Cortisol Circadian Rhythms during the Menstrual Cycle and with Sleep Deprivation in Premenstrual Dysoric Disorder and Normal Control Subjects

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Background: In this study we extended previous work by examining whether disturbances in the circadian rhythms of cortisol during the menstrual cycle distinguish patients with premenstrual dysoric disorder (PMDD) from normal control (NC) subjects. In addition, we tested the differential response to the effects of early and late partial sleep deprivation on cortisol rhythms.

Methods: In 15 PMDD and 15 NC subjects we measured cortisol levels every 30 min from 6:00 PM to 9:00 AM during midfollicular (MF) and late luteal (LL) menstrual cycle phases and also during a randomized crossover trial of early (sleep 3:00 AM–7:00 AM) versus late (sleep 9:00 PM–1:00 AM) partial sleep deprivation administered in two subsequent and separate luteal phases.

Results: In follicular versus luteal menstrual cycle phases we observed altered timing but not quantitative measures of cortisol secretion in PMDD subjects, compared with NC subjects: in the LL versus MF phase the cortisol acrophase was a mean of 1 hour earlier in NC subjects, but not in PMDD subjects. The effect of sleep deprivation on cortisol timing measures also differed for PMDD versus NC subjects: during late partial sleep deprivation (when subjects’ sleep was earlier), the cortisol acrophase was almost 2 hours earlier in PMDD subjects.

Conclusions: Timing rather than quantitative measures of cortisol secretion differentiated PMDD subjects from NC subjects both during the menstrual cycle and in response to early versus late sleep deprivation interventions. Biol Psychiatry 2000;48:920–931 © 2000 Society of Biological Psychiatry

Key Words: Premenstrual dysoric disorder, cortisol, circadian rhythms, women, sleep deprivation, menstrual cycle

Introduction

Because of a growing body of evidence linking the clinical phenomenology and treatment response of premenstrual dysoric disorder (PMDD) to major depressive disorder (MDD; American Psychiatric Association 1996, 317–394), PMDD was classified as a MDD, not otherwise specified, in DSM-IV (American Psychiatric Association 1994). Disturbances of hypothalamic–pituitary–adrenal (HPA) function characterize patients with MDD (Carroll et al 1976; Halbreich et al 1985; Krishnan et al 1990; Linkowski et al 1985a, 1985b; Pfohl et al 1985; Rubin et al 1987; Sachar et al 1973) and have been described in PMDD as well. Although most studies find that basal levels of cortisol and adrenocorticotropic hormone (ACTH) are normal in women with PMDD (Bloch et al 1998; Mortola et al 1989; Parry et al 1994; Rosenstein et al 1996; Rubinow et al 1988; Steiner et al 1984; Su et al 1997), we observed differences in timing measures of cortisol secretion (Parry et al 1994) in normal control (NC) subjects, but not PMDD subjects: a delay in the peak time of the cortisol rhythm occurred in the luteal menstrual cycle phase, as compared with the follicular phase. Differences in cortisol and ACTH responses to a variety of stimuli also have been reported in PMDD subjects, as compared with NC subjects: cortisol responses to corticotropin-releasing hormone are increased in women with PMDD (Facchinetti et al 1994; Rabin et al 1990). Abnormalities, however, frequently are not confined to the symptomatic luteal phase. For example, a blunting of the cortisol and ACTH responses to L-tryptophan (Bancroft et al 1991) and to a serotonin agonist (Su et al 1997) occurs in both phases of the menstrual cycle. Moreover, the increase in cortisol induced by opioid blockade in NC women is almost absent in PMDD patients (Facchinetti et al 1994). Thus, women with PMDD display alterations in the timing of cortisol circadian rhythms and both hypo- and hyper-responsiveness in challenge studies of the HPA axis.

Sleep deprivation improves mood in a majority of patients...
with MDD (Gillin 1983; Kuhs and Tolle 1991; Leibenluft and Wehr 1992; Van den Hoofdakker 1994; Wu and Bunney 1990). Critically timed sleep deprivation interventions also may have promise in providing alternative or adjunctive treatments for the management of PMDD: we previously reported the therapeutic effect of both total (Parry and Wehr 1987) and early (ESD) and late (LSD) partial sleep deprivation (Parry et al 1995) in PMDD. The therapeutic effect of sleep deprivation in PMDD, similar to its effect in MDD and in contrast to its effect in anxiety disorders (Roy-Byrne et al 1986b), further supports the link between PMDD and MDD. It was on the basis of this similarity in clinical phenomenology and treatment response that PMDD was classified as a depressive disorder in DSM-IV (American Psychiatric Association 1994; see sourcebook [American Psychiatric Association 1996, 317–394] for review of database).

The mechanism for the therapeutic effect of sleep deprivation in depressive disorders is unknown. Yamaguchi et al (1978) found that abnormal cortisol circadian rhythms were corrected in MDD subjects who responded to sleep deprivation, and Gerner et al (1979) and Baumgartner et al (1990a, 1990b) reported a greater increase in cortisol levels in responders. According to the internal coincidence model for sleep deprivation and depression (Wehr and Wirz-Justice 1981), the alteration of the timing (phase) relationships between sleep and underlying cortisol rhythms may be one mechanism by which sleep deprivation improves mood in PMDD patients.

Some reports have indicated that sleep deprivation late in the night is more effective than sleep deprivation early in the night (Gillin 1983; Kuhs and Tolle 1991; Leibenluft et al 1993; Parry and Wehr 1987). Our design incorporated both ESD and LSD, allowing us to compare therapeutic efficacy to changes in both quantitative and circadian timing measures of cortisol secretion patterns. A description of the effects of sleep deprivation on mood ratings in PMDD is published in Parry et al (1995). In summary, patient mood ratings showed a significant reduction of depressive symptoms from baseline (without induction of mania) after recovery nights of sleep from both ESD and LSD, but not the day after ESD or LSD (Parry et al 1995). In this study we examine the effects of sleep deprivation on cortisol rhythms. Basing our hypothesis on our previous work, we hypothesize that 1) timing disturbances in cortisol secretion would differentiate PMDD and NC subjects during the menstrual cycle and 2) patient and control groups would have different responses to sleep deprivation interventions as measured by cortisol parameters.

**Methods and Materials**

**Subjects**

Potential PMDD and NC subjects were referred by local professionals or were recruited by advertisement for participation in mood and sleep studies during the menstrual cycle. Screening procedures consisted of a structured menstrual assessment questionnaire (adapted by Parry and Mostifi from the Menstrual Assessment Form described in Roy-Byrne et al 1986a), the Structured Clinical Interview for DSM-III-R (Spitzer et al 1990), a psychiatric interview, a physical examination, and laboratory tests, including chemistry panel, complete blood count, urinalysis, and measurements of thyroid indices. If the subject did not have other major medical, gynecologic, or psychiatric illness; had regular (26- to 32-day) menstrual cycles; reported recurrent premenstrual affective symptoms severe enough to disrupt social or occupational functioning; and was willing to endure the rigors of a long-term research study, she was admitted for a 2- to 3-month prospective evaluation for diagnostic assessment. A past but not recent (within the last year) history of affective illness was permitted for PMDD subjects but not for NC subjects. Normal control subjects had to be without a lifetime history of psychiatric illness (including alcohol abuse) and to have no active medical illnesses. Their first-degree relatives also had to be free of a lifetime history of psychiatric illness with the exception of alcohol abuse (we found that inclusion of the last criterion severely restricted recruitment).

During the 2-month evaluation, both potential PMDD and NC subjects completed twice-daily (morning and evening) mood ratings (100-mm visual analogue scales of depression, anxiety, irritability, fatigue, withdrawal, physical symptoms, and appetite) and visited the clinic weekly for interview-based (21-item Hamilton Rating Scale for Depression [HRSD; Hamilton 1967]) and self-report (Beck Depression Inventory [BDI; Beck et al 1961]) depression ratings. In addition, an addendum to the HRSD to assess atypical items of depression and a hypomania rating scale to determine if sleep deprivation induced manic or hypomanic symptoms were used in evaluation (Rosenthal and Hefferman 1986). On the basis of this examination, to be selected for the study PMDD subjects had to meet DSM-III-R (American Psychiatric Association 1987) criteria for late luteal phase dysphoric disorder and, retrospectively, DSM-IV (American Psychiatric Association 1994) criteria for PMDD. To meet impairment criteria, PMDD subjects had to have a mean score of 14 or more on the HRSD and 10 or more on the BDI; have a 30% increase in daily ratings in the late luteal phase (1 week before the onset of menses); and demonstrate a reduction in mean scores to 7 or less on the HRSD and 5 or less on the BDI, and less than 50 mm on daily ratings by the week after the cessation of menses. All of the PMDD subjects had debilitating affective symptoms that occurred during the late luteal phase of each menstrual cycle throughout the year (i.e., they did not have seasonal premenstrual symptoms). To be selected for the study, NC subjects had to have mean HRSD scores less than 7 and BDI ratings less than 5 at all menstrual cycle phases, and their daily ratings needed to show <30% clinical variation in association with the menstrual cycle. Premenstrual dysphoric disorder and NC diagnosis were not determined until the end of the 2-month evaluation.

Subjects were free of psychoactive medication for at least 2 months before study entry (during the diagnostic evaluation) and for the duration of the study. The use of natural remedies and herbs were excluded on the basis of interviews and questionnaires. Substance abuse and recent prescription medication use
were ruled out by our obtaining urine toxicology screens before admissions. Subjects needed to be off oral contraceptives and to have not been smoking 3 months before entering the evaluation phase of the study, but their use before this time was not exclusionary.

The protocol was approved by the Human Subjects Committee of the University of California, San Diego (UCSD), and all subjects gave written informed consent after the procedures had been explained fully.

**Procedures**

Subjects underwent one night of baseline study during two menstrual cycle phases: 1) the midfollicular (MF; days 6–10 after menses) and 2) late luteal (LL; 2–4 days before the onset of menses based on the midcycle luteinizing hormone (LH) surge, assuming a 14-day luteal phase). The timing of the midcycle LH surge was determined by a colorimetric urinary immunossay (Ovustick, Irvine, CA). Subjects also were studied during a randomized crossover trial of ESD (sleep 3:00 AM–7:00 AM) versus LSD (sleep 9:00 PM–1:00 AM). Each night of sleep deprivation was followed by a night of recovery sleep (ESD-R, LSD-R; sleep 10:30 PM–6:30 AM) in which we primarily obtained sleep electroencephalograms (EEGs) but not hormonal measures (Parry et al 1999). Early and late sleep interventions and their respective nights of recovery sleep were administered in the hospital during the premenstrual (late luteal) phase of separate menstrual cycles.

During each night of study, subjects were admitted to the General Clinical Research Center of the UCSD Medical Center from 4:30 PM to 9:00 AM. A physical examination, screening laboratory tests (chemistry panel, thyroid indices, complete blood count, and urinalysis) were obtained on each admission to rule out the development of other medical conditions that might affect results. Baseline levels of reproductive hormones (estradiol, progesterone, follicle-stimulating hormone, and LH) were measured at 6:00 AM and 6:00 PM on each admission to document menstrual cycle phase and the effect of these hormones on outcome measures. Trained nurses inserted an intravenous catheter at 5:00 PM and drew samples for the cortisol hormone assay every 30 min from 6:00 PM to 9:00 AM in dim light (<100 lux). So as not to disturb sleep, they obtained samples between 10:30 PM and 6:30 AM by a catheter that was threaded through a porthole to an adjoining room. Subjects adhered to their habitual bedtimes and awakening times (except when determined by the sleep deprivation schedules) and slept in rooms by themselves. Blood was drawn for the baseline studies in the MF and LL phases of the menstrual cycle and during ESD and LSD nights in the luteal phase of subsequent menstrual cycles.

**Cortisol Assay**

Plasma cortisol concentrations were measured by radioimmunoassay kits obtained from the Diagnostic Products Corporation (Los Angeles). The intra- and interassay coefficients of variation were 4% and 6%, respectively. Assay sensitivity was 0.3 μg/dL.

**Statistical Analyses**

Cosine analyses of the concentration series of cortisol were performed on each of the 30-min interval data sets for each individual by fitting the general cosine function, $CS(t) = M + A \cos(\omega t + \phi)$, where $CS(t)$ is the hormone concentration at time $t$, $M$ is the mesor (midline value), $A$ is the absolute amplitude, and $\omega$ and $\phi$ are the angular frequency and acrophase, respectively (Nelson et al 1979). As described by Klemfuss and Clopton (1993), this method is one of the most reliable for biological rhythm analyses. The three parameters defining the cosine rhythm are 1) acrophase, the time at which the maxima of the cosine curve occurs; 2) amplitude, half the difference between the highest and lowest value; and 3) mesor, the concentration about which the oscillation occurs. The peak concentration, peak time, nadir concentration, and nadir time (noncosinor functions) also were derived to account for less than 24 hour data. Timing measures (acrophase, peak time, and nadir time) were fixed to 24-hour clock time. To confirm the validity of using cosine rhythmometry analysis for hormone profiles of less than 24 hour duration, 24 hour (obtained at 30-min intervals) cortisol data sets from a previous study (Laughlin and Yen 1996) were analyzed twice—once over the entire 24 hours and once for cortisol values from 6:00 PM to 9:00 AM, corresponding to the sampling interval for this study. The correlation coefficients for the 24-hour versus the 16-hour analyses were .91 for mesor, .91 for amplitude, and .93 for acrophase (all $p < .0001$).

Each plasma cortisol profile was plotted and examined visually by an investigator with extensive experience in the analyses of cortisol rhythms (GAL). For three of the 60 profiles (one PMDD and one NC subject during the luteal phase and one NC during the follicular phase), abrupt and exaggerated increases in cortisol occurred for the duration of three samples. Nurses’ notes indicated that these excursions were coincident with reinsertion of the intravenous catheter. These data were smoothed by interpolation before further analyses. Overall repeated-measures analyses of variance (ANOVAs) were used to test main effects of group (PMDD vs. NC), condition (MF, LL, ESD, and LSD), and their interaction for each of the cortisol measures. When significant main effects or interactions were found, post hoc repeated-measures ANOVAs testing the effect of menstrual cycle phase (MF vs. LL) and the effects of sleep deprivation compared with the baseline LL phase (LL vs. ESD vs. LSD) were performed. Significant interactions for sleep deprivation were delineated further by comparing the delta from the LL baseline to ESD to that from the LL baseline to LSD by repeated-measures ANOVA. Delta acrophase was derived by subtracting ESD or LSD values from baseline values so that, according to convention, phase advances of the cortisol rhythm were calculated as positive values and phase delays as negative values. The significance of deltas for each group was tested by single sample $t$ tests.

Also, because groups may differ in cortisol secretion primarily during quiescent periods at night, we compared mean cortisol levels from 11:00 PM to 7:00 AM in PMDD and NC subjects. Correlations were made between changes in mood ratings and changes in cortisol parameters between baseline and sleep deprivation nights in PMDD patients by linear regression using a
Pearson correlation coefficient. As previous studies indicated effects of, particularly, sleep onset time and sleep latency with cortisol parameters, these sleep variables were correlated with cortisol parameters in NC and PMDD subjects during baseline luteal and ESD and LSD nights. To ascertain effects of reproductive hormonal change on cortisol outcome measures, we examined correlations between the mean of 6:00 PM and 6:00 AM estradiol and progesterone levels and cortisol measures during baseline follicular and luteal menstrual cycle phases. To account for multiple comparisons in these correlations, only results in which \( p < .01 \) were considered statistically significant. To test whether order of treatment (ESD or LSD first) affected cortisol outcome measures, we compared order of treatment (between-group factor) in a repeated-measures ANOVA for ESD and LSD. Finally, we performed a between-group ANOVA to test whether a personal or family history of depression affected cortisol rhythms in PMDD subjects.

For other than the correlational analyses listed above, statistical significance was set at a probability level of \( p < .05 \). Data are presented as means ± SDs.

**Results**

Subjects were recruited from the community by questionnaire: Of 2002 questionnaires sent to interested applicants, 779 were returned; from questionnaires received, 216 women were deemed appropriate for further screening; 103 subjects were evaluated; 41 subjects entered the study—23 subjects with PMDD and 18 NC subjects. Reasons for exclusion were use of medications (including birth control pills), not having regular menstrual cycles, not meeting diagnostic criteria, and not being able to meet the demands of a long-term research study. Three NC subjects and eight PMDD subjects dropped from the study, once entered, because of other time commitments (work or family), anemia, pregnancy, failure to ovulate, or because we were not able to obtain complete or reliable data on them (for further description, see Parry et al 1995). The data from 15 NC and 15 PMDD subjects from whom we were able to obtain complete cortisol profiles are presented in the following analyses.

**Subject Demographics**

The mean age for PMDD subjects (\( n = 15 \)) was 36.0 ± 4.1 years (range 29—43); for NC subjects (\( n = 15 \)) it was 37.2 ± 5.8 years (range 24—45). Premenstrual dysphoric disorder and NC subjects did not differ significantly by age, education, marital status, or parity.

**Mood Rating Scales**

The description of mood rating scales, the nature and severity of depressive symptoms, and treatment response are published in Parry et al (1995). In summary, patient mood ratings showed a significant reduction of depressive symptoms from baseline (without induction of mania) after recovery nights of sleep from both ESD and LSD, but not the day after ESD or LSD (Parry et al 1995).

**Cortisol Rhythm Analyses**

Mean cortisol profiles for PMDD and NC subjects during baseline MF and LL menstrual cycle phases and during nights of ESD and LSD are shown in Figure 1. Results of cortisol rhythm analyses are presented in Table 1.

**OVERALL ANOVA.** In an overall ANOVA to test for main effects of group (PMDD and NC), condition (MF, LL, ESD, and LSD) and their interaction on cortisol rhythm parameters, we found significant main effects of condition for acrophase \( F(3,84) = 14.87, p < .001 \), peak time \( F(3,84) = 9.42, p < .01 \), mesor \( F(3,84) = 6.25, p < .001 \), amplitude \( F(3,84) = 7.51, p < .0001 \), peak concentration \( F(3,84) = 3.28, p < .03 \), and nadir concentration \( F(3,84) = 3.70, p < .02 \) and a significant interaction of group and condition for acrophase \( F(3,84) = 2.89, p < .04 \). There were no statistically significant effects of condition for nadir time and no statistically significant main effects of group for any parameter.

**FOLLICULAR VERSUS LUTEAL MENSTRUAL CYCLE PHASE.** Mesor, amplitude, and peak concentration (quantitative measures) were not significantly affected by menstrual cycle phase. A statistically significant effect of menstrual cycle phase was seen for acrophase \( ANOVA, F(1,28) = 4.48, p < .04 \), with a significant group by phase interaction \( F(1,28) = 4.97, p < .04 \). The cortisol acrophase occurred a mean of 1.00 ± 1.22 hours earlier in the LL menstrual cycle phase as compared with the MF phase for NC subjects, but not for PMDD subjects. The nadir value was higher \( F(1,28) = 5.405, p < .028 \) during the follicular menstrual cycle phase for both NC and PMDD groups.

**LATE LUTEAL PHASE BASELINE VERSUS EARLY AND LATE SLEEP DEPRIVATION.** In a repeated-measures ANOVA comparing LL, ESD, and LSD, there were main effects of condition for mesor \( F(2,56) = 3.43, p < .04 \), amplitude \( F(2,56) = 18.08, p < .001 \), nadir \( F(2,56) = 3.39, p < .04 \), peak time \( F(2,56) = 11.954, p < .001 \), and acrophase \( F(2,56) = 18.29, p < .001 \) and a statistically significant interaction of group and condition for acrophase \( F(2,56) = 3.38, p < .04 \) in that in PMDD subjects, but not in NC subjects, the cortisol acrophase occurred significantly earlier during LSD. During LSD, as compared with the
baseline LL phase and ESD, the mesor and amplitude of the cortisol rhythm were lower and the acrophase and peak time were earlier. The nadir concentration was higher during ESD than during the LL baseline and LSD.

**POST HOC ANALYSES.** For the comparison of LL and ESD there were significant effects of condition for acrophase \([F(1,28) = 4.13, p < .05]\) and peak time \([F(1,28) = 8.92, p < .006]\). For the comparison of LL and LSD there were significant effects of condition for amplitude \([F(1,28) = 18.81, p < .001]\), acrophase \([F(1,28) = 18.40, p < .001]\), and mesor \([F(1,28) = 0.035, p < .04]\) and significant interaction effects for acrophase \([F(1,28) = 5.40, p < .03]\). For the
Table 1. Mean ± SD Values for Cortisol Rhythm Characteristics for 15 Premenstrual Dysphoric Disorder (PMDD) and 15 Normal Control (NC) Subjects during Midfollicular (MF) and Late Luteal (LL) Menstrual Cycle Phases and during Early and Late Partial Sleep Deprivations (ESD and LSD; Administered during Separate LL Menstrual Cycle Phases)

<table>
<thead>
<tr>
<th></th>
<th>MF</th>
<th>LL</th>
<th>ESD</th>
<th>LSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesor (μg/dL)</td>
<td>10.68 ± 2.81</td>
<td>9.70 ± 1.88</td>
<td>9.44 ± 1.63</td>
<td>8.20 ± 1.90</td>
</tr>
<tr>
<td>AM (μg/dL)</td>
<td>10.20 ± 2.25</td>
<td>9.48 ± 2.85</td>
<td>9.68 ± 2.46</td>
<td>9.21 ± 3.06</td>
</tr>
<tr>
<td>Acrophase*</td>
<td>6.58 ± 1.77</td>
<td>7.11 ± 1.64</td>
<td>7.23 ± 1.42</td>
<td>6.10 ± 1.25</td>
</tr>
<tr>
<td></td>
<td>7.30 ± 1.51</td>
<td>7.08 ± 1.39</td>
<td>6.91 ± 2.28</td>
<td>5.38 ± 1.39</td>
</tr>
<tr>
<td>Peak (μg/dL)</td>
<td>9:23 AM ± 1 hr 35 min</td>
<td>9:25 AM ± 1 hr 9 min</td>
<td>10:04 AM ± 1 hr 30 min</td>
<td>7:41 AM ± 1 hr 26 min</td>
</tr>
<tr>
<td></td>
<td>9:58 AM ± 1 hr 17 min</td>
<td>8:58 AM ± 1 hr 25 min</td>
<td>9:29 AM ± 1 hr 50 min</td>
<td>8:28 AM ± 56 min</td>
</tr>
<tr>
<td></td>
<td>22.50 ± 3.66</td>
<td>20.72 ± 3.37</td>
<td>21.90 ± 4.40</td>
<td>18.98 ± 2.74</td>
</tr>
<tr>
<td></td>
<td>22.26 ± 4.45</td>
<td>21.35 ± 4.93</td>
<td>20.37 ± 5.02</td>
<td>20.57 ± 6.00</td>
</tr>
<tr>
<td>Acrophase time</td>
<td>6:30 AM ± 1 hr 39 min</td>
<td>6:14 AM ± 1 hr 53 min</td>
<td>7:34 AM ± 39 min</td>
<td>5:19 AM ± 1 hr 32 min</td>
</tr>
<tr>
<td></td>
<td>6:24 AM ± 1 hr 19 min</td>
<td>5:54 AM ± 1 hr 30 min</td>
<td>6:25 AM ± 1 hr 7 min</td>
<td>4:58 AM ± 1 hr 48 min</td>
</tr>
<tr>
<td></td>
<td>2.55 ± 1.78</td>
<td>1.62 ± 0.69</td>
<td>1.89 ± 0.63</td>
<td>1.67 ± 0.44</td>
</tr>
<tr>
<td></td>
<td>2.08 ± 1.02</td>
<td>1.95 ± 0.94</td>
<td>2.26 ± 0.85</td>
<td>1.92 ± 1.00</td>
</tr>
<tr>
<td>Acrophase (h)</td>
<td>10:56 PM ± 2 hrs 43 min</td>
<td>10:50 PM ± 2 hrs 8 min</td>
<td>10:34 PM ± 2 hrs 1 min</td>
<td>10:34 PM ± 1 hr 46 min</td>
</tr>
<tr>
<td></td>
<td>11:48 PM ± 2 hrs 14 min</td>
<td>10:56 PM ± 1 hr 53 min</td>
<td>11:38 PM ± 1 hr 53 min</td>
<td>11:28 PM ± 1 hr 2 min</td>
</tr>
</tbody>
</table>

*Values are fixed to 24-hour clock time.

Comparison of ESD and LSD there were significant main effects of condition for amplitude \( F(1,28) = 14.90, p < .001 \); acrophase \( F(1,28) = 29.54, p < .001 \); mesor \( F(1,28) = 5.08, p < .03 \); peak time \( F(1,28) = 28.00, p < .001 \); and nadir \( F(1,28) = 7.35, p < .01 \); significant effects of group for peak time \( F(1,28) = 4.72, p < .04 \); and significant interaction effects for acrophase \( F(1,28) = 4.60, p < .04 \).

**DELTA CALCULATIONS.** We calculated change scores for cortisol parameters between the LL baseline and ESD (LL-ESD) and between the LL baseline and LSD (LL-LSD). In a comparison of these two conditions (LL-ESD vs. LL-LSD) we found for cortisol acrophase a statistically significant main effect of condition \( F(1,28) = 29.5, p < .0001 \) and a significant group by condition interaction \( F(1,28) = 4.599, p = .04 \); the cortisol acrophase was delayed for PMDD (delta: −0.63 ± 1.18 hours, \( p = .06 \)) and NC subjects (delta: −0.51 ± 1.82 hours, ns) during ESD (mean delta: −0.57 ± 1.51 hours, \( p = .05 \)) as compared with the LL baseline. In contrast, during LSD the cortisol acrophase was advanced an average of 1.75 ± 1.09 hours (\( p < .001 \)) for PMDD subjects, but was not significantly shifted for NC subjects (0.52 ± 1.74 hours, ns; Figure 2).

**ANALYSES FOR MEAN CORTISOL VALUES FROM 11:00 PM TO 7:00 AM.** In an overall ANOVA, mean levels of cortisol from 11:00 PM to 7:00 AM were compared between groups (PMDD vs. NC subjects) and for the four conditions (MF, LL, ESD, and LSD). There were statistically significant main effects of condition \( F(3,26) = 7.93, p < .001 \) but no significant main effects of group or group by condition interaction. Post hoc ANOVAs comparing menstrual cycle phase (MF vs. LL) showed a
significant effect of group by phase interaction \([F(1,28) = 5.06, p < .04]\) but no significant main effects of group or phase: the mean value of cortisol for NC subjects increased in the LL phase \((9.7 \pm 4.0 \mu g/dL)\), as compared with the EF phase \((8.56 \pm 1.9 \mu g/dL)\), whereas in PMDD subjects the mean value decreased in the LL phase \((8.9 \pm 2.18 \mu g/dL)\), as compared with the EF phase \((10.27 \pm 3.01 \mu g/dL)\).

In an ANOVA comparing LL, ESD, and LSD, there were significant main effects of condition \([F(2,27) = 13.57, p < .001]\) but no significant main effects of group or group by condition interactions. In post hoc comparisons of LL and ESD, and ESD and LSD, there were main effects of condition \([F(1,28) = 11.02, p < .003\) and \(F(1,28) = 24.52, p < .001]\), respectively. The mean cortisol levels from 11:00 PM to 7:00 AM were highest during LSD \((10.12 \pm 2.05 \mu g/dL)\), as compared with ESD \((7.82 \pm 2.76 \mu g/dL)\) or the LL baseline \((9.32 \pm 3.18 \mu g/dL)\).

Correlation of Mood Ratings and Cortisol Parameters

As noted in Methods and Materials, to account for multiple comparisons in these correlational analyses we only considered \(p < .01\) to be statistically significant. With these criteria, there were no statistically significant correlations between baseline cortisol parameters and HRSD or BDI scores in the luteal phase in PMDD subjects and no statistically significant correlations between the change in HDRS or BDI scores and the change in cortisol measures between the LL baseline and the night of ESD or LSD. There was a trend for a negative correlation between the change in BDI ratings and the change in cortisol amplitude between the LL baseline and ESD \((r = -.52, n = 15, p = .05)\). Normal control subjects were not included in these analyses, as they did not have elevated or significant changes in mood ratings.

Reproductive hormones

Baseline levels of reproductive hormones did not differ between groups, as reported by Parry et al (1996). Correlations were made between the mean levels of estradiol and progesterone at 6:00 AM and 6:00 PM and cortisol parameters during the baseline follicular and luteal phases. There was a statistically significant inverse correlation between estradiol levels and cortisol acrophase in the luteal phase, but not the follicular, in PMDD subjects, but not NC subjects \((r = -.71, n = 15, p = .003)\; \text{Figure 3}\). Levels of estradiol and progesterone were not significantly correlated with other cortisol parameters.
amplitude was significantly higher during LSD \( F(1, 13) = 9.04, \ p < .01 \). In PMDD patients with a positive family history for depression the cortisol peak time was later during LSD \( F(1, 13) = 5.82, \ p < .03 \).

**Discussion**

In this study of 15 PMDD and 15 NC subjects during the MF and LL phases of the menstrual cycle and during ESD and LSD in subsequent luteal phases, we found that menstrual cycle phase differentially affected primarily the timing of cortisol secretion, but not the quantitative measures of it, in PMDD and NC subjects: the cortisol acrophase was phase advanced a mean of 1 hour in NC subjects in the LL phase of the menstrual cycle, as compared with the MF phase. This menstrual cycle phase-dependent alteration was absent in PMDD subjects. The effect of sleep deprivation also differed for PMDD and NC subjects primarily in timing rather than in quantitative measures of cortisol secretion: the cortisol acrophase was phase advanced an average of almost 2 hours during LSD (when subjects slept earlier) in PMDD subjects, but not in NC subjects. This finding is in contrast to similar phase delays of about 30 min observed for both PMDD and NC subjects during ESD (when subjects slept later). Thus, both our first hypothesis, that timing disturbances in cortisol secretion would differentiate PMDD and NC subjects during the menstrual cycle, and our second hypothesis, that patient and control groups would have different responses to sleep deprivation interventions as measured by cortisol parameters, were supported.

The normal baseline cortisol levels in PMDD patients seen in this study during both menstrual cycle phases are consistent with our previous report (Parry et al 1994) and most, but not all, other studies: Rabin et al (1990) found low evening cortisol levels in patients with premenstrual syndrome, as compared with NC subjects, as did we when we examined cortisol levels during the nocturnal quiescent hours (11:00 PM–7:00 AM). In a study by Bloch et al (1998), however, examination of morning cortisol levels every 2–3 days failed to identify differences in cortisol at any part of the menstrual cycle. In addition, in frequent (every 20–30 min) sampling studies conducted over extended (18- to 24-hour) time periods, cortisol levels and the circadian amplitude of cortisol (Mortola et al 1989; Parry et al 1994; Steiner et al 1994) were unaltered in women with PMDD. Normal levels of ACTH in PMDD also are seen in most studies (Bloch et al 1998; Rabin et al 1990; Rosenstein et al 1996; Su et al 1997), although Redei and Freeman (1993) found that baseline plasma ACTH levels, but not cortisol levels, were lower in PMS subjects as compared with control subjects. Perhaps the hypercortisolism that often characterizes patients with MDD may be attributed in part to the chronicity of the illness (Halbreich et al 1982). In contrast, PMDD is a more transient disorder and may not be of sufficient duration to elicit a sustained increase in cortisol levels.

In contrast to the lack of substantial differences in quantitative measures of cortisol secretion observed between patient and control groups, we have noted, as in this study, altered timing measures in PMDD and NC subjects during the menstrual cycle: the cortisol peak was phase delayed in the luteal compared with the follicular menstrual cycle phase in NC subjects but not in PMDD subjects (Parry et al 1994). These findings suggest that PMDD subjects may not respond to the hormonal changes of the luteal phase (characterized by the secretion of progesterone) in the same way as do NC subjects. As Young (1999) noted in studies of menstrual cycle phase effects on LH pulsatility in depressed and healthy women, there was a resistance to the frequency-modulating effects of progesterone on LH pulse frequency in depressed women. The fact that in our previous study cortisol peak was phase delayed in the luteal versus follicular phase in NC subjects and that in this study the cortisol acrophase was phase advanced in the luteal versus follicular phase in NC subjects may reflect more a dysregulation of timing functions of cortisol secretion in patients, as compared with control subjects, in the luteal phase, rather than a specific abnormality of direction per se (Siever and Davis 1985).

Other menstrual cycle phase-dependent changes that have been reported to occur (although not differentially in PMDD and NC subjects) include dexamethasone suppression of cortisol and type II glucocorticoid receptor messenger RNA expression in lymphocytes: they are reduced in the luteal phase of the menstrual cycle, as compared with the follicular phase (Altemus et al 1997). As suggested by the authors, premenstrual mood changes may be related to reduced glucocorticoid feedback restraint of central stress response systems during the luteal phase.

Although menstrual cycle phase did affect the nadir value (higher in the follicular phase than in the luteal), it did not have differential effects in PMDD and NC subjects. We attribute this finding to the enhancing effects of estrogen on cortisol secretion (Grant et al 1965) that occur in the follicular phase and that are consistent with our previous findings (Parry et al 1991).

Estradiol was inversely correlated with the cortisol acrophase in PMDD subjects in the luteal phase, but not in NC subjects. This finding suggests that the two groups are differentially responsive to reproductive hormonal change in the luteal menstrual cycle phase, but not the follicular.

From the challenge tests in this study, we find that timing measures of cortisol secretion also are differentially affected between groups: PMDD subjects, but not NC.
subjects, phase advance their cortisol circadian rhythm with LSD (when they advance their sleep to 9:00 PM). The fact that in the luteal phase baseline the cortisol acrophase of PMDD subjects did not advance as it did in NC subjects, but that it did advance with the challenge of LSD (when sleep is advanced), suggests that the resistance to a phase advance of the cortisol rhythm in PMDD subjects in the luteal phase may be corrected by LSD in that it restores the normal phase (timing) relationships between sleep and cortisol circadian rhythms. The baseline differences in cortisol rhythms are not very robust between the two subject groups. With challenge studies using ESD and LSD interventions, however, these cortisol circadian rhythm alterations become more pronounced. Previous studies on the effect of sleep deprivation on cortisol rhythms also suggest that sleep deprivation can affect the timing of the cortisol rhythm: Davidson et al (1991) found that sleep deprivation altered the timing (the nocturnal rise was earlier), but not the average 24-hour levels. Saletu et al (1986) found that partial sleep deprivation late in the night (1:30–6:00 AM), timing similar to LSD in our study, also was associated with an earlier rise in cortisol secretion. Bouhuis et al (1990) found that, in 16 depressed patients, total sleep deprivation (TSD) advanced the time of the maximal cortisol excretion, changes not observed in NC subjects. The time shift, however, was not related to the mood response to TSD in the depressed group. Yamaguchi et al (1978) noted that with 20 depressed patients who underwent one night of TSD, in responders after sleep deprivation, the normal circadian rhythm of cortisol, not evident the preceding day, was restored to that of the NC subjects.

The lower mesor and amplitude of cortisol during LSD probably reflects that with an earlier (phase advanced) sleep onset time, cortisol secretion is decreased. Studies in normal healthy men show that there is a decrease of cortisol during slow-wave sleep (that tends to occur earlier in the night) and an increase during rapid eye movement sleep (that tends to occur later in the night; Weitzman et al 1981). Studies by Pietrosky et al (1994), Weibel et al (1995), and Spath-Schwalbe et al (1993) also suggest that sleep, particularly slow-wave sleep, that occurs during the first hours of nocturnal sleep is associated with decreased cortisol release. The differential effect of ESD and LSD on cortisol during the night (11:00 PM–7:00 AM analyses) also reflects the different times of waking, which increase cortisol levels, during this interval.

Other factors, such as sex, age, genetic factors, stress, and sleep latency, may affect cortisol secretion, and result in differences in study results: studies by Van Cauter et al (1996) showed that in normal premenopausal women the cortisol amplitude is lower than that of men in the same age group. The study by Van Cauter further showed that these younger normal women had a phase delay in their cortisol circadian rhythm in the morning, due to their slower response to the circadian signal, compared with men of the same age group. Thus, our results may differ from those of studies in which men were exclusively or primarily studied, or women of a different age range. Twin studies done by Linkowski et al (1993) showed that apart from environmental factors like meals and sleep, the acrophase and especially the nadir of the cortisol rhythm are genetically controlled. The acrophase, however, is not as robust a marker of the circadian rhythm as the nadir (Linkowski et al 1993). In our study, in patients with a family history of depression the cortisol peak occurred later during LSD. According to Stoney et al (1990), the magnitude of stress responses during three different menstrual phases did not affect cortisol rhythms. If primarily stress factors were involved, we might expect the PMDD patients to have higher cortisol levels rather than lower ones during the quiescent nocturnal hours. Those patients, however, with a personal history of depression did have higher amplitudes of cortisol during LSD, a finding correlated with response to sleep deprivation in previous studies (Baumgartner et al 1990a, 1990b; Gerner et al 1979). Fehm and Born (1991), however, found that it was individual differences in sleep onset latencies that affected the cortisol rise. In our findings, during ESD the later the sleep onset time, the earlier the cortisol peak time, and the shorter the sleep latency, the lower the cortisol nadir concentration.

The strengths of this study include adherence to the rigorous DSM-IV criteria for PMDD: we observed both PMDD and NC subjects for a 2-month period with daily ratings and weekly clinic visits to screen subjects, to exclude subjects who did not meet the criteria for PMDD and to document in a comparison group of NC subjects a lack of clinically significant cyclical mood changes linked to the menstrual cycle. We also excluded a family history of depression in the NC subjects, and the PMDD subjects, although they could have a history of MDD, could not have such an illness in the last year. This approach eliminates confounding our study with women with current MDDs as PMDD subjects. A history of MDD differentiated treatment response, but not baseline cortisol parameters, in PMDD subjects. Other strengths include the frequent sampling of cortisol measures during the 24-hour cycle, the baseline measures in women in symptomatic and asymptomatic menstrual cycle phases, and the measures obtained during challenge paradigms of ESD and LSD that were designed to improve mood in symptomatic subjects during the luteal phase.

A limitation of this study is the relatively small number of subjects in both groups. Thus the findings need to be interpreted with caution. The study needs to be replicated.
with a larger number of subjects to be able to compare the findings with studies done with other depressive disorders. Also, the effects of stress, diet, sleep, and activity, which can affect cortisol secretion, were not minimized by using constant routine conditions. Another limitation of this study is the lack of 24-hour profiles for cosinor analyses. The maximum number of hours needed for a fitted curve has not been determined. Rough estimates of circadian parameters, however, can be gained from samples being drawn overnight from 6:00 PM to 9:00 AM.

From our study’s data, and similar MDD studies by Yamaguchi et al (1978), we find that the primary abnormality in PMDD subjects is the timing of the cortisol circadian rhythm and not the quantity of cortisol secreted. In support of the internal coincidence model for the basis of affective disorders (Wehr and Wirz-Justice 1981), cortisol circadian rhythms may have an abnormal phase position with respect to the timing of sleep in PMDD that is corrected by advancing sleep with LSD. Thus one mechanism by which sleep deprivation may exert its therapeutic effects is by realigning cortisol circadian rhythms with sleep in women with PMDD, with improvements in mood observed the day after recovery nights of sleep (Parry et al 1995). The fact that ESD (in which sleep is delayed until 3:00 AM) also improved mood in PMDD subjects the following night, and was associated with a small delay in the cortisol acrophase (that was not different from that of NC subjects), suggests, however, that it may be the effect of sleep deprivation itself and not its timing that is related to therapeutic efficacy. Although most studies find that improvement of mood occurs after the night of sleep deprivation (day 1 responders; Gillin 1983; Wu and Bunney 1990), other investigators have observed that improvement of mood may not be noted until after at least a partial night of recovery sleep (day 2 responders; Matussek et al 1974; Sack et al 1988; Wirz-Justice et al 1976). Matussek et al (1974) hypothesize that day 1 responders primarily have a serotonergic dysfunction and day 2 responders a noradrenergic dysfunction. Additional studies are warranted examining the effect of ESD and LSD with respect to the timing relationships between cortisol, sleep, and other circadian rhythms during nights of both sleep deprivation and recovery sleep to address these questions further.

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References


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