Premenstrual Dysphoric Disorder Symptoms Following Ovarian Suppression: Triggered by Change in Ovarian Steroid Levels But Not Continuous Stable Levels

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Objective: Premenstrual dysphoric disorder (PMDD) symptoms are eliminated by ovarian suppression and stimulated by administration of ovarian steroids, yet they appear with ovarian steroid levels indistinguishable from those in women without PMDD. Thus, symptoms could be precipitated either by an acute change in ovarian steroid levels or by stable levels above a critical threshold playing a permissive role in expression of an underlying infradian affective "pacemaker." The authors attempted to determine which condition triggers PMDD symptoms.

Method: The study included 22 women with PMDD, ages 30 to 50 years. Twelve women who experienced symptom remission after 2–3 months of GnRH agonist-induced ovarian suppression (leuprolide) then received 1 month of single-blind (participant only) placebo and then 3 months of continuous combined estradiol/progesterone. Primary outcome measures were the Rating for Premenstrual Tension observer and self-ratings completed every 2 weeks during clinic visits. Multivariate repeated-measure ANOVA for mixed models was employed.

Results: Both self- and observer-rated scores on the Rating for Premenstrual Tension were significantly increased (more symptomatic) during the first month of combined estradiol/progesterone compared with the last month of leuprolide alone, the placebo month, and the second and third months of estradiol/progesterone. There were no significant differences in symptom severity between the last month of leuprolide alone, placebo month, or second and third months of estradiol/progesterone. Finally, the Rating for Premenstrual Tension scores in the second and third estradiol/progesterone months did not significantly differ.

Conclusions: The findings demonstrate that the change in estradiol/progesterone levels from low to high, and not the steady-state level, was associated with onset of PMDD symptoms. Therapeutic efforts to modulate the change in steroid levels proximate to ovulation merit further study.

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Premenstrual dysphoric disorder (PMDD) is characterized by distressing mood and behavioral symptoms during the luteal phase of the normal menstrual cycle that disappear within a few days after menses begin (1, 2). No abnormalities of ovarian hormone levels have been consistently identified that distinguish women with PMDD from women who experience no mood or behavioral symptoms during the luteal phase (3). Nonetheless, a critical role for ovarian steroids in the expression of PMDD symptoms is suggested by multiple findings. First, both ovariectomy and ovarian suppression induced by gonadotropin-releasing hormone (GnRH) agonists eliminate symptoms in the majority of women with PMDD (4–15). Second, re-exposure to physiologic doses of either estradiol or progesterone (but not placebo) for 4 weeks' duration resulted in a recurrence of PMDD symptoms after 2–3 weeks of exposure in women with PMDD whose symptoms remitted after GnRH agonist treatment (controls who participated in an identical hormone manipulation study were not symptomatic) (14). Finally, inhibition of the luteal phase increase in the progesterone metabolite allopregnanolone with dutasteride, a 5α-reductase inhibitor, mitigated symptom emergence in PMDD (16).

Reproductive steroids, therefore, appear to play a role in PMDD. What remains unclear is the nature of the ovarian steroid symptom trigger in PMDD. Evidence to date cannot disambiguate the effects of an acute change in the level of ovarian steroid (or metabolite) from those of continuous exposure to elevated levels of ovarian steroids. Preclinical studies suggest that the short-term exposure or withdrawal of progesterone could impact CNS function to induce affective symptoms in an otherwise vulnerable woman. Both increases and decreases in progesterone (and its neurosteroid metabolites) induce changes in the α4 subunit conformation of the γ-aminobutyric acid (GABA) $GABA_A$ receptor sufficient

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to produce anxiety-like behaviors (17–19). Alternatively, studies in rodents demonstrate that estradiol is proconvulsant and accelerates the acquisition of amygdalar-kindled seizures (20, 21). Thus, ovarian steroids can modulate intrinsic neuronal excitation, lower thresholds for neuronal firing, and potentially impact the set points for certain behavioral states. If PMDD is associated with an abnormal infradian *zeitgeber,* the expression of which depends on a critical threshold of exposure to ovarian steroids, then ovarian steroids could play a permissive role in the expression of abnormal neuronal activity within the affective circuits involved with PMDD, thus leading to symptom onset.

In this study, we attempted to define the kinetics of the ovarian steroid event relevant to triggering PMDD symptoms. We selected women with PMDD who responded to treatment with GnRH-agonist-induced ovarian suppression (i.e., whose PMDD symptoms remitted) and who then were exposed to 3 months of combined continuous estradiol and progesterone treatment. If the change in hormone level is critical, then we would expect the initial recurrence of PMDD symptoms in the first month of ovarian steroid exposure followed by a remission of PMDD symptoms once ovarian steroid levels were stable and maintained during months 2–3 of hormone treatment. Alternatively, if the ovarian steroid exposure above threshold levels is the key physiologic event to permit an infradian pacemaker to produce episodic cyclic symptoms during the luteal phase, then we would predict recurrent episodes of affective symptoms reminiscent of luteal-phase-related symptom cyclicity in the context of stable hormone levels during *each* of the three months of ovarian steroid exposures.

METHOD

Participant Selection

We studied 22 women, ages 30 to 50 years, all of whom met study criteria for PMDD, which are based on requirements outlined in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) (1). All women were free of medical illness, had regular menstrual cycles (i.e., 21–35 days in duration), and were not taking any medications (including oral contraceptives and hormonal therapy). All women enrolled had normal physical findings and laboratory test results, were not pregnant, and agreed to use barrier contraception throughout the study. None of the women with PMDD had any axis I psychiatric illness currently or within the previous 2 years as determined by the Structured Clinical Interview for DSM-IV.

Before study enrollment, women prospectively confirmed the timing and severity of their mood symptoms by rating themselves daily for 3 months using a four-item visual analog scale that confirmed the timing and severity of their menstrually related mood symptoms (irritability, sadness, anxiety, and mood swings) as described previously (14, 22). The mean score of at least one of these self-rated negative mood symptoms had to be at least 30% higher (relative to the range of the scale used by each woman) in the week before menstruation compared with the week after the cessation of menstruation in at least two of the three cycles assessed.

Functional impairment was assessed through self-reports of distress and functional impairment on the Daily Rating Form (23). Daily ratings and the results of both a semi-structured interview and a self-report questionnaire were employed to confirm that all women met the required number of symptoms specified in the DSM criteria for PMDD. Women with significant negative mood symptoms occurring during the follicular phase of the menstrual cycle (on the Daily Rating Form) were excluded. Thus, in this study, the diagnostic criteria for PMDD were augmented by the prospectively confirmed severity criterion of a 30% increase in mean negative mood during the week before menses compared with the week after menses, a more stringent criterion than that of DSM-IV or DSM-5 (1, 2).

All women received payment for participation according to the NIH Healthy Volunteer Office guidelines. The study protocol was reviewed and approved by the NIMH Institutional Review Board, and all women provided written consent to study participation.

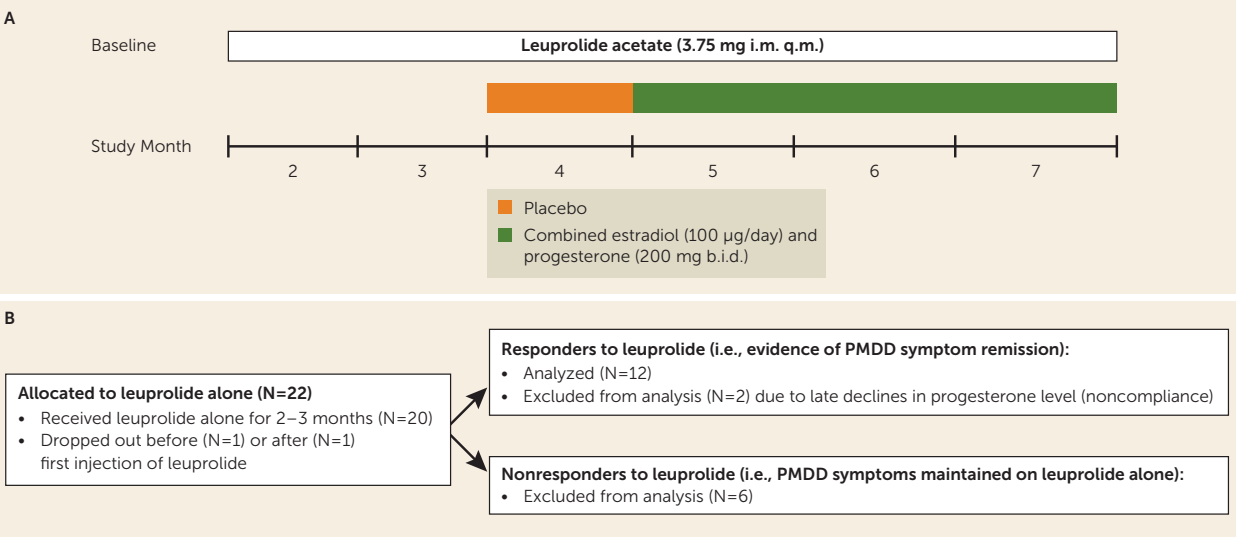
Study Design

Between 2 and 6 days after onset of menses, women with PMDD received six or seven monthly intramuscular injections of 3.75 mg leuprolide, which after an initial stimulation suppresses ovarian function. Clinic visits occurred every 2 weeks. Plasma follicle-stimulating hormone, luteinizing hormone, estradiol, and progesterone levels were measured at each visit to confirm ovarian suppression. Following 2–3 months of leuprolide alone, the women whose PMDD symptoms were in remission (i.e., responders to leuprolide, as determined by self-reported improvement confirmed by Rating for Premenstrual Tension scale [24] scores <5 and the absence of symptom cyclicity on the Daily Rating Form) were selected to continue in the study. Five women with PMDD reported either the experience of distressing life events or a partial symptom response after their second month of leuprolide, and these five subjects were therefore maintained for a third month to evaluate if symptom remission could be demonstrated in each woman. The responders to leuprolide continued to receive monthly leuprolide for another 4 months and received 1 month of single-blind (participant only) placebo (patch and suppository) followed by 3 months of combined estradiol and progesterone replacement (see Figure 1 for details). All women used a patch and a suppository each day during the hormonal add-back to maintain the patency of the blind.

Symptom Rating Scales

Our primary outcome measure was the Rating for Premenstrual Tension observer (rater) ratings and self-ratings (24) completed every 2 weeks during regularly scheduled clinic visits to assess the presence (or absence) of PMDD symptoms. Additionally, Daily Rating Form scores for the core PMDD symptoms of irritability, sadness, and anxiety (2) were evaluated throughout the study. The Daily Rating Form is a 6-point Likert-type scale (1=symptoms absent,

FIGURE 1. Study Design (A) and Patient Flow Chart (B)[a]



[a] After a baseline cycle in which the diagnosis of premenstrual dysphoric disorder (PMDD) was established, all women received open-label leuprolide. Between 2 and 6 days after the onset of menses, the women received six monthly intramuscular injections of 3.75 mg leuprolide. After 2–3 months of leuprolide alone, women whose PMDD symptoms were in remission (responders to leuprolide, i.e., having self-reported improvement confirmed by Rating for Premenstrual Tension scores <5 and the absence of symptom cyclicity on the Daily Rating Form, i.e., weekly [7-day] average daily scores for irritability, sadness, or anxiety of <3, indicating less than moderate severity of a particular symptom [25, 26]) were selected to continue on leuprolide for an additional 4 months. Women not meeting these criteria were considered nonresponders and were not included in the statistical analysis. Responders to leuprolide continued to receive monthly leuprolide injections for another 4 months and received 1 month of single-blind (to participant only) placebo (patch and suppository) followed by 3 months of combined estradiol (100 μg daily by skin patch) and progesterone (200 mg vaginal suppository twice daily) replacement. Functional impairment was assessed through self-reports of distress and functional impairment on the Daily Rating Form (23). The Daily Rating Form criteria for functional impairment were as follows: a score of 2 (minimal) or higher on one of four questions related to functional impairment (i.e., stayed at home or avoided social activities, had conflicts or problems with people, symptoms interfered with relationships at work or home, or symptoms interfered with work productivity) in at least 3 days out of 7 days premenses.

6=symptoms present in the extreme) and measures reported symptoms of PMDD. Responders to leuprolide were defined by Rating for Premenstrual Tension scores of ≤5 during the last month of leuprolide alone as well as the absence of a weekly average daily rating score of ≥3 for irritability, sadness, or anxiety. Women not meeting these criteria were considered nonresponders and were not included in the statistical analysis.

Statistical Analysis

Only women with PMDD who met criteria for symptom remission during the last month of leuprolide alone continued on to the placebo and estradiol/progesterone add-back phases of this protocol. Henceforth, months 1 thru 7 are as follows: month 1=baseline prior to receiving leuprolide (not employed in analysis), month 2=first month of leuprolide (not employed in analysis), month 3=last month of leuprolide, month 4=placebo, month 5=first month of estradiol/progesterone, month 6=second month of estradiol/progesterone, and month 7=third (last) month of estradiol/progesterone. The principal comparisons of our analyses were twofold: first, to examine PMDD symptom severity during each of the 3 months of estradiol/progesterone add-back compared with the last month of leuprolide alone, when PMDD symptoms were in remission (month 5 vs. 3, month 6 vs. 3, and month 7 vs. 3) and, second, to look for potential differences in PMDD symptom severity during the first month of add-back (initial change in estradiol/progesterone levels) compared with symptoms during the subsequent months of add-back (when stable levels of estradiol/progesterone had been established) (month 5 vs. 6 and month 5 vs. 7). Additionally, to evaluate the presence or absence of placebo effects on PMDD symptoms, we compared PMDD symptom severity in the one month of single-blind placebo (month 4) with severity in both the first month of estradiol/progesterone add-back (month 5) and the last month of leuprolide alone (month 3). Finally, we compared the last 2 months of estradiol/progesterone replacement to examine differences in PMDD symptom severity during the months when stable levels of estradiol/progesterone had been established (month 6 vs. 7). Since the focus of this study was to examine the pattern of PMDD symptom "recurrence" during estradiol/progesterone add-back, we did not include in the statistical analyses either the average rating scale scores for baseline preleuprolide (month 1) or for the first month of leuprolide alone (month 2), when in many women estradiol/progesterone levels will vary secondary to the flare of ovarian function induced by the first injection of leuprolide.

In leuprolide responders, both Rating for Premenstrual Tension scores and daily data involved repeated measures on the same woman during five hormone conditions (i.e., months). Rating for Premenstrual Tension scores were analyzed as 2-week measures, and daily symptom ratings were analyzed as weekly averages. Multivariate repeated-measure

analyses were done with SAS version 9.2 software (PROC MIXED, SAS Institute, Cary, N.C.). Separately, for each of the nine symptom ratings, the predictor variable of interest, study month, instead of 2-week or weekly time points, was used because the ratings within each month (rater and self-ratings at weeks 2 and 4 of each month on the Rating for Premenstrual Tension and weeks 1–4 of the Daily Rating Form ratings) showed no significant main or interactive effects of visit within each month or week in these symptom ratings, respectively. We used the Kenward and Roger method for computing the degrees of freedom for tests of fixed effects. The value of the least square means, associated standard errors, and p values are reported. Eight post hoc pairwise comparisons of least square means were compared among hormone conditions by using t tests. To adjust for multiple comparisons, results with p values less than 0.005 (instead of 0.05) are considered statistically significant. Values above this threshold are reported but are considered not significant. This is an informal multiplicity adjustment given the exploratory nature of this study. Formal adjustment of p values in exploratory studies, e.g., Bonferroni adjustment of p values, is not universally accepted because it reduces type I errors at the expense of increasing type II errors (27, 28).

Clinical characteristics in women who did and did not meet the criteria for response to leuprolide were compared with Fisher's exact test for categorical variables and Student's t tests for continuous variables (Table 1).

TABLE 1. Demographic and Clinical Characteristics of Women With Premenstrual Dysphoric Disorder (PMDD) Treated With Leuprolide[a]

Characteristic	Leuprolide Responders (N=12)		Leuprolide Nonresponders (N=6)		p[b]
	Mean	SD	Mean	SD	
Age (years)	38.4	7.4	40.8	3.4	0.56
Body mass index (BMI) (kg/m^2)	31.9	10.8	29.4	4.4	0.77
Duration of PMDD (years)	19.0	10.5	16.8	8.1	0.66
Age at onset of PMDD (years)	19.0	7.1	23.2	6.8	0.25
	N	%	N	%	
Past axis I psychiatric illness	3	25	4	67	0.14
Current medications[c]	1	8	0	0	—
Worst symptom[d]					
Irritability	6	50	4	67	—
Sadness	2	17	0	0	—
Anxiety	1	8	1	17	—
Mood swings	2	17	1	17	—

[a] There were no significant differences in age, BMI, age at onset of PMDD, and duration of PMDD between the women with PMDD who responded to GnRH-agonist-induced ovarian suppression and women who continued to exhibit symptoms during ovarian suppression.
[b] All p values represent the results of Student's t tests except past axis I psychiatric illness, for which the p value is from Fisher's exact test.
[c] One woman received levothyroxine on a regular basis prior to the study.
[d] One woman in the leuprolide responder group self-reported fatigue as her worst symptom.

RESULTS

Participant Characteristics

There were no significant differences in age, body mass index, age at onset of PMDD, and duration of PMDD between the women with PMDD who responded to leuprolide and those who continued to exhibit symptoms during ovarian suppression (Table 1). Twenty-two women with PMDD were enrolled and commenced leuprolide; two women dropped out early in the study, one before and one after the first injection of leuprolide, due to unexpected scheduling conflicts with their work. Thus, 20 women received 2 to 3 months of leuprolide. Six of them did not respond to leuprolide with PMDD symptom improvement/remission, and 14 met the criteria for response to leuprolide and were then continued on leuprolide plus placebo, then estradiol/progesterone add-back. Two of these 14 women were not compliant with the estradiol/progesterone add-back regimen as determined by plasma hormone levels (and subsequent self-report) and, therefore, were not included in the final analyses (Figure 1B).

Symptom Ratings

Rating for Premenstrual Tension. Scores on both the self- and rater-administered Rating for Premenstrual Tension were significantly increased (more symptomatic) during the first month of estradiol/progesterone add-back (month 5) compared with all of the other months (month 5 vs. 3: self, p=0.0003; rater, p<0.0001; month 5 vs. 4: self, p=0.0015; rater: p=0.0013; month 5 vs. 6: self, p=0.0014, rater, p<0.0001; month 5 vs. 7: self, p=0.0006; rater, p<0.0001) (Table 2, Table 3, Table 4, Figure 2). In contrast, there were no significant differences in symptom severity, according to either self or rater scores, between the last month of leuprolide alone (month 3) and scores during the placebo month and the second and third months of estradiol/progesterone add-back. Finally, Rating for Premenstrual Tension scores in the second and third months of estradiol/progesterone add-back also were not significantly different from each other. This pattern of between-month differences in symptom severity reflected the presence of significantly increased Rating for Premenstrual Tension self and rater scores during the first month of estradiol/progesterone compared with all other months (i.e., symptom recurrence in estradiol/progesterone add-back month 1 only).

Daily Rating Form. A pattern similar to that observed in Rating for Premenstrual Tension scores was observed for the daily symptom of irritability. Irritability scores during the first month of estradiol/progesterone add-back were

TABLE 2. Difference in Symptoms Between Leuprolide and Hormone Add-Back Months in 12 Women With Premenstrual Dysphoric Disorder (PMDD) Who Responded to Leuprolide and Then Received Combined Estradiol and Progesterone Add-Back (E/P)[a]

	Month 3 vs. Month 5 (leuprolide − E/P month 1)			Month 3 vs. Month 6 (leuprolide − E/P month 2)			Month 3 vs. Month 7 (leuprolide − E/P month 3)		
Symptom Rating Scale	ΔLSM	SE	p	ΔLSM	SE	p	ΔLSM	SE	p
Rating for Premenstrual Tension[b]									
Self (p=0.0013)	−3.792	0.971	0.0003	−0.458	0.971	0.6392	−0.009	1.030	0.9928
Rater (p<0.0001)	−4.625	0.907	<0.0001	−0.583	0.907	0.5236	0.223	0.932	0.8119
Daily Rating Form[c]									
Sadness (p=0.0158)	−0.272	0.090	0.0036	−0.148	0.090	0.1051	−0.004	0.091	0.9684
Irritability (p=0.0017)	−0.394	0.112	0.0008	−0.212	0.112	0.0634	0.027	0.114	0.8132
Anxiety (p=0.3851)	−0.196	0.116	0.0969	−0.189	0.116	0.1085	−0.058	0.118	0.6266
Mood swings (p=0.5370)	−0.116	0.075	0.1272	−0.073	0.075	0.3351	−0.077	0.076	0.3114
Cravings (p=0.1893)	−0.181	0.090	0.0484	−0.038	0.090	0.6768	0.022	0.092	0.8138
Bloating (p=0.0445)	−0.306	0.131	0.0224	−0.164	0.131	0.2145	−0.397	0.133	0.0040
Breast pain (p=0.2697)	−0.225	0.153	0.1484	−0.255	0.153	0.1020	−0.324	0.154	0.0405
Plasma hormone levels[d]									
Estradiol (pg/ml) (p<0.0001)	−45.854	12.045	0.0004	−52.571	12.045	<0.0001	−72.718	12.352	<0.0001
Progesterone (ng/ml) (p<0.0001)	−12.021	1.529	<0.0001	−12.617	1.529	<0.0001	−12.392	1.571	<0.0001

[a] See Figure 1 for conditions in each study month. LSM, least squares mean; SE, standard error of difference. Symptom severity was compared during each of the three months of estradiol/progesterone add-back with symptom severity during the last month of leuprolide alone, when PMDD symptoms were in remission. To adjust for multiple comparisons, results with p values less than 0.005 are considered statistically significant. This is an informal adjustment given the exploratory nature of this study. Values above this threshold are reported but were considered not significant. The p values in the left-most column represent p values for the omnibus tests for each symptom score or hormone level.

[b] The Rating for Premenstrual Tension consists of both an observer/rater-completed rating and a self-report rating that measures mood, behavior, and physical symptoms on a 36-point scale, with scores <5 consistent with the absence of significant PMDD symptoms (29). Both the self and rater scores were significantly increased (more symptomatic) during the first month of estradiol/progesterone add-back (month 5) compared with leuprolide alone. There were no significant differences in symptom severity scores in either the self or rater scores between the last month of leuprolide (month 3) and scores during the second and third months of hormone add-back (month 6 and month 7).

[c] Daily Rating Form scores for the core PMDD symptoms of irritability, sadness, and anxiety were evaluated throughout the study. Each evening during the 2–3 months of baseline and during the six months on treatment, all women completed the Daily Rating Form. All women were instructed that the ratings should represent a composite score for the previous 12 hours. Scores for irritability and sadness during the first month of estradiol/progesterone add-back were significantly increased compared with the last month of leuprolide alone. Scores for bloating differed significantly between hormone add-back month 3 and the last month of leuprolide.

[d] Plasma progesterone and estradiol levels were measured by electrochemiluminescence immunoassay at the NIH Clinical Center Department of Laboratory Medicine. The lower limits of detectability for the progesterone and estradiol assays were 0.03–0.2 ng/ml and 5.0–10.0 pg/ml, respectively.

significantly increased compared with all other months with the exception of scores during the second month of estradiol/progesterone add-back, i.e., the last month of leuprolide alone (month 5 vs. 3, p=0.0008), the placebo month (month 5 vs. 4, p=0.0031), and the third month of estradiol/progesterone add-back (month 5 vs. 7, p=0.0005) (Tables 2–4). Daily irritability scores remained higher during the second month of estradiol/progesterone, reflecting nonsignificantly higher scores for irritability in the first add-back month that carried over to month 2 of add-back and then remitted during the third add-back month. There were no significant differences in symptom scores between the other months.

Daily symptom severity scores for sadness during the first month of estradiol/progesterone add-back were significantly increased compared with the last month of leuprolide alone (month 5 vs. 3, p=0.0036) and the third month of add-back (month 5 vs. 7, p=0.0046). There were no significant differences in the severity scores of any month for the symptoms of anxiety, mood swings, bloating (except between add-back month 3 and the last month of leuprolide [p=0.004]), breast pain, and cravings (Tables 2–4).

Other Measures

We asked each woman whether she believed she was receiving placebo or estradiol/progesterone replacement. After the placebo month, of the 12 women included in the analysis, three women felt they were on placebo, five thought they were on active estradiol/progesterone, and four did not know what they were receiving. Most of the women based their beliefs on either the severity of their hot flushes or their mood state. Additionally, 10 of these 12 women also reported break-through menstrual bleeding during active add-back but none during placebo add-back; bleeding ranged from occasional spotting in most women to reports of full menses in two women. When menstrual bleeding did occur, it ranged from 2 to 5 days, and it occurred in all 3 months, albeit not in the same individual, of estradiol/progesterone add-back.

Plasma estradiol and progesterone levels were significantly increased during add-back months 1–3 compared with the last month of leuprolide and the month of single-blind placebo (Tables 2 and 3). There were no significant differences between estradiol/progesterone add-back month 1

compared with values during add-back months 2 and 3 (Table 4, Figure 2).

TABLE 3. Differences in Symptoms and Hormone Levels Between Placebo Add-Back and Hormone Add-Back and Between Leuprolide and Placebo Add-Back in 12 Women With Premenstrual Dysphoric Disorder (PMDD) Who Responded to Leuprolide and Then Received Combined Estradiol and Progesterone Add-Back (E/P)[a]

	Month 4 vs. Month 5 (placebo − E/P month 1)			Month 3 vs. Month 4 (leuprolide − placebo)		
Symptom Rating Scale	ΔLSM	SE	p	ΔLSM	SE	p
Rating for Premenstrual Tension[b]						
Self (p=0.0013)	−3.292	0.971	0.0015	−0.500	0.971	0.6092
Rater (p<0.0001)	−3.125	0.907	0.0013	−1.500	0.907	0.1055
Daily Rating Form[c]						
Sadness (p=0.0158)	−0.100	0.090	0.2723	−0.172	0.090	0.0604
Irritability (p=0.0017)	−0.347	0.113	0.0031	−0.047	0.113	0.6773
Anxiety (p=0.3851)	−0.099	0.117	0.3981	−0.097	0.117	0.4105
Mood swings (p=0.5370)	−0.000	0.077	0.9955	−0.115	0.076	0.1356
Cravings (p=0.1893)	−0.167	0.090	0.0704	−0.015	0.090	0.8725
Bloating (p=0.0445)	−0.120	0.131	0.3633	−0.186	0.131	0.1599
Breast pain (p=0.2697)	−0.095	0.153	0.5392	−0.130	0.153	0.4005
Plasma hormone levels						
Estradiol (pg/ml) (p<0.0001)	−44.204	12.045	0.0007	−1.650	12.045	0.8917
Progesterone (ng/ml) (p<0.0001)	−12.063	1.529	<0.0001	0.042	1.529	0.9784

[a] See Figure 1 for conditions in each study month. LSM, least squares mean; SE, standard error of difference. To adjust for multiple comparisons, results with p values less than 0.005 are considered statistically significant. This is an informal adjustment given the exploratory nature of this study. Values above this threshold are reported but were considered not significant. The p values in the left-most column represent p values for the omnibus tests for each symptom score or hormone level.

[b] Both the self and rater Rating for Premenstrual Tension scores were significantly increased (more symptomatic) during the first month of estradiol/progesterone add-back (month 5) compared with placebo add-back (month 4).

[c] Daily Rating Form scores for irritability were significantly increased (more symptomatic) during the first month of hormone add-back (month 5) compared with placebo add-back (month 4).

DISCUSSION

Apart from the ostensible linkage of PMDD symptoms to the luteal phase of the menstrual cycle, the pathophysiologic role of ovarian steroids in this condition is suggested by observations that the short-term add-back of either estradiol or progesterone is sufficient to result in a recrudescence of symptoms in women with PMDD whose symptoms remitted during ovarian suppression (14, 30). These observations left open the possibility that either dynamic hormonal events (i.e., changing ovarian hormone levels) during the menstrual cycle or the prolonged exposure to a threshold level of ovarian steroids was critical to the triggering of PMDD symptoms. In this study, we demonstrated that it was the changes in levels of estradiol and progesterone from low to high levels, and not the steady-state levels, that were associated with the onset of PMDD symptoms. We observed that compared with scores during the leuprolide-alone condition, several symptom rating scores significantly increased during the first month of ovarian steroid add-back but not during the second and third add-back months, when plasma levels of estradiol and progesterone were stable. Additionally, we observed no significant changes in symptoms during single-blind placebo add-back. Thus, our findings demonstrate that the change in level of ovarian steroids from low to high triggers the onset of a negative affective state in women with PMDD. Our results are consistent with several previous publications (14, 30, 31) that have demonstrated an increase in symptoms during the initial ovarian steroid add-back in women whose PMDD responded to ovarian suppression. Interestingly, in the study by Segebladh and colleagues (31), symptom recurrence was observed mainly upon add-back of both estradiol and progesterone, compared with low-dose estradiol alone, suggesting either that progesterone is a critical component of the symptom-triggering hormone event or that levels of ovarian steroids need to reach a specific threshold to trigger symptoms.

The appearance of symptoms in the women who experienced a recurrence of PMDD after the initial add-back was time-limited in all women, and symptoms remitted during the second and third months of hormone add-back, when plasma levels of estradiol and progesterone were relatively stable. Thus, our findings suggest that there is a "half-life" of the affective state that is triggered, following which it remits. The nature of the "switch-out," or termination of the symptomatic state in PMDD, remains to be characterized.

The mechanism whereby a change in ovarian steroid levels induces a recurrence of symptoms in women with a history of PMDD is unclear. Steroid nuclear receptor signaling provides for a wide range of time- and rate-dependent regulatory mechanisms whereby a change in steroid level could impart differential cellular effects compared with those caused by steady-state levels (32). For example, basic science studies suggest that the initial change (i.e., increase or decrease) in progesterone levels can induce alterations in GABA receptor subunit conformation and induce paradoxical anxiety-like behavior in rodents (17–19), and an initial pulse of progesterone activates transcriptional coregulators that differ from those seen after exposure to stable levels (33). Indeed, the timing and pulsatility of a hormone signal may have physiologic relevance in the biology of several clinical phenomena, including the function of the hypothalamic-pituitary-gonadal axis, the stress response, growth and development, and circadian rhythms (34–43). Interestingly,

TABLE 4. Differences in Symptoms and Hormone Levels Among Hormone Add-Back Months in 12 Women With Premenstrual Dysphoric Disorder (PMDD) Who Responded to Leuprolide and Then Received Combined Estradiol and Progesterone Add-Back (E/P)[a]

	Month 5 vs. Month 6 (E/P month 1 – E/P month 2)			Month 5 vs. Month 7 (E/P month 1 – E/P month 3)			Month 6 vs. Month 7 (E/P month 2 – E/P month 3)		
Symptom Rating Scale	ΔLSM	SE	p	ΔLSM	SE	p	ΔLSM	SE	p
Rating for Premenstrual Tension[b]									
Self (p=0.0013)	3.333	0.971	0.0014	3.782	1.030	0.0006	0.449	1.030	0.6649
Rater (p<0.0001)	4.042	0.907	<0.0001	4.848	0.932	<0.0001	0.806	0.932	0.3915
Daily Rating Form[c]									
Sadness (p=0.0158)	0.125	0.090	0.1702	0.268	0.091	0.0046	0.144	0.091	0.1200
Irritability (p=0.0017)	0.182	0.112	0.1105	0.421	0.114	0.0005	0.239	0.114	0.0397
Anxiety (p=0.3851)	0.007	0.116	0.9547	0.138	0.118	0.2441	0.132	0.118	0.2671
Mood swings (p=0.5370)	0.043	0.075	0.5671	0.039	0.076	0.6142	−0.005	0.076	0.9511
Cravings (p=0.1893)	0.143	0.090	0.1157	0.203	0.091	0.0304	0.059	0.091	0.5195
Bloating (p=0.0445)	0.143	0.131	0.2797	−0.091	0.133	0.4977	−0.233	0.133	0.0840
Breast pain (p=0.2697)	−0.030	0.153	0.8435	−0.099	0.154	0.5216	−0.069	0.154	0.6559
Plasma hormone levels									
Estradiol (pg/ml) (p<0.0001)	−6.717	12.045	0.5800	−26.864	12.352	0.0351	−20.147	12.352	0.1101
Progesterone (ng/ml) (p<0.0001)	−0.596	1.529	0.6987	−0.371	1.570	0.8142	0.225	1.571	0.8870

[a] See Figure 1 for conditions in each study month. LSM, least squares mean; SE, standard error of difference. To adjust for multiple comparisons, results with p values less than 0.005 are considered statistically significant. This is an informal adjustment given the exploratory nature of this study. Values above this threshold are reported but were considered not significant. The p values in the left-most column represent p values for the omnibus tests for each symptom score or hormone level.

[b] Both the self and rater Rating for Premenstrual Tension scores were significantly increased (more symptomatic) during the first month of estradiol/progesterone add-back (month 5) compared with the second and third months of hormone add-back (months 6 and 7).

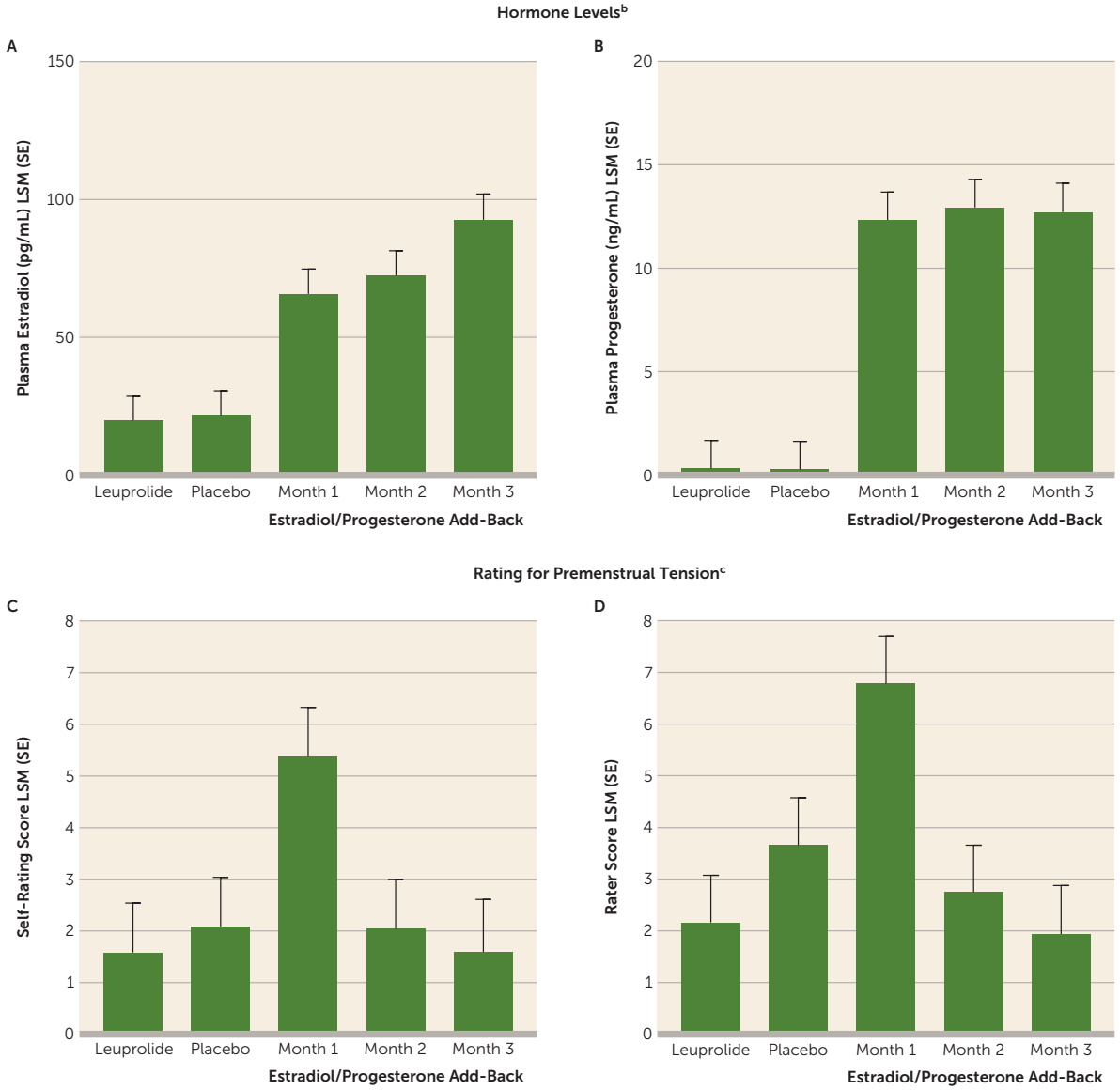
[c] Daily Rating Form scores for irritability were significantly increased (more symptomatic) during the first month of add-back (month 5) compared with the third month of hormone add-back. Daily severity scores for sadness during the first month of hormone add-back were significantly increased compared with the third month of hormone add-back (month 5 vs. 7).

symptoms recurred during the third month of add-back in two women with PMDD proximate to observed declines in progesterone levels. This anecdotal observation suggests that both acute increases and declines in ovarian steroids may trigger a transition from the asymptomatic to the symptomatic state, consistent with the observations of Gulinello and colleagues in rodents (17–19). Regardless of the mechanism underlying the steroid-induced recurrence of symptoms in PMDD, our findings provide a major clue to help decode the process by which clearly defined biological signals are, in susceptible individuals, translated into what is likely network-based affective dysregulation.

These findings have implications for the treatment of women with PMDD. First, a continuous exposure to hormones reminiscent of pregnancy could be an effective treatment for some women with PMDD (44). Studies using oral contraceptives have confirmed their efficacy in some women with PMDD (45–50). However, our data suggest that continuous vs. interrupted oral contraceptive would be more effective, since the latter regimen would recapitulate changes in estrogen and progestin secretion that could induce symptoms, but perhaps at times in the 28-day cycle differing from those in the natural menstrual cycle. Certainly, women who are being treated with either leuprolide with the continuous add-back or those commencing oral contraceptives should be warned about the possible recurrence of symptoms during the first phase of the add-back. Additionally, it is possible, given the findings by Segebladh and colleagues (31), that low-dose estradiol alone could be employed for some women with PMDD with proper monitoring of the endometrium. Finally, preliminary findings from a small trial of the 5α-reductase inhibitor dutasteride suggested that preventing the luteal phase increase in allopregnanolone levels mitigates symptoms in PMDD (16). Thus, treatment strategies to attenuate or eliminate the change in estradiol and progesterone (or their metabolites) could effectively target the hormonal trigger in this condition.

Challenges and limitations of this study include the maintenance of the blind during active and placebo add-backs and the small sample size, which limit generalizability of our findings. First, the presence or absence of hot flushes or menstrual bleeding certainly could have suggested the presence of placebo or combined active add-back. Nonetheless, this was not a traditional clinical trial design to contrast ovarian steroid add-back with placebo add-back. Our main contrast was between the first month of active hormone add-back and months 2 and 3 of active add-back. Consequently, even if participants correctly inferred when they received active vs. placebo add-back (which was often not the case), the presence of PMDD symptoms during month 1 of estradiol/progesterone compared with months 2 and 3 confirms the study's hypothesis. Second, although we observed a recurrence of symptoms in the daily ratings for irritability and sadness, it is possible that had we employed

FIGURE 2. Hormone Levels and Symptom Scores of 12 Women With Premenstrual Dysphoric Disorder Who Responded to Leuprolide and Then Received Combined Estradiol and Progesterone Add-Back[a]



[a] See Figure 1 for conditions in each study month. LSM, least squares mean; SE, standard error of difference.
[b] Plasma estradiol (A) and progesterone (B) were significantly increased in the 3 months of estradiol/progesterone add-back compared with the last month of leuprolide and the month of single-blind placebo.
[c] The pattern of between-month differences in symptom severity reflects the presence of significantly increased self (C) and rater (D) scores during the first month of estradiol/progesterone add-back (study month 5) compared with all other months (i.e., last month of leuprolide alone, placebo, and the second and third hormone add-back months).

a larger sample, we would have identified significant changes in a broader range of PMDD symptoms. Additionally, our observed response rates are similar to those reported in several previous studies by our group (14) and others (4, 5, 9, 51, 52), and they suggest that ovarian suppression is not uniformly effective in PMDD. These observations suggest that additional clinical characteristics of women with PMDD could militate against the beneficial effects of ovarian suppression in PMDD. For example, Pincus et al. (53) suggested the pattern of symptom variability in some women with PMDD was predictive of response to leuprolide. Our approach was to test a specific hypothesis about the role of ovarian steroids in a phenomenon that we identified in a prior publication (14), and a homogeneous sample of women with PMDD with evidence of hormone sensitivity (confirmed by their response to leuprolide) was necessary to achieve this study goal.

Indeed, in addition to identifying the change in ovarian steroids as the relevant symptom-producing stimulus, our findings also emphasize the heterogeneity and complexity of the effects of hormone change in PMDD. Two-thirds of the women with PMDD showed symptom suppression while taking leuprolide, and of those, 58% (seven of 12) showed symptom provocation when receiving estradiol/progesterone add-back. Our findings, therefore, apply only to a subgroup of women with PMDD. Most importantly, these findings advance our understanding of the effects of ovarian steroids in the pathophysiology of PMDD and related conditions.

In conclusion, our findings confirm that the change in ovarian steroids contributes to the onset of negative affective symptoms in women with PMDD. We did not distinguish between the effects of estradiol and progesterone on symptom onset since we did not administer and withdraw these hormones separately. Indeed, in our previous study (14) we observed PMDD symptom recurrence after 2–3 weeks of either estradiol or progesterone, suggesting that both hormones have the capacity to induce symptoms, whereas findings by Segebladh et al. (31) suggest that PMDD recurrence is limited to combined estradiol and progesterone and not induced by low-dose estradiol. These issues remain to be clarified in future studies. What also remains to be determined is why PMDD symptom recurrence is self-limited and symptoms remit despite continuing stable ovarian steroid levels. Presumably, homeostatic mechanisms are activated in relation to either the presence of the negative affective state or the presence of stable levels of ovarian steroids. The latter possibility has been described by Smith et al. in rodents, with alterations in $GABA_A$ subunit conformations occurring after increases or decreases in progesterone or its neurosteroid metabolite allopregnanolone, but with conformations returning to normal during stable levels of these hormones (17–19). Although the mechanisms underlying the mood-destabilizing effects of ovarian steroids in PMDD remain to be better characterized, as does the source of susceptibility to this trigger, our findings provide a new target for interventions. Specifically, therapeutic efforts to inhibit the change in steroid levels proximate to ovulation, similar to those reported by Martinez et al. (16), merit further study.

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