

Prolactin Secretion and Corpus Luteum Function in Women with Luteal Phase Deficiency*

MICHAEL R. SOULES, WILLIAM J. BREMNER, ROBERT A. STEINER,
AND DONALD K. CLIFTON

Departments of Obstetrics and Gynecology (M.R.S., R.A.S., D.K.C.), Medicine (W.J.B.), and Physiology and Biophysics (R.A.S.), University of Washington, and the Veterans Administration Medical Center (W.J.B.), Seattle, Washington 98195

ABSTRACT. Luteal phase deficiency (LPD) as a clinical infertility problem is considered to have a heterogeneous etiology. Hyperprolactinemia has long been considered a causative factor of LPD. In this context we investigated PRL secretion in 18 women with LPD. All of the subjects were infertile with 2 out of phase (>2 days) endometrial biopsies; 10 of the women also had daily blood samples, this latter subgroup had significantly decreased integrated luteal phase progesterone (P) levels compared to normal women with in-phase biopsies. PRL secretion was investigated as follows: 1) daily blood levels; 2) pulsatile secretion patterns in 3 cycle phases [early follicular (12 h); late follicular (12 h); midluteal (24 h)], 3) LH-PRL coupling, and 4) nocturnal patterns. Results were compared to findings in 36 normal women. The mean daily levels of PRL over the menstrual cycle were not different between the two groups (LPD, 12.1 ± 1.5 ; normal, 13.8 ± 0.8 $\mu\text{g/L}$; $P = 0.3$). There was no correlation between luteal phase integrated P and PRL levels for either group. There was a small difference in the PRL pulse amplitude

in the early follicular phase between the LPD and normal women (2.6 ± 0.3 vs. 5.5 ± 1.3 $\mu\text{g/L}$; $P < 0.05$). There were no significant differences between groups in PRL pulse frequency or mean level during the 12 or 24 h in any cycle phase. There was an equivalent amount of LH-PRL pulse coupling in both groups in all three cycle phases. Diurnal and nocturnal PRL secretion was studied by breaking the 24 h data (midluteal) into day (0700–2300 h) and night (2300–0700) segments. Mean PRL levels were higher at night in both groups (LPD, 15.9 vs. 12.6; normal, 15.4 vs. 9.3 $\mu\text{g/L}$; $P < 0.05$), as expected. There were no differences in nocturnal PRL secretory patterns between the two groups. In summary, we have serious reservations whether abnormalities in PRL secretion are a common or integral part of the pathophysiology of LPD. From previous work we know these subtle abnormalities in PRL secretion in LPD are associated with definite abnormalities in gonadotropin secretion. We believe these gonadotropin abnormalities are probably more significant in terms of decreased P secretion. (*J Clin Endocrinol Metab* 72: 986–992, 1991)

NUMEROUS pieces of scientific evidence have linked PRL secretion and corpus luteum function. In rodents, PRL is luteotropic and necessary for nidation and pregnancy (1). PRL receptors are present in human corpora lutea (2). In normal women, suppression of serum PRL with a dopamine agonist medication leads to a significant decrease in progesterone (P) secretion (3). Furthermore, raising serum PRL levels with a dopamine antagonist also leads to decreased P secretion in normal women (4). It would appear that an optimal level (window) of PRL is necessary for normal corpus luteum function. This contention is supported by *in vitro* culture studies with human luteinized granulosa cells, where it has been demonstrated that P secretion can be modulated by varying the PRL concentration in the tissue

culture medium (5).

Luteal phase deficiency (LPD) as a heterogeneous clinical problem is considered causative of infertility and/or habitual abortion (6). LPD is primarily a problem that consists of decreased P secretion after ovulation. Modest elevations of serum PRL have been noted in some women with LPD (7–10). In these patients normalization of PRL with a dopamine agonist has led to a high pregnancy rate. Other studies have focussed on subtle abnormalities in PRL secretion in women with idiopathic LPD (the majority of LPD women fall into this group). These latter studies have found both nocturnal and TRH-stimulated PRL secretion to be elevated in most women with idiopathic LPD (11–13).

It appears a strong case can be made for hyperprolactinemia as a cause of LPD in some women with this reproductive disorder. However, there are some deficiencies in the clinical studies that have linked LPD with PRL: 1) some of the studies were not performed in the same menstrual cycle in which LPD was diagnosed (9, 11, 12); 2) PRL secretion was estimated by only one or

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Address requests for reprints to: Michael R. Soules, M.D., Department of Obstetrics and Gynecology, RH-20, University of Washington, Seattle, Washington 98195.

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several blood samples obtained intermittently (PRL is secreted in a complex manner and is subject to pulsatile, circadian, and environmental variation) (7-10, 12); and 3) a rather small number of subjects (*i.e.* $n = 2$), who were diagnosed as LPD were studied (7).

Therefore, we investigated PRL secretion in a relatively large group of women who demonstrated LPD during the study cycle. The intermittent (pulsatile) secretion pattern of PRL was determined in all of our subjects (73 serum samples over 12-24 h), and many of the women also had daily hormone levels determined throughout the study menstrual cycle. In this manner we were able to take a much closer look at the alleged relationship between PRL secretion and corpus luteum function.

Materials and Methods

Subjects

The subjects in this study have been described previously (14, 15). The LPD study group consisted of 18 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. All had 2 out of phase endometrial biopsies in 2 spontaneous menstrual cycles; these out of phase biopsies were the basis for their 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.* (16) by two 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 2 out of phase endometrial biopsies. An additional (more strict) criterion for this diagnosis is decreased daily (integrated) luteal phase serum P levels (17). All 18 women in this study met the general criteria, a subgroup of 10 women who had daily blood samples 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 (14). Integrated luteal P levels were not available in the other 8 LPD women, since they did not have daily blood sampling.

The control group for this study comprised 36 normal women. These women were between 18-35 yr of age within $\pm 10\%$ of ideal body weight (Metropolitan Life Insurance Co. tables, 1980) had regular menstrual cycles and had one or more normal basal body temperature charts (luteal length, ≥ 12 days). None was taking any medication, and all met the following hormonal criteria in the midluteal phase of a prior menstrual cycle: serum P, less than 38 nmol/L (12 ng/mL); PRL less than 20 $\mu\text{g/L}$ (20 ng/mL); and testosterone, less than 1.4 nmol/L (40 ng/dL). The controls were not all of proven fertility, as many had not ever attempted to conceive. Twenty-four of these women had daily blood samples throughout a complete menstrual cycle that were assayed for PRL and P.

Protocol

Daily blood samples were drawn each morning (0800-1000 h) of the study cycle in subsets of the two study groups (10 of the 18 LPD subjects; 24 of the 36 normal subjects). These samples were assayed for PRL, P, and LH.

All of the women in the LPD group had at least 1 out of phase endometrial biopsy before the study cycle. The 10 LPD subjects with daily blood draws during the study had only 1 previous biopsy. Their second biopsy was performed in the study cycle and was found to be out of phase. The other 8 LPD women had 2 out of phase biopsies in prior cycles. Eleven of the 24 normal subjects undergoing daily blood sampling also had late luteal endometrial biopsies during the study cycle; all 11 were in phase. In this manner we were able to confirm that an endometrial biopsy was a reasonable reflection of luteal serum P levels in our subject population [*i.e.* out of phase biopsies occurred in deficient luteal phases (as determined by integrated P levels) and in-phase biopsies were associated with normal integrated P levels].

Frequent blood sampling was performed in both groups for determination of PRL patterns. Three cycle phases were studied: early follicular (EF), cycle days 1-6; late follicular (LF), cycle days 8-12; and midluteal (ML), cycle days 21-24. Eight of the 18 LPD women underwent frequent sampling on 1 occasion in either the follicular or the luteal phase, while the other 10 were studied once in each phase during the same cycle. In the LPD group, there were 9 frequent sampling studies in the EF phase, 5 studies in the LF phase, and 13 studies in the luteal phase. (The number of women studied in each cycle phase differed due to scheduling constraints.) Sixteen of the normal women were admitted on only 1 occasion in a specific cycle phase for frequent sampling (EF, $n = 5$; LF, $n = 6$; ML, $n = 5$). The follicular phase studies were all performed during daytime hours.

The 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 PRL and LH.

Hormone assays

The NIDDK human PRL RIA kit (RP-1 standard and hPRL-3 anti-PRL serum) was used to determine serum PRL concentrations (18). The intraassay coefficient of variation was 6.5%, and the interassay variability was 14.8%. The sensitivity of the PRL assay was 1 $\mu\text{g/L}$. Serum P was measured directly in duplicate with reagents supplied by Diagnostic Products Corp. (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-hydroxyprogesterone and less than 0.01% with testosterone, estradiol, pregnenolone, and

cortisol. Sensitivity in our laboratory was less than 1.6 nmol/L at a serum volume of 100 μ L. Intra- and interassay coefficients of variation were 9% and 12%, respectively. External quality control used the WHO program, which involves monthly measurements of unknown samples; no significant bias (>10%) was detected, and variabilities were comparable to those described above for internal quality controls. Serum LH was measured by double antibody RIA as described previously (19), using reagents supplied by the NIH with LER 907 as the reference preparation. The sensitivity of the LH assay was 6 μ g/L, with intra- and interassay coefficients of variation of 5.5% and 8.4%, respectively. All samples from an individual women were analyzed in duplicate in a single assay for all hormones.

Pulse analysis technique

For each woman there were 73 data points each for serum PRL and LH during the sampling intervals. The following pulse parameters were calculated: PRL and LH pulse frequency, PRL and LH pulse amplitude, and mean serum PRL and LH levels. An adaptive threshold method (DC3) was used to determine the frequency and amplitude of hormone pulses, as previously described (20). A pulse was defined as an increase from the local minimum to the 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 were 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 $100 \times (\text{number of pulses detected last time}) / (\text{number of samples in the data set})$. 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 PRL and LH data for the occurrence of synchronous secretion (pulses) (20). 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 PRL pulse fell within one data point of a LH pulse. Neither data set was shifted relative to the other before this analysis, as no lag time would be expected in the relationship between these two hormones.

Statistics

The daily hormonal data from both groups were normalized around the day of the LH surge, which was defined as the peak LH value (day 0). Mean PRL levels were calculated for each individual, as were ranges, across the menstrual cycle. An integrated hormone level was calculated for PRL and P for each subject by adding the values for the entire luteal phase.

Each sum represents the area under the curve. These integrated PRL and P levels were compared between the LPD and control groups by correlation analysis and Student's *t* tests. Possible differences in diurnal and nocturnal PRL secretion between the two groups were investigated by empirically dividing the 24-h luteal admissions into two segments: daytime (0700–2300 h) and nighttime (2300–0700 h). (Apparent sleep was observed, but formal electroencephalogram sleep studies were not performed; subjects were encouraged to stay awake during the day, and no extended sleep occurred.) Pulse parameters were broken down accordingly for each segment. All pulse parameters (*i.e.* frequency, amplitude, and mean level) were compared within and between groups in regard to cycle phases and time segments by Student's *t* tests. The results are expressed as the mean \pm SE unless otherwise indicated. $P < 0.05$ was considered significant.

Results

Initial observations of PRL secretion in LPD and normal women were made by examining daily PRL levels over an entire menstrual cycle. The mean PRL levels over a cycle were not different between the LPD and normal groups (LPD, 12.1 ± 1.5 ; normal, 13.8 ± 0.8 μ g/L). One individual in each of the groups had a mean level that slightly exceeded the upper limits of normal (24.6 and 22.9 μ g/L, respectively). The individuals in both groups had a wide range of PRL values; most subjects had one or more daily levels that exceeded 20 μ g/L. The women with LPD had significantly shorter luteal phase lengths than the normal women (11.7 ± 0.4 vs. 12.9 ± 0.2 days; $P \leq 0.01$).

Considering the fact that P secretion varies as a function of PRL concentration in a luteinized granulosa cell culture system (5), we investigated whether total luteal phase P secretion varied with the amount of PRL secreted. In this context a correlation analysis was performed between integrated luteal phase P and PRL levels in both normal and LPD women. In both normal ($n = 24$) and LPD ($n = 10$) women, there was no significant correlation between integrated PRL and P ($r = 0.38$ and -0.31 , respectively). Although the expected difference in integrated P levels between the LPD and normal women was found ($P < 0.01$), there was no difference in integrated luteal PRL levels between the two groups ($P = 0.2$).

PRL is secreted in an intermittent pulsatile fashion throughout the menstrual cycle. Figures 1, 2, and 3 illustrate PRL secretion in representative pairs of normal and LPD women in the EF, LF, and ML cycle phases. Figure 4 summarizes the PRL pulse parameters (frequency, amplitude, and mean level) for the two groups. When directly comparing pulse parameters between the LPD and normal groups the only significant difference was a decreased PRL pulse amplitude in the EF phase in LPD women (2.6 ± 0.3 vs. 5.5 ± 1.3 μ g/L; $P \leq 0.01$).

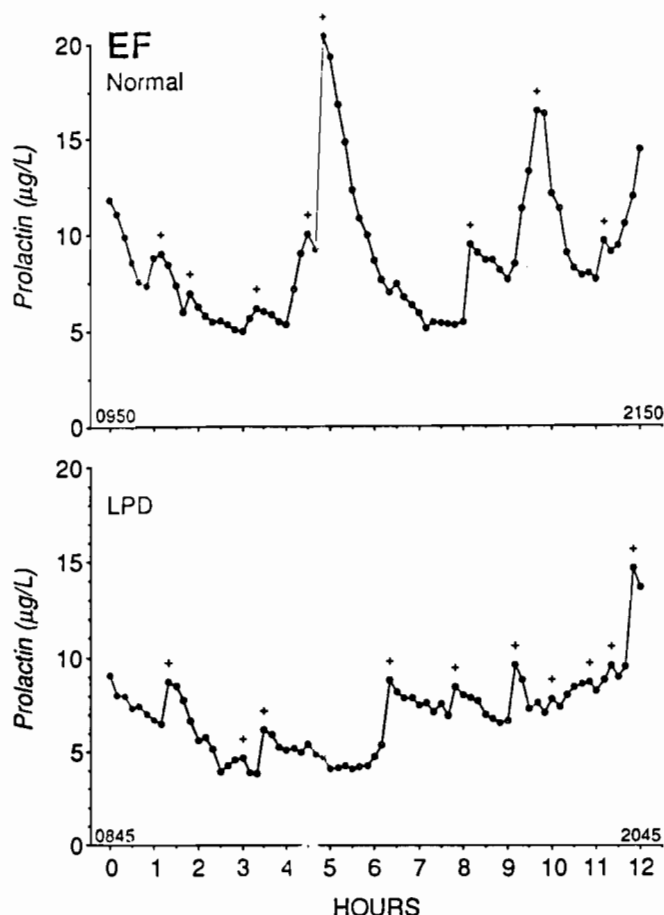


FIG. 1. Intermittent (pulsatile) secretion of PRL in representative normal and LPD women in the EF cycle phase. Secretory episodes (pulses) are indicated by a + on the graphs in this and subsequent figures.

Otherwise, there were no differences in the PRL pulse parameters between the two groups.

There were some subtle differences in the PRL secretion pattern across the menstrual cycle in LPD women (Fig. 4). There was no step up in PRL pulse frequency between the EF and LF phases in LPD women as occurred in normals. In LPD there was a subtle but significant increase in the mean PRL level between the EF and ML phases (9.0 ± 0.9 vs. 13.6 ± 0.9 $\mu\text{g/L}$; $P < 0.01$) that was not present in the normal group.

There is a known coupling between LH and PRL pulses that varies in the degree of synchrony between individuals and phases of the menstrual cycle (20). There were no discernible differences in LH-PRL coincident secretion between normal and LPD women (percentage of subjects in follicular phase with significant coincidence: LPD, 44%; normal, 80%; luteal phase: LPD, 23%; normal, 20%). We also investigated whether there were any differences in diurnal and nocturnal PRL secretion between normal and LPD women in the luteal phase. Both groups demonstrated the expected increase in mean

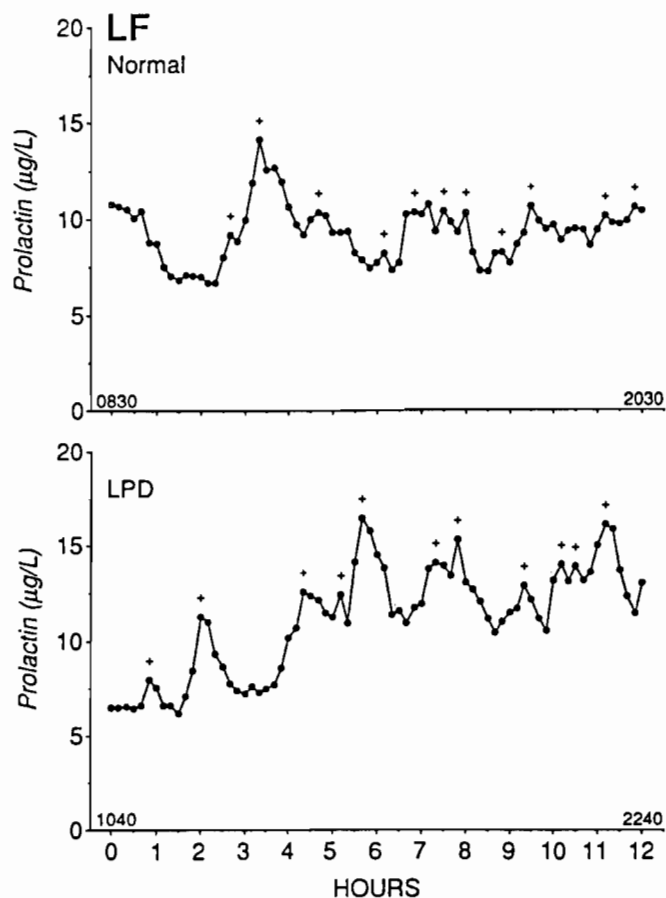


FIG. 2. Intermittent (pulsatile) secretion of PRL in representative normal and LPD women in the LF cycle phase.

PRL levels between the day and night intervals (Table 1). There were no differences between groups in pulse frequency, pulse amplitude, or mean PRL level during the 2300–0700 h interval (Table 1) or during the interval of observed sleep (data not shown).

Discussion

A number of clinical studies have reported abnormalities in serum PRL concentrations in some women with LPD (7–13). In most of these studies the PRL concentration was roughly estimated by obtaining one or several random blood samples. Random blood samples provide only a very rough approximation of the true PRL levels (21), and venipuncture stress alone may contribute to a higher than normal PRL result in women who experience difficulty with blood sampling. Furthermore, the presence or absence of LPD was often inferred from data obtained in prior menstrual cycles and/or by diagnostic methods other than documentation of low P output. Other studies in LPD women have examined PRL secretion in a provocative manner (TRH stimulation; nocturnal changes) and found a high prevalence of abnormali-

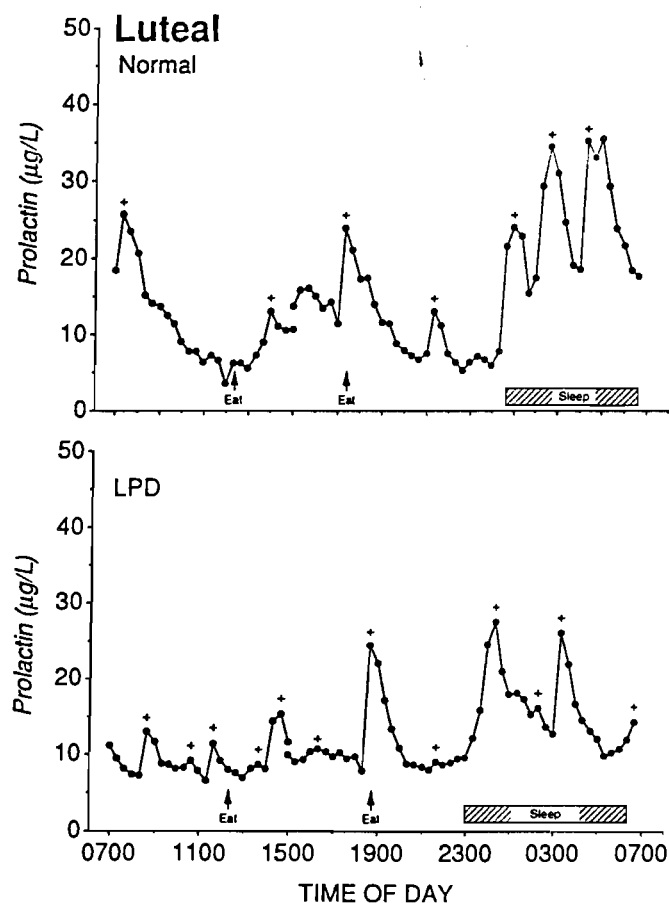


Fig. 3. Intermittent (pulsatile) secretion of PRL in representative normal and LPD women in the luteal cycle phase.

ties (11–13). Considering this information, we hypothesized that most LPD women would demonstrate definite, albeit subtle, abnormalities in PRL secretion. Considering the fact that dopamine is a known modulator of both gonadotropin and PRL secretion, this hypothesis was supported by our recent findings of abnormal LH secretion patterns in LPD (15).

This study examined both daily PRL levels and pulsatile PRL secretion in three cycle phases in a number of women with LPD ($n = 18$). The number of blood samples and the frequency of sampling in the current study would minimize variations in PRL that could occur secondary to pain, stress, or any environmental factors. All of our LPD women had two out of phase endometrial biopsies, and those who had daily sampling had decreased integrated P levels in the study cycle. Our hypothesis was only weakly supported by our findings. The significant changes in PRL secretion in LPD were subtle. The LPD women demonstrated a small decrease in PRL pulse amplitude during the EF phase. Otherwise, there were no significant differences in pulse parameters between the two groups during any phase of the menstrual cycle. Furthermore, we found midnormal range mean PRL

levels in all three cycle phases in LPD (a mean level determined from 73 samples is a very close approximation of the real level). Our finding of no difference in the mean PRL level over the menstrual cycle in a subgroup of LPD women ($n = 10$) compared to that in normal subjects supports the finding of normal mean PRL levels during the pulsatile studies. Together, these results indicate that the ovary, and specifically the corpus luteum, are not exposed to chronic high or low levels of PRL in LPD cycles.

Our additional investigations of PRL secretion in LPD were an attempt to determine whether qualitative secretion differences were present in this disorder. There were no differences in the degree of coupling between LH and PRL secretion when normal and LPD women were compared. In addition, there were no differences in either the nocturnal or diurnal secretion of PRL between these groups in the luteal phase. Due to the expected relatively rapid PRL pulse rate and the associated necessity of 10-min sampling in the follicular phase, we were limited to 12-h study intervals and were unable to investigate nocturnal PRL secretion during this cycle phase. It is possible that LPD women experience exaggerated nocturnal PRL secretion only in the follicular phase; however, their daytime decrease in PRL pulse amplitude in the follicular phase leads us to doubt this possibility.

Finally, we examined whether there was a discernible quantitative relationship between the integrated levels of PRL and P in the luteal phase. McNatty *et al.* (5), using luteinized granulosa cells *in vitro*, found that P secretion varied with the PRL concentration in the culture medium. Our *in vivo* results found no significant changes in P levels as a function of PRL in both normal and LPD women. (Obviously, there are major differences between *in vitro* and *in vivo* studies. For example, the cells studied by McNatty were modified granulosa cells and not true luteal cells.)

These results, taken together, offer little support for abnormalities in PRL secretion as common to the pathophysiology of LPD. Considering that LPD is a disease with a heterogeneous etiology, our study group may not have been large enough to include LPD women with PRL secretion abnormalities. However, this explanation is weak, since this study included more subjects than prior studies that have examined PRL secretion and LPD, and the sampling frequency and intensity employed far exceeded a casual look at PRL levels. Further analysis of the literature on LPD and PRL is necessary to put our study in context. A number of small studies of women with galactorrhea and/or sustained hyperprolactinemia have reported a clear association between normalization of PRL and P levels (7, 8, 10, 22). In these cases, sustained elevations of PRL may very well have a direct suppressive effect on corpus luteum function. However,

FIG. 4. PRL secretory parameters (frequency, amplitude, and mean level) are summarized for LPD and normal women in three phases of the menstrual cycle.

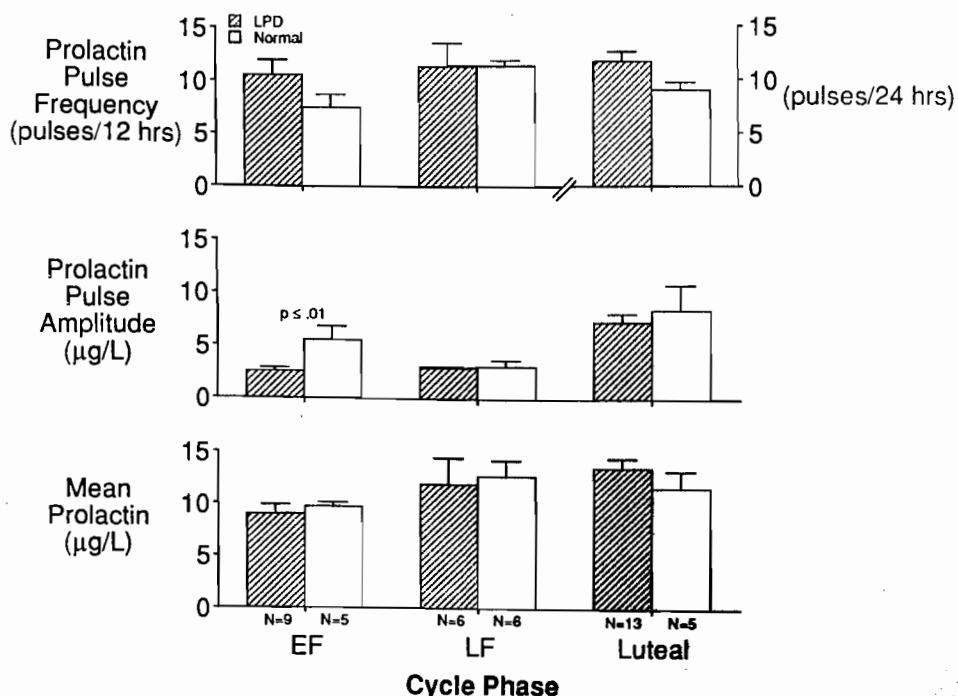


TABLE 1. Nocturnal PRL pulse parameters

	Day (0700–2300 h)	P	Night (2300–0700 h)
PRL pulse frequency			
Normal	5.0 ± 0.5	NS	8.0 ± 1.4
LPD	7.2 ± 0.7	<0.05	8.9 ± 0.8
PRL pulse amplitude			
Normal	5.9 ± 1.5	NS	13.4 ± 5.9
LPD	6.2 ± 1.1	<0.05	8.9 ± 1.0
Mean PRL level			
Normal	9.3 ± 1.5	<0.05	15.4 ± 1.2
LPD	12.6 ± 0.9	<0.05	15.9 ± 0.9

Values are the mean ± SE.

these women were treated with a dopamine agonist medication that is known to have an effect on LH secretion as well (levels of LH and LH secretion patterns were not considered in these studies). Other studies performed in normal women have noted LPD in association with fluctuations in PRL that were induced with either dopamine agonist or antagonist medications (3, 4). Possible dopamine-mediated changes in gonadotropin secretion could also be the explanation for these findings. Another set of studies have reported mild elevations in serum PRL in women with unexplained infertility (9). Most of these patients were treated with bromocriptine, and many conceived. However, most of these studies were uncontrolled, and the hyperprolactinemia was based on a very limited number of random samples. We have previously reported that PRL levels above 20 µg/L are found approximately 20% of the time when daily blood samples were obtained between 0800–1000 h in a large group of normal women (21). Venipuncture stress and

inherent individual variability may both contribute to widely ranging PRL levels in all women. Perhaps LPD women in these prior studies were more reactive in terms of stress and associated increases in PRL than normal women. However, we did not find any differences in the daily variability of PRL levels between the normal and LPD women in this study. Finally, Archer (12) reported increased PRL levels in LPD women stimulated with TRH. While he could differentiate the LPD women as a group, he could not always distinguish their individual PRL response from normal. This finding would appear to indicate that only several women in his study had an exaggerated response. In a similar study we could not distinguish LPD from normal subjects with the use of TRH (23).

The regulatory role of PRL in the nonhuman primate corpus luteum appears to be tenuous as well. Richardson and colleagues (24) studied corpus luteum function during GnRH-induced menstrual cycles in hypothalamus-lesioned monkeys. They found no differences in P secretion among hyper-, eu-, and hypoprolactinemic monkeys. PRL levels that were markedly elevated, normal, or nondetectable had no effect on the time course and levels of P in the luteal phase. Furthermore, PRL did not alter P secretion by monkey or human luteal cells in culture (25, 26).

We suspect that much of the human literature that has linked LPD with hyperprolactinemia has been inadvertently reporting an associated phenomenon rather than a causal factor. We have reported definite but subtle changes in gonadotropin secretion in LPD women (15). Considering dopamine as a neurotransmitter that is

known to modulate gonadotropin and PRL secretion, there may be changes in gonadotropin secretion whenever PRL elevations were reported. To finally determine whether hyperprolactinemia *per se* can cause LPD, it would be necessary to induce a sustained hyperprolactinemic state *in vivo* without modulating the dopamine tone.

In summary, we have serious reservations about whether abnormalities in PRL secretion are an integral or a common component of the pathophysiology of LPD. It would appear that a small subgroup of women with mild, but definite and sustained, hyperprolactinemia may have LPD. Therefore, in the clinical setting, it would still be wise to determine a serum PRL level in patients who have been diagnosed as LPD. If a random PRL measurement is elevated, it should be confirmed by several more samples obtained in a basal state (e.g. morning fasting). Suppression of elevated PRL levels with a dopamine agonist would then be appropriate therapy.

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