen) significantly increased bone mineral density loss compared with combined oral contraceptive (P less than 0.01 for leuprolide acetate *v* estroprogestin; P less than 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 addback oestrogen/progestogen (P less than 0.05 for leuprolide acetate *v* leuprolide acetate plus norethindrone). [22]

Combined oral contraceptives plus danazol versus medroxyprogesterone acetate:
See harms of progestogens at diagnosis., p 8

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

OPTION DANAZOL, GESTRINONE, OR GONADORELIN ANALOGUES AT DIAGNOSIS

Symptoms of endometriosis
Gonadorelin analogues compared with placebo Gonadorelin analogues may be more effective at reducing severe and moderate pain at 6 months (low-quality evidence).

Danazol compared with placebo Danazol seems to be more effective at improving symptom severity at 6 months (moderate-quality evidence).

Danazol compared with gestrinone Danazol and gestrinone seem to be equally effective at reducing dysmenorrhoea (moderate-quality evidence).

Danazol compared with gonadorelin analogues Danazol and gonadorelin analogues are equally effective at reducing menstrual pain and dyspareunia (high-quality evidence).

Gestrinone compared with gonadorelin analogues Gestrinone may be more effective at reducing dysmenorrhoea, dyspareunia, and non-menstrual pain after 6 months' treatment (low-quality evidence).

Danazol compared with medroxyprogesterone acetate Danazol and medroxyprogesterone acetate seem equally effective at improving pelvic pain at 6 months (moderate-quality evidence).

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

Gonadorelin analogues compared with medroxyprogesterone acetate We don't know how gonadorelin analogues and medroxyprogesterone acetate compare at improving symptoms of endometriosis (low-quality evidence).

Gonadorelin analogues compared with dienogest Gonadorelin analogues and dienogest are equally effective at reducing pain (including lower abdominal pain, lumbago, defecation pain, dyspareunia, pain on internal examination) and at improving quality-of-life scores (physical functioning, bodily pain, general health, vitality, social functioning, role emotional and mental health) at 4 months in women with endometriosis (high-quality evidence).

Gonadorelin analogues compared with levonorgestrel-releasing intrauterine system We don't know how gonadorelin analogues and levonorgestrel-releasing intrauterine system compare at reducing chronic pelvic pain at 6 months (low-quality evidence).

Gonadorelin analogues compared with combined oral contraceptives Gonadorelin analogues may be more effective at reducing dysmenorrhoea at 6 months (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).

Endometrial deposits

Danazol compared with gonadorelin analogues Danazol and gonadorelin analogues are equally effective at reducing the number of endometrial deposits after 6 months of treatment (high-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. Addback 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 25 .

Benefits:

We found three systematic reviews (search dates 1998, [24] 2000, [25] and 2007 [26]) 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 [27] and one subsequent RCT. [28]

Danazol, gestrinone, or gonadorelin analogues versus placebo or no treatment:
Two RCTs (98 women) identified by the reviews [24] [25] [26] found that danazol and gonadorelin analogues significantly reduced pain at 3 to 6 months compared with placebo (see table 1, p 24). We found no RCTs assessing the effects of gestrinone versus placebo.

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. [29] It found no significant difference in dysmenorrhoea over 6 months of treatment between danazol and gestrinone (reported as not significant, results presented graphically).

Danazol versus gonadorelin analogues:
The first systematic review identified 15 RCTs (1299 women) comparing gonadorelin analogues versus danazol. [24] After 6 months of treatment, the review found no significant difference in menstrual pain, dyspareunia, or resolution of endometrial deposits (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; resolution of endometrial deposits; 3 RCTs, 426 women; RR 0.84, 95% CI 0.56 to 1.26). [24] 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: –4.2 with nafarelin *v* –4.6 with danazol; P = 0.502). [28]

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) [25] 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 8 .

Danazol plus combined oral contraceptives versus medroxyprogesterone acetate:
See benefits of progestogens at diagnosis, p 8 .

Gonadorelin analogues versus medroxyprogesterone acetate:
See benefits of progestogens at diagnosis, p 8 .

Gonadorelin analogues versus dienogest:
See benefits of progestogens at diagnosis, p 8 .

Gonadorelin analogues versus levonorgestrel-releasing intrauterine system:
See benefits of progestogens at diagnosis, p 8 .

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 13 .

Harms:

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). [24] Gonadorelin analogues are associated with hypo-oestrogenic symptoms, such as hot flushes and vaginal dryness. One review found that danazol significantly increased the risk of acne, muscle cramps, and oedema compared with placebo at 6 months (acne: 11/18 [61%] with danazol *v* 1/17 [6%] with placebo; OR 10.8, 95% CI 2.7 to 42.8; P = 0.0046; muscle cramps: 6/18 [33%] with danazol *v* 0/17 [0%] with placebo; OR 9.7, 95% CI 1.7 to 55.3; P = 0.055; oedema: 8/18 [44%] with danazol *v* 1/17 [6%] with placebo; OR 7.11, 95% CI 1.5 to 31.6; P = 0.025). The review also reported that vaginal spotting and weight gain may occur during treatment. [26]

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). [25] 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). [25]

Gonadorelin analogues versus danazol/gestrinone:
One systematic review found that, after 6 months, danazol/gestrinone increased bone mineral density (BMD) from baseline at the lumbar spine, whereas gonadorelin analogues decreased BMD, and the difference between treatments was significant (search date 2003, 4 RCTs, 287 people; SMD –1.12, 95% CI –1.38 to –0.86). [30] The review found no significant difference between gonadorelin analogues and danazol/gestrinone in percentage change in BMD 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). [25] 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 [standard deviation 8.2] with nafarelin *v* –20.6 [standard deviation 10.4] with danazol). [28]

Gonadorelin analogues versus medroxyprogesterone acetate:
The RCT gave no information on adverse effects. [27]

Gonadorelin analogues versus levonorgestrel-releasing intrauterine system:
See harms of progestogens at diagnosis, p 8 .

Danazol versus medroxyprogesterone acetate:
See harms of progestogens at diagnosis, p 8 .

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 at least 50%). [31] [32] [33] One systematic review found a significantly greater percentage reduction in BMD 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). [30]

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). [34]

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

Gonadorelin analogues versus dienogest:
See harms of progestogens, p 8 .

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%]). [27]

OPTION PROGESTOGENS (OTHER THAN DYDROGESTERONE) AT DIAGNOSIS

Symptoms of endometriosis
Medroxyprogesterone acetate compared with placebo Medroxyprogesterone acetate is more effective at improving symptom severity at 6 months (moderate-quality evidence).

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

Medroxyprogesterone acetate compared with gonadorelin analogues We don't know how medroxyprogesterone acetate and gonadorelin analogues compare at improving symptoms of endometriosis (low-quality evidence).

Dienogest compared with gonadorelin analogues Dienogest and gonadorelin analogues are equally effective at reducing pain (including lower abdominal pain, lumbago, defecation pain, dyspareunia, pain on internal examination) and at improving quality-of-life scores (physical functioning, bodily pain, general health, vitality, social functioning, role emotional and mental health) at 4 months in women with endometriosis (high-quality evidence).

Levonorgestrel-releasing intrauterine system compared with gonadorelin analogues We don't know how levonorgestrel-releasing intrauterine systems and gonadorelin analogues compare at reducing chronic pelvic pain (low-quality evidence).

Medroxyprogesterone acetate compared with danazol Medroxyprogesterone acetate and danazol seem equally effective at improving pelvic pain and total symptoms at 6 months (moderate-quality evidence).

Progestogens compared with combined oral contraceptives We don't know how progestogens and combined oral contraceptives compare at reducing dysmenorrhoea (very low-quality evidence).

For GRADE evaluation of interventions for endometriosis, see table, p 25 .

Benefits: We found three systematic reviews (search dates 1998, [24] 2000, [25] 2007 [26]) 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, [27] and one subsequent RCT. [36]

Medroxyprogesterone acetate versus placebo:
One RCT (33 women with endometriosis diagnosed by laparoscopy, who had had no previous surgical or medical endometriosis treatment) found that medroxyprogesterone acetate significantly improved symptom severity at 6 months compared with placebo (see table 1, p 24). [25]

Medroxyprogesterone acetate versus combined oral contraceptives plus danazol:
One RCT (80 women) identified by the second review [25] compared medroxyprogesterone acetate (150 mg every 3 months) versus combined oral contraceptive plus danazol 50 mg daily. It found that medroxyprogesterone acetate was more effective at reducing dysmenorrhoea, but not dyspareunia or non-menstrual pain (CI not reported).

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. [27] It found that both treatments significantly improved symptoms attributable to endometriosis, sleep disturbances, and anxiety–depression scores from baseline measurements (P less than 0.05 for all outcomes). It found no significant difference between treatments (reported as not significant, CI not reported).

Dienogest versus gonadorelin analogues:
We found one multicentre, double-blind RCT (271 women with endometriosis), which compared dienogest (1 mg orally twice daily) versus gonadorelin analogues (buserelin intranasal spray 900 micrograms/day) for 4 months. [35] The RCT assessed subjective symptoms (lower abdominal pain, lumbago, defecation pain, dyspareunia, and pain on internal examination) by a 5-level rating scale; lower abdominal pain and lumbago were recorded by visual analogue scale (VAS), quality of life (QOL) was rated by the 36-Item Short-Form Health Survey (SF–36). The RCT found no significant difference between groups for subjective non-menstrual pain including lower abdominal pain (difference of mean change: –0.10, 95% CI –0.44 to +0.24), lumbago (difference of mean change: –0.12, 95% CI –0.48 to +0.24), defecation pain (difference of mean change: 0.07, 95% CI –0.50 to +0.64), dyspareunia (difference of mean change: –0.19, 95% CI –0.66 to +0.27) and pain on internal examination (difference of mean change: –0.02, 95% CI –0.32 to +0.28) at 4 months. [35] The RCT found no significant difference between groups in any QOL measures as assessed by the SF–36, including physical functioning, bodily pain, general health, vitality, social functioning, emotional functioning, and mental health (mean difference; physical functioning: +0.9, 95% CI –1.8 to +3.6; bodily pain: +3.6, 95% CI –3.5 to +10.8; general health: –0.8, 95% CI –4.1 to +2.5; vitality: +0.7, 95% CI –4.1 to +5.4; social functioning: +4.8, 95% CI –4.9 to +9.9; emotional functioning: +7.7, 95% CI –1.2 to +16.6; mental health: –0.1, 95% CI –4.3 to +4.0).

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 leuprorelin 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 greater than 0.600). [36]

Medroxyprogesterone acetate versus danazol:
One RCT identified by the second review [25] (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). [25]

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. [27]

Dienogest versus gonadorelin analogues:
The RCT found similar rates of adverse drug reactions for both dienogest and gonadorelin (129/129 [100%] with dienogest *v* 117/126 [93%] with gonadorelin, significance assessment not performed). The RCT found that the most frequent adverse drug reactions included genital bleeding, hot flushes, and headache (genital bleeding: 122/129 [95%] with dienogest *v* 85/126 [67%] with gonadorelin; hot flushes: 64/129 [50%] with dienogest *v* 85/126 [67%] with gonadorelin; headache: 32/129 [25%] with dienogest *v* 43/126 [34%] with gonadorelin); however, no significance assessments were performed between groups for any comparison. The RCT also reported that dienogest significantly reduced the risk of bone mass density loss compared with gonadorelin at 4 months (–1% with dienogest *v* –2.6% with gonadorelin; P = 0.003). [35]

Levonorgestrel-releasing intrauterine system versus gonadorelin analogues:
The RCT found more adverse effects in levonorgestrel-releasing intrauterine system users, with increased breast tenderness (numbers 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). The RCT found no differences in other adverse effects, including abdominal distension and peripheral oedema. [36]

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). [25]

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%]). [27]

OPTION DYDROGESTERONE AT DIAGNOSIS

Symptoms of endometriosis
Dydrogesterone compared with placebo Dydrogesterone may be no more effective at reducing pain (undefined) at 6 months (low-quality evidence).

For GRADE evaluation of interventions for endometriosis, see table, p 25 .

Benefits: We found one systematic review (search date 2000 [25]) of 6 months of continuous ovulation suppression using progestogens.

Dydrogesterone versus placebo:
One RCT (22 women) identified by the review [25] 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 24).

Harms: The review did not report on harms from dydrogesterone. [25]

Comment: None.

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

OPTION PREOPERATIVE HORMONAL TREATMENT

Symptoms of endometriosis
Hormonal treatment before surgery compared with no hormonal treatment Hormonal treatment before surgery seems no more effective at reducing pain scores (moderate-quality evidence).

Hormonal treatment before surgery compared with hormonal treatment after surgery Hormonal treatment given only before surgery and hormonal treatment given only after surgery seem to be equally effective at improving pain scores (moderate-quality evidence).

Ease of surgery
Hormonal treatment before surgery compared with no hormonal treatment Hormonal treatment before surgery seems to be no more effective at improving the ease of surgery for endometriosis (moderate-quality evidence).

For GRADE evaluation of interventions for endometriosis, see table, p 25 .

Benefits: **Hormonal treatment before surgery versus no hormonal treatment:**
We found one systematic review [37] and one additional RCT. [38] 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. [37] 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. [38] 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, [37] which found one RCT [16] comparing 6 months of nafarelin before surgery versus surgery followed by 6 months of nafarelin. It found that 6 months of nafarelin 200 micrograms before surgery significantly reduced symptom scores compared with 6 months of nafarelin 200 micrograms 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). [16] 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). [16] 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). [37]

Hormonal treatment before and after surgery versus hormonal treatment after surgery:
We found one systematic review, [37] which found one RCT [16] 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 greater than 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. [37]

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 [37] did not report on adverse effects. 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). [38] 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 [16] identified by the review [37] found that nafarelin was associated with hot flushes, vaginal dryness, and decreased libido (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; decreased libido: 36% with nafarelin before surgery *v* 36% with nafarelin after surgery). [16]

Hormonal treatment before and after surgery versus hormonal treatment after surgery:
The RCT [16] identified by the review [37] did not report on adverse effects.

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. [16] The additional RCT may also have been too small to detect a clinically important effect. [38]

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

OPTION AROMATASE INHIBITORS New

We found no clinically important results from RCTs about the effects of aromatase inhibitors in women with pain attributed to endometriosis.

For GRADE evaluation of interventions for endometriosis, **see table, p 25 .**

Benefits: **Aromatase inhibitors plus gonadorelin analogues versus gonadorelin analogues alone:**
We found two systematic reviews (search dates 2007 [39] and 2009 [18]), which found no RCTs.

Harms: **Aromatase inhibitors plus gonadorelin analogues versus gonadorelin analogues alone:**
We found no RCTs.

Comment: None.

OPTION NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

Symptoms of endometriosis
Non-steroidal anti-inflammatory drugs (NSAIDs) compared with placebo NSAIDs may be no more effective at reducing pain (undefined) in women with endometriosis (low-quality evidence).

For GRADE evaluation of interventions for endometriosis, see table, p 25 .

Benefits:

Non-steroidal anti-inflammatory drugs (NSAIDs) versus placebo:
We found one systematic review (search date 2005 [40]), which included one crossover RCT (24 women with mild to severe endometriosis) comparing NSAIDs (naproxen) versus placebo. The RCT found no significant difference in overall pain relief between NSAIDs and placebo (OR 3.3, 95% CI 0.6 to 17.7; absolute numbers not reported). [40]

Harms:

Non-steroidal anti-inflammatory drugs (NSAIDs) versus placebo:
The RCT provided insufficient evidence as to whether NSAIDs were associated with more adverse effects compared with placebo (OR 0.46, 95% CI 0.09 to 2.47; absolute numbers not reported). [40]

Comment:

We found one RCT assessing the efficacy of the cyclo-oxygenase 2 inhibitor rofecoxib. [41] 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

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

Laparoscopic removal of endometriotic deposits plus LUNA compared with laparoscopic removal alone Adding LUNA to laparoscopic removal of endometriotic deposits is no more effective than ablation of deposits alone at relieving pain (undefined) at 6 months to 3 years (high-quality evidence).

For GRADE evaluation of interventions for endometriosis, see table, p 25 .

Benefits:

Laparoscopic removal plus laparoscopic uterine nerve ablation (LUNA) versus diagnostic laparoscopy:
We found one systematic review (search date 1999), [42] which identified one RCT (63 women with mild to moderate endometriosis, reported in 2 publications) [43] [44] 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 [VAS]: 2.85 cm with laparoscopic removal *v* 0.05 cm with diagnostic laparoscopy; P = 0.01). [42] Follow-up of the RCT suggested that 90% of the women who responded continued to have pain improvement at 1 year, [43] and 55% continued to have pain improvement at 5 years. [44]

Laparoscopic removal plus LUNA versus laparoscopic removal alone:
We found one systematic review [45] 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. [45] 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). [45] 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 (at least 50% reduction on VAS; 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 [50%] with 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). [46]

Harms:

Laparoscopic removal plus LUNA versus diagnostic laparoscopy:
The RCT identified by the review reported that no adverse effects were observed. [42]

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. [45]

Comment: None.

OPTION LAPAROSCOPIC REMOVAL OF ENDOMETRIOTIC DEPOSITS ALONE

Symptoms of endometriosis
Laparoscopic removal alone compared with diagnostic laparoscopy or no treatment Laparoscopic removal of endometriotic deposits alone is more effective at improving pain symptoms associated with endometriosis and quality of life at 6 months (moderate-quality evidence).

Laparoscopic excision compared with laparoscopic ablation We don't know how laparoscopic excision of deposits and laparoscopic ablation of deposits compare at improving symptoms of endometriosis (low-quality evidence).

Laparoscopic ablation compared with laparoscopic removal plus laparoscopic uterine nerve ablation Laparoscopic ablation of deposits alone and laparoscopic removal plus laparoscopic uterine nerve ablation are equally effective at improving pain relief at 6 months to 3 years (high-quality evidence).

Laparoscopic removal alone compared with laparoscopic removal plus presacral neurectomy Laparoscopic removal of endometriotic deposits is less effective at improving midline dysmenorrhoea at 6 and 12 months (high-quality evidence).

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

Adverse effects
Laparoscopic removal alone compared with laparoscopic removal plus presacral neurectomy Laparoscopic removal alone seems to be associated with a lower rate of adverse effects compared with laparoscopic removal plus presacral neurectomy (moderate-quality evidence).

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

For GRADE evaluation of interventions for endometriosis, see table, p 25 .

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 pre-crossover 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. [47] 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 (VAS) 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 VAS 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). [47]

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. [48] 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). [48]

Laparoscopic removal alone versus laparoscopic removal plus laparoscopic uterine nerve ablation (LUNA):
See benefits of laparoscopic removal plus LUNA, p 12 .

Laparoscopic removal alone versus laparoscopic removal plus presacral neurectomy:
See benefits of laparoscopic removal plus presacral neurectomy, p 14 .

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 goserelin. At 12 months' follow-up, proportionately 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). [49]

Harms:

Laparoscopic removal alone versus laparoscopic removal plus uterine nerve ablation:
See benefits of laparoscopic removal of endometriotic deposits plus uterine nerve ablation, p 12 .
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. [47]

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). [48]

Laser versus diathermy ablation:
We found no RCTs.

Laparoscopic removal alone versus laparoscopic removal plus laparoscopic uterine nerve ablation (LUNA):
See harms of laparoscopic removal plus LUNA, p 12 .

Laparoscopic removal alone versus laparoscopic removal plus presacral neurectomy:
See harms of laparoscopic removal plus presacral neurectomy, p 14 .

Laparoscopic removal versus gonadorelin analogue hormonal treatment:
The RCT gave no information on adverse effects. [49]

Comment:

In the crossover RCT, pre-crossover results are presented, because the effects of pre-crossover treatment may persist after crossover, reducing the reliability of post-crossover results. However, the power calculation in the RCT was based on post-crossover results, so pre-crossover results may be underpowered to detect a clinically important difference in outcomes. [47] 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

Symptoms of endometriosis
Laparoscopic removal plus presacral neurectomy compared with laparoscopic removal alone Laparoscopic removal of endometriotic deposits plus laparoscopic presacral neurectomy is more effective at improving midline dysmenorrhoea at 6 and 12 months (high-quality evidence).

Adverse effects
Laparoscopic removal plus presacral neurectomy compared with laparoscopic removal alone Laparoscopic removal plus presacral neurectomy seems to be associated with a higher risk of adverse effects compared with laparoscopic removal alone (moderate-quality evidence).

For GRADE evaluation of interventions for endometriosis, see table, p 25 .

Benefits: **Laparoscopic removal plus presacral neurectomy versus laparoscopic removal alone:** We found one systematic review [45] 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. [45] 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). [45]

Harms: **Laparoscopic removal plus presacral neurectomy versus laparoscopic removal alone:** The systematic review found a significantly higher incidence of adverse effects in women having 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 adverse effect. [45]

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). [45]

OPTION LAPAROSCOPIC UTERINE NERVE ABLATION ALONE

We found no clinically important results from RCTs 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 25 .

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 13 .

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 13).

Comment: None.

OPTION PRESACRAL NEURECTOMY ALONE

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

For GRADE evaluation of interventions for endometriosis, see table, p 25 .

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 13 .

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 13).

Comment: None.

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

OPTION HORMONAL TREATMENT AFTER CONSERVATIVE SURGERY

Symptoms of endometriosis

Hormonal treatment after surgery compared with surgery alone Hormonal treatment after surgery seems as effective at reducing pain (undefined) at 12 and 24 months (moderate-quality evidence).

Combined oral contraceptive compared with placebo Combined oral contraceptives seem more effective at reducing the rate of dysmenorrhoea at 12 months in women with moderate to severe endometriosis after surgery (moderate-quality evidence).

Danazol compared with placebo Danazol may be more effective at reducing pain (undefined) in women who have had surgery for endometriosis (very low-quality evidence).

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

Medroxyprogesterone acetate compared with placebo Medroxyprogesterone acetate may be more effective at reducing pain (undefined) in women who have had surgery for endometriosis (low-quality evidence).

Levonorgestrel intrauterine device compared with no treatment The levonorgestrel intrauterine device seems more effective than surgery alone at reducing moderate or severe dysmenorrhoea after surgery for endometriosis (moderate-quality evidence).

Danazol compared with gonadorelin analogues We don't know how danazol and gonadorelin analogues compare at reducing pain (undefined) in women who have had surgery for endometriosis (low-quality evidence).

Hormonal treatment after surgery compared with hormonal treatment before surgery Hormonal treatment given only after surgery and hormonal treatment given only before surgery seem to be equally effective at improving pain scores (moderate-quality evidence).

Recurrence of endometriosis

Combined oral contraceptives compared with placebo Combined oral contraceptives for 6 months may be no more effective at preventing recurrence of endometriosis (moderate-quality evidence).

Gonadorelin analogues compared with placebo/expectant management We don't know whether gonadorelin analogues (triptorelin) are more effective at reducing recurrence rates (pain and endometrioma) or increasing time to recurrence at 5 years in women with moderate to severe endometriosis (low-quality evidence).

Aromatase inhibitors plus gonadorelin analogues compared with gonadorelin analogue alone Aromatase inhibitors plus gonadorelin analogues may be more effective at reducing recurrence rates and increasing median time to recurrence at 24 months in women with severe endometriosis post surgery (low-quality evidence).

For GRADE evaluation of interventions for endometriosis, see table, p 25 .

Benefits:

We found two systematic reviews, [37] [39] two subsequent RCTs, [50] [51] and four additional RCTs [52] [53] [54] [55] investigating hormonal treatment after surgery.

Hormonal treatment after surgery versus surgery alone:
The first review (search date 2003, 8 RCTs, 811 people) found no significant difference in pain between hormonal treatment after surgery compared with surgery alone 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). [37] 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 sub-headings.

Combined oral contraceptive versus placebo:
One RCT identified by the first review [37] (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). [56] The RCT may have been underpowered to detect a clinically important difference.

One additional four-arm RCT (222 women post conservative pelvic surgery for endometriosis stage III-IV) compared continuous estroprogestin (ethinyloestradiol 0.03 mg plus gestoden 0.75 mg),

placebo, triptorelin, or leuprorelin (3.75 mg every 28 days) versus dietary treatment (vitamins, mineral salts, lactic germents, fish oil) for 6 months. [54] The RCT found that continuous estroprogestin significantly reduced the rate of dysmenorrhoea compared with placebo (P less than 0.001, absolute numbers not reported) at 12-month follow-up. [54] The RCT found that combined oral contraceptives significantly increased the risk of dyspareunia compared with placebo at 12 months (P less than 0.001, absolute numbers not reported). [54]

Danazol versus placebo or versus expectant management:
One RCT identified by the review [37] (77 women with moderate to severe endometriosis, treated after laparoscopic conservative surgery) compared danazol 600 mg daily versus placebo for 3 months. [57] 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).

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. [52] It found that danazol significantly reduced pain at both 12 months (P less than 0.01) and 24 months (P less than 0.05). Overall, recurrence at 24 months was 44% with danazol compared with 67% with expectant management (P less than 0.05). One RCT identified by the review [37] (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 less than 0.05). [55]

Gonadorelin (gonadotrophin-releasing hormone) analogues versus placebo or expectant management:
The first review [37] identified five RCTs. [58] [59] [60] [61] [62] We found one subsequent RCT [51] and one additional RCT. [54]

The first 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. [58] It found no significant difference in pain at 12 months (assessed by a visual analogue scale [VAS; range 0–10]: 7.0 with nafarelin *v* 6.9 with placebo; reported as not significant, CI not reported). [58]

The 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. [59] 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).

The third RCT identified by the review compared triptorelin for 3 months versus expectant management and found no significant difference in pelvic pain between groups. It was reported only in abstract form, so we could not reliably review its methods. [60]

The fourth RCT identified by the review [37] (109 women with mild to moderate symptomatic endometriosis treated after laparoscopic conservative surgery) found that nafarelin 200 micrograms twice daily after surgery significantly reduced pain after 6 months of treatment compared with placebo (P = 0.001). [61]

The fifth 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. [62] 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. [62]

The subsequent RCT (60 women with moderate to severe endometriosis (stage III and IV) treated after laparoscopic conservative surgery) compared monthly intramuscular triptorelin depot injections after surgery for 3 months versus expectant management with 60 months of follow-up. [51] The RCT found no significant difference in pain recurrence and endometrioma recurrence (pain recurrence: RR 0.94, 95% CI 0.57 to 1.55; P = 1.0; absolute numbers presented graphically; endometrioma recurrence: 4/19 [21%] with triptorelin *v* 2/16 [13%] with placebo; RR 1.29, 95% CI 0.66 to

2.50; P = 0.67). The RCT also found no significant differences between groups for time of pain recurrence (P = 0.79; no further numbers reported). [51]

The additional four-arm RCT (222 women post conservative pelvic surgery for endometriosis stage III-IV) compared continuous estroprogestin (ethinyloestradiol 0.03 mg plus gestoden 0.75 mg), placebo, triptorelin, or leuprorelin (3.75 mg every 28 days) versus dietary treatment (vitamins, mineral salts, lactic germents, fish oil) for 6 months. [54] The RCT found that gonadorelin analogues (triptorelin or leuprorelin) significantly reduced the rate of dysmenorrhoea compared with placebo at 12 months. [54]

Medroxyprogesterone acetate versus placebo:
One RCT identified by the review [37] (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 less than 0.05). [55]

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

Levonorgestrel intrauterine systems after surgery versus surgery alone:
We found one small additional RCT (40 women, treated with conservative laparoscopic surgery). [53] After 1 year of follow-up, it found that a levonorgestrel-releasing intrauterine device (Lng-IUD) inserted after surgery significantly reduced moderate or severe dysmenorrhoea compared with surgery alone (dysmenorrhoea assessed on 0–100-mm VAS [0 = no pain, 100 = most severe pain]; AR for score greater than 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 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. [53]

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 not significant; American Fertility Society score on laparoscopy at end of treatment: 23.6 with danazol *v* 34.8 with triptorelin; P value reported as not significant). [50]

Aromatase inhibitors plus gonadorelin analogues versus gonadorelin analogues alone:
The second systematic review [39] (search date 2007) identified one RCT (97 women with severe endometriosis treated after conservative surgery) [63] comparing aromatase inhibitors plus gonadorelin analogues (anastrozole 1 mg plus goserelin) versus gonadorelin analogues alone (goserelin depot subcutaneous injections of 3.6 mg every 4 weeks) for 6 months. All the patients included in the RCT received elemental calcium (600 mg) and vitamin D (400 IU twice daily). The RCT included in the review found that aromatase inhibitors plus gonadorelin analogues reduced the proportion of women experiencing recurrence of pain at 24 months' follow-up compared with gonadorelin analogue alone (3/40 [8%] with combination treatment *v* 14/40 [35%] with gonadorelin alone; significance assessment not performed). The RCT found that combination treatment significantly increased median time to detect symptom recurrence compared with gonadorelin alone (greater than 2.4 months with combination treatment *v* 1.7 months with gonadorelin alone; RR 4.3, 95% CI 1.3 to 9.8; P = 0.0089). [39]

Hormonal treatment before and after surgery versus hormonal treatment after surgery:
See benefits of preoperative hormone treatment, p 10 .

Hormonal treatment before surgery versus hormonal treatment after surgery:
See benefits of preoperative hormone treatment, p 10 .

Harms:

See also harms of hormonal treatments at diagnosis, p 3 . The first systematic review did not perform meta-analyses of adverse effects. [37] Results from individual RCTs are summarised below.

Combined oral contraceptive versus placebo:
One RCT identified by the review [37] did not report on adverse effects. [56]

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). [52] One RCT identified by the first review [37] 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). [55]

One RCT identified by the first review [37] found that danazol increased hyperandrogenism and weight gain compared with expectant management (hyperandrogenism: 16.7% with danazol; weight gain at least 3 kg: 8.3% with danazol; no adverse effects reported for expectant management). [57]

Gonadorelin (gonadotrophin-releasing hormone) analogues versus placebo or expectant management:
Two RCTs identified by the first review [37] did not report on adverse effects. [61] [62] The additional RCT found that gonadorelin analogues significantly increased the risk of dyspareunia compared with placebo at 12 months (P less than 0.001). [54]

One RCT identified by the first review [37] found that most women on leuprolide acetate experienced menopausal symptoms and all became amenorrhoeic (numbers not reported). [59] A second RCT identified by the first review found that nafarelin increased amenorrhoea compared with placebo (36/36 [100%] with nafarelin *v* 0/39 [0%] with placebo; significance not reported). [58] A third RCT identified by the first review was reported only in abstract form, and it did not report on adverse effects. [60] The additional RCT gave no information on adverse effects. [51]

Medroxyprogesterone acetate versus placebo:
One RCT identified by the review [37] found that medroxyprogesterone acetate increased breakthrough bleeding compared with placebo (65% with medroxyprogesterone acetate *v* 6% with placebo; significance not reported). [55]

Cyproterone acetate versus combined oral contraceptive:
We found no 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. [53] 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). [50]

Aromatase inhibitors plus gonadorelin analogues versus gonadorelin analogues alone:
The RCT included in the second review found that aromatase inhibitors plus gonadorelin significantly increased bone loss compared with gonadorelin alone at 6 months (reported as significant; P value not reported; however, the RCT observed no difference between the two groups at 24 months' follow-up (reported as not significant; P value not reported). Severity of climacteric symptoms (assessed by the modified Greene scale and the Blatt–Kupperman Index) was similar with both treatments. [39] [63]

Hormonal treatment before and after surgery versus hormonal treatment after surgery:
See harms of preoperative hormone treatment, p 10 .

Hormonal treatment before surgery versus hormonal treatment after surgery:
See harms of preoperative hormone treatment, p 10 .

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
Hormone replacement compared with no treatment Hormone replacement therapy may be no more effective at preventing recurrence of endometriosis after oophorectomy (very low-quality evidence).

For GRADE evaluation of interventions for endometriosis, see table, p 25 .

Benefits: We found one systematic review (search date 2008, 1 RCT) assessing the effectiveness of hormone replacement therapy (HRT) after oophorectomy. [64] The RCT (172 women with previous bilateral salpingo-oophorectomy, 92% of whom had total abdominal hysterectomy) identified by the review compared HRT (115 women) versus no treatment (57 women). HRT consisted of sequential administration of oestrogens and progesterone with two 22 cm^2 patches applied weekly to produce a controlled release of 0.05 mg daily (length of treatment is unclear). Micronised progesterone was administered orally (200 mg/day) for 14 days with 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% with HRT *v* 2% with no HRT).

Harms: The RCT included in the review found that surgical re-interventions 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). [64]

Comment: The RCT included in the review had insufficient power to detect clinically important differences. [64]

QUESTION **What are the effects of treatments for ovarian endometrioma?**

OPTION **LAPAROSCOPIC CYSTECTOMY**

Recurrence of endometriosis
Laparoscopic cystectomy compared with laparoscopic ablation Laparoscopic excisional cystectomy is more effective at reducing recurrence of dysmenorrhoea 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 25 .

Benefits: **Laparoscopic cystectomy versus laparoscopic ablative surgery 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). [65] The systematic review found that excisional surgery significantly reduced the recurrence of dysmenorrhoea, dyspareunia, non-menstrual pelvic pain, and endometrioma compared with ablative surgery (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; 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). [65]

Harms: The systematic review of RCTs reported no intraoperative or postoperative complications in either group. [65]

Comment: None.

GLOSSARY

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.

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.

Severity of endometriosis: mild (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 to 15 points; American Fertility Society score of 16 to 40 points; American Fertility Society score of >40 points.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Aromatase inhibitors: New option for which we found two systematic reviews assessing the effects of aromatase inhibitors. [39] [18] The reviews identified no RCTs. Categorised as Unknown effectiveness.

Combined oral contraceptives at diagnosis: One systematic review [18] and two RCTs [19] [17] added. One RCT compared combined oral contraceptives versus placebo. [17] It found that oral contraceptives reduced dysmenorrhoea severity but not non-menstrual pain compared with placebo. [17] The review [18] and second RCT [19] compared combined oral contraceptive versus progestogens. They found similar reductions in dysmenorrhoea, non-menstrual pelvic pain, deep dyspareunia, and dyschezia from baseline in both groups, but did not assess the significance of the difference between groups. [18] [19] One updated systematic review identified no new evidence on the effects of combined oral contraceptives. [20] Categorisation unchanged (Beneficial).

Danazol, gestrinone, or gonadorelin analogues at diagnosis: One updated systematic review identified no new evidence on the effects of gonadorelin analogues given at diagnosis. [26] One RCT added comparing dienogest versus gonadorelin analogues. [35] The RCT found no differences between groups in lower abdominal pain, lumbago, defecation pain, dyspareunia, pain on internal examination, or quality-of-life measures. [35] Categorisation unchanged (Trade-off between benefit and harms).

Hormonal treatment after conservative surgery: One systematic review, [39] one additional RCT, [54] and one subsequent RCT added. [51] The review included one RCT comparing aromatase inhibitors plus gonadorelin analogue compared with gonadorelin analogue alone. It found that combination treatment reduced the rate of recurrence, and increased the median time to recurrence at 24 months in women with severe endometriosis post surgery compared with gonadorelin analogues alone. [39] The additional RCT compared continuous estroprogestin, placebo, triptorelin, or leuprorelin versus dietary treatment for 6 months. [54] The RCT found that continuous estroprogestin and triptorelin or leuprorelin significantly reduced the rate of dysmenorrhoea compared with placebo at 12-month follow-up. [54] The subsequent RCT compared monthly intramuscular triptorelin depot injections after surgery for 3 months versus expectant management with 60 months of follow-up. [51] The RCT found no difference between groups in pain recurrence, endometrioma recurrence or time to pain recurrence. [51] Categorisation unchanged (Likely to be beneficial).

Hormonal treatment after oophorectomy: One systematic review added. [64] The review identified no new evidence on the effects of hormonal treatment after oophorectomy. Categorisation unchanged (Unknown effectiveness).

Progestogens at diagnosis: One RCT added comparing dienogest versus gonadorelin analogues. [35] The RCT found no differences between groups in lower abdominal pain, lumbago, defecation pain, dyspareunia, pain on internal examination, or quality-of-life measures. [35] Categorisation unchanged (Beneficial for progestogens [other than dydrogesterone] compared with placebo).

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TABLE 1 **RCTs comparing hormonal treatment at diagnosis versus placebo.** [24] [25] [26]

Ref	Comparison	Number of RCTs	Population	Outcome	Results (95% CI)
[24]	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
[25]	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, 95% CI 0.29 to 2.21 7/10 (70%) with dydrogesterone 60 mg *v* 5/11 (45%) with placebo; RR 1.54, 95% CI 0.72 to 3.31
[25]	Medroxyprogesterone acetate 100 mg daily *v* placebo*	1	33 women with endometriosis diagnosed by laparoscopy, who had had no previous surgical or medical endometriosis treatment	Symptom severity at 6 months	WMD –5.20, 95% CI –6.80 to –3.60
[26]	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, 95% CI –7.51 to –3.89

Ref, reference. *This RCT was a 3-arm trial: medroxyprogesterone acetate, danazol, and placebo.

TABLE **GRADE evaluation of interventions for endometriosis**

Important outcomes	Symptoms of endometriosis (including chronic pelvic pain, dysmenorrhoea, non menstrual pelvic pain, dyspareunia and dyschezia, and other symptoms), recurrence, endometrial deposits, ease of surgery, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of hormonal treatments given at diagnosis of endometriosis?									
1 (100) [17]	Symptoms of endometriosis	Combined oral contraceptive *v* placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (130) [19] [18]	Symptoms of endometriosis	Combined oral contraceptive *v* progestogens	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for no comparisons between groups
3 (292) [23] [21] [22]	Symptoms of endometriosis	Combined oral contraceptives *v* gonadorelin analogues	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results
2 (98) [24]	Symptoms of endometriosis	Gonadorelin analogues *v* placebo	4	–2	0	0	0	Low	Quality point deducted for sparse data and incomplete reporting of results
1 (35) [26]	Symptoms of endometriosis	Danazol v placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data.
1 (269) [29]	Symptoms of endometriosis	Danazol *v* gestrinone	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
7 (535) [24] [28]	Symptoms of endometriosis	Danazol v gonadorelin analogues	4	0	0	0	0	High	
3 (426) [24]	Endometrial deposits	Danazol v gonadorelin analogues	4	0	0	0	0	High	
1 (55) [25]	Symptoms of endometriosis	Gestrinone *v* gonadorelin analogues	4	–1	–1	0	0	Low	Quality point deducted for sparse data. Consistency point deducted for conflicting results at different end points
1 (33) [25]	Symptoms of endometriosis	Medroxyprogesterone acetate *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (80) [25]	Symptoms of endometriosis	Medroxyprogesterone acetate *v* combined oral contraceptives 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 (48) [27]	Symptoms of endometriosis	Medroxyprogesterone acetate v gonadorelin analogues	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (271) [35]	Symptoms of endometriosis	Dienogest v gonadorelin analogues	4	0	0	0	0	High	
1 (82) [36]	Symptoms of endometriosis	Levonorgestrel-releasing intrauterine system *v* gonadorelin analogue	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (34) [25]	Symptoms of endometriosis	Medroxyprogesterone acetate v danazol	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (22) [25]	Symptoms of endometriosis	Dydrogesterone *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
What are the effects of hormonal treatments before surgery for endometriosis?									

Important outcomes	Symptoms of endometriosis (including chronic pelvic pain, dysmenorrhoea, non menstrual pelvic pain, dyspareunia and dyschezia, and other symptoms), recurrence, endometrial deposits, ease of surgery, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
1 (48) [38]	Symptoms of endometriosis	Hormone treatment before surgery *v* no hormonal treatment	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
2 (123) [38] [16]	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) [16]	Symptoms of endometriosis	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) [40]	Symptoms of endometriosis	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?									
1 (63) [42]	Symptoms of endometriosis	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) [45] [46]	Symptoms of endometriosis	Laparoscopic ablation plus LUNA *v* laparoscopic removal alone	4	0	0	0	0	High	
1 (39) [47]	Symptoms of endometriosis	Laparoscopic removal alone *v* diagnostic laparoscopy or no treatment	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (24) [48]	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) [49]	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) [45]	Symptoms of endometriosis	Laparoscopic removal plus presacral neurectomy *v* laparoscopic removal alone	4	0	0	0	0	High	
1 (67) [45]	Adverse effects (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?									
3 (332 at most) [37]	Symptoms of endometriosis	Hormonal treatment after surgery v surgery alone	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting
1 (222) [54]	Symptoms of endometriosis	Combined oral contraceptives *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting
1 (70) [56]	Recurrence	Combined oral contraceptives *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
3 (165) [52] [55] [57]	Symptoms of endometriosis	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

Important outcomes	Symptoms of endometriosis (including chronic pelvic pain, dysmenorrhoea, non menstrual pelvic pain, dyspareunia and dyschezia, and other symptoms), recurrence, endometrial deposits, ease of surgery, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
6 (at least 764) [61] [62] [58] [59] [60] [54]	Symptoms of endometriosis	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) [55]	Symptoms of endometriosis	Medroxyprogesterone acetates *v* placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (40) [53]	Symptoms of endometriosis	Levonorgestrel intrauterine system *v* no hormonal treatment	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (40) [50]	Symptoms of endometriosis	Danazol *v* gonadorelin analogue	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (60) [51]	Recurrence	Gonadorelin analogues *v* placebo/expectant management	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (97) [39]	Recurrence	Aromatase inhibitors plus gonadorelin analogues *v* gonadorelin analogues alone	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of result
What are the effects of hormonal treatment after oophorectomy (with or without hysterectomy) for endometriosis?									
1 (172) [66]	Recurrence	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?									
2 (164) [65]	Recurrence of endometriosis	Laparoscopic excision of cyst *v* laparoscopic 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.