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Variation of Pituitary Responsiveness to Synthetic LH-RH and T-RH during Different Phases of the Menstrual Cycle*

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The LH and FSH responses to synthetic LH-RH and the prolactin response to synthetic T-RH were evaluated during different phases of the mentrual cycle in order to understand secretory capacity of the pituitary during the menstrual cycle.

Eleven regularly menstruating women between 22 and 35 years of age with a usual cycle length of 27 to 31 days volunteered for this study. Volunteers received an intravenous injection of 100 μg synthetic LH-RH and 200 μg synthetic T-RH during the early and the late follicular phases and during the early and midluteal phases of the menstrual cycle.

LH-RH induced a prompt increase in circulating LH, reaching the peak concentration at 30 minutes following LH-RH administration in all phases of the cycle studied. A change in responsiveness with greater and more sustained LH release from the early to the late follicular phases was observed. The response during the luteal phase was significantly greater than the responses in both the early and the late follicular phases. A concomitant but a much smaller FSH response was observed.

T-RH elicited a prompt increase in circulating prolactin within 30 minutes and decreased gradually thereafter, reaching the baseline level by 2 hours after T-RH administration. Maximum concentration of prolactin was reached in 30 minutes following T-RH during all phases of the menstrual cycle. No variation in pituitary responsiveness to T-RH, however, was observed during different phases of the menstrual cycle.

These data indicate that the sensitivity of the pituitary gonadotrophs to LH-RH varies during different phases of the menstrual cycle.

Key Words: Pituitary responsiveness, Menstrual cycle.

Exogenous estradiol (Yen and Tsai, 1971; Monroe *et al.*, 1972) and clomiphene citrate (Vandenberg and Yen, 1972) have been shown to elicit a greater rise in circulating gonadotropin levels when administrated during the late follicular phase than during the early phase. Evidence has accumulated that the sensitivity of the hypothalamic-pituitary axis to the feedback action of estradiol varies during different phases of the menstrual cycle (Thomas *et al.*, 1973; Jewelewicz *et al.*, 1977; De Kretser *et al.*, 1978). It has also been demonstrated that the response of the pituitary to LH-RH stimulation changes at

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different phases of the menstrual cycle, a phenomenon mediated by the changing concentrations of esradiol-17β and progesterone induced by ovarian activity (Nillius and wide, 1971: Yen *et al.*, 1974b).

Sexual differences in prolactin secretion have been known to be attributed to ovarian secretion (Daughaday *et al.*, 1971; Ehara *et al.*, 1975). There seems to be, however, no difference in basal prolactin levels throughout the cycle (Ehara *et al.*, 1973; Jaffe *et al.*, 1973; Ryu *et al.*, 1971a),while other studies showed higher prolactin levels at midcycle or in the luteal phase (Robyn *et al.*, 1973). The prolactin responses to T-RH administered during different phases of the menstrual cycle have been reported controversially; i.e. no differences in the prolactin response to T-RH during the menstrual cycle (Tyson and Friesen, 1973; McNeilly and Hagen, 1974) and augmentation in prolactin response to T-RH during the luteal phase (Boyd and Sanchez-Franco, 1977).

In the present study we have evaluated the LH and FSH response to synthetic LH-RH and the prolactin response to synthetic T-RH during the different phases of the menstrual cycle.

MATERIALS AND METHODS

1) Subjects

Eleven regularly menstruating women between 22 and 35 years of age with a usual cycle length of 27 to 31 days volunteered for this study. Gonadotropin and prolactin responses were evaluated during the early (day 4 - day 7) and the late (day 11 - day 14) follicular phases of the same cycle in 5 subjects. Additional studies were also made during the early (day 17 - day 19) and the mid (day 20 - day 24) luteal phases of the same cycle in 6 subjects.

The phase of the cycle was determined by the day of the cycle, the basal concentrations of LH, progesterone and estradiol, and the interval from the day of study until the onset of the next menses.

2) Methods

LH-RH and T-RH stimulation test:

Subjects received an intravenous injection of 100 μg of synthetic LH-RH (Hoechst, A.G.) and 200 μg of synthetic T-RH (Hoechst, A.G.).

Blood samples were collected by venipuncture just prior to and 30, 60 and 120 minutes after the injection of LH-RH and T-RH. Serum was separated and frozen at -50°C until assayed.

Assays:

Serum levels of FSH and LH were measured by the radioimmunoassay kit from Daiichi Radioisotope Laboratory (Tokyo, Japan), employing a standard double antibody procedure. Prolactin was also measured by a double antibody radioimmunoassay kit (Abbott Laboratory, Chicago, Ill. U.S.A.).

RESULTS

The mean concentrations of LH and FSH before LH-RH injection and the mean concentration of prolactin before T-RH injection were within the normal range found during different phases of the menstrual cycle in our laboratory.

LH-RH induced a prompt increase in circulating LH and the mean peak concentration was reached in 30 min. following LH-RH administration in all phases of the cycle (Fig. 1). The mean net increase in LH calculated from concentration determined just prior to LH-RH injection (zero time) and the peak response following LH-RH administration was greater during the late (109.0 mIU/ml) than during the early follicular phases (39.0 mIU/ml) of the cycle. This difference was statistically significant ($P<0.01$). The largest net increase (149.9 mIU/ml) was seen during the mid-luteal

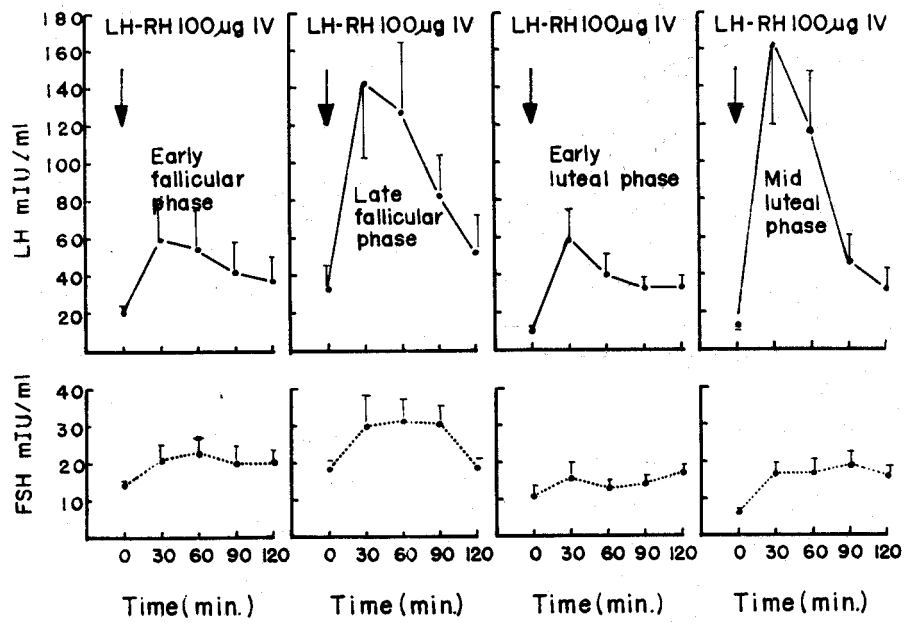

Fig. 1. Serum LH and FSH responses to synthetic LH-RH during different phases of the menstrual cycle.

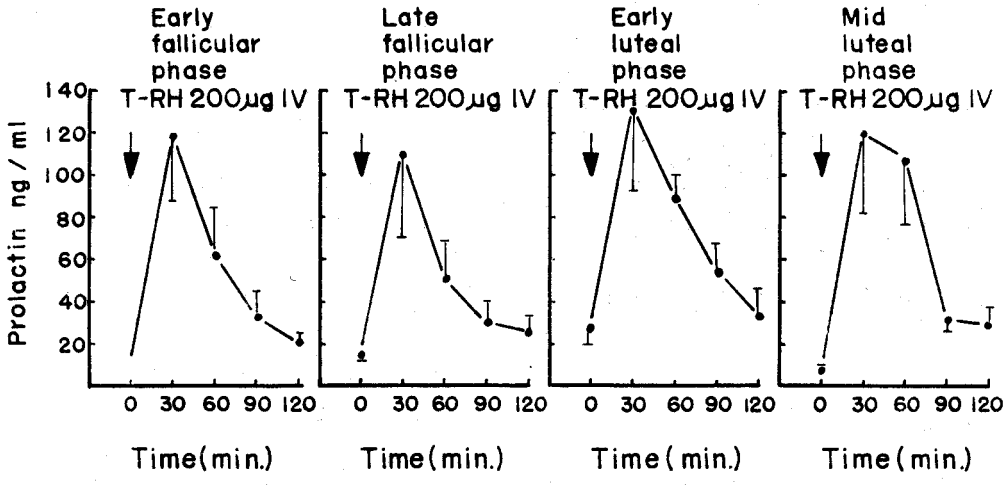

Fig. 2. Serum prolactin response to synthetic T-RH during different phases of the menstrual cycle.

phase and this increase was significantly greater than the values observed during the early ($P < 0.001$) and the late ($P < 0.05$) follicular phases of the cycle.

A concomitant but a much smaller rise in serum FSH levels was observed. The time course and pattern of response were similar to those described for LH (Fig. 1). There was no significant difference in the net increase of FSH during different phases of the cycle.

Figure 2 shows the prolactin response to T-RH stimulation during different phases of the menstrual cycle. Synthetic T-RH elicited a prompt increase in circulating prolactin within

30 min. and decreased gradually thereafter, reaching the baseline level by 2 hours after T-RH administration. Maximum concentration of prolactin was reached in 30 min. following T-RH during all phases of the menstrual cycle. No difference in pituitary responsiveness to T-RH, however, was observed during different phases of the menstrual cycle.

DISCUSSION

The present study indicated that pituitary responsiveness to synthetic LH-RH varied during different phases of the menstrual cycle. This finding is in good accord with the previous data reported (Thomas *et al.*, 1973; Jewelewicz *et al.*, 1977; De Kretser *et al.*, 1978).

The sensitivity of pituitary gonadotrophs to LH-RH is preferentially increased for LH release during the late follicular phase of the cycle. It is likely that this event is brought about by a direct feedback action of the increasing level of serum estradiol. This assumption is supported by the finding that optimal amounts of estradiol enhanced pituitary responsiveness to LH-RH in the human (Jaffe and Keye, 1974; Wang and Yen, 1975; Jewelewicz *et al.*, 1977). Findings in the present study are also compatible with the data that sensitivity of a positive feedback action of estradiol is significantly greater during the late than during the early follicular phase of the cycle (Yen and Tsai, 1971; Yen *et al.*, 1974b) and that estadiol may preferentially promote the release of LH over FSH (Yen and Tsai, 1971). Since a greater response was found during the midluteal phase, the possibility of an additive and synergistic action of progesterone must be considered (Yen *et al.*, 1974b).

The largest net increase in LH response to LH-RH was shown during the mid-luteal phase of the menstrual cycle in the present study. This finding would suggest that the lowered gonadotropin levels observed during this phase of the cycle are not related to a diminished pituitary sensitivity to LH-RH but related to a decrease in LH-RH release. Thus, feedback inhibition on the hypothalamic LH-RH releasing mechanism may be postulated to account for the lowered gonadotropin levels.

No change in prolactin response to T-RH was observed during different phases of the menstrual cycle. McNeilly *et al* (1974) using a combined TRH-LHRH test found the prolactin rise to be similar on day 4 and day 24 of the menstrual cycle. Although not directly comparable to the present study, Tyson and Friesen (1973) studied five patients on day 4 and again on day 9 to 13 and found the T-RH stimulated prolactin rise to be similar. In contrast, it has been reported that pharmacologic doses of estrogen increase serum prolactin (Yen *et al.*, 1974a; Vekemans and Robyn, 1975; Reymond and Le Marchand-Beraud, 1976) and a greater increase in prolactin after T-RH administration was seen at midcycle than in follicular or luteal phases (Reymon and Le March-and-Beraud, 1976). Prolactin response to T-RH was also greater on day 21-22 than on day 7-8 of the menstrual cycle (Boyd and Sanchez-Franco, 1977). They assumed that pharmacologic and physiologic variation in estrogen may modify prolactin secretion.

Such a discrepancy in results from the present study and the others cannot be explained at the present moment.

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