FERTILITY AND STERILITY
Vol. 47, No. 1, January 1987

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

Michael R. Soules, M.D.†‡
Robert A. Steiner, Ph.D.†§‖
Donald K. Clifton, Ph.D.†
William J. Bremner, M.D., Ph.D.¶**

University of Washington and Veterans Administration Medical Center, Seattle, Washington

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 47:000, 1986

The secretory pattern of gonadotropins changes dramatically over the course of the normal menstrual cycle.[1, 2] The follicular phase is characterized by a high-frequency, low-amplitude luteinizing hormone (LH) pulse pattern, whereas the luteal phase is characterized by a relatively low-frequency, high-amplitude LH pulse pattern. These gonadotropin pulse patterns appear to be directed by changes in the frequency and amplitude of pulsatile gonadotropin-releasing hormone (GnRH) secretion together with changes in pituitary responsiveness to GnRH.[3, 4]

Baseline plasma gonadotropin levels, as assessed by measurement of levels in single daily blood samples, also display marked changes over the course of the menstrual cycle. For example, at the end of the luteal phase, plasma follicle-stimulating hormone (FSH) levels increase, remaining elevated well into the early follicular (EF) phase of the next cycle, whereas during the same period, baseline plasma LH levels remain relatively unchanged.

Received February 17, 1986; revised and accepted July 17, 1986.

*Supported by National Institutes of Health grants R01 HD 18967-02 and P50 HD 12629-07; by University of Washington Clinical Research Center National Institutes of Health grant RR-37.

†Department of Obstetrics and Gynecology, University of Washington.

‡Reprint requests: Michael R. Soules, M.D., Department of Obstetrics and Gynecology, RH-20, University of Washington, Seattle, Washington 98195.

§Department of Physiology and Biophysics, University of Washington.

‖Department of Zoology, University of Washington.

¶Department of Medicine, University of Washington.

**Veterans Administration Medical Center.

Recent experiments performed in female rhesus macaques suggest that changes in GnRH pulse frequency can effect changes in the plasma ratio of FSH to LH.[5] 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,[6, 7] although a controversy over this point continues.[8] 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.[9]

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 luteum. 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 (E_2), 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.[2]

Table 1. *Subjects and Protocol*

Subjects	Age	Height/ Weight	IBW[a]	Mean cycle length/luteal length	GnRH (dose, route)	GnRH duration	Cycle 1 cycle days omitted
	yr	*cm/kg*	*%*	*days*	*ng/kg*	*days in relation to LH surge*	
EL group							
A	25	163/56.8	95.4	30/15	75 SC[b]	+2 to +15	+2, +10
B	28	168/57.3	92.0	28/15	100 SC	+3 to +15	+3, +8
C	32	170/62.7	98.6	27/17	75 SC	+5 to +15	+5, +11
ML group							
D	34	168/56.8	91.2	31/15	75 SC	+10 to +18	+10, +14
E	24	175/65.9	99.3	26/14	50 IV[c]	+9 to +15	+9, +14
F	25	163/54.6	92.7	27/14	100 SC	+9 to +17	+9, +15

[a]Ideal body weight; 1980 revised Metropolitan Life Tables.
[b]SC, subcutaneous.
[c]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 intraassay coefficient of variation, determined by analysis of replicate variability in the assay samples, was 6.5%. The interassay coefficient of variation was 18.4%.

The RIA for plasma E_2 was performed with methodology described previously.[12] The sensitivity of the E_2 assay was 12 pg/ml; intraassay and interassay 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. Intraassay variability was 9%, and interassay 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.[13] The mean interassay coefficient of variation was 7%.

PULSE DETECTION

Pulsatile LH patterns were analyzed through a modification of the Santen and Bardin method.[14] 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.[2] 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 ultrasounds 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.[10, 11] 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.

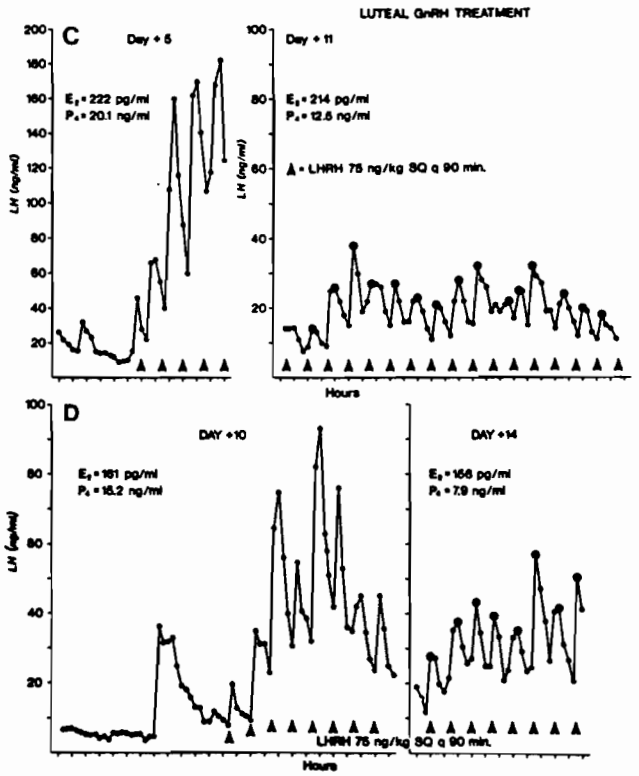

Figure 1
The endogenous EL LH secretory pattern of subject C on cycle day +5 from the LH surge is presented at the top of the graph. Pulsatile GnRH therapy commenced halfway through the day +5 sampling period. Continued GnRH therapy is illustrated on day +11 (ML). The endogenous ML LH secretory pattern of subject D on cycle day +10 is presented at the bottom of the graph. Pulsatile GnRH therapy commenced halfway through the day +10 sampling period. Continued GnRH therapy is illustrated on day +14 (LL). Larger-dot LH values indicate that a pulse was detected. LH-RH, luteinizing hormone-releasing hormone.

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 ± 0.9 versus 4.4 ± 0.7 pulses/24 hrs, $P \leq 0.0001$) and mean LH levels (26.2 ± 2.1 versus 15.0 ± 4.2 ng/ml, $P \leq 0.05$) 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

Table 2. *Endogenous and Induced LH Secretion*

		LH pulse frequency	LH mean amplitude	Mean LH
		pulses/24 hr	*ng/ml*	*ng/ml*
Endogenous (luteal)				
EL group	A	8	27.9	30.8
	B	8	49.3	47.6
	C	8	16.0	18.6
	Mean ± SEM[a]	8.0 ± 0.0	31.1 ± 9.8	32.3 ± 8.4
ML group	D	6	12.8	10.9
	E	4	28.4	9.6
	F	0	—	5.7
	Mean ± SEM	3.3 ± 1.8	20.6 ± 7.8	8.7 ± 1.6
Induced GnRH treatment after 4-8 days				
EL group	A	14	9.0	20.5
	B	12	14.0	31.6
	C	15	11.3	19.4
	Mean ± SEM	13.7 ± 0.9	11.4 ± 1.4	23.8 ± 3.9
ML group	D	16	20.2	30.6
	E	14	19.6	25.9
	F	10	13.3	29.3
	Mean ± SEM	13.3 ± 1.8	17.7 ± 2.2	28.6 ± 1.4
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

[a]SEM, standard error of the mean.

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-

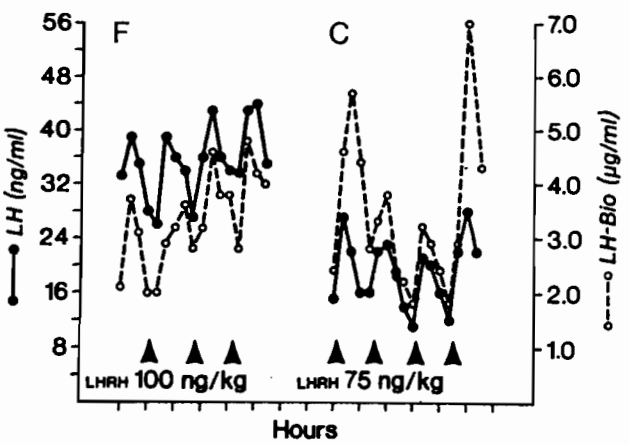

Figure 2
The temporal relationship (1/1) between GnRH-induced LH pulses as measured by the LH RIA (●—●) and LH bioassay (○—○) for selected sampling segments for two subjects is illustrated. LH-RH, luteinizing hormone-releasing hormone.

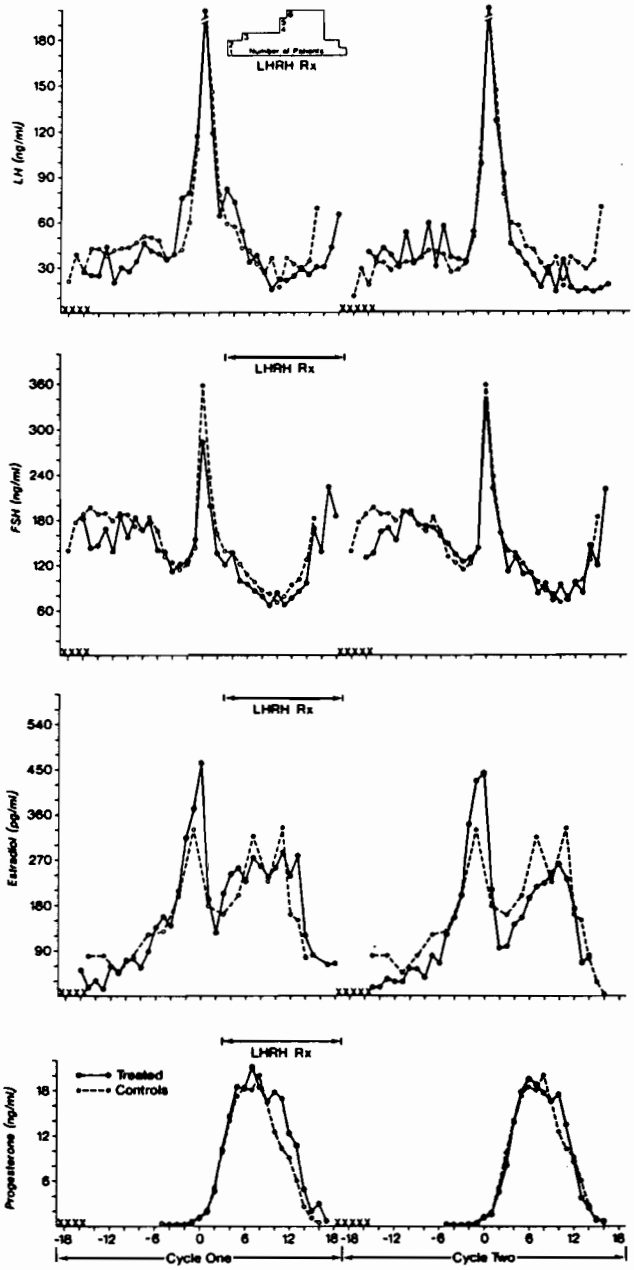

Figure 3
The mean daily serum concentrations of LH, FSH, E_2, and P for normal women (n = 5) (○—○) and women receiving luteal GnRH therapy (n = 6) (●—●) are illustrated. Two complete menstrual cycles of data are presented, with days of menstrual flow indicated by Xs. LH-RH, luteinizing hormone-releasing hormone.

ther the treatment and nontreatment cycles or between the treatment cycle and the untreated control women. The normal decline in daily FSH in the late follicular phase and the FSH rise in the LL phase were present in all cycles. There was no significant difference in the incremental change in FSH from the ML phase to day 1 of the 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).

E_2 SECRETION

There were no differences in E_2 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.

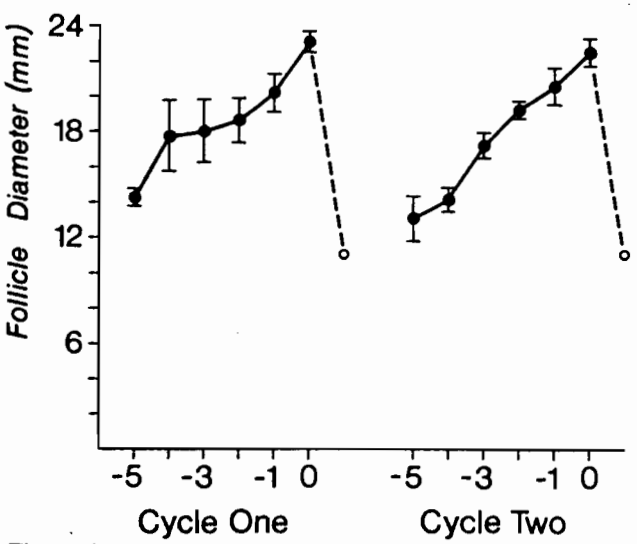

Figure 4
The mean diameters of the dominant ovarian follicle for study cycles one and two for all six subjects are illustrated. The luteal phase of cycle one was treated with GnRH. Ovulation occurred between days −1 and 0.

P SECRETION

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 secretion 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 [159.0 (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 patterns. 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 received intravenous GnRH, was not discernibly different from responses of subjects who received subcutaneous GnRH.

DISCUSSION

Imposition of a follicular phase (high-frequency, low-amplitude) LH secretory pattern (that was indistinguishable from the EF pattern previously described in normal women) was successfully superimposed during the luteal phase in normal ovulatory women. P has been demonstrated to be the cause of the well-described changes in endogenous gonadotropin secretion observed in the luteal phase.[2] 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 evidenced by the results of the LH bioassay. The duration of this superimposed pattern was approximately 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 concentrations, or the LL rise in serum FSH were noted during treatment. Likewise, in the menstrual cycle that immediately followed the luteal treatment, no significant changes were demonstrated in follicular development (follicle size, E_2 levels), gonadotropin levels, or luteal P concentrations.

There is compelling evidence in a nonhuman primate model that the frequency of GnRH pulsation is the principal determinant of baseline gonadotropin concentrations.[5] 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 frequency. It has been postulated that the slow LH pulse rate in the luteal phase was the cause of the intercycle rise in serum FSH. The current study does not support this theory, because a faster LH pulse rate had no discernible effect on the intercycle 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.[15] Inhibin does not appear to be a critical factor: minimal inhibin activity has been reported to be present in the luteal phase.[16] Estrogen is known to suppress FSH secretion readily. The decline in serum E_2 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-associated peptide (GAP) has implications for the differential control of LH and FSH.[17] In rat pituitary cell cultures GAP is a more potent stimulator 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 detrimental to corpus luteum function or subsequent folliculogenesis. In studies conducted in rhesus macaques by Knobil,[18] normal ovulatory menstrual 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 normal luteal phase.[19]

Clinical experience in ovulation induction with intermittent GnRH administration by a portable infusion pump adds some additional information.

Several reports[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.[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[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[18] to support animals with hypothalamic lesions. A study by Collins et al.[23] examined the effects of treating normally cycling monkeys (*Macaca fascicularis*) with moderately high doses of GnRH (18 μg 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.[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.[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

1. Midgley AR Jr, Jaffe RB: Regulation of human gonadotropins. X. Episodic fluctuation of LH during the menstrual cycle. J Clin Endocrinol Metab 33:962, 1971
2. Soules MR, Steiner RA, Clifton DK, Cohen NL, Aksel S, Bremner WJ: Progesterone modulation of pulsatile luteinizing hormone secretion in normal women. J Clin Endocrinol Metab 58:378, 1984
3. Carmel PW, Araki S, Ferin M: Pituitary stalk portal blood collection in rhesus monkeys: evidence for pulsatile release of GnRH. Endocrinology 99:243, 1976
4. Wang CF, Lasley BL, Lein A, Yen SSC: The functional changes of the pituitary gonadotrophs during the menstrual cycle. J Clin Endocrinol Metab 42:718, 1976
5. Wildt L, Hausler A, Marshall G, Hutchison JS, Plant TM, Belchetz PE, Knobil E: Frequency and amplitude of gonadotropin-releasing hormone stimulation and gonadotropin secretion in the rhesus monkey. Endocrinology 109: 376, 1981
6. Groff TR, Madhwa Raj HG, Talbert LM, Willis DL: Effects of neutralization of luteinizing hormone on corpus luteum function and cyclicity in Macaca fascicularis. J Clin Endocrinol Metab 59:1054, 1984
7. Fraser HM, Baird DT, McRae GI, Nestor JJ, Vickery BH: Suppression of luteal progesterone secretion in the stumptailed macaque by an antagonist analogue of luteinizing hormone releasing hormone. J Endocrinol 104:R1, 1985
8. Asch RH, Abou-Samra M, Braunstein GD, Pauerstein CJ: Luteal function in hypophysectomized rhesus monkeys. J Clin Endocrinol Metab 55:154, 1982

9. diZerega GS, Nixon WE, Hodgen GD: Intercycle serum follicle-stimulating hormone elevations: significance in recruitment and selection of the dominant follicle and assessment of corpus luteum normalcy. J Clin Endocrinol Metab 50:1046, 1980
10. Midgley AR: Radioimmunoassay: a method for human chorionic gonadotropin and human luteinizing hormone. Endocrinology 79:10, 1966
11. Bremner WJ, Matsumoto AM, Sussman A, Paulsen CA: Follicle-stimulating hormone and human spermatogenesis. J Clin Invest 68:1044, 1981
12. Matsumoto AM, Paulsen CA, Hopper BR, Rebar RW, Bremner WJ: Human chorionic gonadotropin and testicular function: stimulation of testosterone, testosterone precursors, and sperm production despite high estradiol levels. J Clin Endocrinol Metab 56:720, 1983
13. Steiner RA, Peterson AP, Yu JYL, Conner H, Gilbert M, terPenning B, Bremner WJ: Ultradian luteinizing hormone and testosterone rhythms in the adult male monkey, Macaca fascicularis. Endocrinology 107:1489, 1980
14. Santen RJ, Bardin CW: Episodic luteinizing hormone secretion in man. J Clin Invest 52:2617, 1973
15. Resko JA, Norman RL, Niswender GD, Spies HG: The relationship between progestins and gonadotropins during the late luteal phase of the menstrual cycle in rhesus monkeys. Endocrinology 94:28, 1974
16. Chappel SC, Holt JA, Spies HG: Inhibin: differences in bioactivity within human follicular fluid in the follicular and luteal stages of the menstrual cycle. Proc Soc Exp Biol Med 163:310, 1980
17. Nikolics K, Mason AJ, Szonyi E, Ramachandran J, Seeburg PH: A prolactin-inhibiting factor within the precursor for human gonadotropin-releasing hormone. Nature 316:511, 1985
18. Knobil E: The neuroendocrine control of the menstrual cycle. Recent Prog Horm Res 36:53, 1980
19. Ellinwood WE, Norman RL, Spies HG: Changing frequency of pulsatile luteinizing hormone and progesterone secretion during the luteal phase of the menstrual cycle of rhesus monkeys. Biol Reprod 31:714, 1984
20. Skarin G, Nillius SJ, Wide L: Pulsatile low dose luteinizing hormone-releasing hormone treatment for induction of follicular maturation and ovulation in women with amenorrhoea. Acta Endocrinol (Copenh) 101:78, 1982
21. Liu JH, Durfee R, Muse K, Yen SSC: Induction of multiple ovulation by pulsatile administration of gonadotropin-releasing hormone. Fertil Steril 40:18, 1983
22. Ferin M, Van Vugt D, Wardlaw S: The hypothalamic control of the menstrual cycle and the role of endogenous opioid peptides. Recent Prog Horm Res 40:441, 1984
23. Collins RL, Sopelak VM, Williams RF, Hodgen GD: Pulsatile GnRH treatment in mid-luteal phase: timely luteolysis despite enhanced steroidogenesis. Submitted, 1985
24. Hutchison 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)
25. Handelsman DJ, Jansen RPS, Boylan LM, Spaliviero JA, Turtle JR: Pharmacokinetics of gonadotropin-releasing hormone: comparison of subcutaneous and intravenous routes. J Clin Endocrinol Metab 59:739, 1984