Evidence for a specific role of GnRH pulse frequency in the control of the human menstrual cycle

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Evidence for a specific role of GnRH pulse frequency in the control of the human menstrual cycle. Am. J. Physiol. 257 (Endocrinol. Metab. 20): E930–E936, 1989.—An adequate frequency of gonadotropin-releasing hormone (GnRH) pulses appears to be important for physiological gonadotropin secretion. However, limited information exists on the exact role of this parameter in the regulation of the human menstrual cycle. Thus we studied gonadotropin and gonadal steroid secretion in 32 women with primary hypogonadotropic amenorrhea who received pulsatile GnRH (60 or 120 μg/day) at 60- or 120-min intervals for a total of 64 ovulation induction cycles. Ovulation was achieved in 94% of 60-min and in 70% of 120-min cycles (P < 0.05). In the follicular phase of ovulatory cycles, estradiol (E2) levels did not differ among the four groups; however, mean luteinizing hormone (LH) levels were lower (P < 0.006), and the midcycle LH surge was severely blunted in cycles of subjects receiving 120 μg/day (5 μg/bolus) GnRH every 120 min compared with subjects receiving the same dose of GnRH per day or per bolus every 60 min. Luteal progesterone (only in 60 μg/day GnRH cycles) and E2 levels were lower in 120-min than in 60-min cycles (P < 0.05). The use of the higher daily GnRH dose (120 μg/day) reduced or abolished the frequency-associated hormone level differences. We conclude that a low frequency of pulsatile GnRH in women 1) decreases mean LH levels and blunts the midcycle gonadotropin surge, 2) does not increase follicle-stimulating hormone concentrations, and 3) is associated with a reduced rate of ovulation.

PITUITARY GONADOTROPIN SECRETION is under the control of hypothalamic gonadotropin-releasing hormone (GnRH); a close correspondence exists between endogenous pulsatile GnRH secretion and the episodic pattern of luteinizing hormone (LH) measurable in the peripheral circulation (2, 17). The frequency and amplitude of GnRH-induced LH peaks change dynamically across the normal menstrual cycle (9, 21). Alterations of the pulsatile pattern of LH secretion are present in most patients with hypogonadotropic anovulation (20), thus suggesting that a derangement of endogenous pulsatile GnRH secretion is an important pathogenetic mechanism in this disorder.

Several investigators have studied the effect of changing the frequency of pulsatile GnRH on pituitary gonadotropin secretion in castrated (1, 18) and noncastrated (10, 12, 26) male models. However, the dynamic properties of the menstrual cycle require a longer observation than in males as the endocrine events of one part of the cycle (e.g., the early follicular phase) may impact on a later stage, (e.g., the luteal phase). Only one previous study has examined the effect of pulsatile GnRH frequency in hypothyroidism-lesioned nongonadectomized female monkeys across one or more menstrual cycles (19). No published study in humans has so far addressed the issue of the role of pulsatile GnRH frequency in regulating the hormonal dynamics of the human menstrual cycle. Thus, in women with profound hypogonadotropic hypogonadism, we elected to investigate the effect of different frequencies of pulsatile GnRH administration on gonadotropin secretion, the midcycle surge, ovulation, and corpus luteum function.

METHODS

Patient Population

We studied 32 women, 18–38 yr old, with primary hypogonadotropic amenorrhea. All patients had normal growth hormone (GH) and cortisol response to an insulin tolerance test and normal prolactin (PRL) and thyrotropin (TSH) response to a thyrotropin-releasing hormone test. Base-line serum levels of TSH, thyroid-stimulating hormone (TSH) response to a thyrotropin-releasing hormone test. Base-line serum levels of TSH, 3,5,3′-triiodothyronine, thyroxine, PRL, GH, cortisol, testosterone, androstenedione, dehydroepiandrosterone sulfate were normal. Serum levels of LH (2.5 ± 0.3 IU/l), follicle-stimulating hormone (FSH) (3.0 ± 0.6 IU/l), estradiol (E2, 9 ± 2 pg/ml; 30 ± 10 pmol/l), and progesterone (P, 0.7 ± 0.1 ng/ml; 2 ± 1 nmol/l) were low. Episodic LH secretion was estimated with blood samples drawn at 10-min intervals for 12 consecutive hours (23). Twenty-nine out of 32 patients were apulsatil, whereas in three subjects only a single low-amplitude LH peak could be identified over the entire 12-h period. The gonadotropin response to a single bolus of exogenous GnRH (100 μg) was markedly reduced or absent; however, all patients showed increments of gonadotropin and


**TABLE 1. Pulsatile GnRH regimens**

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of Cycles</th>
<th>Pulse Interval, min</th>
<th>GnRH Dose per Bolus, μg</th>
<th>GnRH Dose per Day, μg</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>15</td>
<td>60</td>
<td>2.5</td>
<td>60</td>
</tr>
<tr>
<td>B</td>
<td>19</td>
<td>60</td>
<td>5.0</td>
<td>120</td>
</tr>
<tr>
<td>C</td>
<td>14</td>
<td>120</td>
<td>5.0</td>
<td>60</td>
</tr>
<tr>
<td>D</td>
<td>16</td>
<td>120</td>
<td>10.0</td>
<td>120</td>
</tr>
</tbody>
</table>

Regimens of pulsatile GnRH administration in 64 cycles of 32 primary amenorrhea patients treated in this study.

E₂ levels when later submitted to low-dose pulsatile GnRH administration, thus indicating normal pituitary function. None of the patients had taken hormonal medications for at least 3 mo preceding the study. Pelvic ultrasound showed reduced uterine (5.9 ± 0.1 cm longitudinal diameter) and ovarian (4.5 ± 0.4 cm³ volume) size. Informed consent was obtained from each subject before participation in this study.

**Protocol**

Pulsatile GnRH (Lutrelief, Ferring, Kiel, FRG) was infused intravenously in all patients using the Zyklomat (Ferring) pump. The dose and frequency of pulsatile GnRH administration was never changed within the same cycle, and treatment was continued until menstruation appeared or β-human chorionic gonadotropin became detectable or for at least 30 days if ovulation did not occur. As shown in Table 1, GnRH doses per bolus (2.5–10.0 μg) and intervals (60–120 min) were combined to obtain two daily GnRH dosages (60 or 120 μg/day).

Four different treatment groups (A–D) resulted, each comprising at least 14 treatment cycles. Thus we were able to investigate the impact of two different frequencies (every 60 or 120 min) while keeping the GnRH dose per day or per bolus (5 μg) constant and to assess the effect of two different daily dosages of GnRH. Each of 32 patients completed at least one pulsatile GnRH cycle (12 completed 1 cycle, 11 completed 2, 6 completed 3, and 3 completed 4 cycles). Patients were assigned to groups randomly, and each time a patient repeated a treatment cycle she received pulsatile GnRH at a different frequency and/or dose, thus rotating between study groups. When cycles were repeated in the same patient, a treatment-free period of at least 2 mo was observed, and data from each cycle were analyzed independently, as previous studies have shown that within 60 days after the removal of the GnRH stimulus, pituitary gonadotroph function reverts to a quiescent state (4).

During treatment, single daily blood samples were drawn ~55 min after a GnRH bolus for the determination of serum LH, FSH, E₂, and P. Pelvic ultrasonography was done at 1- to 4-day intervals during the follicular phase (FP) of all cycles for the measurement of follicle number and size. The day of the midcycle preovulatory surge (day 0) was defined by the concomitant occurrence of serum LH and FSH peaks and a sudden rise of serum P levels above 0.6 ng/ml (14). Ovulation was said to occur when luteal phase (LP) levels rose above 3 ng/ml for at least 1 day after the midcycle surge. Hormone data from anovulatory cycles were not used for mathematical and statistical evaluation; furthermore, when pregnancy occurred, hormone levels measured on or after day +6 of the LP were eliminated. When we calculated mean hormone levels across the FP and the LP, the hormone concentrations measured on the day of the midcycle surge (day 0) were not considered.

Statistical significance between means was assessed with nonparametric methods (Mann-Whitney U test). The Fisher-Yates test (11) was used to verify significance in the different ovulatory rates found in each group. Results are given as the means ± SE.

**Hormone Assays**

Serum LH and FSH were measured in duplicate by radioimmunoassay (RIA) using reagents purchased from Ares Serono (Milan, Italy). Gonadotropin concentrations were expressed as international units per liter of the second international reference preparation of human menopausal gonadotropins. Serum E₂ and P levels were measured by RIA after extraction with diethyl ether and petroleum ether, respectively. All samples from each cycle were analyzed in the same assay.

The precision of the gonadotropin assays was determined by analyzing 5–10 replicates in each assay at each of three displacement levels (20, 50, and 80% B/B). The intra-assay coefficients of variation (CVs) of these quality control samples were 3.8% (20% displacement), 4.3% (50%), and 5.5% (80%) for LH and 3.9% (20%), 4.0% (50%), and 6.6% (80%) for FSH. The interassay CVs were 8.6% (20%), 10.8% (50%), and 17.4% (80%) for LH and 17.6% (20%), 12.3% (50%), and 16.1% (80%) for FSH. In the steroid assays, a single level of quality controls (4–6 replicates) was analyzed. The intra-assay CVs were 5.0% and 5.2% for E₂ and P, respectively; the interassay CVs were 18.8 and 14.7% for E₂ and P, respectively.

**RESULTS**

**Clinical and Ultrasound**

No serious side effects and no clinical signs of ovarian hyperstimulation were reported in any of the 64 cycles. No significant septic complications (high temperature) from the intravenous delivery system were seen, and only occasionally the intravenous catheter had to be changed due to local tenderness. The ovulatory rate (Table 2) was significantly lower in group C (57%) than in group A (100%; P < 0.01) or in group B (89%; P < 0.05); further...
The physiological role of GnRH pulse frequency

### Table 3. Hormonal results

<table>
<thead>
<tr>
<th>Group</th>
<th>LH, IU/l</th>
<th>FSH, IU/l</th>
<th>E2, pg/ml (pmol/l)</th>
<th>LH, IU/l</th>
<th>FSH, IU/l</th>
<th>E2, pg/ml (pmol/l)</th>
<th>P, ng/ml (nmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>14.1±2.0</td>
<td>8.2±0.5</td>
<td>114±26 (420±100)</td>
<td>8.7±1.0</td>
<td>4.4±0.4</td>
<td>145±11 (530±60)</td>
<td>9.7±1.4</td>
</tr>
<tr>
<td>B</td>
<td>14.2±1.3</td>
<td>6.8±0.6</td>
<td>107±25 (390±90)</td>
<td>8.9±1.1</td>
<td>3.8±0.4</td>
<td>173±14* (630±50)</td>
<td>12.2±1.8</td>
</tr>
<tr>
<td>C</td>
<td>8.1±0.4†</td>
<td>6.2±0.6*</td>
<td>105±21 (390±80)</td>
<td>5.0±0.4†</td>
<td>3.9±0.4</td>
<td>93±6† (340±30)</td>
<td>6.3±1.1†</td>
</tr>
<tr>
<td>D</td>
<td>12.8±1.1‡</td>
<td>7.0±0.5</td>
<td>88±19 (320±70)</td>
<td>6.3±0.8‡</td>
<td>4.6±0.4</td>
<td>80±8‡ (390±30)</td>
<td>11.0±2.0‡</td>
</tr>
</tbody>
</table>

Mean ± SE hormone concentrations in follicular (FP) and luteal phase (LP) and LH levels on day 0 of midcycle surge in 64 cycles of 32 primary amenorrhea patients treated with various doses and frequencies of pulsatile GnRH (see Table 1). * P < 0.05 or less vs. same parameter of group A; † P < 0.05 or less vs. same parameter of group B; ‡ P < 0.05 or less vs. same parameter of group C. LH, luteinizing hormone; FSH, follicle-stimulating hormone; E2, estradiol; P, progesterone.

**FIG. 1.** Daily gonadotropin and gonadal steroid levels (mean ± SE) in primary hypogonadotropic amenorrhea patients receiving 60 μg/day GnRH at 60-min intervals (group A, closed circles) or 120-min intervals (group C, open circles). P, progesterone; E2, estradiol; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

**FIG. 2.** Daily gonadotropin and gonadal steroid levels (mean ± SE) in primary hypogonadotropic amenorrhea patients receiving 5 μg of GnRH per bolus at 60-min intervals (group B, closed circles) or 120-min intervals (group C, open circles). See legend to Fig. 1 for abbreviations.

Moreover, the overall ovulatory rate of the groups receiving pulsatile GnRH every 60 min (groups A and B; 94%) was significantly higher than the overall ovulatory rate of the groups receiving pulsatile GnRH every 120 min (groups C and D; 70%; P < 0.05). A total of 14 singleton pregnancies resulted, 5, 3, 4, and 2 in groups A–D, respectively. The duration of the ovulatory nonpregnancy cycles and of FP and LP in each group is shown in Table 2. In addition, when results from groups A and B were pooled and compared with the ones of groups C and D, together, we found that patients receiving pulsatile GnRH at 60-min intervals (groups A and B), had a shorter duration of their induced menstrual cycle (28.3 ± 0.7 vs. 31.1 ± 0.9 days, P < 0.005) and of the FP (13.4 ± 0.6 vs. 17.7 ± 0.8 days, P < 0.0001), whereas the LP was longer (18.1 ± 0.3 vs. 13.3 ± 0.4, P < 0.005) than in

**Hormone Levels (Table 3)**

**FP.** In the FP of ovulatory cycles, mean LH levels were significantly lower in group C (8.1 ± 0.4 IU/l) than in groups A (14.1 ± 2.0 IU/l; P < 0.005; Fig. 1), B (14.2 ± 1.3 IU/l; P < 0.001; Fig. 2), or D (12.8 ± 1.1 IU/l; P < 0.05). Serum FSH concentrations were higher in group A (8.2 ± 0.5 IU/l) than in group C (6.2 ± 0.6 IU/l; P < 0.005). No significant difference in the mean E2 levels...
across the FP was found between any of the treatment groups.

The day-to-day variations of hormone levels in the early FP of ovulatory cycles were also examined (Fig. 3). In the first 7 days of pulsatile GnRH administration, no difference was found in FSH or E₂ levels between any of the groups. However, by the third day of treatment LH levels were already higher in groups A (12.1 ± 1.8 IU/l; P < 0.05) and B (13.3 ± 1.1 IU/l; P < 0.05) than in group C (7.4 ± 0.9 IU/l); this difference further increased in the remaining days of the early FP (Fig. 3). No differences were found in the early FP levels of LH between groups B and D (Fig. 3).

Midcycle surge. The day-to-day variations in hormone levels during the midcycle surge of ovulatory cycles are shown in Fig. 4. No significant difference was found in FSH, E₆, or P concentration between any of the groups. On day 0 LH levels were lower in group C (26.4 ± 7.2 IU/l) than in group A (78.7 ± 12.7 IU/l; P < 0.01), B (69.0 ± 8.9 IU/l; P < 0.001), or D (57.9 ± 12.2 IU/l; P < 0.01). Further statistical analysis of the periovulatory period (days -3 to +3; Fig. 4) showed that LH levels were higher in group A than in group C (60 μg/day groups) between days -3 and +1 and in group B than in group H in group C (5-μg/bolus groups) between days -3 and +3; LH was also greater in group B than in group D (120-μg/day groups) between days +1 and +3.

The remarkable difference in the midcycle LH surge patterns between the 60-min and 120-min frequency of GnRH administration is exemplified in Fig. 5, which shows the same subject who received 60 μg GnRH/day as either 2.5 μg every 60 min or 5.0 μg every 120 min (the 2 cycles were separated by a 7-mo treatment-free period). Although FP, FSH, and E₂ levels were almost superimposable, the 120-min cycle lacked a clear midcycle LH surge and resulted in suboptimal luteal P secretion.
than in pulsatile GnRH to 32 women with primary hypogonadotropic amenorrhea. Most of these patients (29 out of 32) were characterized by an apulsatile pattern of LH secretion; in three subjects only a single LH peak was detectable over an entire 12-h period of frequent blood sampling (every 10 min). This pattern, together with intact pituitary function, indicated a virtually absent endogenous GnRH activity; thus, this human model is comparable to animals with pituitary disconnection (3, 26) or hypothalamic lesions (18, 19, 25), and interference from endogenous GnRH can be discounted.

The regimen of GnRH administration we chose (Table 1) permitted us to test the effect of two different intervals of delivery (60 or 120 min) in subjects receiving either the same GnRH dose per day or per bolus (5 μg); we were also able to assess the effect of two different dose levels (60 or 120 μg/day) of pulsatile GnRH delivery. We chose the lower GnRH dosages (2.5–5.0 μg/bolus) to fall within the physiological range previously assessed by Santoro et al. (22). The 60-min frequency was selected based on the normal LH pulse frequency in the mid and late follicular phase of the human menstrual cycle (9, 21), whereas the 120-min interval approximates the LH pulse frequency of hypothalamic amenorrhea described by Reame et al. (20).

The LH levels in the FP (Table 3) were lower in subjects receiving 60 μg/day of GnRH (5 μg/bolus) every 120 min (group C) than in subjects treated with the same dose of GnRH per day (group A; Fig. 1) or per bolus (group B; Fig. 2) every 60 min. This difference in LH levels could be appreciated within 3 days from the initiation of pulsatile GnRH administration (Fig. 3). No difference in LH levels was present between the 60-min and the 120-min cycles when the GnRH dose/day was increased to 120 μg (Fig. 3), thus suggesting that a greater GnRH dose per day or per bolus can at least partly compensate the frequency-related effects on LH secretion. On the other hand, mean E2 concentrations in the FP (Table 3) were not significantly different between any of the groups, thus indicating that the differences in LH levels we found were not dependent on estrogen modulation at the pituitary level.

It was previously shown that slower pulsatile GnRH frequencies result in higher amplitude LH peaks (4, 10, 18) but lower or stable mean LH levels in male (10, 12, 24, 26) and female (4) hypogonadotropic models. Pohl et al. (19) also found lower LII levels in hypothalamic-lesioned rhesus monkeys when the frequency of GnRH administration (6 μg/bolus) was slowed from every 1 h to every 2 or 3 h. However, the results of this study may have been influenced by the reduction of total daily GnRH dose achieved when a constant GnRH dose per bolus was administered at progressively slower frequencies. Pulsatile GnRH frequency is a critical parameter for adequate pituitary GnRH receptor synthesis (15). Furthermore, Haisenleder et al. (13) recently demonstrated that excessively fast or slow GnRH pulses reduce the gonadotroph mRNA levels for LH, whereas more physiological GnRH frequencies result in optimal mRNA production. In these latter studies (13, 15), the GnRH dose per bolus was adjusted to frequency as in the present report to achieve the same dose per day; this maneuver did not eliminate frequency-induced differences, thus confirming a dose-independent effect of GnRH pulse frequency on the message for LH synthesis. Taken together, these data suggest that although increasing the GnRH interpulse interval causes the release of larger amplitude LH peaks (possibly due to LH accumulation in gonadotrophs), overall LH synthesis may be negatively affected by a slow pattern of GnRH stimulation.

The early FP concentrations of FSH did not differ between the four groups of idiopathic hypogonadotropic hypogonadism (IHH) patients (Fig. 3). Furthermore, the only significant difference throughout the entire FP was lower FSH levels in group C (60 μg/day, every 120 min) than in group A (60 μg/day, every 60 min). These findings contrast with the report of Wildt et al. (28) and others (4, 12) who noticed higher FSH concentrations associated with a slower frequency of GnRH administration. However, most of these studies (4, 25) were carried out in castrated animals; the same group (19) and others could not identify any variation of FSH levels related to frequency when pulsatile GnRH was administered to nongonadectomized (10, 24, 26) or steroid-replaced experimental models (1). A notable exception is represented by the study of Gross et al. (12), who obtained higher FSH levels with the administration of progressively slower GnRH pulse frequencies in males with IHH; this finding was not confirmed by the study of Finkenstein et al. (10) who, however, performed their study in IHH males after the achievement of normal testicular steroidogenesis. Furthermore, the duration of GnRH treatment required to achieve mature gametogenesis is much longer in male than female-IHH (a few weeks vs. several months), thus suggesting that these hypogonadotropic models may not be comparable. These results indicate that the selective FSH increment achieved at a slower frequency of pulsatile GnRH administration can be blocked by inhibin, steroids, or other gonadal factors and that this phenomenon does not occur in eugonadal subjects.

Pelvic ultrasound demonstrated the development of only one dominant follicle of normal size in the ovulatory cycles of all groups, thus confirming that the GnRH regimens we chose did not excessively stimulate the ovary. This finding contrasts with the report of Santoro et al. (22), who noticed the development of multiple follicles in several hypogonadotropic patients treated
with 100 ng/kg of GnRH at 60-min intervals. However, this study included patients with secondary amenorrhea, i.e., a less profound GnRH deficiency than primary hypogonadotropic amenorrhea. It is possible that residual endogenous GnRH secretion may have supplemented the effect of exogenous GnRH and stimulated a more active folliculogenesis.

A significantly lower incidence of ovulation was achieved in the 120-min cycles than in the 60-min cycles (94 vs. 70%; P < 0.05). Similar conclusions were reported by Pohl et al. (19); however, their finding of lower $E_2$ levels in the FP of monkeys receiving pulsatile GnRH at 2- or 3-h intervals suggests that the lack of the midcycle LH surge and anovulation in their model may be related to inadequate pituitary priming by estrogens rather than a specific effect of GnRH pulse frequency on LH synthesis.

Particularly remarkable was the difference in the dynamics of the midcycle LH surge in the ovulatory cycles of our subjects (Fig. 4). Despite superimposable follicular and periovulatory $E_2$ and $P$ concentrations (see also Figs. 1 and 2), LH levels at midcycle were significantly lower in IHH patients receiving 60 $\mu$g/day (5 $\mu$g/bolus) GnRHI every 120 min (group C) compared with the groups receiving the same dose of GnRH per day (group A) or per bolus (group B) every 60 min. A representative example of the effect of pulsatile GnRH frequency on the dynamics of the menstrual cycle is depicted in Fig. 5, which shows the same IHH patient who underwent two treatment cycles at different regimens. Despite a higher GnRH dose per bolus (5.0 vs. 2.5 $\mu$g), and comparable FP $E_2$ levels, the 120-min cycle was characterized by a blunted midcycle LH surge and reduced luteal $P$ concentrations. Endogenous GnRH levels and pulse frequency may be more elevated at midcycle (5), and increments of the frequency of pulsatile LH secretion have been reported during the preovulatory surge in normal women (7). Nevertheless, ovulation can be achieved administering a constant dose and frequency of GnRH across the menstrual cycle of hypothalamic-lesioned female monkeys (16) and of IHH women (6); thus, an increased amount of GnRH stimulation may be facilitatory but is not indispensable for the midcycle LH surge. On the other hand, an appropriately frequent pulsatile GnRH stimulation may be essential to stimulate adequate LH synthesis in the follicular phase (13, 15) so that the pituitary is fully primed and ready to release the massive amounts of LH required for the physiologic preovulatory surge (14).

Mean LH and $E_2$ levels in the luteal phase were lower in the 120-min cycles than in the 60-min cycles (Table 3). Furthermore, $P$ concentrations were significantly reduced in IHH patients receiving 60 $\mu$g/day (5 $\mu$g/bolus) of GnRH at 120-min intervals (Figs. 1 and 2). The finding of reduced corpus luteum steroid secretion associated with the slower frequency regimens was unexpected, considering the physiologic deceleration of LH pulses encountered in the luteal phase of the normal menstrual cycle (8, 9). Our data may indicate that the less frequent and larger LH peaks typical of the LP of the normal menstrual cycle (8) are the result of both a slowing of GnRH pulse frequency (10) and of an increment of the magnitude of endogenous GnRH peaks; the finding of greater $P$ levels in our IHH patients receiving the highest GnRH dose per bolus (10 $\mu$g) every 120 min may support this hypothesis. On the other hand, it is possible that the blunted midcycle LH surge present in lower dose (60 $\mu$g/day) 120-min cycles may have induced follicular luteinization rather than ovulation, thus explaining partial corpus luteum inadequacy.

In conclusion, for the first time in humans we have demonstrated that frequency of pulsatile GnRH by itself can critically affect the midcycle LH surge and ovulation. These findings may be helpful to interpret some apparent discrepancies in the hormonal characteristics of clinical ovulatory disorders. Patients with secondary hypogonadotropic amenorrhea of hypothalamic origin usually present a slower pattern of pulsatile LH secretion (5, 20).

Despite mean gonadotropin levels often within the normal range, these patients do not appear to be able to achieve complete follicular maturation and ovulation. Our data suggest that a slowing of the endogenous GnRH LH pulse generator by blunting the midcycle LH surge may be a central pathogenetic mechanism of anovulation in this disorder.

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