Menstrual Cycle Effects on the Dexamethasone Suppression Test in Major Depression

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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 Spitzer 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 ($F = 9.8$; 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 ($F = 6.3$; 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-

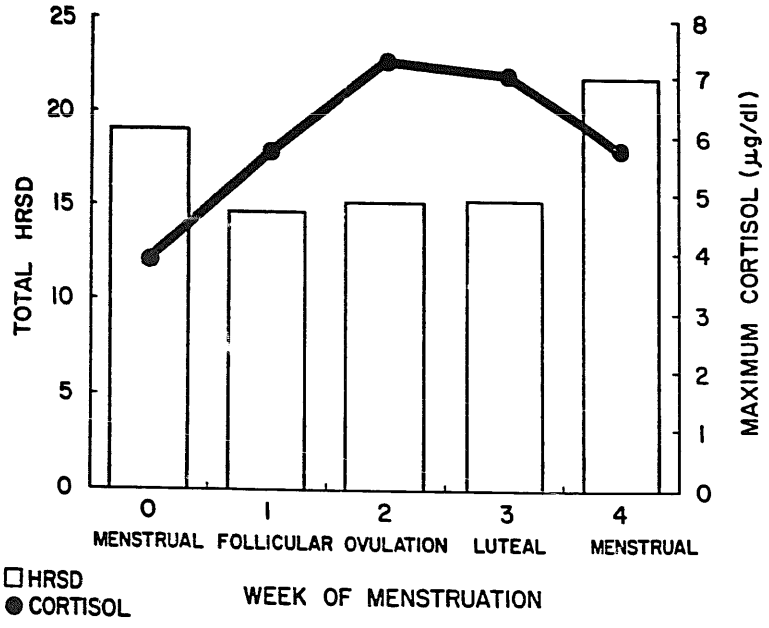

Figure 1. Maximal post-dexamethasone cortisol and HRSD through the menstrual cycle.

Table 1. Menstrual Changes in Maximal Postdexamethasone Cortisol and Hamilton Depression Ratings in Drug-free Patients and Patients on Constant Medication

	Menses-1	Follicular	Ovulatory	Luteal	Menses-2	Significance (ANOVA)
Drug-free (n = 14)						
Post-dex cortisol	4.2 ± 3.2	5.3 ± 4.0	8.6 ± 6.0	6.7 ± 4.7	5.7 ± 3.7	F = 6.1; df = 4,13; $p < 0.01$
17-Item HRSD total scores	20 ± 6	18 ± 6	18 ± 5	18 ± 4	21 ± 8	F = 2.9; df = 4,13; $p < 0.05$
Constant medication (n = 11)						
Post-dex cortisol	3.4 ± 3.0	4.5 ± 4.5	6.3 ± 5.8	6.8 ± 5.0	4.0 ± 3.7	F = 4.5; df = 4,10; $p < 0.05$
17-Item HRSD total scores	15 ± 6	13 ± 7	13 ± 7	13 ± 7	16 ± 8	F = 3.9; df = 4,10; $p < 0.05$

All values expressed as mean ± standard deviation.

sion, performed a 1-mg DST on days 10 and 26 of a 4-week menstrual cycle in 38 women with well-defined premenstrual syndrome. They found no differences in rates of nonsuppression or urinary-free cortisol levels between these timepoints. In the present study, whereas there were significant menstrual changes in postdexamethasone cortisol levels, there were no apparent differences between day 10 (rising) and day 26 (falling). However, the findings are consistent with reports that plasma ACTH levels peak around ovulation and are lowest during menses (Gennazini et al 1975; Burns 1975). They are also consistent with reports that plasma beta-endorphin levels follow a similar pattern, with rising levels through the follicular phase to a periovulatory peak and declining levels through the luteal phase (Wehrenberg et al 1982; Hamilton and Gallant 1988). Collectively, these findings would suggest that proopiomelanocortin (POMC), the precursor molecule of both ACTH and beta-endorphin (Roberts and Herbert 1977) activity, may be increased in the periovulatory phase and decreased during menstruation. The findings of this study further suggest that phase of menstrual cycle is an important variable in the interpretation of results of the DST. It remains to be seen if menstrual fluctuations in HPA axis function occur in all women or are limited to patients with MDD.

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.

Cardona D, Tandon R, Haskett RF, Greden JF (1990): Menstrual effects on neuroendocrine measures. In Woods N, Taylor D, Matteo S (eds), *Menstruation, Health and Illness*. Washington, D.C., Hemisphere Publishing Corporation.

Carroll BJ, Feinberg M, Greden JF, et al (1981): A specific laboratory test for the diagnosis of melancholia. *Arch Gen Psychiatry* 38:15–22.

Endicott J, Spitzer RL (1978): A diagnostic interview: The SADS. *Arch Gen Psychiatry* 35:837–853.

Endicott J, Halbreich U, Schacht S, Nee J (1981): Premenstrual changes and affective disorders. *Psychosom Med* 43:519–528.

Endicott J, Halbreich U, Schacht S, Nee J (1985): Affective disorder and premenstrual depression. In Osofsky HJ, Blumenthal SJ (eds), *Premenstrual Syndrome: Current Findings and Future Directions*. Washington DC: American Psychiatric Press.

Gennazini AR, Lemarchand-Beraud TH, Aubert ML, Felber JP (1975): Pattern of plasma ACTH, hGH and cortisol during the menstrual cycle. *J Clin Endocrinol Metab* 41:431–437.

Graze KK, Nee J, Endicott J (1990): Premenstrual depression predicts future major depressive disorder. *Acta Psychiatr Scand* 81:201–205.

Halbreich U, Endicott J (1985): Relationship of premenstrual changes to depressive disorders. *Acta Psychiatr Scand* 71:331–338.

Hamilton M (1960): Development of a scale for primary depressive illness. *Br J Soc Clin Psychol* 6:278–296.

Hamilton JA, Gallant S (1988): Premenstrual symptom changes and plasma beta-endorphin/beta-lipotropin throughout the normal menstrual cycle. *Psychoneuroendocrinology* 13:505–514.

Haskett RF, Steiner M, Carroll BJ (1984): A psychoneuroendocrine study of premenstrual tension syndrome. A model for endogenous depression. *J Affective Disord* 6:191–199.

McEwen BS (1987): Gonadal and adrenal steroids and the brain: Implications for depression. In Halbreich U (ed), *Hormones and Depression*. New York: Raven Press.

McEwen BS, Biegon A, Fischette CT (1984): Toward a neurochemical basis of steroid hormone action. In Martini L, Ganong WF (eds), *Frontiers in Neuroendocrinology*, Vol 8. New York: Raven Press.

Mortola JF, Girton L, Yen SSC (1989): Depressive episodes in premenstrual syndrome. *Am J Obstet Gynecol* 161:1682–1687.

Murphy BE (1967): Some studies of the protein binding of steroids and their application to the routine micro- and ultra-micro measurement of various steroids in body fluids by competitive protein-binding radioassay. *J Clin Endocrinol Metab* 27:973–990.

Roberts JL, Herbert, E (1977): Characterization of a common precursor to corticotropin and beta-lipotropin: Identification of beta-lipotropin peptides and their arrangement relative to corticotropin in the precursor synthesized in a cell-free system. *Proc Natl Acad Sci USA* 74:5300–5304.

Rubin RT, Poland RE (1984): Pituitary-adrenocortical and pituitary-gonadal function in affective disorder. In Brown GM, Koslow SH, Reichlin S (eds), *Neuroendocrinology and Psychiatric Disorder*. New York: Raven Press.

Rubinow DR, Roy-Byrne P, Hoban MC, et al (1985): Menstrually related mood disorders. In Osofsky HJ, Blumenthal SJ (eds), *Premenstrual Syndrome: Current Findings and Future Directions*. Washington DC: American Psychiatric Press.

Spitzer RL, Endicott J, Robins E (1978): Research diagnostic criteria: Rationale and reliability. *Arch Gen Psychiatry* 35:773–782.

Stokes P, Sikes C (1988): The hypothalamic-pituitary-adrenal axis in major depression. *Endocrinol Metab Clin North Am* 17:1–20.

Wehrenberg WB, Wardlaw SL, Frantz AG, Ferin M (1982): Beta-endorphin in hypophyseal blood: Variations through the menstrual cycle. *Endocrinology* 111:879–881.

Wetzel RD, Reich T, McClure JM, Wald I (1975): Premenstrual affective syndrome and affective disorders. *Br J Psychiatry* 127:219–221.

Yen SS (1980): Neuroendocrine regulation of the menstrual cycle. In Krieger DT, Hughes JC (eds), *Neuroendocrinology*. Sanderland, Massachusetts: Sinauer Association.