CASE STUDY

Infertility Due to Luteal Phase Defects: Options in Diagnosis and Treatment with Natural Progesterone

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Introduction

Infertility is clinically defined as the inability of a person or couple to conceive after one year of unprotected intercourse, or the inability of the female to carry a pregnancy to term. Estimates in the literature of the incidence of infertility in the US range from 10-15%. (1) On seeking help from the medical field as to what is causing the inability to conceive, the individuals are subjected to a barrage of diagnostic exams and screening tests, and may be given any of the diagnoses as listed in Table 1. Even with appropriate therapy, success may be limited. Emotionally, this can be devastating to a couple who have invested much of their time, money, and identity into achieving a viable pregnancy.

Table 1
Causes of Infertility

Male Factor	30-40%
Ovulatory Disorders	15%
Diminished ovarian reserve	
Polycystic ovarian disease	
Hyperprolactinemia	
Thyroid dysfunction	
Cervical Mucus Factor	5-10%
Tubal Adhesion	20%
Luteal Phase Defects	10%
Unknown	10%
Other	
Autoimmune Disease	
Tumors (endocrine)	
Endometriosis	

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Luteal phase defect (LPD) is a recurrent post-ovulatory deficiency in the production of progesterone from the corpus luteum leading to infertility or habitual abortion. The literature estimates a 10% occurrence rate in the normal US population. (2) However, this rate may be inaccurate due to a lack of uniform criteria for the evaluation and differential diagnosis of LPD. The lack of understanding surrounding the succession of events that leads to the progesterone deficiency inherent in LPD has led to some confusion around how it can best be defined. Researchers continue to debate whether the central problem leading to an inadequate endometrium is due to the total amount of progesterone released, the timing or duration of its release, or a decrease in its effect on the endometrial receptors.

This article will examine the problems encountered in diagnosing LPD, as well as evaluating the reliability of the available diagnostic tests for this condition. It will also compare some of the ovulation inducing agents currently available to women experiencing LPD with the option of using various forms and dosages of natural progesterone.

Theories of Causation

Progesterone is produced in two ways by the ovarian cells: it is secreted in a tonic (continuous) fashion by luteinized granulosa cells and it is released in a pulsatile fashion by luteinized theca cells. Tonic release is independent of LH stimuli, and its purpose seems to involve sustaining appropriate endometrial maturation. Exercise and weight loss have been shown to suppress tonic progesterone secretion. Pulsatile release is in direct response to LH stimulation, and is responsible for responding to hCG in the event of conception to assist the corpus luteum in supporting a successful pregnancy. Aging has been shown to effect pulsatile progesterone secretion. (3)

If the corpus luteum is not producing sufficient or timely progesterone, the difficulty could originate from various foci or interactions of foci within the reproductive cycle. A full discussion of the complex intricacies involved in these interactions is beyond the scope of this article. In general, however, these difficulties can involve three areas: insufficient FSH for folliculogenesis and/or the induction of ovarian LH receptors resulting in decreased synthesis of progesterone by the corpus luteum; abnormal frequency or amplitude of the LH surge (or pulses during the luteal phase) resulting in anovulation; or abnormal responses of the hypothalamus and pituitary to ovarian steroid feedback. (4) Both endometriosis and polycystic ovarian syndrome have also been related to LH/FSH ratio imbalances and hypothalamic-pituitary dysfunction. (5,6)

When it is clear that the production of progesterone is not the issue, researchers have examined endometrial factors and the response of the endometrium to progesterone as a possible etiologic source of LPD. One group of considerations examines the effect of estrogen priming on the endometrial progesterone receptors in the follicular phase of the ovulatory cycle. Lack of sufficient amounts of estrogen, too much estrogen, the type of estrogen available, or a defect in the progesterone receptors themselves are all potential foci for infertility problems. (7)

It should be remembered that hypothalamic-pituitary function is greatly influenced by many factors that should be considered before resorting to exogenous treatment for LPD. Stress, sleep, exercise, weight loss, medications and other environmental substances affect the functioning and sensitivity of the hypothalamic-pituitary axis. Therefore, a thorough history is a crucial aspect in the management of the condition.

Effects of Luteal Phase Defects

Progesterone's main function in the body is to induce differentiation of the endometrium in preparation for implantation of the embryo, and to prepare the body for the demands of pregnancy. If either the amount or timing of progesterone release or the response of the endometrium to its stimulation is inadequate, the embryo fails in its attempts to achieve successful implantation resulting in infertility or spontaneous abortion. Recent studies have revealed an additional effect of progesterone on the endometrium that enables implantation. Kaul et al. investigated levels of endometrial Decay Accelerating Factor (DAF), a complement regulatory protein, in women diagnosed with LPD. DAF is involved in protecting the semiallogenic (i.e., partially antigenic, as it also consists of paternal genetic material) fetus from the maternal immune system by binding to activated C4b and C3b fragments and preventing the complement cascade mediated cytotoxic attack. Levels of this protein increase during the secretory phase in the human endometrium. The study found secretory phase DAF levels in women with LPD to be only 25% of the control population. It was discovered that DAF levels increased from a mean value of 12% to 88% in the LPD group after progesterone therapy (vaginal progesterone suppositories 25mg. b.i.d. for 14 days). Thus, a progesterone effect on DAF expression in the secretory phase may be essential for successful implantation. (4)

A few smaller studies demonstrating the positive effect of progesterone on uterine blood flow suggest that progesterone supplementation decreases blood flow impedance and uterine artery pulsatility index in women with LPD treated with ovulation inducing agents. (8) This was hypothesized to improve pregnancy rates secondary to improved uterine perfusion, but whether similar results would be obtained with women not on those specific drugs or in spontaneous cycles was not studied.

Another nonreproductive effect of LPD and diminished progesterone in the luteal phase is on bone loss. In a prospective study by Prior et al., mean luteal length was correlated with percent annual change in vertebral mineral density in premenopausal women. There was an average spinal bone loss of 2.8% - 4% for each anovulatory cycle or each incidence of greater than one short luteal phase. This suggests that lack of adequate progesterone levels (other steroid hormones were not significantly different) corresponds with decreased bone mass in premenopausal women, whether resulting from anovulation or LPD. (9)

Diagnosis of LPD

Many clinical tests have been purported to be useful in diagnosing LPD and various combinations of these have been applied in investigative studies. A list of these diagnostic tools include basal body temperature (BBT) graphs, timed endometrial biopsies, preovulatory pelvic ultrasound (US) for follicle diameter measurements, integrated serum/salivary progesterone levels, mid-luteal serum progesterone levels, luteal phase length, and urinary pregnanediol levels. By consensus, the most common standard in the clinical setting is the timed endometrial biopsy which is used to evaluate endometrial histology for inappropriate phase shifts. Discrepancies arise in the literature as to what is the optimal time in the menstrual cycle for sampling (timing varies from 1-2 days prior to projected menses, to 9 days post-ovulation). Abnormal results range from $\geq$2 day to >4 day lags in maturation of the endometrium. In a study by Batista, et al., it was concluded that disruption of endometrial maturation occurs more frequently in the infertile population and is associated with decreased mean serum progesterone values, yet it is not always associated with a LPD. The study used hCG to stimulate increased progesterone release by the corpus luteum, and as the corpus luteum responded well and this increase in progesterone did not significantly improve endometrial maturation in most cases, they concluded LPD was not the problem. (10) This and another study, which revealed a number of causative factors involved in producing an out-of-phase endometrium (such as mild endometriosis, and ovulatory disorders), raise questions about the efficacy of this technique as a standard diagnostic tool for LPD. (11)

The gold standard test for LPD has been the integrated luteal progesterone level, taken from daily serum samples. Research by Jordan, et al. studied women with low (< 80ng/ml)) and normal integrated progesterone levels and compared the common clinical tests used for diagnosing LPD to this standard to assess the sensitivity and specificity of each. They found that the best test for the prediction of low integrated progesterone was a single midluteal serum progesterone level <10ng/ml or a sum of 3 random midluteal serum progesterone levels <30ng/ml. Other studies have

used or found differing cut-off levels. (22) Basal body temperature charts, preovulatory follicle size, dated endometrial biopsies, and luteal phase length were all shown to have low to marginal sensitivity and specificity. (6)

Salivary progesterone testing has also been shown to be a reliable tool for diagnosing LPD. Finn, et al. determined the optimal frequency of samples to be every 2-3 days during the luteal phase. This frequency corresponded well to the integrated serum progesterone level, and allowed the recognition of short luteal phases and poor post-ovulatory progesterone surges. These two parameters were concomitant with out-of-phase endometrial histology. A single mid-luteal salivary progesterone sample satisfactorily reflected serum levels in women with normal luteal function, but did not adequately reveal abnormal luteal function. (12) A separate study claimed that there was only a 50% correlation between cumulative salivary progesterone and endometrial retarded development (3), as was discussed earlier in this article.

While Jordan, et al. found basal body temperature graphs inadequate in diagnosing LPD (defined as low integrated progesterone) and raised valid concerns regarding their reproducibility, a separate study addressed some of the incongruencies of interpretation. By developing uniform criteria for the classification and evaluation of these graphs, D. Agnes-de-Campes, et al. demonstrated that basal body temperature charts may be accurate tools for assessing ovulation if not LPD. By imposing uniform criteria for classifying the charts as monophasic or biphasic, assessing the adequacy of the thermal shift, and identifying the thermal nadir, interobserver agreement among the experienced observers was 75-81%, depending on the chart feature. (13)

A relatively new aid for evaluating luteal defects currently being investigated is the color flow pulsed Doppler. It is being used to assess the adequacy of the corpus luteum by analyzing the level of impedance in blood flow to the corpus luteum. Increased flow resistance to the corpus luteum has been associated with decreased integrated progesterone levels. (14) No matter which diagnostic test(s) are chosen in the evaluation of women for LPD, it is important to measure more than one cycle in each individual. Research has shown that while luteal defects happen occasionally in women without fertility problems, they are a recurrent issue for some women with infertility. (12)

Identification of the day of ovulation is another important requirement in diagnostic testing, as it influences the time of sampling for all of the above tests. Assessing the status of ovulation serves a dual purpose, allowing the differentiation of LPD from ovulation disorders, which are a separate diagnostic entity requiring different therapeutic options. Determination of the day of ovulation for the purpose of timing progesterone sampling and/or treatment could be done in a number of ways. A simple analysis of basal body temperature graphs, where a rise in temperature of at least 0.2°C (0.5°F) above preceding 6 days that is completed in less than 48 hours and sustained for at least 11 days would indicate ovulation had occurred. (13) Alternatively, a daily follicular phase serum, a urinary LH sample, or a new test measuring the ratio of urinary estrogen and progesterone metabolites could be used to ascertain ovulation time. (15) If differentiating between LPD and an ovulatory disorder is desired, more extensive diagnostic testing is required. This would include pelvic US, where ovulation is defined as the presence of a preovulatory mature follicle at least 18-24mm in diameter with a corresponding serum estrogen level >200ng/ml and serum progesterone <1.5ng/ml, followed by egg release and follicle shrinkage. (16) Explanations for poor luteal functioning include diminished ovarian reserves (a reduction in quantity and quality of follicles available), immature follicle syndrome (IFS), and luteinized unruptured follicle syndrome (LUF; this is often referred to as a follicular cyst). Low midluteal serum progesterone, broad or biphasic LH surges, or a deficiency in prostaglandin F2 are also associated with anovulation. Initial therapy for ovulatory disorders usually involves ovulation inducing agents such as clomiphene citrate, alone or in combination with hMG or progesterone in the luteal phase.

Treatment of LPD

Differing opinions exist as to the proper and most effective treatment for LPD. Much of this controversy can be resolved by effective and accurate diagnosis of LPD as the cause of infertility. Most reproductive specialists advocate the use of assisted reproductive technology. These medications and their indications are listed in Table 2. (17)

When the fertility problem is not secondary to a failure to produce mature follicles, then progesterone (separately or in combination with therapies such as botanicals like Vitex Agnus Castus (18,19), homeopathy, and lifestyle counseling) may be a better and less invasive initial therapy. A study by Check et al. compared pregnancy rates (PR) of infertile women with LPD using clomiphene citrate (CC), hMG, or

Example of Biphasic Basal Body Temperature Graphic (13)

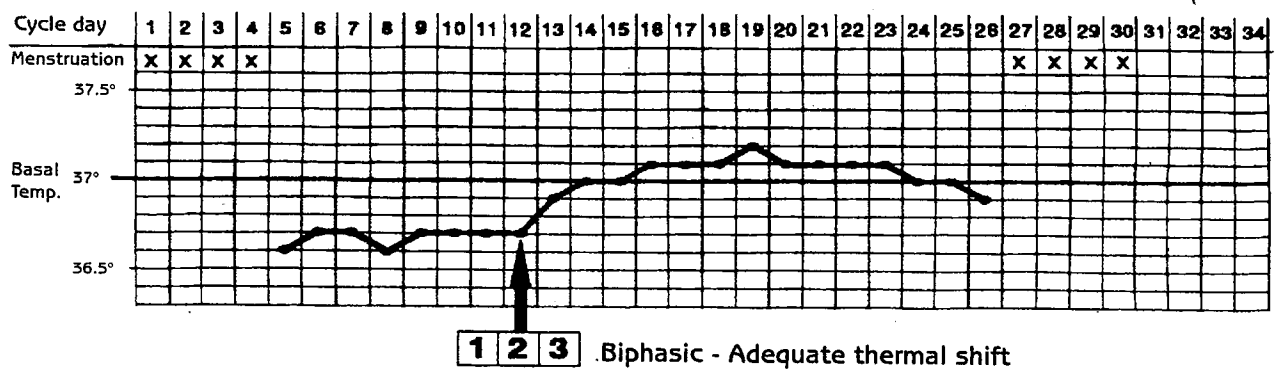

Figure 1

OVULATION INDUCTION AGENTS

Generic Name	Adverse Effects	Indications
Clomiphene	hot flashes, visual disturbances, cervical mucous abnormalities, luteal phase defects, multiple gestation	anovulation, oligoovulation, luteal phase defects
Bromocriptine	nausea, vomiting, postural hypotension, headaches, nasal congestion	hyperprolactinemia
Gonadotropins (hMG, urofollitropin, etc.)	hyperstimulation syndrome, multiple gestation	hypogonadotropic hypogonadism, unexplained infertility, oligoovulation
Gonadotropin-releasing hormone (GnRH)	phlebitis, need for luteal support	hypogonadotropic hypogonadism
Gonadotropin-releasing hormone agonists		pituitary down-regulation prior to gonadotropin therapy

TABLE 2

progesterone. PR for the progesterone treatment group was 77.4% with a 4.1% abortion rate versus 11.1% with a 66.6% abortion rate for the CC and/or hMG group. In addition, the study reported a 64% PR for those who had failed to achieve pregnancy with CC and hMG. (8)

After choosing progesterone as a therapeutic option, one must then ascertain the optimal form, dosage, and timing to use for each individual. Available products include both synthetic and "natural" progesterone. Synthetic progesterone, or progestins, are manufactured chemicals similar to human progesterone but with a different molecular structure. They are not as quickly processed or eliminated by the body, so their activity is prolonged. Progestins have been used extensively in birth control pills and hormone replacement therapy to prevent osteoporosis and to prevent hyperplasia of the endometrium resulting from unopposed estrogen. They are not used in reproductive therapy and research due to their teratogenic effects. Progestins also tend to have both androgenic effects (including adversely altering lipoprotein metabolism and increasing CV risk) and anti-estrogenic or estrogenic effects depending on the product, with increased incidences of withdrawal bleeding, bloating, breast tenderness, and depression/mood changes. (20)

"Natural" progesterone, strictly defined, is not natural but derived from plant based steroid precursors (e.g., wild yam, soy) called sapogenins or diosgenin. The diosgenin (a glycosylated C17-alkyl sterol), through a 4-5 step chemical process, is synthesized first to pregnenalone, then is modified *in vivo* to be identical to the chemical structure of human progesterone (21). Because progesterone is necessary for the survival of the embryo throughout pregnancy, physiological levels are not teratogenic. Natural progesterone may also have side effects such as bloating, breast tenderness, depressed mood, and increased thyroid activity, but to a lesser extent than progestins. For more elaborate comparison between the effects of progesterone versus progestins consult Dr. Lee's book. (21)

Natural progesterone is available in various oral, vaginal/rectal suppository, IM, and transdermal forms (Table 3). (22) Injection and suppositories are the most common forms used in research studies of LPD. IM progesterone provides predicable serum levels, but the injections tend to be painful and difficult to self-administer. Vaginal or rectal suppositories tend to cause a discharge considered unpleasant by many individuals. A creative solution to this problem was recently developed by a group of researchers who employed oral micronized progesterone as a suppository. The cellulose capsules dissolved readily and the lactose-containing vehicle coated the vaginal mucosa instead of melting, which decreased discharge and improved delivery. This route of administration proved superior to IM progesterone in increasing tissue (endometrial) levels of progesterone, enhancing its local effect, and correcting the maturation delay of the endometrium as determined by biopsy. (23) Studies

STRUCTURAL RELATIONSHIP OF VARIOUS PROGESTINS TO PROGESTERONE

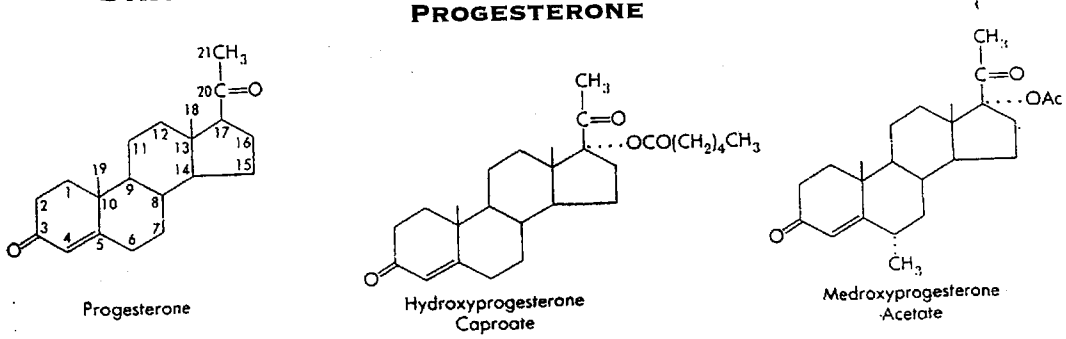

FIGURE 2

using IM progesterone have not been consistent with restoring synchronous endometrial development in out-of-phase biopsies. Using the capsule as a vaginal suppository further optimizes a route of administration of progesterone demonstrated to be effective in increasing pregnancy rates of women diagnosed with infertility due to LPD. Seventy percent of the LPD group (minimum 1.5 years infertility) in one study given suppositories containing 25mg progesterone b.i.d for 14 days each cycle conceived within 6 months, with a 14% abortion rate. (16) While there was no control group, the researchers were attempting to compare progesterone treatment, after pelvic sonography to exclude unruptured follicle syndrome, with previous studies using clomiphene for LPD without this differentiation.

The oral route of progesterone administration has in the past been considered impractical due to poor intestinal absorption and a short biological half-life. However, recent reports have revealed that significant serum levels of progesterone may be achieved by altering particle size and vehicle of progesterone delivery. Studies indicate that the optimum delivery of oral progesterone in terms of absorption and bioavailability is the micronized (decreasing particle size) form utilizing a long-chain fatty acid carrier. This increases uptake by the intestinal lymphatics and avoids extensive prehepatic clearance. Absorption was further enhanced by taking the capsules with high fat or high fiber meals (increasing serum progesterone levels 4.6 and 3.2 times respectively as compared to fasting). However, multiple daily dosing is required due to its short half life, and most individuals experienced drowsiness and/or dizziness as a side effect of the oral progesterone metabolites at dosages necessary to achieve significant serum levels. (24)

Transdermal progesterone (cream or oil) is a less researched alternative in the treatment of LPD. There is less information available regarding the dosages necessary to achieve adequate tissue/serum levels and to synchronize endometrial development. Permeability of progesterone through human skin depends on a number of variables including stratum corneum thickness, lipid content, and keratinocyte dimensions, all of which vary both depending on the individual and depending on the skin location. (22) Thus optimal dosing must proceed in a rather trial and error manner. The differing progesterone content among the various commercially available products adds more uncertainty into the equation. Table 3 (25) provides a dose comparison for the various progestogens and the most effective dosing for each in LPD therapy as gleaned from the literature.

In summary, the management of luteal phase defects as a cause of infertility is an intricate process that requires the integration of several data streams. The cornerstone of the assessment phase lies in a careful history and the choice of the appropriate diagnostic test at the appropriate time in the cycle. Determining the day of ovulation is a crucial variable in this latter aspect. While this area of medicine has seemingly been taken over by high technology and a plethora of chemical agents, the naturopathic practitioner need not be intimidated. There are other options in addition to the use of natural

PROGESTOGEN COMPARISON LIST

Form	Recommended Dose Comparison (daily) for HRT*	Effective Regimen for LPD
Progestins	2.5-10mg (10 mg equals 300mg natural progesterone)	not used
Injectible progesterone	25-100mg	50mg bid during luteal phase
Vaginal suppository	25-600mg	25mg bid during luteal phase (or 100-200mg tid oral micronized progesterone)
Oral micronized	200-800mg	200mg tid during luteal phase for 6 mo
Transdermal cream		unknown
Progest/Progonol/Osteoderm	1/8-1/2 tsp bid (25-44mg P per 1/4 tsp)	
Wild yam ext./Phytogest	1/8-1/2 tsp bid (0.125mg-1mg P per 1/4 tsp)	
Wild yam cream/Progerone	1/4 tsp contains < 0.125mg P	
Sublingual oil	3-6gtts bid (10.1mg/gtt)	unknown

TABLE 3

* HRT= hormone replacement therapy, in which progesterone is often used to reduce hyperplastic effects of unopposed estrogen and/or to aid in prevention of postmenopausal bone loss.

progesterone. Hormone balancing, indeed bringing the entire body more into balance, begins with proper nutrition, exercise, and stress management. These may be further assisted with the use of an indicated homeopathic remedy. Many practitioners have successfully used herbs containing relatively high levels of plant sterols to achieve the balance and timing of hormones necessary for luteal sufficiency and conception. Though many of these, singly or in combination, have not yet been well researched, botanicals used with reported clinical success include *Aletris farinosa, Smilax spp., Dioscorea villosa, Vitex agnus-castus* (26), and *Glycerrhiza glabra.*

Finally, we should not forget, nor let our patients forget, that the *vis medicatrix naturae* continues to be a potent force in resolving infertility. As one study revealed, the spontaneous "cure" rate for infertility was 41% in their treatment group and 35% in their untreated group. (27) Nature, as always, remains a skillful and persevering ally.

SUMMARY: DIAGNOSIS AND TREATMENT OF LUTEAL PHASE DEFECTS

1) Rule out other causes of infertility
2) Rule out anovulation – Basal body temperature graph, pelvic ultrasound, serum midluteal P levels
3) Determine day of ovulation – basal body temperature graph, urine LH level, E/P metabolites
4) Diagnosis of LPD – integrated luteal progesterone level (salivary progesterone q 2 to 3 days during luteal phase or midluteal serum P)
5) Treatment:

Inital approach:

- Stress Management
- Nutritional Counseling
- Constitutional Homeopathy
- Botanical Hormone Balancing

Secondary Measures:

- Natural Progesterone: this should include re-evaluation of integrated luteal P q 2 to 3 months in order to monitor treatment.

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