Pituitary–Adrenal Hormones and Testosterone across the Menstrual Cycle in Women with Premenstrual Syndrome and Controls

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Background: *Premenstrual syndrome (PMS) is a cyclic mood disorder, widely believed, yet not conclusively shown, to be of endocrine etiology. This study examines basal levels of several hormones reported, albeit inconsistently, to differ in women with PMS compared with controls.*

Methods: *Subjects (10 PMS patients and 10 controls) had their blood drawn for one full menstrual cycle. Subjects' mood and behavioral symptoms were assessed by daily self-ratings and objective ratings. Plasma was assayed for total and free testosterone (T), β-endorphin (β-EP), adrenocorticotropic hormone (ACTH), and cortisol.*

Results: *No differences were observed between the PMS and control groups for β-EP, ACTH, or cortisol. PMS subjects had significantly lower total and free T plasma levels with a blunting of the normal periovulatory peak, a finding that may be epiphenomenal to age.*

Conclusions: *This study does not confirm previous reports of abnormalities in plasma levels of either ACTH or β-EP in women with PMS; it also fails to replicate a previous observation of high free T levels in women with PMS. These results are not supportive of a primary endocrine abnormality in PMS patients.* Biol Psychiatry 1998;43:897–903 *Published 1998 Society of Biological Psychiatry*

Key Words: Premenstrual syndrome, testosterone, adrenocorticotropic hormone, β-endorphin, cortisol, androgens

Introduction

Premenstrual syndrome (PMS) is a cyclic phenomenon in which mood and behavioral symptoms occur during the luteal phase of the menstrual cycle, remitting at or close to the onset of menses. While the etiology of PMS is still largely unknown, substantial research efforts have been invested in studying possible hormonal abnormalities in women with PMS. These studies have been inconsistent in the reported differences in certain hormone levels across the menstrual cycle in women with PMS compared with controls. For example, lower adrenocorticotropic hormone (ACTH) and β-endorphin (β-EP) and higher free testosterone levels have been observed in women with PMS in some (but not other) studies (Redei and Freeman 1993; Chuong et al 1985, 1994; Tulenheimo et al 1987; Eriksson et al 1992). Such results, particularly positive ones, tend to become promulgated in an unchallenged fashion and have both theoretical and practical implications for future research. The present study attempts to reevaluate some of the unresolved issues of diagnosis-related differences in basal plasma levels of the androgen testosterone (T) and the hypothalamic–pituitary–adrenal (HPA) axis hormones β-EP, ACTH, and cortisol in women with PMS.

Methods and Materials

Patients and Controls

The subjects in this study were 10 women with prospectively confirmed PMS (mean age 38.4 ± 5.3 years) and 10 women with confirmed absence of PMS (mean age 30.6 ± 5.5 years), who served as the control group. Subjects were self-referred to our clinic in response to advertisements in the local newspaper and hospital newsletters. Subjects had regular menstrual cycles, were free of concomitant medical illness as confirmed by a complete physical examination and laboratory workup, and were not taking any psychoactive medications, hormonal preparations, mineral supplements, or nonsteroidal anti-inflammatory drugs. All subjects were free of current psychiatric illness; the control and patient subjects were also free of any past or recent (past 2 years) psychiatric illness, respectively, as determined by administration of the Structured Clinical Interview for DSM-III-R (SCID) (Spitzer et al 1989). Verbal and written consents were obtained from all participants before their inclusion in the study.

All patient subjects completed daily visual analogue symptom ratings for a screening period of at least 3 months prior to their

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Received November 20, 1996; revised April 16, 1997; revised July 8, 1997; accepted July 24, 1997.

0006-3223/98/$0.00
PII S0006-3223(98)00403-4

entry into the study. PMS was diagnosed if a woman showed a 30% or greater increase (adjusted for the range of the scale employed) in mean negative mood symptoms (anxiety and depression) in the week before menses compared with the week following menses in at least two of three menstrual cycles. Controls had the absence of PMS confirmed in a similar manner. All patients entering our study met the criteria appearing in the appendix to the DSM-IV for premenstrual dysphoric disorder (American Psychiatric Association 1994) when retrospectively applied. Although clinically useful, we find these provisional criteria to be less than optimal for research purposes, given their failure to specify the degree of luteal symptom severity required. To enable our data to be compatible with a long-standing (and current) literature describing patients with PMS, we prefer to employ this term and describe, as above, the operational criteria by which our patients are selected.

Design

Patients and controls who met the study criteria had blood samples drawn between 8:00 AM and 10:00 AM three times a week for a full menstrual cycle, starting within the first few days after the onset of menses. Blood for ACTH was collected in prechilled edetic acid (EDTA)-containing test tubes, β-EP in nonchilled EDTA test tubes, and T and cortisol in test tubes without an anticoagulant. All samples were placed on ice as soon as the blood was drawn and centrifuged within 1 hour. The plasma was then aliquoted and kept frozen at −70°C until thawed for the assay.

Ovulation during the studied cycle was determined by a self-administered ovulation predictor test kit (Clearplan Easy, Unipath Limited, Bedford, U.K.), which was used daily from 5 days prior to the expected luteinizing hormone (LH) surge.

During the studied cycle, all women filled out daily ratings of 24 symptoms rated on a 1–6 scale (Endicott et al 1986), and at every visit the following rating forms were also completed: the Premenstrual Tension Rating Form–Self and Rater Forms (PMT-S, PMT-R) (Steiner et al 1980), and the Beck Depression Inventory (BDI) (Beck et al 1961).

Assays

Plasma was assayed for total and free T, β-EP, ACTH, and cortisol. Total and free T were measured by ethanol–ether extraction, chromatography (celite), and direct radioimmunoassay (RIA), cortisol by direct RIA, and ACTH by immunoradiometric assay (Corning-Hazelton, Vienna, VA). The intra- and interassay coefficients of variation were 11% and 11% for total T, 4% and 14% for free T, 3.7% and 5% for cortisol, and 3% and 14% for ACTH. Sensitivity was 12 ng/dL, 0.7 pg/mL, 0.7 μg/dL, and 2.7 pg/mL, respectively. β-endorphin was measured by an RIA kit (INCSTAR, Stillwater, MN). This assay employs affinity column separation of β-EP from β-lipotropin and related peptides. The antibody employed in this assay is cross-reactive with β-EP-related peptides as follows: human β-EP, 100%; β-lipotropin, less than 5%; dynorphin, enkephalin, and ACTH, less than 0.01%. The intra- and interassay coefficients of variation for this assay were 3.5% and 25% at 17.5 pmol/L, and the sensitivity of the assay was 3.5 pmol/L. Due to insufficient plasma, β-EP data from only 8 out of the 10 PMS patients were available for analysis.

Statistical Analysis

In light of the normal interindividual variability of menstrual cycle length, each hormonal value was assigned to one of seven menstrual cycle phases: the ovulatory phase comprised the 3 days surrounding the LH surge; follicular and luteal phases were divided into thirds (early, mid, and late).

As a result of the assignment of values to menstrual cycle phases, some phases did not have a corresponding hormone value. Estimated values for these missing data points were derived using the BMDP program (5V), which calculates the missing values based on a curve derived from the data distribution (Dixon and Merdian 1992). Only 2% of the values were estimated in this fashion.

Analysis of variance with repeated measures (ANOVA-R) was used to calculate diagnosis, time, and diagnosis-by-time effects for the five hormone measures across the seven menstrual cycle time points. Additionally, the three follicular and three luteal time points were averaged, and an ANOVA-R was used to calculate phase effects across the three main cycle phases—follicular, ovulatory, and luteal. All calculations were repeated after log-transforming the data (due to nonnormal distribution). Post hoc analysis of significant differences found on ANOVA was performed using the Bonferroni *t* test to compare group means at different time points and to compare luteal and follicular phase values.

Age of the two subject groups was compared with a Student's *t* test. The bimodal, discontinuous distribution of ages precluded performance of analysis of covariance (ANCOVA) with age as the covariate; hence, correlations between T levels and age were performed in the patient and control groups separately.

To examine possible relationships between mood symptoms and hormone levels, BDI, PMT-R, and PMT-S rating scale scores of the mid and late luteal phases were correlated with the mid and late luteal phase hormone levels for each of the five hormonal measures using the Spearman rank correlation coefficient. In all cases, statistical significance was set at $p < .05$.

Results

All of the subjects were ovulatory during the studied cycle. Patients experienced significant symptoms during the luteal phase compared with the follicular phase as determined from daily ratings (Endicott et al 1986) [mean premenstrual and postmenstrual week scores for depression 3.0 ± 1.3 and 1.3 ± 0.4, respectively, and for anxiety 2.9 ± 0.7 and 1.2 ± 0.3, respectively ($t_9 = 3.7$ and 6.4, $p < .01$)] and cross-sectional ratings (Table 1). No control subject had significant PMS symptoms.

Figures 1 and 2 show mean plasma hormone levels in patients and controls across the seven menstrual cycle phases.

Table 1. Pre- and Postmenstrual Ratings in Patients versus Controls

	BDI	PMT-R	Depression	Anxiety
PMS				
Follicular	5.5 (8.3)	5.7 (8.9)	1.3 (0.4)	1.2 (0.3)
Luteal	13.0 (5.0)	15.0 (5.3)	3.0 (1.3)	2.9 (0.7)
Control				
Follicular	3.8 (3.3)	3.7 (3.5)	1.1 (0.2)	1.0 (0)
Luteal	3.2 (3.1)	3.5 (3.4)	1.2 (0.3)	1.1 (0.2)

Means and SD for patients and controls for late luteal and early follicular phases. BDI, Beck Depression Inventory; PMT-R, Premenstrual Tension Rating Form–Rater; depression and anxiety symptoms are from daily rating form of Endicott et al (1986).

For ACTH, β-EP, and cortisol, no significant diagnosis [$F(1,18) = 0.09, 0.4, 1.0$, respectively], time [$F(6,108) = 1.6, 1.9, 1.6$, respectively], or diagnosis by time [$F(6,108) = 0.9, 0.5, 0.5$, respectively] effects were seen (Figure 1). (Degrees of freedom for the β-EP were 6,96.) To rule out a type II error, an analysis was performed to calculate, at a power of .8, the number of subjects that would have been needed in each group to demonstrate as significant the difference in hormone levels that we observed: 135 subjects in each group for ACTH and 120 for β-EP.

For both total and free T, significant diagnosis [$F(1,18) = 7.4$, $p < .01$ and $F(1,18) = 7.3$, $p < .01$, respectively], time [$F(6,108) = 14.9$, $p < .01$ and $F(6,108) = 4.9$, $p < .01$, respectively], and diagnosis by time [$F(6,108) = 3.3$, $p < .01$ and $F(6,108) = 2.2$, $p < .05$, respectively] effects were seen. Post hoc analysis showed that the PMS patients had significantly lower total and free T levels at the periovulatory time points ($p < .05$) compared to the controls, with differences at the other time points across the cycle reaching a trend level ($p < .1$) (Figure 2). Similar significant differences were maintained when the data were log transformed.

The patient group was found to be significantly older than the control group (38.4 ± 5.3 versus 30.6 ± 5.5 years, $t_{18} = 4.1$, $p < .01$). No significant correlation was found in either patient or control groups between age and either total or free T plasma levels. To further examine the possible contribution of age to our results, we selected the 5 patients for whom we had age-matched controls (34.6 ± 4.3 years for controls, 34.6 ± 4.2 years for patients). A student's *t* test between these age-matched group means for the ovulatory phase showed a trend for decreased free T levels in patients ($t_8 = 2.2$, $p = .06$); while total T levels were in the same direction (lower in patients), differences between groups were not significant.

Phase effects on hormonal measures appear in Table 2. A significant phase effect appeared for plasma β-EP levels [$F(2,28) = 4.5$, $p < .05$], reflecting significantly higher levels during the follicular phase (see Table 2). A significant phase effect was also observed for total [$F(2,36) = 22.0$, $p < .01$] and free T [$F(2,36) = 7.7$, $p < .01$], which reflects a periovulatory peak in the control group (see Table 2). A significant diagnosis by phase effect [$F(2,36) = 4.2$, $p < .05$ and 3.9, $p < .05$ for total and free T] was seen due to a blunting of the periovulatory peak in the patient group for both total and free T.

No correlation was found between hormonal measures at the follicular, ovulatory, or luteal time points and BDI or PMT-R and PMT-S scores at the mid and late luteal phases.

Discussion

The first finding in this study is the lack of any group differences in plasma levels of ACTH, β-EP, or cortisol between women with and without PMS. Our ACTH data are consistent with those from several studies (Rabin et al 1990; Rosenstein et al 1996), but contrast with those of Redei and Freeman (1993), who reported low plasma ACTH concentrations in women with PMS across the menstrual cycle (although significantly so only during the luteal phase) compared with controls. In their study low luteal phase ACTH levels were found in the "low symptom cluster" subgroup ($n = 6$) consequent to a luteal phase increase in ACTH levels seen in the controls but not in the patients. Our data, as well as data from Mauri et al (1990), would suggest that luteal phase increases in ACTH are not normally observed and therefore call into question the source of the change observed by Redei and Freeman. Further, we divided our patient sample into low and high symptom groups (as a rough approximation of the classification of Redei and Freeman) and again were unable to detect differences in ACTH levels between the subgroups or between either subgroup compared with controls. Given that our subsamples are small (albeit identical to the subsample sizes described by Redei and Freeman), our observations can only be generalized with the greatest of caution. Finally, our data are also consistent with recent data by Su et al (1997) showing no significant differences between baseline ACTH levels in the follicular and luteal phases or between PMS patients and controls (in fact,

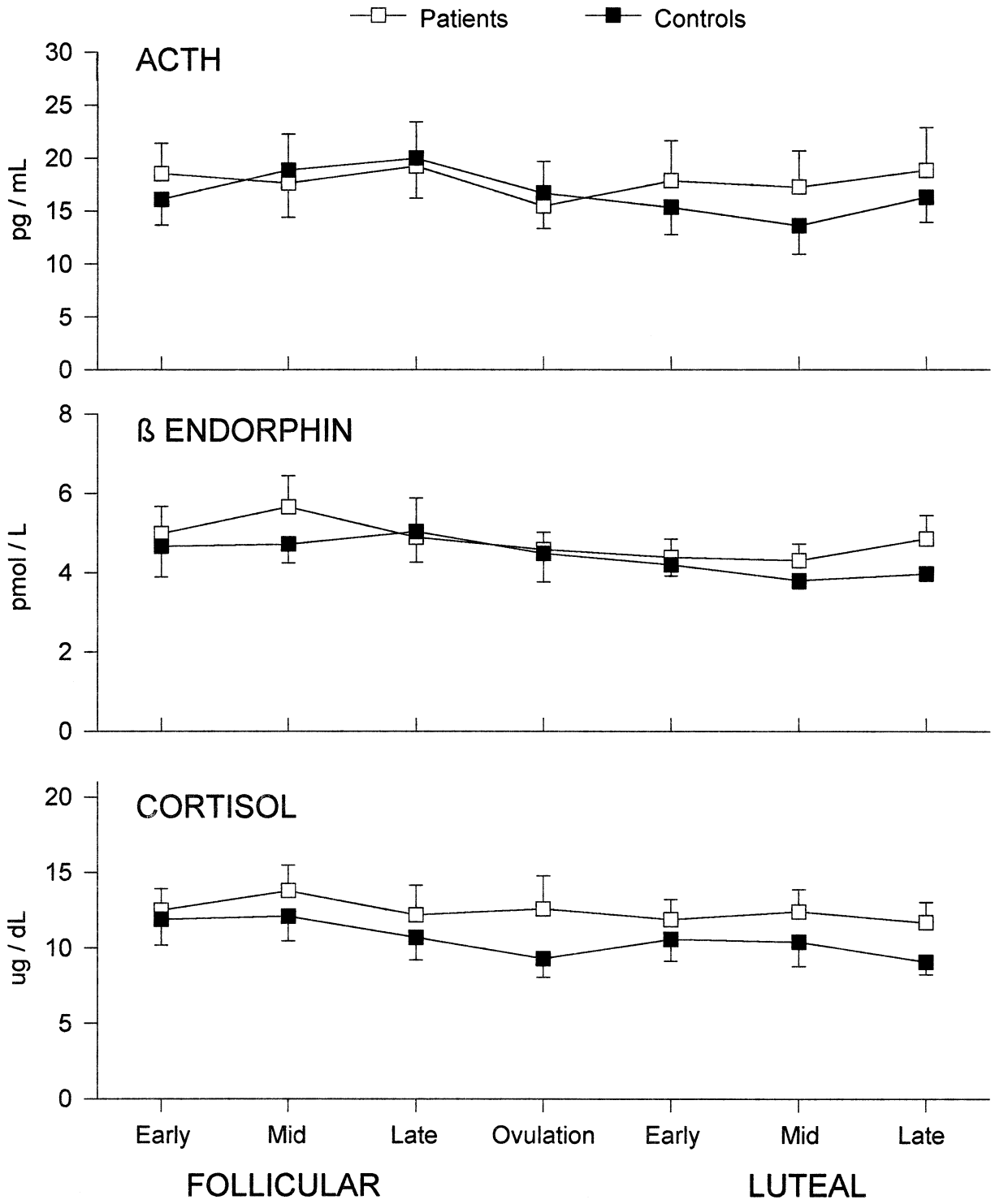

Figure 1. Plasma β-endorphin, ACTH, and cortisol (mean ± SE) across the menstrual cycle in women with PMS ($n = 10$) and controls ($n = 10$).

ACTH was higher in the PMS patients than controls at a trend level).

Studies of plasma β-EP levels in women with PMS have produced conflicting results, including low levels during the late luteal (Chuong et al 1985; Facchinetti et al 1987; Giannini et al 1990) or periovulatory (Chuong et al

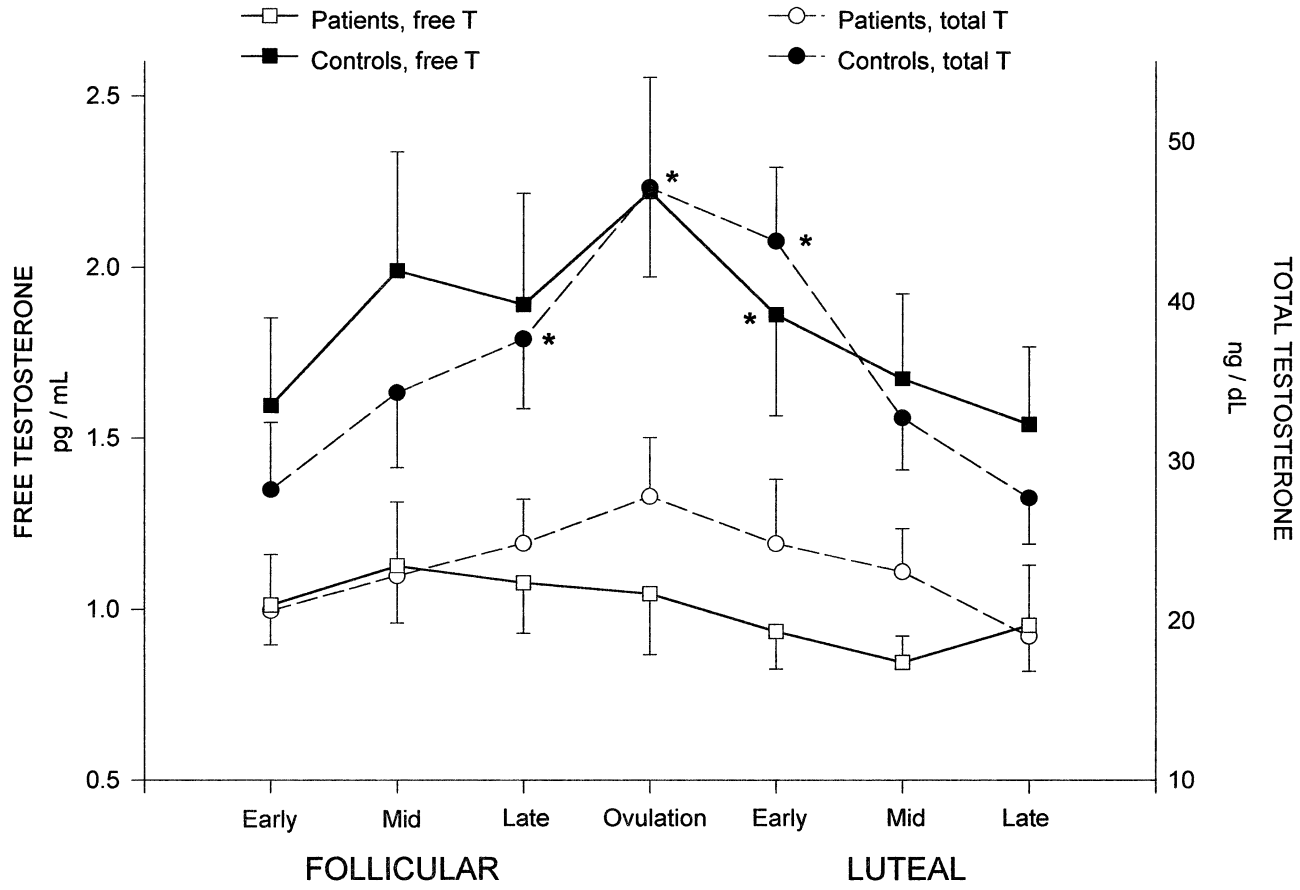

Figure 2. Plasma total and free testosterone (mean ± SE) across the menstrual cycle in women with PMS ($n = 10$) and controls ($n = 10$). *Bonferroni t test (patients vs. controls), $p < .05$.

1994) phases, low levels during the early but not the late luteal or the periovulatory phases (Tulenheimo et al 1987), or absence of significant differences (Hamilton and Gallant 1988). Facchinetti et al (1987) suggested that the failure of Tulenheimo et al (1987) to observe significant differences during the late luteal phase may have reflected their use of a nonspecific, cross-reactive antibody, as Facchinetti et al (1987) observed differences in β-EP but not β-lipotropin. Like Facchinetti et al, we employed an extraction procedure enabling us to measure β-EP, but we found no significant differences between patients and controls. Several factors complicate interpretation of our data. First, while our assay was specific, the values measured were near the limit of detection of the assay, thus potentially obscuring the magnitude of differences between high and low values. Further, while the performance characteristics [intraassay coefficients of variation (CVs)] were excellent, the interassay CV was high. The potential impact of this large CV was to some extent mitigated, because each assay contained samples from 1 patient and 1 control, so that the between-assay variability was equally distributed across patients and controls. Third, our patient group was significantly older than our controls, although this is unlikely to have affected our results, as there is evidence that age does not influence basal levels of β-EP, ACTH, or cortisol, particularly in premenopausal women (Akil et al 1993; Parker 1995; Tanaka et al 1993; Gelfin et al 1995). Fourth, our sample sizes are small; however, sizes of the samples required (by power analysis) to demonstrate the group differences observed in this study for ACTH and β-EP as statistically significant are so large as to suggest their lack of clinical relevance. Additionally, our data are in the opposite direction to that reported for ACTH (Redei and Freeman 1993) or for β-EP (Tulenheimo et al 1987; Chuong et al 1985, 1994; Facchinetti et al 1987) in that plasma levels of both are lower (nonsignificantly) in the controls than in patients. Finally, β-EP and ACTH are secreted in an equimolar fashion, so that the absence of diagnostic group-related differences in ACTH lends support to our failure to demonstrate group-related differences in β-EP. Differences across studies in the sampling methods for subject selection may also have contributed greatly to the discrepancies described above.

Studies of plasma T levels across the menstrual cycle

Table 2. Phase Effects across One Cycle in PMS Patients versus Controls [Concentration, Mean (SD)]

Assay	Follicular phase	Ovulation phase	Luteal phase
Free testosterone (pg/mL)[a]			
Patient	1.07 (0.49)	1.05 (0.56)	0.91 (0.36)
Control	1.82 (0.95)	2.22 (1.05)[b]	1.69 (0.77)
Total testosterone (ng/dL)[a]			
Patient	22.75 (7.76)	24.80 (12.84)	22.29 (8.82)
Control	33.36 (13.08)	47.10 (17.65)[c]	34.71 (10.24)
ACTH (pg/mL)			
Patient	18.5 (8.9)	15.5 (6.8)	18.0 (11.5)
Control	18.3 (7.9)	16.7 (9.4)	15.1 (7.3)
Cortisol (μg/dL)			
Patient	12.8 (4.8)	12.56 (6.9)	12.0 (3.9)
Control	11.6 (4.6)	9.26 (3.9)	10.0 (3.7)
β-Endorphin (pmol/L)[d]			
Patient	5.2 (1.5)	4.6 (1.3)	4.5 (1.3)
Control	4.8 (1.5)	4.5 (2.0)	4.0 (0.5)

[a]Post hoc Bonferroni *t* test, patients vs. controls at ovulation, $p < .05$.
[b]Post hoc Bonferroni *t* test comparison with the follicular phase, $t_{18} = 3.3$, $p < .05$; with the luteal phase, $t_{18} = 4.4$, $p < .05$.
[c]Post hoc Bonferroni *t* test comparison with the follicular phase, $t_{18} = 6.1$, $p < .05$; with the luteal phase, $t_{18} = 5.5$, $p < .05$.
[d]Post hoc Bonferroni *t* test, patients and controls in follicular phase, comparison with the luteal phase, $t = 3.4$, $p < .01$; with the ovulatory phase, $t = 2.2$, $p < .05$.

have failed to find significant differences between women with PMS and controls (Eriksson et al 1992; Backstrom and Aakvaag 1981; Watts et al 1985; Rubinow et al 1988). Eriksson et al, however, reported higher free T in women with PMS, despite the absence of differences in total T (Eriksson et al 1992). We were unable to confirm this finding and, in fact, observed significantly lower T and free T levels in women with PMS compared with controls. Decreases in T (Zumoff et al 1995) and free T (Mushayandebru et al 1996) have been observed with aging in older premenopausal women, particularly during the periovulatory phase. The significantly older age of our patients and the conspicuous absence of a periovulatory peak in this group suggest that the differences we observed may simply be epiphenomenal to age. Because a linear increasing function of age in the full sample was lacking, covariance for age could not be performed. The lack of correlation that we observed between T levels and age in both subject groups and the trend for lower free T levels in the smaller age-matched patient group could argue for an independent diagnostic effect. Nonetheless, we are confident only in reporting our inability to confirm the observation by Eriksson et al of increased free T levels in PMS, an observation that is perplexing given the absence of diagnostic differences they report in total T and sex hormone-binding globulin levels, the main determinants of free T.

A significant phase effect was found for T, consistent with reports of a periovulatory peak reported in normally cycling women (Judd and Yen 1973). This peak is blunted in the women suffering from PMS, which accounts for the group-by-phase effect observed in the present study. As noted above, this blunting may be an epiphenomenon of the older age of our patients (Mushayandebru et al 1996).

A significant phase effect for β-EP and a trend toward a phase effect for ACTH were found, reflecting higher levels of these hormones during the follicular phase compared with the luteal phase. These data contrast with previous reports in normally cycling women showing either the absence of menstrual cycle effects (Facchinetti et al 1987; Chuong et al 1989) or a periovulatory peak and a postovulatory trough of plasma β-EP levels (Vrbicky et al 1982). These discrepancies again may reflect methodological differences (e.g., specificity of the antibody or assay variability). Additionally, our data contrast with a small study reporting a midcycle peak of plasma ACTH (Genazzani et al 1975), but are consistent with a more recent and larger study by Mauri et al (1990) showing slightly higher ACTH plasma levels in the follicular phase of the menstrual cycle that do not reach statistical significance. Our cortisol data are consistent with a number of reports that found no group differences or phase effects in women with PMS and controls (Rubinow et al 1988; Facchinetti et al 1987; Rubinow and Schmidt 1995).

In conclusion, our data do not confirm previous reports of abnormalities in plasma levels of either ACTH or β-EP in women with PMS, nor do they support the observation of increased free T in women with PMS. Our data are consistent with the hypothesis that PMS reflects an abnormal response to normal hormone levels rather than a manifestation of endocrine dysfunction.

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