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The Corpus Luteum: Determinants of Progesterone Secretion in the Normal Menstrual Cycle

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Fourteen normal volunteers were studied during one menstrual cycle. Follicular development, the luteinizing hormone (LH) surge, and the relationship between LH and progesterone secretion in the luteal phase were studied to determine the factors that control corpus luteum function. Follicular development was assessed by measuring follicle size and daily estradiol (E2) levels; the LH surge was quantified by determining the area under the curve. Although there was a significant positive correlation between mean follicle diameter and E2, these same parameters did not correlate with postovulatory progesterone secretion; nor did the LH surge correlate with progesterone secretion. A decrease in LH pulse frequency occurred in moving from the follicular to the luteal phase. There was a trend toward an increase in the late luteal LH pulse frequency compared with the midluteal phase, but this was not significant. Progesterone was secreted in an intermittent (pulsatile) fashion in the midluteal and late luteal phases. The general decrease in progesterone in the latter days of the menstrual cycle appears to be due to a decrease in the progesterone pulse amplitude. A significant correlation between LH and progesterone was present when the data were "smoothed"; however, there was not a significant synchrony for LH and progesterone pulses for most of the subjects when the initial data were analyzed by objective criteria. Progesterone secretion in the luteal phase is quite complex and leads to highly variable serum levels of progesterone when samples are obtained at random from normal women. *(Obstet Gynecol 71:659, 1988)*

In primate species, the corpus luteum is the principal source of progesterone, and provides the essential hormone support for implantation and the maintenance of early pregnancy.[1] We examined the factors external to the corpus luteum that are putative determinants of corpus luteum function.

Normal luteal function appears to be dependent upon adequate follicular development. Inadequate preovulatory follicular development may be a common pathophysiologic mechanism for luteal phase deficiency (a controversial, yet widely recognized, abnormality of corpus luteum function).[2] Several studies have reported decreased gonadotropin concentrations

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Table 1. Normal Study Subjects

Subject	Age	Percent ideal body weight*	Menstrual cycle (luteal phase) length (d)	Daily follicular sonograms performed	24-hr frequent sampling admissions			
					Menstrual cycle day	Cycle day relative to LH surge	Cycle day relative to Next menstrual period	Cycle phase
A	33	100	30 (14)		24	+8	−7	ML
B	23	96	28 (14)		21	+7	−7	ML
C	31	90	31 (15)		25	+9	−7	ML
D	29	97	33 (14)		28	+9	−6	ML
E	25	107	36 (14)	X	32	+10	−5	ML
F	31	104	29 (13)	X	28	+12	−2	LL
G	23	100	27 (14)	X	25	+12	−3	LL
H	28	91	28 (14)	X	26	+12	−3	LL
I	31	90	28 (14)	X	27	+13	−2	LL
J	28	93	26 (12)	X	25	+11	−2	LL
K	33	92	27 (13)	X				
L	29	101	26 (12)	X				
M	23	99	28 (12)	X				
N	26	93	33 (14)	X				

LH = luteinizing hormone; ML = midluteal phase (cycle days 20–24, days +6 to +10 from LH surge); LL = late luteal phase (cycle days 25–28, days +11 to +14 from LH surge).

* Metropolitan Life Tables, 1980.

in the follicular phase in "normal" women who were found to have decreased luteal progesterone secretion.[3,4] Decreased preovulatory follicular size has been reported in women with luteal phase deficiency as well.[5] These studies support the argument that preovulatory follicular development, which is dependent on gonadotropin secretion, is a principal determinant of corpus luteum function.

Another possible external determinant of corpus luteum function in women could be the midcycle luteinizing hormone (LH) surge. It has been postulated that luteal phase deficiency could occur from an inadequate (eg, improperly timed or insufficient) LH surge.[2] However, spontaneous luteal phase deficiency secondary to an inadequate surge has not been reported.

The role of LH as a determinant of corpus luteum function after ovulation remains in question. A long-held concept (based on ovulation induction studies) considered a small quantity of luteal LH as necessary for normal corpus luteum function.[6] The report of normal progesterone levels after postovulatory hypophysectomy in monkeys concluded that gonadotropins, and more specifically LH, were not necessary for normal corpus luteum function.[7] However, more recent studies in nonhuman primates and women indicate that the corpus luteum requires at least a minimum amount of LH support for normal progesterone secretion.[8–10]

In consideration of these issues regarding corpus luteum function and progesterone secretion, we examined follicular development, the LH surge, and luteal gonadotropin levels in spontaneous menstrual cycles in normal women. We addressed specific questions regarding the control of corpus luteum function by extrinsic factors: 1) Does the degree of follicular development determine the quantity of progesterone secreted after ovulation? 2) Does the magnitude of the LH surge determine the quantity of progesterone secreted after ovulation? 3) Is there a relationship between LH and progesterone secretion in the luteal phase? Is progesterone secretion pulsatile and coupled with LH secretion?

Materials and Methods

Each normal volunteer was studied during the course of a complete menstrual cycle. To ascertain the determinants of corpus luteum function in question, all women had daily blood samples drawn and participated in one or more additional procedures—preovulatory ovarian sonography and/or frequent blood sampling in the luteal phase.

Fourteen normal women aged 23–33 years participated as volunteers in this study (Table 1). Each volunteer had a history of normal menstrual cycles and a biphasic basal body temperature (BBT) chart before entering the study. These women were within 10% of ideal body weight (Metropolitan Life Tables, 1980) and were taking no medications. Table 1 lists the level of participation of each volunteer in the various parts of the protocol.

A BBT chart was kept, and daily venous blood samples were obtained from each volunteer between 8 and 10 AM. These blood samples were analyzed for LH, follicle-stimulating hormone (FSH), progesterone, and estradiol (E2) by radioimmunoassay (RIA). Ten of the subjects had daily transabdominal sonograms of the ovaries to assess follicular size from cycle day 10, until two of the following three sonographic criteria for ovulation were observed: 1) an abrupt decrease in size or disappearance of a preovulatory-size follicle, 2) a hyperechoic border or increased echoes in a follicle-like structure, and 3) an acute increase in free intraperitoneal fluid. The sonograms were performed with mechanical real-time sector scanners, each having both 3- and 5-MHz transducers.

Eleven of the 14 women were also studied in the luteal phase of their menstrual cycle during a 24-hour admission to the Clinical Research Center, University of Washington. Five women were admitted in the midluteal phase and five in the late luteal phase (one additional volunteer started her menstrual period during the 24-hour sampling study). During each admission, blood samples were obtained every 20 minutes through a heparinized indwelling intravenous line. Serum was separated, frozen at −20C, and stored until analysis for LH, FSH, and progesterone.

Serum samples were analyzed for LH and FSH by double-antibody RIA.[11,12] Standard National Institutes of Health reagents were used, including the LER-907 reference preparation. The sensitivity of the LH assay was 6 ng/mL at a volume of 200 μL; intra- and interassay coefficients of variation were 5.5 and 8.4%, respectively. The sensitivity of the FSH assay was 25 ng/mL at a volume of 200 μL; intra- and interassay coefficients of variation were 7.3 and 9.7%, respectively.

The RIA for serum E2 was performed using previous methodology, as described.[13] The sensitivity of the E2 assay was 12 pg/mL at a serum volume of 150 μL; intra- and interassay coefficients of variation were 8.2 and 8.8%, respectively.

Serum progesterone was measured by RIA with reagents supplied by Diagnostic Products Corporation (Los Angeles, CA). Cross-reactivity data supplied by the producer indicated less than 2.4% cross-reaction with all steroids tested, including 0.3% with 17 alpha-OH progesterone and less than 0.01% with testosterone, E2, pregnenolone, and cortisol. Sensitivity in our laboratory was less than 0.5 ng/mL at a serum volume of 100 μL. Intra- and interassay coefficients of variation were 9 and 12%, respectively. External quality control used the World Health Organization program, which involves monthly measurements of unknown samples; no significant bias (greater than 10%) was detected, and variabilities were comparable to those described above for internal quality controls.

An adaptive-threshold method was used to determine the time and amplitude of hormone pulses.[14] A pulse was defined as an increase from local minimum to local maximum that was greater than a threshold value. The correct threshold was determined in an iterative manner.

The daily hormone data were arranged relative to the day of the midcycle LH peak (surge), which was designated as day 0. Integrated values for follicular E2 secretion were determined from days −6 to 0, and for luteal progesterone secretion from day 0 to the first day of the next menstrual period. These integrated values were calculated by multiplying the mean daily hormone concentration times the number of days for each individual. The integrated area under the LH surge was calculated by adding the three LH levels for days −1, 0, and +1 (day 0 = LH peak) for each individual. Correlation coefficients were calculated between the following pairs of data: integrated follicular E2 and mean follicle diameter, integrated follicular E2 and integrated luteal progesterone, integrated luteal progesterone and mean follicle diameter, and integrated luteal progesterone and LH surge area. Other statistical comparisons among groups were made by analysis of variance and Student's t tests. Pulse parameters (ie, frequency, amplitude, and mean levels) were compared between groups by Student's t tests.

A newly derived technique was used to analyze the LH and progesterone data for the occurrence of synchronous secretion (pulses). This technique, derived from Monte Carlo simulations,[15] takes into account the statistical probability of "simultaneous" pulses occurring by chance, dependent upon the number of observed pulses for each of the hormones. Simultaneity was considered present if a progesterone pulse fell within one data point of an LH pulse. This criterion was applied after shifting the entire set of progesterone data 40 minutes relative to the LH data.

After analyzing the data for simultaneous pulses, we further evaluated the correlation of LH and progesterone secretion by "smoothing" (averaging sets of three consecutive data points to obtain an hourly mean level) the 24-hour data to focus on up and down trends rather than specific pulses. More general changes (trends) could be identified with these hourly means. Cross-correlations were calculated by determining correlation coefficients with the set of progesterone data shifted relative to the LH data at one-hour intervals. (The shift of progesterone data that resulted in the best overall correlation with LH was one hour after the LH data points.)

A 24-hour cosine regression analysis was performed

Table 2. Luteal Phase: Luteinizing Hormone and Progesterone Secretory Parameters in Normal Women (24-Hour Frequent Sampling Admissions)

Cycle phase	Subject	LH pulses (no./24 hr)	LH pulse amplitude (ng/mL)	Mean LH (ng/mL)	P pulses (no./24 hr)	No. of P pulses within 20 min of an LH pulse	P pulse amplitude (ng/mL)	Mean P (ng/mL)	P range, 24 hr (ng/mL)	Variation in P over 24 hr (%)*
ML	A	7	12.9	10.0	12	4	6.9	23.9	14.6–33.2	79
	B	7	13.5	14.9	11	5	3.8	14.0	8.8–25.7	121
	C	5	42.8	30.7	5	4†	5.9	9.4	4.8–15.3	112
	D	4	26.4	12.9	9	3	3.8	10.5	5.0–14.7	92
	E	8	11.3	8.5	9	5	4.4	11.4	7.1–17.3	89
		6.2 ± 0.7	21.4 ± 6.0	15.4 ± 4.0	9.2 ± 1.2	4.2 ± 0.4	5.0 ± 0.6	13.8 ± 2.6	8.1–21.2	99
LL	F	8	5.8	8.5	1	1	0.2	0.5	0.2–0.9	140
	G	9	12.3	6.7	3	2	2.7	3.3	1.4–6.4	152
	H	13	7.4	14.7	11	8	1.1	4.6	2.2–9.1	150
	I	6	20.8	12.3	10	4	0.5	1.7	0.8–2.9	124
	J	7	23.7	13.8	5	4‡	1.9	3.7	1.6–6.2	124
		8.6 ± 1.2	14.0 ± 3.6	11.2 ± 1.6	6.0 ± 2.0	3.8 ± 1.2	1.3 ± 0.5†	2.8 ± 0.7†	1.2–5.1	138

LH = luteinizing hormone; P = progesterone; ML = midluteal phase; LL = late luteal phase.
* Calculated by subtracting the range minimum from the range maximum and dividing this difference by the 24-hour mean P value.
† $P \leq .01$.
‡ $P \leq .05$.

on hourly mean progesterone concentrations in each subject to investigate for possible circadian rhythms.[16]

Data are expressed in terms of mean ± standard error of the mean (SEM) unless otherwise indicated.

Results

One complete menstrual cycle was studied for each subject. The average cycle length was 29.3 ± 0.8 days. When the integrated E2 level in the late follicular phase for each subject was compared with the mean follicular diameter on the day before ovulation, there was a significant ($r = 0.65$, $P < .05$) correlation (Figure 1). This finding indicates that there is a positive correlation between follicle size and E2 secretion. However, when both of these parameters of follicular development were compared with integrated progesterone levels in the luteal phase, there was no correlation ($r = 0.27$ and $r = 0.004$, not significant; data not shown). Furthermore, there was no correlation between the area under the LH surge and integrated luteal progesterone secretion ($r = 0.30$, not significant; data not shown). These data indicate that the degree of follicular development and the height of the LH surge are not quantitative determinants of corpus luteum function in normal menstrual cycles.

Table 2 lists the secretory parameters for LH and

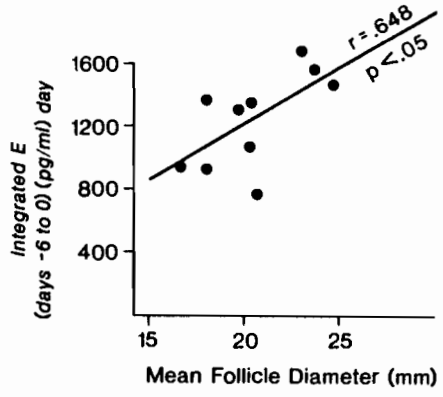

Figure 1. A significant correlation ($P < .05$) between integrated follicular estradiol (E) levels and mean follicle diameter is illustrated.

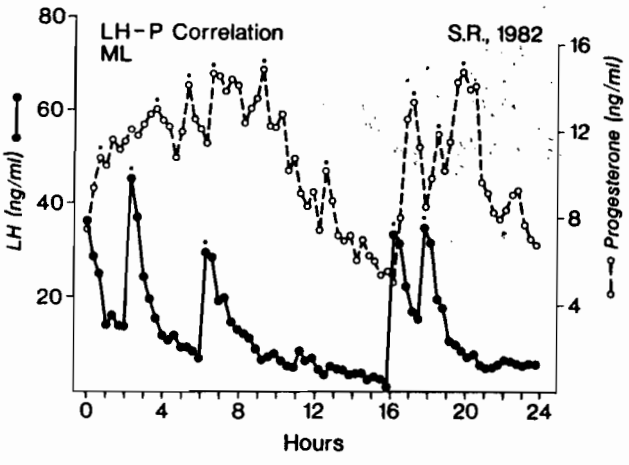

Figure 2. Simultaneous LH and progesterone (P) secretion patterns in the midluteal (ML) cycle phase in a normal woman. Shifts in data that were identified as pulses are indicated by asterisks for both LH and progesterone.

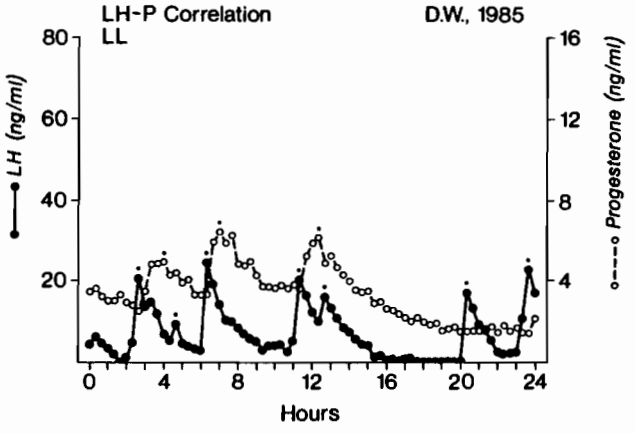

Figure 3. Simultaneous LH and progesterone (P) secretion patterns in the late luteal (LL) cycle phase in a normal woman. Shifts in data that were identified as pulses are indicated by asterisks for both LH and progesterone.

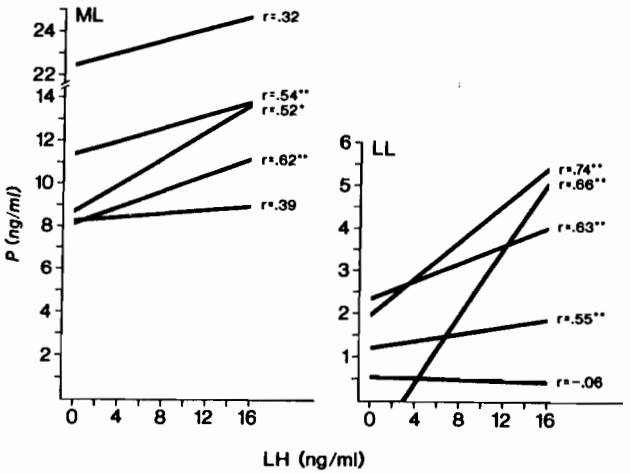

Figure 5. Cross-correlation values of LH and progesterone (P) secretion for five women each in the midluteal (ML) and late luteal (LL) phases. Twenty-four LH and progesterone data points were cross-correlated for each subject; the lines on the figure represent the best fit of these data points for each subject (* $P \leq .05$, ** $P \leq .01$).

progesterone in the midluteal and late luteal phases, respectively. Individual graphs of the LH and progesterone secretory pattern in the midluteal and late luteal phases in two different subjects are presented in Figures 2 and 3. The LH pulse frequency exhibited a tendency (not significant) to be slower, with an increase in LH pulse amplitude in the midluteal phase compared with the late luteal phase. There was a significant positive correlation ($P \leq .05$) in the midluteal phase between the duration of the interpulse interval and the amplitude of the ensuing LH pulse; this relationship was not present in the late luteal phase. The late luteal pattern of LH secretion appeared to continue into day 1 of the ensuing cycle which, by definition, was the early follicular phase (Figure 4). However, when LH pulse data from the early follicular phase were compared with the late luteal phase, the LH pulse frequency (14.6 versus 8.6 pulses per 24 hours) and mean LH levels (35.1 versus 11.2 ng/mL) were increased in the early follicular phase.[17]

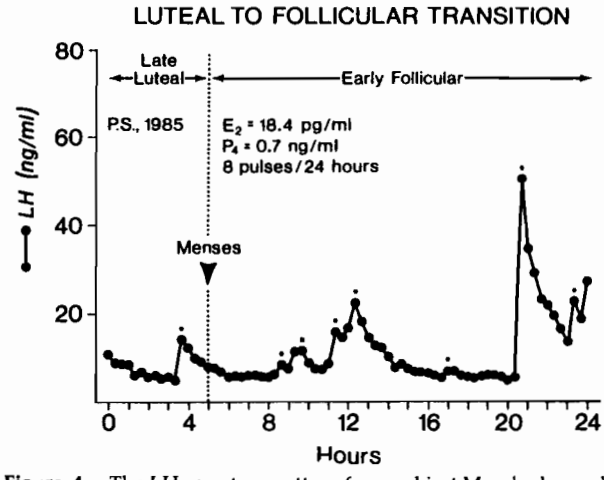

Figure 4. The LH secretory pattern from subject M, who began her menstrual period during a 24-hour sampling study. (Therefore, she proceeded from the late luteal phase of one cycle to the early follicular phase of her next cycle.) Pulses are indicated by asterisks.

The progesterone pulse frequency tended to be slower in the late luteal compared with the midluteal phase (6.0 versus 9.2 pulses per 24 hours; $P = .20$). The average amplitude of progesterone pulses and the mean progesterone level over 24 hours was lower in the late luteal than in the midluteal phase ($P < .01$) (Table 2). The pulsatile nature of progesterone secretion caused wide fluctuations in serum progesterone levels in each subject. In the midluteal phase, the average range of serum progesterone over 24 hours was 8.1–21.2 ng/mL; in the late luteal phase, the average range was 1.2–5.1 ng/mL. The percent variation in serum progesterone levels in each individual was quite marked (Table 2).

We investigated LH and progesterone secretion in the midluteal and late luteal cycle phases for a possible relationship in terms of coupled secretion. In most graphs of simultaneous LH and progesterone secretion data, it would appear from scanning the data that there is a one-to-one relationship between LH and progesterone secretion (Figures 2 and 3). Although our technique, which considers the statistical probability of pulses occurring simultaneously by chance, confirmed there were many simultaneous LH and progesterone pulses, a significant relationship was noted in only one

subject in each cycle phase (Table 2). To further investigate this potentially coupled relationship, we smoothed the LH and progesterone secretory data by calculating an hourly mean value for each hormone. A cross-correlation analysis was run on the 24-hour smoothed LH and progesterone data from the midluteal and late luteal cycle phases. There was a significant correlation between LH and progesterone in three of five subjects in the midluteal phase and four of five subjects in the late luteal phase (Figure 5). The *r* value was at a maximum when the progesterone data was shifted one hour later than the LH data, indicating a probable response time for the corpus luteum. Furthermore, Figure 5 indicates that most of the women studied had a significant quantitative relationship between LH and progesterone secretion.

The progesterone secretion data were analyzed to determine whether there were circadian variations in corpus luteum function. A cosine regression analysis was used on the hourly mean progesterone data for each subject in the midluteal and late luteal cycle phases. There was no consistent nocturnal-diurnal pattern to progesterone secretion in either of the cycle phases studied.

Discussion

A substantial number of studies indicate that normal corpus luteum function is dependent upon normal follicular development. The role of the LH surge in terms of corpus luteum function is more theoretical. Our current findings, that follicular development (as assessed by serum E2 levels and follicle size) and the LH surge do not correlate with progesterone secretion after ovulation in normal cycles, would appear to contradict the existence of a functional relationship between the follicle and the corpus luteum. In an attempt to explain what appears to be contradictory findings, we hypothesize that minimum thresholds for follicular development and the LH surge must be met to achieve normal corpus luteum function. Once the minimum threshold for follicular development has been reached, other factors (eg, luteal phase LH) determine the quantity of progesterone secreted.

Studies that have examined the pulsatile pattern of gonadotropin secretion over the menstrual cycle have all noted a slowing of LH secretion in the luteal compared with the follicular phase. This current report examines the LH secretion pattern in two specific segments (midluteal, late luteal) of the luteal phase. There was a trend toward a faster LH secretion rate, LH pulses of lower amplitude, and lower 24-hour mean LH levels in the late luteal phase than in the midluteal phase. However, there were no significant differences in any of these parameters. Filicori et al[18] studied the LH secretion patterns in the midluteal, late luteal, and the early luteal cycle phases, and concluded that there was a progressive decrease in the number of LH pulses over the luteal phase. However, this study did not find a significant difference (increase) in LH interpulse interval between the midluteal and late luteal phases. Our data, which point toward an increase in the LH pulse rate in the late luteal phase, differ from those of Filicori et al in that our late luteal subjects were closer to their next menstrual period, as evidenced by the difference in the mean 24-hour progesterone level between the studies (2.8 versus 7.0 ng/mL). Since the LH pulse frequency is increased in the early follicular phase, there has to be an increase somewhere between the luteal and follicular phases. (Figure 4 depicts the actual LH pulse pattern in a woman who went from the late luteal to the early follicular phase over the course of the 24-hour study). Because progesterone has been demonstrated to slow the LH pulse frequency,[17] it would make sense that the frequency would increase as progesterone levels decline in the late luteal phase. Therefore, we believe that the LH pulse frequency increases between the midluteal and late luteal phases.

Awareness that progesterone is secreted in an episodic fashion in the luteal phase has only recently developed. Reports by Younglai et al[19] and Backstrom et al[20] briefly described progesterone secretion as pulsatile. Filicori et al[18] reported intermittent secretion of progesterone in the midluteal and late luteal phases, but not in the early luteal phase. However, they studied only two women in each cycle phase, and thus were not able to describe a meaningful progesterone secretion pattern over the luteal phase. Separate nonhuman primate studies by Healy et al[21] and Ellinwood et al[22] also reported intermittent secretion of progesterone in the luteal phase.

Our study examined progesterone secretion in the luteal phase in a sufficient number of normal subjects to describe a pattern. There was no difference in the progesterone pulse frequency between the midluteal and late luteal phases, with a progesterone pulse occurring approximately every three hours in both phases. There was a significant decrease in the progesterone pulse amplitude and mean level of progesterone in moving from the midluteal to late luteal cycle phase. Therefore, the lower serum concentrations of progesterone in the premenstrual interval appear to be caused by smaller amplitude rather than less frequent progesterone pulses. The pulsatile nature of luteal phase progesterone secretion results in rather wide variations in single random serum levels of progesterone. This variation would indicate that the use of

serum progesterone levels to assess quantitatively the adequacy of ovulation (eg, diagnose luteal phase deficiency) is difficult at best. We recommend that random luteal progesterone levels be used only in a qualitative manner; that is, to indicate whether ovulation has occurred.

It would appear from examination of simultaneous LH and progesterone secretion data in most subjects (in both the midluteal and late luteal phases) that the secretion of these two hormones may be coupled. The studies by Healy et al[21] and Ellinwood et al[22] reported that bioactive luteal LH pulses in rhesus monkeys were usually associated with progesterone pulses. Filicori et al[18] noted a significant LH-progesterone cross-correlation in both of the two subjects they studied in the midluteal and late luteal phases. However, Beitins and Dufau[23] concluded that LH and progesterone secretion were not correlated when they found quite different luteal pulse frequencies for progesterone and biologically active LH. These studies all pose some interpretation difficulties, either because they involved only a small number of subjects and/or because they used a statistical method that did not consider the chance occurrence of simultaneous pulses. (The shorter the interpulse interval for any two hormones being compared, the greater the likelihood that any two unrelated hormone pulses will coincide.) When we analyzed our LH-progesterone pulse data using a method that considered the statistical probability of chance simultaneity, we found only two of ten data sets with significant synchrony. However, when our data were smoothed by calculating the hourly mean for LH and progesterone, there was a significant correlation coefficient for most patients. This latter finding indicates that major shifts in LH secretion beyond individual LH pulses (many of the pulses were of small amplitude) are responsible for progesterone secretion.

The mainstream of current scientific opinion regarding the functional role of LH in the luteal phase considers LH to be necessary for corpus luteum function in a qualitative-permissive sense. Recent studies in women and monkeys that examined the effects of anti-LH antibodies,[8] transient withdrawal of luteal LH,[9] and luteal phase administration of a gonadotropin-releasing hormone antagonist[10] have all indicated that LH is qualitatively necessary for normal function of the corpus luteum. Our LH-progesterone cross-correlation data in this study indicated a quantitative relationship between LH and progesterone secretion. (Figure 5 demonstrates that seven of ten women had a statistically significant positive relationship between LH and progesterone levels over a 24-hour period of sampling.) This apparent quantitative relationship requires further study because it casts LH in a new role as a major determinant of corpus luteum function.

Some reproductive hormones display circadian secretion rhythms; for instance, we previously reported a nocturnal slowing of LH secretion in the follicular phase.[16] A diurnal rhythm has been reported for progesterone secretion in the luteal phase of rhesus macaques (which varied with exposure to light).[24] Healy et al[21] observed a nocturnal increase in progesterone secretion in some of the rhesus monkeys they studied. Two recent studies in women that used only daytime sampling intervals reported that progesterone levels were significantly increased in the morning compared with the afternoon.[25,26] We failed to find a significant circadian rhythm with a consistent phase for progesterone secretion in either the midluteal or late luteal cycle phase. The use of a cosine regression analysis on 72 data points obtained over 24 hours amounted to a major examination for cyclicity. We do not understand the apparent discrepancy between our study and the previous reports in terms of circadian secretion of progesterone. However, we remain unconvinced that women secrete progesterone in a circadian manner.

References

1. Csapo AI, Pulkkinen MO, Wiest WG: Effects of luteectomy and progesterone replacement therapy in early pregnant patients. Am J Obstet Gynecol 115:759, 1973
2. Jones GS: The luteal phase defect. Fertil Steril 27:351, 1976
3. Strott CA, Cargille CM, Ross GT, et al: The short luteal phase. J Clin Endocrinol Metab 30:246, 1970
4. Sherman BM, Korenman SG: Measurement of serum LH, FSH, estradiol and progesterone in disorders of the human menstrual cycle: The inadequate luteal phase. J Clin Endocrinol Metab 39:145, 1974
5. Geisthovel F, Skubsch U, Zabel G, et al: Ultrasonographic and hormonal studies in physiologic and insufficient menstrual cycles. Fertil Steril 39:277, 1983
6. Vande Wiele RL, Bogumil J, Dyrenfurth I, et al: Mechanisms regulating the menstrual cycle in women. Recent Prog Horm Res 26:63, 1970
7. Asch RH, Abous-Samra M, Braunstein GD, et al: Luteal function in hypophysectomized rhesus monkeys. J Clin Endocrinol Metab 55:154, 1982
8. Groff TR, Madhwa Raj HG, Talbert LM, et al: Effects of neutralization of luteinizing hormone on corpus luteum function and cyclicity in macaca fascicularis. J Clin Endocrinol Metab 59:1054, 1984
9. Hutchison JS, Zeleznik AJ: The corpus luteum of the primate menstrual cycle is capable of recovering from a transient withdrawal of pituitary gonadotropin support. Endocrinology 117: 1043, 1985
10. Mais V, Kazer RR, Cetel NS, et al: The dependency of folliculogenesis and corpus luteum function on pulsatile gonadotropin secretion in cycling women using a gonadotropin-releasing hormone antagonist as a probe. J Clin Endocrinol Metab 62:1250, 1986

11. Midgley AR Jr: Radioimmunoassay: A method for human chorionic gonadotropin and human luteinizing hormone. Endocrinology 79:10, 1966
12. Bremner WJ, Matsumoto AM, Sussman A, et al: Follicle-stimulating hormone and human spermatogenesis. J Clin Invest 68:1044, 1981
13. Matsumoto AM, Paulsen CA, Hopper BR, et al: 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
14. Soules MR, Clifton DK, Bremner WJ, et al: Corpus luteum insufficiency induced by a rapid gonadotropin-releasing hormone-induced gonadotropin secretion pattern in the follicular phase. J Clin Endocrinol Metab 65:457, 1987
15. Moore PG: Principles of Statistical Techniques. London, Cambridge University Press, 1969, pp 216–220
16. Soules MR, Steiner RA, Cohen NL, et al: Nocturnal slowing of pulsatile luteinizing hormone secretion in women during the follicular phase of the menstrual cycle. J Clin Endocrinol Metab 61:143, 1985
17. Soules MR, Steiner RA, Clifton DK, et al: Progesterone modulation of pulsatile luteinizing hormone secretion in normal women. J Clin Endocrinol Metab 58:378, 1984
18. Filicori M, Butler JP, Crowley WF: Neuroendocrine regulation of the corpus luteum in the human: Evidence for pulsatile progesterone secretion. J Clin Invest 73:1638, 1984
19. Younglai EV, Smith SL, Cleghorn JM, et al: Variation in ovarian steroid levels during the luteal phase of the menstrual cycle. Clin Biochem 8:234, 1975
20. Backstrom CT, McNeilly AS, Leask RM, et al: Pulsatile secretion of LH, FSH, prolactin, oestradiol and progesterone during the human menstrual cycle. Clin Endocrinol (Oxf) 17:29, 1982
21. Healy DL, Schenken RS, Lynch A, et al: Pulsatile progesterone secretion: Its relevance to clinical evaluation of corpus luteum function. Fertil Steril 41:114, 1984
22. 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
23. Beitins IZ, Dufau ML: Pulsatile secretion of progesterone from the human corpus luteum: Poor correlation with bioactive LH pulses. Acta Endocrinol 111:553, 1986
24. Spies HG, Mahoney CJ, Norman RL, et al: Evidence for a diurnal rhythm in ovarian steroid secretion in the rhesus monkey. J Clin Endocrinol Metab 39:347, 1974
25. Syrop CH, Hammond MG: Diurnal variations in midluteal serum progesterone measurements. Fertil Steril 47:67, 1987
26. Hughes CL, Fleming R, Coutts JRT, et al: Pulsatile hormone secretion late in the luteal phase of normal and infertile women during diurnal hours, Regulation of Ovarian and Testicular Function. Edited by VB Mahesh, DS Dhindsa, E Anderson. New York, Plenum, 1987, pp 629–634

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