Luteal Phase Defects and Progesterone Supplementation

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Importance: Luteal phase defects (LPDs), or an insufficiency of progesterone production during the luteal phase of the menstrual cycle, have been identified as a potential cause of recurrent pregnancy loss (RPL), but its exact contribution to RPL is not well-defined. In addition, the role of exogenous progesterone supplementation during pregnancy remains controversial.

Objective: The goal of this review is to provide an updated, evidence-based summary of LPD, including prevalence and potential pathophysiologic mechanisms, and to explore the current controversies regarding progesterone supplementation for management and treatment of RPL.

Evidence Acquisition: A literature review identified relevant research using a PubMed search, Cochrane summaries, review articles, textbook chapters, databases, and society guidelines.

Results: Endogenous progesterone plays a crucial role in the first trimester of pregnancy, and therefore, insufficiency may contribute to RPL. However, the precise relationship between LPD and RPL remains unclear. Luteal phase defect is primarily a clinical diagnosis based on a luteal phase less than 10 days. Although there may be a possibility of incorporating a combined clinical and biochemical approach in defining LPD, the current lack of validated diagnostic criteria creates a challenge for its routine incorporation in the workup of infertility. Moreover, no treatment modality has demonstrated efficacy in improving fertility outcomes for LPD patients, including progesterone supplementation, whose inconsistent data do not sufficiently support its routine use, despite its minimal risk. It is imperative that women diagnosed with LPD should be worked up for other potential conditions that may contribute to a shortened luteal phase. Future work needs to focus on identifying a reproducible diagnostic test for LPD to guide treatment.

Conclusions and Relevance: Currently, the perceived relationship between LPD and RPL is challenged by conflicting data. Therefore, patients with an abnormal luteal phase should undergo a thorough workup to address any other potential etiologies. Although supplemental progesterone is commonly utilized for treatment of LPD and RPL, inconsistent supporting data call for exogenous hormone therapy to be only used in a research setting or after a thorough discussion of its shortcomings.

Target Audience: Obstetricians and gynecologists, family physicians

Learning Objectives: After completing this activity, the learner will be better able to explain the various definitions, diagnostic criteria, and potential pathophysiologic mechanisms of LPD; discuss the current controversies surrounding the role of LPD within RPL; and delineate the current studies and recommendations for treatment, specifically the use of progesterone supplementation.

Luteal phase defects (LPDs) are a clinical diagnosis related to an abnormally shortened luteal phase, characterized by low progesterone levels. Because progesterone is vital to the maintenance of pregnancy, LPD is commonly considered as a part of an evaluation of recurrent pregnancy loss (RPL).
Numerous controversies exist regarding LPD, its impact on fertility and fecundity, and the role of therapeutic progesterone supplementation. In part due to its relative safety profile, supplemental progesterone is often used empirically and outside professional recommendations. This review will thus consider the current state of evidence as well as professional guidelines for the diagnosis and treatment of LPD.

**PHYSIOLOGY AND ASSOCIATION WITH RPL**

Progesterone is vital for successful implantation, placental formation, and maintenance of pregnancy. Seminal studies have confirmed progesterone's importance in pregnancy as removal of the corpus luteum before 7 weeks (or antagonizing progesterone's activity via the administration of mifepristone) will result in pregnancy loss. Throughout the first 7 to 9 weeks of pregnancy, administration of mifepristone will result in pregnancy loss. Seminal studies have confirmed progesterone's importance in implantation, nutrition, and pregnancy maintenance (particularly in the first 7 to 9 weeks), luteal phase deficiency (LPD) has consistently been proposed as an important cause of early isolated and RPL. First described in 1949, LPD refers to an abnormally shortened luteal phase that is often characterized by lower-than-normal maternal serum progesterone levels. As a clinical diagnosis, LPD is most often defined as a luteal phase lasting less than 10 days, although other definitions make this distinction at less than 9 or 11 days. Multiple studies have reported an association between LPD and infertility. For example, one study involving 3674 pregnancies found that first-trimester progesterone levels of <5 ng/mL and >20 mg/mL were associated with pregnancy loss rates of 85.5% and 7.7%, respectively. Another study of 32 healthy women reported that menstrual cycles resulting in conception have a sharper and earlier rise in progesterone levels during the luteal phase compared with cycles not ending in conception (of note, the impact of human chorionic gonadotropin from the embryo could not be excluded in this study).

Despite these reports supporting a connection between RPL and LPD, a conflicting study found that the same woman's preimplantation luteal phase is similar between a successful pregnancy and one that resulted in early miscarriage, whereas a separate meta-analysis of 19 studies involving women with threatened miscarriage between 5 and 23 weeks' gestation reported serum progesterone levels as an unhelpful marker for predicting pregnancy outcomes. In summary, the current data present inconsistencies when it comes to establishing a definitive association between LPD and pregnancy loss.

Moreover, RPL is common—affecting 1% to 2% of couples trying to conceive—and 80% of fetal losses occur during the first trimester. However, because of controversies surrounding the clinical definition of RPL, its etiologies and treatments largely remain controversial. It is not surprising then that, because of a perceived but unproven association between LPD and RPL, various doses and preparations of progesterone supplementation have been utilized by clinicians during the first trimester to reduce the risk of early spontaneous pregnancy loss. However, reports concerning the association of LPD and RPL and of the efficacy of progesterone therapy to improve pregnancy outcomes in patients with RPL remain inconsistent.

**EPIDEMIOLOGY**

Reporting the prevalence of LPD is difficult because no diagnostic criteria have been demonstrated to be clinically reliable, and those criteria that are used differ among studies. Whereas some—including the American Society for Reproductive Medicine (ASRM)—utilize clinical criteria that document LPD based on luteal phase duration (<10 days), others use biochemical criteria, most commonly serum progesterone concentrations less than 5 ng/mL during the luteal phase. For example, the BioCycle study examined 463 women and found that almost all women diagnosed with LPD using duration-based clinical criteria also had peak luteal progesterone concentrations less than 10 ng/mL.

Further confounding the ability to link LPD and RPL are inconsistent diagnostic criteria for pregnancy loss that are exacerbated when defining RPL. For instance, in their most recent position statements, ASRM states that RPL can be defined as 2 or more miscarriages; the European Society of Human Reproduction and Embryology (ESHRE) uses similar criteria of 2 or more pregnancy losses; and the Royal College of Obstetricians and Gynecologists defines RPL as 3 or more consecutive pregnancy losses. Furthermore, these 3 societies do not
agree on how to best define or which terms are optimal for describing early pregnancy losses, and the rates of both miscarriages and reported pregnancy loss are, of course, contingent on how these pregnancy losses are categorized.

To summarize, there are variable definitions of pregnancy loss, which jeopardizes accurate quantification of the number of pregnancies used to be considered “recurrent.” Despite this challenge, RPL’s prevalence has been approximated to be between 1% and 4% of all women based on reports in Europe and the United States.6,15,25,26

ETIOLOGIES AND DIAGNOSIS OF LPD

The 2 potential mechanisms for the pathophysiology of LPD include the insufficient production of and insufficient duration of progesterone activity, both of which can impact downstream processes, including a diminished endometrial response27–30 and decreased follicular-stimulating hormone levels.31 Collectively, current studies suggest that a shortened luteal phase can impact the quantity and duration of hormone secretion, which can then affect endometrial development for embryo implantation.

In addition, some or most cases of LPD may be secondary to additional pathophysiologic endocrine processes that occur at the level of the hypothalamic-pituitary axis or the thyroid. For example, several studies have provided evidence that women of advanced age have diminished estrogen, progesterone, and estradiol metabolite levels during the luteal phase.32,33 Moreover, hypothyroidism can increase prolactin levels, which, in turn, inhibit gonadotropin secretion and disturb the luteal phase, as well as overall menstrual cyclicity.34 Other conditions that have been reported to affect fertility such as eating disorders,35 polycystic ovarian syndrome,36 endometriosis,37 obesity,38 and more have also been reported to be associated with LPD. However, primary etiologies such as these are typically detected in a standard diagnostic workup (such as abnormal thyroid-stimulating hormone or prolactin levels) and/or prompted by clinical findings.

Currently, no diagnostic test for LPD has been validated. Several testing criteria that rely on clinical, biochemical, and biopsy findings have been suggested.39–42 However, LPD remains primarily a clinical diagnosis.

A clinical LPD diagnosis is based on a luteal phase lasting less than 10 days.20 However, duration-based criteria for diagnosing LPD have been challenged by numerous reports that suggest a shortened luteal phase may be a part of a healthy woman’s menstrual cycle. For example, one study found that 13% of fertile women had a luteal phase lasting less than 10 days.20 Therefore, although 10 days has been acknowledged as a diagnostic criterion for LPD, normally menstruating women may also exhibit a shortened luteal phase; this overlap often obscures interpretation of the duration-based criteria in clinical studies. In addition, utilizing length of luteal phase duration as an indicator of infertility is challenging because such data can only be ascertained from menstrual cycles that do not lead to fertilization.4

Given the challenges of a clinical diagnosis, efforts have been made to determine reliable biochemical criteria for LPD—most often using luteal phase serum progesterone levels. Considering progesterone’s fundamental role in facilitating a successful pregnancy, it is not surprising that luteal phase serum progesterone levels have most often been targeted for use in diagnosing LPD. Still, there have been difficulties in establishing a definitive reference range for luteal serum progesterone because of its normal pulsatile secretory response to luteinizing hormone in a normal menstrual cycle. This minute-to-minute variability in progesterone levels dramatically decreases the utility of a single biochemical measurement as a diagnostic criterion for LPD. Although the aforementioned BioCycle study utilized a luteal serum progesterone value of less than 5 ng/mL to diagnose LPD, an alternative study proposed either a midluteal phase progesterone value less than 10 ng/mL or a cumulative sum of 3 separate serum progesterone levels of less than 30 ng/mL during the luteal phase.41 Although this summative approach might be predicted to better reflect the average circulating progesterone levels in the luteal phase, it has not yet been clinically proven to be useful for LPD diagnosis. The BioCycle study proposed an alternative LPD definition that integrated both the chemical and biochemical criteria, but this also has not yet been validated.20 Of note, ASRM has suggested the potential future use of the BioCycle’s integrated diagnostic approach but stressed the need for further studies to examine its potential reliability in diagnosing LPD.4

In summary, it should be reemphasized that although luteal phase duration continues to be the most widely utilized method to diagnose LPD, it is imprecise, and a need for a reliable tool to accurately detect LPD and appropriately interpret these findings in relation to fertility and pregnancy maintenance remains.

PROPOSED TREATMENTS FOR LPD

Without a reliable method to diagnose LPD, evaluation of its association with adverse reproductive outcomes, including preclinical and clinical pregnancy loss, and its utility in treating these disorders is a protean task. However, there are several best practices that...
can be used when approaching a patient who presents with a clinical history suggestive of LPD. In a woman with irregular menses or with a history of short menstrual cycles and a history of infertility or early isolated pregnancy loss or RPL, it is imperative to first address and rectify other underlying conditions that may be contributing factors, such as obesity or hypothyroidism. In the treatment of couples with RPL, alternative etiologies that may include genetic, anatomic, infectious, and other hormonal conditions should also be sought and addressed before consideration of treatment for LPD.4

Historically, LPD treatment options have all been essentially empiric, involving luteal phase supplementation with progesterone, estrogen, human chorionic gonadotropin, or a combination thereof. Ovarian stimulation has also been suggested as a treatment for LPD. Each of these interventions has been designed to enhance endometrial development, ovulatory function, and implantation, but none have been definitively proven to do so in response to an assumed diagnosis of LPD.4 For instance, the use of clomiphene or gonadotropins for ovarian stimulation has been frequently used in an effort to promote corpus luteum function and maturation in women experiencing subfertility. Although these approaches have exhibited some efficacy in addressing other etiologies of subfertility, the available data are inadequate to support their specific use for LPD.4

The most prevalent “treatment” approach for presumed LPD has utilized progesterone, in a great variety of dosing regimens and routes of administration, including oral, vaginal, and intramuscular. Although supplementation with progesterone has been associated with favorable outcomes in women with abnormal menstrual cycles being treated for subfertility, it has no demonstrable benefits in women with normal menstrual cycles and subfertility. Given the prevalence of abnormal luteal phases by dating and using serum progesterone testing in women with normal fertility and normal menstrual cycles, this might not be surprising.

CRITICAL STUDIES ON PROGESTERONE SUPPLEMENTATION

There is a significant body of literature on the use of progesterone supplementation in couples with RPL. Much of this literature consists of small and uncontrolled reports, and the methodologies for diagnosis of LPD, as well as RPL, and modes of supplementation vary widely, making comparisons exceedingly challenging. There are, however, some meta-analyses and a few recent large randomized, placebo-controlled trials available that give us some insight into the role of progesterone supplementation in treating women with infertility or RPL.

One relatively informative study conducted in 2017 examined the effectiveness of supplemental vaginal progesterone in a well-defined population of women who had encountered 2 or more unexplained pregnancy losses before reaching 10 weeks of gestation. The participants were administered 100 to 200 mg of vaginal progesterone every 12 hours, starting 3 days after the luteinizing hormone surge. Among the cohort of 59 women who qualified to receive progesterone supplementation, 69% achieved a subsequent successful pregnancy (gestation >10 weeks). In this study, the women served as their own historical controls, and only 6% had achieved pregnancy success in their prior pregnancies in the absence of progesterone supplementation. Although the use of historical controls can be considered suboptimal, the investigators concluded that vaginal micronized progesterone was significantly associated with improved success in this well-defined cohort of women experiencing RPL.45

The findings of this study, however, were not reproducible. In a larger multicenter, randomized, placebo-controlled study of 836 women with unexplained RPL, defined as at least 3 consecutive or nonconsecutive first-trimester pregnancy losses, exposed women to either 200 mg vaginal progesterone twice daily (twice a day) or a placebo. The investigators of this study, called the Progesterone in Recurrent Miscarriages (PROMISE) trial, used intention-to-treat analysis to show that live birth rates beyond 24 weeks' gestation were comparable between the 2 cohorts, with 65.8% in the progesterone group and 63.3% in the placebo group. The study concluded that the use of progesterone supplementation conferred no significant therapeutic benefit in women experiencing unexplained RPL.46 In similar findings to the PROMISE trial, another large, multicenter, randomized, placebo-controlled study called the Progesterone in Spontaneous Miscarriage (PRISM) trial, examined 4153 women with first-trimester vaginal bleeding (considered up to 16 weeks' gestation). The women in this study were randomly divided into 2 groups, receiving either 200 mg vaginal progesterone twice a day or a placebo. The findings of this large trial revealed that 75% of the progesterone group had a successful live birth after 34 weeks compared with 72% in the placebo group. Once again, the conclusion was that progesterone supplementation during the first trimester did not yield a significant improvement in live birth rates.47

Although the PROMISE and PRISM trials are the largest studies, both have subsequently been criticized for the timing of initiation of progesterone supplementation, with critics suggesting that supplementation began at a gestational age potentially too late for optimal efficacy.48 It is also important to note that both trials highlighted the
favorable safety profile associated with progesterone supplementation as neither reported any adverse effects, including increased rates of preeclampsia or small-for-gestational-age infants.46,47

Notably, although neither the PROMISE nor the PRISM trial endorsed progesterone supplementation to mitigate adverse reproductive outcomes, an ensuing meta-analysis of both studies concluded that there was a statistically significant increase in subsequent live birth rates in progesterone-treated women who had experienced a minimum of 3 pregnancy losses and presented with vaginal bleeding. However, this recommendation was cautionary—stating that although there may be benefit, shared decision-making between providers and patients should still be used when considering initiation of progesterone supplementation.16

In 2013, a Cochrane meta-analysis was conducted involving 14 separate randomized controlled trial or quasi-randomized trials (2158 total participants) involving progesterone supplementation in women with recurrent miscarriages. The studies included in the review were notable for variability in the doses and routes of progesterone administration. This 2013 review reported that there was no significant improvement in the rate of miscarriage when women were given supplemental progesterone versus a placebo or no medication at all.49 However, a subsequent 2019 Cochrane review that included additional interim studies and a more rigorously defined patient population disagreed with the prior report. The 2019 meta-analysis focused on progesterone supplementation in women experiencing recurrent miscarriages; it included 12 independent trials, 8 of which compared progesterone supplementation to a placebo; the remaining 4 compared progesterone to no treatment (1856 women in total). The findings of this 2019 Cochrane report indicated that progesterone supplementation may potentially reduce the occurrence of miscarriages, demonstrating a slight increase in live birth rate in those receiving progesterone.50

Interestingly, since this 2019 review was published, there has been considerable controversy regarding the reliability of the included studies. Notably, one of the analyzed trials within the review has since been retracted.51 Further concerns have emerged over other studies incorporated in the analysis.52 In response, Cochrane conducted another meta-analysis in 2021, including 7 randomized trials with a total cohort of 5682 women. The findings of this updated review suggested that there is likely minimal to no improvement in live birth rate associated with progestogens for women dealing with threatened or recurrent miscarriage.53 Again, critics have stated that many of the participants may have started progesterone too late in gestation to have seen benefit.

To summarize, the available data on progesterone supplementation for the treatment of RPL continue to yield conflicting results. There have been no randomized controlled trials on progesterone supplementation conducted in women with LPD, given the ambiguity in the diagnosis itself, so any data pertaining to progesterone use in RPL may not directly translate to utility in LPD treatment. Moreover, the absence of strong evidence-based data establishing a clear association between LPD and RPL further complicates our understanding of progesterone supplementation in either condition.

PROFESSIONAL SOCIETY GUIDELINES

With inconsistent diagnostic criteria and equivocal data, professional society guidelines regarding LPD are, by consequence, also inconsistent.

The ASRM published “Diagnosis and Treatment of Luteal Phase Deficiency: A Committee Opinion” in 2021. The committee opinion focuses on diagnosis, treatments, and future directions. It clearly states that LPD is a clinical diagnosis because biochemical and histologic tests are unable to differentiate between fertile and infertile women. The committee opinion supports a clinical diagnosis of LPD in the presence of a luteal phase that lasts less than 10 days. The committee opinion paper then later goes on to state that a biochemical test assessing serum progesterone is “clinically impractical.”4 Of note, ASRM makes a clear distinction between the use of progesterone as a supplement for a natural menstrual cycle (as in the case of LPD) and its use as a fertility treatment (as in the case of endometrial preparation for in vitro fertilization). Despite this, the committee falls short of recommending against supplemental progesterone and instead notes that progesterone use in patients with RPL is “conflicting.”

The American College of Obstetricians and Gynecologists takes a harder stance in Practice Bulletin No. 200, “Early Pregnancy Loss,” stating that “there are no effective interventions to prevent early pregnancy loss.” Citing a 2008 Cochrane review regarding how progestins have shown no effect at preventing early pregnancy loss,49 the American College of Obstetricians and Gynecologists asserts that the use of progestins is controversial and that conclusive evidence supporting its use is lacking.4

The ESHRE published the most recent professional guideline and takes the most ardent stance against routine use of progesterone. In their 2023 guideline on RPL, the ESHRE recommends against luteal phase testing in women with RPL (strong evidence). Furthermore, the guideline primarily uses the results of the PROMISE trial to state, “The guideline development
group recommends not to prescribe progesterone in women with unexplained RPL.²⁻¹

CONCLUSIONS
At present, LPD is primarily a clinical diagnosis in women with luteal phases lasting less than 10 days' duration, and this definition is neither inclusive nor exclusive enough to be of great clinical utility. Because a shortened luteal phase could potentially result in abnormal corpus luteum function and lower than normal levels of serum progesterone during the luteal phase, LPD has been intuitively, but not scientifically linked to RPL. However, current research has failed to identify a discernible relationship between LPD and RPL. Furthermore, no diagnostic tests for LPD have been reliable in differentiating between fertile and infertile women. A potentially promising diagnostic approach could involve combining the clinical (luteal phase length) and biochemical (progesterone levels) criteria, but such validation will require further carefully designed research. Similarly, no treatment modality has proven effective in improving fertility outcomes in patients with presumed LPD. Although exogenous progesterone has long been utilized to treat LPD and RPL, and safety of supplementation is fairly clear, efficacy has not been definitively shown. Therefore, future research should focus on developing a better understanding of LPD's impact on fertility and early pregnancy maintenance, determining whether treatment is necessary and/or beneficial, including assessing optimal timing for initiating treatment.

In clinical practice, LPD can have many etiologies, so patients should thoroughly be evaluated for potential known underlying conditions that could result in a shortened luteal phase. Considering our present understanding of safety and efficacy, exogenous progesterone should be used only by clinicians through shared decision-making and following a comprehensive conversation with prospective recipients about its limitations.

REFERENCES
Obstetrical & Gynecological Survey CME Activity Examination: February 2024

Please answer the questions on page 129 by filling in the appropriate circles below. Please mark the one best answer and fill in the circle until the letter is no longer visible. To process your exam, you must also provide the following information:

Name (please print): ________________________________

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City/State/Zip ____________________________________

Daytime Phone ____________________________________

Specialty _________________________________________

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Your completion of these activities includes evaluating them. Please respond to the questions below.

• Please rate these activities (1 — minimally, 5 — completely)

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• CME 1: Giouleka et al.
Postnatal Care: A Comparative Review of Guidelines
After participating in this activity, the learner should be better able to:
Describe all the aspects of postnatal care; explain the appropriate clinical evaluation plan during the postnatal period; and assess the available postpartum care promotion techniques.
Luteal Phase Defects and Progesterone Supplementation

After completing this activity, the learner will be better able to: Explain the various definitions, diagnostic criteria, and potential pathophysiologic mechanisms of LPD; discuss the current controversies surrounding the role of LPD within RPL; and delineate the current studies and recommendations for treatment, specifically the use of progesterone supplementation.

• How many of your patients are likely to be impacted by what you learned from these activities?
  ○ <20%  ○ 20%–40%  ○ 40%–60%  ○ 60%–80%  ○ >80%

• Do you expect that these activities will help you improve your skill or judgment within the next 6 months? (1 – definitely will not change, 5 – definitely will change) 1 2 3 4 5

• How will you apply what you learned from these activities (mark all that apply):
  ○ In diagnosing patients  ○ In making treatment decisions
  ○ In monitoring patients  ○ As a foundation to learn more
  ○ In educating students and colleagues  ○ In educating patients and their caregivers
  ○ As part of a quality or performance improvement project  ○ To confirm current practice
  ○ For maintenance of board certification  ○ For maintenance of licensure

• Please list at least one (1) change you will make to your practice as a result of this activity: ________________________________________________

• Did you perceive any bias for or against any commercial products or devices? Yes  ○  No  ○
  If yes, please explain:

• How long did it take you to complete these activities? _______ hours _______ minutes

• What are your biggest clinical challenges related to obstetrics and gynecology?

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