Diagnosis and treatment of luteal phase deficiency: a committee opinion

Practice Committees of the American Society for Reproductive Medicine and the Society for Reproductive Endocrinology and Infertility

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Luteal phase deficiency (LPD) is a clinical diagnosis associated with an abnormal luteal phase length of ≤10 days. Potential etiologies of LPD include inadequate progesterone duration, inadequate progesterone levels, or endometrial progesterone resistance. LPD has not only been described in association with medical conditions but also in fertile, normally menstruating women. Although progesterone is important for the process of implantation and early embryonic development, LPD has not been proven to be an independent entity causing infertility or recurrent pregnancy loss. Controversy exists regarding the multiple proposed measures for diagnosing LPD and, assuming it can be diagnosed accurately, whether treatment improves outcomes. This document replaces the document entitled "Current clinical irrelevance of luteal phase deficiency: a committee opinion," last published in 2015 (Fertil Steril 2015;103:e27–e32). (Fertil Steril® 2021;115:1416–23. ©2021 by American Society for Reproductive Medicine.)

El resumen está disponible en Español al final del artículo.

PHYSIOLOGY OF NORMAL LUTEAL FUNCTION

In medically unassisted cycles, progesterone secreted by the corpus luteum is essential for the establishment and maintenance of pregnancy, until the placenta becomes competent to secrete sufficient progesterone. An example of this necessity is that the removal of the corpus luteum before the development of adequate placental function results in spontaneous pregnancy loss (1). Considering normal luteal phase physiology, the following observations have been made:

- A typical luteal phase length is relatively fixed at 12–14 days but may range from 11–17 days.
- Progesterone levels peak in nonpregnancy cycles 6–8 days after ovulation.
- Progesterone is secreted in pulses under the control of luteinizing hormone (LH).
- Progesterone production by the corpus luteum is pulsatile, secreted in response to LH pulses; progesterone pulses are more pronounced in the midluteal to late luteal phase, and progesterone levels may fluctuate up to eightfold within 90 minutes (2).
- The endometrial response is a reflection of follicular-phase estrogen and luteal phase estrogen and progesterone. In turn, the production and secretion of these hormones depend on follicular phase follicle development, ovulation, and luteal phase corpus luteum function.
- Once implantation occurs, progesterone secretion by the corpus luteum depends on rising human chorionic gonadotropin (hCG) levels.
- Failure of hCG levels to increase results directly in corpus luteum failure and a decline in progesterone levels (3).

DEFINITION OF LUTEAL PHASE DEFICIENCY

Luteal phase deficiency (LPD) was first described in 1949 (4) and LPD broadly refers to an abnormal luteal phase. Given the importance of the luteal phase in the establishment of a normal pregnancy, a defect in the luteal phase (i.e., LPD) has been suggested as a cause of pregnancy, and most notably, recurrent pregnancy loss. Classically, clinically detected LPD refers to a luteal phase of ≤10 days in length, but alternate definitions include ≤11 days and ≤9 days. Alternative biochemical definitions have also been proposed; for example, a low integrated progesterone level across the luteal phase. Clinical and biochemical tests have been proposed to diagnose LPD.

POTENTIAL CLINICAL IMPLICATIONS OF LPD

Since ovarian progesterone is required for a normal intrauterine pregnancy, the potential for ovarian inadequacy to cause infertility or pregnancy failure is plausible. Despite the wide fluctuations observed in circulating

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progesterone levels during the luteal phase, some investigators have found a more rapid rise of progesterone and higher midluteal estrogen and progesterone levels in cycles, resulting in conception compared with cycles in which conception does not occur (5), although early effects of the embryonic hCG during a conception cycle cannot be completely ruled out. Alternatively, other studies demonstrate that luteal phase profiles are similar within the same woman in cycles that resulted in successful pregnancy versus cycles that resulted in early pregnancy loss (6, 7).

LPD has also purportedly been associated with infertility and subfertility (8–10), first-trimester pregnancy loss (11), short menstrual cycles (12–15), and premenstrual spotting (16). Importantly, LPD has also been diagnosed in random cycles of normally menstruating women (14). Overall, it is unclear if abnormal luteal function is an independent cause of implantation failure or early pregnancy loss in natural cycles.

PATHOPHYSIOLOGIC BASIS FOR LPD

The pathophysiology of LPD may include several different mechanisms that ultimately affect endometrial development. LPD has been described as a condition in which ovarian hormone production is not of a sufficient quantity or temporal duration to maintain a functional secretory endometrium and allow normal embryo implantation and growth. A short luteal phase has been associated with low follicular phase follicle stimulating hormone (FSH) levels, low follicular phase estradiol levels, altered follicular phase FSH/LH ratios, and abnormal FSH and LH pulsatility (17). These follicular phase abnormalities have been associated with subsequent reductions in luteal phase estrogen and progesterone levels (14, 15, 18–20).

Alternatively, LPD may develop as a result of an inadequate endometrial response to adequate hormone levels. For example, it has been proposed that some patients demonstrate an endometrium that has an altered (deficient) response to progesterone, thereby reducing fertility (21–24). With such progesterone resistance, it is the endometrial response to the steroid rather than the amount or duration of progesterone exposure that is defective.

Idiopathic LPD implies an abnormality of the luteal phase in the absence of an identifiable disease process. Given the requirement of progesterone for normal pregnancy, it would be assumed that there should be a threshold serum progesterone concentration necessary for the establishment and maintenance of pregnancy. However, because of the pulsatile nature of serum progesterone, it has not been possible to define a normal threshold peak, trough, or average concentration for progesterone in natural cycles. Modeled cycles, after the administration of exogenous estradiol and progesterone, have suggested that the threshold serum progesterone levels for a normal endometrial histology may be as low as 2.5 ng/mL, but that normal gene expression may require a peak threshold between 8 and 18 ng/mL (25). Idiopathic LPD has not been proven to cause infertility (8, 26).

CONDITIONS THAT ALTER THE LUTEAL PHASE

Pathologic conditions that disrupt normal gonadotropin-releasing hormone (GnRH) and LH pulsatility can hypothetically lead to LPD. Examples of conditions that have been associated with LPD include hypothalamic amenorrhea (27–31), eating disorders (32), excessive exercise (27), significant weight loss (33), stress (34, 35), obesity (36), polycystic ovary syndrome (34), endometriosis (37), aging (38), undiagnosed or inadequately treated 21-hydroxylase deficiency (39), thyroid dysfunction (40), hyperprolactinemia (40), ovarian stimulation alone (41), and assisted reproductive technology use (42). These studies vary in how LPD was defined and are limited by the challenges already described in diagnosing LPD.

Thyroid and prolactin disorders may disrupt GnRH secretion and alter the hypothalamic-pituitary-ovarian axis. The increased secretion of thyrotropin-releasing hormone in hypothyroidism may result in hyperprolactinemia by stimulating lactotroph 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 (43, 44).

Additional conditions that have been associated with altered luteal progesterone levels include renal transplantation (45), increased beta-endorphin levels (46), and lactation (47). Obesity has been associated with a reduction in fertility and an increased pregnancy loss rate (48). This negative impact is particularly evident in the morbidly obese. A study evaluated LH pulsatility and urinary progesterone metabolites in obese women compared with normal-weight control subjects (49). As with women with anorexia, an alteration in LH pulsatility (a reduction in LH pulse amplitude) and a reduction in luteal phase pregnanediol glucuronide (the major metabolite of progesterone) excretion was observed in these obese women. Whether this abnormality, possibly via LPD, contributes to the lowered fecundity rates of obese women is unknown.

Advanced reproductive age has also been associated with abnormalities in luteal phase function. Studies have demonstrated decreased progesterone production and deficiencies in luteal phase progesterone and estradiol metabolites in women of late reproductive age (50, 51). Whether these abnormalities contribute to the lower pregnancy rates and higher pregnancy loss rates associated with aging is unclear. Interestingly, an isolated, diminished ovarian reserve has not been associated with LPD, following adjustment for age (52).

Because conditions that alter normal gonadotropin secretion 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 would correct the abnormal luteal estrogen and progesterone secretion. An evaluation of the underlying medical causes should be initiated in any woman with clinical evidence of LPD.

PROPOSED DIAGNOSTIC TESTS FOR LPD

Diagnosis of LPD is made clinically. Multiple diagnostic tests have been proposed, including clinical, biochemical, and histologic tests, but none have been able to reliably differentiate between fertile and infertile women (53–56). In order of increasing invasiveness, the different methods proposed for diagnosing LPD include a shortened luteal phase based on menstrual cycle length; a shortened luteal phase based on basal body temperature (BBT) charting or urinary LH surge detection kits; the measurement of a single or multiple serum progesterone levels; and an endometrial biopsy.

Menstrual Cycle Length

Monitoring of BBT or urinary LH surge detection, and monitoring of luteal length, may substantiate normal ovulation and adequate luteal length. The average luteal phase length is 14 days, with a normal variation of 11–17 days (14, 57, 58). A short luteal phase has been described as an interval of less than 9–11 days from the LH peak to the onset of menstrual flow (14, 17, 57). However, there are multiple definitions of how many days constitute LPD, which makes assessing the literature difficult.

Short luteal phases have also been diagnosed in noninfertile women with regular menstrual cycles. One study demonstrated that 13% of ovulatory menstrual cycles were associated with a luteal length <10 days (17). Another study demonstrated that 18% of menstrual cycles had a luteal phase length <12 days (59). Although women with a shortened luteal phase in this latter study were less likely to conceive in the subsequent month, their overall fecundity at 12 months was not lower.

Given the above limitations of describing the short luteal phase, it may be reasonable to consider LPD when clinically indicated in the presence of a luteal phase of <10 days. However, the above findings also suggest that a shortened luteal phase length is relatively common and not associated with decreased fecundity over 12 months. Assessing an adequate luteal phase is complicated further by the fact that the luteal phase length cannot be measured in cycles that result in pregnancy, but only in cycles that do not result in pregnancy.

Progesterone Levels

While luteal serum progesterone levels are commonly used to assess luteal function in the absence of pregnancy, progesterone levels typically peak 6–8 days after ovulation (3). A luteal progesterone value of >3 ng/mL is considered indicative of ovulation. Therefore, random serum progesterone levels can be used to establish that ovulation occurred in a menstrual cycle; however, no minimum serum progesterone concentration defines normal or fertile luteal function.

Progesterone is secreted in pulses in response to LH pulses, with progesterone values oscillating between 5 and 40 ng/mL over short periods of time in normally ovulatory women, making a single random measurement difficult to interpret (2). In ovulatory cycles, luteal progesterone values of <5 ng/ml occur 8.4% of the time, and values of <10 ng/mL occur 31.3% of the time (17). Furthermore, corpus luteum function varies from cycle to cycle in normal fertile women. Therefore, there are substantial limitations to diagnosing LPD using a single progesterone level.

Some studies have suggested that the best marker of luteal phase progesterone production is obtained by measuring serum progesterone daily during the luteal phase and adding the values to produce an integrated luteal progesterone value. An integrated luteal phase progesterone value of <80 ng/mL represents the bottom 10th percentile of cycles and has been proposed as a diagnostic test for LPD (53). Given the impracticality of daily serum testing, 3 daily luteal progesterone values, obtained between luteal phase days 5–9, totaling <30 ng/mL also have been proposed as an alternate diagnostic criterion for LPD. Although pooled luteal progesterone values may better reflect the overall luteal phase progesterone production, this test has not been clinically validated and may be clinically impractical.

Combined Menstrual Cycle Length and Midluteal Progesterone Testing

In the BioCycle Study, 8.9% of cycles in normally menstruating women had a luteal phase of <10 days, which the investigators defined as "clinical" LPD (17). Similarly, 8.4% of women had a midluteal serum progesterone measurement of <5 ng/mL, which the investigators defined as "biochemical" LPD. Clinical and biochemical LPD were associated with lower follicular estradiol, lower luteal estradiol, lower luteal progesterone, and lighter menstrual flow. Almost all the women with a clinical LPD of <10 days also had a midluteal serum progesterone value <10 ng/mL. Therefore, the investigators proposed using the combination of these two thresholds to define LPD, which when defined as such had a prevalence of 8.2% in their study (17). Although combined testing has not been validated further, this method may provide a tool for future clinical research assessment of LPD.

Endometrial Biopsy

Abnormalities of endometrial maturation have been viewed historically as the gold standard to diagnose LPD (60, 61). In theory, whether the maturation of the endometrium is delayed by inadequate ovarian hormone secretion or is delayed because of an intrinsic endometrial abnormality, the resulting defect is thought to prevent normal implantation or early placental development (61). Studies that have defined the diagnostic criteria for LPD using endometrial biopsy have relied on the traditional microscopic appearance of luteal phase endometrial development (60). However, implantation is associated with changes in a number of factors beyond endometrial histology, including steroid receptors, structural proteins, growth factors, cytokines, receptors, and pinopodes (62–67). Additionally, maturation may differ across various sections of the endometrium and a single endometrial biopsy may not be able to assess global endometrial development. Defining clinically applicable criteria for normal luteal phase endometrial development is complex and evolving.

Prospective, blinded, clinical trials demonstrate that endometrial biopsy is an imprecise tool for differentiating fertile from infertile women. In two randomized trials of healthy, regularly menstruating, fertile women, histologic assessment of endometrial maturation was delayed in up to 25% of biopsy cycles. Furthermore, the variability within individuals from one cycle to the next was high and there was also a high variability in histologic dating as assessed by different reviewers (55, 56). In a multicenter randomized clinical trial (RCT) of 847 women with regular menstrual cycles, 49% of midluteal and 35% of late luteal biopsies were ''out of phase,'' and there was no difference when comparing fertile and infertile women (56). Together, these reports confirm that endometrial biopsy for histologic endometrial dating is not a valid clinical diagnostic tool for the identification of an infertile population or the diagnosis of LPD.

Consistent with these findings are studies designed to test the hypothesis that low progesterone levels lead to inadequate endometrial development (25, 68). In these studies, multiple doses of intramuscular progesterone were given on the background of supplemental estradiol following the suppression of ovarian function with a GnRH agonist. The exogenous hormone cycles were compared with natural cycles and each other. Normal endometrial histology was seen with peak serum levels as low as 2.5 ng/mL, but completely normal gene expression required a peak threshold >8–18 ng/mL (25).

Other Endometrial Markers

Because the histologic evaluation of the endometrium is imprecise, many additional biochemical, morphologic, and molecular markers of endometrial function have been proposed to assess endometrial receptivity to implantation (61, 67). However, no marker of endometrial receptivity has been validated in a RCT or demonstrated the ability to distinguish normal fertile from infertile women. At this time, molecular markers of receptivity remain experimental and are not considered valid clinical diagnostic tools.

In summary, there is currently no reproducible and clinically practical standard to diagnose LPD and distinguish fertile from infertile women. The roles of luteal phase progesterone levels, endometrial biopsy, and other diagnostic studies have not been fully established, and the performance of these tests cannot be recommended. Furthermore, given the lack of a clear correlation between LPD by alternative definitions and clinically relevant outcomes, no test can be considered the gold standard.

PROPOSED TREATMENTS

Given the lack of clear diagnostic criteria for LPD and the overlapping results in most tests between fertile and infertile women, it is not surprising that quality data are lacking for treating LPD. The first approach to the treatment of potential LPD is the correction of any underlying condition, such as hypothalamic or thyroid dysfunction, or hyperprolactinemia. If no underlying abnormality is identified, then treatment becomes empiric and is not generally recommended. This should be interpreted in the context that LPD is difficult to define and there has been scant quality literature investigating treatment for LPD. The aim of empiric treatment has historically been to improve ovulatory function, promote endometrial maturation, enhance endometrial receptivity, and support implantation and development of an early pregnancy. Empiric strategies have included supplemental luteal progesterone, luteal progesterone plus estrogen, luteal hCG, or ovarian stimulation with clomiphene or gonadotropins.

Ovarian Stimulation

The use of agents to stimulate the ovaries may improve the fertility of subfertile women. The biologic plausibility of this treatment strategy is based on the physiologic continuity between the developing follicle and the corpus luteum. Improved preovulatory follicular dynamics should improve corpus luteum function. However, attempts to link poor fertility outcomes to these surrogate endpoints have been unsuccessful and ovulation induction has not been demonstrated to treat LPD (69–72).

Progesterone

Progesterone can be administered via oral, vaginal, and intramuscular routes. The use of progesterone after fertility treatments is distinctly different from using it to supplement the natural menstrual cycle. Although progesterone is beneficial after various therapeutic infertility treatments, there is no evidence that progesterone is beneficial for fertility in natural cycles. Similarly, there is no evidence that progesterone is beneficial for treating LPD.

There are no RCTs investigating progesterone supplementation for women with LPD. Studies have investigated progesterone supplementation for recurrent pregnancy loss, which theoretically may overlap with LPD due to inadequate progesterone support for early pregnancy. A systematic review and meta-analysis also suggested that progestogen supplementation reduced the miscarriage rate in women with unexplained recurrent miscarriage (73). However, in another study, progesterone supplementation initiated after a positive pregnancy test was not shown to decrease miscarriage risk (74). The data on the use of progesterone supplementation for recurrent pregnancy loss are conflicting and may not necessarily be reflective of patients with LPD.

FUTURE DIRECTIONS

Despite LPD being proposed as a clinical entity causing infertility and early pregnancy loss for over 70 years, there is a lack of quality research on the diagnostic criteria and treatment of LPD. Controversy remains regarding the definition, diagnosis, and clinical significance of LPD outside of a known pathologic condition suppressing LH pulsatility. There is a need for research to determine if isolated LPD is a clinical entity that leads to infertility. If LPD can be demonstrated, then further research to develop diagnostic tests that differentiate fertile from infertile women with LPD is needed. Finally, randomized trials could be performed to evaluate therapeutic options for women with proven LPD. Present limited data do not support LPD as a clinical entity that causes infertility

or early pregnancy loss, or that treatment can improve clinical outcomes.

SUMMARY

- LPD is a clinical diagnosis and may be present with a luteal phase $\leq$10 days in length.
- Abnormal luteal function may occur as the result of several medical conditions.
- True isolated LPD implies an underlying pathologic abnormality of the luteal phase in the absence of an identifiable disease process negatively affecting normal LH support of the corpus luteum.
- No diagnostic test for LPD has proven to be reliable in the clinical setting or in differentiating fertile from infertile women.
- Endometrial biopsies only have the precision to distinguish the early luteal, midluteal, and late luteal phases, and have been shown to not discriminate between fertile and infertile women.
- No treatment for LPD has been shown to improve pregnancy rates in natural, unstimulated cycles.

CONCLUSION

- Infertile women suspected of having abnormal luteal function due to an underlying medical condition should be evaluated and appropriately treated for an identified abnormality.
- Histologic dating of the endometrium with endometrial biopsies is not recommended.
- Additional research is needed to determine if testing modalities, such as combined testing (i.e., luteal progesterone measurement and luteal phase length $<$10 days for the diagnosis of LPD), identifies a subgroup of patients with poorer reproductive outcomes and, if so, whether treatment improves outcomes.

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Diagnóstico y tratamiento del defecto de fase lútea: una opinión del comité.

El defecto de fase lútea (LPD) es un diagnóstico clínico asociado a una duración anormal de la fase lútea de $\leq$ 10 días. Las potenciales etiologías del LPD incluyen duración inadecuada de progesterona, niveles inadecuados de progesterona o resistencia endometrial a la progesterona. El LPD no sólo ha sido descrito como asociado a condiciones médicas, sino también en mujeres fértiles con menstruación normal. Aunque la progesterona es importante para el proceso de implantación y el desarrollo temprano del embrión, no se ha demostrado que el LPD sea una entidad independiente causante de infertilidad o aborto de repetición. Existe controversia sobre las múltiples medidas propuestas para el diagnóstico de LPD y, asumiendo que se pueda diagnosticar con acierto, sobre si el tratamiento mejora los resultados. Este documento sustituye al documento titulado "Current clinical irrelevance of luteal phase deficiency: a committee opinion," publicado por última vez en 2015.