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Assessment of the Effects of the Herbal Remedy Femal on the Symptoms of Premenstrual Syndrome: A Randomized, Double-Blind, Placebo-Controlled Study

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ABSTRACT

Background: Current treatments for premenstrual syndrome (PMS) appear to offer, at best, a 25% to 50% reduction in symptoms, and many of these treatments have substantial side effects. Femal, an herbal remedy containing a pollen extract, a pollen and pistil extract, and Royal Jelly, has been used in Scandinavia for the treatment of PMS for >4 years.

Objective: The aim of this study was to assess the effect of Femal on the symptoms of PMS.

Methods: This was a randomized, double-blind, placebo-controlled, crossover trial of the effects of Femal in women with PMS. The symptoms of PMS were evaluated using well-established questionnaires and daily body weight measurement.

Results: Thirty-two women (mean age, 39.4 years; range, 27–50 years) with regular menstrual cycles of 24 to 34 days entered the trial. Three women dropped out of the study, leaving 29 for final evaluation. Two months of active treatment lowered overall symptom indices significantly and lowered 6 of 9 individual symptom scores by 27% to 57%. Evidence for a slow onset of action and protracted effect was provided by the finding that all symptom indices studied declined significantly (by 48%–88%) in the group that received placebo before Femal ($P < 0.01$). In contrast, the group that received Femal before placebo showed no significant differences between Femal and placebo, except in sleep quality ($P < 0.04$). Premenstrual weight gain was reduced 50% by active treatment compared with placebo. There were no reported unwanted or adverse effects during Femal treatment.

Conclusion: The findings suggest that the herbal therapy Femal provided substantial symptomatic relief of PMS to the women in this study, with minimal risk of unwanted or adverse effects.

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INTRODUCTION

The herbal remedy Femal®* has been available for >4 years in Scandinavia for the treatment of premenstrual syndrome (PMS). Much favorable anecdotal information about Femal has accumulated during that time. Moreover, the preparation has a positive safety record, with few adverse effects reported to date.

Femal contains 3 active ingredients: a pollen extract (GC Fem), a combined pollen and pistil extract (PI 82), and Royal Jelly, which is produced by honeybees. Each tablet contains 36 and 120 mg of the respective extracts and 6 mg of Royal Jelly. The pollen and pistil extract contains mimics of the antioxidant enzyme superoxide dismutase,[1] and Royal Jelly is rich in pantothenic acid, thiamine, riboflavin, pyridoxine, folic acid, and sterols.[2] The pollen and pistils are selected and harvested primarily from members of the grass (Poaceae) family, including rye (*Cecale cereale*), and provided in a standardized formulation. The pollens are treated with their own enzymes to achieve germinal opening and avoid the risk of an allergic reaction to the pollen.

Given the favorable reports on Femal during its >4 years of use in Scandinavia, as well as its positive safety record, a placebo-controlled trial seemed warranted. Based on a search of the literature, the present study is the first controlled trial of Femal. The objective was to assess the effect of Femal on symptoms of PMS.

PATIENTS AND METHODS

The trial protocol was approved by the local ethics committee. Volunteers were recruited through an advertisement and provided their written informed consent before entering the study. Although all respondents had been diagnosed with PMS by their general practitioner or gynecologist an average of 11.5 years earlier, they were interviewed again in the month preceding the trial to confirm the diagnosis and determine whether they were eligible for the study.

Women aged 20 to 54 years with regular menstrual cycles and a previous diagnosis of PMS who met the criteria of Steiner et al[3] for primary recurrent premenstrual tension syndrome were eligible for the study. The exclusion criteria were as follows: pregnancy or lactation; menstrual cycle irregularity; unstable medical illness; seizure disorder within the past year; history of multiple drug reactions; menstrual cycle length shorter than 24 days or longer than 35 days; major psychiatric disorder; suicidal ideation or intent; and use of psychoactive drugs, investigational drugs, or specific medication for PMS in the past 2 months. To exclude psychiatric disorders, the women were evaluated by a psychologist, with support from a psychiatrist.

*Trademark: Natumin Pharma, Huskvarna, Sweden.

Study Design

This was a randomized, double-blind, placebo-controlled, crossover trial (Figure). Half of the patients (group A) took 2 Femal tablets twice daily starting on the first day after menstruation had finished and continued the same treatment daily throughout 2 consecutive menstrual cycles. The other half (group B) took the same number of placebo tablets for 2 consecutive cycles. The groups then crossed over to the alternative treatment for the next 2 menstrual cycles. The 2 groups began their treatment at the same time.

Study Measures

Each patient kept a diary card on which she recorded her daily body weight, days of menstruation, and days on which PMS symptoms were present. Each patient brought her diary card to the clinic 4 times, just after each menstrual cycle had ended, and reported in detail on the symptoms experienced during the most recent cycle.

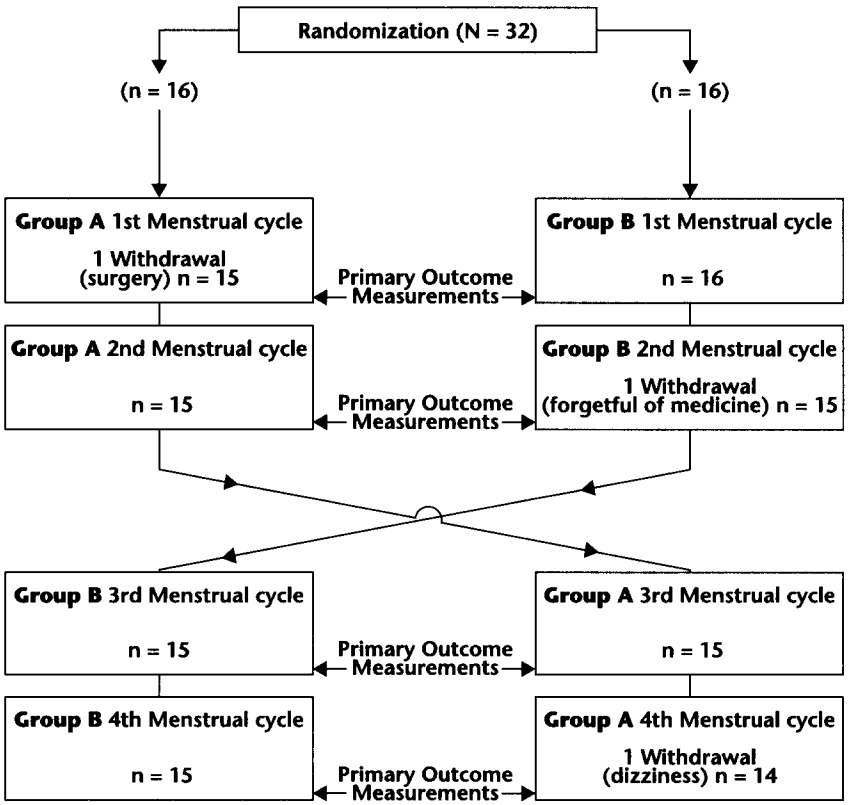

Figure. Study design and number of patients at each phase of the study. Group A = Femal (Natumin Pharma, Huskvarna, Sweden) before placebo; group B = placebo before Femal.

Three instruments were used in recording and assessing symptoms. On the Premenstrual Tension Syndrome Self-rating[3] (PMTS-S) scale, patients gave "yes" or "no" answers to 36 questions about the severity of such PMS symptoms as mental tension, irritability, efficiency, dysphoria, motor coordination, mental/cognitive function, eating habits, sexual drive and activity, physical symptoms, and social impairment. The questions are given equal weight and phrased so that the more "yes" answers are given, the more severe the PMS symptoms are. The score is calculated from the number of "yes" answers, with the maximum score being 36. Administration of the questionnaire was supervised and the results recorded by the clinic nurse, who was blinded to treatment assignment.

On the Premenstrual Tension Syndrome Observer Rating[3] (PMTS-O) scale, the clinical investigator asked the patient to rate the severity of the 10 major symptoms of PMS noted in the previous paragraph. Each symptom was graded on a scale of increasing severity (0–4), except for eating habits and sexual activity, which were graded on a scale from 0 to 2. The final score was the sum of scores for all 10 symptoms, with the maximum possible score (greatest severity of symptoms) being 36. The investigator was blinded to treatment assignment.

On the Premenstrual Symptom Evaluation, patients assessed 10 symptoms of PMS on a 100-mm visual analog scale (VAS), from 0 = least severe to 100 = most severe. These included mental tension, irritability, dysphoria, raw luteal-phase score[3] (derived from mean VAS scores for the first 3 symptoms), headache, bloating, breast tenderness, edema, sleep disturbance, and interference with social or professional life.

Finally, an overall assessment of well-being was made using a scale from 1 to 5, with 5 being the worst possible. Side effects were elicited by general and direct questioning on the part of the clinical investigator. There were no formal criteria for discontinuing the study. However, patients were withdrawn immediately at their request or if severe side effects occurred.

Patients were randomly assigned to treatment groups in clusters of 4 through the use of a computer-generated list. The code was broken only after the clinical trial had been completed and all results had been handed over for statistical analysis. The drug formulations were labeled as 1 month's treatment, periods 1 through 4. The clinical investigator supplied 4 bottles to each patient, 1 at the beginning of each menstrual cycle. Active drug and placebo were supplied as tablets that were indistinguishable from each other in size, shape, color, taste, and odor. No patient or staff member detected any difference in the 2 tablet types.

Statistical Analyses

Two analyses were performed on an intent-to-treat basis. In the combined-group analysis, the sums of the 2 groups' symptom scores (ie, the separate scores on each instrument) at the end of the first and second months of active treatment were labeled F1 and F2, respectively. The corresponding results with

placebo were labeled P1 and P2. Thus, the 4 sets of results represented all patients, allowing comparison of both active treatment with placebo and the first month of active therapy with the second month. In the separate-group analysis, each group was examined separately for differences between the 4 successive months of the trial.

A nonparametric method, the Wilcoxon signed-rank, matched-pairs analysis, was used for all analyses of the significance of differences between treatment groups. $P \leq 0.05$ was considered significant. All analyses were performed by an independent organization.

RESULTS

Thirty-two women (mean age, 39.4 years; range, 27–50 years) with regular menstrual cycles of 24 to 34 days entered the trial. One woman withdrew just after the first cycle because of nongynecologic surgery. Another woman withdrew after the first 2 cycles because of difficulties remembering to take medication according to the study protocol. A third woman withdrew after 2 weeks of the final cycle because of dizziness, a symptom the patient thought was related to a viral infection and not to PMS (Figure). The remaining 29 patients completed the trial.

All patients included in the study met the Steiner et al[3] criteria for premenstrual tension. On the day of inclusion, the women were asked to grade the severity of their PMS symptoms using a scale from 0 (no complaint) to 5 (almost unbearable symptoms). The mean score was 3.9 (range, 2–5).

The results of the combined-group analysis are shown in Table I. The 4 indices of the effect of Femal on PMS symptoms revealed a statistically significant (PMTS-O, $P = 0.029$; PMTS-S, $P = 0.036$; raw luteal-phase score, $P = 0.018$; change in body weight, $P = 0.009$) reduction in symptom severity during active treatment compared with placebo. Based on VAS scores, active treatment significantly affected 6 of the 10 major symptoms constituting the patient's assessment of PMS symptoms ($P \leq 0.036$) (Tables I and II).

Patients' perception of a reduction in edema ($P = 0.012$) corresponded with a 50% decrease in premenstrual weight gain ($P = 0.009$). For 3 symptoms—breast tenderness, sleep disturbance, and interference with social or professional life—Femal had no statistically significant effect, although there were reductions of 29%, 19%, and 41%, respectively. For headache, there was a nonsignificant worsening (5%).

No significant effect of active treatment versus placebo (F1 vs P1) was observed after the first cycle of treatment (Table I). However, after 2 months of treatment (F2 vs P2), changes in 8 of the major symptoms achieved significance ($P \leq 0.036$). These results suggest that Femal had a gradual onset of action, requiring >1 month of therapy to exert its full effect.

When the results in the 2 groups were analyzed separately for differences between active treatment and placebo, group B (placebo before Femal) showed

Table I. Scores for symptoms of premenstrual syndrome in 32 women during the 1st and 2nd cycles of treatment with Femal (Natumin Pharma, Huskvarna, Sweden) and the 1st and 2nd cycles of treatment with placebo. Data are given as mean (95% CI).

	Femal		Placebo					
	1st Cycle	2nd Cycle	1st Cycle	2nd Cycle	*P*			
Treatment	(F1)	(F2)	(P1)	(P2)	P1 vs P2	P1 vs F1	F1 vs F2	P2 vs F2
PMTS-O rating	11.3 (8.1–14.5)	9.6 (6.0–13.1)*	13.6 (10.5–16.7)	14.4 (10.8–17.9)	0.616	0.185	0.131	0.029
PMTS-S	12.6 (9.3–15.9)	10.6 (7.1–14.2)*	15.2 (11.7–18.7)	15.8 (12.2–19.5)	0.447	0.342	0.148	0.036
Raw luteal-phase score	2.9 (1.8–3.9)	2.5 (1.4–3.5)*†	3.7 (2.7–4.6)	4.2 (3.1–5.2)	0.356	0.155	0.036	0.018
Weight change, kg	1.1 (0.7–1.5)	0.7 (0.4–0.9)*†	1.1 (0.7–1.6)	1.4 (0.9–1.8)	0.278	0.989	0.025	0.009
Mental tension	3.0 (1.8–4.2)	2.7 (1.5–3.9)	3.2 (2.2–4.1)	3.8 (2.7–4.9)	0.406	0.234	0.138	0.060
Irritability	3.5 (2.3–4.6)	3.0 (1.8–4.2)*†	4.4 (3.3–5.6)	4.5 (3.3–5.7)	0.964	0.147	0.036	0.029
Dysphoria	2.7 (1.6–3.9)	2.2 (1.2–3.3)†	3.0 (2.0–3.9)	4.0 (2.8–5.1)	0.136	0.152	0.173	0.017
Edema	2.6 (1.4–3.9)	1.9 (0.8–2.9)*†	3.1 (1.9–4.4)	3.1 (1.8–4.4)	0.750	0.276	0.042	0.012
Bloating	2.8 (1.6–4.0)	2.5 (1.3–3.6)	3.7 (2.6–4.8)	3.9 (2.6–5.3)	0.875	0.057	0.469	0.054
Overall well-being	2.3 (1.7–2.8)	2.2 (1.6–2.7)†	2.8 (2.3–3.3)	3.0 (2.5–3.5)	0.608	0.178	0.945	0.035

PMTS-O = Premenstrual Tension Syndrome Observer rating scale (maximum score 36, with higher scores indicating greater severity); PMTS-S = Premenstrual Tension Syndrome Self-rating scale (maximum score 36, with higher scores indicating greater severity).
*$P \leq 0.05$ vs P2.
†$P \leq 0.05$ vs F1.

Table II. Percentage decline in symptom indices* after the use of Femal (Natumin Pharma, Huskvarna, Sweden) for 2 menstrual cycles.

Symptom	% Decline	*P*
Well-being	27	0.035
Mental tension	29	0.060
PMTS-S	33	0.036
PMTS-O	33	0.029
Irritability	33	0.029
Raw luteal-phase score	41	0.018
Dysphoria	45	0.017
Bloating	36	0.054
Edema	57	0.012
Weight change	50	0.009

PMTS-S = Premenstrual Tension Syndrome Self-rating; PMTS-O = Premenstrual Tension Syndrome Observer Rating.
*Percent drug effect was calculated as follows: (mean score Femal − mean score placebo) × 100/mean score placebo.

highly significant reductions during active treatment in body weight change, PMTS-O, PMTS-S, and raw luteal-phase scores ($P < 0.01$). For the 10 symptoms included in the PMTS-S, a significant reduction was seen ($P < 0.01$). Significant reductions were also observed in 10 individual self-rated symptoms, including headache, breast tenderness, sleep disturbance, and interference with social or professional life (all, $P < 0.01$; data not shown). The mean decline in symptom score was 68% (range, 48%–88%).

By contrast, in group A (Femal before placebo), there was a significant difference in favor of Femal in the 1- and 2-month treatment scores for sleep disturbance only ($P < 0.04$). These differences suggest a carryover effect. Protocol deviations did not occur.

During the first treatment period, menstruation lasted a mean of 5.0 days with placebo and 5.4 days with active treatment. In the second treatment period, menstruation lasted 5.1 days and 5.6 days, respectively. Neither difference was statistically significant. During placebo treatment, the mean number of days with PMS symptoms was 5.7, compared with 3.5 with Femal (39% decrease during active therapy); the difference was not statistically significant.

Neither systolic nor diastolic blood pressure, as measured using a mercury sphygmomanometer, was affected by treatment. Heart rate, counted over 15 seconds, also remained unchanged throughout the study.

During the first and second active-treatment periods, 3 and 5 women, respectively, commented on a shortening of the menstrual cycle. There was 1 complaint of dizziness; otherwise, Femal was well tolerated.

The combined-group analysis indicated that 8 of 10 PMS symptoms decreased by 27% to 57% during active treatment. Again, the fact that >1 month

of therapy was required to achieve the full treatment effect suggests that Femal had a slow onset of action. In the separate-group analysis, group B had substantial and significant decreases in scores for all symptoms tested with Femal (mean 68% decrease; range, 48%–88%). Although the reason for the unexpectedly level response in group A is uncertain, a possible explanation is that the prolonged action of Femal had a carryover effect sufficiently large and protracted to obscure any differences between the 2 treatments in group A. In this analysis, all 4 cycles of treatment were, in effect, active treatments.

DISCUSSION

A crossover design was chosen for this study of Femal because, in a satisfactorily completed trial of this design, all patients will have received a course of both placebo and active treatment, thus serving as their own controls. A trial of this design carries the risk of a carryover effect when, as in our study, no washout period intervenes between the active-treatment and placebo phases of the trial. The results did, in fact, show strong evidence of a protracted carryover effect. In the group that received placebo before Femal, the change in individual VAS scores was always between 3 and 4 points ($P < 0.01$). In contrast, in the group that received Femal before placebo, the change in individual VAS scores was <1 point, with only sleep disturbance showing a significant change ($P < 0.04$). The present data also suggest an order effect. Intent-to-treat analysis of the combined data for both groups showed significant changes in scores for the majority of symptoms.

This study might be criticized for failing to include an initial phase designed to eliminate all placebo responders, particularly in view of the known tendency of patients with PMS to show a placebo response.[4] However, if the incidence of placebo response were to prove as high overall as that reported by Magos et al,[5] assembling a study group free of placebo response would involve preliminary screening of hundreds of patients.

Within these limitations, the trial methodology appears to have been reasonably satisfactory. The results indicate that Femal had a beneficial effect, achieving 27% to 57% reduction in 8 of 10 PMS symptoms while being well tolerated. It is encouraging that on the single relevant objective measure used—body weight gain—Femal was associated with 50% less premenstrual weight gain compared with placebo.

Based on the assumption that PMS is a medical disorder and must, therefore, have a definable cause, the condition has been investigated using a multitude of physiopathologic approaches, many offering a possible line of rational treatment. The etiology of the condition is, however, still obscure, and hopes of a single effective drug therapy have remained unfulfilled. The early belief that PMS was associated with water or electrolyte retention has been challenged by actual measurements,[6] and several variations on the sex hormone imbalance theory have not been supported by any consistent pattern in measured hor-

mone concentrations.[7] Argument about the causative role of progesterone continues,[8] but the consensus appears to be that women with PMS have normal menstrual hormonal patterns. However, normal hormonal variations in some women may generate central neuroendocrine disturbances that provoke PMS symptoms, although the source of the predisposition is not known. A review presents the central neuroendocrine mechanisms and potential treatments of PMS.[9] The most promising approach appears to be use of selective serotonin reuptake inhibitors.[10] However, treatment with these drugs has resulted in only 25% to 50% improvement in PMS symptoms, with frequent side effects and a high dropout rate.[4,11,12] Furthermore, trials have often been confined primarily to women with premenstrual dysphoric disorder, with few results available for women with the more common varieties of PMS, as in the present study.

More holistic aspects of PMS (eg, social, cultural, anthropologic) have also been widely examined, as in the review by Richardson.[13] The many personal strategies (eg, regular exercise, avoiding certain foods) that British women have devised to relieve PMS symptoms have been described by Choi and Salmon.[14]

Based on a search of the published literature, no comprehensive, up-to-date review of the drug treatment of PMS is available. The difficulties associated with such a project are illustrated in the study by Budeiri et al,[15] who set out to identify the most appropriate treatments for PMS but had to settle for a critical examination of the inclusion criteria and methods of assessment in use. In 350 trials of 115 drugs, they encountered 65 questionnaires or scales used for assessing symptoms, of which 47 were adequate for formal analysis. They stressed the need for future limitation and standardization of methods.

CONCLUSIONS

Our findings suggest that the herbal remedy Femal provided substantial symptomatic relief of PMS symptoms, with minimal risk of side effects, in the women in this study. Compared with the results reported for selective serotonin reuptake inhibitors,[9–11] Femal appears to be at least as efficacious in reducing the symptoms of PMS. It also was associated with a reduction in PMS-related weight gain.

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