COMPARISON OF PLASMA AND MYOMETRIAL TISSUE CONCENTRATIONS OF ESTRADIOL-17β AND PROGESTERONE IN NONPREGNANT WOMEN

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ABSTRACT

Plasma and myometrial tissue concentrations of estradiol (E_2) and progesterone (P) were measured by radioimmunoassay techniques in samples obtained from women with regular menstrual cycles and from women in pre- or postmenopausal age. In women with regular cycles, the tissue concentration of E_2 ranged from 0.13 to 1.06 ng/g wet weight, with significantly higher levels around ovulation than in follicular or luteal phases of the cycle. The tissue concentration of P ranged from 2.06 to 14.85 ng/g wet weight with significantly higher level in luteal phase than in follicular phase. The tissue/plasma ratio of E_2 ranged from 1.45 to 20.36 with very high values in early follicular phase and the lowest in mid-luteal phase. The ratio for P ranged from 0.54 to 23.7 and was significantly lower in the luteal phase than in other phases of the cycle. One woman in premenopausal age with an ovarian cyst was the only case with a tissue/plasma ratio of $E_2 < 1$, since her plasma E_2 levels were exceptionally high. In postmenopausal women, the tissue concentration of E_2 was not significantly lower than in menstruating women in follicular phase, and the tissue concentration of P was not significantly lower than in fertile women in any of the phases. Neither in these women nor in menstruating women was there a close correlation between tissue and plasma levels. The present data indicate that the myometrial uptake capacity for ovarian steroids may be saturated, and also that a certain amount of these steroids is bound to tissue even if plasma levels are low.

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INTRODUCTION

Ovarian steroids are known to profoundly influence the function of the myometrium as of other target organs. Although in recent years, considerable data on estradiol (E_2) and progesterone (P) concentrations in the pregnant myometrium have been published, there is relatively little information on the endogenous levels of E_2 and P in the nonpregnant myometrium in the different endocrine states (1-3). The available data on E_2 and P concentrations in various target tissues have on the whole shown that there is a poor correlation between plasma and tissue concentrations of these steroids. In the present study we have measured E_2 and P concentrations in fertile women at different stages of the menstrual cycle, as well as in pre- and postmenopausal women.

MATERIAL AND METHODS

Clinical material. Myometrial tissue pieces were obtained from 43 nonpregnant women, aged 27 to 56 years, who underwent hysterectomy because of myomas, adenomyosis, hypermenorrhea, incontinence, cancerous preinvasion or microinvasion of the cervix, or premalignant changes of the endometrium. Thirty-five of the women had regular spontaneous menstrual cycles with an inverval of 25 to 35 days, three were in premenopausal age and had menstrual irregularities, and five women were two to twelve months postmenopausal. None of the women included in the study was on any hormonal treatment.

Sampling procedures. The women were operated upon under general anesthesia and in all cases a total hysterectomy was performed. Venous blood samples for the determination of plasma concentrations of estradiol-17β (E_2) and progesterone (P) were taken in heparinized tubes immediately before operation. The blood was centrifuged and plasma stored at -20°C until assayed. Directly after removal of the uterus, myometrial tissue pieces, approximately 3 mm wide, 8 mm deep, and 20 mm long, were taken from the ventral side of the uterine body. In no instance were samples taken from, or in the vicinity of, myomas. After removal of the serosa, pieces weighing 200 to 400 mg were obtained, and stored frozen at -20°C until analyzed.

Extraction of steroids and radioimmunoassay. After thawing and digestion with sodium dodecyl sulphate and NaOH (4,5), the digested material was extracted with ethyl acetate and run through Sephadex LH-20 columns to remove the sodium dodecyl sulphate (6). After evaporation the residue was diluted to suitable amount for radioimmunoassay (RIA) of E_2 (7) and P (8). The hormone concentrations in plasma were also determined by these RIAs. Extensive data on reliability of these assay methods have been reported previously (4-6). The intra- and inter-assay coefficients of variation for tissue E_2 were 5 and 10 %, respectively, and the corresponding figures for P 10 and 18 %, respectively. Protein concentration in the digested tissue was determined according to Lowry et al. (9).

Definition of cycle stage. On the basis of plasma steroid levels, material from women with regular menstrual cycles was divided into three groups (6). The follicular phase included women with plasma $P < 2$ ng/ml and $E_2 < 100$ pg/ml; the ovulatory phase, women with the

same plasma levels but E_2 > 100 pg/ml; and the luteal phase, those with P > 2 ng/ml. In all cases this grouping according to plasma hormones concurred well with the cycle data and histopathological examination of the endometrium of the removed uterus.

Statistics. Comparison between groups of data was performed using the Student's t-test.

RESULTS

Women with regular menstrual cycles. Data in Table I show that the protein content does not change in the different phases.

Table I. Protein content per gram of myometrial tissue at different phases of the menstrual cycle

Phase	Protein (mg/g wet weight)
Follicular (14)	138.1 ± 13.6
Ovulatory (6)	135.8 ± 17.5
Luteal (15)	142.0 ± 12.9

Mean values ± SEM; number of determinations in parenthesis

The plasma and tissue concentrations of E_2 and P in the different cycle stages are shown in Figs. 1 and 2. The tissue concentrations in these figures are expressed in amount of hormone per gram wet weight.

The plasma and tissue concentrations of E_2 in ovulatory phase were significantly higher ($p < 0.001$ and $p < 0.05$, respectively) than in follicular phase or luteal phase ($p < 0.05$ and $p < 0.01$, respectively). The plasma levels ranged from 25 to 280 pg/ml and the tissue concentrations from 0.13 to 1.06 ng/g wet weight.

The mean P concentrations in plasma and tissue during luteal phase were significantly higher than those in follicular phase ($p < 0.001$ in both instances) and the plasma concentration also higher than in ovulatory phase ($p < 0.001$). The plasma concentrations ranged from less than 0.1 to 12.02 ng/ml and the tissue concentrations from 2.06 to 14.85 ng/g wet weight.

The ratios between tissue and plasma concentrations of E_2 and of P at the different stages of the menstrual cycle are shown in Table II. The differences in E_2 ratio between the follicular phase and the ovulatory and luteal phases were not statistically significant. The P ratio in luteal phase was significantly lower than in follicular and ovulatory phases ($p < 0.001$ in both instances).

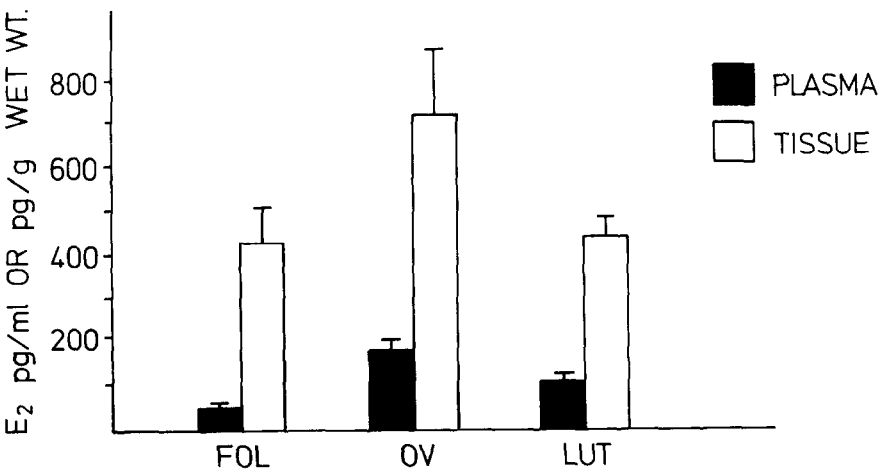

Fig. 1. Plasma and myometrial tissue concentrations of estradiol-17β during the follicular (Fol), ovulatory (Ov), and luteal (Lut) phases. Bar indicates SEM; number of determinations were 14, 6 and 15 in Fol, Ov and Lut phases, respectively.

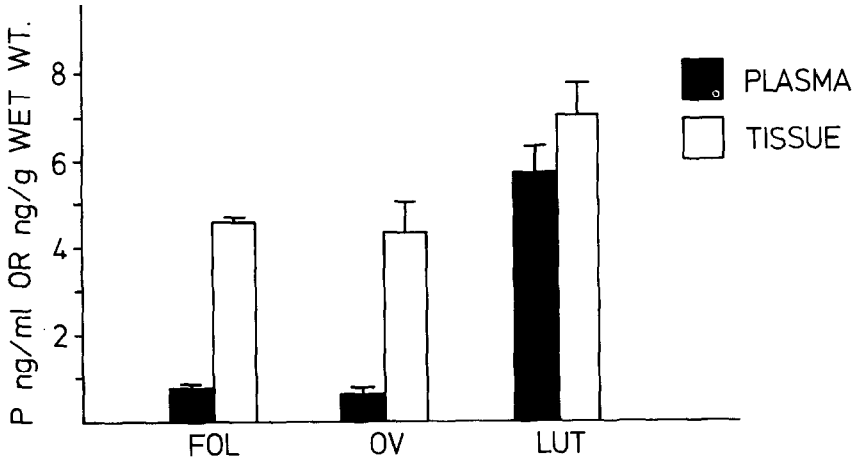

Fig. 2. Plasma and myometrial tissue concentrations of progesterone during the follicular (Fol), ovulatory (Ov), and luteal (Lut) phases. Bar indicates SEM; number of determinations were 14, 6 and 15 in Fol, Ov and Lut phases, respectively.

Table II. Ratios between estradiol (E_2) and progesterone (P) concentrations in tissue (per gram wet weight) and plasma (per ml) at different phases of the menstrual cycle

Phase	E_2 ratio	P ratio
Follicular (14)	9.95 ± 1.96	8.17 ± 0.16
Ovulatory (6)	4.52 ± 0.77	7.99 ± 1.50
Luteal (15)	5.98 ± 1.14	1.44 ± 0.21

Mean values ± SEM; number of determinations in parenthesis

An examination of tissue plasma ratios within the follicular phase showed a clear tendency for a decrease in the E_2 ratio with the advancing phase. The ratio values as high as 20.36 were found in the very early follicular phase. The lowest ratio, however, 1.45 was found in mid-luteal phase. The P concentration in tissue was higher than in plasma in all but four women who were in the early luteal phase at the operation. In these the plasma concentration ranged from 7.40 to 11.6 ng/ml and the tissue concentration from 4.76 to 6.72 ng/g wet weight.

Pre- and postmenopausal women. Plasma and myometrial tissue concentrations of ovarian hormones in three women with menstrual irregularities in premenopausal age are shown in Table III. Of particular interest is the observation of the highest plasma and tissue concentrations of E_2 found in the woman with an ovarian cyst, since this was the only case with a higher E_2 concentration in plasma than in tissue.

Table III. Concentrations of estradiol (E_2) and progesterone (P) in blood plasma and myometrial tissue in three premenopausal women with menstrual irregularities

Pat.	Histopathological diagnosis	E_2		P	
		Plasma pg/ml	Tissue pg/g wet weight	Plasma ng/ml	Tissue ng/g wet weight
1.	Adenomyosis. Endometrial hyperplasia. Follicular cyst in the left ovary	1 118	1 038	< 0.1	5.31
2.	Myoma. Endometrial hyperplasia. Teratoma in the left ovary	108	583	0.72	5.94
3.	Endometrial hyperplasia. Bilateral cystadenofibromas in ovaries	143	532	0.25	3.44

Table IV. Concentrations (mean ± SEM) of estradiol (E_2) and progesterone (P) in blood plasma and myometrial tissue in five postmenopausal women 2 to 12 months after the last menstrual bleeding

	E_2			P			Protein content
	Plasma pg/ml	Tissue pg/g wet weight	Ratio tissue/ plasma	Plasma ng/ml	Tissue ng/g wet weight	Ratio tissue/ plasma	mg/g wet weight
Hormone concentrations	37.2±16.2	232.1±27.4	14.58±6.21	0.23±0.67	4.84±0.44	28.06±8.04	125.06±15.31
Difference from							
follicular phase	*ns*	*ns*	ns	**	ns	***	*ns*
ovulatory phase	***	***	ns	*	ns	*	*ns*
secretory	*	**	*	***	ns	***	ns

* = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$; *ns = no significant difference*

Table IV shows ovarian hormone concentration in five postmenopausal women. Neither the plasma nor the tissue concentrations of E_2 were significantly lower than in follicular phase. Plasma P concentration in these women was significantly lower than in fertile women in any of the phases (Fig. 2). The tissue concentration, however, was not significantly different from any of the phases. Consequently, tissue/plasma ratio was highest in this group and significantly higher than in any of the phases of fertile women. Protein contents in the postmenopausal group did not differ from fertile women.

DISCUSSION

In women with normal menstrual cycles the hormone concentrations differed between different phases, but there was no close correlation between tissue and plasma levels in the same individual. One explanation for a poor correspondence between tissue and plasma hormone levels could be a time lag in the decline of tissue hormonal concentrations when plasma concentrations were declining. The present data indicating high tissue/plasma ratio of E_2 in early follicular phase, which tended to decline later in the phase, supports this view. Furthermore, it is likely that a certain amount of the hormone is so tenaciously bound to the tissue that it would not depart in spite of very low or zero level in the circulation. The fact that the uterine receptors have a very high affinity for the respective hormone (4, 5) is in line with this notion. The present data showing that tissue P in both pre- and postmenopausal women remained comparable to those in the menstruating women (not significantly lower than in luteal phase) in spite of a substantial decline in plasma levels, lend further support to this view.

It is also interesting to note that E_2 concentration in the myometrium of the woman with an ovarian cyst was lower than the concentration in the plasma. This would indicate saturation of the myometrial binding capacity. However, although the plasma P concentration in this case was minimal, the tissue level was relatively high, which could have contributed to the reduction of the E_2 binding in the tissue by lowering E_2 receptor concentration (10). The tissue/plasma ratio of P decreased significantly in the luteal phase (1.44 ± 0.21) and in fact in four cases this ratio was even lower than one. This is compatible with the previous suggestion that following accumulation of P in the tissue, the P receptors are depressed by P itself (11). Studies of myometrial receptor concentration in menstruating women have shown that the highest P receptor content is found at midcycle, which declines rather rapidly thereafter (3). The tissue concentration of P in these studies (3) seemed to follow the receptor pattern, although lagging behind (3-4 days) in tissue.

The data presented in our study may not only be important for elucidating mechanisms that regulate tissue concentration of these steroids, but can provide useful information on functional aspects. It is well-known that the pattern of uterine activity varies considerably during the menstrual cycle (12). However, most investigators have

failed to correlate the myometrial activity to the plasma concentrations of ovarian hormones. It is more reasonable to think that the physiological activity of the myometrium will be governed by the tissue concentrations, rather than those in the plasma, of these hormones.

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