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DIFFERENTIAL BEHAVIORAL EFFECTS OF GONADAL STEROIDS IN WOMEN WITH AND IN THOSE WITHOUT PREMENSTRUAL SYNDROME

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ABSTRACT

Background The symptoms of women with premenstrual syndrome improve in response to suppression of ovarian function, although these women have no evidence of ovarian dysfunction. We undertook a study to determine the role of estrogen and progesterone in this syndrome.

Methods We first studied the effect of ovarian suppression with leuprolide, an agonist analogue of gonadotropin-releasing hormone, or placebo on symptoms in 20 women with premenstrual syndrome. Ten women whose symptoms improved during leuprolide treatment were given estradiol and progesterone in a double-blind, crossover design, each for four weeks, during continued leuprolide administration. Women without premenstrual syndrome (normal women) participated in a similar protocol. Outcomes were assessed on the basis of daily self-reports by the patients and biweekly rater-administered symptom-rating scales.

Results The 10 women with premenstrual syndrome who were given leuprolide had a significant decrease in symptoms as compared with base-line values and with values for the 10 women who were given placebo. The 10 women with premenstrual syndrome who were given leuprolide plus estradiol or progesterone had a significant recurrence of symptoms, but no changes in mood occurred in 15 normal women who received the same regimen or in 5 women with premenstrual syndrome who were given placebo hormone during continued leuprolide administration.

Conclusions In women with premenstrual syndrome, the occurrence of symptoms represents an abnormal response to normal hormonal changes. (N Engl J Med 1998;338:209-16.)

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PREMENSTRUAL syndrome is a cyclical disorder characterized by mood-related and somatic symptoms that occur during the luteal phase of the menstrual cycle and disappear at or soon after the onset of menstruation. The pathophysiologic role of the luteal phase in premenstrual syndrome is unclear, as are the roles of the ovarian steroids estrogen and progesterone. Truncation of the luteal phase with the progesterone-receptor antagonist mifepristone does not alter the symptoms of the syndrome,¹ but ovarian suppression with agonist analogues of gonadotropin-releasing hormone usually reduces them.²⁻⁵ Taken together, these results are consistent with the view that premenstrual syndrome is triggered by hormone-related events occurring before the midluteal phase of the menstrual cycle.

The purpose of this study was to test the hypothesis that estradiol and progesterone induce symptoms resembling those due to the premenstrual syndrome in women with premenstrual syndrome. We further sought to determine whether the response to suppression and replacement of gonadal hormones differed between women with and those without the syndrome.

METHODS

We studied 20 women with premenstrual syndrome and 15 women who did not have the syndrome (hereafter referred to as normal women). They ranged in age from 27 to 45 years (mean, 37) and from 21 to 39 years (mean, 30), respectively. All reported regular menstrual cycles (range, 22 to 34 days), and all had a negative urine pregnancy test. None were taking any medications or

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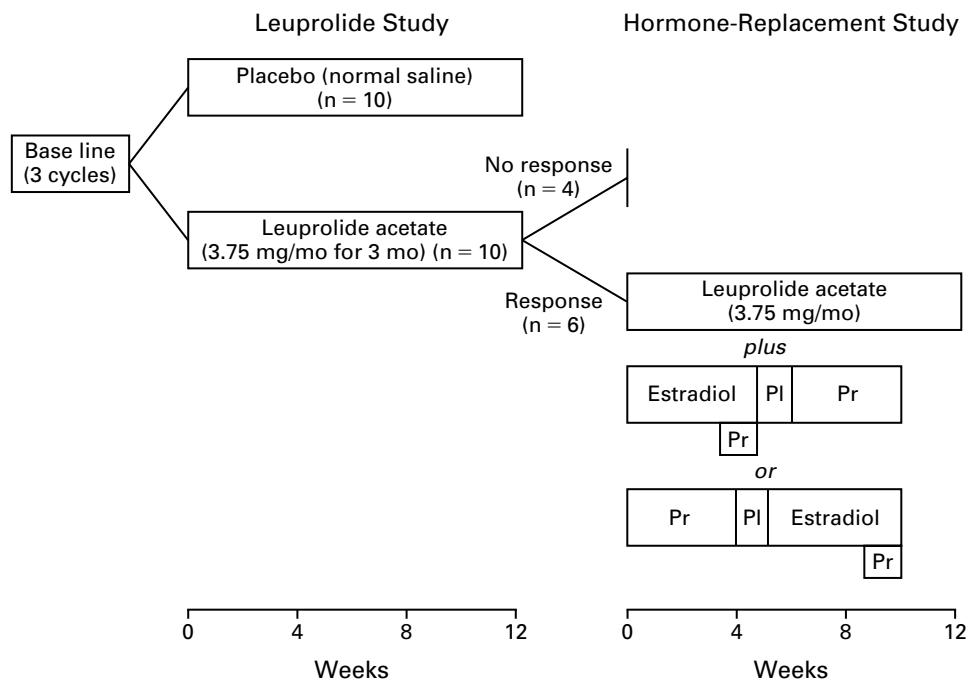


Figure 1. Design of the Studies of Ovarian Suppression with Leuprolide and Subsequent Estradiol or Progesterone Administration in Women with Premenstrual Syndrome.

In the leuprolide study, between days 2 and 6 after the onset of menses, women meeting criteria for premenstrual syndrome were randomly assigned to receive three monthly intramuscular injections of either 3.75 mg of leuprolide or normal saline. In the hormone-replacement study, women with premenstrual syndrome whose symptoms improved during ovarian suppression continued to receive leuprolide and also received in random order four weeks each of 17 β -estradiol (0.1 mg per day) and progesterone (Pr; 200 mg twice daily) in a double-blind crossover design. After the four weeks of estradiol replacement, all the women received both estradiol and progesterone for one week to precipitate progesterone-withdrawal-induced shedding of the endometrium. PI denotes placebo.

had any current medical illness, and all had a normal physical examination. None of the women with premenstrual syndrome had had any psychiatric illness within the previous two years, and none of the normal women had ever had a psychiatric illness, as determined by a structured diagnostic interview, the Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders* (third edition, revised).⁶ Four women with premenstrual syndrome had a history of affective disorder.

The women with premenstrual syndrome came to our clinic in response to advertisements in the local newspapers or were referred by their physicians. All these women confirmed the timing and severity of their mood-related symptoms prospectively by rating themselves daily for three months using a three-item visual-analogue scale, as described elsewhere.⁷⁻⁹ Each woman had an increase of at least 30 percent (relative to the range of the scale used) in her mean self-ratings of negative moods (depression, anxiety, and irritability) in the seven days before her menses as compared with the ratings for the seven days afterward in at least two of the three base-line cycles. The normal women were recruited by advertisement to participate in a study of the role of hormones in behavior. None had any premenstrual symptoms using the same daily rating scales during a two-month base-line period.

The protocol was approved by the National Institute of Mental Health Intramural Research Subpanel and the Food and Drug Administration, and written informed consent was obtained

from all the women. The normal women were paid for their participation according to the schedule of payment issued by the National Institutes of Health Normal Volunteer Office.

Study Design

Leuprolide Study

After the initial base-line screening period and between days 2 and 6 after the onset of menses, the women with premenstrual syndrome were randomly assigned to receive three monthly injections of either the gonadotropin-releasing hormone agonist leuprolide acetate (3.75 mg) or an equal volume of saline placebo in a double-blind fashion (Fig. 1). If a woman subsequently had two normal menstrual periods and no hot flashes, she was considered to have received placebo and the treatment code was broken. Women who received placebo (all of whom were considered to have had no response as defined below) and who wished to participate in the hormone-replacement study received 3.75 mg of leuprolide per month on an open-label basis for an additional three months (commencing between days 2 and 6 after the onset of the menstrual period after the completion of the placebo trial).

Hormone-Replacement Study

In a follow-up study, women with premenstrual syndrome whose symptoms responded to ovarian suppression during the first three

months (under either double-blind or open-label conditions) continued to receive leuprolide for an additional three months to investigate the effects on mood of separately adding back physiologic doses of estradiol and progesterone. The women were randomly assigned to receive four weeks each of transdermal 17β -estradiol (Ciba-Geigy, Raritan, N.J.) at a dose of 0.1 mg per day and progesterone vaginal suppositories (Upsher-Smith Laboratories, Minneapolis) at a dose of 200 mg twice daily in a double-blind, placebo-controlled, crossover study with a one-week washout period between the periods of hormone administration. In addition, after the four weeks of estradiol administration, all the women received one week of both estradiol and progesterone to induce shedding of the endometrium. All the women received both active or placebo patches and suppositories each day for 10 weeks.

To determine whether estradiol and progesterone affected the behavior of only the women with premenstrual syndrome, the normal women participated in a similar protocol except that they received leuprolide alone for only two months before starting the hormone-replacement protocol.

Finally, a subgroup of five women with premenstrual syndrome received placebo hormone replacement (i.e., both placebo patches and suppositories) for one month before the administration of estradiol or progesterone. This modification of the protocol was intended to control for the woman's awareness that she was taking something during the hormone-replacement period. This was done after two rather than three months of leuprolide administration to avoid extending the duration of leuprolide treatment.

Assessment of Symptoms

Symptom-rating forms assessing the severity of common symptoms of premenstrual syndrome were completed daily by all the women during both studies. The forms included a 16-item extended version of the visual-analogue scale used during the three-month base-line phase that was completed each evening (the women were instructed to rate how they felt at the moment they were completing the form) and a modification of the Daily Rating Form,^{10,11} also completed each evening (the women were instructed that the ratings should represent a composite rating for the previous 12 hours). The ratings on both the Daily Rating Form and the visual-analogue scale assessed the severity of common symptoms of premenstrual syndrome.^{12,13} Specifically, the Daily Rating Form measured the severity of symptoms such as sadness, anxiety, irritability, cravings for food, impaired function, bloating, and breast pain; the variables assessed by the visual-analogue scale included sadness, anxiety, mood swings, appetite, and global feelings (i.e., "feel best ever" vs. "feel worst ever"). In addition, the women recorded the presence and severity of hot flashes (a potential side effect of leuprolide) daily. The following standardized rating scales were completed during each clinic visit: the Beck Depression Inventory¹⁴; the Spielberger Anxiety Inventory-State Form¹⁵; and both the patient and observer forms of the Rating Scale for Premenstrual Tension Syndrome.¹⁶

Blood samples were drawn every two weeks throughout the study. The samples were centrifuged, and aliquots of plasma were frozen at -20°C until the time of assay.

Hormone Assays

Plasma progesterone and estradiol (after extraction and Celite chromatography) were measured by radioimmunoassay as described previously.^{17,18} All samples from each woman with premenstrual syndrome were paired with the samples from at least one normal woman and analyzed in a single assay. The values are reported as the means (\pm SD) of four samples (one obtained every two weeks for eight weeks) before and after the initiation of hormone replacement.

Statistical Analysis

The daily ratings for each symptom were averaged for each of the four weeks preceding the leuprolide or saline injections and

for the four weeks of estradiol and progesterone replacement in the hormone-replacement study. In the leuprolide study the means of the daily symptom ratings were compared by analysis of variance with repeated measures (SPSS/Systat, Chicago), with treatment (leuprolide vs. placebo) as the variable between groups and study phase (base line vs. treatment), month, and week as the variables within groups. The efficacy of leuprolide as compared with placebo was further determined in post hoc comparisons of symptoms during weeks 2 and 4, which were the weeks with maximal variation in symptoms (postmenstrual vs. premenstrual) during base line. Since the blinding could not be maintained in those receiving placebo for more than two months, we selected the last two months of treatment to compare the effects of leuprolide and placebo. The results presented are the weekly symptom scores averaged across the last two months of each study phase (base line and treatment). The absence of a response to leuprolide or saline was defined as the persistence of symptoms of sadness, anxiety, or irritability during any two weeks during the last two months of treatment as reflected by weekly mean scores on the Daily Rating Form of 2.5 or greater (on a scale of 1 to 6).

In the hormone-replacement study, symptom ratings were analyzed by repeated-measures analysis of variance, with the study group (women with premenstrual syndrome or normal women) as the variable between groups and treatment (leuprolide alone, estradiol plus leuprolide, or progesterone plus leuprolide), month, and week as the variables within groups. Standardized scores (e.g., for the observer form of the Rating Scale for Premenstrual Tension Syndrome) were analyzed in a similar manner. Finally, repeated-measures analysis of variance was used to examine the effects of placebo replacement in the subgroup of women with premenstrual syndrome. Symptom ratings during weeks 2 and 3 of hormone replacement (the weeks in which symptoms were maximal) were contrasted with comparable weeks during the period in which leuprolide alone was given in women with premenstrual syndrome and normal women.

Since there were no main or interactive effects of the month on analysis of variance, we did not perform separate analyses for progesterone and estrogen (since statistically they were equivalent). Hence, we present mean values for the two months during each of the treatment phases (leuprolide alone and leuprolide with replacement hormone). The data obtained during the months with estrogen and progesterone replacement are nonetheless given separately.

RESULTS

Two women with premenstrual syndrome who were assigned to receive placebo withdrew from the study for personal reasons at the end of the leuprolide study; therefore, only 18 women with premenstrual syndrome were potentially eligible to participate in the hormone-replacement study. The results of both the daily visual-analogue scale and standardized symptom scores (i.e., the Beck Depression Inventory and the Spielberger Anxiety Inventory) were similar to those of the Daily Rating Form and to the scores on the observer form of the Rating Scale for Premenstrual Tension Syndrome, respectively; consequently only results from the last two scales are presented.

Leuprolide Study

In the women with premenstrual syndrome who were receiving leuprolide, almost all symptom scores for week 4 were significantly lower than those for both week 4 of the base-line period and week 4 in the women with premenstrual syndrome who were

TABLE 1. SYMPTOM RATINGS DURING BASE-LINE PERIOD AND DURING THE ADMINISTRATION OF LEUPROLIDE OR PLACEBO IN 20 WOMEN WITH PREMENSTRUAL SYNDROME.*

SYMPTOM AND GROUP	BASE LINE		TREATMENT		P VALUE†
	WEEK 2 (POSTMENSTRUAL)	WEEK 4 (PREMENSTRUAL)‡	WEEK 2	WEEK 4	
	mean ±SD				
Sadness					
Leuprolide	1.8±0.5	3.7±1.0	1.6±0.6	1.5±0.4§¶	0.01
Placebo	1.8±0.3	3.4±1.2	1.6±0.5	2.8±1.0	
Anxiety					
Leuprolide	1.5±0.5	3.6±0.9	1.3±0.3	1.4±0.3§¶	0.04
Placebo	1.7±0.7	3.9±0.9	1.8±0.8	3.2±0.8§	
Bloating					
Leuprolide	1.6±0.4	3.8±1.0	1.3±0.3	1.5±0.6§¶	0.06
Placebo	1.2±0.4	3.9±1.0	1.9±1.2	3.6±1.0	
Breast pain					
Leuprolide	1.2±0.4	3.0±1.2	1.0±0.1	1.1±0.3§¶	0.07
Placebo	1.0±0.1	2.9±1.2	1.3±0.5	2.3±1.2	
Food cravings					
Leuprolide	1.6±0.7	3.3±1.5	1.9±0.7	1.7±0.7§**	0.009
Placebo	1.7±0.6	3.6±1.5	1.7±0.8	3.0±1.1	
Impaired function					
Leuprolide	1.7±0.4	3.5±1.2	1.5±0.4	1.5±0.6§**	0.005
Placebo	1.7±0.6	2.8±1.2	1.6±0.7	2.5±1.1	
Irritability					
Leuprolide	1.6±0.5	3.6±0.9	1.7±0.6	1.5±0.5§¶	0.009
Placebo	2.0±0.8	4.0±0.9	2.0±0.8	3.3±0.9	

*There were 10 women in each group. Scores range from 1 (symptoms not present) to 6 (symptoms present in the extreme). The Bonferroni t-test was used for all post hoc comparisons. All P values are two-tailed.

†The P value is for the interaction between treatment (leuprolide or placebo), study phase (base line or treatment), and week by repeated-measures analysis of variance.

‡P<0.05 for all paired comparisons with week 2.

§P≤0.05 for the comparison with base-line values at week 4.

¶P<0.05 for the comparison with the placebo group at week 4.

||P<0.05 for the comparison with values at week 2.

**P≤0.1 for the comparison with the placebo group at week 4.

receiving placebo (Table 1). Moreover, the symptom scores among the women who were receiving leuprolide did not differ significantly between week 2 and week 4, indicating that cyclicity of symptoms was eliminated. There were no significant differences in symptom scores between week 4 of the placebo period and week 4 of the base-line period, except for the symptom of anxiety, and there were significant differences in symptom scores between weeks 2 and 4 during placebo administration (Table 1). No woman responded to placebo. Eight of 18 women who received leuprolide under double-blind (4 of 10) or open-label (4 of 8) conditions had no response; therefore, only the remaining 10 women were included in the hormone-replacement study.

Hormone-Replacement Study

As shown in Figure 2 for the symptom of sadness, women with premenstrual syndrome had significant

increases in symptoms during treatment with leuprolide plus replacement hormone as compared with treatment with leuprolide alone. The normal women, in contrast, remained asymptomatic during hormone replacement. Both the daily symptom scores and the scores on the Rating Scale for Premenstrual Tension Syndrome were significantly higher in women with premenstrual syndrome than in the normal women during the periods of estradiol and progesterone replacement (Tables 2, 3, and 4 and Fig. 2). The symptoms that increased significantly in women with premenstrual syndrome (but not normal women) were sadness, anxiety, bloating, impaired function, and irritability (Table 2). The findings were similar when the most symptomatic week in each study (highest weekly mean score during treatment with leuprolide alone or leuprolide and hormone replacement) or when the average of the four weekly mean symptom scores was analyzed.

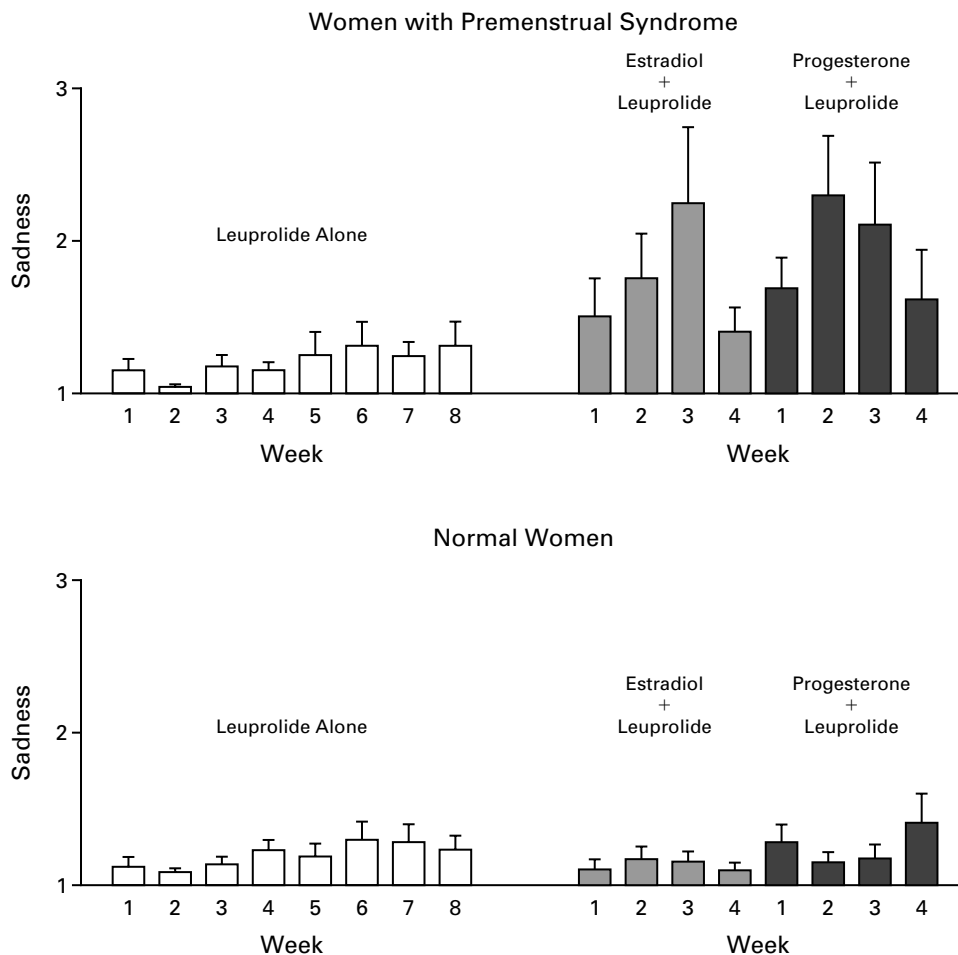


Figure 2. Recurrence of Symptoms of Premenstrual Syndrome during the Addition of Estradiol or Progesterone to the Leuprolide Regimen.

Ten women with premenstrual syndrome and 15 normal women had minimal mood and behavioral symptoms while receiving leuprolide. In contrast, the women with premenstrual syndrome but not the normal women had a significant increase in sadness during the administration of either estradiol or progesterone. Values are the means (\pm SE) of the seven daily scores on the sadness scale of the Daily Rating Form for each of the eight weeks preceding hormone replacement (leuprolide alone) and during the four weeks of estradiol (plus leuprolide) and progesterone (plus leuprolide) replacement. A score of 1 indicates that the symptom was not present, and a score of 6 indicates that it was present in the extreme.

In contrast to the return of symptoms during replacement with estradiol or progesterone, there was no significant increase in symptom scores during placebo replacement in the five women with premenstrual syndrome who received a month of leuprolide plus placebo in addition to the active replacement regimens. For example, the scores for the Rating Scale for Premenstrual Tension Syndrome were significantly higher during the active-replacement phase (progesterone and estradiol) than during the placebo-replacement phase; scores during the latter phase did not significantly differ from the

low scores during the period of leuprolide treatment alone (Table 4).

Plasma Hormone Concentrations

The mean (\pm SD) plasma concentrations of both estradiol (8.1 ± 5.6 pg per milliliter [30 ± 21 pmol per liter]) and progesterone (0.3 ± 0.1 ng per milliliter [1.0 ± 0.3 nmol per liter]) were in the hypogonadal range (signifying ovarian suppression) during the administration of leuprolide alone and were elevated during the respective period of hormone replacement (estradiol, 110 ± 45 pg per milli-

TABLE 2. SYMPTOM RATINGS DURING THE ADMINISTRATION OF LEUPROLIDE AND LEUPROLIDE PLUS HORMONE REPLACEMENT IN 10 WOMEN WITH PREMENSTRUAL SYNDROME AND 15 NORMAL WOMEN.*

SYMPTOM AND GROUP	LEUPROLIDE ALONE		LEUPROLIDE + HORMONE REPLACEMENT		P VALUE†
	WEEK 2	WEEK 3	WEEK 2	WEEK 3	
	mean ±SD				
Sadness					
Women with premenstrual syndrome	1.2±0.3	1.2±0.2	2.0±0.8	2.2±0.9‡§	0.003
Normal women	1.2±0.3	1.2±0.3	1.2±0.2	1.2±0.3	
Anxiety					
Women with premenstrual syndrome	1.3±0.3	1.2±0.2	2.0±0.6	2.1±0.9‡§	0.01
Normal women	1.2±0.2	1.2±0.3	1.1±0.2	1.1±0.1	
Bloating					
Women with premenstrual syndrome	1.2±0.2	1.2±0.2	2.2±1.1	2.3±1.1‡§	0.10
Normal women	1.1±0.2	1.2±0.2	1.3±0.5	1.2±0.3	
Food cravings					
Women with premenstrual syndrome	1.5±0.8	1.5±0.7	1.3±0.5	1.6±1.0	0.30
Normal women	1.1±0.1	1.1±0.1	1.3±0.2	1.2±0.3	
Impaired function					
Women with premenstrual syndrome	1.2±0.2	1.3±0.3	1.7±0.7	1.8±0.8‡§	0.10
Normal women	1.2±0.4	1.2±0.3	1.1±0.3	1.2±0.4	
Irritability					
Women with premenstrual syndrome	1.3±0.2	1.4±0.5	2.1±0.7	2.2±0.8‡§	0.02
Normal women	1.3±0.4	1.3±0.3	1.3±0.2	1.3±0.3	

*Scores range from 1 (symptoms not present) to 6 (symptoms present in the extreme). The Bonferroni t-test was used for all post hoc comparisons. All P values are two-tailed. When consistent with hypothesized interactions between study group and study phase, selected trend differences were assessed with post hoc comparisons. For this analysis, symptoms during estradiol and progesterone therapy were averaged, given the absence of main or interactive effects of the month of treatment.

†The P value is for the interaction between treatment (leuprolide alone or leuprolide plus hormone replacement), study group (women with premenstrual syndrome or normal women), and week by repeated-measures analysis of variance.

‡P<0.05 for the comparison with leuprolide alone at week 3 in the women with premenstrual syndrome.

§P<0.05 for the comparison with leuprolide plus hormone replacement at week 3 in the normal women.

liter [407±166 pmol per liter]; and progesterone, 11.8±5.7 ng per milliliter [38±18 nmol per liter]. The mean plasma concentrations of estradiol and progesterone did not differ significantly between women with premenstrual syndrome and the normal women.

DISCUSSION

Apart from the temporal linkage of symptoms of premenstrual syndrome to the luteal phase of the menstrual cycle, the possible role of gonadal steroids in the etiology of premenstrual syndrome has been suggested by reports of the efficacy of ovarian suppression with agonists of gonadotropin-releasing hormone^{2-5,21-24} and the androgen danazol.²⁵ In contrast, the occurrence of symptoms despite the elimination of the mid-to-late luteal phase of a menstrual cycle suggests the lack of pathophysiologic relevance

of the luteal phase in premenstrual syndrome,¹ a suggestion consistent with the lack of efficacy of progesterone therapy.²⁶ Nevertheless, the possibility remained that hormonal events during either the follicular or periovulatory phase of the menstrual cycle may initiate the onset of the symptoms of premenstrual syndrome.

In this study we first identified women with premenstrual syndrome whose symptoms were linked to changes in gonadal steroids by selecting only women who had a remission of symptoms during ovarian suppression. In women meeting this criterion, we replaced estrogen and progesterone separately in an attempt to determine the specificity of their effects on the symptoms of premenstrual syndrome.

The administration of leuprolide to women with premenstrual syndrome decreased the severity of symptoms and eliminated the cyclicity of symptoms,

further confirming the efficacy of agonists of gonadotropin-releasing hormone in this condition. Only 10 of 18 women with premenstrual syndrome who were receiving leuprolide responded, results consistent with the majority of studies showing the efficacy of short-term therapy with a gonadotropin-releasing hormone agonist in some, but not all, women.⁵

In the women with premenstrual syndrome, the symptoms returned and were maximal one or two weeks after the initiation of either estradiol or progesterone replacement, confirming previous reports by Muse (personal communication, 1989) and Mortola et al.²² These results are also consistent with observations that changes in gonadal steroids early in the menstrual cycle are correlated with symptoms appearing later in the cycle in women with premenstrual syndrome.²⁷⁻²⁹ With our prior findings that symptoms of premenstrual syndrome occur independently of the mid-to-late luteal phase of the menstrual cycle,¹ these results suggest that follicular or periovulatory²⁷ changes in either estradiol or progesterone secretion may be critical to the onset of symptoms of premenstrual syndrome. Given the attenuation of symptoms during the last week of replacement with estradiol or progesterone, we cannot predict whether long-term (or low-dose) estrogen or progesterone replacement would continue to precipitate adverse mood symptoms.

The most striking finding in this study is that although women with premenstrual syndrome had few symptoms during ovarian suppression and recurrence of symptoms during ovarian steroid hormone replacement, the normal women had no perturbation of mood during either manipulation. These observations, in conjunction with the normal pituitary-gonadal function in these women, suggest that normal plasma concentrations of gonadal steroids can trigger an abnormal response — deterioration in mood state — in susceptible women.

We are indebted to TAP Pharmaceuticals, Deerfield, Ill., for providing depot leuprolide acetate; to Ciba-Geigy, Raritan, N.J., for providing estradiol skin patches; to Upsher-Smith Laboratories, Minneapolis, for providing progesterone suppositories; to Ms. Candace Davis for expert assistance with figure preparation; and to Dr. John Bartko for statistical consultation.

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