Efficacy of progesterone and progestogens in management of premenstrual syndrome: systematic review

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Authors' objectives
To assess the efficacy of progesterone and progestogens in the treatment of premenstrual syndrome.

Searching
MEDLINE (from 1966 to 2000), EMBASE (from 1988 to 2000), PsycINFO (from 1988 to 2000) and the Cochrane Controlled Trials Register were searched. The search terms were stated. In addition, the reference lists from relevant papers were examined and relevant pharmaceutical companies were contacted. Studies published in any language were eligible.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were included. Most of the included studies were crossover RCTs.

Specific interventions included in the review
Comparisons of progesterone or progestogens with placebo were eligible for inclusion. The included studies used progesterone suppositories or pessaries (200 to 800 mg), oral micronised progesterone (300 or 1,760 mg) and progestogens (15 mg medroxyprogesterone, 15 mg norethisterone and 20 mg dydrogesterone). The duration of treatment ranged from 2 to 6 months.

Participants included in the review
Women with a pre-treatment diagnosis of premenstrual syndrome were eligible for inclusion.

Outcomes assessed in the review
The inclusion criteria were not defined in terms of the outcomes. The primary outcome in the review was the change in the overall symptoms of premenstrual syndrome. Side-effects were also assessed.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
Study quality was assessed using the Jadad scale, which assesses randomisation, blinding, treatment of drop-outs and withdrawals. The authors also used their own quality scale which assessed study design, reproducibility and statistical analysis. At least one reviewer assessed validity.

Data extraction
Two reviewers independently extracted the data and resolved any disagreements through discussion with a third reviewer. The data extracted and tabulated included: study design, the number of participants, details of the intervention, outcome measures, results, withdrawals, side-effects, and funding source. The proportion of women who improved was also extracted. Where possible, the data were extracted on an intention-to-treat basis. Standardised mean differences were calculated for continuous data.

Methods of synthesis
How were the studies combined?
Studies of progesterone therapy and progestogen therapy were analysed separately. An overall standardised mean difference (SMD) and 95% confidence interval (CI) for the proportion of women who improved was calculated using a random-effects model, then converted to an odds ratio (OR). Publication bias was assessed using regression analysis.

How were differences between studies investigated?
Statistical homogeneity was assessed using the chi-squared test, taking a P-value of less than 0.05 to indicate significant heterogeneity. Results for progesterone were analysed separately according to the mode of administration (suppositories or pessaries, and oral).

Results of the review
Ten RCTs (531 women) of progesterone therapy and four RCTs (378 women) of progestogen therapy were included.

Progesterone.
Placebo was marginally more effective at reducing symptoms than progesterone suppositories or pessaries. The SMD (8 RCTs) was 0.04 (95% CI: 0.03, 0.05) and the OR was 0.93 (95% CI: 0.91, 0.95). Micronised progesterone significantly reduced symptoms compared with placebo. The SMD (3 RCTs) was -0.15 (95% CI: -0.17, -0.12) and the OR was 1.30 (95% CI: 1.25, 1.36). For all routes of administration combined, there was no clinically significant difference between progesterone and placebo, though progesterone was statistically significantly better than placebo. The SMD was -0.028 (95% CI: -0.040, -0.017) and the OR was 1.05 (95% CI: 1.03, 1.08). No significant heterogeneity was found (P=0.999).

Progestogen.
Progestogen significantly reduced symptoms compared with placebo. The SMD was -0.036 (95% CI: -0.059, -0.014) and the OR was 1.07 (95% CI: 1.03, 1.11). No significant heterogeneity was found (P=0.999).

There was no evidence of publication bias.

Side effects.
The most common side-effects reported for progesterone were an alteration in the length of menstrual cycle with progesterone suppository or pessary, and fatigue or sedation with oral micronised progesterone. There was no significant difference between progesterone and placebo or between progestogens and placebo in the proportion of withdrawals due to side-effects. The ORs were 1.66 (95% CI: 0.43, 6.79) and 1.65 (95% CI: 0.86, 3.21) in the progesterone and progestogen groups, respectively.

Authors' conclusions
There was no evidence from the review that progesterone or progestogens are more effective than placebo in treating premenstrual syndrome.

CRD commentary
The review question was clear in terms of the study design, intervention and participants. The participants were required to have a pre-trial diagnosis of premenstrual syndrome, but no criteria were stated as a requirement for this diagnosis. Several relevant databases were searched, the search terms were stated and no language limitations were applied. Two reviewers extracted the data and this reduced the potential for bias and errors. However, the methods used to select the studies were not described. Validity was assessed using defined criteria and some relevant information on the included studies was tabulated. It was not clear which of the many outcomes assessed in the individual studies were used to calculate the main outcome (proportion with improved symptoms) in the review. The studies were appropriately grouped by type of therapy and combined in a meta-analysis, and statistical heterogeneity was tested. The authors commented on the clinical significance of the results, but it was unclear whether this level had been determined a priori. The evidence presented tends to support the authors' conclusions.
Implications of the review for practice and research
Practice: The authors state that there is no evidence that progesterone or progestogens improve symptoms of premenstrual syndrome.

Research: The authors did not state any implications for further research.

Bibliographic details

PubMedID
11588078

Original Paper URL
http://bmj.bmjournals.com/cgi/content/full/323/7316/776

Indexing Status
Subject indexing assigned by NLM

MeSH
Female; Humans; Odds Ratio; Premenstrual Syndrome /drug therapy; Progesterone /therapeutic use; Progestins /therapeutic use; Randomized Controlled Trials as Topic; Treatment Outcome

AccessionNumber
12001008383

Date bibliographic record published
30/11/2003

Date abstract record published
30/11/2003

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.