Patterns of Circulating Gonadotropins (LH and FSH), Prolactin and Ovarian Steroids (Estradiol and Progesterone) during the Menstrual Cycle in Korean Women

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Serum levels of LH, FSH and prolactin and plasma levels of estradiol and progesterone were measured by radioimmunoassay from 8 healthy volunteers on no medication for at least 3 months prior to study and with histories of regular menstrual cycle. The following criteria were used to define a normal menstrual cycle: 1) mid-cycle LH surge, 2) luteal phase duration between 12 and 16 days, 3) plasma progesterone levels above 5 ng/ml 5–10 days after LH surge.

Six of eight cycles studied were considered normal. Serum levels of LH from 6 women were fairly constant through the cycle, except at midcycle, when a surge occurred. The rapid increase of LH secretion was during the late follicular phase with a mean peak value of 147.5 mIU/ml. Concentration of FSH started to rise after the onset of menses and decreased slightly during the late follicular phase. FSH rose sharply at midcycle with a mean peak value reaching 36.8 mIU/ml. Following the midcycle FSH and LH surge, FSH and LH decreased sharply and remained at lower concentration during the luteal phase than during the follicular phase.

Serum prolactin concentrations fluctuated throughout the menstrual cycle. There was no peak value of prolactin concomitant to the LH peak.

Plasma estradiol gradually increased during the follicular phase reaching a maximum of 354.3 pg/ml prior to the midcycle LH surge. Following its peak, the level of estradiol dropped sharply and started to increase from the 3rd day after LH peak, rising to 235.9 pg/ml during the midluteal peak. Plasma progesterone levels remained consistently low during the follicular phase and started to rise after the midcycle surge of LH. This rise persisted from day 5 to day 9 after the LH surge, showing a mean value of 26.1 ng/ml. Afterward, a sharp decline occurred resulting in menstruation.

Two cycles studied were considered abnormal. Both cycles showed a “short luteal phase”.

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The availability of sensitive and specific radioimmunoassay for gonadotropins and ovarian steroids has prompted an explosion of knowledge concerning the physiologic interrelationship between hypophysial and gonadal function during the menstrual cycle.

The patterns of follicle stimulating hormone (FSH) and luteinizing hormone (LH) during the menstrual cycle have been well established by a number of investigators (Midgley, 1966; Catt et al., 1968; Midgley and Jaffe, 1968; Abraham et al., 1969; Abraham et al., 1972) and levels of estradiol and progesterone have also been determined (Abraham, 1969; Abraham et al., 1971; Abraham et al., 1972). Circulating prolactin has been measured during the menstrual cycle (Ehara et al., 1973; Tamura and Igarashi, 1973; McNeilly and Chard, 1974; Epstein et al., 1975; Vekemans et al., 1977) but contradictory data have been reported.

The present report represents an initial attempt to relate the daily levels of gonadotropins (LH and FSH), prolactin and ovarian steroids (estradiol and progesterone) during the same menstrual cycle in Korean women.

MATERIALS AND METHODS

Subjects

Eight healthy, nulliparous volunteers with histories of regular menstrual cycle were studied. Subjects had no endocrine or gynecological disease and no medication, including oral contraceptives, for at least 3 months prior to study.

Blood was drawn at a regular time each day (between 10 and 11 a.m.) from each subject. The first day of menstrual bleeding was considered to be the first day of the cycle. Blood was usually collected every other day from cycle day 1-11 and then daily until cycle day 18, followed by every other day until the onset of menses. The follicular phase (pre-LH peak duration) was defined as the time interval between the first day of menses and the LH peak. The luteal phase (post-LH peak duration) was the interval between the LH peak and the first day of menses. The following criteria were used to define a normal menstrual ovulatory cycle.

1. mid-cycle LH peak
2. luteal phase duration between 12-16 days
3. plasma level of progesterone above
   5 ng/ml 5-10 days after LH peak

Method

Serum and plasma were stored at -50°C until assayed. Each cycle was assayed as a unit so that fluctuations would represent intra-rather than interassay variation.

The serum FSH and LH were measured by a radioimmunoassay kit employing a standard double antibody procedure provided by Daiichi Radioisotope Laboratory (Tokyo, Japan). Prolactin was also measured by the double antibody radioimmunoassay kit provided by Abbott Laboratory (Chicago, Illinois, U.S.A.). Radioimmunoassay kit from Daiichi laboratory was employed to determine the plasma value of estradiol and progesterone. Student t-test was used for the statistical analysis.

RESULTS

Based on the above defined criteria for a normal menstrual cycle, six of the eight were considered normal, showing an indirect evidence of ovulation (Table 1).

The day of the LH surge was designated as day zero and used as a reference point for plotting the mean of six normal cycles. The patterns of serum FSH and LH (Fig. 1 and Table 2) agree well with previously pub-
Table 1. Summary of the menstrual cycle data in eight women

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Age (years)</th>
<th>Cycle length (days)</th>
<th>Pre-LH peak duration (days)</th>
<th>Post-LH peak duration (days)</th>
<th>Plasma progesterone 5-10 Days post LH peak (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18</td>
<td>27</td>
<td>13</td>
<td>13</td>
<td>29.8±4.2</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
<td>28</td>
<td>14</td>
<td>13</td>
<td>41.2±1.9</td>
</tr>
<tr>
<td>3</td>
<td>24</td>
<td>30</td>
<td>15</td>
<td>14</td>
<td>26.2±2.7</td>
</tr>
<tr>
<td>4</td>
<td>26</td>
<td>27</td>
<td>14</td>
<td>12</td>
<td>24.6±1.7</td>
</tr>
<tr>
<td>5</td>
<td>25</td>
<td>29</td>
<td>16</td>
<td>12</td>
<td>13.6±4.8</td>
</tr>
<tr>
<td>6</td>
<td>23</td>
<td>31</td>
<td>18</td>
<td>12</td>
<td>30.5±1.2</td>
</tr>
<tr>
<td>7</td>
<td>18</td>
<td>27</td>
<td>20</td>
<td>6</td>
<td>2.8</td>
</tr>
<tr>
<td>8</td>
<td>22</td>
<td>24</td>
<td>18</td>
<td>5</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Table 2. Serum LH, FSH and prolactin concentrations (mean±S.E.) in six women at different stages of the normal menstrual cycles

<table>
<thead>
<tr>
<th>Hormones</th>
<th>Phases of the menstrual cycle</th>
<th>Follicular</th>
<th>Midcycle</th>
<th>Luteal</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSH (mIU/ml)</td>
<td></td>
<td>16.0±0.6</td>
<td>36.8±6.2</td>
<td>11.6±1.2</td>
</tr>
<tr>
<td>LH (mIU/ml)</td>
<td></td>
<td>29.5±1.5</td>
<td>147.5±29.7</td>
<td>22.0±2.0</td>
</tr>
<tr>
<td>Prolactin (ng/ml)</td>
<td></td>
<td>12.5±2.3</td>
<td>14.9±3.8</td>
<td>15.2±3.9</td>
</tr>
</tbody>
</table>

Fig. 1. Serum FSH and LH concentrations obtained from a composite of the six individual normal menstrual cycles: Mean±S.E. Plotted the time of maximal LH concentration as day 0.

Published data (Catt et al., 1968; Midgley and Jaffe, 1968; Abraham et al., 1972). Serum levels of LH from six women were fairly constant through the cycle, except at midcycle, when a sharp surge occurred. LH concentration during the follicular phase was 25.9 mIU/ml. During the late follicular phase LH level started to rise rapidly reaching a peak value of 147.5 mIU/ml. Serum FSH concentration rose after the initial menses and maintained a slight decrease during the late follicular phase. The peak level of FSH occurred at the same day as the midcycle surge of LH occurred. The concentration of FSH at midcycle was 36.8 mIU/ml. Following the midcycle LH and FSH surge, levels of LH and FSH during the luteal phase were 22.0 mIU/ml and 11.6 mIU/ml respectively.

The patterns of plasma estradiol and prog...
Table 3. Plasma estradiol and progesterone concentrations (mean±S.E.) in six women at different stages of the normal menstrual cycles

<table>
<thead>
<tr>
<th>Hormones</th>
<th>Phases of the menstrual cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Follicular</td>
</tr>
<tr>
<td>Estradiol (pg/ml)</td>
<td>99.4±11.0</td>
</tr>
<tr>
<td>Progesterone (ng/ml)</td>
<td>2.1±0.2</td>
</tr>
</tbody>
</table>

**Fig. 2.** Plasma estradiol and progesterone concentrations obtained from a composite of the six individual menstrual cycles: Mean ±S.E. Plotted the time of maximal LH concentration as day 0.

**Fig. 3.** Serum prolactin concentration obtained from a composite of the six individual normal menstrual cycles: Mean±S.E. Plotted the time of maximal LH concentration as day 0.

Estradiol during the six normal cycles studied are depicted in Fig. 2 and Table 3. Plasma estradiol had a mean value of 99.4 pg/ml during the early follicular phase. From 4 day prior to the LH peak, plasma estradiol began to rise sharply, reaching the maximum of 354.3 pg/ml one day prior to the LH peak. The estradiol peak occurred one day prior to the LH surge in 5 subjects and on the day of LH surge in one subject. The peak levels ranged from 197.4-407.8 pg/ml. Immediately after the estradiol surge, a sharp drop occurred, reaching a level of approximately 90.0 pg/ml on day 2 post LH peak. Thereafter, estradiol rose slowly to a plateau at 235.9 pg/ml between day 5 and day 10 post LH peak. Following this, the estradiol level began to fall to reach the lowest level before the onset of menses. During the follicular phase, the progesterone level was 2.1 ng/ml. Prior to the midcycle surge of LH, progesterone started to increase gradually being followed by a plateau on day 7 to day 9 post LH peak. Afterward, a sharp decline occurred to reach the lowest level on the first day of menses.

Average curve of serum prolactin concentration during the menstrual cycle (Fig.3) was obtained after plotting day zero being the day...
of the LH peak. Serum prolactin levels fluctuated throughout the menstrual cycle. There was no peak value of prolactin concomitant to the LH peak. During the follicular phase the mean level of prolactin was 12.5 ng/ml (Table 2). The mean value during the luteal phase was slightly higher than the mean value during the follicular phase but the difference is not statistically significant.

The cycle studied in subjects 7 and 8 (Table 1) was of a type called "short luteal phase". It is not settled whether ovulation occurred in such a cycle or whether this pattern is associated with luteinization of atretic follicles without ovulation. In both subjects, LH and FSH reached serum levels in the range seen during the normal midcycle surge. LH surge coincided with a peak of estradiol. Plasma progesterone levels were below normal luteal phase levels and the luteal phase lasted only 7 and 5 days respectively.

**DISCUSSION**

This study reports for the first time simultaneous measurement of FSH, LH, prolactin, estradiol and progesterone during the same menstrual cycles in Korean women.

The patterns of serum FSH and LH concentrations during the menstrual cycle found in the present study are, qualitatively and quantitatively, remarkably similar to those reported previously (Vande Wiele, 1970; Miggley and Jaffe, 1971; Abraham et al., 1972). During the late follicular phase, the rise of plasma estradiol level is accompanied by a decrease in FSH level and a small but steady increase in basal LH secretion. This divergence in the secretion of FSH and LH is probably related to 1) a preferential inhibitory action of estradiol on FSH release (Yen and Tsai, 1971) and 2) an increase in "inhibin" secretion by mature follicles with selective inhibition of FSH secretion (De Jong and Sharpe, 1976). Progesterone levels show no significant change prior to the midcycle surge although one study has reported a small rise on the day before (Laborde et al., 1976).

During the midcycle there is a surge in serum LH level which leads to the final maturation of the graafian follicles and follicular rupture 16 to 24 hours after LH peak. Although there is a general agreement on the presence of a single midcycle peak in LH levels during the menstrual cycle, French-mont (1966) has observed a proliferative peak as well. Our data confirmed the presence of a single midcycle peak in serum LH. There is a simultaneous peak in FSH level during the midcycle but physiologic significance of the FSH peak has not been understood. A possible role for the FSH peak might be to augment the ovulatory effect of LH. It is well recognized that the effects of FSH and LH are synergistic in many respects. Furthermore, from works in a number of animal species, it remains unclear as to what the "ovulatory hormone" really is.

In all the normal cycles studied, estradiol was elevated just prior to and/or on the day of the midcycle peak of gonadotropins. Odell and Swerdloff (1966) have suggested that in women an ovarian signal may trigger the ovulatory surge of gonadotropins. A positive correlation between concentrations in serum LH and estradiol during the normal cycle was reported by several investigators (Korenman and Sherman, 1973; Baird and Franser, 1974). They noted that the concentration of estradiol in plasma starts to rise at least 8 day before the LH peak (Baird and Franser, 1974) reaching a maximum within
48 hours prior to the LH peak, most commonly within 24 hours (Korenman and Sherman, 1973) and suggested that a certain critical concentration of estradiol may be necessary to induce the midcycle release of LH from the pituitary. Vande Wiele et al. (1970) also found that plasma estradiol reached a peak level prior to or on the day of the LH peak. They designed a mathematical model to explain the relationship between plasma estradiol and the midcycle surge of gonadotropins.

The finding by Odell et al. (1967) of lower LH levels in the luteal phase compared to proliferative levels was also observed in the present study although Faiman and Ryan (1967) and Midgley and Jaffe (1968) failed to show any difference. The reason for this discrepancy is not apparent. The serum FSH was maintained at a lower concentration during the luteal phase than during the follicular phase. The most remarkable feature of the luteal phase of the menstrual cycle is a marked increase in progesterone output reaching a maximum during the midluteal phase. There is a parallel but smaller increase in estradiol levels. As progesterone and estradiol increase, serum level of FSH and LH decrease throughout the most of the luteal phase but FSH begins to rise at the end of the luteal phase to initiate follicular growth for the next cycle.

Serum prolactin levels at various stages in the menstrual cycle have shown no consistent differences between the follicular and luteal phases in the present study. This result agrees well with previous findings (Friesen et al., 1972; Ehara et al., 1973; McNelly and Chard, 1974; Epstein et al., 1975). Robyn et al. (1977) and Vekemans et al. (1977), however, have reported a midcycle prolactin peak with continued high levels during the luteal phase. Further, prolactin release in response to TRH appeared to be greater during the luteal phase than during the midfollicular phase of the menstrual cycle (Boyd and Sanchez-Franco, 1977). The absence of striking changes in prolactin concentration during the menstrual cycle should not be taken as evidence that prolactin exerts no influence on ovarian function or that ovarian steroids fail to augment prolactin secretion.

Although the number of subjects in our study was small, it might be concluded that the circulating patterns of gonadotropins and ovarian steroids during the menstrual cycle in Korean women are, qualitatively and quantitatively, comparable to the previous findings from other countries.

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