0021-972X/89/6904-0813$02.00/0
Journal of Clinical Endocrinology and Metabolism

Vol. 69, No. 4
Printed in U.S.A.

Luteal Phase Deficiency: Abnormal Gonadotropin and Progesterone Secretion Patterns*

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ABSTRACT. Luteal phase deficiency (LPD) is a reproductive disorder associated with infertility and spontaneous abortion. This study was undertaken to determine whether LPD might be related to an abnormal pattern of gonadotropin secretion. We tested this hypothesis by evaluating the pattern of pulsatile LH secretion in both the follicular and luteal phases of the menstrual cycle in normal women (n = 21) and women with LPD (n = 20), which was diagnosed on the basis of two out of phase endometrial biopsies. In addition, we sought to determine whether changes in progesterone (P) pulse patterns could account for the decrease in average serum P levels in women with LPD. To this end, we examined the pulse patterns of P and compared these patterns between normal women and those with LPD. Frequent blood sampling was performed in both groups to determine their respective hormone secretion patterns. In the follicular phase, blood samples were obtained every 10 min for 12 h; in the luteal phase the samples were obtained every 20 min for 24 h. Serum LH, FSH, and P were assayed in each sample. Pulse detection was performed by an adaptive threshold method of pulse analysis. The LH pulse frequency was significantly higher in the women with LPD than in the normal women in the early follicular phase [$P < 0.05$; LPD, 12.8 ± 1.4 (±SE); normal, 8.2 ± 0.7 pulses/12 h]. LH pulse frequency was similar in the early and late follicular phases in the women with LPD, whereas it was higher in the late follicular phase in normal women. Mean serum FSH levels were not different between groups in both the early and late follicular phases. In the luteal phase the P pulse amplitude and mean serum P level were significantly lower in the LPD group than in the normal women ($P < 0.01$). We conclude that 1) a too rapid LH pulse pattern in the early follicular phase may lead to inadequate LH support of the corpus luteum and become manifest as LPD; 2) the mechanism for inadequate P secretion in LPD is decreased P pulse amplitude; 3) the finding of similar serum FSH levels in the two groups in both the early and late follicular phases did not support compromised folliculogenesis as an etiological factor for LPD. (*J Clin Endocrinol Metab* **69:** 813, 1989)

LUTEAL phase deficiency (LPD) is an enigmatic endocrine disorder associated with infertility and spontaneous abortion (1, 2). The diagnosis of this condition is generally made by the finding of repeated out of phase endometrial biopsies (3). It is believed that the infertility and pregnancy wastage associated with this disorder are caused by inadequate maturation and development of the endometrium, rendering it incapable of supporting the implanting blastocyst. The failure of the endometrium is thought to be attributable to insufficient progesterone (P) production by the corpus luteum. This hypothesis is supported by two related clinical observations. First, mean integrated serum P levels in the luteal phase are lower in women with LPD than in normal women (4, 5). Second, P treatment of women with LPD improves their fertility (6). Together, these observations support the concept that inadequate P secretion plays the major role in LPD-associated infertility. However, the mechanism underlying the defect in P secretion is unknown.

Follicular phase events are known to affect subsequent luteal phase P production. Suppression of folliculogenesis leads to decreased serum P levels and LPD (7), while ovulation induction with multiple follicle development results in supraphysiological serum P levels in the ensuing luteal phase (8). Furthermore, subtle changes in gonadotropin secretion in the follicular phase can subsequently affect corpus luteal function. For example, we found a significant increase in LH pulse frequency in the early follicular phase in four women with LPD (9). These findings were confirmed by a subsequent study of five women with LPD performed at another institution (10). They also found the integrated serum LH and FSH response to a single bolus dose of GnRH was increased in LPD women in the early follicular phase (11). We were able to induce LPD in normal women by imposing a rapid gonadotropin secretion pattern in the follicular phase with small frequent intermittent doses of exoge-

Received December 7, 1988.
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* This work was supported by NIH Grants R01-HD-18967, R01-HD-12625, and P50-HD-12629; Clinical Research Center Grant RR-37, and the VA.

nous GnRH (12). Based on these preliminary findings we hypothesized that an abnormal follicular phase gonadotropin secretion pattern might occur in women with LPD.

In the luteal phase LH is the major luteotropic hormone, and any defect in the pattern of luteal gonadotropin secretion could have a deleterious effect on the functioning of the corpus luteum (13). P is also secreted in an episodic (pulsatile) manner from the corpus luteum. P and LH secretion appear to be coupled, with most major LH pulses followed by a P pulse (14–16), and a positive quantitative correlation between LH and P has been described (16). Consequently, we hypothesized that the low serum P levels in women with LPD could be due to an abnormality in the luteal phase secretion patterns of LH or P or in the secretory relationship between these hormones.

With these considerations in mind, this study was undertaken to examine gonadotropin and P secretion in LPD and normal women. Specifically, we studied 1) the LH secretion pattern in four cycle phases, 2) the pattern of P secretion by the corpus luteum, and 3) the relationship between the LH and P secretion patterns in the luteal phase.

Materials and Methods

Subjects (Table 1)

The LPD study group consisted of 20 women (age range, 21–37 yr), who had presented to the Reproductive Endocrinology clinic with a diagnosis of either infertility (primary or secondary) or recurrent spontaneous abortion. Nine of the women had mild hyperprolactinemia (average serum PRL, >20 μg/L; range, 21–36 μg/L) and/or galactorrhea. All 20 women with LPD had 2 out of phase endometrial biopsies in 2 spontaneous menstrual cycles; these out of phase biopsies were the basis for the diagnosis of LPD. The biopsies were performed in the late luteal phase and were assigned a menstrual cycle day according to the criteria of Noyes *et al.* (17) by 2 pathologists who reread all of the slides in a blind fashion at the completion of the study. Biopsies more than 2 days out of phase in relation to the subsequent menstrual period, according to both pathologists, were used to define the LPD study population.

The general clinical criteria for diagnosing LPD have been infertility coupled with two out of phase endometrial biopsies. An additional (more strict) criterion for this diagnosis is decreased daily (integrated) luteal phase serum P levels (3). All 20 women in this study met the general criteria, and 10 of these 20 women met the more strict criterion for LPD; that is, in addition to having 2 out of phase biopsies and infertility, these 10 women had decreased integrated serum P levels compared to normal women (4). The women with LPD had an average luteal phase length of 11.7 ± 0.5 (±SE) days.

The control group for this study comprised 21 normal women. These women were between 18–35 yr of age, within ± 10% of ideal body weight (Metropolitan Life Insurance Co. tables, 1980), had regular menstrual cycles, and had one or more normal basal body temperature charts. None were taking any medication, and all met the following hormonal criteria in the midluteal phase of a prior menstrual cycle: serum P, > 38 nmol/L (12 ng/mL); PRL, < 20 μg/L; testosterone, < 1.4 nmol/L (40 ng/dL). Nine of the normal women had a late luteal endometrial biopsy during the study cycle, all 9 were in phase. The average luteal length in this group was 13.5 ± 0.2 days ($P < 0.001$, compared with the LPD group).

Protocol

Frequent blood sampling was performed in both groups for determination of the LH, FSH, and P secretion patterns. The study design focused on a comparison of LH and P pulse patterns between normal women and the women with LPD. Four cycle phases were studied: early follicular, cycle days 1–6; late follicular, cycle days 8–12; midluteal, cycle days 21–24; and late luteal, cycle days 25–28. Eleven of the LPD women underwent frequent sampling on 1 occasion in either the follicular or the luteal phase, while the other 9 were studied once in each phase during the same cycle. In the LPD group, there were 11 frequent sampling studies in the early follicular phase [mean serum estradiol (E_2), 81 pmol/L (22 pg/mL)], 5 studies in the late follicular phase [mean serum E_2, 407 pmol/L (111 pg/mL)], and 13 studies in the luteal phase. (The number of women studied in each cycle phase differed due to variations in their schedules.) Each of the normal women was admitted in a specific cycle phase for frequent sampling on only 1 occasion (early follicular, n = 5; late follicular, n = 6; midluteal, n = 5; late luteal, n = 5). The follicular phase studies were all performed between 0800–2000 h.

In reference to defining the luteal phase for the LPD patients, these women were admitted in the midluteal phase, on cycle days 21–24; however, there were some unavoidable discrepancies in categorizing the luteal phase admissions of the LPD women dependent upon the point of reference. For example, six LPD women were in the late luteal phase based on their ensuing menstrual period.

All women in both groups were admitted to the Clinical Research Center at the University of Washington for the frequent blood-sampling studies. In the follicular phase, 5-mL venous blood samples were obtained every 10 min for 12 h through an indwelling iv line; in the luteal phase samples were obtained every 20 min for 24 h. (These sampling intervals were selected based on the known variation in gonadotropin pulse frequency during the menstrual cycle; more frequent sampling is necessary to characterize the faster follicular phase secretion pattern.) Each blood sample was allowed to clot, and the serum was separated and frozen at −20 C until assayed for LH, FSH, and P. Pooled samples from each admission were assayed for E_2. All samples from an individual woman were analyzed in duplicate in a single assay.

RIAs

LH and FSH. Serum LH and FSH were measured by double antibody RIAs as described previously (12), using reagents supplied by the NIH with LER 907 as the reference preparation. The sensitivity of the LH assay was 6 μg/L, with intra- and interassay coefficients of variation (CVs) of 5.5% and 8.4%, respectively. The sensitivity of the FSH assay was 25 μg/L, with intra- and interassay CVs of 7.3% and 9.7%, respectively.

TABLE 1. Patient characteristics

Subjects	Age (yr)	%IBW[a]	Average cycle length (days)	Study cycle length (days)	Diagnosis[b]	Serum PRL (μg/L)	Galactorrhea	Endometrial biopsy (days out of phase)	
								Cycle 1	Cycle 2
A[c]	21	139	28.5	26	1°	11	−	2.25	3.75
B[c]	35	95	27	26	2°	14	−	5	4
C[c]	32	91	25.5	24	Spon ab	9	−	4	3.75
D[c]	33	99	26.5	25	2°	3	−	4	3.25
E[c]	32	131	23.5	25	2°	15	−	7	6
F[c]	28	92	29	30	Spon ab	9	−	3	4
G[c]	29	87	27	25	1°	21	+	3	2.5
H	31	103	30.5	29	1°	25	−	2.25	2.25
I	35	93	28	32	2°	23	−	7	4
J	32	95	32	NA[d]	1°	16	−	2.25	3.5
K	35	96	30	27	1°	23	−	2.5	4
L[c]	35	111	30	28	2°	10	−	2.75	6.5
M[c]	33	86	23	23	2°	11	+	4	4.5
N	32	NA	28	NA	1°	36	−	3	3
O	37	106	28	NA	2°	17	−	4.5	4.5
P	35	91	26.5	35	1°	8	−	4	3.5
Q[c]	31	100	26.5	27	2°	13	+	6	6
R	34	126	26.5	29	2°	7	+	2.75	2.25
S	34	99	26	25	2°	5	+	2.25	3.75
T	37	94	26.5	28	2°	15	−	2.25	5.5

[a] Percent ideal body weight, by Metropolitan Life tables, 1980.
[b] 1°, Primary infertility; Spon ab, spontaneous abortion; 2°, secondary infertility.
[c] Second endometrial biopsy and daily blood samples performed in study cycle.
[d] Not available.

E_2. Serum E_2 was measured by RIA as previously described (12). The sensitivity of the E_2 assay was 44 pmol/L (12 pg/mL), with intra- and interassay CVs of 8.2% and 8.8%, respectively.

P. Serum P was measured by RIA using reagents supplied by Diagnostic Products Corp. (Los Angeles, CA). This assay had a cross-reactivity of 0.3% with 17-hydroxyprogesterone and less than 0.01% with testosterone, E_2, pregnenolone, and cortisol. The assay sensitivity was 1.6 nmol/L (0.5 ng/mL), and intra- and interassay CVs were 9% and 12%, respectively.

Pulse analysis technique

For each woman there were 73 data points each for serum LH and FSH during the sampling intervals (this applied to P in the luteal phase as well). The following pulse parameters were calculated: LH and P pulse frequency, LH and P pulse amplitude, and mean serum LH, FSH, and P levels. An adaptive threshold method (DC3) was used to determine the frequency and amplitude of hormone pulses as previously described (18). A pulse was defined as an increase from local minimum to local maximum that was greater than a threshold value. The threshold was determined in an iterative manner. Initially, the threshold was set at 2.5 times the SD of the sample replicates, and the number of pulses in the data set was determined. Based on the estimated number of pulses, the threshold was readjusted according to the following formula: $T = S^*(5.518 + F^*[-0.3519 + F^*(0.01339 - 0.0002478^*F)])$, where T is the threshold, S is the SD of the replicates, and F is 100 × (number of pulses detected last time)/(number of samples in the data set). The analysis was then repeated with the new threshold. If the number of pulses detected was different from the number found on the previous pass, a new threshold was calculated according to the above formula, and the procedure was repeated. This iterative procedure was continued until the number of pulses detected stabilized. The formula for threshold was determined empirically based on computer simulations.

A recently described technique was used to analyze the LH and P data for the occurrence of synchronous secretion (pulses) (18). This technique, derived from Monte Carlo simulations, takes into account the statistical probability of simultaneous pulses occurring by chance, dependent upon the number of pulses for each of the hormones. Simultaneity was considered present if a P pulse fell within one data point of a LH pulse. This criterion was applied after shifting the entire set of P data by two points (40 min) relative to the LH data. (This maneuver was performed under the assumption there would be a response time to LH by the corpus luteum. The best fit in terms of simultaneous pulses for most of the women was 40 min, rather than 20 or 60 min.)

Statistics

Pulse parameters (*i.e.* frequency, amplitude, and mean level) were compared between groups by Student's *t* tests. The results are expressed as the mean ± SE unless otherwise indicated. $P \leq 0.05$ was considered significant.

Results

Follicular phase

In the early follicular phase, the LH pulse frequency

was significantly higher in the LPD women than in the normal women ($P \leq 0.05$; 12.8 ± 1.4 *vs.* 8.2 ± 0.7 pulses/12 h; Fig. 1). There were no detectable differences between the LPD and the normal groups for the other pulse parameters in the early follicular phase (mean serum LH level: LPD, 25.4 ± 3.1; normal, 17.7 ± 3.9 μg/L; LH pulse amplitude: 8.8 ± 1.3 *vs.* 10.5 ± 1.6 μg/L). Representative LH pulse patterns for a woman with LPD and a normal woman in the early follicular phase are shown in Fig. 2.

There was a significant increase in LH pulse frequency across the transition between the early and late follicular cycle phases in the normal women, consistent with other reports ($P \leq 0.001$) (19). This increase in LH pulse frequency in the late follicular phase did not occur in the LPD women studied (Fig. 1). There were no significant differences detected between the normal and the LPD women in any of the gonadotropin pulse parameters in the late follicular phase. The mean serum FSH levels in both the early and late follicular cycle phases were not significantly different in the normal and the LPD women (Fig. 3).

Luteal phase

In the women with LPD, LH pulse frequency decreased significantly between the follicular and luteal phases ($P \leq 0.001$; 12.9 ± 1.1 pulses/12 h *vs.* 5.9 ± 0.7 pulses/24 h), as occurs in normal women (19). Furthermore, in the LPD women during the luteal phase there were no significant differences in LH pulse parameters (LH pulse frequency, LH pulse amplitude, and mean serum LH level) compared to the corresponding values in the normal women (Fig. 1). There was no correlation between the mean P level and LH pulse frequency in either group (data not shown).

P was secreted in an episodic fashion in the women with LPD and the normal women (Fig. 4). During the 24-h sampling interval, the women with LPD had between 4–12 serum P pulses, and the normal women had between 5–12 serum P pulses; thus, the mean P pulse

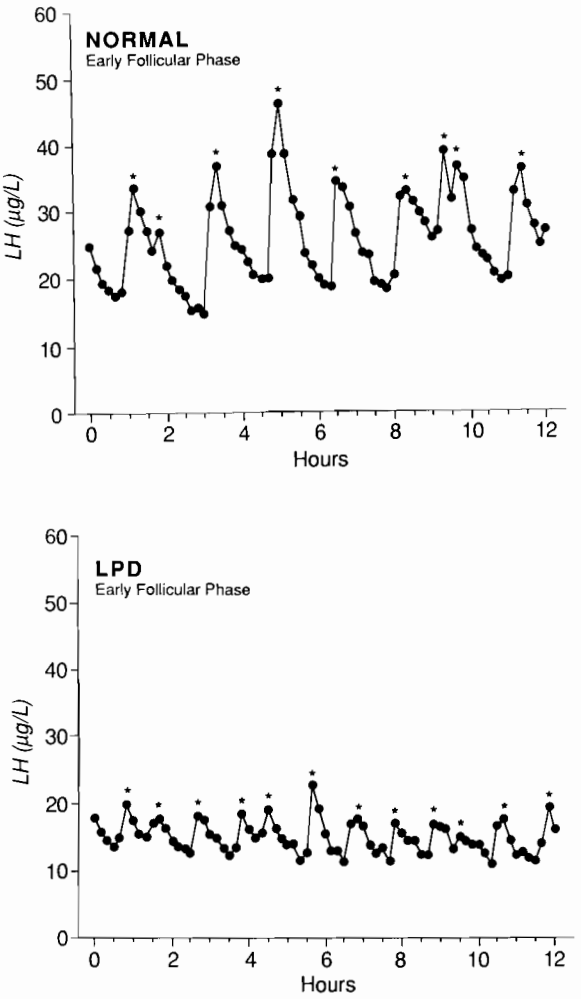

FIG. 2. The LH secretory pattern in a normal woman (*top*) and a woman with LPD (*bottom*). Each woman was studied for 12 h, with a 10-min sampling interval. Note the more frequent LH pulses of lower amplitude in the woman with LPD compared to the normal woman. Each identified pulse is indicated by a *star*.

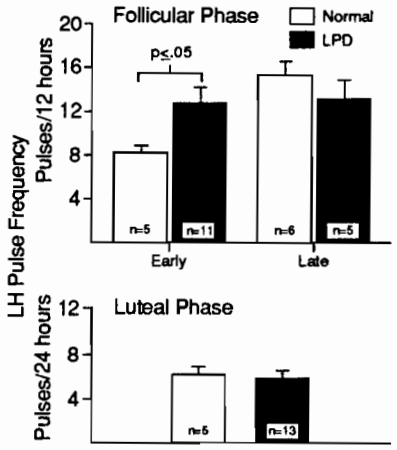

FIG. 1. Mean (±SE) LH pulse frequency in normal women and women with LPD during the follicular and luteal cycle phases. The size of each group is shown at the *bottom of each bar*.

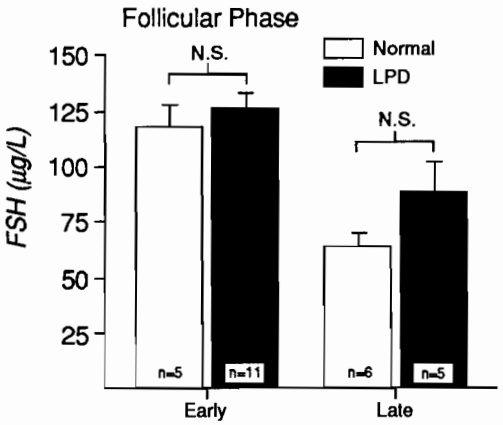

FIG. 3. Mean (±SE) serum FSH levels for 12 h in the early and late follicular phases in LPD and normal women. The size of each group is shown at the *bottom of each bar*.

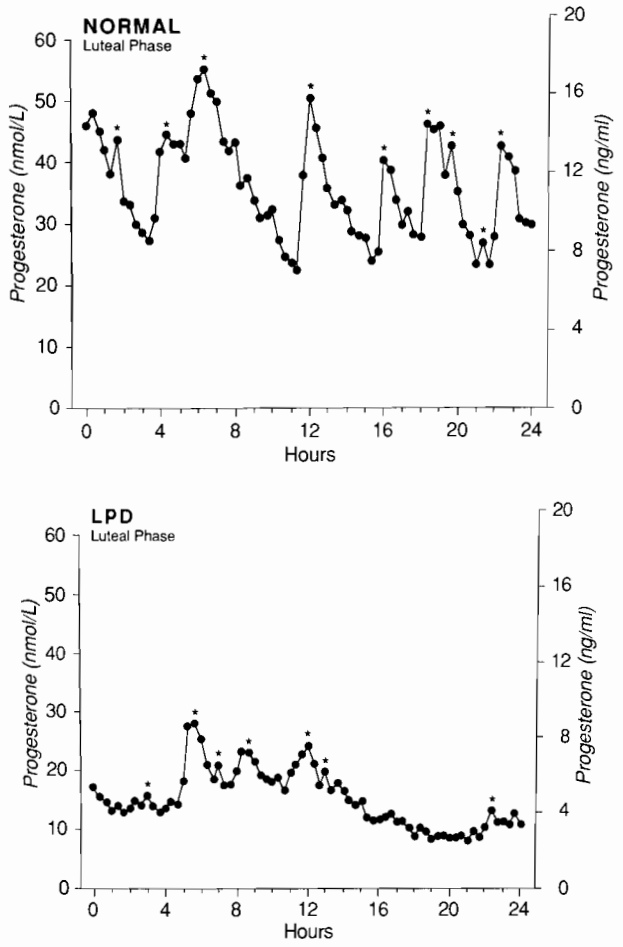

FIG. 4. The pulsatile patterns of P secretion in the midluteal phase in a normal woman (*top*) and a woman with LPD (*bottom*). Serum P values were determined at 20-min intervals for 24 h. Identified pulses are indicated by a *star*. Note the similar number of P pulses, but the P pulse amplitude was less in the woman with LPD.

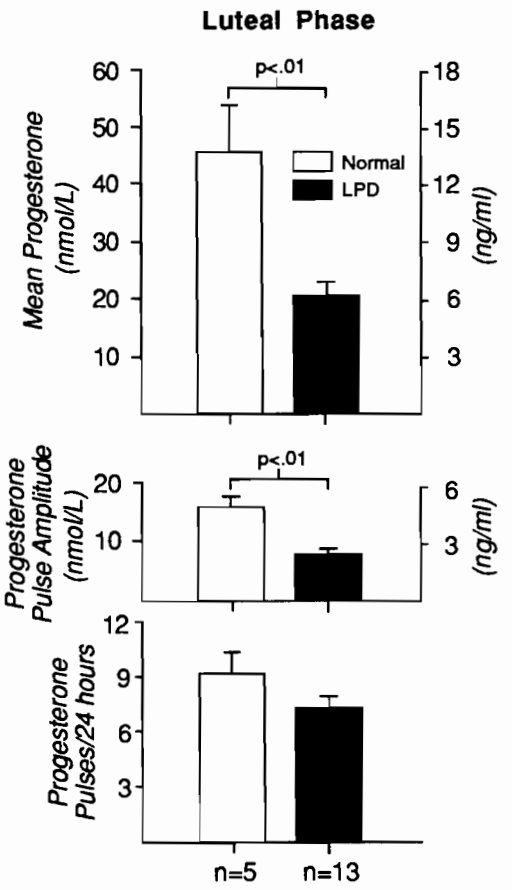

FIG. 5. Mean (±SE) P pulse frequency, P pulse amplitude, and mean serum P level in normal women and women with LPD in the midluteal phase. The size of each group is indicated at the *bottom*.

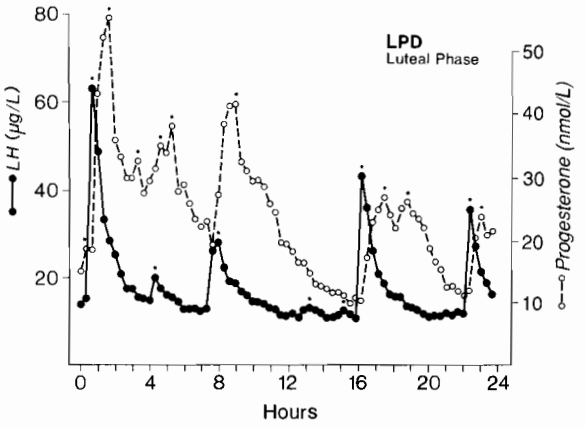

FIG. 6. The 24-h patterns of LH and P secretion in the luteal phase in a woman with LPD. Identified pulses are marked with an *asterisk*. Note that most LH pulses are temporally associated with a P pulse.

frequencies in the 2 groups were similar (7.3 ± 0.7 *vs.* 9.2 ± 1.2 pulses/24 h; Fig. 5). However, the average P pulse amplitude and the 24-h mean serum P level were significantly lower in the LPD women (Fig. 5). The mean P pulse amplitude in the women with LPD was 8 ± 1 nmol/L (2.5 ng/mL) compared to 16 ± 2 nmol/L (5.0 ng/mL) in the normal women ($P \leq 0.01$). Similarly, the 24-h mean serum P level in the LPD women was 20 ± 3 nmol/L (6.3 ng/mL) *vs.* 44 ± 8 nmol/L (13.8 ng/mL) in the normal women ($P \leq 0.01$). Since most of the studies in the LPD women could be classified relative to the woman's next menstrual period as occurring in the late luteal phase, comparisons were also made with late luteal phase values in 5 normal women. Both the P amplitude and the mean serum P level were significantly ($P \leq 0.05$) higher in the LPD group (data not shown).

A relationship between LH and P secretion patterns in the luteal phase has been reported in normal women (14–16). This coupling of pulses appeared to be present in some LPD women (Fig. 6). A statistical method that analyzes paired pulse data for the presence of significant simultaneity was used to examine the LPD luteal phase LH-P data (shifted 40 min) (18). While the majority of LH and P pulses were within 1 data point of each other in the LPD women, the coupling of LH and P secretion was significant in only 5 of the 13 women studied during the luteal phase.

Discussion

We examined the episodic patterns of gonadotropin secretion in a large number of women with LPD and compared their secretory profiles to those in a group of normal women. In an earlier preliminary study we found evidence for the occurrence of a more rapid LH pulse frequency during the early follicular phase in a small number of women with LPD (9). The results of this study confirmed the earlier findings in a larger number of women. We now extend the comparison to demonstrate that in women with LPD, LH pulse frequency is increased beginning early in the follicular phase and that LH pulse frequency does not undergo further acceleration with the approach of the periovulatory period, in contrast to normal women. Thus, it would appear that in women with LPD, the LH pulse pattern is fixed throughout the follicular phase at an inappropriately high frequency (at a time when the follicle is undergoing important maturational changes). The reason for the accelerated early follicular phase LH pulse frequency in women with LPD is unknown, but it is conceivable it is the result of their relatively lower serum P levels in the luteal phase of the immediately preceding cycle; this suggestion is based on the premise that P is responsible for slowing LH secretion in the luteal phase (20). Whatever the reason, the abnormally high early follicular phase LH pulse frequency may have untoward effects on follicular development and subsequent luteal function.

The physiological significance of the prolonged rapid LH pattern in the follicular phase in women with LPD is open to speculation. In earlier studies, we found only subtle evidence for compromised folliculogenesis in women with LPD (normal serum FSH and E_2 and follicle size, but decreased serum inhibin) (4). However, the sustained rapid LH pattern in the follicular phase in these women may have effects in other cycle phases. An induced supraphysiological LH pulse pattern in the follicular phase in normal women induced a significant decrease in luteal phase serum bioactive LH and P levels (LPD) (12). In this study the subgroup ($n = 10$) of women who had daily blood sampling during their cycle had a small but significant decrease in serum bioactive LH in the luteal phase (4); therefore, it is possible that diminished LH bioactivity may be responsible for the reduced P pulse amplitude and the reduced mean serum P levels in women with LPD. Together, these observations suggest that events in the preceding follicular phase contribute to diminished secretion of bioactive LH in the luteal phase, which could, in turn, help to explain the reduced P pulse amplitude that characterizes the women with LPD.

While our finding of a rapid LH pulse frequency in the early follicular phase has been confirmed by others (10), a recent report from Germany noted a slower early follicular LH pulse frequency in 16 women with LPD (21). We can only speculate in regard to these opposite findings. The German report studied a different group of patients—relatively younger women whose etiology for LPD appeared to be exercise and/or dieting. The women in our study were older and presented with infertility or habitual abortion. Although both studies incorporated a 12-h sampling interval, our study obtained samples every 10 rather than 15 min during the day as opposed to nocturnal sampling in the other study. It is interesting that both groups found an abnormal gonadotropin secretion pattern in the same cycle phase—early follicular. Perhaps a change in either direction (fast or slow) in the LH secretion rate in the early part of the menstrual cycle can lead to LPD.

Other than the increased early follicular phase LH pulse frequency, gonadotropin secretion was normal in the follicular phase in the women with LPD. It is noteworthy that the mean serum FSH concentrations in both the early and late follicular phases were similar in the LPD women and the normal women. There is considerable evidence that inadequate follicular development (both spontaneous and induced) in women and nonhuman primates can induce LPD (7, 22–24), and in some early studies LPD women were found to have abnormalities in serum FSH concentrations or LH/FSH ratios (based on daily measurements) in the follicular phase (22, 23). We found no abnormalities in follicular phase serum bioactive or immunoactive LH or FSH levels in the subgroup of 10 women with LPD who had daily blood sampling (4), and the finding of similar mean serum FSH levels in the LPD and normal women in both the early and late follicular phase extends this recent report (4). Since the mean serum FSH levels reported here were an average of 73 samples collected in 12 h, these values should represent a close approximation of the true average level. While there is no doubt that follicular phase FSH deficiency is capable of causing LPD, we found no evidence for FSH deficiency in the LPD women we studied.

Adequate serum LH levels in the luteal phase are required for normal corpus luteal function (13), and there is some evidence that LH quantitatively determines the amount of P and inhibin secreted by the corpus luteum (16, 25). We, therefore, determined the LH secretory pattern in the luteal phase in the women with LPD. Their LH secretion pattern at this time was similar to that in normal women; that is, LH pulse frequency was slower and LH pulse amplitude was higher than in the follicular phase. If P were the primary factor slowing the GnRH pulse generator in the luteal phase, then given the lower mean serum P levels in the women with LPD, the occurrence of normal luteal phase LH pulse parameters in the women with LPD implies enhanced sensitivity to P-mediated negative feedback.

The corpus luteum secretes P in an intermittent manner in both normal and LPD women (14–16). The P pulse frequency in the LPD women was similar to that in the normal women. However, the mean P pulse amplitude and the mean serum P level during the 24-h sampling interval was decreased in the LPD women. Thus, the deficient P secretion by the corpus luteum in the LPD women was the result of less P secretion per episode.

LH and P secretion are coupled in the midluteal and late luteal cycle phases in normal women (14–16). This coupling represents both a temporal and a quantitative relationship. Approximately half of the LPD women had a significant temporal coupling of their LH and P secretion patterns; the coupling pattern in the others was similar, although not statistically significant. Thus, we found no breakdown in the secretory linkage between LH and P in women with LPD.

Deducing the site of the initial abnormality in women with LPD is exceedingly difficult. Indeed, there may be several pathogenic mechanisms for LPD. One possibility is a derangement in P feedback on the hypothalamic-pituitary axis. However, this argument can be circular. On the one hand, an increased LH pulse frequency in the early follicular phase may set up the follicle for failure after its transformation into a corpus luteum; on the other hand, failure of the corpus luteum to produce adequate amounts of P may lead to an inappropriately high LH pulse frequency in the ensuing follicular phase of the next cycle. These are not mutually exclusive scenarios, and indeed, they may interact to perpetuate the condition, given, for example, an abnormal set-point for P feedback control of pulsatile GnRH secretion. A reasonable next step would be careful assessment of the sensitivity of the steroid feedback control of gonadotropin secretion in women with LPD. If the rapid LH secretion pattern in the early follicular phase in women with LPD is not secondary to inadequate P feedback, an equally plausible explanation would be disruption in the normal functioning of the GnRH pulse generator. There are clinical examples of abnormal suprahypothalamic input affecting the menstrual cycle, *e.g.* hypothalamic amenorrhea, and various activities, such as dieting (26) and exercise (27), are associated with LPD. It is conceivable, therefore, that in some women a stress-induced alteration in neurotransmitter modulation, *e.g.* endogenous opioid peptides, of the GnRH pulse generator could lead to a disruption in the gonadotropin pulse pattern and subsequent LPD.

Acknowledgments

The authors gratefully acknowledge the laboratory assistance of Dianne Schoenberg, Dorothy McGuinness, Arlen Sarkissians, and Florida Flor; the artwork assistance of Jan Hamanishi; and the secretarial assistance of Cynthia Schuler.

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