Abnormal Patterns of Pulsatile Luteinizing Hormone in Women With Luteal Phase Deficiency

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

Luteal phase deficiency is usually a problem of inadequate progesterone production associated with inadequate ovarian follicular development. The hypothesis that luteal phase deficiency results from an abnormal secretion pattern of luteinizing hormone (LH) was tested in these women. To this end, the early follicular LH secretion pattern in four women with luteal phase deficiency was characterized and compared with patterns in normal women. Blood samples were obtained through indwelling catheters every ten minutes for eight hours (10 AM to 6 PM), and plasma levels of LH and FSH were measured. Luteinizing hormone and FSH secretion profiles were analyzed for pulse frequency, amplitude, and mean plasma level. A significantly greater LH pulse frequency in women with luteal phase deficiency was observed when compared with the frequency in normal controls (luteal phase deficiency, 10.5 pulses/eight hours; normal, 5.2 pulses/eight hours; $P \leq .05$). The mean FSH concentration was less in the women with luteal phase deficiency, but the level was not significant. These data suggest that the abnormal LH secretion pattern observed in women with luteal phase deficiency is responsible for their inadequate luteal phase progesterone secretion and their infertility. *(Obstet Gynecol 63:626, 1984)*

Normal function of the corpus luteum is dependent upon the proper ripening of the preovulatory follicle,[1] which is directed by a precise patterning of gonadotropin signals emanating from the pituitary gland.[2] Inadequate progesterone secretion or luteal phase deficiency is a cause of infertility and habitual abortion in the clinical setting.[3] Several studies have noted abnormal concentrations of baseline (daily samples) gonadotropins in the follicular phase of women with luteal phase deficiency.[4,5] In this study, the pattern of gonadotropin secretion in the early follicular phase in women with luteal phase deficiency was investigated and compared with the pattern observed in normal women.

From the Division of Reproductive Endocrinology, Departments of Obstetrics and Gynecology, Physiology and Biophysics, Zoology, and Medicine, University of Washington and Veterans Administration Medical Center, Seattle, Washington.

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Methods

The subjects were four infertile women with luteal phase deficiency as diagnosed by results of out-of-phase endometrial biopsy specimens in two separate menstrual cycles. The biopsy specimens were read according to the criteria of Noyes et al,[6] and all were more than two days out-of-phase when correlated with the next menstrual period. Table 1 lists pertinent details regarding these patients. Table 2 provides details regarding endometrial biopsies. Prolactin levels in these women were normal to slightly elevated (Table 1). As estimated from basal body temperature charts, the lengths of the follicular phase, the luteal phase, and the total cycle were normal in three of the four patients (Table 1). Each patient was admitted for pulse studies in the early follicular phase (cycle days 4 to 6) of the menstrual cycle, after the second biopsy and before any therapy. The serum estradiol value of 115 on cycle day 6 in patient D was an upper normal value for this laboratory in the early follicular phase. Endometrial biopsies were not performed in the pulse study cycles. Each patient subsequently demonstrated an in-phase endometrial biopsy after progesterone therapy was administered in the luteal phase; two of the patients have subsequently been placed on bromocriptine, as well, for failure to conceive.

During each early follicular phase admission, blood samples were obtained every ten minutes for eight hours (10 AM to 6 PM) through an indwelling intrave-

Table 1. Luteal Phase Deficiency Patients

Patient	Age	Gravidity/ parity	% IBW*	Prolactin (ng/mL)	Average cycle length (days)			Early follicular cycle day studied	E_2† at admittance (pg/mL)
					Follicular phase	Luteal phase	Total		
A	35	3/3	97.7	23	14	9	23	4	60
B	32	0/0	98.8	16	18	13	31	5	50
C	35	0/0	94.3	15, 34	15	15	30	6	60
D	31	0/0	91.3	22, 16, 37	16	15	31	6	115

* Ideal body weight (according to Metropolitan Life Tables, 1957).
† E_2 = estradiol.

nous line. Blood samples were analyzed for plasma concentrations of LH and FSH with the use of a double antibody radioimmunoassay technique, as modified from the original procedure described by Midgley.[7,8] Standard National Institutes of Health reagents were used, and results are expressed in nanograms per milliliter as per the LER-907 reference preparation. The sensitivity of the LH assay was 6 ng/mL; intra- and interassay coefficients of variation were 5.5 and 8.4%, respectively. The sensitivity of the FSH assay was 25 ng/mL; intra- and interassay coefficients of variation were 7.3 and 9.7%, respectively.

Pulsatile LH patterns were analyzed, using a modification of the method of Santen and Bardin.[9] For each sample set, the measurement error was assessed based on replicate variability. A "pulse" was defined as an increase from nadir to peak that was two standard deviations greater than assay variability. Statistical comparisons between the normal women ($N = 5$) and those with luteal phase deficiency were made by the Mann-Whitney U test.

Gonadotropin data from the same eight-hour time segments in the early follicular phase (10 AM to 6 PM) used in the luteal phase deficiency study patients were extracted and analyzed from 24-hour studies performed in normal controls.[10] Pertinent information regarding the five control women include age range 24 to 34 years (somewhat younger than the study patients), within five percent of ideal body weight (according to 1957 Metropolitan Life Tables); average cycle length 27 to 31 days; demonstrated a normal luteal phase progesterone secretion curve (did not have endometrial biopsies performed); and were admitted for early follicular pulse studies on or between cycle days 4 to 6 (mean = -11.6 ± 1.1 days from LH surge). This early follicular control gonadotropin data had been collected at a 20-minute sampling interval with four hours of superimposed ten-minute sampling. There was no difference in either LH or FSH pulse number between the ten- and 20-minute data base when this four-hour segment was subjected to pulse analysis. Comparable pulse analysis of simultaneous ten-minute versus 20-minute segments of LH data from normals in the late follicular phase also demonstrated no differences between them.[10] These findings indicate that the 20-minute sampling interval in normal controls was of sufficient frequency to accurately describe patterns of pulsatile secretion.

Table 2. Results of Endometrial Biopsies of Patients With Luteal Phase Deficiency

Patient	Cycle day of biopsy	Cycle length	No. of days biopsy out-of-phase	Successive cycles biopsied
A				
First biopsy	21	22	3	No
Second biopsy	23	24	4	
B				
First biopsy	28	31	3	Yes
Second biopsy	29	30	4	
C				
First biopsy	26	27	3	No
Second biopsy	26	27	4	
D				
First biopsy	24	33	3	Yes
Second biopsy	30	31	3	

Results

Women with luteal phase deficiency displayed a significantly greater LH pulse frequency when compared with normal women (10.5 versus 5.2 pulses/eight hours; $P \leq .05$) (Figure 1). Extrapolated to 24 hours, the luteal phase deficiency patients would have 31.5 LH pulses/day contrasted with 15.6 daily LH pulses in normals. Patients with luteal phase deficiency also demonstrated a lower LH pulse amplitude when compared with normal controls (11.2 versus 12.3 ng/mL), but this difference was not statistically significant (Figure 1). The mean LH level over the eight-hour period was roughly equivalent in the two groups (36.0 ± 4.9

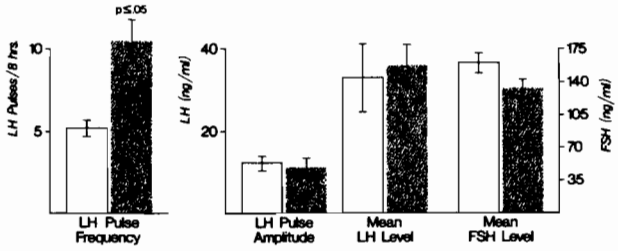

Figure 1. Bar graphs present comparative (mean ± SEM) LH and FSH pulse data for normal women (N = 5, 20-minute sampling interval) versus women with luteal phase deficiency (N = 4, ten-minute sampling interval). Open bars = normal control subjects. Shaded bars = luteal phase deficiency.

versus 33.1 ± 8.2 ng/mL); the mean FSH level was lower, again not significantly (P = .10), in the patients with luteal phase deficiency (133.3 ± 9.9 versus 159.7 ± 10.5 ng/mL) (Figure 1). Representative LH pulsatile patterns from a patient with luteal phase deficiency and from a normal woman are presented in Figure 2.

Discussion

Luteal phase deficiency has been clearly described in the research setting by decreased progesterone concentrations in multiple blood samples obtained in the luteal phase.[4,5] The diagnosis of luteal phase deficiency in the clinical setting has been more controversial (daily blood samples for progesterone are impractical in the clinical setting). The controversy stems primarily from the use of various diagnostic techniques, including basal body temperature charts, single and multiple serum progesterone levels, and endometrial biopsies. The sensitivity and accuracy of these clinical tests have not been well established. Endometrial biopsy currently appears to be the best clinical method by which to diagnose luteal phase deficiency.[11] Out-of-phase luteal endometrial biopsies have been correlated with decreased progesterone secretion,[12] but more studies need to be done. The patients in this study were diagnosed as having luteal phase deficiency by endometrial biopsy criteria alone; luteal serum progesterone levels were not determined in these women.

A growing body of experimental evidence implicates inadequate preovulatory follicular development in the pathogenesis of luteal phase deficiency. Strott et al[4] first noted a significant decrease in the FSH/LH ratio in the follicular phase of women with spontaneous luteal phase deficiency. In a similar study, Sherman and Korenman[5] found decreases in follicular phase baseline plasma FSH and estradiol levels in women with spontaneous luteal phase deficiency. In both of these studies, baseline plasma LH levels and the midcycle LH peak were normal. These reports on the endocrine pathology associated with luteal phase deficiency were published in the mid-1970s and were soon extended by important nonhuman primate studies. The existence of spontaneous luteal phase deficiency in the rhesus monkey was first reported by Wilks and colleagues.[13] They found significant changes in the preovulatory FSH/LH ratio and decreased follicular phase plasma estradiol levels in rhesus monkeys with this condition. Work by Stouffer and Hodgen[14] corroborated the concept of preovulatory determination of corpus luteum function. By inducing transient early follicular decreases in baseline FSH with the administration of porcine follicular fluid to rhesus monkeys, they were able to effect decreases in follicular phase estradiol and luteal phase progesterone production.[14] In an extension of Stouffer's study, diZerega and Hodgen[1] reported that porcine follicular fluid-induced luteal phase deficiency in rhesus monkeys could be partially reversed with human menopausal gonadotropins. A recent study by Sheehan and Yen[15] reported that women given a potent luteinizing hormone-releasing hormone agonist early in the follicular phase of spontaneous menstrual cycles have decreased follicular FSH and estradiol, followed by short luteal phase.[15] These studies argue for preovulatory gonadotropin abnormalities (primarily, decreased FSH) as a pathophysiologic basis of luteal phase deficiency.

There are well-described changes in the LH secretory (pulsatile) patterns over the course of the human menstrual cycle.[16,17] Likewise, there are well-known changes in baseline LH and FSH throughout the menstrual cycle. Recent studies in rhesus monkeys show that luteinizing hormone-releasing hormone pulse fre-

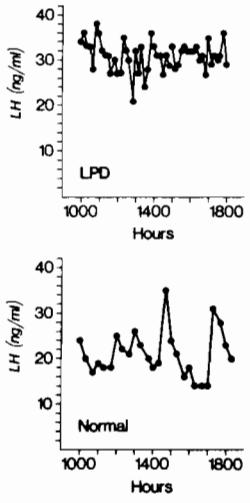

Figure 2. The LH secretory pattern in the early follicular phase in a normal woman (five pulses) and a woman with luteal phase deficiency (nine pulses) at 20-minute and ten-minute sampling intervals, respectively.

quency can influence the LH/FSH secretion ratio, demonstrating that a decrease in the luteinizing hormone-releasing hormone pulse frequency may cause a selective increase in baseline FSH levels over that of LH; conversely, an increase in the luteinizing hormone-releasing hormone's pulse frequency leads to a decrease in baseline FSH.[18] Lincoln and Short[19] have also reported that changes in luteinizing hormone-releasing hormone pulse frequency and amplitude can differentially regulate baseline LH and FSH levels in the ram. Inferences drawn from these studies led to the hypothesis that the decrease in baseline FSH in the follicular phase in women with luteal phase deficiency would be associated with a relatively higher LH pulse frequency in the early follicular phase of women with luteal phase deficiency compared with normal women; the results provide evidence to support this hypothesis. The gonadotropin secretory pattern associated with luteal phase deficiency in other phases of the menstrual cycle needs to be carefully investigated. Significantly decreased mean plasma FSH levels during the early follicular phase of these four women with luteal phase deficiency were not observed. Previous reports[4,5] suggest that, in women with luteal phase deficiency, plasma FSH levels are lower than controls, most notably in the middle and late follicular phases—phases not studied in the present work.

It has recently been demonstrated that progesterone is responsible for the decrease in LH pulse frequency in the luteal phase.[10] Based on the assumption that luteal phase deficiency, as diagnosed by endometrial biopsy, is associated with inadequate progesterone secretion, two hypotheses, not mutually exclusive, could account for the difference in LH pulse pattern between normal women and those with luteal phase deficiency. On the one hand, inadequate progesterone production in luteal phase deficiency may be responsible for the increased LH pulse rate in the early follicular phase, with the problem perpetuating itself in the subsequent early follicular phase, after the decrease in progesterone in the preceding luteal phase. On the other hand, a primary disturbance in the luteinizing hormone-releasing hormone pulse generator, leading to an increased LH pulse frequency (and, consequently, decreased baseline FSH levels), could be the cause of luteal phase deficiency. Further study will be required to clarify the relative importance of these, and possibly other, mechanisms in the etiology of luteal phase deficiency.

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Address reprint requests to:
Michael R. Soules, MD
Department of Obstetrics and Gynecology RH-20
University of Washington
Seattle, WA 98195

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