Investigation of the efficacy of progesterone pessaries in the relief of symptoms of premenstrual syndrome

P J MAGILL

PROGESTERONE STUDY GROUP

SUMMARY

Background. *A variety of definitions have been applied to premenstrual syndrome. The severity of the syndrome is also variable.*

Aim. *A study was undertaken to compare progesterone pessaries with placebo in the relief of symptoms of premenstrual syndrome. In this study the condition was characterized by a wide range of symptoms recurring in the late luteal phase but absent in the follicular phase (that is, the specific definition published by Dalton in 1953).*

Method. *A multicentre, prospective, double-blind, randomized, parallel group study was undertaken by 45 general practitioners. Patients were deemed eligible after two prospective menstrual cycles of observation (selection phase) in which a precise definition of symptoms was applied. Patients were randomized to use either progesterone pessaries (400 mg twice a day) or matching placebo, by vaginal or rectal administration, from 14 days before the expected onset of menstruation until the onset of vaginal bleeding, for four consecutive cycles. Baseline data for the outcome variables were determined in the selection phase. The main outcome variables were changes in the severity (categorized as none, mild, moderate or severe) of each patient's most severe symptom, and in the average score of all the patient's symptoms characteristic of premenstrual syndrome. Spontaneous reports of adverse events were recorded.*

Results. *A total of 281 patients were screened for premenstrual syndrome; of these, 141 patients were randomized to treatment or placebo groups. Efficacy was evaluated in 93 patients. Reductions in the scores of the highest scoring, most severe, symptoms and in the average symptom score, were consistently observed in patients receiving progesterone pessaries and in those receiving placebo. The response to progesterone was greater than to placebo during each cycle; the differences were clinically and statistically significant. Adverse events were reported by 51% of patients in the progesterone treatment group and by 43% in the placebo group. Irregularity of menstruation, vaginal pruritus and headache were reported more frequently by patients taking active therapy.*

Conclusion. *In this study, progesterone, given as pessaries by vaginal or rectal administration, was more effective than placebo in the relief of symptoms of premenstrual syndrome in a population of patients selected by strict entry criteria.*

Keywords: progesterone; premenstrual syndrome; management of disease; clinical trials in general practice.

P J Magill, PhD, FRCPath, FFPM, head of clinical research, Hoechst UK Ltd, Hounslow, Middlesex.

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Introduction

PREMENSTRUAL syndrome has been defined by Dalton[1] as a condition characterized by symptoms which recur in the late luteal phase of successive menstrual cycles but are absent in the early or mid-follicular phase. The time course of the syndrome rather than the symptoms themselves (the nature of which are varied) therefore distinguished this definition from others. For example, other investigators have defined premenstrual syndrome as the presence of symptoms which are less severe but not completely resolved after onset of menstruation, termed 'menstrual distress' by Dalton.[2]

The published incidence of premenstrual syndrome has varied according to methodology and definition. For example, Taylor and colleagues carried out a covert investigation of 608 women contacted through urban general practices.[3] Although 92% were symptomatic during menstruation, 78% were also symptomatic during the first five postmenstrual days, suggesting an incidence of premenstrual syndrome of 14% according to Dalton's criteria.[2] The severity of the syndrome is also variable between patients and between menstrual cycles, but it can be disabling.[2]

The biochemical changes responsible for the syndrome are uncertain. Some studies have shown plasma progesterone levels to be lower in patients with premenstrual syndrome than in controls,[4-6] whereas others have reported either higher levels in patients[7] or no difference.[8,9] Despite these uncertainties, relief of symptoms has been reported after supplementation of oestradiol[10] and, in uncontrolled studies, of progesterone.[1,11,12] One study of orally administered progesterone has shown active treatment to be more effective than placebo.[13] In contrast, five controlled studies of vaginal administration demonstrated symptom relief with progesterone or placebo and failed to demonstrate a difference between the two.[14-18] In general the entry criteria for these trials did not emphasize the absence of symptoms after onset of menstruation, and included patients whose condition might have been described as menstrual distress.[2] Freeman and colleagues, for example, stated that postmenstrual symptoms (from day six to day 12) were low or absent, with total premenstrual symptoms at least 50% greater than postmenstrual symptoms.[18]

A multicentre, prospective, double-blind, randomized, parallel group study was designed to investigate the effectiveness of progesterone pessaries in patients selected using the entry criteria specified by Dalton's definition of premenstrual syndrome — 'the recurrence of symptoms in the premenstruum with absence of symptoms in the postmenstruum'.[2]

Method

Patient selection and baseline variables

A total of 45 general practitioners screened women patients aged between 18 and 45 years who attended complaining of symptoms characteristic of premenstrual syndrome during their previous three menstrual cycles. Exclusion criteria were: recent history of menstrual irregularity; psychotic illness; suicidal tendency; drug or alcohol misuse; or recent use of antidepressants, vitamin B_6

preparations, benzodiazepines, or therapy interfering with normal ovarian function. Eligible patients agreed to use non-hormonal contraception and to discontinue any medication for premenstrual syndrome on admission to the trial.

Pre-study meetings of the 45 general practitioner investigators were aimed at ensuring maximum consistency. All eligible patients gave signed informed consent. The protocol was accepted by the PMR ethics committee, Sale, Cheshire.

At study entry, each patient's age, height, weight, medical and menstrual history and description of symptoms were recorded. Each day of the study, patients scored symptoms of premenstrual syndrome on diary cards as: not present (0 points), mild (1), moderate (2) or severe (3). The selection phase of the study consisted of two prospective menstrual cycles of observation. At the end of the selection phase, daily symptom scores for each symptom, in each cycle, for the seven days before menstruation and the first three days of bleeding were added together to give the total for the late luteal phase; daily symptom scores for the seven days immediately following cessation of menstruation were added together to give the total for the follicular phase. For the purposes of the trial, a symptom was defined as characteristic of premenstrual syndrome if a total of seven points or more was recorded in the late luteal phase and if no more than one point was recorded in the follicular phase of each cycle. For each symptom, the baseline score was calculated as the mean of the scores in the two selection phase cycles. Patients were not eligible to participate in the study if they recorded characteristic symptoms during only one cycle. Any of the 150 symptoms listed by Dalton[1] were eligible if the appropriate time course was confirmed.

Randomization and treatment

This study was a multicentre comparison of progesterone pessaries (Cyclogest®, Hoechst UK Ltd) and placebo. Patients with at least one premenstrual syndrome symptom were randomized to use either one 400 mg progesterone pessary or placebo, identical in appearance to the progesterone pessary, twice a day starting 14 days before the estimated date of onset of menstruation, and continuing until menstruation, for four successive months. Randomization was stratified by investigator with a block size of four. Patients used only pre-packed trial supplies labelled with their trial numbers. Patients were given the choice of vaginal or rectal administration of the pessaries; treatment was self-administered either vaginally or rectally according to the preference of the patient, as previous investigation has shown absorption of progesterone (Cyclogest®) by these routes to be comparable (internal report, Charterhouse Clinical Research Unit Ltd, for Hoechst UK Ltd, 1988).

During the four treatment cycles patients continued to record and score daily the symptoms identified during the selection phase. Route of administration was recorded each day of treatment. Adverse events were also recorded by the patients. During each cycle, patients' blood pressure, weight and height were measured at the surgeries by the investigators. Patient participation ended with completion of the fourth treatment cycle. The random code was not broken until all patients had finished the trial.

Statistical analysis

For each patient, the baseline highest symptom score was the single most severe symptom, and therefore the one with greatest clinical importance. The baseline average symptom score, also calculated for each patient, was the mean of her eligible symptoms. Medians of the scores at baseline were calculated for the patient population in each group. Medians of reductions in these scores were calculated for the treatment and placebo groups in each of the four treatment cycles.

Descriptive statistics were used to summarize all baseline, demographic and safety data (recordings of adverse events, blood pressure and weight). The Wilcoxon rank sum test was used to compare changes in symptom scores during treatment and differences between groups. In a covariate analysis the Wilcoxon rank sum test was adjusted for imbalance observed between the incidences of some symptoms by stratifying by the presence or absence of individual symptoms. The analysis was carried out using *StatXact Turbo.*

Results

Patient selection

Forty five general practitioners identified a total of 281 patients who reported symptoms suggestive of premenstrual syndrome. The patients were entered into the selection phase. On the basis of results from the selection phase, 141 patients were thought to have eligible symptoms and were randomized to use progesterone pessaries (80 patients) or placebo (61 patients), and 140 patients were excluded from the study. Of the 141 patients who started therapy, results from 93 (50 patients in treatment group and 43 in placebo group) were available for analysis according to the study protocol. Results from the other 48 patients were not evaluable because: symptoms were recorded in only one cycle of the selection phase (cyclicity was therefore not confirmed) — six patients using progesterone pessaries and four using placebo; symptom severity was too low in the luteal phase or too high in the follicular phase — 16 patients using progesterone pessaries and 10 using placebo; or patients were taking medication not permitted by the protocol — eight patients using progesterone pessaries and four using placebo. Data on 93 patients were therefore available for statistical analysis according to the protocol, but data on 141 patients were used for the 'intention to treat' statistical analysis.

Baseline variables

All patients randomized to active treatment and placebo groups, and also patients eligible for evaluation assigned to these groups, were similar in terms of age, height, weight and menstrual history at baseline (Table 1). Patients in the treatment group eligible for evaluation showed tendencies to have greater severity of dysmenorrhoea and shorter history of premenstrual syndrome than patients in the placebo group eligible for evaluation, although the differences were not marked. The 141 randomized patients did not differ from the 281 patients screened in terms of baseline variables.

A total of 144 symptoms were recorded in the selection phase by the 50 patients in the treatment group eligible for evaluation and 105 by the 43 patients in the placebo group (Table 2). Most patients recorded more than one symptom. Some symptoms, notably bloatedness, depression, irritability and tension, appeared to be over-represented in the treatment group.

The highest scoring symptoms among patients eligible for evaluation, that is, each patient's most severe symptom at baseline, are described in Table 3. Baseline median highest scoring symptom scores were 18 points (interquartile range 14 to 21 points) and 17 points (interquartile range 14 to 21 points) in the progesterone treatment group and placebo group, respectively; baseline medians of the average symptom scores were 16 points (interquartile range 13 to 19 points) and 15 points (interquartile range 13 to 19 points) in the two groups, respectively. Thus, the scores were similar at baseline.

Table 1. Baseline characteristics of patients randomized (intention to treat) and those evaluated (per protocol) for efficacy of treatment.

Characteristic	Patients in group receiving pessaries			
	Intention to treat		Evaluable	
	Progesterone (n = 80)	Placebo (n = 61)	Progesterone (n = 50)	Placebo (n = 43)
Mean (SD) age (years)	36.1 (5.1)	34.9 (5.9)	35.4 (5.3)	34.8 (6.0)
Mean (SD) height (cm)	162.8 (7.3)	161.4 (10.2)	161.0 (6.9)	161.1 (11.9)
Mean (SD) weight (kg)	63.7 (9.1)	62.5 (7.4)	64.1 (10.1)	62.3 (8.1)
Mean (SD) age at menarche (years)	12.8 (1.6)	12.6 (1.6)	12.7 (1.6)	12.5 (1.5)
Mean range of menstrual cycle length (days)	26.2 to 29.1	26.6 to 29.8	26.3 to 28.9	26.6 to 30.1
Median range of duration of menstruation (days)	4 to 6	5 to 7	4 to 6	5 to 7
Dysmenorrhoea (no. of patients reporting)[a]				
None	19	24	11	17
Mild	21	11	12	10
Moderate	23	21	17	12
Severe	14	5	9	3
Median no. of pregnancies	2	2	2	2
Median (IQ) duration of symptoms (months)	42 (3 to 96)	54 (3 to 92)	36 (3 to 84)	60 (3 to 96)

n = number of patients in group. [a]Data missing for some patients. SD = standard deviation. IQ = interquartile range.

Patients eligible for evaluation: symptom scores during treatment

Reductions from baseline in scores of the highest scoring symptoms (Table 4) and in average symptom scores (Table 5) were noted in both groups in all four treatment cycles. Reductions in scores of the highest scoring and the average of each patient's symptoms were consistently greater in the treatment group than in the placebo group. Reductions in scores (that is, in symptom severities) in the treatment group were about twice those in the placebo group, underlining the clinical significance of the improvement. Some differences between groups were significant at the 1% level (P<0.01) and most were significant at the 5% level (P<0.05).

Six patients in the treatment group and eight in the placebo group failed to attend all their clinic visits.

Covariate adjustment

Bloatedness, depression, irritability and tension appeared to be over-represented in the treatment group at baseline. The analysis was therefore adjusted to allow for this by stratification: these symptoms were used as covariates in a covariate adjustment of the statistical significance of differences in reductions from baseline during treatment, to confirm the efficacy analysis. The supplementary calculation produced little change in P values.

Table 2. All eligible symptoms recorded by patients in the progesterone treatment group (50 patients) and placebo group (43 patients).

Symptom	No. of symptoms reported in group	
	Progesterone pessaries	Placebo
Aching legs	0	1
Aggression	5	4
Anxiety	5	2
Argumentativeness	2	2
Backache	7	6
Bloatedness	20	12
Breast tenderness	12	13
Change in libido	3	2
Clumsiness	3	1
Constipation	0	1
Depression	12	6
Disturbed sleep	0	1
Dry mouth and throat	1	0
Food cravings	5	7
Headache	3	2
Heaviness in the head	1	0
Irritability	22	16
Loss of concentration	5	6
Loss of self control	1	0
Mood change	1	0
Nausea	0	1
Night sweats	1	0
Oedema	3	5
Palpitation	0	1
Stomach ache	1	0
Tension	13	6
Tiredness	13	9
Weepiness	4	1
Withdrawal	1	0

Table 3. Highest scoring eligible symptoms of premenstrual syndrome recorded by patients in the progesterone treatment group (50 patients) and placebo group (43 patients).

Highest scoring symptom	No. of patients recording symptom in group	
	Progesterone pessaries	Placebo
Aggression	3	0
Anxiety	1	1
Backache	1	2
Bloatedness	9	6
Breast tenderness	3	9
Change in libido	0	1
Clumsiness	1	0
Depression	2	2
Food cravings	1	4
Irritability	10	5
Loss of concentration	3	3
Mood change	1	0
Oedema	1	1
Palpitation	0	1
Stomach ache	1	0
Tension	4	2
Tiredness	9	6

Table 4. Changes from baseline in the highest scoring symptoms at the four treatment cycles for patients randomized to use progesterone pessaries or placebo.

Treatment cycle	Median reductions (interquartile range) in scores of highest scoring symptoms in group using: Progesterone pessaries	Placebo
1 (*n* = 50/43)	-9 (-16 to -5)	-4 (-12 to 0)**
2 (*n* = 49/43)	-9 (-15 to -6)	-5 (-10 to -1)**
3 (*n* = 42/38)	-10 (-16 to -5)	-8 (-13 to -2)
4 (*n* = 41/31)	-10 (-16 to -5)	-5 (-12 to 0)*

n = number of patients in progesterone pessaries/placebo group. Differences in reductions between groups: *$P<0.05$, **$P<0.01$.

Table 5. Changes from baseline in average symptom scores at the four treatment cycles for patients randomized to use progesterone pessaries or placebo.

Treatment cycle	Median reductions (interquartile range) in average symptom scores in group using: Progesterone pessaries	Placebo
1 (*n* = 50/43)	-7 (-12 to -4)	-4 (-10 to 0)**
2 (*n* = 49/43)	-7 (-12 to -5)	-5 (-9 to 0)*
3 (*n* = 42/38)	-10 (-12 to -5)	-6 (-11 to -2)*
4 (*n* = 41/31)	-10 (-14 to -2)	-4 (-10 to 0)

n = number of patients in progesterone pessaries/placebo group. Differences in reductions between groups: *$P<0.05$, **$P<0.01$.

All patients: intention to treat analysis of symptom scores

Average symptom scores were analysed for all symptoms in all 141 patients irrespective of eligibility according to study definitions. The medians of the average symptom scores at baseline were 13 points in the progesterone treatment group and 12 points in the placebo group. Reductions in symptom scores were noted in both groups in all of the four treatment cycles (Table 6). Reductions in the treatment group were generally greater than in the placebo group although the differences were not significant at the 5% level, except in the first treatment cycle. Changes from baseline in the intention to treat analysis were smaller than those in the analysis as per protocol (Table 5).

Route of administration

As patients were given the choice of vaginal or rectal administration, some patients varied the route of administration of the pessaries. Vaginal administration was used by 69% of those in the treatment group and by 63% of those in the placebo group.

Adverse events

No clinically significant changes in blood pressure, weight or the severity or duration of menstrual bleeding were noted in either group.

Forty one of the 80 patients randomized to the treatment group reported a total of 101 adverse events, while 26 of the 61 patients randomized to the placebo group recorded a total of 53 adverse events. Those that were reported by three or more patients in either group are listed in Table 7. Incidences of nausea, abdominal pain, influenza syndrome, dysmenorrhoea, breast pain and rectal pain were similar in each group. In contrast, menstrual disorder (mostly changes in cycle length), vaginal pruritus and headache were more common in patients who used progesterone pessaries than in those who used placebo, although the difference was statistically significant only for menstrual disorder ($P<0.05$). The severities of adverse events were generally mild, although two patients in each group withdrew from the study after reporting adverse events: irregular menstruation and an ovarian cyst in the treatment group and respiratory infection and depression in the placebo group. Two patients stopped using placebo because of dislike of the pessaries. One patient using progesterone pessaries became pregnant after having had a long interval of infertility.

Table 6. Changes from baseline in average symptom scores at the four treatment cycles for all patients in intention to treat analysis, randomized to use progesterone pessaries or placebo.

Treatment cycle	Median reductions (interquartile range) in average symptom scores in group using: Progesterone pessaries	Placebo
1 (*n* = 73/57)	-5 (-9 to -1)	-2 (-7 to 2)*
2 (*n* = 66/57)	-5 (-10 to -2)	-3 (-8 to 1)
3 (*n* = 58/51)	-6 (-10 to 0)	-3 (-8 to 1)
4 (*n* = 57/43)	-4 (-10 to 1)	-4 (-10 to 2)

n = number of patients in progesterone pessaries/placebo group, in intention to treat analysis. Differences in reductions between groups: *$P<0.05$.

Table 7. Adverse events recorded at any time during treatment by at least three patients using either progesterone pessaries or placebo.

	No. of patients reporting (no. of reports of) adverse event in group using: Progesterone pessaries	Placebo
Menstrual disorder	11 (17)	2 (3)*
Vaginal pruritus	8 (10)	2 (4)
Headache	6 (10)	3 (3)
Nausea	6 (7)	4 (6)
Abdominal pain	4 (5)	2 (2)
Influenza syndrome	4 (4)	1 (1)
Dysmenorrhoea	3 (4)	1 (1)
Breast pain	3 (4)	0
Rectal pain	3 (3)	3 (5)
Diarrhoea	2 (2)	4 (7)

Difference between groups: *$P<0.05$.

Discussion

This study provides the first evidence of the effectiveness of progesterone pessaries as treatment for premenstrual syndrome in a double-blind trial. The results are believed to be important despite flaws in the conduct of the study which included the randomization of 141 patients when only 93 were confirmed as being eligible for evaluation of efficacy of the pessaries. In total, 48 patients did not, on close inspection, meet the specified entry criteria and therefore should not have been entered in the study. The randomization of these patients suggests that the inclusion criteria were not set out with sufficient clarity or were not adhered to rigorously enough.

Differences in the patient populations at baseline were also present, although these were unlikely to have affected the results of the trial. Dysmenorrhoea, the severity of which was greater in the treatment group at baseline, cannot occur as part of premenstrual syndrome. Covariate adjustment for symptoms apparently over-represented at baseline did not materially change levels of statistical significance, suggesting that such imbalances had not affected the study outcome. The comparability of symptom scores at baseline between groups, on the other hand, provides reassurance that the reductions that occurred during treatment can be interpreted with confidence. Levels of statistical significance for changes in symptom scores have not been corrected for multiple testing but are shown clearly in Tables 4 and 5.

The study had facets not used in previous trials[14-18] which may explain why progesterone pessaries were shown to be effective here but not in earlier studies. Although subject to protocol violation, the entry criteria aimed, by documenting postmenstrual symptom severity, to select a patient population as similar as possible to those used with success in previous anecdotal series.[2] In other controlled trials, symptoms were more severe in the luteal phase but could still be present after the onset of menstruation, although Maddocks and colleagues[16] used the criteria of Steiner and colleagues:[19] 'symptoms only during the premenstrual period with relief soon after onset of menses'.

The patients in this study selected the symptoms that they considered to be of greatest importance. Previous trials used questionnaires, such as that of Moos,[20] which seek to document all symptoms characteristic of premenstrual syndrome; such an approach could dilute changes in the symptoms of greatest importance to the patient or could miss them altogether. The present study is also unusual in using a parallel group design, thus avoiding the potential problem of carry-over effects which can confound crossover studies. In previous studies only Dennerstein and colleagues[13] tested for, and excluded, such an effect.

Three adverse events — changes in the length of menstrual cycle, vaginal pruritus and headache — were more common in patients using progesterone pessaries than in those using placebo. Changes in menstrual cycle length may reflect feedback effects of progesterone or a direct effect on the endometrium. Progesterone also appeared to increase the incidence of pruritus, presumably reflecting a direct effect or changes in vaginal flora, although a few cases were reported in the placebo group. The reports of headache were few. Comparable numbers of patients failed to return to the clinic or stopped treatment because of dislike of, or adverse events during, treatment with progesterone pessaries or placebo.

Debate continues about the choice of treatment for premenstrual syndrome. In the present study, patients meeting all specified entry criteria who were treated with progesterone pessaries showed greater benefit than those on placebo. The difference between the groups was reduced when results from all patients were analysed (intention to treat analysis). This provides an indication that patients selected using a wider definition than that of Dalton[2] may respond in a different way to those chosen within the definition, although this needs to be confirmed in a trial specifically designed to test response in patients selected using different definitions. Such a finding would also stimulate the need for a community-based survey of the incidences of premenstrual syndrome according to different definitions.

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Address for correspondence

Dr P J Magill, Nuffield Department of Obstetrics and Gynaecology, John Radcliffe Hospital, Maternity Department, Headington, Oxford OX3 9DU.

Food for thought...

'Sixty per cent of the variance in the number of heartsink patients that general practitioners reported on their lists could be accounted for by the following four explanatory variables: greater perceived workload; lower job satisfaction; lack of training in counselling and/or communication skills; and lack of appropriate postgraduate qualifications.'

Mathers N, Jones N, Hannay D. Heartsink patients: a study of their general practitioners. June *Journal,* p.293.