Luteal phase defect: myth or reality

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Luteal phase defect (LPD) was described by Jones in 1949\cite{1}; it is characterized by failure to develop fully mature secretory endometrium. This entity is defined as a defect of the corpus luteum to secrete progesterone in high enough amounts or for too short a duration. This results in an inadequate or out-of-phase transformation of the endometrium which precludes embryo implantation. Therefore, LPD is believed to be a cause of infertility and spontaneous miscarriage. Abnormalities of the luteal phase have been found in 3\% to 10\% of the female population that has primary or secondary infertility and occurs in up to 35\% of those who have recurrent abortion\cite{2}.

As a clinical entity, however, LPD is poorly characterized. LPD may be identified in many women who have proven fertility. There is no definite consensus in the diagnosis of the condition. Some investigators emphasize the importance of endometrial histology in diagnosis and claim that the actual serum progesterone levels have no value as long as the endometrium is in-phase. Other investigators however, believe that only progesterone levels that are greater than a certain threshold can assure the optimal preparation of endometrium for implantation. LPD also has been believed to be one of the stages of ovulatory disturbance that starts with anovulation and continues as oligo-ovulation, LPD, and normal ovulation\cite{3}. This article reviews the controversies that surround LPD.

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Issues in etiopathogenesis

The proposed mechanisms of LPD include decreased levels of follicle-stimulating hormone (FSH) in follicular phase, abnormal luteinizing hormone (LH) pulsatility, decreased levels of LH and FSH during the ovulatory surge, decreased response of endometrium to progesterone, and elevated prolactin levels [4]. Furthermore, LPD has been linked to several factors (eg, inadequate endometrial progesterone receptors and endometritis) and drugs (eg, clomiphene citrate, gonadotropin releasing hormone (GnRH) agonists and antagonists).

Some investigators reported increased LH pulse frequency and abnormal follicular phase LH:FSH ratio [5], whereas others claimed inadequate LH surge [6] as possible etiologic factors for LPD. These findings were not confirmed in other studies [7,8]. Reported follicular phase FSH deficiency with decreased preovulatory estradiol levels as a cause for LPD [6] also was not demonstrated by other investigators [8,9].

Approximately one half of all LPDs have been attributed to the improper function of the GnRH pulse generator in the hypothalamus [10]. Following ovulation, the increased serum progesterone levels oversuppress the GnRH pulse generator which results in too few LH pulses, and therefore, improper luteal function. Hyperprolactinemia has also been implicated in LPD by interfering with GnRH secretion. Latent hyperprolactinemia by interfering with GnRH also has been associated with LPD [10].

In a primate model, 12-day physical and psychologic stress challenge induced LPD which was marked by the decrease in area under the curve for luteal phase serum progesterone levels. The reduction in overall luteal phase progesterone secretion was not associated with a shorter luteal phase which indicated that premature luteolysis did not occur. This reduction however was attributed to the observed decrease in luteal LH levels, which was ultimately related to the stress-induced dysfunction of the hypothalamic-pituitary-adrenal axis [11]. Mild hyperprolactinemia and exaggerated prolactin release in response to stress also has been associated with LPD [10,12].

Experimental interference with the profile of gonadotropic stimulation during the follicular phase of the cycle by either using a GnRH agonist [13] or administering a crude follicular fluid preparation [14] reduced the progesterone secretion during the luteal phase. Other investigators demonstrated a decrease in immunoreactive FSH levels during the follicular phase in patients with LPD diagnosed by endometrial histology [15]. After the normal folliculogenesis, progesterone secretion can be decreased by interference with gonadotropic support by GnRH antagonist administration during the midluteal phase [16,17].

Abnormal LH pulse frequency has been linked to LPD [18]. LPD also has been associated with decreased inhibin levels in the follicular phase and a subnormal midcycle LH surge [4].

In the corpus luteum, the most abundant cell types are endothelial cells and the pericytes. Resident cells that stem from white blood cell line and fibroblasts also are present [19]. Only a minority of cells are the steroidogenic cells which are of
two types [20,21]. The large luteal cells originate from the follicular granulosa cells. These cells are not responsive to LH but produce several autocrine and paracrine peptides and eicosanoids. They also produce progesterone and estradiol, in turn, guaranteeing the basal production of these two hormones. The second cell type is the small luteal cells that are derived from the follicular theca cells. These cells acquire LH receptivity and respond to LH pulses with increased estradiol and progesterone secretion. In some patients, LPD is believed to be related to the failure of small luteal cells to respond to LH [10]. An ovarian cause for LPD—in the form of accelerated luteolysis—was suggested as one of the mechanisms [9]. The reasons for early luteal regression were linked to white blood cells and cytokines that are involved actively in the corpus luteum [22,23].

It is clear that any disturbance of ovulatory function may produce LPD in the research setting. The question remains whether each or some of these factors in a given individual is persistent enough to cause "chronic" LPD that leads to infertility or recurrent miscarriage.

Diagnosis

The optimal means of diagnosing LPD is controversial. It is defined historically as a lag of more than 2 days in the histologic development of endometrium compared with the day of the cycle. This lag should occur in more than one cycle. Several indicators and laboratory findings have been proposed for the diagnosis of LPD. These include shortened luteal phase in basal body temperature (BBT) charts, decreased luteal phase serum progesterone levels, and discrepancies in endometrial histologic findings.

**Basal body temperature chart**

BBT measurements were claimed to be useful in the diagnosis of short luteal phase; however, controversy exists regarding the appropriate criteria to use [9]. Progesterone increases the set-point of the hypothalamic thermoregulatory center. A serum progesterone level that is greater than 2.5 ng/mL may increase the BBT up to 1°F; this forms the basis of the BBT chart. Traditionally, a biphasic BBT chart with sustained increased temperature for 12 to 15 days is considered to be normal. Determining the length of the luteal phase was proposed to be the simplest approach for the evaluation of luteal function, although its predictive values have been questioned [24].

It was reported that 5.2% of women who have normal ovulatory cycles have luteal phases that are shorter than 9 days [7]. Such luteal phases were observed commonly in women who were younger than 24 and older than 45 years of age. When the temperature elevation is maintained for less than 11 days, the quality of ovulation and the resulting corpus luteum has been considered to be inadequate [7]. In 95 patients who had unexplained infertility, however, there were no differences in the length of the luteal phase when compared with 92 control
women who had normal ovulatory cycles [24]. The occurrence of luteal phase duration of up to 11 days were 9% and 8% in women who had unexplained infertility and in controls, respectively [24].

In 30 regularly menstruating women, different BBT patterns and luteal phase lengths were found in 36% and 67% of the observed consecutive cycles, respectively [25]. In addition, estrogen and progesterone levels and endometrial dating showed substantial variability in the consecutive cycles of each patient. This indicates that the conditions of the luteal phase are not the same in every cycle.

In studies, neither the rate of increase in the postovulatory temperature nor the magnitude of temperature elevation correlated with endometrial histology. The overall correlation of BBT charts with endometrial histology was as low as 25% [26]. BBT charts are not reliable enough to be considered as the diagnostic tool for LPD.

Endometrial histology

The original description of LPD in 1949 incorporated BBT charts, urinary pregnanediol levels, and endometrial biopsy as diagnostic tests [1]. The classic approach to diagnose LPD uses the histologic dating method of Noyes et al [27,28] in endometrial biopsy specimens. This original criterion was described in relation to BBT charts. Reproducibility to within 2 days of BBT charts was obtained in more than 80% of the 8000 biopsy specimens that were studied. The diagnosis is made histologically when endometrial maturation lags 2 or more days behind the expected day of ovulation and the subsequent onset of menses [29,30]. With this technique, the prevalence of LPD in an infertile population has ranged from 3.5% to 38.9% [30–32].

The optimal time for performing an endometrial biopsy has not been determined. In an earlier study, nearly one half of the abnormal endometrial biopsies that were performed during the midluteal phase had reverted to normal when repeated in the late luteal phase [33]. Some investigators recommended late luteal biopsy 11 to 12 days after positive urinary LH testing, although the endometrial histology may be increasingly variable as menstruation approaches [3]. When retrospective and prospective dating methods for the diagnosis of LPD were compared, the retrospective method (determination of LH peak by daily assay) identified 42% of biopsy specimens as out-of-phase, whereas the prospective method (calculation based on the onset of next menstrual period) identified only 10% as out-of-phase [34]. The results of repeat endometrial biopsies vary during each cycle in the same patient by 15 to 30% [35]. Therefore, two out-of-phase endometrial biopsies from two cycles have been recommended for the diagnosis of LPD.

There also has been a disagreement over whether to use a 2-day lag or a greater than 2-day lag to diagnose LPD. Five regularly menstruating women of proven fertility underwent a total of 39 endometrial biopsies [36]. Using a 2-day or greater lag in endometrial maturity to define LPD, the incidence of single and sequential out-of-phase endometrial biopsies was 51.4% and 26.7%, respectively.
Using a 3-day or greater lag to define a LPD, the incidence of single and sequential out-of-phase endometrial biopsies was 31.4% and 6.6%, respectively. Furthermore, these incidences in normal, fertile women were close to the rates observed in infertile populations [36].

There is significant inter- and intraobserver variability in the results of histologic dating. The duplicate endometrial biopsies from 25 women were dated by five evaluators on two separate occasions [37]. Inconsistencies between the evaluators accounted for 65% of the observed variability, whereas 27% was due to inconsistencies in duplicate readings by the same evaluator [37]. The significant inter- and intraobserver variability in the results of histologic dating, the issue of cycle-to-cycle variation of biopsy results, the debates in the proper timing of the biopsy, the disagreements over the diagnostic criteria of days of lag in the specimen, and the similar biopsy findings in fertile and infertile women compromise the dependability of endometrial histology in the diagnosis of LPD.

**Progesterone levels**

The serum progesterone levels are subject to large fluctuations as a result of pulsatile hormone release [38]. On the basis of a single progesterone determination during the midluteal phase, a false LPD may be diagnosed approximately 15% of the time [10]. Some investigators suggest that because the decreased progesterone levels are seen regularly before the occurrence of an LH pulse, it is more appropriate to draw two or three blood samples within a 3-hour period to decrease the probability of a falsely diagnosed LPD down to 2% to 0.5% [10].

In 457 patients who had regular menstrual cycles and normal ovulation as confirmed by transvaginal ultrasound, the distribution of midluteal phase serum progesterone levels were bimodal with two peaks at approximately 7 ng/mL and 11 ng/mL. The arbitrary cut-off for a normal progesterone level was set at greater than 8ng/mL. Life table analysis of the data showed that the patients who had decreased midluteal progesterone levels had decreased spontaneous fecundity [10].

Studies that compared daily luteal serum progesterone levels in women who had unexplained infertility with those who had normal ovulatory or conception cycles reported different cut-off values to define abnormal progesterone levels [39,40]. Some investigators defined abnormal progesterone levels as less than 5 ng/mL for 5 or more days in the luteal phase, whereas other investigators concluded that an abnormal level during the luteal phase was less than 10 ng/mL.

The corpus luteum is unresponsive to LH pulses during the early luteal phase. The response to LH develops between Day 4 and Day 6 after ovulation [41]. It has been suggested that if a single determination of progesterone level can be done on one of the days when the corpus luteum becomes responsive to LH, a correct diagnosis of LPD may be more likely [10]. When a midluteal progesterone level of less than 10 ng/mL was considered to be abnormal, the probability of falsely diagnosing LPD was as low as 4% [10]. The same group
concluded that LPD may occur in infertile patients at irregular and unknown intervals and may be chronic in only approximately 6% of these women [8].

The use of a single or serial progesterone levels as a diagnostic test has been criticized because of the pulsatile nature of progesterone secretion and the transient decrease in progesterone levels following daily events like food ingestion [42]. Progesterone levels vary up to 10-fold during the 2- to 3-hour pulse interval in the luteal phase [43]. In this respect, multiple daily progesterone measurements with the calculation of integrated progesterone levels during the luteal phase may be more accurate but are not applicable clinically.

The sensitivity and specificity of common clinical tests that are used for the diagnosis of LPD were assessed in 58 strictly defined normal women and 34 women who were evaluated for various reasons, including infertility and recurrent abortion [5]. BBT charts, maximum preovulatory follicle sizes, dated endometrial biopsies, and serum progesterone levels (single and multiple) were used in an attempt to predict which patients had decreased integrated progesterone levels during the luteal phase. Luteal integrated progesterone levels—an estimate of total progesterone output over the luteal phase—were determined by summing daily serum progesterone levels starting with the day after the LH surge and ending with the day before the next menstrual period. First, the normal range of integrated progesterone values was determined in a pool of 58 normal volunteers. The investigators calculated an arbitrary cut-off that was inspired from an earlier article that stated the prevalence rate of LPD as 10% [9]. Because 10% of the women in this pool had integrated progesterone values less than 80 ng · days/mL, the cut-off was set as such; however, various cut-off values that were reported in the literature were calculated in a variety of ways in different female populations and were higher than this threshold [12,44,45]. The patient population that was studied, however, had a prevalence rate of LPD of 21% with the cut-off value of less than 80 ng · days/mL [5].

In the study detailed above, unacceptably low sensitivity and/or specificity values were calculated for BBT chart, luteal phase length, and preovulatory follicle diameter for the diagnosis of LPD. Timed endometrial biopsy had marginal sensitivity (29%–57%) and specificity (44%–56%)—whether dated by next menstrual period or midcycle events, which included the day of LH surge or ovulation as determined by ultrasound. The best test for the prediction of decreased integrated progesterone was a single serum progesterone level from the midluteal phase (5 to 9 days after ovulation) that was less than 10 ng/mL (31.8 nmol/L) (sensitivity 86%, specificity 83%) or a sum of three random serum progesterone measurements that was less than 30 ng/mL (95.4 nmol/L) (sensitivity 100%, specificity 80%). The out-of-phase timed endometrial biopsy combined with a single midluteal progesterone level that was less than 10 ng/mL had a sensitivity of 71% and specificity of 93% [5]. In this study, the best dating criterion for endometrial biopsies was next menstrual period rather than the midcycle events. The endometrial biopsy was recommended as a second-line test, especially when LPD needs to be evaluated in a cycle that is treated with ovulation induction or supplemental progesterone [5]. Along with the concerns
that were described earlier, this study was criticized for using daily measurement of plasma progesterone as the reference test against all other tests that should be assessed [46]. The issues raised were that the receptivity of endometrium to progesterone could vary independent of serum progesterone levels and that histologic delay could be present with physiologic progesterone [47] or despite supraphysiologic progesterone levels [48]. Furthermore, the integrated serum progesterone is not a good indicator of endometrial histology [49].

Measuring urinary pregnanediol glucuronide, a metabolite of progesterone, in the first urine voided daily during the luteal phase was recommended to diagnose LPD. This approach may eliminate variability that is due to pulsatile secretion and may be more indicative of the total progesterone production by the corpus luteum [50–52]. Although this approach is an attractive tool in the research setting, its clinical applicability is difficult. In addition, the proportion of progesterone that is converted and excreted as pregnanediol glucuronide varies with age, stage of menstrual cycle, and other factors [3].

Ultrasound

It was recommended to monitor ovarian follicle size with pelvic sonography during the cycle to detect LPD. The follicle diameter was monitored throughout the follicular phase until the day of ovulation; this was indicated by an acute decrease in follicle diameter, abrupt increase in free intraperitoneal fluid, or appearance of intrafollicular echoes. A maximum mean preovulatory follicle diameter of less than 17 mm was considered to indicate LPD [53,54]. In a more recent study, however, a maximum preovulatory follicle size of 17 mm or less was unacceptably insensitive in the diagnosis of LPD [5]. There is no minimum follicle size that separates all normal women from those who have LPD. Studies regarding the assessment of the luteal phase by using transvaginal color and pulsed Doppler ultrasound did not show any significant benefit [55,56].

Clinical conditions that are associated with luteal phase defect

Recurrent abortion

Recurrent abortion is defined as the loss of three or more consecutive pregnancies before the twentieth week of gestation. This condition may be associated with LPD that is marked by retarded endometrial development in the peri-implantation period.

The diagnosis of LPD has been based on the histologic study of a timed luteal phase biopsy according to the method of Noyes et al [27]. In studies that examined timed endometrial biopsy specimens in women who had recurrent abortion, the incidence of LPD ranged from 17.4% [57] to 28% [58]. The evaluation of late luteal phase endometrial biopsies that were performed on regularly
menstruating, fertile women who had no history of pregnancy loss demonstrated a 26.7% incidence of at least a 2-day lag in sequential cycles [36].

In a prospective case series of 197 women who had a history of two consecutive first-trimester spontaneous abortions, preconceptional, single midluteal (5 to 9 days after ovulation) phase serum progesterone (cut-off level for progesterone was less than 10 ng/mL for LPD diagnosis) and estrogen levels did not predict future pregnancy loss [59].

In a recent study that aimed to investigate whether endometrial expression of specific cellular and molecular markers differ in women who have in-phase and out-of-phase endometrium that is consistent with LPD, endometrial biopsies were obtained from 36 women who had unexplained, recurrent first-trimester abortion. Endometrial biopsies were obtained accurately between 6th and 11th days following LH surge (LH + 6 to + 11). There were no differences in endometrial expression of CD45, CD4, and CD3 cells; estrogen receptor; progesterone receptor; leukemia inhibitory factor; and interleukin-6 between in-phase and retarded endometrium [60]. Although an earlier study showed increased epithelial cell expression of progesterone receptor in women who had recurrent abortion and LPD [61], this study did not find any difference in progesterone receptor and estrogen receptor expression between in-phase and LPD endometrium [60]. The differences between the two studies have been related to the variability of the timing of endometrial biopsies and the use of a newer progesterone receptor antibody. Most importantly, the study showed no difference in luteal progesterone levels in women who had in-phase or retarded endometrium [60]. In contrast, LPD was associated with decreased mid-cycle plasma estrogen levels which may indicate poor oocyte quality and a poorly functioning corpus luteum, although it secreted normal amounts of progesterone.

The observations on the artificial cycles suggested that optimum estrogen priming is essential during the follicular phase to achieve appropriate endometrial development during the luteal phase [62]. Because most cases of LPD were not associated with decreased progesterone, but rather, with an abnormal response of endometrium to progesterone, treatment has been targeted at improving the endometrial responsiveness by enhancing the priming of endometrium in the follicular phase. In a small retrospective study, controlled ovarian stimulation with human menopausal gonadotropin improved the endometrial maturation and increased pregnancy rate in patients who had recurrent miscarriage [63]. Although various treatments have been described for LPD, including ovulation induction with clomiphene citrate or gonadotropins, human chorionic gonadotropin injection at the time of expected ovulation, and progesterone supplementation during the luteal phase and the first trimester of the pregnancy, the data are inadequate to support any conclusion [64,65]. A meta-analysis of randomized trials of pregnancies that were treated with progestational agents failed to find any evidence for their positive effect on the maintenance of pregnancy [66]. In view of the uncertainties in establishing the diagnosis of LPD, the empiric treatment of unexplained recurrent abortion with clomiphene citrate was suggested, again without any valid scientific evidence [67].
Despite the many controversies that surround the association of recurrent abortion and LPD, the work-up recommendation for recurrent pregnancy loss still includes luteal phase endometrial biopsy 10 days after the LH surge for endometrial dating [68]. This recommendation and practice should be readdressed.

Infertility

The frequency of LPD in women who have infertility—when strictly defined—is no greater than that found by chance in normal cycles [69]. In a series of 1492 biopsies in 1055 women, 26 biopsies were in conception cycles [70]. With an in-phase biopsy, 15 of 20 pregnancies went to term; however, 4 of 6 pregnancies in women who had an out-of-phase biopsy also went to term. Furthermore, the term pregnancy rates were identical in women who had treated or untreated LPD that was diagnosed with endometrial dating [70].

In 126 cases of unexplained infertility, serial study of plasma hormones and midluteal endometrial biopsies revealed retarded endometrium in 34.1% of the patients. Approximately 78% of the patients who had retarded endometrium showed normal progesterone levels [71].

It was suggested that there may be degrees of LPD. With a lag of 5 days or more, treatment with clomiphene citrate yielded a conception rate of 79%; however, in women who had less severe defects, the same treatment was associated with a conception rate of 8.9% [72].

If a patient has persistent LPD that is accompanied by hyperprolactinemia, bromocriptine is recommended as a treatment option [68]. Although vaginal progesterone and oral dehydrogesterone have been used successfully to induce endometrial maturation in patients who were diagnosed with LPD [73,74], the association between the treatment for out-of-phase endometrium and pregnancy in infertile patients is lacking [70,75].

The assessment of endometrial function is a highly controversial area in infertility. Inducing ovulation may improve the hormonal profile of the patient; this may not be associated with a receptive endometrium for implantation [76]. Conversely, postmenopausal and hypogonadal women who are given hormone replacement therapy and donor oocytes can achieve higher implantation rates than women who have normal cycles, even if the respective donors for both groups have comparable pregnancy rates [77].

The pathogenesis of LPD has been linked to inadequate corpus luteum function or inadequate endometrial response. The former has been explained further as due to impaired follicle development, insufficient LH surge, impaired luteotropic system, increased luteolysis, or primary dysfunction of the corpus luteum [78]. The pathogenesis-oriented treatments include estrogen or progesterone replacement, ovulation induction, luteal phase support with human chorionic gonadotropin, progesterone, GnRH pulse, and bromocriptine. In terms of achievement of successful pregnancies, little efficacy was associated with progesterone replacement; however, acceptable pregnancy rates were accom-
plished with ovulation induction. This scenario suggests that the primary cause of LPD in infertility is poor oocyte quality that is due to impaired follicle development. Although clinicians have considered LPD to be one of the most important causes of infertility for several decades, no convincing evidence exists for this relationship.

**Luteal suppression in assisted reproduction**

GnRH agonists increase pregnancy rates for in vitro fertilization (IVF) cycles by preventing premature surges of endogenous LH through pituitary suppression during controlled ovarian stimulation [79]. In this way, time is allowed for a larger number of oocytes to reach maturity before retrieval. GnRH agonists also work by increasing the length of time for gonadotropin-independent follicular growth resulting in synchronous development of a large cohort of follicles with the ability to respond to exogenous gonadotropins. In spite of these favorable effects, GnRH agonists may create an iatrogenic LPD [80]. The use of GnRH agonists causes the suppression of pituitary LH secretion for as long as 10 days after the last dosage. Without an LH signal, the corpus luteum may be dysfunctional. Without proper progesterone and estrogen stimulation, endometrial receptivity may be compromised [81]. Therefore, luteal supplementation with various agents has been used to prevent this abnormality.

In a recent meta-analysis, luteal supplementation with human chorionic gonadotropin and intramuscular (IM) progesterone significantly improved fertility outcomes as compared to no treatment in women undergoing IVF [82]. Oral progesterone supplementation during the luteal phase had less benefit than vaginal progesterone or IM human chorionic gonadotropin. The oral progesterone, however, also had decreased efficacy and a greater number of side effects than the IM progesterone.

It was hypothesized that IM human chorionic gonadotropin might be superior to progesterone alone as luteal support. Because human chorionic gonadotropin rescues the corpus luteum, it allows the continuation of estrogen and progesterone secretion and may maintain the secretion of other unknown products from the corpus luteum [83]. In a recent meta-analysis, no differences were found between IM human chorionic gonadotropin administration during the luteal phase when compared with IM or vaginal progesterone [82]. Some studies reported significant increases in hyperstimulation rates when human chorionic gonadotropin was used for luteal support [84,85]. Hence, there is no evidence that i.m. human chorionic gonadotropin as luteal support is superior to progesterone alone. The meta-analysis also showed that IM progesterone contributed to higher cumulative pregnancy and delivery rates than vaginal progesterone [82]. The optimal length of treatment for luteal support is still controversial; it may be limited to the luteal phase or through 10 to 12 weeks’ gestation.

The recent availability of GnRH antagonists for the prevention of a premature LH increase in IVF was believed to be advantageous because gonadotropin levels recover within 24 hours after stopping the GnRH antagonist [86]. It was
speculated that luteal phase supplementation may not be required in cycles in which GnRH antagonist cotreatment is applied [87]. In a recent prospective study, the nonsupplemented luteal phase characteristics in patients who were cotreated with GnRH antagonists were analyzed in women who were randomized to recombinant human chorionic gonadotropin, recombinant LH, or an endogenous LH surge that was induced by a GnRH agonist bolus for the induction of final oocyte maturation. The luteal phase was inadequate in all groups that had decreased pregnancy rates. The investigators strongly recommended luteal support with GnRH antagonist cotreatment [88].

Recent concepts in endometrial evaluation

For a long time the premenstrual dating of endometrium was considered to be the gold standard for the evaluation of LPD. Recently, the relationship between the histologic changes and the endometrial receptivity has been questioned [89].

The evaluation of endometrial dating by Noyes criteria [27,28], was derived from observations in a predominantly infertile population; scant validating evidence exists despite its widespread use over 5 decades. The flaws of timed endometrial biopsy include its dependence on a subjective histologic interpretation; variation in the handling of glandular stromal disparity among different investigators; and a moderate reproducibility of readings, even when the same specimen is read several times by a single pathologist [5,34]. In addition, timed endometrial biopsy has been validated as the definitive test for LPD by comparing its results with unproven criteria, such as BBT charts and single progesterone measurements with various methods [27,90]. Therefore, histologic dating seemed to be a crude index of endometrial receptivity. Recent studies have been directed to find more objective measures of endometrial receptivity.

The midluteal assessment of endometrium with relevant markers was evaluated to define better endometrial receptivity. The measurement of glycodelin A (previously called placental protein, PP14) in endometrial flushings was recommended in the identification of an endometrial defect [91]. In this regard, $\alpha_v\beta_3$ integrin expression and pinopod formation have been the proposed markers for uterine receptivity [92,93].

It is accepted that the endometrium is receptive to blastocyst implantation during a short period during the luteal phase that is known as the implantation window. Based on the IVF and embryo transfer data, this period lasts for approximately 4 days (between Days 5.5 and 9.5 following ovulation) [94]. Traditionally, this putative window of implantation has been defined by histologic features [27,75]. Because there have been many discrepancies in this definition, studies have focused on molecular markers that are believed to be important in endometrial receptivity. In a recent study, an increased level of $\alpha_v\beta_3$ integrin expression and pinopods were found on postovulatory Days 6 to 7, irrespective of whether endometria were in-phase or out-of-phase [95].
The diminished endometrial receptivity that results in failed or defective implantation has been proposed as a mechanism of infertility that is not related to anovulation or tubal or male factors. LPD has been considered to be one of the many causes of an unreceptive endometrium. The studies of the biochemical markers of endometrial receptivity demonstrated that even when the morphologic development of endometrium proceeds normally, its functional maturation may be impaired. This discrepancy between endometrial histology and its functional maturation was observed in patients who had mild endometriosis [96] and unexplained infertility [97]. Progesterone receptor is down-regulated differentially in endometrial epithelium and stroma and loss of epithelial progesterone receptor coincides with the time of embryo implantation [98,99]. Several other studies have been published regarding the patterns of endometrial estrogen and progesterone receptor expression in LPD. The results of these studies varied widely [74,100–102]; small sample size, different patient populations, and differences in the timing of endometrial biopsies and the methodologies that were used may explain the conflicting results. The development and use of monoclonal antibodies that were more specific to steroid receptors seemed to make the findings of recent studies more valid.

In a more recent study, histologic delay that was consistent with LPD was associated with a failure of progesterone receptor down-regulation and a lack of \(\alpha v \beta 3\) integrin expression [61]; however, in patients who had minimal or mild endometriosis, the down-regulation of progesterone receptor was not associated with the timely expression of \(\alpha v \beta 3\) integrin. Hence, many alternate routes may affect endometrial receptivity at the molecular level; this complicates further the evaluation and diagnosis of LPD.

Among the patterns of integrin expression that were studied in human endometrium, \(\alpha v \beta 3\) integrin appears precisely as the implantation window begins (~cycle Day 20) [103]. This marker may not be expressed in patients who have LPD as diagnosed by histologic dating as well as in some infertile women who have normal endometrial dating [96,97].

The potential significance of the newly proposed markers of endometrial receptivity was challenged recently. A study was conducted to investigate the intra-subject variability and inter-cycle reproducibility of histologic dating and endometrial receptivity markers, which included \(\alpha v \beta 3\) integrin expression determined by immunohistochemistry and pinopod formation that was assessed under scanning electron microscopy [104]. Fifteen patients who had primary infertility underwent three endometrial biopsies in consecutive spontaneous cycles on postovulation Day 7 as determined by serial transvaginal ultrasound. \(\alpha v \beta 3\) Integrin expression and pinopod formation in the endometrium of infertile patients were poorly reproducible and were highly variable from one cycle to another. Furthermore, the reproducibility for the new markers of endometrial receptivity was similar to that for traditional histologic dating [104]; hence, their potential usefulness as targets for infertility treatments was debated.

In another study, the correlation of midluteal endometrial histologic dating and \(\alpha v \beta 3\) integrin expression with subsequent fecundity was examined [105].
One hundred consecutive infertile patients underwent two endometrial biopsies, 4 days apart (mid- and late luteal); these were timed from the day of ovulation as determined by transvaginal ultrasound. All patients were followed for 18 to 24 months. Twenty five midluteal biopsies were out-of-phase. Endometrial glandular \( \alpha v \beta 3 \) integrin expression was observed in 50% of midluteal specimens; expression was more frequent among in-phase biopsies. All late luteal biopsies expressed integrin. Thirty-eight women had spontaneous pregnancy. There was a lack of correlation between the presence or absence of \( \alpha v \beta 3 \) integrin and the outcome for infertile women, irrespective of whether endometrial biopsies were in-phase or out-of-phase [105]. The value of endometrial evaluation, histologically and immunohistochemically, for \( \alpha v \beta 3 \) integrin in patients who had infertility was questioned.

Summary

Although the diagnosis of LPD has been described convincingly in the research setting, it remains a controversial clinical entity. In clinical practice, the diagnosis of LPD has been attempted by several methods—BBT charts, progesterone levels indirectly, and endometrial biopsy as a direct and invasive method. All of these methods are retrospective; the interpretation of endometrial biopsies—even with the recently proposed molecular markers—has not been satisfactory. Therefore, no reliable method exists to diagnose LPD. When LPD is found, most physicians are inclined to incriminate it as the cause of infertility or recurrent abortion, although there is no convincing scientific evidence to support these associations. Does the LPD appear consecutively or sporadically? This question further complicates discussions on the diagnosis and treatment of LPD.

No specific treatment is intended to manage LPD. The treatment of LPD with progestin replacement has not been correlated with conception. The treatment decisions mostly are empiric. Treatment modalities that are recommended for unexplained infertility (eg, ovulation induction, assisted reproduction) have been successful in achieving pregnancy in women who have LPD. These issues undermine the efforts to diagnose the condition.

LPD is a reality in assisted reproduction cycles with GnRH agonist/antagonist suppression. Otherwise, there is no convincing evidence to define LPD as a distinct clinical entity that leads to reproductive problems. It is not justified to include costly and cumbersome tests to diagnose LPD in patients who have infertility or recurrent abortion.

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