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FSH, LH, TeBG-CAPACITY, ESTROGEN AND PROGESTERONE IN WOMEN WITH PREMENSTRUAL TENSION DURING THE LUTEAL PHASE

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SUMMARY

Plasma immunoreactive estrogen was significantly lower on days 9 and 8 before menstruation in a group of 15 women with premenstrual tension (PMT) syndrome, than in a control group of 17 women. Estrogen thereafter started to increase and was significantly higher in the PMT-group than in the controls on day 5 before menstruation. This increase was significant until day 1 before menstruation. Progesterone levels were constantly lower in the PMT-group than in the controls.

The mean FSH level in plasma in PMT patients was significantly increased above controls on day 9, 8, 7 and 6 before menstruation. No difference between groups was seen in LH levels nor in serum albumin and binding capacity of testosterone-estradiol binding globulin (TeBG), neither could changes in LH, albumin or TeBG capacity explain the increase seen in estrogen concentration. The possible role of FSH in the PMT syndrome is discussed in order to explain the increased estrogen secretion.

INTRODUCTION

In a recent report [1] it was shown that plasma concentrations of radioimmunologically determined estrogen (mainly estradiol-17β) were significantly increased on days 5–2 before the onset of menstruation in women suffering from premenstrual tension (PMT) with anxiety as the main symptom. On days 6–4 there was a significant decrease of plasma concentrations of progesterone in these women. In order to elucidate the origin of these changes in steroid hormone concentrations we decided to determine the concentrations in blood plasma of FSH and LH, the most important stimulators of ovarian steroid secretion. We also wanted to know whether this increase in plasma estrogen concentrations is concomitant with a corresponding increase in plasma binding capacity of estrogen, in order to thus explain the higher estrogen concentrations in women with PMT. This can be done by measuring the testosterone-estradiol binding globulin (TeBG) and albumin concentrations in plasma. It would also be of interest to investigate an extended period of the luteal phase in order to acquire more information of the factors behind the higher concentrations of estrogen and lower concentrations of progesterone.

EXPERIMENTAL

Patients. Blood samples were taken daily from one of the antecubital veins during ten days preceding menstruation in fifteen women aged 23–45 years, diagnosed as suffering from the premenstrual tension syndrome, with anxiety as their main symptom. Diagnoses were made by a psychiatrist and a gynecologist. Criterias for diagnoses and participation in the investigation were: 1. Psychiatric symptoms developing during the week preceding menstruation; 2. Cessation of symptoms at the start of menstruation; 3. No history of psychiatric illness; 4. No hormonal treatment. All patients were suffering from slight to moderate symptoms. In the cycle when the blood samples were taken four patients reported less disturbances than usual. As a control group seventeen women without PMT-symptoms aged 24–45 were serving.

Hormone determinations. Estrogen and progesterone were measured by radioimmunoassay as described earlier [1], except that saturated $(NH_4)_2SO_4$ is used instead of charcoal. FSH and LH were determined by a radioimmunosorbent technique [2]. See this reference for normal range of FSH and LH during the menstrual cycle.

TeBG capacity and albumin concentrations. TeBG capacity was determined with two-phase technique [3] using a simplified method with addition of 4 ng of unlabelled 5α-dihydrotestosterone [4]. Plasma albumin was determined according to Rodkey [5].

Statistical calculations. Comparisons between groups were carried out according to Wilcoxon's rank method and within groups to Wilcoxon's matched pairs signed-ranks test.

RESULTS

During days 9 and 8 before menstruation the PMT group had a significantly lower mean estrogen con-

Table 1. Mean ± S.E. concentrations of estrogen and progesterone in the PMT-group compared to the control group

	Estrogen pg/ml					Progesterone ng/ml				
Day	No	PMT	No	Control	Difference	No	PMT	No	Control	Difference
10	8	114.6 ± 14.2*	10	125.3 ± 10.0	NS	7	6.48 ± 1.6	11	10.95 ± 1.6	0.025
9	10	114.8 ± 13.5*	11	145.9 ± 10.0	$P < 0.05$	10	10.19 ± 1.5	10	13.55 ± 1.2	NS
8	11	118.0 ± 11.8	11	153.4 ± 12.9	$P < 0.05$	11	10.40 ± 1.5	11	15.89 ± 1.8	0.025
7	11	130.7 ± 11.3	12	141.8 ± 11.8	NS	11	10.12 ± 1.1	12	15.36 ± 1.7	0.025
6	12	139.3 ± 13.1	13	135.2 ± 12.0	NS	12	9.04 ± 1.1	13	15.48 ± 2.0	0.005
5	14	156.8 ± 14.0*	17	115.7 ± 9.2	$P < 0.005$	14	9.17 ± 1.3	17	16.69 ± 1.7	0.005
4	15	142.8 ± 9.5	17	108.5 ± 8.6	$P < 0.005$	15	8.91 ± 0.8	17	12.20 ± 0.7	0.005
3	15	132.1 ± 6.9	17	99.2 ± 9.6	$P < 0.005$	15	7.56 ± 0.9	17	9.23 ± 1.3	NS
2	15	103.4 ± 10.9	17	78.0 ± 8.1	$P < 0.05$	15	4.38 ± 0.7	17	5.68 ± 1.3	NS
1	15	91.0 ± 10.3	16	63.2 ± 6.2	$P < 0.025$	14	3.04 ± 0.8	16	3.64 ± 0.7	NS

* Days 10 and 9 to day 5. $P < 0.05$ and 0.02 resp.

centration in plasma than the controls (Table 1 and Fig. 1). The estrogen level started to increase and became significantly increased on day 5 before menstruation (Table 1). From day 5 on the estrogen levels in the PMT-group were also significantly higher than in the controls until day one before menstruation (Table 1, Fig. 1).

The progesterone levels in plasma were significantly lower in the PMT-group than in the control group. The mean level of progesterone was significantly lower from day 10 to day 4 before the onset of menses, except day 9 (Table 1, Fig. 1). The mean levels of progesterone in plasma in the PMT-group never exceeded 10.5 ng/ml (Table 1, Fig. 1) while the control group showed mean values up to 16 ng/ml (Table 1, Fig. 1).

The plasma FSH concentrations in the PMT-group were significantly higher than in the control group on days 9, 8, 7 and 6 (Table 2, Fig. 1). Within the PMT-group the mean plasma FSH concentration decreased significantly from day 9 and 8 to day 7 (Table 2, Fig. 1). Between days 10, 9 and 8 there were no significant differences. The decrease seen between days 9, 8, 7 and day 4 was also significant (Table 2, Fig. 1).

In the control group the difference between days 10 and 9 was not significant. However between day 8 and 7 a significant decrease was noted (Table 2). Also between days 10, 9 and 8 to day 6 there was a significant difference (Table 2). Thus the steepest decrease in FSH concentrations was noted one day earlier in the control group than in the PMT-group (Fig. 1, Table 2). Furthermore concentrations of FSH below 0.60 ng/ml occurred three days earlier in the control group than in the PMT-group (Table 2, Fig. 1). In both groups there was a significant increase from day three to day one (Table 2, Fig. 1) with no difference between groups.

No significant differences occurred in mean plasma LH concentrations between the two groups (Table 2, Fig. 1) in any day measured. The decrease seen from

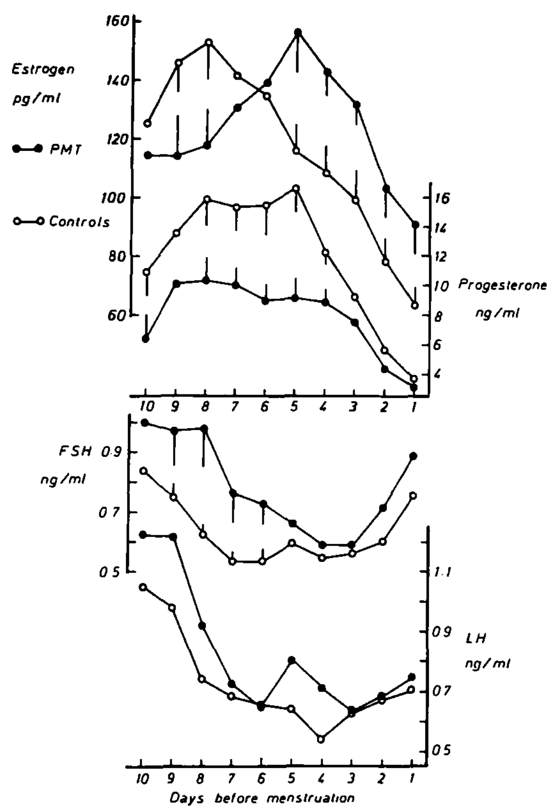

Fig. 1. Estrogen, progesterone, FSH and LH during the luteal phase. S.E. plotted as vertical bars in days showing significant difference between groups. ●——● PMT group. ○——○ control group.

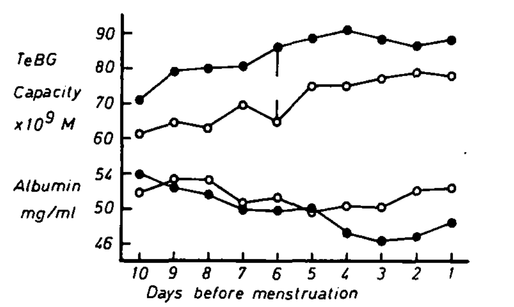

Fig. 2. TeBG binding capacity and albumin concentrations during the luteal phase. S.E. plotted as vertical bars in days showing significant difference between groups. ●——● PMT group. ○——○ control group.

Table 2. Mean ± S.E. concentrations of FSH and LH in the PMT group compared to the control group

		FSH ng/ml					LH ng/ml			
Day	No	PMT	No	Control	Difference	No	PMT	No	Control	Difference
10	7	1.03 ± 0.17	11	$0.84 \pm 0.07^{\gamma}$	NS	8	$1.23 \pm 0.20^{\omega}$	11	$1.05 \pm 0.09^{\psi}$	NS
9	10	$0.97 \pm 0.12^{*\lambda}$	11	$0.75 \pm 0.05^{\alpha\gamma}$	$P < 0.05$	10	$1.22 \pm 0.27^{\omega}$	11	$0.98 \pm 0.12^{\psi}$	NS
8	11	$0.98 \pm 0.13^{*\lambda}$	11	$0.63 \pm 0.03^{\alpha\beta\gamma}$	$P < 0.01$	10	$0.92 \pm 0.17^{\omega}$	11	0.74 ± 0.06	NS
7	11	$0.76 \pm 0.10^{*\lambda}$	12	$0.54 \pm 0.03^{\beta}$	$P < 0.025$	11	$0.73 \pm 0.11^{\omega}$	12	$0.69 \pm 0.08^{\psi}$	NS
6	11	0.73 ± 0.07	12	$0.54 \pm 0.03^{\gamma}$	$P < 0.05$	12	0.65 ± 0.11	13	0.66 ± 0.07	NS
5	13	0.66 ± 0.07	17	0.60 ± 0.06	NS	13	0.81 ± 0.15	17	0.64 ± 0.07	NS
4	15	$0.59 \pm 0.07^{\lambda}$	16	0.55 ± 0.04	NS	15	0.71 ± 0.10	16	0.54 ± 0.08	NS
3	15	$0.59 \pm 0.06^{\xi}$	17	$0.56 \pm 0.04^{\sigma}$	NS	15	0.64 ± 0.08	17	0.63 ± 0.06	NS
2	15	0.72 ± 0.07	17	0.61 ± 0.04	NS	15	0.69 ± 0.07	17	0.67 ± 0.08	NS
1	15	$0.89 \pm 0.09^{\xi}$	16	$0.76 \pm 0.05^{\sigma}$	NS	15	0.75 ± 0.06	16	0.71 ± 0.06	NS

* 9 and 8 to day 7. $P < 0.025$ and 0.005 resp. $^{\lambda}$ days 9, 8 and 7 to day 4. $P < 0.005$, 0.005 and 0.01 resp. $^{\xi}$ day 3 to 1 $P < 0.01$.

$^{\alpha}$ Day 9 to day 8 $P < 0.005$; $^{\beta}$ day 8 to day 7 $P < 0.005$; $^{\gamma}$ days 10, 9 and 8 to day 6 $P < 0.005$, 0.005 and 0.025; $^{\sigma}$ day 3 to day 1 $P < 0.005$; $^{\omega}$ days 10, 9 and 8 to day 7 $P < 0.01$, 0.025 and 0.01 resp.; $^{\psi}$ days 10 and 9 to day 7 $P < 0.005$ and 0.025 resp.

day 10 and 9 to day 7 was significant in both groups (Table 2, Fig. 1). In the PMT-group the decrease from day 8 to day 7 was also significant. After day 7 there was no significant variation within either group.

The mean binding capacity of testosterone-estradiol binding globulin (TeBG) was somewhat higher in the PMT-group, this difference being significant only on day 6 before menstruation (Fig. 2, Table 3). There was a small increase in the mean concentrations from about 80×10^{-9} M on days 9, 8 and 7 to about 90×10^{-9} M on day 4 (Fig. 2, Table 3). This increase was not significant. A similar trend was noted in the control group (Fig. 2, Table 3) showing a small increase from about 65×10^{-9} M on days 9, 8 and 6 to 75–80 $\times 10^{-9}$ M on days 5–1, neither increase being significant.

The albumin concentrations in the PMT-group showed no significant differences from the control group, and no significant deviation within the groups.

DISCUSSION

On days 10, 9 and 8 before menstruation a low production of estrogen and progesterone was noted in the PMT patients compared to the control group. However on day 7 plasma estrogen levels started to rise and showed a maximum on day 5. On this day the mean estrogen level in the PMT group was significantly increased compared to the control group. After this day the estrogen levels of the PMT group continued to be higher than those of the control group. Progesterone levels in the PMT group showed no corresponding increase and were of a low concentration throughout the luteal phase. During the initial luteal phase when both estrogen and progesterone levels were low, an increase in plasma FSH concentration was observed in the PMT patients. The mean FSH level started to decrease on day 7 before menstruation simultaneously with an increase of the estrogen levels. The increase in FSH levels of the PMT group subsided on day 5, the day when the estrogen levels of the PMT group were maximal.

The significant rise in the estrogen levels from days 9 or 8 to day 5 before menstruation suggests an increased activity of secretory cells in the ovary. The increase in estrogen secretion of the PMT-group is preceded by an increase in FSH concentrations about three days earlier. This is similar to the events normally occurring at the beginning of the follicular phase [6–9] where FSH concentrations start to increase about three days before menstruation and rise up to about 1.5 ng/ml [2, 9] during the first or second day of the menstrual cycle. On the fourth to fifth day of the menstrual cycle the estrogen concentrations start to increase [4, 8, 9], *i.e.* four to five days

Table 3. Mean ± S.E. TeBG binding capacity and albumin concentrations in PMT-group compared to the control group

		TeBG capacity 10^9 M					Albumin mg/ml			
Day	No	PMT	No	Control	Difference	No	PMT	No	Control	Difference
10	7	71.4 ± 9.3	11	61.6 ± 8.3	NS	7	54.0 ± 1.5	11	51.8 ± 1.9	NS
9	10	79.4 ± 11.3	9	64.5 ± 6.2	NS	10	52.4 ± 1.5	9	53.3 ± 1.9	NS
8	11	80.0 ± 10.2	9	62.9 ± 6.7	NS	11	51.6 ± 1.6	9	53.2 ± 1.5	NS
7	11	80.9 ± 9.7	11	69.6 ± 7.6	NS	11	49.5 ± 1.8	11	50.7 ± 2.2	NS
6	12	86.0 ± 8.6	13	64.8 ± 5.9	$P < 0.05$	12	49.9 ± 1.5	13	51.2 ± 1.8	NS
5	13	88.6 ± 9.3	17	74.8 ± 7.0	NS	13	49.7 ± 1.3	17	48.7 ± 2.2	NS
4	15	90.9 ± 9.2	17	74.6 ± 6.0	NS	15	47.3 ± 2.6	17	50.3 ± 1.5	NS
3	15	88.2 ± 9.9	17	76.9 ± 6.5	NS	15	46.4 ± 2.6	17	50.2 ± 1.4	NS
2	15	86.2 ± 10.3	17	78.8 ± 5.6	NS	15	46.8 ± 2.6	17	52.1 ± 1.1	NS
1	14	88.1 ± 10.4	15	77.5 ± 6.5	NS	14	48.4 ± 2.0	15	52.4 ± 1.1	NS

after FSH reached beyond 1 ng/ml [9]. The rise of plasma estrogen in the PMT patients was observed one to two days after the plasma FSH was significantly increased compared to controls. Clomiphene is reported to induce an FSH rise within 3–4 days [10, 11] while urinary estradiol-17β and estrone starts to rise on day 4 to 5 after starting clomiphene administration, *i.e.* one to two days after the FSH peak obtained with the same dose of clomiphene [11, 12]. The FSH concentration increased about 150% after clomiphene. In our results mean FSH concentrations were about 165% higher in the PMT-group on days 10, 9 and 8 than the concentration on day 4. Even after injections of HMG there is a delay of two to three days before an increase in estrogen levels is seen [13].

The increase in FSH levels of the PMT group during the luteal phase on days 10, 9 and 8 before menstruation may stimulate proliferation of a second set of follicles which in turn starts to produce estrogen. This estrogen will be added to the estrogen originating in the corpus luteum. No progesterone will however be produced in the follicles. Accordingly a constant low level of progesterone was observed. What then may be the reason for the increased FSH level found in the PMT group? The inhibition of FSH secretion by estrogen is well known [11, 14, 15] but also progesterone seems to have an inhibiting effect [16–18] at least together with estrogen. In the PMT-group there were lower concentrations of both estrogen and progesterone in the beginning of the luteal phase. This may have caused the increased FSH secretion in the PMT group during the luteal phase. At increasing estrogen levels FSH secretion may become inhibited, causing the decrease seen from day 8 to day 4 before menstruation. This may bring the follicular development and estrogen secretion during the luteal phase to a stop simultaneously with normal functional luteolysis with induction of the normal FSH secretion and of menstruation. In this cross-sectional study the variations caused by episodic secretion are minimised and can be disregarded when significant differences are obtained between patient and control groups.

No changes occurred in the levels of LH that could explain the increase of the estrogen levels in the PMT group. The levels were similar between both groups and rather constant during the time of increasing estrogen levels in the PMT group.

The mean binding capacity of TeBG in both groups showed no significant variations during the luteal phase and the differences between the groups were in general insignificant. At the same time the albumin concentrations showed no significant differences either within or between groups. It has also been shown that levels of testosterone are fairly constant during the latter part of the menstrual cycle [19]. This makes it unlikely that the increase in plasma estrogen in the PMT group during the luteal phase was due to elevated binding capacity. The changes seen in the total estrogen concentrations may therefore truly reflect changes in the unbound estrogen, which is assumed to be the biologically most active part. In conclusion, we suggest that in the PMT syndrome an increased secretion of estradiol may originate from newly formed ovarian follicles under the stimulation of pituitary FSH.

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