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ESTROGEN AND PROGESTERONE IN PLASMA IN RELATION TO PREMENSTRUAL TENSION*

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SUMMARY

Plasma concentration of estrogen and progesterone were measured during the last 6 days of the menstrual cycle in women with premenstrual tension, and compared with a group of healthy women. Those women with anxiety as the main symptom (PMT-a) had significantly higher estrogen levels on days 5–2 before the onset of menstruation. On days 6–4 they had lower levels of progesterone. Estrogen–progesterone ratios were significantly higher on days 6–3 before menstruation. The PMT-a group also showed increases in body wt. during the last days of the menstrual cycle.

INTRODUCTION

It is clinically known that fluctuations in mental state can be correlated to the menstrual cycle. In a survey conducted by Dalton [1] on 276 female psychiatric patients, it was shown that over half (53%) of all suicide attempts occurred premenstrually or during menstruation. Likewise, the admission of patients to the psychiatric clinic was twice as great premenstrually and during menstruation than at other times in the menstrual cycle. Cooke [2] reported that 84% of all violent crimes committed by women occurred shortly before or during the early menstrual phase. Coppen and Kessel [3] observed that about 25% of all women suffered, more or less, from the premenstrual tension syndrome, that is to say, much more frequently than previously believed.

Clinical studies carried out by, among others, Logothetis *et al.* [4] on epileptic women have shown that it is possible to correlate both the frequency and duration of the seizures with phases in ovarian activity.

What then are the most important symptoms of premenstrual tension? Stieglitz and Kimbel [5] showed that in the case of 67 patients 68% suffered from emotional instability and 50% from headaches. Rees [6], in a study of 30 patients, found that 100% suffered from irritability, 80% from emotional instability, 73% from anxiety and 63% from headaches.

The etiology of the premenstrual tension syndrome has been the subject of much debate. As early as 1931 Frank [7] suggested that it could be due to a rise in "female sex hormone" (estrogen) levels. Gillman [8], on the other hand, was of the opinion that progesterone was the causative factor. An abnormal estrogen–progesterone ratio has also been suggested by Israel [9], Morton [10] and others. It is of interest, in this light, that Morton [10] was able to induce similar symptoms by the administration of large doses of estrogen. Water and sodium retention has also been implicated as the actual cause of the syndrome by, among others, Greenhill and Freed [11]. Russel [12] has, however, shown that there is no correlation between water and sodium retention and the presence and seriousness of the premenstrual tension syndrome.

EXPERIMENTAL

Daily measurements of estrogen and progesterone levels, in duplicate plasma samples during the last 6 days before the onset of the menstruation, were made using a radioimmunoassay technique.

Twelve women suffering from premenstrual tension were compared with a group of eight healthy women from whom the syndrome was known to be absent. Ten of the premenstrual tension group had suffered mainly from anxiety and irritability (PMT-a) and two had merely suffered from headaches (PMT-h). The diagnosis was established by a senior psychiatrist and a gynecologist. The age range was 25–43 yr for the control group and 31–47 yr for the experimental group. The difference between the groups was evaluated using Student's *t*-test.

Radioimmunoactive estrogen, mainly estradiol-17β, was determined using an antibody prepared by Caldwell [13]. The antibody used for the assay of progesterone was prepared against the 11-oxime derivative and

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Table 1. Precision of the determinations for duplicate plasma samples

Estrogen (pg/ml)	Mean difference (concn ± S.E.)	No. of pairs	Coefficient of variation (%)
60	11·0 ± 2·9	18	23·8
60	18·8 ± 2·5	39	11·0
Progesterone (ng/ml)			
5	1·34 ± 0·20	28	25·5
5–10	2·31 ± 0·32	25	17·1
10	3·40 ± 0·54	20	11·5

was obtained commercially (Endocrine Science, Tarzana, Cal.). The progesterone assay was carried out according to the procedure of Furuyama and Nugent [14]. Estrogen and progesterone were both assayed directly, omitting the column chromatography step [15, 16]. Separation of bound and unbound steroid was achieved by using dextran-coated charcoal.

The standard curve has been fitted to an equation worked out by Leclercq, Täljedal and Wold [17]. The results were calculated using a Hewlett–Packard Model 9810-A calculator.

The variation between duplicate samples is shown in Table 1. The recovery for the extraction of estrogen was 75·6 ± 0·58% (n = 91) and for progesterone 76·8 ± 1·20% (n = 99). The mean blank for estrogen was 7·6 ± 1·0 (S.E.) pg/ml (n = 23) and for progesterone 4·0 ± 1·0 (S.E.) pg/ml (n = 20). In both cases the values obtained for healthy females agreed with results in the literature [14, 18–21].

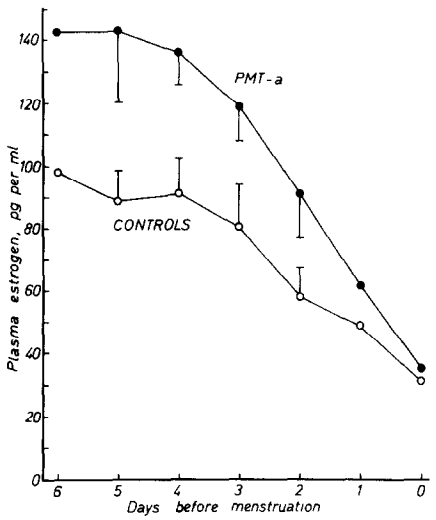

Fig. 1. Mean ± S.E. plasma estrogen levels prior to menstruation. Patients with anxiety as main symptom; PMT-a. S.E. plotted as vertical bars to indicate significance.

RESULTS

Estrogen levels in the PMT-a group were higher than those of the controls on days 2–5 before the onset of menstruation (p = 0·05, 0·025, 0·01, 0·05 on the respective days). The increase observed on day 6 was not significant. The mean concn on day 4 was 136·4 ± 10·4 pg/ml compared with 91·7 ± 12·4 pg/ml in the controls (Fig. 1). The progesterone concentration on days 1–3 were not significantly different from those of the controls. On days 4–6 a significant decrease (p = 0·05, 0·01, 0·05) occurred in the PMT-a group (Fig. 2). It is noteworthy that the estrogen–progesterone ratio was higher in the PMT-a group on days 3, 4, 5 and 6 (p = 0·05, 0·05, 0·05, 0·025) (Table 2). On days 4, 5 and 6 none of the patients' ratios was less than the mean of the controls. On day 3 only two values were less than the mean of the controls. One of the two values on day 3 was noted in subject 5 and she had low ratios as a whole. Subjects S5 and S11 (Table 2) were noted to have less disturbances than usual.

The women were weighed daily during the investigation and it was seen that the PMT-a group increased in wt. during the 3 last days of the menstrual cycle, that is to say, under those days when both estrogen and progesterone showed their greatest decrease in plasma concn. The change in wt. on days 6, 5, 4, 3 and 2, compared with day 1 before menstruation, was clearly significant (p = 0·005, 0·025, 0·005, 0·01, 0·01). The control group showed no significant wt. changes (Fig. 3).

DISCUSSION

Our results show that those women who exhibit anxiety as the chief symptom of premenstrual tension have higher levels of estrogen and, on certain days, lower levels of progesterone in plasma. It is also known from the work of Woolley and Timiras [22], on rats, that estradiol decreases the electroshock seizure threshold and that progesterone counteracts this decrease.

Table 2. Estrogen progesterone ratios × 10^4

Patient	Days before menstruation 1	2	3	4	5	6
S2	268	59	259	214	176	286
S3	946	709	194	161	220	
S4	190	121	135	85	126	174
S5	372	303	92	91	133	97
S6		149	146	145	99	145
S8	136	135	81	140	132	176
S9	6200	824	577	402	732	219
S11	1195	338	168	133	71	105
S12	338	223	271	690		
S13	399	202	243	177	185	216
Mean ± S.E. patients	1116 ± 646	306 ± 82	217 ± 45	224 ± 59	208 ± 67	177 ± 22
Mean ± S.E. controls	220 ± 51	161 ± 33	114 ± 13	84 ± 13	58 ± 5	89 ± 24
Significance	NS	NS	$P = 0.05$	$P = 0.05$	$P = 0.05$	$P = 0.025$

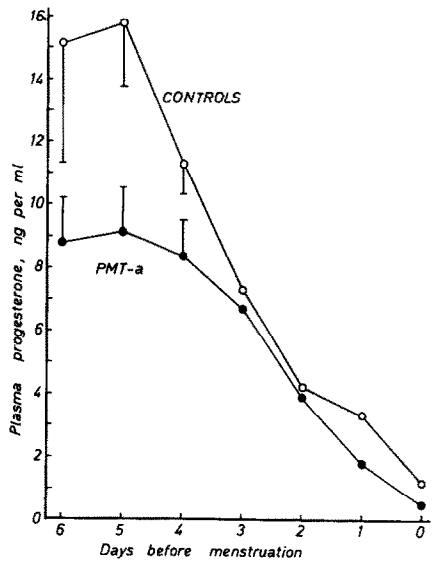

Fig. 2. Mean ± S.E. plasma progesterone levels prior to menstruation. Patients with anxiety as main symptom; PMT-a. S.E. plotted as vertical bars to indicate significance.

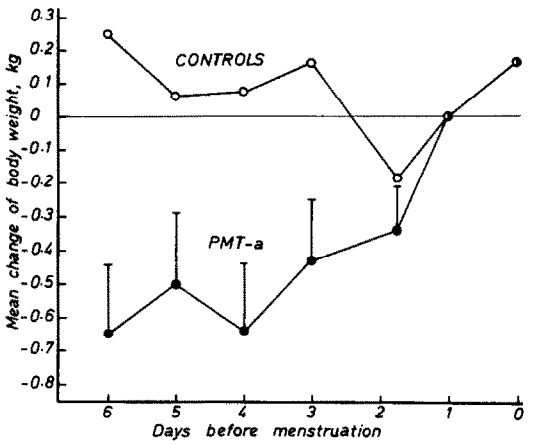

Fig. 3. Mean ± wt. changes compared with the wt. on day 1 before menstruation. S.E. plotted as vertical bars to indicate significance.

Timiras [23] has also shown that the excitability of the dorsal hippocampus is increased by estradiol. This result is of greater interest in the light of the work of Zigmond and McEwen [24], and others, showing that estradiol accumulates in the limbic system, that part of the brain which is considered, to a great extent, to control the emotions. It may be of relevance, in this context, that Kobayashi *et al.* [25] have been able to show that estradiol decreases the activity of MAO and choline acetylase activity in certain parts of hypothalamus. It is, however, not known if this is the case in the whole central nervous system (CNS).

All evidence so far indicates that estradiol has a direct exciting effect on the CNS, and that this effect is counteracted by progesterone. Symptoms such as anxiety and irritability could, to a certain extent, depend upon overexcitability in the limbic system due to a superfluity of estradiol which accumulates there. We have also investigated two women suffering only from headaches. These women had hormone levels within the range of the controls. In a study of Somerville [26] on six women with premenstrual headaches it seemed to be the withdrawal of estrogen which caused the headaches. This indicates that there are differences in the etiology of PMT-headache and PMT-anxiety.

A therapeutic study by Rees [6] showed that diuretic treatment of PMT-patients did not always remove

symptoms such as irritability, anxiety and depression. Progesterone therapy did, however, remove these symptoms. These observations are in accordance with our results, showing that estrogen and progesterone blood levels are indeed changed during PMT.

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