The effectiveness of GnRHa with and without 'add-back' therapy in treating premenstrual syndrome: a meta analysis
Wyatt K M, Dimmock P W, Ismail K M, Jones P W, O'Brien P M

CRD summary
This review concluded that gonadotrophin-releasing hormone analogues, with and without hormonal add-back therapy, appear to be effective for the management of premenstrual syndrome. The authors' conclusions follow from the evidence presented, although they are based on a small number of participants and further research is required to confirm long-term safety.

Authors' objectives
To assess the effectiveness of gonadotrophin-releasing hormone analogues (GnRHa), with and without hormonal add-back therapy, for the management of premenstrual syndrome.

Searching
MEDLINE, EMBASE, PsycINFO, CINAHL, British Nursing Index and the Cochrane Controlled Trials Register were searched from inception to 2002, with no language restrictions; the search terms were provided. In addition, pharmaceutical companies were contacted and the reference lists of the included studies were checked.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) that were double-blind were eligible for inclusion.

Specific interventions included in the review
Studies comparing GnRHa with placebo were eligible for inclusion. The included studies were of GnRHa with or without hormonal add-back therapy. The GnRHa used were zoladex, leuprolide, buserelin and oestradiol, administered by monthly depot injection, daily intravenous injection and daily intranasal spray. The majority of the studies used a dosing regimen that suppressed ovulation. The length of treatment ranged from three to six cycles. The studies of add-back hormone therapy used different regimens.

Participants included in the review
Studies of participants with a diagnosis of premenstrual syndrome prior to treatment were eligible for inclusion. Details of how the included studies established a diagnosis were not reported. Data from one study that included women with a premenstrual exacerbation of a depressive disorder but did not meet American Psychiatric Association DSM-IV criteria for premenstrual dysphoric disorder were excluded.

Outcomes assessed in the review
Studies with sufficient extractable results were eligible for inclusion. The main outcome of interest was the overall symptoms of premenstrual syndrome. Physical and behavioural symptoms were investigated as secondary outcomes. Side-effects were also investigated. The outcome measures used in the included studies were premenstrual assessment calendar, premenstrual distress questionnaire, Penn Daily Symptom Report, Hamilton Depression Rating Scale, Premenstrual Tension Syndrome Scale, Target Symptom Scale, Clinical Global Impressions Scale, visual analogue scales and premenstrual syndrome symptom chart.

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

Assessment of study quality
Two methods were used to assess study validity. The studies were assessed for method of randomisation, blinding, and reports of drop-outs and withdrawals using the Jadad scale. Studies scoring three or more points on this scale were classified as high quality. Studies were also assessed for the following criteria: confirmation that the participants were not receiving psychiatric or hormonal medication or oral contraceptives during the trial; reporting of a power calculation to justify the sample size, or more than 65 participants in each arm; a single, clearly stated drug dose; use of a reproducible premenstrual symptom measurement; clear presentation of the results; a description of the number of withdrawals and reasons; the exclusion of women with a major psychiatric disorder, or a separate analysis of these participants; and whether the trial was supported by independent funding. One point was awarded for each criterion and the maximum score possible was eight. Two independent reviewers assessed the validity of the studies, and any disagreements were resolved by discussion with a third reviewer.

Data extraction
Two reviewers extracted the data in duplicate, and any disagreements were resolved by discussion with a third reviewer. Where individual premenstrual symptoms were reported in the primary studies, these were combined to give an overall symptom score. Intention-to-treat data were used where available. Authors were contacted for further details when sufficient information was not available in the paper. When the trials were of a crossover design, only the first arm was used. The standardised mean difference (SMD) and 95% confidence interval (CI) were calculated for the outcomes of interest for individual studies where data were continuous, otherwise the odds ratio (OR) was calculated. Where only medians and ranges were available, these were converted to means and standard deviations.

Methods of synthesis
How were the studies combined?
Studies of GnRHa alone and GnRHa plus add-back therapy were pooled separately using a random-effects model. The pooled SMD was converted to an OR. Publication bias was investigated by regression analysis of a funnel plot.

How were differences between studies investigated?
In addition to pooling studies of GnRHa therapy with and without add-back therapy separately, a subgroup analysis of studies that used a dose of GnRHa sufficient to cause anovulation was conducted. Separate analyses were conducted for the three outcomes: overall symptoms, physical symptoms and behavioural symptoms. Statistical heterogeneity was investigated using the chi-square test, with a P-value of less than 0.05 indicating significant heterogeneity.

Results of the review
Five RCTs (n=107) of GnRHa alone and 3 RCTs (n=66) of GnRHa plus add-back therapy were included.

Using a cut-off point of three points on the Jadad scale, all the studies were classified as high quality, though only one study achieved the maximum possible score. All of the studies scored six points on the second scale; none of the studies were classified as having sufficient power to detect a small effect and none were conducted independently of the pharmaceutical industry.

Overall premenstrual symptoms were reduced with GnRHa alone compared with placebo (pooled SMD -1.19, 95% CI: -1.88, -0.51). The equivalent OR was 8.66 (95% CI: 2.52, 30.26). GnRHa alone remained more effective than placebo when only studies that used a dose sufficient to cause anovulation were pooled (SMD -1.43, 95% CI: -2.11, -0.75). When physical and behavioural symptoms were considered separately, there was a reduction in both for GnRHa compared with placebo. There was no evidence of statistically significant heterogeneity for any of these analyses. There was no statistically significant difference between GnRHa and placebo for withdrawal rates due to side-effects (OR 1.95, 95% CI: 0.71, 3.63), although women receiving treatment were three times more likely to report side-effects than those receiving placebo.

When GnRHa with add-on hormonal therapy was compared with GnRHa with placebo, there was no statistically significant difference in the effectiveness of the treatments (SMD 0.12; 95% CI: -0.34, 0.59). There were conflicting data on side-effects. The authors stated that the results seemed to suggest that women were more likely to drop out while receiving add-on therapy (OR 1.60, 95% CI: 0.71, 3.63), though this was not statistically significant.
There was no evidence of publication bias based on a regression analysis of the funnel plot.

Authors' conclusions
GnRHa appeared to be an effective treatment in the management of premenstrual syndrome. The addition of hormonal add-back therapy did not reduce efficacy.

CRD commentary
The review addressed a clear research question using defined inclusion criteria. Several relevant databases were searched without any language restrictions and specific attempts were made to locate unpublished studies, thereby reducing the risk of language and publication bias. Apart from the study selection process, the review methodology was described and included measures to avoid the introduction of error and bias. The methodological quality of the primary studies was assessed and reported, though there was limited consideration of the results in the context of study quality. The statistical analysis seemed appropriate, though statistical heterogeneity did not appear to be investigated for the analysis of GnRHa plus add-back therapy and it was unclear to what extent the analyses were based on intention-to-treat data. The authors' conclusions appear to follow from the evidence presented. However, the conclusions are based on a fairly small number of participants and further research is required to confirm the long-term safety of GnRHa in combination with add-back therapy.

Implications of the review for practice and research
Practice: Until further data are available to establish the safety of using hormonal add-on therapy with GnRHa, this combination can be administered to provide a short-term break from the symptoms of premenstrual syndrome.

Research: Further research is required on the long-term safety of GnRHa combined with hormonal add-back therapy. Research is also required on the use of GnRHa with and without add-back therapy as a predictive test for individuals severely affected by premenstrual syndrome who may have to decide between ovarian conservation and ovarian removal if they are to undergo a hysterectomy.

Bibliographic details

PubMedID
15198787

DOI
10.1111/j.1471-0528.2004.00135.x

Indexing Status
Subject indexing assigned by NLM

MeSH
Female; Gonadotropin-Releasing Hormone /adverse effects /analsogs & derivatives /therapeutic use; Humans; Premenstrual Syndrome /drug therapy; Randomized Controlled Trials as Topic; Regression Analysis

AccessionNumber
12004009785

Date bibliographic record published
31/05/2006
Date abstract record published
31/05/2006

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.