

The clinical relevance of luteal phase deficiency: a committee opinion

The Practice Committee of the American Society for Reproductive Medicine

American Society for Reproductive Medicine, Birmingham, Alabama

Luteal phase deficiency (LPD) has been described in healthy normally menstruating women and in association with other medical conditions. While progesterone is important for the process of implantation and early embryonic development, LPD, as an independent entity causing infertility, has not been proven. (*Fertil Steril*® 2012;98:1112–7. ©2012 by American Society for Reproductive Medicine.)

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Maintenance of pregnancy requires production of progesterone from the corpus luteum after ovulation and during the early first trimester until placental function is established. Removal of the corpus luteum prior to the development of adequate placental function results in spontaneous pregnancy loss (1). Given the importance of ovarian progesterone production to implantation and early pregnancy, the potential for ovarian inadequacy as a cause of infertility or pregnancy failure seems plausible. Studies in support of the need for adequate progesterone during the luteal phase (2) suggest that cycles in which conception occurs have a more rapid rise of progesterone and higher mid-luteal estrogen and progesterone levels compared to cycles in which there is no conception. However, similarly increased luteal phase progesterone levels have been observed in cycles with normal and biochemical pregnancies suggesting the pregnancy losses do not always result from ovarian insufficiency (3). Delayed implantation has been associated with a higher rate of pregnancy loss, although

the delayed implantation was more likely a result of an embryonic problem with inadequate early human chorionic gonadotropin (hCG) production, rather than an inappropriate ovarian response (4).

Given the importance of the luteal phase in the establishment of a normal pregnancy, luteal phase deficiency (LPD) has been described as a condition in which endogenous progesterone is not sufficient to maintain a functional secretory endometrium and allow normal embryo implantation and growth. The condition was first described in 1949 (5). Controversy regarding the clinical significance of LPD is due in part to the lack of a reliable test to diagnose this disorder. Luteal phase deficiency has purportedly been associated with infertility (6, 7); first trimester pregnancy loss (8); short cycles (9–12); premenstrual spotting (13); anorexia, starvation, and eating disorders (14); excessive exercise (15); stress (16, 17); obesity and polycystic ovary syndrome (PCOS) (18); endometriosis (19); aging (20); inadequately treated 21-hydroxylase deficiency (21); thyroid dysfunction and hyperprolactinemia

(22); ovulation stimulation alone (23); ovulation induction with or without gonadotropin-releasing agonists; and assisted reproductive technologies (ART) (24). Luteal phase deficiency has been shown to occur during the postpartum period, with significant weight loss or exercise (25), and in random cycles of normally menstruating women (11). Although there appears to be an association with infertility, it has not been established that persistent LPD is a cause of infertility. Moreover, LPD is only clinically relevant if it is consistently present in most cycles. This report will address controversies regarding the diagnosis and potential treatment of luteal inadequacy.

MEDICAL CONDITIONS WITH POTENTIAL IMPACT ON LUTEAL PHASE FUNCTION

Abnormalities in gonadotropin-releasing hormone (GnRH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH) pulsatility may be found in recovery from hypothalamic amenorrhea and may result in diminished luteal estrogen and progesterone secretion (15, 26–28). Diminished LH pulsatility with resulting abnormal progesterone secretion may also be problematic in ovulation induction cycles in women with hypothalamic amenorrhea (28, 29).

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Correspondence: American Society for Reproductive Medicine, 1209 Montgomery Highway, Birmingham, AL 35216 (E-mail: asrm@asrm.org).

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Thyroid and prolactin disorders also may disrupt GnRH secretion and alter the hypothalamic-pituitary-ovarian axis. The increased secretion of thyrotropin-releasing hormone in hypothyroidism may cause hyperprolactinemia by stimulating lactotrope prolactin production and secretion. Hyperprolactinemia can inhibit GnRH secretion directly by acting on GnRH neuronal prolactin receptors or indirectly by increasing hypothalamic dopamine and opioid peptide levels (30, 31). Other conditions that have been associated with altered luteal progesterone levels include renal transplantation (32), increased beta-endorphin (33), and lactation (34). Because conditions that alter normal gonadotropin secretion will impair follicular development and ultimately corpus luteum function, resultant changes in the amount and duration of luteal sex steroid secretion may compromise endometrial development. Presumably, correcting these underlying conditions will correct the abnormal luteal estrogen and progesterone secretion.

Obesity

Obesity has been associated with a reduction in fertility and increased pregnancy loss rate (35). This negative impact is particularly evident in the morbidly obese. A recent study (36) has evaluated LH pulsatility and urinary progesterone metabolites in obese women compared with normal weight controls. As with anorexic women, there is an alteration of LH pulsatility (here a reduction in pulse amplitude), and there is a significant reduction in luteal phase pregnanediol glucuronide (the major metabolite of progesterone) excretion. Whether this abnormality contributes to the lowered fecundity rates is unknown at this time.

Ovarian Aging

Ovarian aging also has been associated with abnormalities in luteal phase function. Early studies demonstrated deficient progesterone production in the luteal phase (37), and, more recently, deficiencies in both luteal phase progesterone and estradiol metabolites have been identified in women of late reproductive age (38). Whether these abnormalities contribute to the lowered pregnancy rates and higher loss rates with aging is unclear.

The pathophysiology of luteal inadequacy may include several different mechanisms that ultimately affect endometrial development. The “short luteal phase” was initially described as an interval of 8 or fewer days from the LH peak to the onset of menstrual flow (11). The short luteal phase has been associated with low follicular FSH levels, altered follicular FSH/LH ratios, or abnormal FSH and LH pulsatility, and these follicular phase abnormalities lead to reduced luteal estrogen and progesterone levels (11, 12, 39–41). However, a short luteal phase may occur in young healthy women with regular cycle length (11), so the clinical consequences of the short luteal phase are unclear.

During cycles in which *in vitro* fertilization is performed, the luteal phase may be abnormal. Cycles utilizing both GnRH agonists and antagonists have been associated with deficient luteal phase hormonal production. GnRH agonists appear to cause luteal phase inadequacy and subfertility by prolonged

suppression of pituitary LH secretion (i.e., up to 3 weeks after downregulation is achieved, suppression occurs) (42–44). In the case of GnRH antagonists, significant reductions in pregnancy rates have also been identified (45). Although the recovery of LH production from the pituitary is quite rapid following cessation of GnRH antagonists, a clear negative clinical impact in the luteal phase may be seen. It has been hypothesized that endogenous LH may be suppressed by the high gonadotropin levels in the stimulatory phase (45). The result of inadequate LH stimulation of the corpus luteum may lead to diminished progesterone secretion and premature luteolysis (24, 46). Interestingly, adding GnRH agonists to superovulation and intrauterine insemination (SO-IUI) cycles or gonadotropin ovulation induction (OI) cycles for PCOS did not reduce the pregnancy rate luteal estrogen or progesterone levels or alter endometrial dating (47, 48).

ARE THERE DIAGNOSTIC CRITERIA FOR INADEQUATE LUTEAL FUNCTION?

Diagnostic tests are influenced by and based upon the following physiologic observations:

1. Normal luteal phase length is relatively fixed at 12–14 days.
2. Progesterone levels peak in non-pregnancy cycles 6 to 8 days after ovulation.
3. Progesterone is secreted in pulses.
4. The endometrial response is a reflection of the follicular phase estrogen and the luteal phase estrogen and progesterone.
5. Once implantation occurs, progesterone secretion by the corpus luteum is dependent upon rising hCG levels.
6. Failure of hCG levels to increase directly causes corpus luteum failure and a decline in progesterone levels (49).

The different methods proposed for diagnosing LPD include, in order of increasing invasiveness, basal body temperature (BBT) charting, serum progesterone levels, and endometrial biopsy. Because of its inaccuracy and because of the inconvenience to patients, the measurement of BBT is of historical significance only and should be discouraged.

The addition of urinary LH surge detection and monitoring of luteal length substantiates ovulation and adequate luteal length. An interval of 11–13 days from LH surge to menstruation is considered normal, while an interval of 8 or fewer days from the time of an LH surge is considered evidence of a short luteal phase (11, 50). However, as noted, a short luteal phase may occur in healthy young women (11).

Progesterone Levels

Another common method used for the diagnosis of LPD is measurement of serum progesterone levels. Progesterone is secreted in pulses that reflect LH pulses, and levels may fluctuate up to 8-fold within 90 minutes (51). In the absence of pregnancy, progesterone levels peak 6 to 8 days after ovulation (49). In order to determine peak progesterone levels, it is necessary to determine the time of ovulation, but this, too, may be problematic. Although urine LH tests may be used

to determine ovulation, a false-positive LH surge is found when testing urine in over 70% of cycles in women with regular menstrual cycles (52).

Unfortunately, there is no standard characterization of progesterone secretion during the luteal phase in normal fertile women (53). No minimum serum progesterone concentration defines “fertile” luteal function. Furthermore, corpus luteum function varies from cycle to cycle in normal fertile women. Therefore, random serum progesterone levels are not a valid clinical diagnostic tool to evaluate luteal phase adequacy. Once pregnancy has been established, the corpus luteum is stimulated by hCG to produce progesterone, and progesterone levels have some value in determining if the pregnancy is nonviable or extrauterine (54). Since low progesterone levels in early pregnancy likely reflect abnormal hCG stimulation of the corpus luteum by a nonviable or extrauterine pregnancy, a low progesterone level, obtained at the time of, or after, diagnosis of early pregnancy should not be used to initiate therapy with exogenous progesterone.

Endometrial Biopsy

Abnormalities of endometrial maturation have been viewed as the “gold standard” to diagnose luteal inadequacy (55). In theory, whether the maturation is delayed by inadequate ovarian hormone secretion or is delayed because of an intrinsic endometrial abnormality, luteal phase inadequacy is thought to prevent normal implantation or early placental development (56). Studies that have defined the diagnostic criteria for LPD have relied upon the traditional microscopic appearance of luteal phase endometrial development (55). However, implantation is associated with changes in a number of factors that have been incompletely described, including steroid receptors, structural proteins, growth factors, cytokines, receptors, and pinopodes (57–62). Therefore, defining clinically applicable criteria for normal luteal phase endometrial development is complex and evolving.

Many have considered the endometrial biopsy to be the most important diagnostic test to evaluate for LPD (56). However, recent prospective, blinded, randomized clinical trials (RCTs) suggest that the endometrial biopsy is an imprecise tool for differentiating fertile women from women with a LPD (infertility). In two randomized trials of healthy, regularly menstruating, fertile women, endometrial maturation was delayed in up to 25% of biopsy cycles, the variability for individuals from one cycle to the next was high, and there was high variability in histologic dating by various reviewers (63, 64). In a multi-center RCT of 847 women with regular menstrual cycles, 49% of mid-luteal and 35% of late-luteal biopsies were “out of phase,” and there was no difference comparing fertile and infertile women (65). Together, these reports confirm that the endometrial biopsy for histologic endometrial dating is not a valid clinical diagnostic tool for the identification of an infertile population or diagnosis or treatment of LPD.

Consistent with these findings is a recent, novel study designed to test the hypothesis that low progesterone levels would lead to inadequate endometrial development (66). In this study, two doses of intramuscular progesterone were

given on the background of supplemental estradiol following suppression of ovarian function with a GnRH agonist. Both “model” cycles were compared to the natural cycle in the study participants. No impact of lowering the progesterone to 3–10 ng/mL was evident with histological dating.

Since the histologic evaluation of the endometrium is so imprecise by itself, many additional biochemical, morphological, or molecular markers of endometrial function have been proposed to reflect when or if the endometrium is receptive to implantation (56, 62). However, no marker of proposed receptivity has been validated to confirm its accuracy in distinguishing normal fertile women from infertile women. Interestingly, in the study described above (66), endometrial protein expression appeared to differ in the subjects with lowered progesterone replacement, suggesting a potentially more subtle deficiency. At this time, however, molecular markers of receptivity remain experimental and are not valid clinical diagnostic tools.

In summary, currently there is no reproducible, physiologically relevant, and clinically practical standard to diagnose LPD and distinguish fertile from infertile women. The roles of BBT, luteal progesterone levels, endometrial biopsy, and other diagnostic studies have not been established, and performance of these tests cannot be recommended.

IF DIAGNOSIS IS NOT POSSIBLE, IS TREATMENT FOR LUTEAL INADEQUACY EVER APPROPRIATE?

The first approach to treatment of potential luteal inadequacy is the correction of any underlying condition. If no underlying abnormality (e.g., hypothalamic dysfunction, thyroid dysfunction, or hyperprolactinemia) is identified, treatment becomes empiric and is based on limited reliable data. Treatment has been given empirically to promote endometrial maturation, to enhance endometrial receptivity, and to support implantation and development of an early pregnancy. Strategies include supplemental progesterone, progesterone plus estrogen, human chorionic gonadotropin (hCG) in the luteal phase, or ovulation induction with clomiphene or gonadotropins. A Practice Committee guideline (67) may be utilized for further detail.

Ovulation Induction

Use of agents that induce ovulation may improve the fertility of subfertile women. The biologic plausibility of this hypothesis is based on the physiologic continuity between the developing follicle and the corpus luteum. Improved preovulatory follicular dynamics should improve corpus luteum function. However, two problems must be addressed before accepting a cause-effect relationship between use of agents that induce ovulation and improved corpus luteum function and fertility outcomes. The first problem is linked to the definition of luteal insufficiency. By necessity, luteal insufficiency has been defined by surrogate endpoints such as progesterone deficiency or out-of-phase endometrium in ovulation induction studies. To date, all attempts to link poor fertility outcomes to these surrogate endpoints have been unsuccessful (68–71). Therefore,

the only practical way to define or diagnose a LPD is to demonstrate that luteal support alone increases pregnancy and live birth rates. There have been few studies to determine if agents that induce ovulation “treat” LPD by improving the quality or quantity of follicles. One of the few studies to determine if use of agents that induce ovulation “treated” LPD by improving the quality of the follicle or increasing the quantity of follicles prospectively evaluated 18 women with prior out-of-phase endometrial biopsy in clomiphene cycles (72). Luteal phase inadequacy was corrected by biopsy criteria in 8/10 women with more than one preovulatory follicle and in 2/8 women with a single follicle. It can be argued that “ovulation induction strategies” improve fertility by inducing multiple ovulation and not by correcting LPD.

Progesterone

Supplementation of progesterone can be given orally, vaginally, or by the intramuscular route. Currently, there is no evidence that progesterone is beneficial in natural, unstimulated cycles. The question of whether supplementation in the face of reproductive aging may be appropriate has not been addressed in a rigorous scientific manner.

Currently, the only well-documented indication for supplemental vaginal or intramuscular (IM) progesterone is for the improvement of ART outcomes in GnRH agonist or antagonist stimulation cycles (42, 43, 67). Intramuscular progesterone is associated with the highest serum levels, and vaginal progesterone increases endometrial tissue levels (73). It has been agreed that oral progesterone should not be used for luteal support because only approximately 10% of micronized progesterone is absorbed intact through the gastrointestinal tract, and pregnancy rates are lower in ART cycles in which oral progesterone was administered compared to those in which vaginal or intramuscular progesterone was used (42, 43, 74). Progesterone supplementation should be administered until placental progesterone production is adequate, around 8–10 weeks of gestation.

hCG

Luteal supplementation with hCG stimulates the ovaries (or corpora lutea) to boost production of endogenous progesterone and estradiol in GnRH agonist/antagonist ART cycles. ART delivery rates are higher, and spontaneous abortion rates are lower, when supplemental hCG is compared to unsupplemented GnRH agonist/antagonist cycles (42, 43). However, the incidence of moderate or severe ovarian hyperstimulation (OHSS) is significantly higher when supplemental hCG is administered. Low-dose hCG (500 IU every other day) may provide luteal support with minimal risk of inducing OHSS (75). Because of the clinical equivalence with intramuscular progesterone and higher incidence of side effects with hCG, luteal progesterone is generally preferred in GnRH agonist/antagonist IVF cycles.

Once pregnancy is established, supplemental hCG is not beneficial. An RCT of supplemental hCG in 183 women with first-trimester vaginal bleeding and ultrasound-confirmed cardiac activity found that the miscarriage rate was 11% with the placebo and 12% with hCG (76).

SUMMARY

- Abnormal luteal function may occur as the result of a medical condition (e.g., elevated prolactin, abnormal thyroid function), and infertile women should be investigated for these disorders with appropriate treatment of identified conditions.
- No diagnostic test for luteal phase insufficiency has been proven reliable in a clinical setting. The roles of BBT, luteal progesterone levels, endometrial biopsy, and other diagnostic studies have not been established, and performance of these tests cannot be recommended.
- No treatment for luteal phase insufficiency has been shown to improve pregnancy outcomes in natural, unstimulated cycles.
- Luteal support after ART procedures with progesterone or hCG improves pregnancy outcomes, but hCG increases the risk of OHSS.
- There is no proven role in adding progesterone or hCG for luteal support once a pregnancy has been established. Use of supplemental progesterone, in a non-ART cycle beyond the time of expected menses (i.e., 2 weeks after ovulation), is not proven beneficial.

CONCLUSIONS

While progesterone is important for the process of implantation and early embryonic development, LPD, as an independent entity causing infertility, has not been proven.

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Samantha Pfeifer, M.D.; Marc Fritz, M.D.; Jeffrey Goldberg, M.D.; R. Dale McClure, M.D.; Roger Lobo, M.D.; Michael Thomas, M.D.; Eric Widra, M.D.; Glenn Schattman, M.D.; Mark Licht, M.D.; John Collins, M.D.; Marcelle Cedars, M.D.; Catherine Racowsky, Ph.D.; Michael Vernon, M.D.; Owen Davis, M.D.; Kurt Barnhart, M.D., M.S.C.E.; Clarisa Gracia, M.D., M.S.C.E.; William Catherino, M.D., Ph.D.; Robert Rebar, M.D.; Andrew La Barbera, Ph.D.

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