

Luteal Phase Deficiency: Characterization of Reproductive Hormones over the Menstrual Cycle*

MICHAEL R. SOULES, ROBERT I. McLACHLAN†, MARIT EK,
KRISTINE D. DAHL, NANCY L. COHEN, AND WILLIAM J. BREMNER

Departments of Obstetrics and Gynecology (M.R.S., N.L.C.), Medicine (R.I.M., K.D.D., W.J.B.), and Pathology (M.E.), University of Washington, and Veterans Administration Medical Center (R.I.M., K.D.D., W.J.B.), Seattle, Washington 98195

ABSTRACT. The recurrent deficiency of progesterone (P) secretion by the corpus luteum has been associated with infertility and habitual abortion and given the clinical diagnosis of luteal phase deficiency (LPD). There is evidence that both follicular and luteal phase abnormalities can result in LPD cycles. In this study we have examined reproductive hormone levels and preovulatory follicular size in women with LPD (n = 10). For the purposes of this study, LPD was determined by an endometrial biopsy in the studied cycle that was more than 2 days out of phase. These biopsies were performed in women with infertility or habitual abortion who exhibited an out of phase biopsy in a prior cycle. The control group consisted of 28 normal women. Daily serum levels of the following hormones were determined in each subject: LH and FSH [immuno- and bioactive (LH-immuno and LH-bio)], P, estradiol (E₂), and inhibin. The LPD women exhibited significant decreases in integrated luteal phase levels of inhibin [10,615 ± 898 vs. 13,560 ± 662 (U/L)·days; P < 0.02] and E₂ [5,015 ± 275 vs. 6,435 ± 393 (pmol/L)·days (1366 vs. 1753 (pg/mL)·days); P < 0.05] in addition to the expected decrease in P [280 ± 23 vs. 420 ± 23 (nmol/L)·days (88 vs. 132 (ng/mL)·days); P < 0.01]. On days 6–11 after the LH surge (day 0), there was a significant (P < 0.05) decrease in mean LH-bio levels in LPD compared with those in normal

women (146 ± 26 vs. 212 ± 24 µg/L). The midcycle LH surge was deficient in LPD when both LH-immuno [482 ± 30 vs. 672 ± 43 (µg/L)·days; P < 0.01] and LH-bio [1711 ± 179 vs. 2248 ± 226 (µg/L)·days; P < 0.05] levels were compared with normal values. When comparing the follicular phase in LPD with that in normal women, similar follicle size, peak and integrated E₂ levels, and mean LH and FSH (immuno and bio) levels were found. The only follicular phase abnormality noted in this study was decreased mean levels of serum inhibin in the early and midfollicular phases (221 ± 19 vs. 308 ± 25 U/L; P < 0.01). In this group of women with LPD, low levels of inhibin in the follicular phase were consistent with the concept of a defect in function of the preovulatory follicle, possibly as a result of previously described defects in gonadotropin secretion in this condition. Our findings of decreased LH levels by both immuno- and bioassay at midcycle and in the luteal phase may also be causal in the deficiencies of corpus luteal function.

We conclude that 1) the corpus luteum in LPD exhibits multiple hormone deficiencies, and 2) the pathogenesis of LPD is complex and includes decreased inhibin levels in the follicular phase, a subnormal midcycle LH surge, and abnormal levels of LH-bio in the luteal phase. (*J Clin Endocrinol Metab* 69: 804, 1989)

THE LUTEAL phase of the normal menstrual cycle is characterized by progesterone (P) secretion by the corpus luteum. P acts to stimulate endometrial gland maturation (secretory change) and decidual transformation of the endometrial stroma, thereby providing the hormonal basis for embryo implantation. The clinical entity of luteal phase deficiency (LPD) has been considered to exist when there is recurrent deficiency of luteal phase P secretion and/or action, leading to infertility or habitual abortion (1, 2). LPD has been suggested to be a

common cause of infertility, although the data are variable (3), probably as a result of differences in definition and patient groups studied.

The pathogenesis of LPD is not well understood. As the corpus luteum is anatomically derived from the post-ovulatory follicle, events before ovulation may influence subsequent corpus luteal function. Experimental interference with the profile of gonadotropic stimulation during the follicular phase of the cycle using a GnRH agonist (4) or crude follicular fluid preparation (5) has been shown to interfere with P secretion during the luteal phase. Other investigations have reported decreased immunoactive FSH (FSH-immuno) levels during the follicular phase (6–9). On the other hand, after normal folliculogenesis, P secretion can also be decreased by interference with the gonadotropic support during the midluteal phase by GnRH antagonist administration (10, 11) and interference with pulsatile LH secretion (12). A

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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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further potential mechanism of LPD may include abnormalities of LH pulse frequency during the follicular phase (13–17). It is clear that follicular and/or luteal phase abnormalities may produce LPD.

Inhibin is a glycoprotein heterodimer consisting of two dissimilar disulfide-linked subunits, termed α and β (18, 19), which is believed to have an important role in the physiological regulation of FSH release. Inhibin is produced by the granulosa cell under the influence of FSH (20, 21) and by the luteal cell of the human ovary. Serum inhibin levels during the normal menstrual cycle show both a late follicular and a prominent midluteal rise (22, 23). In addition, inhibin may have a local role within the ovary (24). Since inhibin is secreted by both the follicle and the corpus luteum, we hypothesized that there would be decreased levels of circulating inhibin in the follicular and/or luteal phase of the cycle in LPD.

This study was undertaken as an attempt to further characterize the pathogenesis of LPD. Daily serum levels of reproductive hormones (including inhibin) were determined in a group of LPD women. Daily measurements of preovulatory follicle size were made until ovulation occurred. We sought to determine in LPD women 1) whether abnormalities in follicular development were present; 2) whether gonadotropin levels or relative ratios were different in the follicular, periovulatory, and/or luteal phases; 3) whether the follicle and corpus luteum were deficient in the secretion of hormones other than P; and 4) whether there was inadequate LH support of the corpus luteum.

Materials and Methods

LPD subjects

The women who participated in this study (Table 1) had presented to the reproductive endocrinology/infertility clinic with a complaint of either infertility or recurrent abortion. Those women with an initial late luteal endometrial biopsy

more than 2 days out of phase were eligible to participate in this study. Twelve women met these criteria and volunteered. The endometrial biopsies were assigned a menstrual cycle date according to the criteria of Noyes *et al.* (25) by 2 pathologists, each of whom reread all of the slides in a blind fashion at the completion of the study. Biopsies that were more than 2 days out of phase in relation to the subsequent menstrual period according to both pathologists were used to define the study population. Ten (83%) of the 12 volunteers had an out of phase biopsy during the study cycle; their data were compared to corresponding data from normal controls. Other groups have reported a lower incidence of a second out of phase biopsy (49–79%) (26, 27); however, our higher rate is a rather consistent finding in our clinic population. The 10 LPD subjects had endometrial biopsies in the study cycle that varied from 2.5–6.5 days out of phase (Table 2). In this manner the endometrial biopsy was used to select a population that would be expected to have decreased integrated P concentrations in the luteal phase (Fig. 1). [We consider decreased integrated luteal P levels to be the primary diagnostic feature of LPD (3).]

These women were studied over one menstrual cycle in the following manner. 1) Daily venous blood samples were drawn between 0800–1000 h from cycle day 1 until cycle day 5 of the subsequent menstrual cycle. 2) Daily pelvic sonography was performed to determine follicle size and identify ovulation from cycle day 10 until ovulation. 3) An endometrial biopsy was performed in the late luteal phase of the study cycle. The blood samples were assayed for LH, FSH, P, estradiol (E_2), and inhibin by RIA. Biologically active LH (LH-bio) was measured across the entire cycle; for FSH-bio, only samples from the follicular phase were assayed.

The daily sonograms were performed using an Acuson (Mountain View, CA) model 128 sector scanner with a 5-mHz abdominal transducer. A mean follicle diameter was sonographically determined as $(x + y + z)/3$; the ultrasound criteria for ovulation were the presence of at least two of the following findings: an acute decrease in follicle diameter, an abrupt increase in free ip fluid, and/or the appearance of intrafollicular echoes.

Normal subjects

Twenty-eight normal women were used as controls for this study. These women were between 18–35 yr of age, within \pm

TABLE 1. Clinical characteristics of study subjects

Subject	Age (yr)	%IBW ^a	Diagnosis [duration (yr)] ^b	Cycle length (days) ^c	Luteal length (days) ^c	Galactorrhea	PRL (random sample; ng/mL)
A	33	86	2° inf (1)	23	12	+	11
B	21	139	1° inf (2)	28	13	–	11
C	31	100	2° inf (3)	26	12	+	13
D	33	99	2° inf (4)	26	13	–	3
E	32	131	2° inf (5)	23	10	–	15
F	32	91	Recurrent ab	25	13	–	9
G	35	95	2° inf (1)	27	13	–	14
H	28	92	Recurrent ab	29	16	–	9
I	35	111	2° inf (3)	30	13	–	10
J	29	87	1° inf (4)	27	14	+	21

^a Ideal body weight, Metropolitan Life tables 1980.

^b 2° inf, Secondary infertility; 1° inf, primary infertility; ab, abortion.

^c Average of two or more basal body temperature charts from cycles before the actual study cycle.

TABLE 2. Characteristics of study cycle in LPD women

Subject	Cycle length (days) ^a		Endometrial biopsies [initial; study cycle (days out of phase)]	Max. follicle diameter (mean)	Peak follicular E ₂ (pg/mL) ^b	Peak luteal P (ng/mL) ^b
	Follicular phase	Luteal phase				
A	13	10	4; 4.5	24.7	443	33.3
B	14	12	2.5; 4	15.7	331	17.1
C	16	11	6; 6	16.7	292	12.0
D	13	12	4; 3.5	14.0	307	17.0
E	15	10	7; 6	21.3	313	11.2
F	12	12	4; 4	^c	335	11.2
G	13	13	5; 4	20.7	362	11.8
H	17	13	3; 4	^c	265	10.7
I	18	10	3; 6.5	25.0	296	10.6
J	11	14	3; 2.5	^c	322	13.4
Mean ± SEM	14.2 ± 0.7	11.7 ± 0.5 ^d	4.2; 4.5 ^d	19.7 ± 1.6	327 ± 15	14.8 ± 2.2 ^e
Normal (n = 28; mean ± SEM)	15.6 ± 0.6	13.1 ± 0.2	0.25 ± 0.25	20.3 ± 0.5	335 ± 21	19.4 ± 0.9

^a Follicular phase includes and luteal phase excludes the day of the LH surge.

^b SI unit conversion: E₂, 1 pg/mL = 3.67 pmol/L; P, 1 ng/mL = 3.18 nmol/L.

^c Subject did not have ultrasounds performed.

^d P < 0.01.

^e P < 0.05.

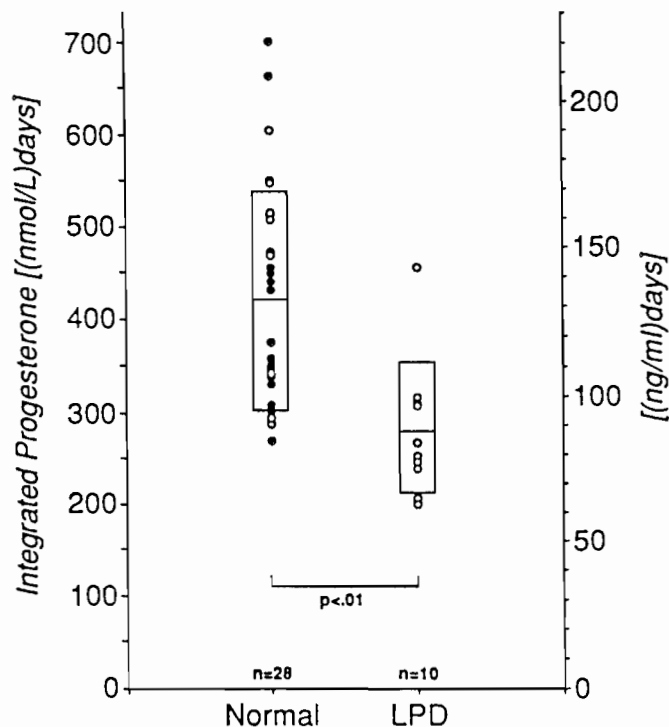


FIG. 1. Integrated P levels calculated over the duration of the luteal phase are shown for 28 normal (left) and 10 LPD (right) women. The size of each box indicates ± 1 SD. \circ , Values for those subjects who also had endometrial biopsies in the study cycle. The 8 normal women had in phase biopsies; the 10 LPD women had out of phase biopsies.

10% ideal body weight (Metropolitan Life Insurance Co. tables), had regular menstrual cycles (26–35 days), had at least one normal basal body temperature chart, were taking no

medications, and met the following hormonal criteria in the midluteal phase of a screened menstrual cycle [P, >38 nmol/L (12 ng/mL); PRL, <20 μ g/L; testosterone, <1.4 nmol/L (40 ng/dL)]. These controls had daily blood samples, hormonal assays, and ovarian follicular sonographic examinations in the same manner as the study patients. A randomly selected subgroup of these women (n = 8) had late luteal endometrial biopsies in the control cycle. These biopsies were determined to be in-phase by two pathologists who interpreted the histology in the same manner as described for the study subjects. (The integrated P levels in the biopsied normal women were significantly higher than those in the LPD women, but not significantly different from the integrated P levels in the other controls).

Serum was frozen and stored at -20°C before the measurement of FSH, LH, E₂, P, and inhibin. Selected samples were also assayed for LH- and FSH-bio. For all assays, samples from one woman were assayed simultaneously.

RIAs

LH and FSH. Serum LH and FSH were measured by double antibody RIAs as described previously (15), 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 (CVs) of 5.5% and 8.4%, respectively. The sensitivity of the FSH assay was 25 μ g/L, with intra- and interassay CVs of 7.3% and 9.7%, respectively.

E₂. Serum E₂ was measured by RIA as previously described (15). The sensitivity of the E₂ 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.

Inhibin. Serum inhibin was measured in a heterologous double antibody RIA based on purified 31K bovine follicular fluid inhibin as described previously (28). The rabbit antiserum (As 1989) was raised to 31K bovine inhibin, which was also iodinated for use as tracer. Transforming growth factor- β , bovine activin-A, bovine Mullerian inhibitory substance, and free inhibin subunits obtained after reduction and alkylation of 31K bovine inhibin showed less than 1% cross-reactivity in the assay. A partially purified human follicular fluid inhibin preparation was prepared and calibrated in terms of its *in vitro* inhibin bioactivity as described previously (22). Serum samples (200 μ L) were assayed in duplicate; the sensitivity of the assay was 100 U/L, and the ED_{50} was 650 U/L. The interassay CV was derived from the repeated measurements of multiple dilutions of a quality control serum (obtained from women during the midluteal phase) covering the range 90–20% bound to free ratio, and was 10.9% from 10 assays. The intraassay CVs in the upper (ED_{12}), mid (ED_{50}), and lower (ED_{88}) regions of the standard curve were 10.7%, 2.8%, and 6.0%, respectively, from 10 assays.

Bioassays

LH. Serum LH-bio levels were measured by using a modification (29) of procedures described by Van Damme *et al.* (30) and Dufau *et al.* (31). The mean intra- and interassay CVs were 8% and 12%, respectively. The sensitivity of the LH bioassay was 1.5 μ g/L. All of the samples for LH-bio were run in three assays. Samples from both normal and LPD women were run in each of these assays, with all of the samples from an individual in the same assay.

FSH. Serum FSH-bio was measured using an *in vitro* granulosa cell bioassay which measures FSH-stimulated estrogen production by rat granulosa cells obtained from diethylstilbestrol-primed rats (32). The reference preparation was LER 907. 17β - E_2 was measured using reagents supplied by Diagnostic Products Corp. The intra- and interassay CVs for the estrogen assay were 4% and 9%, respectively. The sensitivity of the FSH bioassay was 1.5 ng/culture well, with intra- and interassay CVs of 10% and 14%, respectively.

Statistics

Before statistical comparisons 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). Cycle days were numbered from the LH surge, the follicular phase in negative numbers and the luteal phase in positive numbers.

Cycle length was determined for the study cycle as the number of days elapsed from the first day of menses to and including the day before the onset of the next menses. Follicular phase length was calculated as the number of days from the onset of menses to and including the day of the LH surge.

Luteal phase length was defined as the number of days between the LH surge and the onset of the next menses.

Mean follicle diameter was determined for each subject for a minimum of 3 days before ovulation. Daily mean follicle size was compared between LPD and controls by analysis of variance with repeated measures.

An integrated hormone level was calculated for follicular phase E_2 and luteal phase E_2 , inhibin, and P for each subject by adding the values for days -6 to 0 in the follicular phase and for day 0 to the day before menses in the luteal phase, respectively. Each sum represents the area under the curve for the chosen days. Integrated levels were compared between the LPD and control groups by Student's *t* test.

For gonadotropin comparisons a mean LH (immuno and bio) and a mean FSH (immuno only) were calculated for the follicular and luteal phases of each cycle in each individual. To avoid the midcycle surge these mean LH and FSH levels did not include the interval from day -2 to day 2. Mean LH and FSH levels were compared between normal and LPD groups by Student's *t* test.

Specific segments of the cycle were selected for comparisons of FSH- and LH-bio. While we were interested in FSH-bio in the early and midfollicular phases, only limited remaining serum samples were available. Therefore, serum samples from days -12 to -5 were pooled for each patient. We were able to measure FSH-bio in daily samples from days -6 to -1, means were compared between the groups by Student's *t* test. LH-bio was measured in daily serum samples for cycle days 6–11 (allowing for short luteal phases in some LPD subjects, these were the common days that could be analyzed for both the study and control subjects), and comparisons were made between the groups by Student's *t* test. The second half of the luteal phase was selected for comparison of LH-bio levels because we hypothesized if inadequate LH support of the corpus luteum was part of the pathogenesis of LPD, then it would manifest itself at the time when P levels were decreased relative to normal.

A LH surge integrated value was calculated for each subject by adding the LH (immuno and bio) values on days -1, 0, and 1 and compared between the groups by Student's *t* test.

The intercycle interval was studied in the LPD women and in five normal women by rearranging the data relative to the onset of the next menstrual period after the study cycle. The intercycle interval was considered to be -5 to 5 days relative to the onset of menses, which was considered day 1.

Results are expressed as the mean \pm SE; $P \leq 0.05$ was considered significant.

Results

Luteal phase

In the luteal phase a certain level of corpus luteum function is necessary for implantation and the maintenance of early pregnancy. Luteal phase duration was significantly decreased in LPD compared to normal women (11.7 ± 0.5 vs. 13.1 ± 0.2 days; $P < 0.01$). P concentrations were decreased in LPD compared to normal women (Fig. 2A). Peak serum P in LPD was 47 ± 7

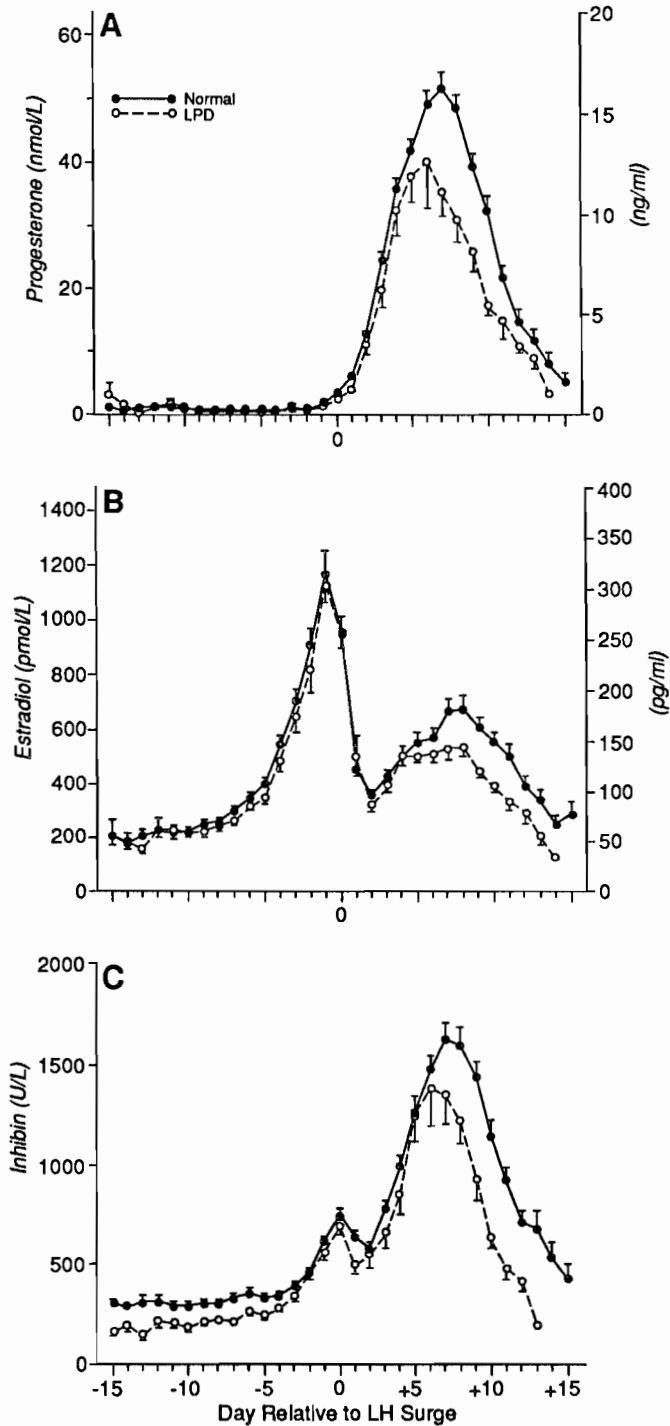


FIG. 2. The daily mean (\pm SE) levels of serum P (A), E_2 (B), and inhibin (C) over the menstrual cycle are indicated for the normal (\bullet — \bullet) and LPD (\circ — \circ) groups. There was a significant decrease compared with normal values in the luteal phase integrated levels of these three hormones in the LPD group. There was also a significant decrease in follicular phase (days -12 to -5) mean serum inhibin levels in the LPD group compared with normal values.

nmol/L compared to 62 ± 3 nmol/L in controls (14.8 vs. 19.4 ng/mL; $P < 0.05$); integrated P over the duration of

the luteal phase was 280 ± 23 (nmol/L)·days in LPD vs. 420 ± 23 (nmol/L)·days in normal women [88 vs. 132 (ng/mL)·days; $P < 0.01$; Fig. 1). Likewise, luteal phase E_2 concentrations were decreased in LPD [Fig. 2B; peak luteal E_2 , 624 ± 33 vs. 782 ± 51 pmol/L (170 vs. 213 pg/mL); $P = 0.07$ (NS); integrated luteal E_2 , $5,015 \pm 275$ vs. $6,435 \pm 393$ (pmol/L)·days ($1,366$ vs. $1,753$ (pg/mL) days); $P < 0.05$]. The luteal phase rise of inhibin was attenuated in LPD women, reaching an earlier peak on day 6 or 7, but was not significantly lower than that in normal cycles (1496 ± 176 vs. 1675 ± 74 U/L; $P =$ NS). Inhibin levels then fell prematurely along with P toward an early menses (Fig. 2C). Thus, the integrated inhibin level was significantly lower in LPD cycles [$10,615 \pm 898$ vs. $13,560 \pm 662$ (U/L)·days; $P < 0.02$].

There were several patterns of deficient P and inhibin secretion in LPD: 1) some women ($n = 2$) maintained normal daily levels of P and inhibin until the midluteal phase, which then fell rapidly; 2) most LPD women ($n = 7$) had persistently lower P and inhibin levels throughout the luteal phase, and 3) one woman with LPD secreted higher than normal levels of P and inhibin during the early luteal phase, followed by a precipitous decline and a 10-day luteal phase.

Insufficient LH support of the corpus luteum is a possible pathophysiological mechanism for LPD. The daily LH-immuno levels over the luteal phase were not different between LPD and normal women. During the latter stages of the luteal phase (days 6–11) both the normal and LPD women had daily LH-immuno levels that bordered on the lower level of assay sensitivity. When the individual mean LH-bio levels on days 6–11 were compared, the levels were significantly lower (146 ± 26 vs. 212 ± 24 μ g/L; $P < 0.05$) in the LPD group compared to normal values (Fig. 3).

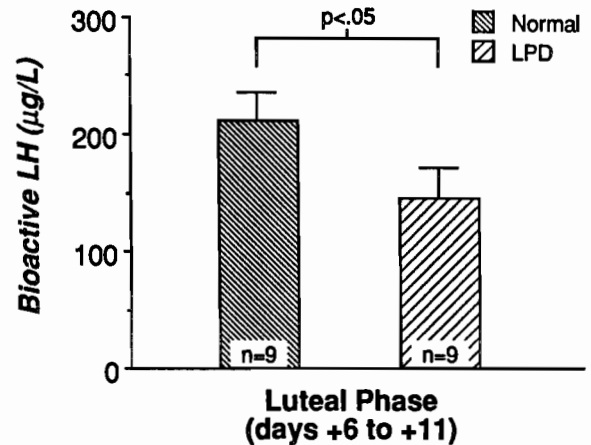


FIG. 3. The mean LH-bio levels across days 6–11 are indicated for the normal and LPD groups. There was a significant decrease in LH-bio levels in the LPD women compared with normal values. The size of each group and 1 SE are indicated.

Midcycle surge

The midcycle events pertaining to ovulation were evaluated in both groups. There was a trend toward lower peak levels of serum LH- and FSH-immuno in LPD cycles. The integrated LH surge (days -1 to 1) was significantly ($P < 0.01$) decreased in LPD [482 ± 30 vs. 672 ± 43 ($\mu\text{g/L}) \cdot \text{days}$; Fig. 4]; the integrated midcycle FSH value was lower than normal in LPD [662 ± 57 vs. 732 ± 39 ($\mu\text{g/L}) \cdot \text{days}$], but failed to reach significance. To further investigate this apparent decrease in the LH surge in LPD, daily serum samples from days -1 to 1 in the normal and LPD women were appropriately diluted, and LH-bio measured in a single assay. There was a significant decrease in both the peak LH-bio level (751 ± 93 vs. 1189 ± 143 $\mu\text{g/L}$; $P < 0.02$) and the integrated LH-bio surge [1711 ± 179 vs. 2248 ± 226 ($\mu\text{g/L}) \cdot \text{days}$; $P < 0.05$] in the LPD women (Fig. 4). Nonetheless, this attenuated LH surge in LPD led to ovulation (as determined by sonographic criteria) at an appropriate time (within 24 h of the LH peak in 71% of LPD patients compared with 79% of normal women).

Follicular phase

Indices of follicular development were studied (inadequate preovulatory follicular development can cause decreased P secretion after ovulation). The length of the follicular phase in the LPD women varied from 11–18 days (average, 14.2 ± 0.7 days) compared to 15.6 ± 0.6 days in normal women ($P = \text{NS}$). While the mean daily serum levels of LH- and FSH-immuno were lower in the LPD group (LH, 30.6 ± 2.3 vs. 39.1 ± 3.1 $\mu\text{g/L}$; FSH, 156.4 ± 12.0 vs. 161.6 ± 4.8 $\mu\text{g/L}$), there were no significant differences. The mean daily LH-bio levels on days

-15 to -2 tended to be lower in LPD women (249.3 ± 22.7 vs. 326.2 ± 40.6 $\mu\text{g/L}$), but failed to reach significance ($P = 0.07$). FSH-bio in individual patients' pooled sera from days -12 to -5 was not different between the LPD and normal groups. Daily FSH-bio levels on days -6 to -1 were also not different between the groups (Fig. 5).

Follicular growth was examined in terms of both E_2 secretion and follicle size. Peak serum E_2 levels and preovulatory integrated E_2 concentrations were not different between the groups (Table 2 and Fig. 2B). Neither the size of the dominant follicle nor its pattern of growth differed between LPD and normal women (Table 2).

In normal women inhibin begins a distinct rise after day -5, toward a midcycle peak. Therefore, we chose to compare inhibin levels in the respective groups during the interval preceding this rise. Mean serum inhibin levels from days -12 to -5 were significantly lower in the LPD group than in the normal group (221 ± 19 vs. 308 ± 25 U/L; $P < 0.01$; Fig. 2C). Inhibin levels in the LPD group rose after day -5 toward a peak on day 0, which was not significantly different from normal cycles (697 ± 49 vs. 771 ± 41 U/L; $P = \text{NS}$).

Intercycle interval

The intercycle interval encompasses the demise of the corpus luteum and the initiation of new follicular development. The endometrium in LPD women demonstrated an altered sensitivity to steroid withdrawal. In the women with LPD, menstrual bleeding began despite significantly ($P \leq 0.05$) increased P levels compared with those in normal women. In LPD cycles, the mean serum P was 9.5 ± 1.6 and 8.9 ± 3.5 nmol/L (3.0 and 2.8 ng/

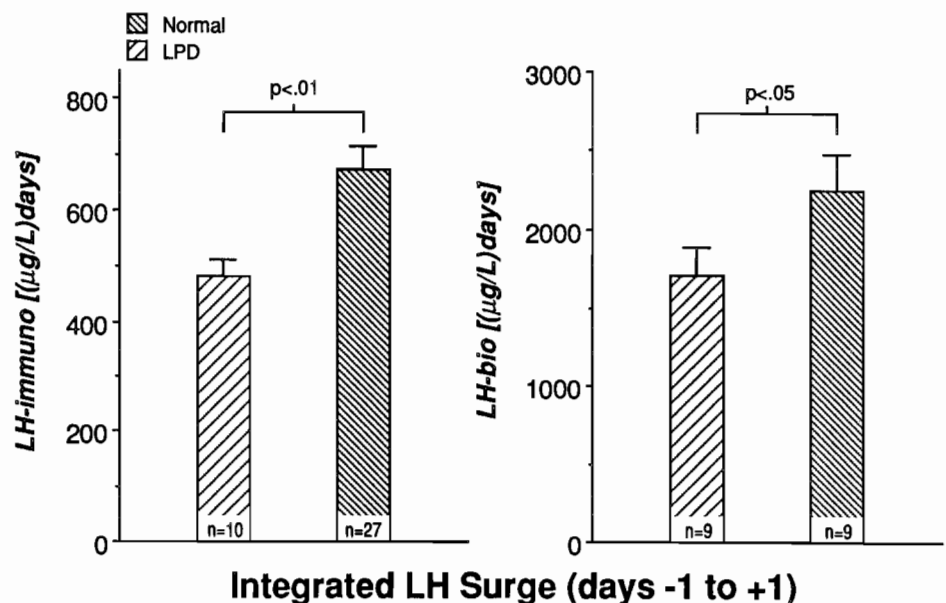


FIG. 4. The integrated LH-immuno and LH-bio levels over the midcycle surge (days -1, 0, and 1) are indicated for the normal and LPD groups. Both LH-immuno and bio levels were significantly decreased in the LPD group. The size of each group and 1 SE are indicated.

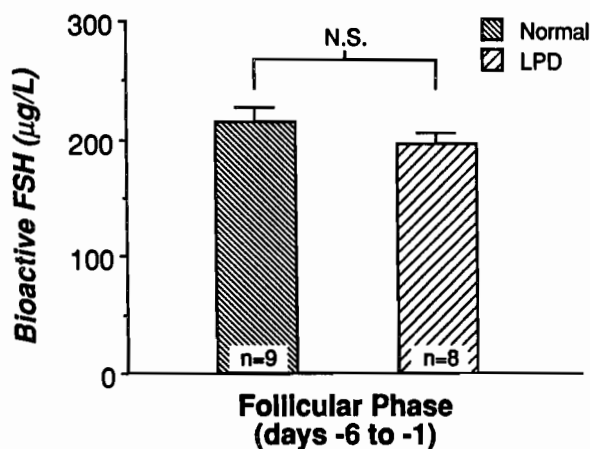


FIG. 5. The mean levels of FSH-bio over days -6 to -1 are indicated for the normal and LPD women. There was no significant difference between the groups. The size of each group and 1 SE are indicated.

mL) on the day preceding and the day of onset of menses, respectively, compared to corresponding levels of 6.0 ± 0.6 and 3.2 ± 0.6 nmol/L (1.9 and 1.0 ng/mL) in normals. Corresponding serum E_2 levels were not different between the two groups. Daily levels of serum LH and FSH were not different between LPD and normal groups over the intercycle interval.

Discussion

While LPD has been proposed as the cause of 10–30% of infertility and 30% of habitual abortion (3), its pathogenesis is not well understood (perhaps because of problems with its definition, patient group selection, and evidence for a number of possible etiological mechanisms). Based on our present knowledge, LPD should be viewed as a syndrome with a multifactorial etiology. A further difficulty has been in the prospective identification of spontaneous LPD cycles. Patients in the current study were selected on the basis of their clinical history of infertility and abnormal histology on endometrial biopsy in a screening cycle. The various clinical methods used to diagnose LPD (e.g. selected serum P levels) remain controversial (3). Of these methods, a timed endometrial biopsy as an *in vivo* bioassay of luteal phase P effect appeared to us to be the most reliable. We hypothesized that women with an out of phase biopsy would show hormonal evidence of decreased corpus luteal function. Indeed, in our hands, the endometrial biopsy identified a group of women with significant deficiencies in luteal P, E_2 , and inhibin secretion.

While in a physiological sense, P is presumed to be the dominant hormone secreted by the corpus luteum, the ovary does secrete other hormones in the luteal phase. The human corpus luteum secretes inhibin, as evidenced by a marked luteal phase rise in normal women in parallel with P (22, 23). In addition, inhibin bioactivity is secreted

by cultured human granulosa-lutein cells (33), and inhibin subunit gene expression has been found in corpus luteal tissue (34). The luteal phase of LPD women was characterized by decreased levels of inhibin and E_2 in addition to the P deficiency. Deficient secretion of these other hormones (especially inhibin as a nonsteroidal secretory product) indicates a generalized deficiency of the corpus luteum in LPD. While implantation and early pregnancy can be prevented or interrupted by P deficiency, it is not clear whether there are specific pathophysiological sequelae to the deficiencies in E_2 and inhibin. There have been two cell types described in the human corpus luteum, each having different capabilities in terms of P and E_2 secretion (35); the cellular origin of corpus luteum inhibin is unknown. It is not clear whether one or both cell types exhibit deficiencies in hormone secretion in LPD.

Normal corpus luteal function is dependent upon sufficient circulating levels of LH. When LH is suppressed in women or monkeys in the luteal phase, premature luteolysis occurs (10–12). We have recently demonstrated that inhibin as well as the sex steroids are primarily under LH control in the luteal phase (11). There is a qualitative relationship between LH and P secretion from the normal human corpus luteum which is probably quantitative as well (36, 37). In this study we found decreased LH-bio levels from days 6–11 after the LH surge in the women with spontaneous LPD. This interval was selected because all of the LPD women had decreased P levels at this time in the menstrual cycle. We have previously reported a decrease in luteal LH-bio levels (with a concomitant decrease in P) after a supraphysiological gonadotropin pulse frequency was induced in the follicular phase (15). Since LPD women demonstrate an increase in LH pulse frequency in the early follicular phase of their cycles, this may be the basis for their low LH-bio levels in the luteal phase (13, 14, 16). It would appear that decreased LH support of the corpus luteum is an integral part of the pathophysiology of LPD.

Previous isolated observations of some individual LPD cycles have noted what appeared to be an attenuated midcycle LH surge (38). The midcycle LH surge was deficient in magnitude and duration in the LPD women in this study. Despite the presence of a deficient LH surge in LPD, a timely ovulation occurred, as determined sonographically. It is possible that an inadequate gonadotropin surge could lead to an impaired corpus luteum despite the presence of a normal follicle; however, this hypothesis has never been directly tested. The physiological basis for reduced LH secretion at midcycle in LPD is unknown; its understanding would be facilitated by a study of the midcycle surge in LPD in more detail than can be afforded by single daily blood samples.

It is clear that inadequate follicular development (both

spontaneous and induced) in women and monkeys can lead to LPD (4, 5). Abnormalities in the LH/FSH ratio in the follicular phase have been reported in both women and monkeys with LPD cycles (6-9). Decreased preovulatory follicle size has previously been noted in LPD women (39). However, most indices of follicular development were normal in the LPD women we studied; there were no abnormalities in follicular phase levels of immuno- or bioactive LH or FSH, follicular phase duration, peak or integrated E_2 levels, or follicle size. Decreased inhibin levels in the early and midfollicular phases represented the only detectable follicular phase abnormality in our LPD subjects. The subnormal serum inhibin levels suggest a problem with granulosa cell response to FSH, which is not reflected by serum E_2 levels. In addition, the fact that FSH and E_2 in LPD women were not different from normal values despite approximately 30% lower levels of inhibin would also argue against a dominant negative feedback role for inhibin during the early to midfollicular phase. The measurement of follicular phase inhibin is unlikely to be an accurate predictor of subsequent deficient luteal function in individual cycles since there was considerable overlap between the normal and LPD groups. It would appear that decreased levels of inhibin represent a subtle abnormality of folliculogenesis in LPD that, presumably, is corrected when LPD is successfully treated with ovulation-inducing medications (40).

Increased mean serum P concentrations were noted at the onset of menses in the LPD women studied. This finding has been previously reported (41). Apparently the endometrium is less stable and more sensitive to steroid hormone withdrawal in LPD. Perhaps the tendency toward a decreased E_2/P ratio in the late luteal phase in these women with LPD is the source of this instability.

LPD can occur under a variety of circumstances and appears to be a heterogeneous disease. Based on our findings in spontaneous LPD cycles, the pathogenesis of LPD includes a variety of elements: 1) subnormal inhibin levels in the early and midfollicular phases; 2) an attenuated LH surge; and 3) decreased luteal LH-bio levels in the mid- and late luteal phases. We have previously reported an increased LH pulse frequency in the early follicular phase of LPD menstrual cycles (13, 14). Further studies are necessary to sort out the complex interactions these findings represent between the hypothalamic-pituitary unit and the ovary in LPD.

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