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

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Abstract

Objective To evaluate the efficacy of progesterone and progestogens in the management of premenstrual syndrome.

Design Systematic review of published randomised, placebo controlled trials.

Studies reviewed 10 trials of progesterone therapy (531 women) and four trials of progestogen therapy (378 women).

Main outcome measures Proportion of women whose symptoms showed improvement with progesterone preparations (suppositories and oral micronised). Proportion of women whose symptoms showed improvement with progestogens. Secondary analysis of efficacy of progesterone and progestogens in managing physical and behavioural symptoms.

Results Overall standardised mean difference for all trials that assessed efficacy of progesterone (by both routes of administration) was -0.028 (95% confidence interval -0.017 to -0.040). The odds ratio was 1.05 (1.03 to 1.08) in favour of progesterone, indicating no clinically important difference between progesterone and placebo. For progestogens the overall standardised mean was -0.036 (-0.059 to -0.014), which corresponds to an odds ratio of 1.07

(1.03 to 1.11) showing a statistically, but not clinically, significant improvement for women taking progestogens.

Conclusion The evidence from these meta-analyses does not support the use of progesterone or progestogens in the management of premenstrual syndrome.

Introduction

Premenstrual syndrome is defined as the recurrence of psychological and physical symptoms in the luteal phase, which remit in the follicular phase of the menstrual cycle. It is estimated that up to 1.5 million women in the United Kingdom experience such severe symptoms that their quality of life and interpersonal relationships are greatly affected. Over 35% of these women will seek medical treatment.¹

The rationale for the use of progesterone and progestogens in the management of premenstrual syndrome is based on the unsubstantiated premise that progesterone deficiency is the cause.² There is no consistent evidence that low concentrations of progesterone are found in women with the premenstrual syndrome.^{3,4} However, as premenstrual syndrome

occurs in ovulatory cycles progesterone may be the underlying cause or at least the trigger for symptoms in susceptible women.⁵

Studies of prescribing patterns from the United Kingdom and the United States in the 1990s have shown that 60-70% of prescriptions for premenstrual syndrome are progesterone or progestogens based.^{6,7}

Progestogens are also prescribed for premenstrual syndrome on the basis of their "progesterone-like" action. Dydrogesterone, norethisterone, and levonogestrel have pharmaceutical licences in the United Kingdom, despite the apparent paradox of claimed effectiveness of treatment versus their ability to generate side effects similar to those seen in the premenstrual syndrome.⁵ The continued popularity in prescribing these treatments for premenstrual syndrome led us to undertake a detailed review of clinical trials of all types of progestogens and progesterone therapy in the management of premenstrual syndrome.

Methods

Trials

We searched Embase (1988-2000), Medline (1966-2000), PsychINFO (1988-2000), and the Cochrane controlled trial register for reports of published clinical trials of progesterone and progestogens in the management of premenstrual syndrome. MeSH terms used were premenstrual syndrome, progesterone, and progestogen, as well as the individual drug names, together with title and abstract searches for keywords progesterone, progestogen, premenstrual syndrome, premenstrual tension, late luteal phase dysphoric disorder, premenstrual dysphoria, and premenstrual dysphoric disorder. References cited in all trials were searched to identify missing studies. All languages were included. Pharmaceutical companies who manufacture progesterone preparations and progestogens were contacted. We included only those trials that included patients with a pretreatment diagnosis of premenstrual syndrome.

Data extraction and outcome measures

All the data were extracted independently in duplicate. Disagreements were resolved by discussion with a third investigator. We collected data on the dosage and preparation of treatment. The main outcome measure was a reduction in overall symptoms of premenstrual syndrome. When possible we quoted results using intention to treat.

Quality assessment

We assessed trial quality using a scale developed by Jadad et al,⁸ which assesses the randomisation, double blinding, reports of drop outs, and withdrawals for the trials, and our own quality scale, which assesses the quality of the trials for study design, reproducibility, and statistical analysis.

Statistical analysis

When continuous data were presented we calculated a standardised mean difference. This is equivalent to an effect size, which is a dimensionless quantity representing the difference between two means as a number of SDs; 0.3 represents a small effect, 0.5 a medium effect, and 1.0 a large effect.⁹ A negative effect size means a

reduction in symptoms. We calculated an overall standardised mean difference using random effects models. The overall standardised mean difference was converted to an odds ratio.¹⁰ Homogeneity was tested for with a χ^2 test, with $P < 0.05$ indicating significant heterogeneity. We used the method of Egger et al to detect bias.¹¹

Results

We identified 14 published trials that assessed the efficacy of progesterone in the management of premenstrual syndrome but excluded four from analysis. Ten trials remained, representing 531 women with data suitable for inclusion in the analyses.¹²⁻²¹ One trial compared both progesterone suppositories and oral micronised progesterone with placebo, and the data were analysed as two studies.¹² We identified 15 published trials that assessed progestogen in the management of premenstrual syndrome but excluded 12 from analysis. Of the three remaining trials²²⁻²⁴ one compared two different progestogens (each with their own placebo) and so this trial was treated as two separate studies.²² Table 1 gives details of the included trials for both treatments.

Progesterone—The overall standardised mean difference for a reduction in premenstrual syndrome symptoms with progesterone suppositories or

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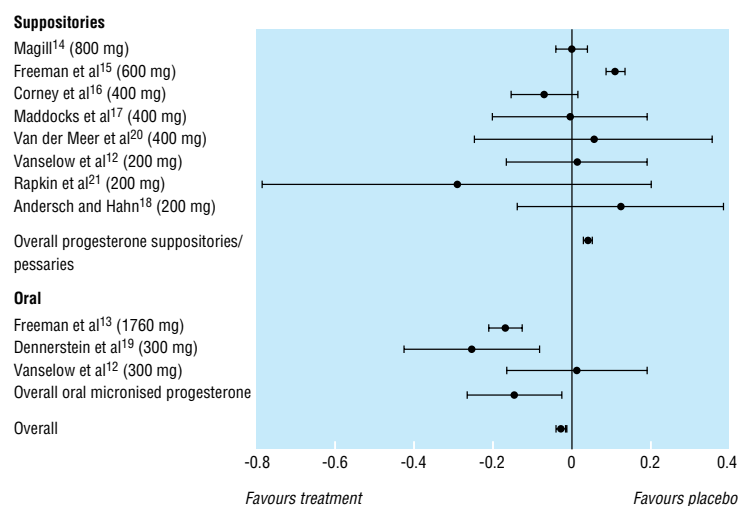


Fig 1 Standardised mean differences and 95% confidence intervals for proportion of patients who showed improvement in overall premenstrual syndrome (progesterone versus placebo). Negative values indicate reduction in symptoms, favouring active treatment

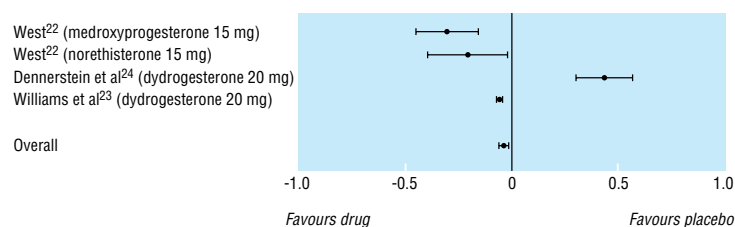


Fig 2 Standardised mean differences and 95% confidence intervals for proportion of patients who showed improvement in overall premenstrual syndrome (progestogen versus placebo). Negative values indicate reduction in symptoms, favouring active treatment

Table 1 Characteristics of studies included in meta-analysis of treatment of premenstrual syndrome

Study	Participants	Intervention	Outcome measures	Reported results	Withdrawals/side effects	Source of funding	Quality score (Jadad/own)	Comments
Progesterone								
Van der Meer et al, 1983 ²⁰	20 completed crossover	2x200 mg/day rectal suppositories for 4 months	4 point scale for: depression, irritability, fatigue, concentration, anxiety, aggression, headache, breast pain, abdominal pain, nausea, obstipation, oedema	No more effective than placebo	7 drop outs, no reported side effects	Not stated	3/7	
Dennerstein et al, 1985 ¹⁹	23 completed crossover	3x100 mg/day oral micronised progesterone for 4 months	Moos MDQ, BDI, SSAI, daily symptom record	Appreciable benefit over placebo	1 drop out, none due to side effects	Not stated	4/6	
Andersch and Hahn, 1985 ¹⁸	20 randomised 15 completed crossover	2x100 mg/day vaginal suppositories for 2 months	CPRS scale	No difference over placebo	5 drop outs, no reported side effects	Not stated	3/6	
Maddocks et al, 1986 ¹⁷	48 randomised 20 completed	2x200 mg/day luteal phase suppositories for 6 months	Moos MDQ, BDI, SSAI, PMS self rating scale	Not significantly different from placebo	28 drop outs, 2 due to side effects, 1 placebo, 1 progesterone	Not stated	3/7	
Rapkin et al, 1987 ²¹	8 randomised 8 completed crossover	200 mg/day luteal phase suppositories for 6 months	Daily diary scores for psychological, behavioural, and somatic symptoms, POMS	Not significantly different from placebo	No drop outs, no reported side effects	Not stated	5/6	
Corney et al, 1990 ¹⁶	47 randomised 19 completed	2x200 mg/day continuous suppositories for 6 months	PMS self rating scale, GHQ, social problem questionnaire	Not significantly different from placebo	28 drop outs due to side effects (individual numbers not presented)	Independent	3/6	Trial compared progesterone, placebo and behavioural therapy. Neither treatment better than placebo
Freeman et al, 1990 ¹⁵	187 randomised 121 completed crossover	400 mg/day cycle 1, 800 mg/d cycle 2 luteal phase suppositories	DSR, clinical global rating, HAM-D, Hopkins symptom checklist, PAF	Not significantly different from placebo	8 drop outs due to side effects (individual numbers not given)	Independent (pharmaceutical company provided progesterone)	4/8	
Magill, 1995 ¹⁴	141 randomised 93 completed	2x400 mg/day luteal phase suppositories for 4 months	150 symptom checklist	Not significantly different from placebo when results analysed as intention to treat	4 drop outs due to side effects (2 in each arm)	Trial funded by pharmaceutical company	4/7	
Freeman et al, 1995 ¹³	106 randomised 93 completed	4x300 mg/day luteal phase up to 12x300 mg/d flexible dosing oral micronised	Daily symptom report, clinical and patient global rating, symptom severity	Oral micronised progesterone no better than placebo	Individual drop out numbers not presented: reasons and numbers for drop outs did not differ between treatment arms	Independent (pharmaceutical company provided progesterone)	3/7	Alprazolam was another treatment arm. Alprazolam was significantly better than progesterone and placebo
Vanselow et al, 1996 ¹²	39 randomised 25 completed crossover	3x100 mg/day luteal phase oral progesterone 2x100 mg/day luteal phase progesterone pessary 3x2 months	Menstrual distress questionnaire, BDI, state anxiety and anger scales	No difference between either active treatment and placebo	4 drop outs due to side effects (1 placebo; 3 progesterone pessary; 0 oral progesterone)	Funded by Laboratoires Besins-Iscovesco, France	4/7	
Progestogen								
West, 1990 ²² (medroxyprogesterone)	19 completed crossover	3x5 mg/day medroxyprogesterone 21 days of each cycle for 3 cycles	VAS for 7 symptoms	Significant improvement in psychological and breast symptoms	8 drop outs, 3 due to side effects	Independent	3/6	Breakthrough bleeding occurred in 74% of the cycles treated with medroxyprogesterone
West, 1990 ²² (norethisterone)	16 completed crossover	3x5 mg/day norethisterone for 21 days of cycle for 3 cycles	VAS for 7 symptoms	Significant improvement for breast symptoms only	5 drop outs, 3 due to side effects	Independent	3/6	
Dennerstein, 1986 ²⁴	24 completed crossover	2x10 mg/day dydrogesterone on day 12-26 of cycle for 4 cycles	MDQ, mood adjective checklist, DSR, BDI, SSAI	No more effective than placebo	6 drop outs, 3 due to side effects	Independent	3/7	
Williams, 1983 ²³	260 completed parallel	2x10 mg/day dydrogesterone on day 12 to menses for 3 cycles	Daily symptom diary	No significant difference	40 drop outs due to side effects		4/6	

Moos MDQ=Moos menstrual distress questionnaire; BDI=Beck depression inventory; CPRS=clinical psychiatric rating scale; POMS=profile of mood states; GHQ=general health questionnaire; DSR=daily symptom record; SSAI=Spiegelberger state anxiety inventory; VAS=visual analogue scale; HAM-D=Hamilton rating scale for depression; PAF=premenstrual assessment form.

pessaries was 0.04 (95% confidence interval 0.03 to 0.05) and hence was marginally in favour of placebo. This difference corresponds to an odds ratio of 0.93 (0.91 to 0.95). The figures for oral micronised progesterone were -0.15 (-0.17 to -0.12), marginally in favour of oral micronised progesterone,

corresponding to an odds ratio of 1.30 (1.25 to 1.36), showing a slight improvement for women taking oral micronised progesterone. When we combined all the trials of progesterone (by both routes of administration) the overall result showed no clinically significant difference between progesterone and placebo,

although the result was statistically significant (-0.028 , -0.040 to -0.017 ; corresponding odds ratio 1.05, 1.03 to 1.08) in favour of progesterone. The pooled trials were statistically homogeneous ($P=0.999$) (figure 1).

Progestogens—The overall standardised mean difference for reduction in symptoms showed a slight difference between progestogens and placebo in favour of progestogens (-0.036 , -0.059 to -0.014), the corresponding odds ratio being 1.07 (1.03 to 1.11). The pooled trials were statistically homogeneous ($P=0.999$). Figure 2 shows the individual standardised mean difference for each trial, the type of progestogen used in the trial, and the pooled standardised mean difference with 95% confidence intervals.

Bias—Regression analysis of the plots indicated no evidence of bias (intercept = 2.97, -3.88 to 9.82, $P=0.45$, for progesterone and intercept = 0.80, -9.79 to 11.4, $P=0.85$, for progestogens).

Side effects—We extracted data on side effects (when reported) from the included trials (table 2). The data in the trials were incomplete; five of the trials of progesterone did not give a detailed breakdown of side effects or the number of participants who suffered from them. The most commonly reported side effect for progesterone administered as a suppository or pessary was an increase or decrease in the length of the menstrual cycle; the most commonly reported side effect for oral micronised progesterone was fatigue or sedation. There was an increased but not significant risk of drop out due to side effects in the progesterone group (odds ratio 1.66, 0.43 to 6.79). None of the included trials gave a detailed breakdown of side effects for progestogens. We noted withdrawals from trials due to side effects, comparing placebo with progestogens. This showed a non-significant higher dropout rate in the treatment group due to side effects (1.65, 0.86 to 3.21).

Discussion

This systematic review shows that there is no published evidence to support the use of either progesterone or progestogens in the management of the premenstrual syndrome.

The premenstrual syndrome has been considered to be an endocrine disorder as symptoms are eliminated during pregnancy and are absent during non-ovulatory cycles and after the menopause.²⁵ No research, however, has convincingly shown a progesterone deficiency in women with premenstrual syndrome.⁴

Many therapeutic interventions have been claimed to be effective due to a high placebo effect and the large number of poorly controlled trials in women without a pretrial diagnosis of premenstrual syndrome. It is because of these factors that one of the stated inclusion criteria for this review was a diagnosis of premenstrual syndrome before randomisation. There are no published trials of topical progesterone cream, which has been popularised through the media and the internet.²⁶ Of the eight trials of progesterone suppositories, all but one showed a negative result. The only study that claimed to show a positive result was the study by Magill.¹⁴ When we examined the data on

Table 2 Side effects reported in included studies of progesterone according to method of administration

Side effect	Suppository/pessary		Oral micronised	
	Drug	Placebo	Drug	Placebo
Cycle length changes	40	42	5	5
Breast swelling/bloating	28	20	5	8
Change in blood loss	24	28		
Nausea	19	14	2	1
Vaginal pruritus	19	13		
Cramps	13	15	4	2
Headache	12	5	9	0
Flu-like symptoms	7	3		
Pregnancy	6	0	1	0
Dysmenorrhoea	5	5		
Depression	3	8	3	0
Dizziness/lightheadedness	3	4	24	6
Rectal pain	3	3		
Anxiety	2	5		
Acne	2	3	3	4
Fatigue/sedation	2	2	46	23
Insomnia	2	0	2	4
Hot flushes	1	4	0	1
Confusion/memory problems	1	3	17	1
Body hair growth	1	2		
Decreased libido	1	1	0	1
Night terrors			1	1
Increased appetite			1	1
Altered taste			1	1
Dry skin			1	1
ringing in ears			1	0
Totals	194	180	126	60

an intention to treat basis, however, we could not show a beneficial effect.

We found a small positive effect of progesterone over placebo in the three trials that assessed oral micronised progesterone. This may be due to the ability of this treatment to increase concentrations of allopregnanolone and pregnanolone (metabolites of progesterone), which have a positive effect on the central nervous system similar to that of GABA (γ -aminobutyric acid). Progesterone administered as a suppository or pessary does not increase concentrations of these metabolites.^{15 27} This standardised mean difference (-0.147) could be compared with that for selective serotonin reuptake inhibitors (SSRIs), which was -1.066 in favour of treatment. These standardised mean differences correspond to an odds ratio of 1.3 and 6.91, respectively.²⁸ It should also be noted that oral micronised progesterone is not available in the United Kingdom.

The published evidence for progestogen treatment is not of high quality. Of the 15 published trials, only three trials met quality criteria, representing 378 women in total. A sensitivity analysis on the three trials (266 women) that were excluded because of lack of a prospective diagnosis slightly improved the standardised mean difference (-0.182 , -0.044 to 0.320) but it did not make it clinically significant. Poorly controlled, low quality trials often have positive results, often due to an imprecise definition of premenstrual syndrome in the study population and a subsequent uncertainty as to what condition is being treated.

Of the four included studies, two used dydrogesterone, one used norethisterone, and one used medroxyprogesterone. Low numbers of participants and trials

What is already known on this topic

The premenstrual syndrome affects about 1.5 million women in the United Kingdom

There are numerous treatment options, progesterone being one of the most strongly advocated

Progesterone and progestogens are among the most widely prescribed treatments for premenstrual syndrome in the United Kingdom and the United States

What this study adds

There is no evidence to support the claimed efficacy of progesterone in the management of premenstrual syndrome

There is insufficient evidence to make a definitive statement about progestogens, but current evidence suggests that they are not likely to be effective

meant that a comparative analysis of individual progestogens could not be undertaken.

While the role of endogenous progesterone and its metabolites in the aetiology of premenstrual syndrome remains unclear, it is evident from this meta-analysis that exogenous administration of either progestogens or progesterone does not improve symptoms. This is not surprising as there are reliable data to refute the theory that premenstrual syndrome is caused by a progesterone deficiency. With this review, there is now no convincing evidence to support the continued prescription of progesterone or progestogens for the management of premenstrual syndrome.

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Competing interests: SO'B has been reimbursed for lectures and conferences by Hoechst Marion Roussel, Shire Pharmaceuticals, SmithKline Beecham, Eli Lilly, Searle, Sanofi Winthrop, Zeneca, Galen Laboratories, Solvay Pharmaceuticals, and Novo Nordisk. He has also received funds for research staff from Searle, SmithKline Beecham, Eli Lilly, and Sanofi Winthrop. He is married to a member of the research department of Zeneca Pharmaceuticals.

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Corrections and clarifications

Tobacco litigation worldwide

A reader queried the absence of a competing interests statement in this Education and Debate article by R A Daynard, C Bates, and N Francey (2000;320:111-3). Professor Daynard would like to declare that he has been involved as counsel in suing tobacco companies and has received grants for research into the use of litigation to control tobacco use.

Joint British recommendations on prevention of coronary heart disease in clinical practice: summary

The authors would like to clarify one point in these summary recommendations from the British Cardiac Society, the British Hyperlipidaemia Association, the British Hypertension Society, and the British Diabetic Association (2000;320:705-8). In the guidance on "Using the coronary risk prediction chart for primary prevention" the first sentence states that the charts are for estimating the risk of coronary heart disease and defines that as "non-fatal myocardial infarction and death from coronary heart disease." In fact the end points should have been described as "non-fatal myocardial infarction, coronary death, and new angina pectoris." The *British National Formulary* will include the correct definitions of the end points from March 2002. The recommendations of the joint British Societies and of the NHS Framework are unaffected, and the end point for coronary heart disease including new angina pectoris is the same as for all Framingham based methods of coronary risk prediction.