Inhibitory Effect of Progesterone on the Postcastration Gonadotrophin Rise in Women

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Abstracts

This study was designed to investigate the effects of progesterone on the gonadotrophin rise after bilateral salpingo-oophorectomy (BSO). Twenty-eight regularly menstruating women underwent hysterectomy and BSO during the follicular phase of the menstrual cycle. They were divided into 5 groups depending on the treatment after BSO. Plasma LH and FSH were studied serially for 14 days after BSO and the patterns of LH and FSH rises were contrasted to those observed in the control group which received neither progesterone nor estrogen. LH and FSH levels in the group which were given low dose progesterone only, rose consistently after BSO and these patterns were similar to those seen in the control group. However, the addition of estrogen reduced gonadotrophin rises significantly more than estrogen did alone. Further, the luteal phase level of progesterone solely has a suppressive effect on the gonadotrophin rises after BSO. Our observations suggest that synergism of progesterone with estrogen may exist in suppressing gonadotrophin secretion in the normal luteal phase and should help in understanding why gonadotrophin levels in the luteal phase are lower than those in the follicular phase of the menstrual cycle.

It is widely accepted that under normal physiological conditions gonadotrophin secretion is subjected to the negative feedback actions of circulating sex steroid hormones. Gonadotrophin rise after ovariectomy is thought to be due in part to the decrease in circulating sex steroid hormones. Although the inhibitory effect of estrogen on the gonadotrophin rise after ovariectomy is well known it still remains undetermined whether or not progesterone plays a significant role in suppressing gonadotrophin rise after ovari-

ectomy in women. In animals and women it has been observed that the maintenance of circulating estradiol alone at concentrations characteristic of the normal follicular phase was insufficient to prevent the rise in circulating gonadotrophins following ovariectomy (Karsch *et al.*, 1973, Simon & diZerega 1982). We previously reported that a luteal phase level of progesterone alone decreases the frequency of LH pulses, augments their amplitude, and lowers the basal levels of LH and FSH in hypogonadal women (Minakami *et al.*, 1984). Our observations are in good agreement with the report by Karsch

et al. (1980) that in sheep, simulation of the luteal phase pattern of progesterone alone could reduce LH concentrations which were intermediate between the elevated levels in ovariectomized non-treated controls and the basal levels in intact controls. These findings suggest that progesterone alone has an inhibitory effect on the gonadotrophin rise after castration in women. Since few data are available concerning this issue, we designed the present study.

Materials and Methods

Twenty-eight regularly menstruating patients aged 36–51 yr with uterine fibroids were studied. These women had not received any hormonal medication for at least 3 months. The full na-

ture of the study was explained to them. They consented to take part in this study and to have bilateral salpingo-oophorectomy (BSO) performed at the time of hysterectomy. Hysterectomy and BSO was performed in all patients in the early to mid-follicular phase of the menstrual cycle. Five patients were treated with intra-muscular(im) injections of 250 mg hydroxyprogesterone caproate (HPC) at 0800h on the day of surgery and on day 7 after BSO (Group HPC). The second group of 5 patients were given im injections of 10 mg progesterone at 0800 and 2000h, (twice daily) beginning on the day of surgery, for 15 consecutive days (Group P). The third group of 5 patients were treated with im injections of 2.0 mg of estradiol benzoate (E_2B) at 0800h on the day of surgery and on days 3, 6, 9 and 12 after BSO (Group E_2B). The fourth group of 5 patients received the combined treatment as Group HPC and Group E_2B (Group HPC+ E_2B). The remaining 8 patients, who received neither

Fig. 1. Daily plasma progesterone concentrations achieved in Group P (●) and Group HPC (○) (upper panel). Daily plasma estradiol concentrations achieved in Group E_2B (○) (lower panel). Group P (n=5) was given im injections twice daily of 10 mg progesterone beginning on the day of bilateral salpingo-oophorectomy (day 0). Group HPC (n=5) was given im injections of 250mg hydroxyprogesterone caproate (HPC) on day 0 and 7. Group E_2B was given im injections of 2.0mg of estradiol benzoate (E_2B) on day 0, 3, 6, 9 and 12. All values are expressed as the mean $\pm$ SEM.

progesterone, HPC nor E_2B acted as controls. The mean ages ($\pm$ SD) for Group P, Group HPC, Group E_2B , Group HPC+ E_2B and the control group were 45.4 ± 2.0 , 44.0 ± 3.2 , 45.6 ± 3.0 , 46.6 ± 2.5 and 45.1 ± 4.5 , respectively. They did not differ significantly. For 16 consecutive days, beginning 2 days before the operation, blood samples were collected once a day between 0900–1100h in all patients. All plasma samples were separated immediately and stored at -20°C until analyzed for LH, FSH, progesterone and estradiol by radioimmunoassay, as previously described (Minakami *et al.*, 1984). Intra- and interassay coefficients of variation for both LH and FSH did not exceed 7% and 11%, respectively. To minimize the effects of interassay variation all samples obtained from a single patient were assayed in a single radioimmunoassay for LH and FSH. Data were analyzed using analysis of variance, with subsequent Student's *t*-testing when applicable.

Results

The circulating levels of progesterone and estradiol achieved in Groups P, HPC and E_2B are shown in Fig. 1. The twice daily im injections of 10 mg progesterone resulted in maintaining high levels of circulating progesterone (9.3 ± 1.4 – 15.8 ± 2.8 ng/ml). In contrast, the concentration of progesterone in the group given 250 mg HPC intramuscularly on days 0 and 7 remained at low levels (1.3 ± 0.4 – 1.9 ± 0.4 ng/ml) (Fig. 1 upper panel). 2.0 mg of E_2B im injections on days 0, 3, 9 and 12 resulted in considerable daily fluctuation in the circulating estradiol level. However, it remained relatively high (Fig. 1. lower panel).

Fig. 2. Daily plasma LH concentrations before and after bilateral salpingo-oophorectomy (BSO, day 0) in groups HPC (■), P (○), E_2B (▲), HPC+ E_2B (◐) and control (●). The control group ($n=8$) received neither E_2B nor progestin after BSO. Group HPC+ E_2B ($n=5$) was given the combined treatment as Group HPC and Group E_2B . The shaded area shows the $\pm$ SEM of plasma LH in the control group. Other explanations same as for Fig. 1.

rise was modest and a significant increase in LH was not found until day 13 post-operation (Table 1). Further, LH levels in Group P were significantly lower than those in Group HPC and the control group from day 4 on postoperation (Table 2). In Group E₂B, a significant increase in LH above the preoperation value occurred only on days 4 and 5 (Table 1). When compared with the control group, significant low levels of

Treatment		Days from BSO													
		1	2	3	4	5	6	7	8	9	10	11	12	13	14
Control	LH	*	*	b	c	c	c	d	d	d	d	d	d	d	d
	FSH	*	*	b	c	c	c	d	d	d	d	d	d	d	d
HPC	LH	*	*	b	c	d	d	d	d	d	d	d	d	d	d
	FSH	*	*	c	c	d	d	d	d	d	d	d	d	d	d
P	LH	*	*	*	*	*	*	*	*	*	*	*	*	c	c
	FSH	*	*	*	*	*	*	*	*	*	*	*	*	a	a
E ₂ B	LH	*	*	*	a	b	*	*	*	*	*	*	*	*	*
	FSH	*	*	*	*	*	*	*	*	*	*	*	*	a	a
HPC+E ₂ B	LH	*	*	*	*	*	*	*	*	*	*	*	a	b	a
	FSH	*	*	*	*	*	*	*	*	a	a	c	b	c	c

[illegible]

LH were observed from day 7 on post-operation (Table 2). In Group HPC+E₂B, LH levels did not show a significant increase above the preoperation value and they decreased significantly from day 13 (Table 1). In addition, from day 12 on, an LH level in Group HPC+E₂B was significantly lower than that in Group E₂B (Table 2).

Plasma FSH changes

Changes in plasma FSH in the 5 groups before and after BSO are shown in Fig. 3. The mode of plasma FSH change was similar in both the control group and Group HPC to that in LH changes. The first significant rise in FSH above the preoperative level was seen by day 3 in both groups (Table 1). Also, FSH levels in Group P rose con-

sistently after BSO, but the course of the plasma FSH rise was modest. Consequently, a significant rise in FSH above the preoperative level was not seen until day 13. In Groups E₂B and HPC+E₂B, FSH levels after BSO never exceeded the preoperative levels and dropped significantly by day 12 and 9, respectively (Table 1).

Discussion

Our results show that the low level of plasma progesterone does not affect the postcastration gonadotrophin rise. The low level of plasma progesterone does, however, facilitate the suppressive effect of estrogen, while the luteal phase level of progesterone acts solely to suppress the gonadotrophin

Fig. 3. Daily plasma FSH concentrations before and after bilateral salpingo-oophorectomy (BSO, day 0). Other explanations are the same as for Fig. 2.

rise after castration in women. In control subjects and Group HPC, a prompt and significant increase in the gonadotrophins was observed during the first 14 days after castration. In contrast, distinctly different patterns in the postcastration gonadotrophin rise were observed in the other 3 groups from that seen in the control group. It has been reported that some differences in the pattern of the postcastration gonadotrophin rise could be observed relative to the ovarian phase of the menstrual cycle, with a more rapid and greater rise in gonadotrophin during the initial phase after castration in preovulatory than postovulatory subjects (Fioretti *et al.*, 1982, Yen & Tsai 1971). To avoid the influences of ovarian steroids, all patients who participated in this study underwent surgery during the follicular phase of the menstrual cycle. Therefore, the differences in the patterns of gonadotrophin rise after castration between groups seen in our study may be attributable to differences in treatment.

An increase in plasma LH was observed during the first few days after surgery followed by a gradual decline in plasma LH in Groups E₂B and HPC+E₂B. This initial rise in LH might be due to the well-known positive feedback effect of estrogen (Araki *et al.*, 1978, Keye & Jaffe 1975, Nillius & Wide 1971b, Yen & Tsai 1972). In the human as well as rhesus monkey, it is well known that at midcycle progesterone starts to rise before LH and FSH reach their maximum values (Guerrero *et al.*, 1976, Hoff *et al.*, 1983, Laborde *et al.*, 1976, Weick *et al.*, 1973). This progesterone rise has been thought to advance and augment the following LH peak (Aono *et al.*, 1976, Caligaris *et al.*, 1968, Chang & Jaffe 1978, Helmond *et al.*, 1981, March *et al.*, 1979). In our study, earlier appearance of an LH peak was seen in the Group HPC+E₂B than in the Group E₂B. This finding can be explained by an advancing effect of a low progesterone level. Lack of an LH

peak in Group P is probably due to shorter duration of exposure of the hypothalamo-pituitary system to estrogen than in Groups E₂B and HPC+E₂B. This interpretation is based on reports that an initiation of a positive feedback effect of sex steroids on gonadotrophin secretion seems to need a certain duration of exposure of the hypothalamo-pituitary system to estrogen (Araki *et al.*, 1978, Keye & Jaffe 1975). Also, a relatively large dose of progesterone is rather ineffective in inducing an LH peak in estrogen-treated hypogonadal women and monkeys (Helmond *et al.*, 1981, Nillius & Wide 1971a).

It is recently reported that progesterone administered in the normal follicular phase of the menstrual cycle in women slowed LH pulse frequency, augmented pulse amplitude, and lowered mean plasma LH levels (Soules *et al.*, 1984). Our results show that even low levels of plasma progesterone, which alone were unable to modify gonadotrophin secretion, facilitated the suppressive effect of estrogen. Thus, our findings confirm the report of Soules *et al.*, (1984) and further indicate that subthreshold levels of progesterone in suppressing gonadotrophin secretion can synergize with estrogen in this regard.

The most interesting and novel finding of this report is seen in the effect of progesterone alone on the gonadotrophin rise after castration. To our knowledge, there is no literature concerning this issue. In the present study, we demonstrated that the luteal phase level of progesterone alone can reduce LH and FSH concentrations which are intermediate between the elevated levels in control subjects and the preoperative value. This result is in agreement with our previous report (Minakami *et al.*, 1984) and others (Bullock *et al.*, 1975, Schiff *et al.*, 1980) that progesterone alone administered to hypogonadal women lowers plasma LH and FSH levels moderately. In contrast, a low level of progesterone did not sup-

press the gonadotrophin rise after castration.

In summary, the luteal phase level of progesterone alone suppresses the gonadotrophin rise after castration in women. Furthermore, even low levels of progesterone, which alone are unable to suppress gonadotrophin secretion, facilitate the suppressive effect of estrogen. These observations may help in understanding why gonadotrophin levels in the luteal phase are lower than those in the follicular phase of the menstrual cycle (Santen & Bardin 1973, Sherman & Korenman 1975).

Acknowledgements

We wish to thank Miss Yoko Sato and Miss Yasuko Sato for technical assistance, and Miss Mariko Kato for secretarial assistance.

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