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Circadian hormone secretory profiles in women with severe premenstrual tension syndrome.

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Summary. The circadian secretory profiles of serum prolactin, growth hormone and cortisol were measured in two women suffering from severe premenstrual tension syndrome and in two asymptomatic control subjects. Subjects and controls were screened and included after a rigorous selection process. Blood samples were obtained every 30 min over a period of 24 h in each woman both on day 9 (follicular phase) and day 26 (luteal phase) of the menstrual cycle. There was no relationship between the hormonal secretory profiles and the premenstrual tension syndrome.

Many biological theories have been suggested to explain the premenstrual tension syndrome (PMTS) (Steiner & Carroll 1977). We have recently described the psychological changes that occur with severe PMTS (Haskett *et al.* 1980; Steiner *et al.* 1980), but the aetiological significance of the hormonal changes during the menstrual cycle is as yet unclear. The pattern of circulating sex steroid hormones and gonadotrophins in the course of the normal menstrual cycle have been well described in recent years (Punnonen *et al.* 1976; Kaulhausen *et al.* 1978). Studies which have attempted to demonstrate a link between PMTS and a relative imbalance of hormones, including not only oestrogens and progesterone but also aldosterone, have produced conflicting results (Smith 1975; Backstrom & Mattsson 1975; Janowsky *et al.* 1973).

Earlier reports of elevated prolactin (PRL) levels during the late luteal phase in women with PMTS (Halbreich *et al.* 1976; Horrobin *et al.* 1976) have not been confirmed by other investigators (Backstrom & Aakvaag 1981; Steiner *et al.* 1983*a*, *b*).

In the present study we measured the circadian secretory profile of PRL at two points in the menstrual cycle in two women with severe PMTS, and compared them with two asymptomatic control subjects. In addition, we examined the secretory profiles of growth hormone (GH) and cortisol to assess their relation to the severity of psychological distress and the possible contribution of a non-specific stress effect on these hormonal systems.

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Subjects and methods

The project was approved by the Human Subject Review Committee of the University of Michigan and only subjects willing and able to give informed consent were included in the study.

Two women with extremely severe PMTS were carefully selected from a large group of volunteers. They were 28 and 30 years of age, with no recent change in gynaecological function and no significant physical or psychiatric disorder. They had taken no drugs for 1 month before the study and took none during the study. They had premenstrual dysphoric symptoms for at least six consecutive menstrual cycles. The 'Menstrual Distress Questionnaire—Today Form' (MDQ-T) (Moos 1969) was used to demonstrate severity of symptoms and the on/off nature of the disturbance. Two women, matched for age, who were completely asymptomatic volunteered to be studied as controls. Ovulation was investigated in all four subjects using basal body temperature charts for 1 month before, and throughout, the month of the study.

The two subjects with PMTS and the two asymptomatic healthy controls were admitted to the clinical research centre for 24 h on days 9 and 26 of their menstrual cycle (where day 1 was the onset of menses). The studies on day 9 (follicular phase) preceded those on day 26 (late luteal phase) in all subjects. Blood samples for PRL, GH and cortisol were collected every 30 min for 24 h from an indwelling catheter in the antecubital vein. The severity or the absence of symptoms in each subject was established by completing the MDQ-T form on the morning of each study day. The MDQ lists 47 symptoms each scored on a scale from 1 to 6 (minimum total score of 47 to a maximum total score of 282) and the 'Today Form' (MDQ-T) is rated according to the symptoms present on the day of completing the scale.

Serum PRL was measured by an established double antibody radio-immunoassay technique (Sinha *et al.* 1973) with intra-assay variability of 8·9%, inter-assay variability of 13·8% and sensitivity of 0·1 ng/tube. Human PRL (hPRL, AFP 1562-C) for iodination and standard was kindly provided by Dr Albert F. Parlow. The glucose oxidase–lactoperoxidase method described by Tower *et al.* (1977) was used for iodination and the suitability of the ^{125}I-PRL was verified by the talc–resin–TCA technique (Tower *et al.* 1978). Anti-hPRL (AFP-1) was supplied by the National Pituitary Agency. Values are reported as ng/ml of hPRL AFP 1562-C (see also Hays & Rubin 1979).

GH was measured by a modified radio-immunoassay technique (Odell *et al.* 1967). Human GH standard preparation was HS-840; the iodination preparation was HS-1147-BC; and the GH antibody had no number designation. These materials were received from the National Pituitary Agency through the courtesy of Dr Albert F. Parlow. All samples were tested in duplicate, and samples from each subject were tested in the same assay. Mean intra-assay variability was 5% and mean inter-assay variability was 20%. The 50% intercept and $(B/T)_0$ (percentage bound in the absence of unlabelled hormone) values were well within the tolerance ranges for our laboratory.

Plasma cortisol was measured by the competitive protein-binding method of Murphy (1967) modified as described by Carroll *et al.* (1976).

The data were analysed statistically using an analysis of variance with repeated measures.

Results

The cortisol, GH and PRL circadian secretory profiles are presented in Figs 1–3. The mean daily serum levels for these three hormones and the corresponding MDQ-T scores are shown in Table 1.

The plasma cortisol levels showed a typical circadian secretory profile in the two subjects with PMTS and in the two controls on both occasions of sampling (Fig. 1). All eight cortisol profiles were well within normal limits as described by Krieger *et al.* (1971). The timing of the major circadian rise in cortisol secretion and the extent of spontaneous nocturnal inhibition of cortisol levels were similar in the follicular and late luteal phases. The one exception was the unexplained lack of nocturnal inhibition during the follicular phase in one of the controls (no. 3, D.F.D.). The mean daily plasma cortisol levels (Table 1) showed statistically significant differences between days 9 and 26 but the direction of change was not consistent in either the PMTS subjects or the controls and these differences probably have no physiological significance.

The growth hormone secretory profiles were not remarkably different between days 9 and 26 (Fig. 2). Nocturnal GH elevations were seen in each woman, as were some spontaneous diurnal peaks. The mean daily plasma GH levels are shown in Table 1. The mean differences between days 9 and 26 were weakly significant in one PMTS and in one control subject and although highly significant in the other control subject the change was in the opposite direction.

The prolactin secretory profiles are shown in Fig. 3. A general elevation of PRL values throughout the circadian cycle was found in all the four women in the late luteal (premenstrual) phase. In one woman with PMTS (no. 2, A.B.L., Fig. 3*b*) this increase was substantial and was recorded at a time when she had severe symptoms, with an extremely high MDQ-T total score of 194 (for comparative data see Moos 1968; Gruba & Rohrbaugh 1975; Rouse 1978). A much smaller change was seen in the other woman with PMTS (no. 1, R.P.R., Fig. 3*a*) who was almost as symptomatic with a very high MDQ-T score of 171.

It is notable that although both the asymptomatic control subjects denied any features of PMTS, confirmed by their low MDQ-T score control subject no. 4 (S.E.S., Fig. 3*d*) had

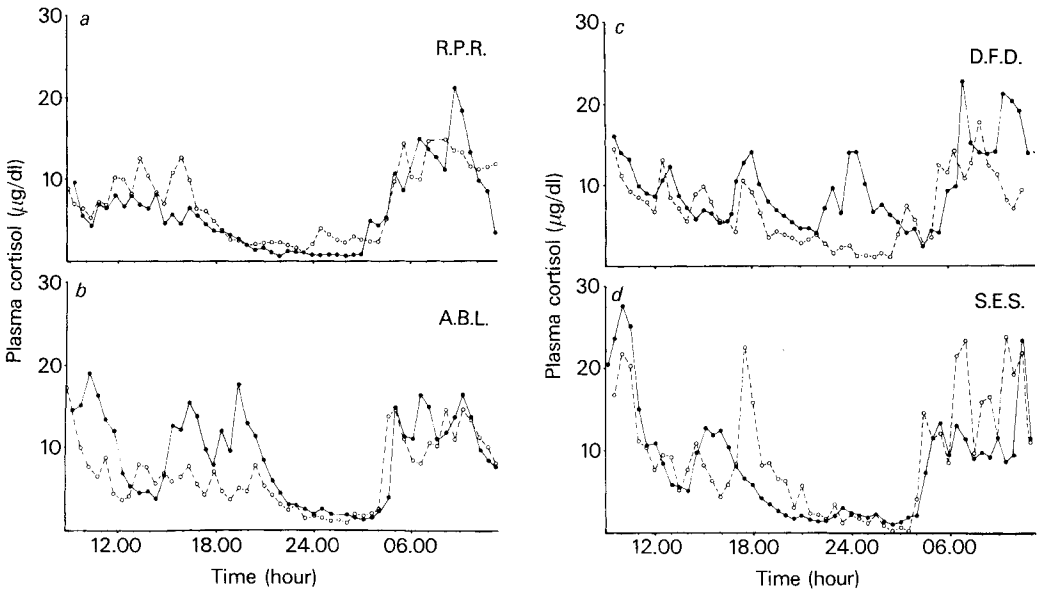

Fig. 1. Circadian cortisol profiles in two women with severe premenstrual tension syndrome (*a* & *b*) and two asymptomatic control subjects (*c* & *d*) during the follicular (●——●) and luteal (○- - - - -○) phases of the menstrual cycle.

marked elevation of PRL during the late luteal (premenstrual) phase.

Well-defined early morning maxima of PRL levels were present in only some women and were inconsistent between phases.

The mean daily PRL levels (Table 1) were significantly higher in the two women with PMTS during the late luteal phase but the most significant difference in the same direction was seen in one of the asymptomatic control subjects.

Discussion

The cortisol and GH results in our study do not indicate a major neuro-endocrine stress or arousal response associated with PMTS. The elevated

Table 1. Mean 24-h plasma levels of prolactin (PRL), growth hormone (GH) and cortisol in two women with severe premenstrual tension syndrome (PMTS) and two asymptomatic control subjects

Subject	Day of cycle	24-h plasma levels			MDQ-T score
		PRL (ng/ml)	GH (ng/ml)	Cortisol (μg/dl)	
PMTS					
no. 1 (R.P.R.)	9	8·0±0·4	1·92±0·95	5·97±0·67	63
	26	11·0±0·7***	3·27±0·85*	7·06±0·58***	171
no. 2 (A.B.L.)	9	10·5±0·6	1·14±0·26	9·14±0·71	76
	26	25·3±1·1***	1·69±0·29NS	6·89±0·59***	194
Control					
no. 3 (D.F.D.)	9	19·1±0·7	2·46±0·59	9·78±0·66	48
	26	20·4±0·6NS	3·90±1·19*	7·00±0·57***	55
no. 4 (S.E.S.)	9	29·8±0·8	4·43±1·31	8·39±0·99	74
	26	49·5±1·0***	1·92±0·6***	9·40±0·97**	59

Results are mean ±SEM.
Significance of differences: *$P<0·05$; **$P<0·01$; ***$P<0·001$; NS, not significant.
MDQ-T, 'Menstrual Distress Questionnaire—Today'.

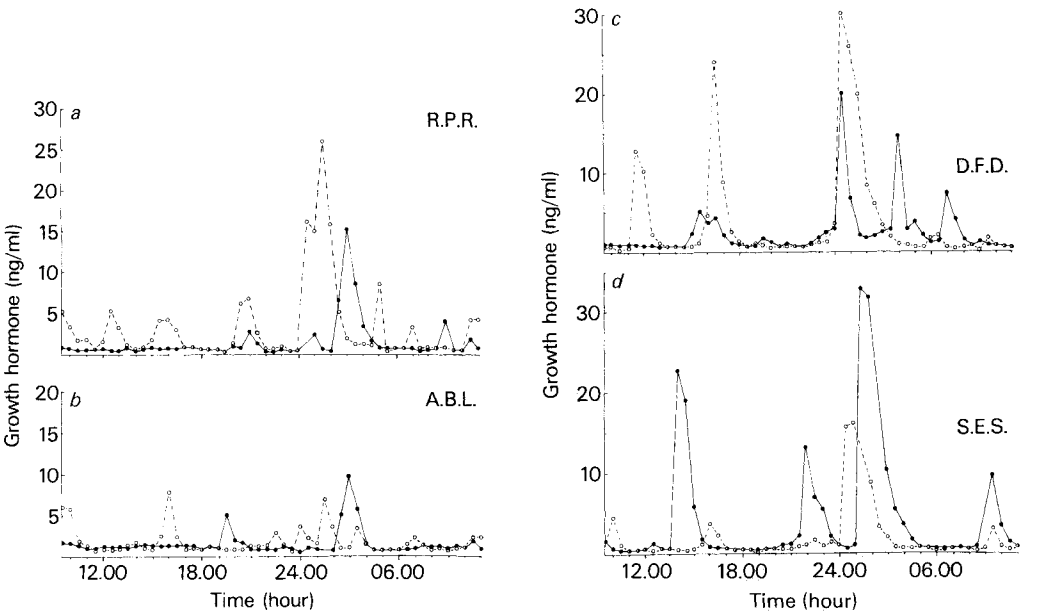

Fig. 2. Circadian growth hormone profiles in two women with severe premenstrual tension syndrome (*a* & *b*) and two asymptomatic control subjects (*c* & *d*) during the follicular (●——●) and luteal (○- - - - -○) phases of the menstrual cycle.

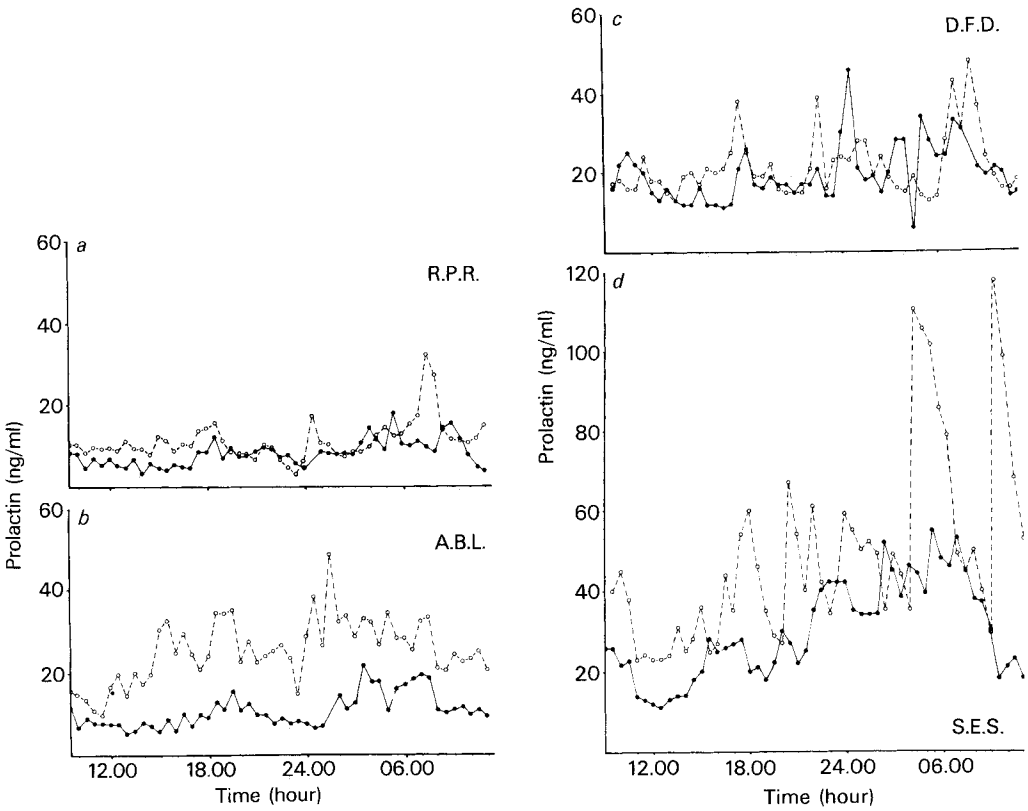

Fig. 3. Circadian prolactin profiles in two women with severe premenstrual syndrome (*a* & *b*) and two asymptomatic control subjects (*c* & *d*) during the follicular (●——●) and luteal (○- - - - -○) phases of the menstrual cycle.

PRL levels are also unlikely to be the result of nonspecific stress of PMTS. We found no support for the hypothesis that PMTS is associated with hyperprolactinaemia (see also O'Brien & Symonds 1982). Markedly elevated PRL levels were seen in the absence of PMTS.

It is clear from our data that measurement of circadian profiles is superior to plasma level estimation in single samples. The pulsatile secretion pattern of these hormones clearly demonstrates the difficulties of interpreting values obtained from single samples. We have also demonstrated that the comparison of mean daily hormone levels with behavioural observations that are scored once a day does not appear to be meaningful. The relation between changes in hormonal secretion and PMTS remains unclear.

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