Authors' objectives
To obtain estimates of the effectiveness of progestin treatment for pelvic pain associated with endometriosis.

Searching
MEDLINE was searched from 1966 to 1996 for studies published in the English language, using the MeSH terms 'endometriosis', 'pelvic pain', 'dysmenorhoea', 'dyspareunia', 'infertility' and 'medical therapy'. In addition, selected speciality journals and Current Contents (Clinical Medicine) were handsearched (January 1976 to June 1996 and January 1986 to June 1996, respectively). References from retrieved articles, and from books and monographs on endometriosis published in the previous 10 years, were examined for additional studies.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs), cohort and observational studies were included. Proceedings of scientific meetings were excluded. Studies were included if the results were presented as the proportion of treatment responders per nonresponder. Trials were excluded if it was not possible to categorise the outcome of interest, if it was not specified how many patients were symptomatic at baseline, if progestins were combined with surgery or use of other drugs, or if ‘ad interim’ results were reported in advance of a full report. The period of follow-up stated in four studies varied from 2 to 15 months.

Specific interventions included in the review
Treatments included were medroxyprogesterone acetate given orally or parenterally in a depot formulation (dose ranging from 10 to 50 mg/day over a duration ranging from 1.5 to 13.5 months); progestogen (norethynodrel 98.5%, desogestrel 0.15 mg/day, or cyproterone acetate 27 mg) combined with oestrogens in the form of oral contraceptive (ethinyl estradiol-3-methyl ether, 1.5% 0.035 to 40 mg/day) over a duration ranging from 6 to 13.5 months; dydrogesterone (dose of 10 to 60 mg/day for a range of 12 to 21 days per cycle for 6 or 9 months); lynestrenol (5 to 7.5 mg/day for 1.5 to 7 months); norethisterone (600 to 4,800 mg for a duration of 1.8 to 7 months); and megestrol acetate (40 mg/day for 2 months).

Participants included in the review
Women with pelvic pain associated with endometriosis were included.

Outcomes assessed in the review
The main outcome measure was response (absence or amelioration of pain) or nonresponse (persistence, worsening or recurrence of pain) to treatment. Also assessed were the effects on dysmenorrhoea or, when types of symptoms were not specified, the effect on any pelvic pain. When treatments caused a high frequency of amenorrhoea, the persistence of symptoms during therapy was assessed on the basis of pain not associated with menstruation. In addition, the frequency of side-effects and the pregnancy rate in women who want children were assessed.

How were decisions on the relevance of primary studies made?
Two authors screened articles on title and abstract, and excluded any that they agreed were irrelevant.

Assessment of study quality
The authors do not report the criteria used to assess validity, or how the validity assessment was performed.

Data extraction
Two authors extracted data unblinded onto standardised forms, with any discrepancies resolved by consensus. Only one
trial analysed data on an intention to treat basis, and patients excluded from the primary studies were not included in the
review's data analysis.

**Methods of synthesis**

How were the studies combined?
The studies were combined using odds ratios (ORs) with 95% confidence intervals (CIs) calculated by the Mantel-
Haenszel method.

How were differences between studies investigated?
Differences were assessed qualitatively and quantitatively using chi-squared statistics.

**Results of the review**

Fourteen studies (380 patients) were included: of these, 4 were RCTs (122 patients), 1 was quasi-experimental (23
patients) and 9 were noncomparative studies (235 patients).

The pooled frequency of nonresponders at the end of treatment was 9% (95% CI: 5.3, 13.6) for all noncomparative
studies. Combining the two doses of progestin in one RCT showed that dydrogesterone was no more effective than
placebo in reducing pelvic pain symptoms during treatment (OR 0.8, 95% CI: 0.2, 3.3) and after 1-year follow-up (OR
1.2, 95% CI: 0.2, 5.6). For the other 4 randomised trials of progestins versus either danazol, danazol and oral
contraceptive or goserelin, the treatment effects were equivalent (OR 1.1, 95% CI: 0.4, 3.1). The pooled frequency of
pelvic pain at the end of follow-up in 4 studies was 50% (95% CI: 37.8, 62.2). The conception rate after treatment in 8
studies ranged from 36 to 50%. Combined incidence of side-effects from progestin therapy showed that one-third of
patients experienced menstrual irregularities, whereas other adverse effects (weight gain, breast tenderness edema and
mood changes) were reported less frequently.

There appeared to be no significant statistical heterogeneity (Breslow-Day chi-squared=3.53, d.f.=3, P=0.32).

**Cost information**
The cost of a 6-month course of therapy in Italy is about $1,300 for gonadotropin-releasing hormone agonists (GnRH-a)
in depot formulations and $590 for danazol (600 mg daily).

**Authors' conclusions**
The methodological quality of studies, although not formally assessed in the review, was poor and raised doubts about
the potential for bias. In addition, studies were limited in terms of information about the condition of patients, stage of
disease and any previous treatments provided. These shortcomings, and the potential effects of publication bias, lead
the authors to question the suitability of the studies for meta-analysis. From the evidence available, the authors conclude
that progestins (with or without oestrogens) seem effective in most patients with symptomatic endometriosis, and show
no significant differences when compared with danazol and GnRH-a for temporary pain relief. In view of their
tolerable side-effects and limited cost, progestins could be considered as first-line medical treatment for long-term
therapy in women who do not want children.

**CRD commentary**
This is a well-conducted systematic review, providing sufficient information on the subject and methodology of the
review. The criticisms focus on the quality of the primary studies and the extent of the literature search. The authors
discuss the validity of the primary research, but there is no discussion of the validity criteria or methods of their
application. The literature search strategy was limited to published English language studies, which may have been the
cause of the limited amount of quality literature found. The authors' conclusions should be viewed with caution, as they
themselves suggest, being based on the results of observational studies and a limited number of experimental studies.
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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.