Papers

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 (−0.014 to −0.060), 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] Although initial data suggest there to be abnormal concentrations of metabolites of progesterone (pregnanolone and allopregnanolone),[3] there is no consistent evidence that low concentrations of progesterone are found in women with the premenstrual syndrome. Indeed, published studies have shown progesterone to be the same in women with and without premenstrual syndrome.[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. Women taking hormone replacement therapy experience typical symptoms seen in premenstrual syndrome (progestogen induced premenstrual syndrome).[5]

In 1989 the National Association of Premenstrual Syndrome sent a questionnaire to general practitioners and found that over half prescribed progesterone pessaries or suppositories and over 60% prescribed progestogens[6] for women with premenstrual syndrome. In the United States and Canada an earlier study found that 70% of prescriptions for premenstrual syndrome were for progesterone suppositories or pessaries.[7] From 1993 to 1998 progestogens and progesterone remained the most widely prescribed treatments for premenstrual syndrome in the United Kingdom (unpublished data).

In the United Kingdom, the only licensed preparation of progesterone is Cyclogest, administered as a suppository or pessary. Oral micronised progesterone has been available for some time in Europe and the United States but not in the United Kingdom. Crinone, a vaginal progesterone gel, does not have a UK pharmaceutical licence, but it is listed for treatment of premenstrual syndrome in the *Monthly Index of Medical Specialties* (*MIMS*). Topical, "natural" progesterone cream has, without evidence, been extensively marketed through the internet and lay media as a reputedly effective treatment for premenstrual syndrome.[8]

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] This, together with the seeming lack of evidence from clinical trials for the efficacy of progesterone or progestogens, the known failure of

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transdermal preparations of progesterone to achieve measurable increase in blood concentrations of progesterone,[9 10] and 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 medical databases 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 (PMT), late luteal phase dysphoric disorder (LLPDD), premenstrual dysphoria (PMD), and premenstrual dysphoric disorder (PMDD). We searched Embase (1988-2000), Medline (1966-2000), PsychINFO (1988-2000), and the Cochrane controlled trial register. References cited in all trials were searched iteratively to identify missing studies. All languages were included. Pharmaceutical companies who manufacture progesterone preparations (oral micronised, intramuscular, vaginal gel, topical cream, or suppositories) and progestogens were contacted. We included trials that investigated the effect of progesterone or progestogens on premenstrual symptoms if they were randomised, placebo controlled, double blind studies that included patients with a pretreatment diagnosis of premenstrual syndrome, for which all data from the trials could be acquired.

Data extraction and outcome measures

All the data were extracted independently in duplicate by two investigators (PWD, KMW) by means of a standardised protocol and data collection form. Disagreements were resolved by discussion with a third investigator (SO'B). When there were insufficient data presented for inclusion, we contacted authors for further details. We collected data on the dosage and preparation of treatment. The main outcome measure was a reduction in overall symptoms of premenstrual syndrome. Combined or overall symptoms was chosen in an attempt to overcome the clinical heterogeneity associated with the measurement and scoring of symptoms used in individual trials. When possible we quoted results using intention to treat, as such results represent an accurate means of determining the efficacy of a drug. We undertook separate analyses of micronised oral progesterone and progesterone pessaries or suppositories versus placebo. We carried out a secondary analysis of the treatment of behavioural and physical symptoms. Withdrawals from treatment and side effects were recorded.

Quality assessment

We assessed trial quality using a scale developed by Jadad et al,[11] 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. This eight point scale comprised the following: confirmation that no other medications or oral contraceptives were being taken; a power calculation to justify patient numbers or more than 65 participants in each arm (enabling detection of a small effect size of 0.3, see below); a single, clearly stated dose of drug; reproducible measurement of premenstrual symptoms; clear presentation of results; a description of the number and reason for trial withdrawals; exclusion of, or a separate analysis of, participants with a major psychiatric disorder; and whether or not the trial was supported by independent funding. We awarded one point for each category present in the trial. Each trial was independently scored by two investigators and the third investigator arbitrated on any disagreements. We used predetermined criteria for the recognition of the highest quality trials. A score of 3 or more was required in the Jadad score for the trial to be designated "high quality" and included in the meta-analysis[11]; a score of less than 3 meant that the trial was designated "low quality." We have given results for our quality score, but we did not use it as a criterion for inclusion because the score has not been validated.

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. The magnitude of an effect size has been described by Cohen[12]; 0.3 represents a small effect, 0.5 a medium effect, and 1.0 a large effect. A negative effect size means a reduction in symptoms. When medians and ranges were presented the values were converted to means (SD).[13] When comparisons were made between pooled standardised mean differences for different subanalyses, we assessed statistical differences using a z test; $P < 0.05$ was considered significant. We calculated an overall standardised mean difference using both fixed and random effects models. The overall standardised mean difference was converted to an odds ratio with the association described by Hassleblad and Hedges.[14] Homogeneity was tested for with a χ^2 test, with $P < 0.05$ indicating significant heterogeneity.

We used the method of Egger et al[15] to detect bias (such as publication and location bias) in the included trials with a funnel plot. We assessed the asymmetry of the funnel plot quantitatively by plotting a linear regression of the standard normal deviate (standardised mean difference divided by SE) against precision (inverse of SE). A regression line that passes through the origin of the plot (within error limits) indicates symmetry and hence the absence of bias.

Results

We identified 14 published trials that assessed the efficacy of progesterone in the management of premenstrual syndrome.[16–29] We excluded four: two because of their low quality score on the Jadad scale,[26 27] one because the data could not be extracted,[29] and one because the trial failed to make a prospective diagnosis of premenstrual syndrome before randomisation.[24] Ten trials remained, representing 531 women with data suitable for inclusion in the analyses. One trial compared both progesterone suppositories and oral

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[25]	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[23]	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[22]	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[21]	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[28]	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[20]	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[19]	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[18]	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[17]	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[16]	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 Laboritoires Besins-Iscovesco, France	4/7	
Progestogen								
West, 1990[30] (medroxy-progesterone)	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[30] (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[32]	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[31]	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=Spielberger state anxiety inventory; VAS=visual analogue scale; HAM-D=Hamilton rating scale for depression; PAF=premenstrual assessment form.

micronised progesterone with placebo, and the data were analysed as two studies.[16]

We identified 15 published trials that assessed progestogen in the management of premenstrual syndrome.[30–44] We excluded 12: three were open studies,[41–43] four did not include a prospective diagnosis of premenstrual syndrome,[34 36–38] three were preliminary reports of included trials,[35 40 44] and in two data

Table 2 Characteristics of studies excluded from meta-analysis of treatment of premenstrual syndrome

Study	Participants	Intervention progesterone	Reason for exclusion	Reported results	Side effects	Comments
Richter et al, 1984[24]	40 women referred from general practice	400 mg/day progesterone suppository luteal phase	No prediagnosis of PMS; women recruited with self diagnosis	More women believed that progesterone gave symptom relief than placebo	No withdrawals due to side effects	No difference in improvement seen between treatment groups
Smith et al, 1975[29]	14 randomised	50 mg intramuscular progesterone every other day in luteal phase	Insufficient published results for data analysis	3 women felt better on progesterone, 3 women felt better during progesterone free months; 8 women found no difference	No withdrawal, side effects not mentioned	Trial was a crossover of 4 treatment regimens: progesterone; progesterone plus spironolactone; spironolactone; placebo injections and tablets
Sampson, 1979[27]	32 randomised, 24 completed crossover	2x200 mg/day, 2x400 mg/day suppositories luteal phase for 2 months	Low Jadad score	No significant difference from placebo	400 mg: 7 drop outs; 800 mg: 9 drop outs; none due to side effects	
Baker et al, 1995[26]	17 completed multiple crossover	2x200 mg/day vaginal suppositories luteal phase for 7 months	Low Jadad score	No overall difference from placebo; significant improvement for tension, mood swings irritability, control	None reported	Trial assessed only psychological symptoms
Coppen, 1969[33]	17 completed parallel trial	2x7.5 mg/day norethisterone on day 16-25 of cycle	Data presented not suitable for extraction	Not effective in improving premenstrual symptoms	None reported	Norethisterone was also compared with diuretic, Dytide
Hoffmann, 1988[34]	161 completed parallel trial	2x10 mg/day dydrogesterone on day 12-menses for 3 cycles	No prospective diagnosis of PMS	No clinically relevant effect	38 drop outs, 3 due to side effects	
Haspels, 1980[35]	123 completed parallel trial	2x10 mg/day dydrogesterone on day 12-menses for 4 cycles	Subgroup of patients from included study[15]	Significantly better than placebo for psychological symptoms and clinically better for somatic symptoms	27 drop outs, none due to side effects	British arm of European study
Jordheim, 1972[36]	35 completed parallel trial	3x2.5 mg medroxyprogesterone 10 days before menstruation	No placebo arm, no prospective diagnosis of PMS	No significant effect	None stated	Medroxyprogesterone compared with medroxyprogesterone plus diuretic
Kerr, 1980[37]	67 completed	2x10 mg/day dydrogesterone on day 12-menses for 4 cycles	No preliminary diagnosis; single blind trial	Unclear: "dydrogesterone is a useful agent"	36 drop outs, 3 due to side effects	Trial funded by pharmaceutical company
Hellberg, 1991[38]	38 completed crossover	5 mg/day medroxyprogesterone acetate for 3 cycles	No prospective diagnosis of PMS	Significantly better than placebo	5 drop outs, none due to side effects	2 interventions compared with placebo; spironolactone (50mg/day) also better than placebo
Sampson, 1988[39]	69 completed crossover	2x10 mg/day dydrogesterone for 14 days of cycle for 4 cycles	Data presented not suitable for extraction	Significant decrease in pain with menstrual bleeding and breast symptoms only	39 drop outs, 5 due to side effects	
Sampson, 1982[40]			Same patient group as above			
Taylor, 1977[42]	50 completed	2x10 mg/day dydrogesterone on day 12-26 of cycle for 2 or more cycles	Open trial; no prospective diagnosis	Measureable improvement in 70% of patients	None	
Strecker, 1981[43]	31 completed	20 mg/day dydrogesterone on day 15-25 of cycle	Open trial; no prospective diagnosis	Beneficial for relief of some symptoms	No side effects reported	
Strecker, 1980[44]			Same patient group as above			
Morse, 1991[41]	14 completed	20 mg/day dydrogesterone on day 17-27 for 3 cycles	Open trial	Some short term symptom relief	No drop outs due to side effects	Dydrogesterone *v* cognitive therapy and relaxation therapy

could not be extracted.[33 39] Of the three remaining trials one compared two different progestogens (each with their own placebo) and so this trial was treated as two separate studies.[30]

Table 1 gives details of the included trials for both treatments, and table 2 lists the excluded trials and their reason for exclusion.

Quality assessment of trials

All the included trials of progesterone and progestogens scored ⩾3 on the Jadad scale. On our quality score four of the 10 progesterone trials[20 22 23 28] and two of the three progestogen trials[30 31] scored 6, five progesterone trials[16–18 21 25] and the other progestogen trial[32] scored 7, and one trial of progesterone scored the maximum of 8.[9]

Data extraction

All the included trials for either treatment presented continuous data and so an overall standardised mean difference was calculated with both fixed and random effects models. Because we found only minimal differences between the fixed and random effects models we used the more conservative random effects model.

Progesterone

The overall standardised mean difference for a reduction in premenstrual syndrome symptoms with progesterone suppositories or 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, −0.017 to −0.0408; 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 shows the individual standardised mean difference for each trial, the type of preparation and dosage for that trial, and the pooled standardised mean difference with 95% confidence intervals for trials that used progesterone suppositories and those that used oral micronised progesterone. The inclusion of the data from the two low quality trials[25 26] did not significantly affect the overall result.

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

We investigated bias using a funnel plot.[15] Regression analysis of the plots indicated no significant asymmetry (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) and thus no evidence of bias.[15]

Subanalyses

We carried out a subanalysis of the effectiveness of the treatments in managing either physical or behavioural symptoms. Figure 3 shows the overall standardised mean difference for behavioural and physical symptoms from eight of the trials of progesterone, which represented 371 women. The overall standardised mean difference was 0.011 (−0.003 to 0.024) for behavioural symptoms and −0.088 (−0.061 to −0.115) for physical symptoms. There was no significant variation in the overall standardised mean differences (P = 0.357). This was also true when the treatments were further divided into progesterone suppositories and oral micronised progesterone.

Figure 4 shows the individual standardised mean difference for the progestogen trials that reported behavioural and physical symptoms separately. The overall standardised mean difference was −0.06 (−0.04 to −0.07) for behavioural symptoms compared with −0.16 (−0.13 to −0.19) for physical symptoms. Progestogens seem to be more effective in alleviating physical symptoms than behavioural symptoms (P < 0.0001), although the magnitude of the effect size for physical symptoms is not considered to be clinically significant.

Side effects

We extracted data on side effects (when reported) from the included trials (table 3). The data in the trials were incomplete; five of the trials 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. We analysed withdrawals from progesterone trials due to side effects, comparing placebo with treatment. This

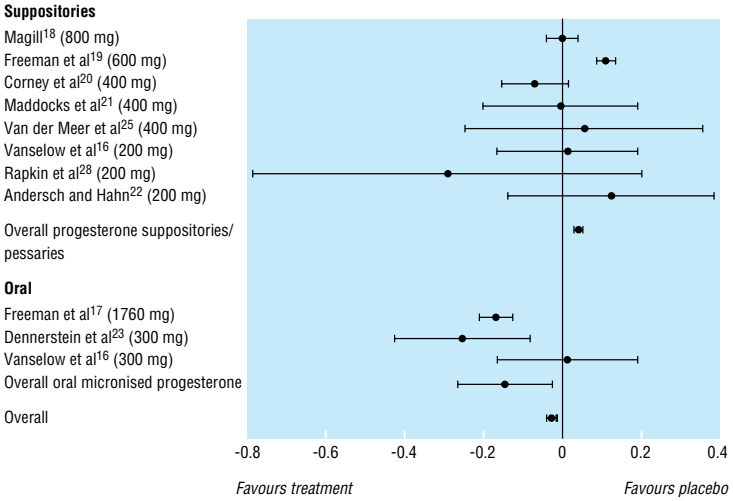

Fig 1 Standardised mean differences and 95% confidence intervals for proportion of patients who showed improvement in overall premenstrual syndrome (progesterone versus placebo). Negative values indicate reduction in symptoms, favouring active treatment

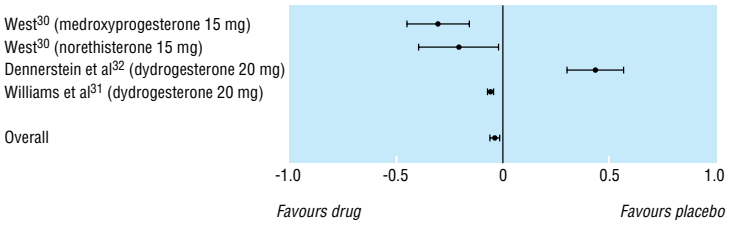

Fig 2 Standardised mean differences and 95% confidence intervals for proportion of patients who showed improvement in overall premenstrual syndrome (progestogen versus placebo). Negative values indicate reduction in symptoms, favouring active treatment

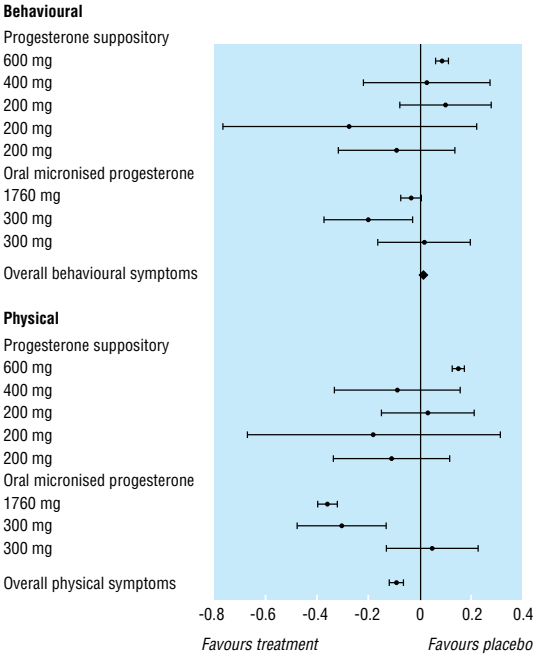

Fig 3 Standardised mean differences and 95% confidence intervals for proportion of patients who showed improvement in behavioural and physical symptoms (progesterone versus placebo)

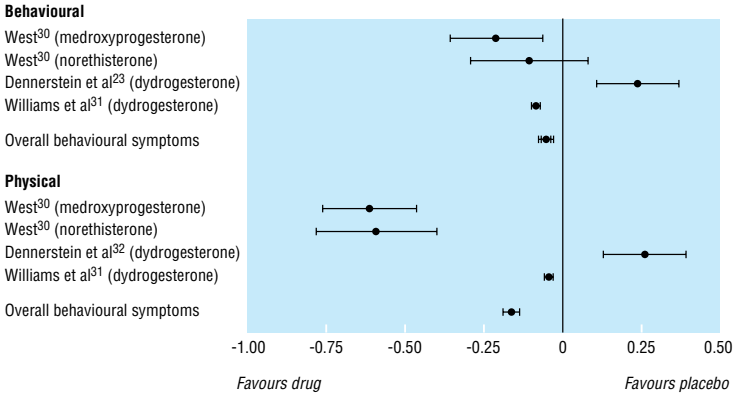

Fig 4 Standardised mean differences and 95% confidence intervals for proportion of patients who showed improvement in behavioural and physical symptoms (progestogen versus placebo)

showed an increased but not significant risk of drop out due to side effects in the treatment 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

The meta-analyses that we carried out in this systematic review show 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. This is based on the observation that symptoms are reduced or eliminated during pregnancy (when progesterone concentrations are high and non-cyclical) and are absent during non-ovulatory cycles and after the menopause.[44] As early as 1938 it was proposed that premenstrual syndrome was caused by relative, unopposed oestrogen during the luteal phase.[45] Dalton and Green developed this theory further in the 1950s, and Dalton still remains one of the main proponents of the progesterone deficiency theory. No research, however, has convincingly shown a progesterone deficiency in women with premenstrual syndrome.[46]

Many therapeutic interventions have been claimed to be effective. This may be attributed 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 the known high placebo response associated with premenstrual syndrome that one of the stated inclusion criteria for our meta-analyses was that in all trials the women should have had premenstrual syndrome diagnosed before randomisation. We also considered only randomised, double blind placebo controlled trials suitable for analysis. It could be argued that women with self diagnosed premenstrual syndrome would, in fact, be the population that the clinician treats. However, in a meta-analysis it is essential that the trials have defined the disorder precisely before treatment to permit definitive statements on the efficacy of the given treatment to be made.

Table 3 Side effects reported in included studies of progesterone according to method of administration

	Suppository/pessary		Oral micronised	
Side effect	**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

Progesterone

Of the ten trials of progesterone treatment that met the inclusion criteria, eight assessed progesterone suppositories and three used oral micronised progesterone (one trial compared both suppositories and oral micronised preparations and the two arms were treated as two separate trials). There are no published trials of topical progesterone cream, which has been popularised through the media and the internet.[8] One trial of intramuscular progesterone was identified, but the data were presented in a textbook review chapter in a format that was not extractable.[29] This placebo controlled trial involved only 14 women with premenstrual syndrome and concluded that progesterone did not produce a significant beneficial effect. Of the eight adequately controlled 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.[18] However, when we examined the data on an intention to treat basis, as opposed to an analysis of "completers," 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.[16 47]

The positive result for oral micronised progesterone was due mainly to one trial conducted by Freeman et al in 1995, which involved 170 women.[17] Although it seems significantly positive in this meta-analysis, the conclusion by the authors of that trial was that "oral micronised progesterone therapy was no better than placebo." This standardised mean difference (−0.147) should be compared with the overall standardised mean difference from another meta-analysis of treatment for premenstrual syndrome, which used the same inclusion criteria.[48] The overall standardised mean difference for selective serotonin reuptake inhibitors (SSRIs) was −1.066 in favour of treatment. These standardised mean differences correspond to an odds ratio of 1.3 for oral micronised progesterone and 6.91 for selective serotonin reuptake inhibitors.[49] It should also be noted that oral micronised progesterone is not available in the United Kingdom.

The overall result showed that progesterone was slightly better than placebo for treating physical symptoms but was no better than placebo in managing behavioural symptoms, although this difference was not significant. This is true for both progesterone suppositories and oral micronised progesterone.

The published evidence for progestogen treatment is not of high quality. Of the 15 published trials, only four trials met quality criteria. They represented 378 women in total, of whom 159 received the active treatment. We carried out a sensitivity analysis on the three trials (266 women) that were excluded because of lack of a prospective diagnosis. The inclusion of the low quality trials slightly improved the effect size (overall standardised mean difference −0.182, −0.044 to 0.320) but not to the extent of making it clinically significant. Poorly controlled, low quality trials often have positive results. In the case of premenstrual syndrome this is often due to an imprecise definition of 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. The lack of trials and the low numbers of participants in each trial meant that a comparative analysis of individual progestogens could not be undertaken. Progestogens were slightly more effective at treating physical compared with behavioural symptoms, but again there was no clinically significant improvement.

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.

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

Contributors: SO'B originated the idea for the study and co-authored the paper. SO'B and MO provided clinical input to the text. KMW was the lead author of the paper, extracted and assessed the trial data, and assisted in the literature searches, reference collation, data entry, and statistical analysis. PWD undertook the literature searches, located the references, and assisted KMW in the data extraction and scoring of the trials. He coordinated the data analysis and statistical calculations in collaboration with KMW and under the guidance of PWJ. PWJ gave statistical input on the data extraction, validity of statistical tests, conversion of statistical measures, and assessment of the heterogeneity of the collated data. He also performed the heterogeneity tests and advised on the statistical methods used in the meta-analysis. All the authors contributed to the writing of the paper. PWD and KMW are guarantors.

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