Menstrual Cycle Effects on the Dexamethasone Suppression Test in Major Depression

Rajiv Tandon, Roger F. Haskett, Daniel Cardona, Kirsten Alcser, and John F. Greden

Introduction

Patients with major depressive disorder (MDD) frequently exhibit dysregulation of the hypothalamo-pituitary-adrenal (HPA) axis reflected in elevated basal cortisol levels as well as resistance to feedback inhibition, which is typically manifested by resistance to suppression by dexamethasone (Carroll et al 1981; Stokes and Sikes 1988). Alterations in and interactions between the HPA and hypothalamo-pituitary-gonadal (HPG) axes in MDD have also been documented (Rubin and Poland 1984; McEwen 1987). Systematic fluctuations of gonadal steroid levels through the menstrual cycle have been well described (Yen 1980), with maximal estrogen activity in the periovulatory phase and maximal progesterone activity in the early to mid-luteal phase. In view of the interactions between the HPG and HPA axes, the relationship between premenstrual syndrome and mood disorders (Endicott et al 1985; Rubinow et al 1985; Mortola et al 1989; Graze et al 1990), and the systematic menstrual oscillations in gonadal steroid activity, it would be important to evaluate possible menstrual effects on HPA function. Early studies in this regard have failed to find differences in cortisol secretory parameters between the follicular and luteal phase (Haskett et al 1984; Mortola et al 1989). To further study possible menstrual changes in the HPA axis, we conducted serial dexamethasone suppression tests (DSTs) through one complete menstrual cycle in 25 inpatients with MDD.

Methods

The sample consisted of 25 hospitalized menstruating women with a Schedule for Affective Disorders and Schizophrenia/Research Diagnostic Criteria (SADS/RDC) diagnosis of MDD (Endicott and Slaitzer 1978; Spitzer et al 1978). Subjects who met the following inclusion/exclusion criteria were retrospectively identified from the University of Michigan Depression program dataset collected over 5 years: (1) all subjects had one complete, carefully documented, 4-week menstrual cycle during which they were medication free (n = 14) or had no change of antidepressant medication (n = 11); and (2) all subjects had weekly valid 1 mg DSTs (Carroll et al 1981) through the menstrual cycle. Menstrual cycle status was ascertained weekly by a research nurse based on patient report of onset of menses. Twenty five patients fulfilling these criteria were retrospectively identified from among 140 hospitalized menstruating women with MDD. Subjects ranged in age from 19 to 45 years, mean ± SD age 34 ± 7. Cortisol was assayed by Murphy's competitive protein binding method (Murphy 1967). Patients were also rated weekly on the Hamilton Rating Scale for Depression (HRSD) (Hamilton 1960).

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Five weekly DSTs were conducted in which week 0 corresponded to week of menses, week 1 to the follicular phase, week 2 to the periovulatory phase, week 3 to the luteal phase, and week 4 to menses. Maximal postdexamethasone cortisol levels at these five timepoints were compared by a repeated measures analysis of variance (ANOVA).

Results
We found that the maximal postdexamethasone cortisol levels were lowest at week 0 (menses-1), with a mean of 3.84 μg/dl, rose to 4.94 μg/dl at week 1 (follicular), reached a peak of 7.61 μg/dl at week 2 (periovulatory), declined marginally to 6.76 μg/dl at week 3 (luteal) before declining to 5.00 μg/dl at week 4 (menses-2). As illustrated in Figure 1, these differences were highly significant ($F = 9.8; \text{df} = 4.24; p < 0.001$). Scheffe F-tests showed the following group differences to be significant ($p < 0.05$): menses-1 versus ovulatory; menses-1 versus luteal; follicular versus ovulatory; ovulatory versus menses-2; other comparisons showed no significant group differences. The drug-free group ($n = 14$) and the group of patients on a constant dose of antidepressant ($n = 11$) showed the same pattern (Table 1).

These findings could not be explained by changes in severity of depression, weight, or other known sources of variance in HPA function. In fact, the HRSD scores showed an inverse pattern to postdexamethasone cortisol levels through the menstrual cycle (see Fig. 1), with a significant menstrual increase in the severity of depression ($F = 6.3; \text{df} = 4.24; p < 0.01$). Again, both the drug-free and constant-medication groups showed this pattern, although mean 17-item total Hamilton scores were lower in the medicated group (Table 1).

In terms of categorization as DST suppressors or nonsuppressors (defined by a cutoff of 5 μg/dl), 19 patients (10 suppressors and 9 nonsuppressors) did not change through the menstrual cycle. The remaining 6 patients were DST nonsuppressors only during the periovulatory and/or luteal weeks, but suppressed normally at other timepoints.

Discussion
The pattern of menstrual changes in postdexamethasone cortisol levels noted in our study differ from the findings of Haskett et al (1984). Haskett et al, evaluating premenstrual syndrome as a possible neuroendocrine model for depres-
Table 1. Menstrual Changes in Maximal Postdexamethasone Cortisol and Hamilton Depression Ratings in Drug-free Patients and Patients on Constant Medication

<table>
<thead>
<tr>
<th></th>
<th>Menses-1</th>
<th>Follicular</th>
<th>Ovulatory</th>
<th>Luteal</th>
<th>Menses-2</th>
<th>Significance (ANOVA)</th>
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<tbody>
<tr>
<td>Drug-free (n = 14)</td>
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<tr>
<td>Post-dex cortisol</td>
<td>4.2 ± 3.2</td>
<td>5.3 ± 4.0</td>
<td>8.6 ± 6.0</td>
<td>6.7 ± 4.7</td>
<td>5.7 ± 3.7</td>
<td><em>F</em> = 6.1; df = 4.13; <em>p</em> &lt; 0.01</td>
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<tr>
<td>17-item HRSD total scores</td>
<td>20 ± 6</td>
<td>18 ± 6</td>
<td>18 ± 5</td>
<td>18 ± 4</td>
<td>21 ± 8</td>
<td><em>F</em> = 2.9; df = 4.13; <em>p</em> &lt; 0.05</td>
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<tr>
<td>Constant medication (n = 11)</td>
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<tr>
<td>Post-dex cortisol</td>
<td>3.4 ± 3.0</td>
<td>4.5 ± 4.5</td>
<td>6.3 ± 5.8</td>
<td>6.8 ± 5.0</td>
<td>4.0 ± 3.7</td>
<td><em>F</em> = 4.5; df = 4.10; <em>p</em> &lt; 0.05</td>
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<tr>
<td>17-item HRSD total scores</td>
<td>15 ± 6</td>
<td>13 ± 7</td>
<td>13 ± 7</td>
<td>13 ± 7</td>
<td>16 ± 8</td>
<td><em>F</em> = 3.9; df = 4.10; <em>p</em> &lt; 0.05</td>
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All values expressed as mean ± standard deviation.

Menstrual fluctuations in the severity of depression observed in this study are consistent with reports of a premenstrual exacerbation of depressive symptomatology (Rubinow et al 1985) and support the relationship between menstrual mood changes and major depression (Wetzel et al 1975; Endicott et al 1981; Halbreich and Endicott 1985; Graze et al 1990).

Findings of our study are limited by the retrospective design and identification of menstrual cycle phase on the basis of patient report of onset of menses. Gonadal hormone levels would have provided a more reliable index of the phase of menstrual cycle. Similarly, dexamethasone levels would have permitted a more comprehensive evaluation of the DST response; these were not obtained, however, as the subjects were selected retrospectively from a database of patients in the early 1980s. Finally, our inclusion/exclusion criteria may have biased the patient sample by including more treatment-refractory patients (particularly in the constant-medication group). As a consequence, our results must be considered preliminary.

Menstrual changes in DST cortisol levels theoretically may stem from menstrual fluctuations in basal HPA activity or central neurotransmitters (Cardona et al 1990), gonadal steroid modulation of central neurotransmitters or steroid receptors at hypothalamic or pituitary levels (McEwen et al 1984), alteration of adrenal corticosteroid metabolism, or interference with cor-
tisol assay. Possible mechanisms underlying menstrual fluctuations in HPA activity and their relationship to mood and other psychobiological changes through the menstrual cycle warrant further exploration.

References
Burns JK (1975): Variation in plasma ACTH levels during the human menstrual cycle. J Physiology (London) 249:36 P.