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Onset and Characteristics of the Midcycle Surge in Bioactive and Immunoactive Luteinizing Hormone Secretion in Normal Women: Influence of Physiological Variations in Periovulatory Ovarian Steroid Hormone Secretion*

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ABSTRACT

Limited studies in nonhuman primates suggest that the midcycle LH surge is characterized by distinctly different patterns of bioactive (LH-BIO) and immunoactive (LH-RIA) LH secretion. To further examine the patterns of midcycle LH-BIO and LH-RIA secretion and explore the influence of physiological variations in steroid hormone feedback on LH surge dimensions we studied seven normal ovulatory women over the periovulatory interval. In each, blood samples were obtained every 3 h and transvaginal ultrasonography was performed every 12 h over a 5–7 day interval at midcycle. Serum levels of LH-RIA, FSH, estradiol (E_2), progesterone (P_4), and 17-hydroxyprogesterone were determined by RIA; LH-BIO was estimated using a mouse leydig cell bioassay. Hormone data were standardized to the time of surge onset in LH-RIA (time zero), defined as a 100% increase above a 6-point running mean baseline value; surge cessation was defined as a decline to below baseline concentration.

Mean LH-RIA surge duration was 54.0±4.0 h. LH-BIO surge onset was simultaneous with that of LH-RIA and coincident with the peak in E_2 levels (mean data). Mean P_4 and 17-hydroxyprogesterone rose in a parallel, phasic manner; an abrupt increase in slope occurred between −6 h and +30 h but an acute rise in P_4 was not consistently observed among individuals. The surge onset to follicle rupture interval (mean 37.6±4.2 h) positively correlated with peak LH-RIA ($r=0.76$, $P<0.05$), surge amplitude ($r=0.74$, $P<0.05$) and surge onset to peak interval ($r=0.87$, $P<0.02$), but not surge duration. There were no significant relationships between E_2 or P_4 (mean, peak, integrated, slope) and surge amplitude or duration (LH-RIA, FSH), peak value, or surge onset to peak interval (LH-RIA, LH-BIO, FSH).

These data suggest that in women, 1) onset of the midcycle surge in LH-RIA and LH-BIO is simultaneous, and 2) surge characteristics are not influenced by physiological variations in steroid hormone secretion that occur beyond the thresholds required for surge initiation. (*J Clin Endocrinol Metab* **75:** 489–493, 1992)

THE MIDCYCLE gonadotropin surge is the most dramatic endocrinological event in the normal menstrual cycle and is responsible for initiation of the complex sequence of secondary events that culminates in ovulation. The dynamics of the spontaneous immunoactive LH (LH-RIA) surge are well described (1–3), but data regarding the pattern of bioactive LH (LH-BIO) secretion at midcycle are quite limited (4, 5). Evidence from earlier nonhuman primate studies suggests that the patterns of midcycle LH-RIA and LH-BIO secretion are temporally, quantitatively and/or qualitatively distinct (4); comparable human data are lacking.

Numerous studies have helped to define the complex hypothalamic-pituitary-ovarian feedback interactions that combine to induce the midcycle gonadotropin surge (6–12); both estradiol (E_2) and progesterone (P_4) play an important role. Whereas the obligatory stimulus is clearly the rapid rise in E_2 levels that accompanies the latter stages of preovulatory follicular maturation, periovulatory P_4 influences both the time of onset and ultimate magnitude of the surge. Both the minimum strength/duration requirements for effective estrogen positive feedback (6–8) and the manner in which P_4 influences the timing and dimensions of the surge (8–12) are established. However, whether the timing, composition, and/or magnitude of the surge are influenced by the wide range of physiological variations in midcycle steroid hormone secretion is not clear.

The design of a previous study (3) in which we obtained frequent blood samples throughout the immediate periovulatory interval in a group of normal cycling women afforded us the opportunity to reexamine certain aspects of the endocrine dynamics that surround the midcycle gonadotropin surge and ovulation. Specifically, in the current study we sought to examine: 1) the relative patterns of LH-RIA and LH-BIO secretion during the periovulatory interval, 2) the

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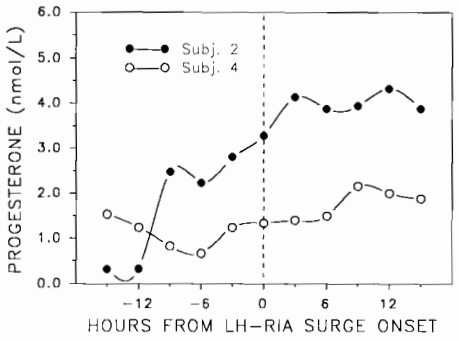

FIG. 3. Serum concentrations of P_4 in serum samples drawn every 3 h between −15 h and +15 h relative to onset of the LH-RIA midcycle surge in two individuals. In one (subject 2), an acute increase in serum P_4 occurred before surge onset; the pattern is representative of that seen in three of seven women studied. In others (*e.g.* subject 4), surge onset was accompanied only by a gradual increase in serum P_4 concentration.

TABLE 2. Follicular ultrasound

Subject	Maximum mean follicle diameter (mm)	Surge onset-follicle rupture interval (h)
1	24.0	43.5
2	23.0	22.5
3	20.5	45.5
4	25.0	48.0
5	25.5	35.75
6	20.5	46.0
7	21.0	22.0
Mean ± SEM	22.8 ± 0.8	37.6 ± 4.2

dominant follicle before rupture (mean 22.8 ± 0.8 mm) and the time interval between LH-RIA surge onset and follicle rupture (mean 37.6 ± 4.2 h) are presented in Table 2. The surge onset to follicle rupture interval positively correlated with LH-RIA surge amplitude ($r = 0.74$, $P < 0.05$), peak LH-RIA ($r = 0.76$, $P < 0.05$), and the LH-RIA surge onset to peak interval ($r = 0.87$, $P < 0.02$), but not with surge duration.

Discussion

In this study in women, onset of the midcycle surge in LH-RIA and LH-BIO secretion was simultaneous and coincident with the observed peak in E_2 concentrations (mean data). These data contrast with earlier observations in nonhuman primates (4) which suggested that LH-BIO undergoes transition from a tonic to surge mode of secretion 4–6 h earlier than does LH-RIA. Although our study employed a less frequent sampling interval (3 h *vs.* 15 min) and could therefore be less sensitive to a subtle difference between the times of LH-RIA and LH-BIO surge onset, even the temporal sequence of the two events was inconsistent among individuals.

The patterns and levels of periovulatory steroid hormones observed in our group of normally ovulating women were typical of the normal cycle and uniformly exceeded accepted threshold concentrations. Each subject also had a characteristic, spontaneous LH surge but none of the surge parameters we examined appeared to be influenced by the wide range of physiological variations in ovarian steroid secretion observed among subjects. Neither the pattern nor level of E_2 or P_4 secretion was related to the timing, composition, or magnitude of the midcycle gonadotropin surge. These data suggest that once minimum threshold requirements for induction of a normal gonadotropin surge are met, surge characteristics are not further influenced by physiological variations in steroid hormone secretion.

Previous studies have suggested that the periovulatory rise in P_4 may trigger an LH surge firing mechanism that is first cocked by an interval of incremental E_2 exposure (2). We did observe a phasic rise in mean periovulatory P_4 and 17OHP levels that closely approximates the pattern previously described (2), but the putative acute preovulatory increase in P_4 did not occur in all individuals. Only three subjects experienced a sudden increment in serum P_4; a less striking increase was detected in a pair of others, but the rise in P_4 was only very gradual in the remaining two subjects.

Correlations between the surge onset to follicle rupture interval and LH-RIA peak, surge amplitude, and surge onset to peak interval are of interest. However, follicle rupture was arbitrarily defined as occurring at the time of that sonogram demonstrating follicular collapse when, in fact, it may have occurred at any time in the preceding 12-h interval. Any conclusions regarding the influence of surge dimensions on the time of ovum release must take into account the interval between scans. Nevertheless, our data suggest that a more abrupt LH surge may accelerate follicle rupture and imply that initiation of the ovulatory sequence may require a threshold level of LH.

In summary, frequent blood sampling throughout the periovulatory phase demonstrated a simultaneous onset of the midcycle surge in LH-BIO and LH-RIA that occured coincident with the peak in preovulatory E_2 concentrations. Onset and dimensions of the LH surge did not correlate with the patterns or levels of midcycle steroid hormone secretion but did relate to the time of follicle rupture. These data contrast with earlier observations in the nonhuman primate and suggest that characteristics of the midcycle gonadotropin surge are not sensitive to physiological variations in steroid hormone feedback but may influence the ovulatory sequence within the follicle.

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References

1. **Thorneycroft IH, Sribyatta B, Tom WK, Nakamura RM, Mishell Jr DR.** 1974 Measurement of serum LH, FSH, progesterone, 17-hydroxyprogesterone and estradiol-17β levels at 4-hour intervals during the periovulatory phase of the menstrual cycle. J Clin Endocrinol Metab. 39:754–8.
2. **Hoff JD, Quigley ME, Yen SSC.** 1983 Hormonal dynamics at midcycle: a reevaluation. J Clin Endocrinol Metab. 57:792–6.
3. **McLachlan RI, Cohen NL, Dahl KD, Bremner WJ, Soules MR.** 1990 Serum inhibin levels during the periovulatory interval in

normal women: relationships with sex steroid and gonadotropin levels. Clin Endocrinol (Oxf). 32:39–48.

4. **Marut EL, Williams RF, Cowan BD, Lynch A, Lerner SP, Hodgen GD**. 1981 Pulsatile pituitary gonadotropin secretion during maturation of the dominant follicle in monkeys: estrogen positive feedback enhances the biological activity of LH. Endocrinology. 109:2270–2.
5. **Veldhuis JD, Beitins IZ, Johnson ML, Serabian MA, Dufau ML**. 1984 Biologically active luteinizing hormone is secreted in episodic pulsations that vary in relation to stage of the menstrual cycle. J Clin Endocrinol Metab. 58:1050–8.
6. **Knobil E**. 1974 On the control of gonadotropin secretion in the rhesus monkey. Recent Prog Horm Res. 30:1–46.
7. **Young JR, Jaffe RB**. 1976 Strength-duration characteristics of estrogen effects on gonadotropin response to gonadotropin-releasing hormone in women. II. Effects of varying concentrations of estradiol. J Clin Endocrinol Metab. 42:432–42.
8. **Liu JH, Yen SSC**. 1983 Induction of midcycle gonadotropin surge by ovarian steroids in women: a critical evaluation. J Clin Endocrinol Metab. 57:797–802.
9. **Terasawa E, Rodriguez-Sierra JF, Dierschke DJ, Bridson WE, Goy RW**. 1980 Positive feedback effect of progesterone on luteinizing hormone (LH) release in cyclic female rhesus monkeys: LH response occurs in two phases. J Clin Endocrinol Metab. 51:1245–50.
10. **Helmond FA, Simons PA, Hein PR**. 1980 The effects of progesterone on estrogen-induced luteinizing hormone and follicle-stimulating hormone release in the female rhesus monkey. Endocrinology. 107:478–85.
11. **Aono T, Miyake A, Kinugasa T, Kurachi K**. 1976 Progesterone advancement of estrogen-induced luteinizing hormone release during the midfollicular phase in normal cyclic women. J Endocrinol. 71:451–4.
12. **Chang RJ, Jaffe RB**. 1978 Progesterone effects on gonadotropin release in women pretreated with estradiol. J Clin Endocrinol Metab. 47:119–25.
13. **Steiner RA, Peterson AP, Yu JYL, Conner H, Gilbert M, ter-Penning B, Bremner WJ**. 1980 Ultraradian luteinizing hormone and testosterone rhythms in the adult male monkey, macaca fascicularis. Endocrinology. 107:1489–93.