The evidence for the management of endometriosis
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Authors' objectives
To summarise the effectiveness and safety of medical and surgical management of endometriosis.

Searching
The search strategy of the Cochrane Menstrual Disorders and Subfertility Group was used to identify trials on MEDLINE and EMBASE (years not stated). The database of the Cochrane Menstrual Disorders and Subfertility Group was also available to the authors. Thirty key journals were handsearched and the reference lists of other RCTs were also searched. Unpublished studies were identified from abstracts and conference proceedings, and from pharmaceutical companies.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) which compared an ovulatory suppressive agent in the treatment of endometriosis-associated pain with placebo; compared other ovulatory suppressive agents with danazol in the treatment of endometriosis-associated pain; compared surgery with medical therapy; compared surgery with no treatment.

Specific interventions included in the review
Medical: danazol, medroxyprogesterone acetate (MPA), gestrinone, combined oral contraceptive pills (including ethinyl oestradiol, cyproterone acetate), gonadotrophin-releasing hormone (GnRH) analogues and add-back therapy, pre and postoperative therapies. No specific dose ranges were specified. Medical therapies were compared with each other or with placebo.

Surgical: ablation by laser or thermal techniques, excisional techniques, presacral neurectomy (including laparoscopic uterine nerve ablation (LUNA)), ovarian cystectomy, adhesion barriers. Studies of assisted reproductive technologies were not included. Surgical techniques were compared with placebo (investigational surgery only) or conservative treatment.

Participants included in the review
Women with visually diagnosed endometriosis either by laparoscopy or laparotomy, in association with dysmenorrhoea, dyspareunia, other pelvic pain or infertility.

Outcomes assessed in the review
Improvement of pain, American Fertility Society (AFS) scores, recurrence of symptoms after stopping treatment, side-effects.

How were decisions on the relevance of primary studies made?
Studies were assessed for relevance by either author.

Assessment of study quality
The authors do not state that they assessed validity.

Data extraction
Data were extracted by one author for medical trials and the other author for surgical trials. Data were extracted on the following variables: intervention type, participant number, outcome measures and results.
Methods of synthesis
How were the studies combined?
Where possible data were entered into RevMan and a summary statistic (odds ratio) was calculated. When data were not suitable for combination as a meta-analysis only the odds ratio and the 95% confidence intervals for individual studies were presented.

How were differences between studies investigated?
The authors do not state how differences between the studies were investigated.

Results of the review
Placebo versus medical therapy: 7 RCTs (n=464).
Comparisons of medical treatments: 7 RCTs (n=541).
GnRH analogue versus danazol: 33 RCTs (n=3223).
Danazol versus danazol: 3 RCTs (n=97).
Add-back trials: 16 RCTs (n=1095).
Oral contraceptive pill trials: 2 RCTs (n=99).
Endometrioma treatment: 4 RCTs (n=315).
Preoperative medical treatment: 1 RCT (n=41).
Surgical trials: 6 RCTs (n=578).
Placebo versus medical therapy: in 4 trials (2 of GNRH, 1 of danazol and one of MPA) ORs vary from 0.001 to 0.4 for the symptom of having severe or moderate pain. In a trial of duphaston however the OR was 0.76 (95% CI: 0.18, 3.21).
In one trial, total or partial resolution of peritoneal implants was observed in 60% of patients receiving danazol (p<0.01) and 63% of patients receiving MPA (p<0.01), versus 18% in the placebo group.
In one trial medical treatment was associated with a lower recurrence of pain at 12 months.
GnRH analogue versus danazol: In 5 trials there was no difference between groups at the end of 6 months therapy in occurrence of moderate or severe pain. Eight studies showed no difference between groups for AFS scores at 6 months. Four studies showed no difference between groups for recurrence of symptoms at 12 months. In five trials people in the GnRH group were more likely to discontinue treatment (OR 0.32, 95% CI: 0.21, 0.49). Acne and weight gain occurred more frequently on danazol and hot flushes and vaginal dryness occurred more on GnRH.
Oral contraceptive pill versus GnRH analogues (1 trial): After 6 months dysmenorrhea was more effectively treated by the GnRH analogue than the contraceptive pill. Hot flushes and vaginal dryness were experienced more on GnRH analogue.
GnRH analogues versus GnRH analogues and ‘add back’ therapy (13 trials): Add back therapy led to a lesser reduction in spinal bone mineral density than GnRH alone initially but there was no difference at 6 months. A consistent reduction in the reported number of hot flushes was noted.
Postoperative medical therapy (3 trials): Danazol and provera were more effective than placebo in reducing pain and AFS scores at the end of treatment and 6 months later. Results on use of GnRH analogues were inconclusive.
Medical therapy (without surgery) for endometriotic cysts (4 trials): No difference between groups were noted except for GnRH analogue used for 3 months after surgical drainage which showed a 50% reduction in cyst diameter.
Laparoscopic ablation (1 trial): laser laparoscopy was compared with diagnostic laparoscopy. At 6 month follow-up 62.5% in the laser group were improved compared to 22.6% in the placebo group. Median decrease in pain score at 6 months was significantly greater in the laser group than the control group.

LUNA (1 trial): 0/10 people in the control group reported relief from dysmenorrhoea compared to 9/11 in the LUNA group at 3 months. At 1 year 5/11 in LUNA group still had relief from dysmenorrhoea.

Presacral neurectomy (2 trials): In one trial 4/4 patients in treatment group reported relief of central dysmenorrhoea at 6 months compared to 0/4 in control group. In another trial at 1 year after surgery 80% of patients in presacral neurectomy + conservative surgery group had successful pain relief compared to 75% in the conservative surgery only group.

Management of subfertility associated with endometriosis: Medical therapy (4 trials) showed no improvement versus placebo. Eight trials showed no difference between danazol and other medical therapy. Laparascopic surgery (2 trials) one trial showed improvement compared to diagnostic laparoscopy (p=0.006).

Authors’ conclusions
Currently available medical therapies are all equally effective in controlling dysmenorrhoea, dyspareunia and pelvic pain. Medical therapy has been shown to result in an improvement in AFS scores when compared with placebo and in recurrence rates. There is no difference in the effectiveness of the different therapies currently available for the relief of symptoms or recurrence rates or AFS scores. Side-effect profiles need to be taken into consideration when prescribing. The GnRH analogues have a better side-effect profile than danazol for weight gain and acne, whereas danazol has a better side-effect profile for hot flushes and bone mineral density. GnRH analogue is, however, better tolerated than danazol overall. The oral contraceptive pill is effective in managing many of the painful symptoms of endometriosis. 'Add back therapy' reduces the loss of bone mineral density and does not interfere with effectiveness. There is inadequate evidence of the effectiveness of preoperative medical therapy. Evidence for postoperative medical therapy is conflicting. Medical therapy is not effective in the long-term treatment of endometriotic cysts.

Surgical treatment has been shown to be effective in pain relief compared with expectant management and has shown an increased fecundity with minimal complications in the treatment of stages I and II endometriosis. Some of the best pregnancy rates and pain alleviation have been found in stages III to IV disease but these have never been tested by RCTs. The controls of national drug agencies such as the Food and Drug Administration have ensured that medical therapies have to be carefully scrutinised before they are approved and pharmaceutical companies have had to pay large amounts of money to researchers to pay for the necessary prospective trials. Because of the absence of such controls in surgical operations it is vital that surgeons exercise the same diligence before introducing new procedures for the treatment of endometriosis.

CRD commentary
The research question and inclusion criteria are clear and the literature search is comprehensive, not restricted to English language publications, and attempts to find unpublished literature. More details of included studies could have been given. Validity is not assessed and heterogeneity between studies is not formally assessed although the authors appropriately do not pool studies of different interventions. Reporting of the results is rather unclear as for some interventions the results of cohort studies (which do not appear in the list of included studies, or meet the inclusion criteria) are reported along with the results of RCTs. A more structured style would have been easier to interpret. The authors’ conclusions should be treated with caution given the above methodological limitations.

Implications of the review for practice and research
Practice: The authors state that presacral neurectomy should only be attempted by very skilled and highly trained laparoscopic surgeons who also have experience in conventional presacral neurectomy.

Research: The authors state that presacral neurectomy requires future assessment in the form of a randomised controlled trial. Further RCTs of pre- or post-operative treatment with GnRH analogues are needed to assess their value in women with endometriomas. The authors summarise with the statement that RCTs in the future should be directed to...
look for further effectiveness of the following interventions: oral contraceptive pill, medical therapy versus surgical
therapy, depo provera versus GnRH analogue, long term therapies, long term fertility protection, pre and post-operative
medical therapies, and the role of laparoscopic procedures such as LUNA, presacral neurectomy and excision of
peritoneal deposits.

Bibliographic details
Farquhar C, Sutton C. The evidence for the management of endometriosis. Current Opinion in Obstetrics and
Gynecology 1998; 10(4): 321-332

PubMedID
9719884

Indexing Status
Subject indexing assigned by NLM

MeSH
Endometriosis /drug therapy /surgery; Estrogen Antagonists; Female; Gonadotropin-Releasing Hormone /analog &
derivatives; Humans; Laparoscopy; Randomized Controlled Trials as Topic; Recurrence

AccessionNumber
11998001468

Date bibliographic record published
30/09/2000

Date abstract record published
30/09/2000

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract
contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on
the reliability of the review and the conclusions drawn.