LACK OF EFFECT OF INDUCED MENSES ON SYMPTOMS IN WOMEN WITH PREMENSTRUAL SYNDROME

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Abstract *Background.* No physiologic abnormality of the luteal phase has been consistently demonstrated in women with premenstrual syndrome (PMS). Using the progesterone antagonist mifepristone, we truncated the late luteal phase of the menstrual cycle in a blinded fashion to evaluate the relation of the events of the late luteal phase to the symptoms of PMS.

Methods. Fourteen women with PMS were given mifepristone (12.5 or 25 mg per kilogram of body weight) by mouth on the seventh day after the surge of luteinizing hormone. On the sixth through the eighth days after the surge, they also received injections of either placebo or human chorionic gonadotropin (2000 IU). Seven women with PMS received placebo instead of both mifepristone and human chorionic gonadotropin. All the women completed daily questionnaires measuring a variety of mood-related and somatic symptoms.

Results. Mifepristone consistently induced menses. The women receiving only mifepristone had plasma progesterone levels like those of the follicular phase (<3 nmol per liter) within four days, whereas all the other women had plasma progesterone levels characteristic of the luteal phase (>8 nmol per liter) for at least seven days after treatment. In all three groups, the severity of symptoms was significantly higher after treatment than before, according to an analysis of variance with repeated measures. The level and pattern of the ratings of symptom severity were similar in all treatment groups.

Conclusions. Neither the timing nor the severity of PMS symptoms was altered by mifepristone-induced menses or luteolysis. The temporal association of typical PMS symptoms with an artificially induced follicular phase suggests that endocrine events during the late luteal phase do not directly generate the symptoms of PMS. (N Engl J Med 1991; 324:1174-9.)

THE premenstrual syndromes (PMS) are a group of disorders characterized by affective, behavioral, and somatic symptoms that occur consistently during the luteal phase of the menstrual cycle. The linkage of the symptoms of PMS to a specific phase of the cycle has led to the assumption that PMS reflects either a physiologic abnormality or an abnormal response to the normal hormonal changes during the luteal phase. Numerous etiologic hypotheses have been proposed, based on the cyclic variation of gonadal steroids or other factors during the menstrual cycle. No physiologic abnormalities of basal[1,2] or stimulated[3-6] plasma hormone levels have been consistently identified, however, that could mediate the development or expression of symptoms of PMS. Nonetheless, most treatments recommended for this condition are purported to correct a hypothesized physiologic abnormality of the luteal phase by either furnishing a substance that is believed to be deficient or suppressing cyclic ovarian function.

If an unidentified physiologic abnormality during the late luteal phase causes PMS, then the elimination of this phase should prevent its appearance. If, however, typical PMS symptoms appeared despite the elimination of the middle and late parts of the luteal phase, this would suggest that hormonal events during that phase are not the proximal cause and that treatments designed to normalize function during the late luteal phase have no rational basis. The purpose of this study was to test the hypothesis that the occurrence of the late luteal phase is not necessary for the development of the symptoms of premenstrual syndrome. With the antiprogestin agent mifepristone, one can block the actions of progesterone, produce regression of the corpus luteum, and terminate the luteal phase. The simultaneous administration of human chorionic gonadotropin (hCG) preserves the corpus luteum (and thus prevents the mifepristone-induced truncation of the luteal phase) but does not interfere with the progesterone-blocking (and menses-inducing) action of the antiprogestin agent. Thus, by administering mifepristone with or without hCG, one can either eliminate or preserve the hormonal events of the luteal phase. If the late luteal phase of the menstrual cycle is not essential for the development of the mood-related and behavioral symptoms of women with PMS, then the pattern and severity of these symptoms should not differ significantly between women in whom the phase has been truncated and those in whom it has been preserved.

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METHODS

Background

Mifepristone (17β-hydroxy-11β-[4-dimethyl-aminophenyl-1]-17α-[prop-1-ynyl]-estra-4,9-dien-3-one) is a 19-norsteroid congener of the progestin norethindrone with a high affinity (approximately five times that of progesterone) for the human progestin receptor and potent antiprogestational activity in laboratory animals and humans.[7-13] A single oral midluteal dose of 10 mg per kilogram of body weight was associated with luteolysis and vaginal bleeding within 72 hours in all women tested; during the next menstrual cycle, the pattern of progesterone secretion was normal and the mean (±SD) length of the cycle was 30±2 days.[13] Thus, the luteal phase was truncated and the cycle rhythm advanced. If, however, in addition to the administration of mifepristone, hCG was given in a dose of 2000 IU intramuscularly for three days (the day before, the day of, and the day after the administration of mifepristone), vaginal bleeding occurred within 72 hours and again 8 to 10 days after the mifepristone-induced menses; the menstrual cycle subsequent to

the second episode of bleeding lasted approximately 28 days. Thus, despite midluteal vaginal bleeding, the luteal phase was maintained and the cycle was not reset. Therefore, administering mifepristone alone caused luteolysis; with the administration of hCG, mifepristone induced menses by blocking the support of the endometrium provided by progesterone, but luteal function was preserved, and physiologic luteolysis occurred later at the expected time. In addition, after the induced vaginal bleeding, the women were unaware of the presence or absence of hCG (and hence of their actual menstrual-cycle phase) for 8 to 10 days, until they had (or did not have) the second episode of vaginal bleeding.[13]

Selection of Subjects

The subjects of this study were 18 women with prospectively confirmed PMS. They all came to our clinic in response to advertisements in the local newspapers and a hospital newsletter or were referred by their personal physicians. All reported menstrual cycles of regular length, which in the individual women ranged from 21 to 35 days. None were taking psychoactive medications, hormonal preparations (including oral contraceptives), mineral or vitamin supplements, or nonsteroidal antiinflammatory drugs (all putative treatments for PMS). None had any medical illness currently (either when recruited or at the time of testing) or within the previous year or any psychiatric illness within the previous two years, as determined by the administration of a semistructured diagnostic interview, the Modified Schedule for Affective Disorders and Schizophrenia — Lifetime (SADS-L).[14] The presence of Axis II psychiatric diagnoses[15] was not determined. Before the study, all the 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.[16] Each woman had an increase of at least 30 percent in her mean self-ratings of negative moods (depression, anxiety, and irritability) in the seven days before menses, as compared with the ratings for the seven days afterward, in at least two of three cycles during this three-month period. As described by Schnurr,[17] this method correlates highly with the method of measuring the effect size in order to establish that the severity criteria for PMS have been met. Women were excluded from this study if they had mood symptoms during the follicular phase of the cycle — i.e., postmenstrual mean mood ratings below the midpoint of the rating scale. These criteria were slightly more stringent than those adopted by the working group of the National Institute of Mental Health (NIMH) PMS Research Workshop; the differences were the specification of an interval of seven rather than five days before and after menses and the requirement that serious postmenstrual mood symptoms (i.e., during the follicular phase) be absent. Approximately 30 percent of the women presenting to our clinic with symptoms of PMS met these diagnostic criteria. We retrospectively examined the records of the women participating in the study and found that all those selected for participation also met the criteria for late luteal phase dysphoric disorder of the *Diagnostic and Statistical Manual of Mental Disorders* (third edition, revised).[15]

The protocol was approved by the NIMH intramural research review subpanel. Before the beginning of the study, written informed consent was obtained from all subjects for participation in a study investigating the relation between hormonal changes and menstrually related disorders of mood.

Protocol

After the initial three-month screening period, and six days after the luteinizing hormone surge (as determined by daily rapid plasma measurements in 10 women and an Ovuquick [Monoclonal Antibodies] urinary test in 11 women), the women were randomly assigned to one of three groups. These groups represented combinations of mifepristone (Roussel–UCLAF, Paris) (12.5 or 25 mg per kilogram) administered by mouth, hCG (Organon, Boxtel, the Netherlands; 1000 IU per milliliter) (2000 IU) administered by intramuscular injection, and placebo tablets or injections containing placebo (normal saline). Group 1 received mifepristone (25 mg per kilogram) orally on day 7 after the luteinizing hormone surge and placebo administered intramuscularly on days 6 through 8. Group 2 was identical to group 1, except that the oral dose of mifepristone was 12.5 mg per kilogram, and hCG (2000 IU) was given intramuscularly. This lower dose (12.5 mg per kilogram) was selected for administration in group 2 because it was sufficient to induce menses within 48 to 72 hours (by blocking progesterone receptors in the uterus) but insufficient to induce luteolysis and thus terminate the luteal phase in the presence of hCG. The higher dose used in group 1 (25 mg per kilogram) was sufficient to ensure both the induction of menses (blockade of uterine progesterone receptors) and luteolysis in all women. To control for the effects of the medications on the symptoms of PMS, a third group was included. Group 3 was identical to groups 1 and 2, except that placebo was substituted for both mifepristone and hCG. Because group 3 was designed purely to control for the immediate effects of a pharmacologic intervention on the symptoms of PMS, the study was stopped in these women after the onset of their normal menstrual period, and they were offered the opportunity of random assignment to either group 1 or group 2.

Urinary hCG levels were determined in all women immediately before the administration of mifepristone to ensure that no woman was pregnant. Daily ratings of self-reported symptoms were completed during the menstrual cycle in which medication was administered and during the following cycle. The rating instruments included a 16-item extended version of the visual-analogue scale report form used during the three-month screening phase and a 21-item, six-point scale representing a slight modification of the daily rating form developed by Endicott and Halbreich.[18,19] The ratings on both the visual-analogue scale and the daily rating form assess the severity of common symptoms of PMS, including sadness, anxiety, irritability, mood lability, cravings for food, impaired concentration, bloating, and breast pain. The visual-analogue scale was completed at the same time each evening, and the women were asked to rate how they felt at the moment they were completing the form. The modified daily rating form was completed at the same time, but the women were told that their ratings should represent a composite rating for the previous 12 hours. In addition, they completed the following standardized rating scales on the day each blood sample was drawn: the Beck Depression Inventory,[20] a self-reported measure of the severity of depression; the Spielberger State–Trait Anxiety Inventory — State form,[21] a self-reported measure of the severity of anxiety; and both the self and observer (rater) forms of the Rating Scale for Premenstrual Tension Syndrome (PMTS).[22] The raters saw the women in the clinic and were not aware of their group assignments.

Blood samples were drawn each morning for the first 11 days after the administration of hCG or placebo began and then three times a week until the beginning of the next menstrual cycle (except group 3, in which blood was drawn only until the first menses after the administration of placebo). The blood samples were centrifuged, and aliquots of plasma were frozen at −20°C until the time of assay.

Plasma Progesterone and Estradiol Assays

The plasma samples were assayed for progesterone by a method described elsewhere.[23] The intraassay coefficients of variation in the low and high regions of the standard curve were 4.6 percent and 8.5 percent, respectively, and the interassay coefficients of variation were 14.2 percent and 14.5 percent. The samples were purified with Celite chromatography and assayed for estradiol by a method described elsewhere.[24] The intraassay coefficients of variation in the low and high regions of the standard curve were 7.5 percent and 5.2 percent, respectively, and the respective interassay coefficients of variation were 11.6 percent and 12.3 percent. All samples from an individual woman were analyzed in a single assay.

Statistical Analysis

The daily self-ratings of symptoms (on the visual-analogue scale and the daily rating form) were analyzed as follows: the seven days before the luteinizing hormone surge, representing the follicular-phase days (phase 1), were compared with days 5 to 11 after the administration of mifepristone or placebo (phase 2). By day 5, plasma levels of mifepristone (half-life, approximately 24 hours), though not measured in this study, would be expected to be negligible. In this comparison, phase 2 distinguished the women in

group 1 (with plasma progesterone levels ≤3.0 nmol per liter) from those in groups 2 and 3 (with plasma progesterone levels >3.0 nmol per liter). The daily self-ratings of symptoms during the nine days before the luteinizing hormone surge were also compared with the ratings for the nine days after the administration of mifepristone or placebo. This period was selected for analysis because most of the women in groups 2 and 3 had either a second menses (group 2) or their regular menses (group 3) within nine days of the administration of mifepristone and hCG (in group 2) or of placebo (in group 3). The daily self-ratings were compared by analysis of variance with repeated measures, with day and phase as the within-subjects factors and treatment group as the between-subjects factor. In addition, the scores on the Beck Depression Inventory, the Spielberger State–Trait Anxiety Inventory, and the PMTS-Self and PMTS-Rater scales during the nine days after the administration of mifepristone or placebo were compared between treatment groups by analysis of variance with repeated measures, with the number of days after mifepristone or placebo as the within-subjects factor and treatment group as the between-subjects factor. The variables were expressed as means ±SD.

Correlations between plasma hormone levels and ratings of symptoms were performed with the Spearman correlation coefficient. This analysis was performed for each woman, for all women, and for women grouped according to treatment group or menstrual-cycle phase.

Results

Characteristics of the Subjects

The women ranged in age from 31 to 44 years (mean, 38±5). Seven of the 18 women were parous, and all reported menstrual-cycle lengths of 21 to 35 days. The lengths of the menstrual cycle according to treatment group during the three months before the study were as follows: group 1 (mifepristone and placebo), 28±3 days; group 2 (mifepristone and hCG), 27±2 days; and group 3 (placebo and placebo), 27±2 days. The duration of recorded menstrual bleeding was 4±1, 4±1, and 5±1 days in groups 1, 2, and 3, respectively. The luteinizing hormone surge occurred on menstrual-cycle day 14±2. According to the modified SADS-L diagnostic interview, 8 of the 18 women had a history of affective disorder — 4 in group 1, 3 in group 2, and 1 in group 3.

Characteristics of the Menstrual Cycle

Seven women participated in each of the three groups. Three of the women originally in group 3 were randomly assigned to group 1 or 2 during the next menstrual cycle (one to group 1 and two to group 2). Menses occurred within 72 hours of the administration of mifepristone in all 14 women (after 48 hours in 13 and after 72 hours in 1). The seven women who received placebo instead of both mifepristone and hCG had menses within 10 days of the oral administration of placebo (range, 9 to 10). No woman had clinically important side effects after either active medication. The plasma progesterone levels were ≤3.0 nmol per liter in all seven women in group 1 (mifepristone only) four days after the administration of the drug. In groups 2 and 3 the plasma progesterone levels remained at luteal-phase levels (>8 nmol per liter) for 7 to 8 days and above follicular-phase levels (≤3.0 nmol per liter) until 10 to 11 days after the administration of mifepristone or placebo (Fig. 1).

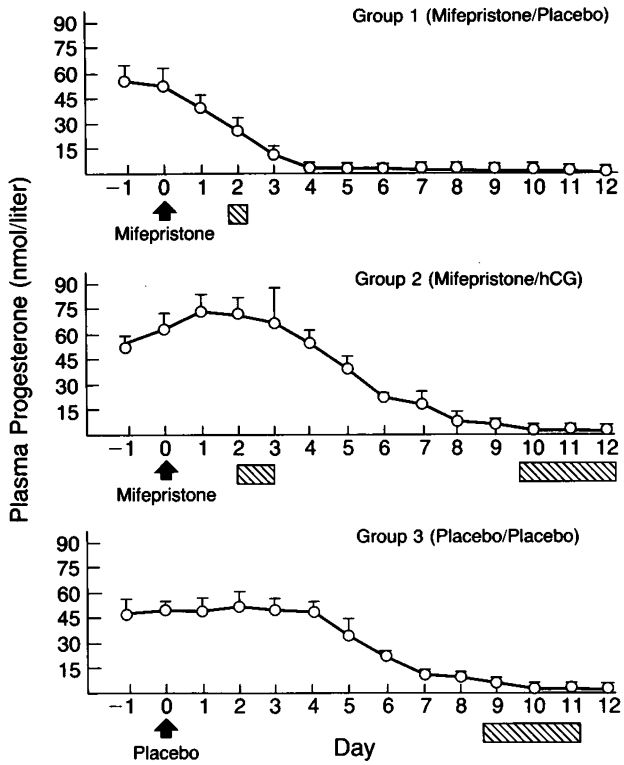

Figure 1. Mean (±SE) Plasma Progesterone Concentrations in the Study Groups after the Administration of Mifepristone or Placebo.

In the women in group 1, plasma progesterone levels were uniformly less than 3.0 nmol per liter four days after treatment, whereas the levels in the women with preserved luteal phases were higher (groups 2 and 3). The hatched bars indicate the day of onset of menses, and bars spanning several days indicate the range of dates of onset.

The mean menstrual-cycle lengths (defined as the interval between the onset of successive follicular phases) during the cycle in which mifepristone or placebo was administered were 22±3 days in group 1, 28±4 days in group 2, and 27±4 days in group 3. The menstrual-cycle lengths after mifepristone-induced menses were 33±7 days in group 1 and 26±2 days in group 2. All post-treatment cycles were ovulatory, as indicated by the fact that serum progesterone levels during the cycles reached the luteal-phase range (>8 nmol per liter).

Ratings of Symptoms

There was a significant increase in all daily ratings of symptoms (on the visual-analogue scale and the daily rating form) during the seven-day period (days 5 to 11) after the administration of mifepristone or placebo, as compared with the ratings for the seven days before the luteinizing hormone surge (i.e., phase 2 compared with phase 1). This effect was observed regardless of the medication administered (P not significant for the interaction of treatment with phase). No significant differences were found in the ratings of severity of symptoms during phase 2 among the three

groups. In fact, the ratings on the visual-analogue scale for sadness, anxiety, irritability, bloating, breast pain, and appetite and on the daily rating form for sadness, anxiety, irritability, bloating, and cravings all showed significant effects of phase but no significant effects of treatment or of the interaction of treatment with phase. This pattern of change in symptoms was also evident when we compared the nine days before the luteinizing hormone surge (the follicular phase) with the nine days after the administration of mifepristone. The results were similar with all the rating scales used, including the Beck Depression Inventory, the Spielberger Anxiety Inventory, and both the PMTS-Self and PMTS-Rater forms. The group means for anxiety, a representative PMS symptom, are shown in Table 1. In addition, the patterns of change in ratings are shown in Figure 2 for three selected symptoms, specifically anxiety and bloating on the daily rating form (representing a composite rating for the whole day) and anxiety on the visual-analogue scale (representing a rating at a fixed time each day). Figure 3 shows the daily mood ratings of one woman whose typical premenstrual symptoms began 10 days after the administration of mifepristone, when she had follicular-phase plasma levels of estradiol and progesterone.

It should be noted that the second randomization of three of the women in group 3 (placebo) to groups 1 (one woman) and 2 (two women) violated the presupposition of independence for the analysis of variance with repeated measures. The critical comparison in this study design was between groups 1 and 2, however; the women in these groups had a menstrual period after mifepristone and then entered either an artificially induced follicular phase (group 1) or a preserved luteal phase (group 2). Thus, we analyzed the same symptom ratings as described above, but with groups 1 and 2 alone, excluding the women who were randomized a second time. The results were identical to those of the original analysis — i.e., significant effects of phase and nonsignificant effects of treatment and interaction of treatment with phase.

Table 1. Summary of Daily Self-Ratings of Anxiety Symptoms.*

Test/Group†	Before Treatment	After Treatment	Both Phases
		mean ±SD	
Daily rating form			
Group 1	1.8±1.2	3.0±1.1	2.4±0.9
Group 2	1.2±0.3	2.1±0.9	1.6±0.4
Group 3	1.6±0.7	3.6±1.2	2.6±0.6
All groups	1.5±0.8	2.9±1.2	—
Visual-analogue scale			
Group 1	25.0±9.6	50.4±13.4	37.7±8.4
Group 2	28.0±9.6	35.2±17.9	31.6±15.9
Group 3	23.9±9.4	40.5±20.6	32.0±11.0
All groups	25.6±12.4	42.0±17.3	—

*This table summarizes the findings obtained by analysis of variance with repeated measures — i.e., significant effects of treatment phase (before and after treatment) in the ratings on the daily rating form ($F = 24.9$, $P<0.0001$, $df = 1,18$) and the visual-analogue scale ($F = 11.0$, $P = 0.004$, $df = 1,18$). However, the pattern and severity of symptoms after the administration of mifepristone (follicular phase), mifepristone and hCG (luteal phase), or placebo (luteal phase) were not significantly different (absence of effects of group and of interaction of group with phase). After mifepristone or placebo, therefore, symptoms developed independently of menstrual-cycle phase.

†There were seven women in each group.

Symptom–Hormone Correlations

There was no correlation between any of the symptoms and the plasma levels of progesterone or estradiol, regardless of the medication received or the menstrual-cycle phase. Furthermore, there was no significant correlation between the levels of these gonadal steroids and the mood or behavior ratings in any individual woman.

Discussion

Neither blockade of the action of progesterone alone nor truncation of the luteal phase of the cycle altered the course or severity of the symptoms of PMS, and these symptoms developed and progressed during the hormonal conditions of the follicular phase. This was true not only of mood-related symptoms, but also of a number of the somatic symptoms typically associated with PMS. A significant effect of phase was found, consistent with the usual temporal appearance of PMS symptoms; thus, the absence of a significant treatment effect was not due to the absence of symptoms of PMS during the study. The results were independent of the frame of reference (composite or cross-sectional) or type of rating instrument used. We also found no relation between PMS symptoms and plasma levels of progesterone and estradiol.

Although PMS is partly defined by its synchronization with the normal hormonal changes of the menstrual cycle, no direct effect of any of these hormones on the symptoms of PMS has been identified. Thus, the timing of these symptoms is open to at least two explanations. First, the symptoms could be caused directly by hormonal changes that are as yet unidentified, or alternatively they could represent abnormal sensitivity or responsiveness to the normal physiology of the menstrual cycle. The symptoms of PMS may be triggered by hormonal events occurring earlier in the cycle than the late luteal phase, in a manner consistent with reports that the suppression of ovulation results in remission of PMS symptoms.[25-28] Second, PMS symptoms may be part of a cyclic mood disorder that is synchronized with the menstrual cycle but not caused by it. This mood disorder could then become temporarily desynchronized from the rhythm of the menstrual cycle in a manner analogous to the phenomenon of jet lag in travelers, in which circadian rhythms temporarily become desynchronized or dissociated from the diurnal cues of the new time zone.

Post hoc analysis revealed a history of affective disorder in four of the five women in whom PMS was relatively dissociated from the late luteal phase of the menstrual cycle. This observation is consistent with either the "triggering" or "synchronization" mecha-

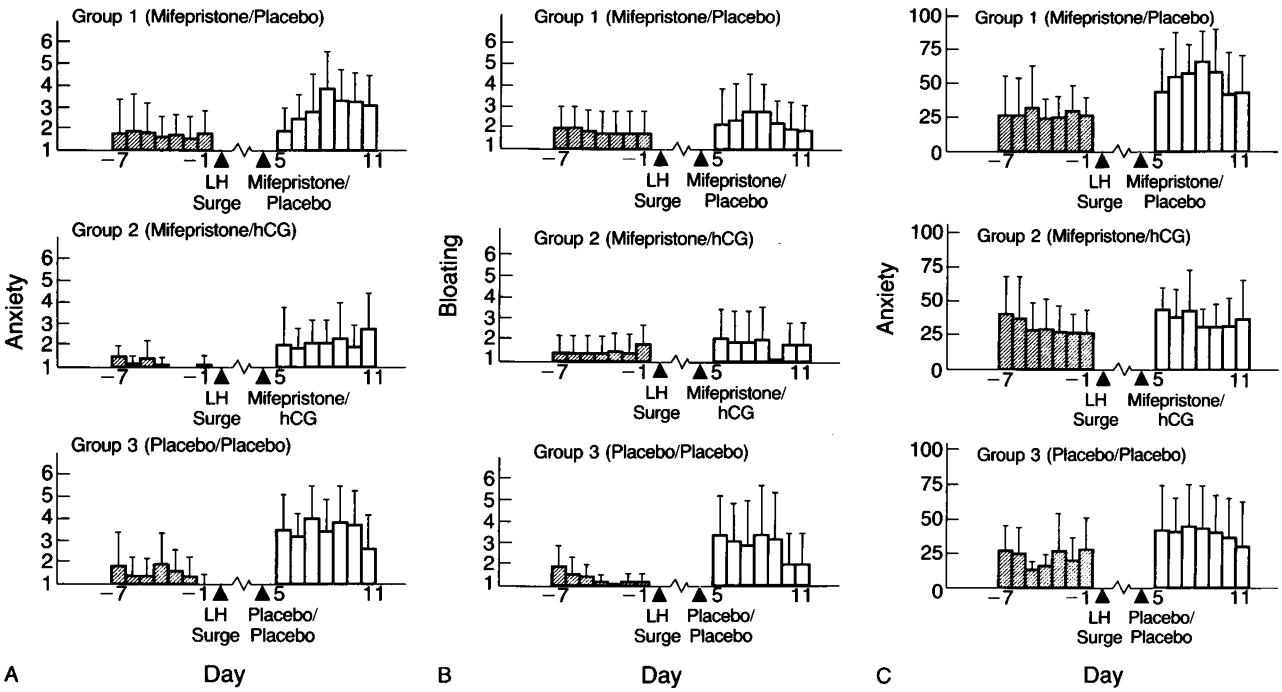

Figure 2. Absence of Effect of Truncation of the Late Luteal Phase on the Appearance of PMS Symptoms, According to Mean (±SD) Self-Rating Scores for the Three Groups.

Analysis of variance with repeated measures showed significant increases in all daily self-ratings of symptoms from day 5 through day 11 after the administration of mifepristone or placebo (open bars), as compared with the ratings from the seven days before the luteinizing hormone surge (the follicular phase; shaded bars). The patterns of change in the symptom ratings for anxiety (effect of phase: $F = 24.9$, $P<0.001$, $df = 1,18$) and bloating (effect of phase: $F = 13.3$, $P = 0.002$, $df = 1,18$) on the daily rating form are shown in Panels A and B, respectively; a score of 1 indicates that the symptom was not present, and a score of 6 indicates that it was present in the extreme. The patterns of change in the ratings for anxiety on the visual-analogue scale (effect of phase: $F = 11.04$, $P = 0.004$, $df = 1,18$) are shown in Panel C; a score of 0 on this scale denotes least anxious ever, and a score of 100 most anxious ever. The increase in symptoms was comparable in all three groups despite the truncation of the luteal phase in group 1. (There were nonsignificant effects of treatment group and interaction of treatment group with phase in all daily ratings of symptoms.)

nisms. A hormonal event occurring before the late luteal phase of the menstrual cycle might trigger PMS symptoms in women whose history of depression increased their vulnerability to subsequent mood disturbances. Alternatively, the menstrual cycle might act to entrain an otherwise autonomous cyclic affec-

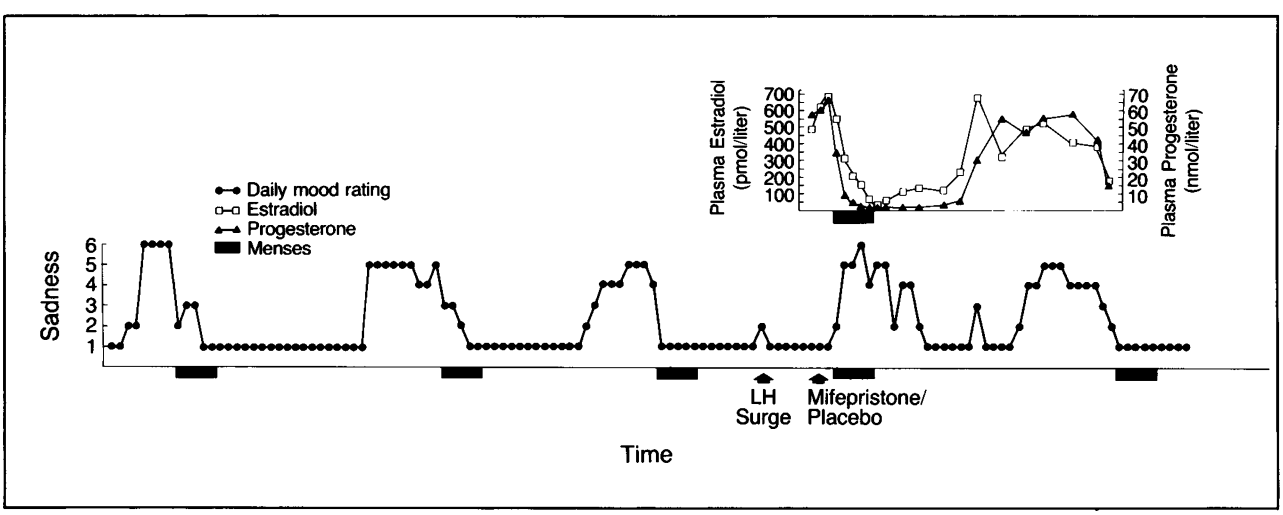

Figure 3. Occurrence of PMS Symptoms during a Mifepristone-Induced Follicular Phase in One Woman in Group 1.

The pattern of ratings for sadness on the daily rating form is shown at left for one woman during three base-line menstrual cycles. A rating of 1 denotes no sadness, and a rating of 6 extreme sadness. After the administration of mifepristone, the woman had typical premenstrual mood symptoms during the drug-induced follicular phase of the menstrual cycle, as confirmed by the plasma levels of gonadal steroids shown above.

tive disorder in some of these women. Two of the women who received mifepristone alone, however, did not have PMS symptoms when the menstrual cycle was reset, although these individual effects were obscured in the group statistics. The possibility still exists, therefore, that in some women with PMS there is an obligatory relation between PMS and the endocrine events of the late luteal phase.

One might hypothesize that the changes in mood in group 1 during the experimentally induced follicular phase resulted from the blockade of central progesterone receptors by mifepristone. Several factors militate against this explanation. First, in at least one study there were no changes in mood in women after the administration of mifepristone.[29] Second, the symptoms of PMS typically begin during the early-to-mid-luteal phases, a time when plasma progesterone levels are either increasing or at their plateau, and thus it is unlikely that blockade of the action of progesterone would trigger the onset of premenstrual symptoms. Furthermore, if mifepristone caused symptoms due to a blockade of progesterone receptors in the central nervous system, it would be expected that all the women receiving mifepristone alone would have had their typical symptoms of PMS, but they did not. Finally, the drug has a plasma half-life of 24 hours; thus, at the time that many of the women in group 1 were experiencing their symptoms (five or more days after the administration of mifepristone), the medication would be undetectable in the plasma and unlikely to have a direct effect on symptoms occurring at that time.

In conclusion, we have shown the lack of relevance of late-luteal-phase biology to the causation of PMS by observing no change in the predicted development of symptoms despite truncation of the late luteal phase. Our data suggest that investigations of physiologic abnormalities of the late luteal phase in PMS are unlikely to identify pathophysiologic processes relevant to the disorder. Furthermore, there appears to be no physiologic rationale for the widespread use of progesterone therapy in PMS during the late luteal phase. Finally, our results suggest that for some women PMS may represent either a disorder of mood state that is triggered by hormonal events occurring before the late luteal phase or an autonomous mood-state disorder that is linked to but not caused by events of the menstrual cycle.

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