Pulsatile secretion of progesterone from the human corpus luteum: poor correlation with bioactive LH pulses

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Abstract. Having previously established that biologically active luteinizing hormone (LH) is secreted in episodic pulsations that vary in relation to the menstrual cycle, we investigated the possibility that a temporal relationship could exist between the bioactive LH pulses and progesterone secretion from the late corpus luteum. In 4 young women blood was withdrawn every 15 min for 8 h. Serum progesterone concentrations fluctuated at a mean frequency of 0.9 h with a wide range of amplitudes (13.8 to 1.7 ng/ml). Serum bioactive LH pulse frequency in contrast was 0.25 pulses/h in all subjects. The pulse amplitude was 18.2 to 12.4 mIU/ml (2nd IRP-hMG). These data reveal that within the 8 h-period studied, progesterone secretory pulses occurred four times more frequently as those for bioactive LH. Therefore it is unlikely that a temporal relationship exists between individual bioactive LH and pulses of progesterone secreted by the late corpus luteum.

Corpus luteum function is of utmost importance in the hormonal regulation of the normal menstrual cycle, nidation, implantation and maintenance of early pregnancy (Jewelewicz et al. 1974a). In various animal species, there is a wide spectrum of the degree of dependence of corpus luteum function on pituitary trophic support with sheep being totally dependent but sows independent (Nalbandov 1970). In the hypophysectomized rhesus monkey with induced ovulation, corpus luteum function continues in the presence of undetectable endogenous LH levels (Asch et al. 1982).

The importance of pituitary LH for human corpus luteum function has not yet been conclusively proven. Early studies regarding serum progesterone fluctuations showed insignificant (Younglai et al. 1975) or small (Bäckström et al. 1982) pulses during the luteal phase of the normal menstrual cycle. There was some suggestion that concentrations of progesterone increased in response to the rise of immunoreactive LH. These results were based on small numbers of subjects studied for relatively short periods of time (6 h). Recently the duration of the study has been extended and blood samples collected every 10 min for 24 h-periods (Filicori et al. 1984). From the results in two women studied during the mid and late luteal phases Filicori et al. (1984) concluded that progesterone secretion was episodic and correlated with pulsatile immunoreactive LH release. We have previously demonstrated that bioactive LH is secreted in episodic pulsations that vary in relation to the phase of the menstrual cycle (Veldhuis et al. 1984). This study was undertaken to examine the question of whether bioactive LH influenced human corpus luteum progesterone secretion during the late luteal phase of the menstrual cycle.

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Materials and Methods

Subjects and protocol

Studies were conducted in 4 healthy young women (mean age 27.3 years) with carefully documented normal menstrual cycles based upon daily basal body temperature estimates and luteal phase serum progesterone concentrations over at least 2 consecutive months. Each woman had a normal developmental history, including age of menarche, and normal serum concentrations of thyroid hormones, prolactin, immunoreactive LH and FSH, oestradiol and testosterone. No subject was receiving medications, had experienced weight loss or was engaged in strenuous sports. All women provided written informed consent approved by the Human Investigation Subcommittee of the Massachusetts General Hospital.

Blood was collected during each of the three phases of the same menstrual cycle: follicular (day 3 and 4), late follicular (day 11–14) and luteal (3 to 6 days before onset of menses). The results of the immunoreactive and bioactive LH patterns obtained during these times have been included in a larger sample of women and have been published (Veldhuis et al. 1984).

In this study blood was collected every 15 min from an antecubital vein for a total of 8 h. All studies were conducted 3 to 6 days before the onset of menses, starting at 9 a.m. The subject remained semirecumbent and ate a light lunch. The serum was separated and kept frozen at −20°C until assayed for bioactive LH and progesterone.

Assays

Serum progesterone was measured by the method of Abraham et al. (1971). All samples from each subject for all hormone determinations were within the same assay. The sensitivity of the assay was 0.1 ng/ml. The intra-assay coefficient of variation was 5% and the inter-assay coefficient 10%.

The bioactivity of serum LH was measured by means of the previously described rat interstitial cell testosterone (RICT) production assay (Dufau et al. 1976). The standard used was 2nd IRP-hMG. The within-assay coefficient of variation averaged 8.8%.

Statistics

The pulse frequency and amplitude of serum bioactive LH and progesterone were analyzed by the computerized pulse-detection method of Clifton & Steiner (1983). The details of the application of this method for evaluation of bioactive LH pulses have been previously described (Dufau et al. 1983).

Results

The mean serum progesterone and bioactive LH values, pulse frequency and amplitude are shown in Table 1. The individual values for serum progesterone and bioactive LH throughout the study

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Day of study</th>
<th>Progesterone</th>
<th>Bioactive LH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>days in cycle*</td>
<td>Mean ± sd (ng/ml) (range)</td>
<td>Pulse frequency per hour</td>
</tr>
<tr>
<td>1</td>
<td>25/30</td>
<td>13.8 ± 6.5 (26.1 to 4.7)</td>
<td>1.25</td>
</tr>
<tr>
<td>2</td>
<td>24/31</td>
<td>11.6 ± 1.0 (16.9 to 7.6)</td>
<td>0.25</td>
</tr>
<tr>
<td>3</td>
<td>25/30</td>
<td>7.4 ± 3.8 (14.7 to 2.1)</td>
<td>1.38</td>
</tr>
<tr>
<td>4</td>
<td>27/30</td>
<td>3.7 ± 1.7 (7.0 to 1.8)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

* Days in current study cycle.

Table 1.

Pulse characteristics of serum progesterone and bioactive LH during the luteal phase of the normal menstrual cycle.
The 4 subjects whereas bioactive LH pulses occurred every 4 h in all \( P < 0.05 \). The pulse amplitude for serum progesterone varied from 13.8 to 1.7 ng/ml whereas for bioactive LH 18.2 to 12.4 mIU/ml. Relatively infrequent yet large pulses of LH have been previously documented by using immunoassays (Yen et al. 1972; Filicori et al. 1984) and bioassay (Veldhuis et al. 1984). Others have reported the presence of small but discrete immunoreactive LH pulses preceding the large pulsations (Reame et al. 1984). In this study we were unable to detect such small pulsations of LH by means of the RICT bioassay. During the luteal phase 78% of the bio- and immunoreactive LH peaks were coincident and the immunoreactive and bioactive LH peak frequencies were not significantly different (Veldhuis et al. 1984).

### Discussion

Normal corpus luteum function is a direct continuum beginning with follicle growth and maturation. The first morphologic signs of luteinization begin concurrently with the preovulatory LH surge. Thus ovulation transforms the dominant follicle from being primarily an oestrogen source to a transient endocrine tissue secreting primarily progesterone (DiZerega & Hodgen 1981). Pituitary gonadotrophins, especially FSH, and locally secreted oestradiol are essential for the maintenance, viability, growth and steroid biosynthesis of the granulosa cells of the developing antral follicles (McNatty 1978). Once the corpus luteum is formed the granulosa-luteal cells maintain progesterone secretion in the presence of minimum but constant amounts of LH (Jewelewicz et al. 1974b). hCG/LH binding capacity of human corpora lutea is maximal during the midluteal phase, which is also the time of maximal progesterone secretion (McNeilly et al. 1980). Therefore hCG/LH binding declines along with progesterone secretion unless pregnancy occurs. The foetal trophoblast then supplies the corpus luteum with chorionic gonadotrophin which prolongs its secretion of progesterone.

This study examines the question of whether the pulsatile secretion of progesterone during the mid and late luteal phase of the menstrual cycle is directly related to pulsatile bioactive LH secretion.
from the pituitary. Though it has been stated that progesterone increments in the serum are closely attended by episodes of LH release (Filicori et al. 1984), in this study we were unable to establish any type of correlation. In spite of the fact that the study time was considerably shorter than in the previously quoted report (Filicori et al. 1984), it was clearly evident that serum progesterone pulses were significantly more frequent than those for bioactive LH (Fig. 1). It can also be seen from Fig. 1 that during a long period of relative apulsatility of bioactive LH secretion, progesterone secretion continued in a pulsatile mode. A large pulse of progesterone actually preceded the large bioactive LH pulse and thus could not have been a result of the bioactive LH stimulation. Therefore though low levels of bioactive LH with infrequent large pulses may be essential for the overall maintenance of corpus luteum function, individual bioactive LH pulses did not influence the relatively independent mode of progesterone secretion. Added support to this concept is derived from the knowledge that the corpus luteum of pregnancy is maintained by placental hCG. This hormone has a long half-life and would provide a continuous rather than pulsatile mode of stimulation. The episodic progesterone secretion appears to be either dependent on other, yet unrecognized factors or represent inherent properties of primed and stimulated steroid secreting cells.

At the present time it is not known whether the presence of oestradiol and progesterone in fluctuating concentrations in the blood provides a biologic advantage for the development and maintenance of endometrium and other steroid responsive cells. In vitro progesterone stimulates the release of LRH from superfused hypothalamic tissue from ovariectomized oestradiol-primed prepubertal rats only if delivered in an intermittent mode (Kim & Ramirez 1982). A 4-fold increment over basal LRH is observed about every 2 h which is reminiscent of the pattern of bioactive LH secretion during the luteal phase of the human menstrual cycle. Continuous progesterone infusion is not effective in increasing LRH release (Kim & Ramirez 1982). Thus progesterone secreted by the corpus luteum of pregnancy and later the placenta in high and relatively constant concentrations (Ryan 1980) may contribute to the low secretion of hypothalamic LRH during pregnancy.

References

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