The effects of inducing a follicular phase gonadotropin secretory pattern in normal women during the luteal phase

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It has been hypothesized that the slowing of the luteinizing hormone (LH) pulse frequency in the luteal phase may be necessary for the demise of the corpus luteum, the intercycle rise in baseline follicle-stimulating hormone (FSH), or ovarian follicular development in the subsequent cycle. For assessment of the physiologic role of the luteal phase LH pulse pattern, this pattern was converted to a follicular pattern in six normal women who used exogenous gonadotropin-releasing hormone administered with a portable pump (dose 50 to 100 ng/kg subcutaneously every 90 minutes beginning in the early luteal [n = 3] and midluteal [n = 3] cycle phases). There was no significant difference between the treated and the subsequent cycle for luteal progesterone production (186.3 versus 159.0 (ng/ml) day), preovulatory follicular size (23.1 versus 22.5 mm), estradiol levels, luteal phase length (15.6 versus 14.3 days), and daily gonadotropin concentrations including the intercycle FSH rise (160.5 versus 139.1 ng/ml). A follicular phase gonadotropin pulse pattern (increased frequency, decreased amplitude) in the luteal phase had no discernible effects on the corpus luteum or on follicular development in the subsequent cycle. Fertil Steril 47:900, 1986

The secretory pattern of gonadotropins changes dramatically over the course of the normal menstrual cycle. The follicular phase is characterized by a high-frequency, low-amplitude luteiniz-

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Recent experiments performed in female rhesus macaques suggest that changes in GnRH pulse frequency can affect changes in the plasma ratio of FSH to LH. In these experiments, castrated monkeys were rendered deficient in the production of endogenous GnRH by placement of discrete lesions in the vicinity of the arcuate nucleus and then supported on various regimens of exogenous GnRH. In this work it was observed that a slow frequency of GnRH pulses produced a selective increase in plasma FSH levels. In light of the selective increase in plasma FSH levels in the luteal phase (the intercycle FSH rise) that occurs at the same time as or just after a slowing of LH pulse frequency, the decreasing frequency of GnRH pulses during this time could be responsible for mediating the observed selective FSH increase.

In women, the primary target organ of gonadotropin secretion is the ovary. It has been generally accepted that LH is necessary to support adequate progesterone (P) secretion from the corpus luteum, although a controversy over this point continues. Whether the secretion pattern of LH (low-frequency, high-amplitude) during the luteal phase affects corpus luteum function has not been specifically addressed. Ovarian follicular development is also under the control of circulating gonadotropins, notably FSH. It appears that normal corpus luteum function depends on adequate preovulatory follicular development. However, the role of the intercycle rise in FSH as a determinant of ovarian folliculogenesis remains controversial.

After consideration of all these findings, we hypothesized that the luteal gonadotropin secretion pattern did not quantitatively determine, but only permitted P secretion from the corpus lut
teum. We further hypothesized that the change (slowing) in the gonadotropin secretion pattern in the luteal phase was responsible for the late luteal (LL) rise in baseline FSH, follicular recruitment and development in the ensuing cycle, and ultimately corpus luteum function (P secretion) in the next cycle. As a test of these hypotheses, a high-frequency, low-amplitude (follicular) gonadotropin pattern was induced with exogenous GnRH in the luteal phase of normal women. We monitored the effect of this treatment on daily hormone levels—LH, FSH, estradiol (E2), P, and prolactin (PRL)—and ovarian folliculogenesis throughout both the treated menstrual cycle and the subsequent cycle.

**MATERIALS AND METHODS**

**SUBJECTS**

The study subjects (Table 1) were six normal women, 24 to 34 years of age, who were within ±10% of ideal body weight (Metropolitan Life Tables 1980). They had achieved menarche at a normal age, had regular menstrual cycles, were taking no medications, had normal medical histories and physical examinations, and had biphasic basal body temperature (BBT) charts.

**CONTROLS**

The normal group for comparison of gonadotropin secretion and daily hormone concentrations were five women aged 18 to 35 years who met the same criteria as the subjects in this study. These normal women were described previously.

**Table 1. Subjects and Protocol**

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Age</th>
<th>Height/Weight</th>
<th>IBW*</th>
<th>Mean cycle length/luteal length</th>
<th>GnRH (dose, route)</th>
<th>GnRH duration</th>
<th>Cycle 1 cycle days omitted</th>
<th>days in relation to LH surge</th>
</tr>
</thead>
<tbody>
<tr>
<td>EL group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>25</td>
<td>163/56.8</td>
<td>95.4</td>
<td>30/15</td>
<td>75 SC</td>
<td>+2 to +15</td>
<td>+2, +10</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>28</td>
<td>168/57.3</td>
<td>92.0</td>
<td>28/15</td>
<td>100 SC</td>
<td>+3 to +15</td>
<td>+3, +8</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>32</td>
<td>170/62.7</td>
<td>98.6</td>
<td>27/17</td>
<td>75 SC</td>
<td>+5 to +15</td>
<td>+5, +11</td>
<td></td>
</tr>
<tr>
<td>ML group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>34</td>
<td>168/56.8</td>
<td>91.2</td>
<td>31/15</td>
<td>75 SC</td>
<td>+10 to +16</td>
<td>+10, +14</td>
<td>-20, +14</td>
</tr>
<tr>
<td>E</td>
<td>24</td>
<td>175/65.9</td>
<td>99.3</td>
<td>26/14</td>
<td>50 IV</td>
<td>+9 to +15</td>
<td>+9, +14</td>
<td>-19, +15</td>
</tr>
<tr>
<td>F</td>
<td>25</td>
<td>163/54.6</td>
<td>92.7</td>
<td>27/14</td>
<td>50 SC</td>
<td>+9 to +17</td>
<td>+9, +15</td>
<td></td>
</tr>
</tbody>
</table>

*Ideal body weight; 1980 revised Metropolitan Life Tables.

**SC, subcutaneous.

**IV, intravenous.
PRL concentrations were determined by a double-antibody RIA, with the use of an NIADDK (National Institute of Arthritis, Diabetes, Digestive and Kidney Disease) human PRL kit (RP-1 standard, hPRL-3 anti-PRL serum). The intra assay coefficient of variation, determined by analysis of replicate variability in the assay samples, was 6.5%. The inter assay coefficient of variation was 18.4%.

The RIA for plasma $E_2$ was performed with methodology described previously. The sensitivity of the $E_2$ assay was 12 pg/ml; intra assay and inter assay coefficients of variation were 8.2% and 8.8%, respectively.

$P$ was measured with reagents supplied by Diagnostic Products Corporation, Los Angeles, CA. Cross-reactivity data supplied by the producer indicated < 2.4% cross-reaction with all steroids tested, including 0.3% with 17-hydroxyprogesterone and < 0.01% with testosterone, $E_2$, pregnenolone, and cortisol. Sensitivity in our laboratory was 0.5 ng/ml. Intra assay variability was 9%, and inter assay variability was 12%. External quality control used the World Health Organization program, which involves monthly measurements of unknown samples; no significant bias (> 10%) was detected, and variabilities were comparable with those described for internal quality controls.

Bioactive plasma LH levels were measured in a single assay as previously described with a modification of procedures described by Van Damme et al. and Dufau et al. The mean inter assay coefficient of variation was 7%.

PULSE DETECTION

Pulsatile LH patterns were analyzed through a modification of the Santen and Bardin method. For each sampling series, measurement error was assessed on the basis of assay replicate variability. A "pulse" was defined as an increase from nadir to peak that was two standard deviations greater than the assay variability.

STATISTICS

Daily gonadotropin concentrations in cycle 1 were compared with those in cycle 2 for each treatment group by analysis of variance. The same method was used to compare the daily gonadotropins of each treatment group with those of the untreated (control) group as well.

Comparisons of $E_2$ secretion in the follicular phase and $P$ secretion in the luteal phase were made between cycles 1 and 2 of each treatment group by paired $t$-tests of the integrated areas under the respective secretion curves [integrated $E_2$ area expressed as (pg/ml) day, and integrated $P$ area expressed as (ng/ml) day]. The same method was used to compare the steroid secretion of the cycles of the treated women with those of the untreated controls.

Comparisons of the cycle length (days), luteal phase length (days), and mean ovarian follicular diameter for a given cycle day (mm) were made between cycles, treatment groups, and controls by Student's $t$-test. The LH pulse parameters (frequency, amplitude, mean level) of treated and control groups were likewise compared by Student's $t$-test.

The change in FSH secretion in the LL phase between cycles 1 and 2 for the treated subjects and between the treatment and control groups was determined by subtraction of the FSH concentration on cycle day −6 preceding the next menstrual period from the FSH concentration on the first day of the subsequent menstrual period. The differences were compared by Student's $t$-test for the various groups.

RESULTS

LH SECRETION

The endogenous and induced LH secretion pattern for two representative subjects is presented in Figure 1. These women had an exaggerated LH response when GnRH was initially administered. The induced LH secretory pattern was more uniform 4 to 6 days later when the women were admitted in the ML or LL phases.

The endogenous LH secretion pattern in the EL phase (subjects A through C sampled for 6 hours) and the ML phase (subjects D through F sampled for 12 hours) was determined before introduction of GnRH therapy (Table 2). For comparison the endogenous LH secretory parameters were extrapolated to 24 hours. The LH secretory parameters of the ML group and the previously described ML normal women were not different. No endogenous LH pulses were detected in patient F during 12 hours of sampling (Table 2). In light of the infrequent occurrence of LH pulses in the ML phase (mean = 4.4/24 hr), the absence of pulses for 12 hours is within the normal range.
PROTOCOL

The study encompassed two complete menstrual cycles. Daily venous blood samples were obtained from the participants over two cycles, and the following hormone concentrations were determined: E$_2$, P, PRL, LH, and FSH. During exogenous GnRH therapy the daily blood samples were taken between GnRH pulses. Pelvic ultrasonography was begun on menstrual cycle day 10 in both cycles and continued at a daily interval until apparent ovulation had occurred. During each pelvic sonogram attention was focused on the ovary with the largest (dominant) follicle; measurements were taken in three planes, and a mean diameter was calculated $[(a + b + c)/3]$. Ovulation was presumed to have occurred within the daily interval bracketed by two sonograms when two or more of the following changes were demonstrated: acute decrease in follicular size, the appearance of internal echoes, a thickening of the follicular membrane, and an acute increase in the quantity of peritoneal fluid. For pelvic-ovarian ultrasonography, one of several real-time sector scanners was used, each having both 3 and 5 MHz transducers.

On attaining presumptive ovulation in the first study cycle, the subjects were subdivided into two treatment groups: early luteal (EL) (subjects A through C) and midluteal (ML) (subjects D through F). The EL group began GnRH therapy within 2 to 4 days of presumptive ovulation, whereas the ML group began within 6 to 8 days. The EL and ML phases were considered to be $+ 3$ to $+ 6$ and $+ 7$ to $+ 10$ days, respectively, after the LH surge. Although the subjects each began GnRH therapy within one of these phases, they did not each begin treatment on the same day after the surge in consideration of scheduling limitations regarding their research center admission. GnRH (Factrel, Ayerst Pharmaceuticals, New York, NY) was administered at a dose of 50 to 100 ng/kg by means of an intermittent (pulsatile) infusion pump (Autosyringe Pump model A6H, Autosyringe Division, Travenol Laboratories, Hooksett, NH). The dose and frequency of GnRH administration was chosen to mimic the LH pulse pattern normally found in the EF phase of the cycle. The GnRH dose was varied somewhat among the volunteers in an attempt to induce an LH pulse amplitude similar to a follicular phase pulse amplitude in each subject. The GnRH was administered over 4 seconds every 90 minutes to all subjects, by a subcutaneous route in five subjects and by an intravenous route in one of the ML volunteers (subject E). Intravenous GnRH was administered to one subject in an attempt to ascertain whether the route of administration would change the pattern of response. GnRH therapy was continued in each volunteer until the first day of her next menstrual cycle. The dose and duration of GnRH therapy (calculated from the peak of the LH surge) for each subject is presented in Table 1.

Each volunteer experienced two hospital admissions (total duration, 36 hours) during the luteal phase of her first study cycle. Over the duration of each admission, venous blood samples were obtained from the subjects every 20 minutes through an indwelling intravenous line while they remained at bed rest. The LH and PRL concentrations were determined in these samples by radioimmunoassay (RIA) followed by analysis for pulsatile secretion. Selected samples encompassing several LH pulses were analyzed for LH biologic activity in two of the volunteers. For each treatment group the first admission occurred on the day that GnRH pump therapy was instituted, with therapy commencing halfway into the sampling interval. The second admission occurred during ongoing GnRH therapy for each subject. For the EL treatment group the two hospital admissions occurred in the EL and ML cycle phases; for the ML group the two admissions occurred in the ML and LL cycle phases. The exact cycle days of each admission for each subject are given in Table 1.

With the onset of the next menstrual cycle (cycle 2), the GnRH therapy was stopped, and there were no further admissions. During the second cycle the subjects kept temperature charts, had daily blood samples, and had pelvic ultrasonograms from cycle day 10 until presumptive ovulation. The study was complete for each volunteer with the onset of her third menstrual cycle.

RADIOIMMUNOASSAYS

Blood samples were analyzed for LH and FSH by double-antibody RIA. Standard National Institutes of Health reagents were used, including the LER-907 reference preparation. The sensitivity of the LH assay was 6 ng/ml; intraassay and interassay variability were 5.5% and 8.4%, respectively. The sensitivity of the FSH assay was 25 ng/ml; intraassay and interassay variability were 7.3% and 9.7%, respectively.
The LH secretory pattern induced by GnRH during the luteal phase was a good approximation of the normal EF pattern and was different from the normal ML pattern. For comparison the induced LH secretory parameters were from the second admission only. For all LH secretory parameters (frequency, amplitude, mean level) the induced pattern was not significantly different from the normal EF pattern ($P = 0.5$). However, when the induced pattern was compared with the normal ML pattern, the LH pulse frequency (13.5 $\pm$ 0.9 versus 4.4 $\pm$ 0.7 pulses/24 hrs, $P \leq 0.0001$) and mean LH levels (26.2 $\pm$ 2.1 versus 15.0 $\pm$ 4.2 ng/ml, $P \approx 0.05$) were significantly different (Table 2). These were the same differences noted when the normal EF phase was compared with the normal ML phase.\(^2\) In two subjects undergoing GnRH treatment, segments of LH pulsatile activity, as determined by RIA, were selected and measured in the LH bioassay. There was one-for-one correspondence of the induced LH secretory activity as measured on both assays (Fig. 2).

The daily (morning) serum concentrations of LH and FSH were measured throughout both menstrual cycles studied (Fig. 3). There was no significant difference in the pattern or absolute levels of the baseline gonadotropins between ei-

Table 2. Endogenous and Induced LH Secretion

<table>
<thead>
<tr>
<th></th>
<th>LH pulse frequency</th>
<th>LH mean amplitude</th>
<th>Mean LH</th>
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<tbody>
<tr>
<td></td>
<td>pulses/24 hr</td>
<td>ng/ml</td>
<td>ng/ml</td>
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<tr>
<td>Endogenous (luteal)</td>
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</tr>
<tr>
<td>EL group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>8</td>
<td>27.9</td>
<td>30.8</td>
</tr>
<tr>
<td>B</td>
<td>8</td>
<td>49.3</td>
<td>47.6</td>
</tr>
<tr>
<td>C</td>
<td>8</td>
<td>16.0</td>
<td>18.5</td>
</tr>
<tr>
<td>Mean ± SEM</td>
<td>8.0 ± 0.0</td>
<td>31.1 ± 9.8</td>
<td>32.3 ± 8.4</td>
</tr>
<tr>
<td>ML group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>6</td>
<td>12.8</td>
<td>10.9</td>
</tr>
<tr>
<td>E</td>
<td>4</td>
<td>28.4</td>
<td>9.6</td>
</tr>
<tr>
<td>F</td>
<td>0</td>
<td>—</td>
<td>5.7</td>
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<tr>
<td>Mean ± SEM</td>
<td>3.3 ± 1.8</td>
<td>20.6 ± 7.8</td>
<td>8.7 ± 1.6</td>
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<td>Induced GnRH treatment after 4-8 days</td>
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<td>A</td>
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<td>9.0</td>
<td>20.5</td>
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<tr>
<td>B</td>
<td>12</td>
<td>14.0</td>
<td>31.6</td>
</tr>
<tr>
<td>C</td>
<td>15</td>
<td>11.3</td>
<td>19.4</td>
</tr>
<tr>
<td>Mean ± SEM</td>
<td>13.7 ± 0.9</td>
<td>11.4 ± 1.4</td>
<td>23.8 ± 3.9</td>
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<tr>
<td>ML group</td>
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<td>F</td>
<td>10</td>
<td>13.3</td>
<td>25.3</td>
</tr>
<tr>
<td>Mean ± SEM</td>
<td>13.3 ± 1.8</td>
<td>17.7 ± 2.2</td>
<td>26.6 ± 1.4</td>
</tr>
</tbody>
</table>

Normal (n = 5) (Mean ± SEM)

| EF         | 14.4 ± 1.0         | 15.0 ± 2.4        | 32.8 ± 8.2 |
| ML         | 4.4 ± 0.7          | 24.7 ± 6.6        | 15.0 ± 4.2 |

\(^*SEM,\) standard error of the mean.

Figure 2
The temporal relationship (1/1) between GnRH-induced LH pulses as measured by the LH RIA (---) and LH bioassay (○-○) for selected sampling segments for two subjects is illustrated. LH-RH, luteinizing hormone-releasing hormone.

Soules et al. Rapid LH/FSH secretion in luteal phase
next cycle between treatment and control groups and between cycles 1 (84.0 ng/ml) and 2 (60.9 ng/ml) \( (P = 0.15) \).

**PRL Secretion**

There were no changes observed in daily serum PRL levels during GnRH therapy or differences in daily PRL concentrations between cycles 1 and 2 (data not shown).

**Follicle Diameter**

The daily mean diameter of the dominant ovarian follicle as imaged by ultrasound was determined. The follicle data were organized so that follicle day 0 was the day before sonographic detection of ovulation (Fig. 4). Ovulation, according to ultrasound criteria, was determined to have occurred between the peak day of the LH surge and the following day in all cycles. There was no difference in preovulatory follicular diameter between cycles 1 and 2 for both treatment groups. The mean follicular diameter on day 0 was 23.1 ± 0.55 for all subjects in cycle 1 and 22.5 ± 0.73 in cycle 2 \( (P = 0.36) \).

**E₂ Secretion**

There were no differences in \( E₂ \) secretion, as determined by integrated area under the curve across the entire cycle, between cycles 1 [5382.8 (pg/ml) day] and 2 [4389.3 (pg/ml) day] \( (P = 0.12) \) or between these cycles and in those in the controls.

Figure 3
The mean daily serum concentrations of LH, FSH, \( E₂ \), and \( P \) for normal women \((n = 5)\) (○—○) and women receiving luteal GnRH therapy \((n = 6)\) (■—■) are illustrated. Two complete menstrual cycles of data are presented, with days of menstrual flow indicated by Xs. LH-RH, luteinizing hormone-releasing hormone.

Figure 4
The mean diameters of the dominant ovarian follicle for study cycles one and two for all six subjects are illustrated. The luteal phase of cycle one was treated with GnRH. Ovulation occurred between days -1 and 0.
P secretion during treatment (cycle 1) and in
the ensuing cycle (cycle 2) appeared normal (Fig.
3). For both the EL and ML treatment groups
there was no difference in the integrated P secre-
tion in the luteal phase when cycle 1 and cycle 2
were compared with those in controls. There
appeared to be a slight decrease in luteal P secretion
in cycle 2 [150.0 (ng/ml) day] versus cycle 1
[186.3 (ng/ml) day], but this apparent difference
was not significant (P = 0.07).

None of the women who participated in this
study had abnormal vaginal bleeding or acute or
chronic changes in their menstrual cycle pat-
terns. The subjects' BBT charts during the study
were unchanged from previous temperature
charts. There was no difference in the length of
their luteal phase (from the LH surge to the day
before the onset of the next menstrual period)
between cycle 1 (15.6 days) and cycle 2 (14.3 days)
(P = 0.36). The response of patient E, who re-
ceived intravenous GnRH, was not discernibly
different from responses of subjects who received
subcutaneous GnRH.

DISCUSSION

Imposition of a follicular phase (high-frequen-
cy, low-amplitude) LH secretory pattern (that
was indistinguishable from the EF pattern previ-
ously described in normal women) was success-
fully superimposed during the luteal phase in nor-
mal ovulatory women. P has been demonstrated
to be the cause of the well-described changes in
endogenous gonadotropin secretion observed in
the luteal phase. The brain is the apparent site
for this negative feedback effect of P in that this
suppression was circumvented with exogenous
GnRH during this study. These induced pulses
were capable of inducing biologic activity as evi-
denced by the results of the LH bioassay. The
duration of this superimposed pattern was ap-
proximately 1 week in one-half of the subjects
(ML to end of cycle) and 2 weeks (EL to end of
cycle) in the other half. Despite this pronounced
change in gonadotropin secretion, no discernible
effects in daily gonadotropin levels, P concentra-
tions, or the LL rise in serum FSH were noted
during treatment. Likewise, in the menstrual cy-
cle that immediately followed the luteal treat-
ment, no significant changes were demonstrated
in follicular development (follicle size, E2 levels),
gonadotropin levels, or luteal P concentrations.

There is compelling evidence in a nonhuman
primate model that the frequency of GnRH pulsa-
tion is the principal determinant of baseline go-
adotropin concentrations. An increased GnRH
pulse rate has been associated with an increase in
serum LH and a decrease in serum FSH levels; an
opposite effect on baseline gonadotropin levels
was noted with a decreased GnRH pulse frequen-
cy. It has been postulated that the slow LH pulse
rate in the luteal phase was the cause of the in-
tercycle rise in serum FSH. The current study
does not support this theory, because a faster LH
pulse rate had no discernible effect on the intercy-
cle FSH rise. The control of the intercycle FSH
rise remains to be determined. The release of
the negative feedback effects of P does not appear
to be the sole determinant, because extended P
treatment beyond the normal luteal phase length
did not prevent an FSH rise. Inhibin does not
appear to be a critical factor: minimal inhibin
activity has been reported to be present in the
luteal phase. Estrogen is known to suppress
FSH secretion readily. The decline in serum E2 in
the LL phase alone or in combination with P may
be a principal determinant of the intercycle rise
in serum FSH. The description of the GnRH-asso-
ciated peptide (GAP) has implications for the
differential control of LH and FSH. In rat pitu-
itary cell cultures GAP is a more potent stimu-
tor of FSH than LH secretion. Unidentified
factors may be determinants of the intercycle
FSH rise as well.

Previous studies offer evidence that imposition
of a more rapid (follicular) rate of gonadotropin
secretion in the luteal phase may not be detri-
mental to corpus luteum function or subsequent
folliculogenesis. In studies conducted in rhesus
macaques by Knobil, normal ovulatory men-
strual cycles could be restored in hypothalamic-
lesioned animals maintained with an hourly
GnRH pulse. This intermittent GnRH regimen
was maintained constantly throughout several
consecutive menstrual cycles, in each of which
normal luteal serum P concentrations were
achieved, which suggested that a slowing of
GnRH pulse frequency is not an essential feature
for sustaining normal luteal function. Female
macaques, like women, exhibit a pronounced
slowing of LH pulse frequency during their nor-
mal luteal phase.

Clinical experience in ovulation induction with
intermittent GnRH administration by a portable
infusion pump adds some additional information.
Several reports\textsuperscript{20,21} have noted normal luteal phase length, normal luteal P levels, normal pregnancies when ovulation was induced with GnRH administered every 90 to 120 minutes throughout the cycle, including the luteal phase. A subgroup of these patients who received luteal GnRH therapy were reported as having inadequate P production, but most appeared to have adequate luteal phase function as assessed by clinical criteria. The study by Skarin et al.\textsuperscript{20} noted normal luteal function when GnRH therapy was administered over several consecutive cycles. The monitoring of luteal phase P secretion in these clinical studies was not intensive.

However, some controversy attending this issue remains. Ferin and colleagues\textsuperscript{22} noted prolonged intervals (135 to 190 days) until ovulatory cycles were restored in rhesus monkeys treated with GnRH. These cycling monkeys received hourly doses of GnRH throughout a luteal phase after a spontaneous ovulation. The dose of GnRH used to treat these intact monkeys was less than the dose used by Knobil\textsuperscript{18} to support animals with hypothalamic lesions. A study by Collins et al.\textsuperscript{23} examined the effects of treating normally cycling monkeys (\textit{Macaca fascicularis}) with moderately high doses of GnRH (18 \( \mu \)g every 3 hours) beginning on cycle day 20 until the onset of the next menstrual period. There were increases in serum levels of LH and P in these monkeys, but the luteal phase was not prolonged. The ovulating status of the animals after this study was apparently not examined. This study demonstrated that luteal phase GnRH treatment in supraphysiologic doses can augment P secretion by the corpus luteum. A detrimental effect on the primate corpus luteum has been demonstrated when the GnRH pulse frequency was slowed to one pulse/24 hrs in rhesus macaques with hypothalamic lesions.\textsuperscript{24} Therefore, the corpus luteum is capable of recognizing a variation in luteal phase LH secretion.

The findings from the current study would indicate that a relatively rapid LH secretion pattern in the luteal phase has no effect on pituitary or ovarian function. Although this may be true, the study's design might have prevented the discovery of some real differences. Studies that use human volunteers and employ intensive protocols usually involve a relatively small number of subjects. The small number of subjects (\( n = 6 \)) in this study may have been insufficient to uncover any subtle differences that may have been present. For instance, the integrated serum P in cycle 2 was lower than in cycle 1 and approached statistical significance (\( P = 0.07 \)). Another aspect of study design was that the gonadotropin pulses were induced with subcutaneously administered GnRH in five of the six subjects. Intravenously administered GnRH appears to approximate the characteristics of endogenous pulses more closely.\textsuperscript{25} However, the SC route induced a discrete LH pulse pattern very similar to the normal follicular phase (Fig. 1). Furthermore, no difference in any of the measured variables was noted in the intravenously treated volunteer. That only one luteal phase, as opposed to luteal phases in several consecutive cycles, was treated may also have been a reason that no effects were found.

There has been a general physiologic presumption that the luteal decline in gonadotropin pulsation was a signal from the pituitary to the ovary that was necessary to maintain normal ovulation and menstrual cyclicity. The results of this study demand that this presumption be questioned. The physiologic significance, if any, of the relatively slow luteal gonadotropin pulse pattern remains to be elucidated.

REFERENCES


24. Hutchinson JS, Zeleznik AJ: Effects of varying gonadotropin pulse frequency on corpus luteum function and lifespan during the menstrual cycle of rhesus monkeys. Presented at the 67th Annual Meeting of The Endocrine Society, Baltimore, Maryland, June 19-21, 1985 (Abstr 613)