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A Psychoendocrine Study of Premenstrual Tension Syndrome

A Model for Endogenous Depression?

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Summary

We studied 42 women with severe Premenstrual Tension Syndrome (PMTS) and compared their clinical features and adrenocortical function with those seen in major depressive disorders. Self-report scales demonstrated that PMTS was very distressing, but the disturbance did not meet the RDC for Major Depressive Disorder — endogenous subtype. Twenty-four hour urinary free cortisol estimation did not indicate cortisol hypersecretion and abnormal Dexamethasone Suppression Test results occurred much less frequently than is usual in endogenous depression. Adrenocortical function did not differ significantly between follicular and premenstrual phases. PMTS does not appear to be a psychoendocrine model for endogenous depression.

Key words: *Dexamethasone Suppression Test – Endogenous depression – Premenstrual Tension Syndrome – Psychoendocrine study*

Introduction

Women suffering from severe Premenstrual Tension Syndrome (PMTS) experience a number of distressing emotional and behavioral changes during the premenstruum. This disturbance, by definition, shows a temporal relationship to the

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cyclic fluctuations by the pituitary-gonadal system and it was anticipated that endocrine studies might increase our understanding of PMTS. Unfortunately, the measurement of various hormone plasma levels associated with this syndrome has not yielded particularly reliable or informative results (see Abplanalp et al. 1980 for review). An alternative strategy would be a search for those endocrine abnormalities that have been noted to be associated with specific forms of psychopathology. The presence of such phenomena might suggest some similarity between the pathophysiology of PMTS and other psychiatric disorders.

The hypothalamic-pituitary-adrenocortical (HPA) axis is the most intensively studied endocrine system in situations of altered psychological state and some specific associations have been described. Adrenocortical activity is noted to increase in response to various stressful stimuli and is persistently elevated in many patients during an episode of endogenous depression (ED) (see Carroll 1977 for review). The clinical similarities between PMTS and some depressive disorders would be of greater heuristic significance if these women also demonstrated disinhibition of the HPA axis, similar to that seen in patients with ED. Although estrogen or progesterone treatment, or pregnancy, alter adrenocortical function (Bulbrook et al. 1973; Lindholm and Schultz-Moller 1973; Hellman et al. 1976), evaluation of this system in PMTS is facilitated by the apparent absence of cyclic fluctuations in baseline cortisol secretion in medication-free women with normal menstrual cycles (Aubert et al. 1971; Saxena et al. 1974; Carr et al. 1979).

Urinary measures of cortisol excretion during a 24-h period provide an integrated measure of adrenocortical functioning over time. This is preferred to the measurement of plasma cortisol levels, since the pulsatile release pattern of cortisol limits the amount of information provided by the latter method unless frequent blood samples are obtained. Urinary free cortisol (UFC) is reported to reflect the effective level of free plasma cortisol better than any other urinary parameter (Greaves and West 1960; Rosner et al. 1963, 1964; Burke and Beardwell 1973; Beisel et al. 1964).

This study compared the clinical features of severe PMTS with the syndrome of ED. Indices of adrenocortical function that are abnormal in many patients with ED, such as 24-h UFC (Carroll et al. 1976a) and the 1 mg Dexamethasone Suppression Test (DST) (Carroll et al. 1981), were also assessed in these women. In addition, to evaluate the possible contribution of a non-specific stress response to HPA axis activation, we examined the relationship between cortisol excretion and reported levels of psychological distress.

Material and Method

Forty-two women between the ages of 22 and 42 years were selected from more than 250 volunteers for a study of severe PMTS. Each woman gave informed consent, reported at least moderate or severe emotional and physical symptoms during the premenstrual phase and noted rapid remission of the disturbance soon after the onset of menses. Subjects were free of other significant physical or psychiatric disorders, had regular menstrual cycles for at least the preceding 6

months and were not taking oral contraceptives or other medications known to affect endocrine functioning. The selection process extended over 2–4 cycles and included interviews during both follicular *and* premenstrual phases (Haskett et al. 1980).

Clinical interviews, self-report scales and endocrine measurements were performed for each subject at each of two visits during the menstrual cycle. A follicular phase visit occurred on Day 9, where Day 1 was the first day of menses, and a late-luteal phase visit was on Day 26 which always occurred 3–7 days premenstrually. During each clinical interview, subjects were asked about the presence of the features of PMTS. In addition, information was obtained on the symptoms and signs necessary for psychiatric syndromal categorization according to the Research Diagnostic Criteria (RDC) (Spitzer et al. 1977).

Before each interview, subjects were instructed to record their current state on the following self-report scales: Visual Analogue Scale (VAS) (Aitken 1969; Maxwell 1978), Menstrual Distress Questionnaire-Today form (MDQ-T) (Moos 1968), Multiple Affect Adjective Checklist (MAACL) (Zuckerman and Lubin 1965), and the State form of the State/Trait Anxiety Inventory (STAI-STATE) (Spielberger et al. 1970). The Visual Analogue Scale is a 100 mm line labelled 'no symptoms' at one end and 'worst ever' at the other. The subject marked this line at an appropriate point to make a subjective estimate of global discomfort. The MDQ-T is a scale on which women can rate their current experience of 47 symptoms at any point in the menstrual cycle. The STAI-STATE and MAACL have been used and validated extensively.

Thirty-eight women completed a 1 mg DST at the time of the follicular and premenstrual phase visits. UFC was measured in urine collected during the 24-h periods immediately before and after the 11:30 p.m. dose of 1.0 mg dexamethasone. Total plasma cortisol was estimated from a blood sample drawn at 4 p.m. on the second day according to the standard DST procedure for outpatients (Carroll et al. 1981). Cortisol was measured in plasma and urine by the competitive-protein-binding methods of Murphy (1967, 1968) with modifications described by Carroll et al. (1976b).

Results

All 42 subjects complained of a prominent dysphoric mood when interviewed during the premenstrual visit. The clinical disturbance reported by each woman at that time, only met the RDC for Major Depressive Disorder (MDD) if the duration of symptoms criterion in this diagnostic category was reduced from 2 weeks to 2 days. None, however, met criteria for the endogenous subtype. At the follicular visit, psychopathology was either absent or minimal and no subject met RDC for any category of psychiatric illness.

The self-report scales completed by this group of women demonstrated that PMTS was associated with a marked increase in symptoms (Tables 1 and 2). During the *follicular* phase, the mean score on the STAI-STATE was comparable to the

TABLE 1

MEAN TOTAL SCORES ON SELF-REPORT SCALES AT FOLLICULAR AND PREMENSTRUAL VISITS

	Follicular phase (day 9)	Premenstrual phase (day 26)
MDQ-T	74	135
STAI-STATE	34	55
VAS	7.7	61.4
MAACL-D	11	22
MAACL-A	5	12
MAACL-H	6	14

MDQ-T: Menstrual Distress Questionnaire — Today form
STAI-STATE: State/Trait Anxiety Inventory — State form
VAS: Visual Analogue Scale
MAACL-D: Multiple Affect Adjective Checklist — Depression Scale
MAACL-A: Multiple Affect Adjective Checklist — Anxiety Scale
MAACL-H: Multiple Affect Adjective Checklist — Hostility Scale

scores obtained from an asymptomatic group of female volunteers on Day 14 of their menstrual cycle (Golub 1976). By comparison, the *premenstrual* phase score from the women in this study was much higher than that reported in the group studied by Golub (1976). The severity of the disturbance experienced by these women is evident from a comparison of the mean premenstrual STAI-STATE score in this study (55) with the scores obtained from psychiatric patients with an anxiety reaction (49) or depressive reaction (54) (Spielberger et al. 1970).

Twenty-four-hour UFC values obtained during the DST are summarized in Table 3. Mean values for the group showed no evidence of cortisol hypersecretion before dexamethasone (< 100 μg/24 h) and indicated normal suppression of cortisol secretion after dexamethasone (< 25 μg/24 h). The mean baseline UFC excretion values of 46.7 and 47.9 μg/24 h were no different than those found by Murphy

TABLE 2

COMPARISON OF SCORES ON STAI-STATE WITH NORMATIVE DATA

		Mean score
PMTS subjects (this study)	Follicular phase (Day 9)	34
	Premenstrual phase (Day 26)	55
Asymptomatic female volunteers (Golub 1976)	Intermenstrual phase (Day 14)	34
	Premenstrual phase	38
Male psychiatric patients (Spielberger et al. 1970)	Anxiety reaction	49
	Depressive reaction	54

(1968) in normal subjects (48 μg/24 h). Despite the definitive premenstrual increase in symptoms, UFC values obtained in the premenstrual and follicular phases were not significantly different.

Predexamethasone 24-h UFC values were compared with total scores on the VAS, MDQ-T, STAI-STATE, and each of three subsets of items on the MAACL representing the dimensions of depression (MAACL-D), anxiety (MAACL-A) and hostility (MAACL-H). Results from the follicular and premenstrual phase visits were

TABLE 3

URINARY FREE CORTISOL EXCRETION (μg/24 h)

Results are means with S.D. range in parentheses.

	Follicular phase	Premenstrual phase	*P*
Predexamethasone (Normal < 100)	46.7 (30.9–70.8)	47.9 (29.5–77.6)	NS
Postdexamethasone (Normal < 25)	4.7 (1.9–10.3)	5.8 (2.3–12.6)	NS

TABLE 4

CORRELATIONS BETWEEN PRE-DEXAMETHASONE (BASELINE) 24-H UFC AND TOTAL SCORES ON SELF-REPORT SCALES

	Follicular phase						
	UFC	MDQ-T	STAI-STATE	VAS	MAACL-D	MAACL-A	MAACL-H
UFC		−0.1216	0.0917	−0.1294	−0.0193	0.0791	−0.0157
MDQ-T			0.3505 [b]	0.1897	0.0911	0.1951	0.2185 [a]
STAI-STATE				0.2921 [a]	0.2293 [a]	0.4200 [b]	0.4154 [b]
VAS					0.2748 [a]	0.2681 [a]	0.3177 [a]
MAACL-D						0.6971 [a]	0.6567 [b]
MAACL-A							0.6448 [b]

[a] $P < 0.05$.
[b] $P < 0.005$.

TABLE 5

CORRELATIONS BETWEEN PRE-DEXAMETHASONE (BASELINE) 24-H UFC AND TOTAL SCORES ON SELF-REPORT SCALES

	Premenstrual phase						
	UFC	MDQ-T	STAI-STATE	VAS	MAACL-D	MAACL-A	MAACL-H
UFC		0.000	0.0943	−0.0305	−0.0117	0.0418	−0.0176
MDQ-T			0.3034 [a]	0.3755 [b]	0.2349 [a]	0.2620 [a]	0.1470
STAI-STATE				0.3822 [b]	0.4103 [b]	0.5408 [b]	0.3354 [b]
VAS					0.4716 [b]	0.5040 [b]	0.3993 [b]
MAACL-D						0.4555 [b]	0.3497 [b]
MAACL-A							0.6203 [b]

[a] $P < 0.05$.
[b] $P < 0.005$.

considered separately. Five subjects were not included in this analysis because of incomplete data. Kendell's tau_b correlation coefficient was used to characterize the relationship between UFC measurements and concurrent ratings of self-reported distress. Significance of tau_b was tested using the normal distribution and z scores. A rank-order correlation coefficient was used because there were large numbers of tied scores on the rating scales during the follicular phase. A summary of the results is presented in Tables 4 and 5. Tau_b calculated for the relationship between UFC and the total scores on each of the self-report scales did not reach significance during either phase of the menstrual cycle. Significant associations were found between the scores obtained on many of the rating scales during the same cycle phase.

Four women showed an abnormal DST result in the follicular phase and three women in the premenstrual phase. An abnormal result is indicated by a 4 p.m. postdexamethasone plasma cortisol value greater than 5 μg/dl. No woman had an abnormal result on both occasions.

Discussion

Our subjects were women with unusually severe emotional and behavioral disturbance during the premenstruum. This was demonstrated by the marked phase-related change in the mean total score on each of the self-report scales (Table 1). Details of these findings have been reported separately (Haskett et al. 1980). The presence of definite score changes on all scales reflects the broad range of symptoms that may be seen in PMTS. Despite the severity of symptoms, the endocrine results were remarkably normal.

The frequent presence of depressed mood in PMTS has raised questions about the relationship between this disturbance and the depressive disorders. Demonstration of such a link would be of therapeutic and heuristic importance. In this study we used a criterion-based diagnosis (RDC) and a neuroendocrine marker (DST) to compare PMTS with ED. The study subjects met the criteria for the relatively heterogeneous category of MDD during the premenstruum but only after the arbitrary abbreviation of the duration criterion. Their clinical features did not, however, resemble the typical syndrome of ED.

In addition, the typical HPA axis dysfunction reported in many patients with ED was only occasionally seen in these subjects. There was no association between the premenstrual disorder and hypercortisolemia or resistance of cortisol secretion to suppression by dexamethasone. The rate of abnormal DST result was much lower than that reported in patients with ED and did not significantly change between follicular and premenstrual phases of the menstrual cycle (Fig. 2). Thus, in these women with no other psychiatric disorder, PMTS did not appear to be a model for ED.

The HPA axis is also a sensitive marker of physiological responsivity to a variety of noxious events (see Mason 1968 for review). Some reports have suggested that the symptoms of PMTS occur in response to psychological stressors and many different intrapsychic and environmental stimuli have been proposed (Benedek 1952; Fortin

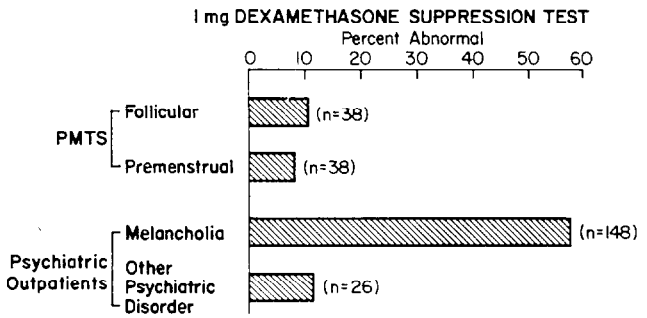

Fig. 1. Frequency of abnormal result for Dexamethasone Suppression Test administered to 38 women with PMTS during the follicular and premenstrual phases of their cycles. This is compared with results obtained from two groups of psychiatric outpatients.

et al. 1958; Paulson 1961; Paige 1971; Rees 1976; Taylor 1979). We were unable to show a significant relationship between 24-h baseline UFC excretion and the severity of symptoms, as measured by total scores on any of the self-report scales. This was noted during the follicular phase, when subjects were relatively asymptomatic, as well as during the premenstrual phase when all subjects were severely affected by PMTS. This is particularly intriguing, since Marinari et al. (1976) reported that asymptomatic women had a greater response of plasma cortisol to a stressful stimulus given during the premenstrual phase compared with 'mid-cycle'. Even a study which could not show a difference in cortisol responsivity between midcycle and menstrual phases, did note that the adrenocortical response was closely related to the anxiety level experienced after the stressful stimulus (Abplanalp et al., 1977). In our subjects, neither the currently unidentified cause of PMTS, nor the experience of the disturbance resulted in a significant mean difference in cortisol excretion between follicular and premenstrual phases of the cycle. HPA axis functioning does not appear to be a useful neuroendocrine marker of the distress that is reported by women suffering from severe PMTS.

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