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Progesterone and the Luteal Phase:

A Requisite to Reproduction

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INTRODUCTION

The normal menstrual cycle can be divided into two phases: follicular and luteal, which are separated by ovulation and bookended by the first day of menstrual bleeding. The follicular phase is dominated by the development of the preovulatory follicle, resulting in estrogen-stimulated endometrial proliferation, whereas the corpus luteum (CL) of its namesake luteal phase produces progesterone, which inhibits endometrial proliferation and determines endometrial receptivity. Without both phases working in series, natural reproduction is not possible. This article focuses on the normal physiology of the luteal phase, investigates the controversy surrounding luteal phase defect, and describes the role of luteal phase support in assisted reproductive technology (ART).

LUTEAL PHASE PHYSIOLOGY

In the natural menstrual cycle, the follicular phase culminates with the maturation of the dominant follicle. Increasing estradiol, secreted from the granulosa cells inside the dominant follicle, triggers a surge of luteinizing hormone (LH) from the anterior pituitary. The LH surge propagates a series of events, beyond the scope of this article, that result in the breakdown of the connections of granulosa cells comprising the cumulus oophorous, reentry of the oocyte into the diplotene stage of prophase I of meiosis, and eventual rupture of the follicle and extrusion of the oocyte into the pelvis. While the oocyte is captured by the fimbria and possibly fertilized in the fallopian tubes, the postovulatory, deflated, and eggless follicle can easily be forgotten. However, the remaining follicular cells play an essential role in facilitating reproduction and maintaining normal menstrual cyclicity by forming the CL.

Before ovulation, the granulosa cells of the dominant follicle begin their transformation into the CL by enlarging and becoming vacuolated.[1] The vacuoles take up the pigment lutein

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(from the Latin *luteus*, meaning “yellow”) giving developing CL its characteristic yellow color. Before ovulation the granulosa cells are separated from the circulation by the basal lamina, necessitating nutrients and communications travel through gap junctions. With luteinization, the basal lamina regresses and the theca cells migrate into the forming CL. In addition, there is prompt neovascularization of the developing CL,[2] mainly under the control of vascular endothelial growth factor and fibroblast growth factor, which are upregulated in the luteinized granulosa cells.[3] The result of the impressive neovascularization is one of the highest blood flows per unit mass in the body,[1] a fact clinically apparent to a gynecologist managing a hemorrhagic CL.

Although the CL secretes many different hormones, the sex steroid, progesterone, is of primary importance because it is necessary and sufficient to transform the endometrium to a state receptive to blastocyst implantation and to maintain early pregnancy.[1] The production of progesterone by the luteal cells depends on the availability of its circulating cholesterol substrate and is facilitated by a low-level LH stimulation.[4] To accomplish steroidogenesis, the luteal cells develop into 2 morphologic appearances, small and large cells, with distinct functions.[5] The small cells, likely derived from the theca cells,[6] contain LH and human chorionic gonadotropin (HCG) receptors.[7] The LH receptor regulates low-density lipoprotein cholesterol receptor binding and internalization of the cholesterol.[1] The large luteal cells are thought to arise from the granulosa cells.[6] These cells have a greater steroidogenic capacity but lack the LH and HCG receptors needed to stimulate growth and provide cholesterol substrate.[8] The small and large cells are linked by gap junctions facilitating rapid transport of signals between cells, providing a mechanism by which the large luteal cells, devoid of LH receptors, respond to LH stimulation and provide the primary source of progesterone.

Multiple experimental designs and clinical experience in patients undergoing ART treatment illustrate the importance of tropic LH secretion to progesterone production from the CL. In one classic experiment, rhesus monkeys with an obliterated median basal hypothalamus, and, therefore, absent gonadotropin-releasing hormone (GnRH) secretion, were given exogenous GnRH pulses of a uniform amplitude and frequency via a mechanical pump. When the GnRH pump was active during the luteal phase, LH and progesterone were secreted. Within hours of discontinuing GnRH pulses, LH and progesterone levels were undetectable.[9] In women, lacking GnRH due to hypophysectomy, progesterone from the CL can be maintained with LH infusion.[10] In women undergoing in vitro fertilization (IVF) with pituitary downregulation (lacking significant LH production), early ovarian progesterone production can be stimulated with supplementation of HCG, an LH analog. Further, the profound and rapid variation in progesterone levels throughout the luteal phase closely mimics LH pulsatility in the human[11] and rhesus macaque.[12]

The individual CL seems to have a programmed lifespan independent of LH secretion. The normal lifespan of the CL is 11 to 17 days (mean 14.2 days) from the time of ovulation to the onset of menses.[13] If not rescued by HCG production from a newly implanted pregnancy, the CL will regress into an avascular scar known as a corpus albicans, via a process termed luteolysis.[14] Studies in rhesus monkeys have illustrated LH stimulation can be removed for up to 3 days without luteolysis. When it is reinstituted, progesterone

production returns, which suggests luteolysis is not an LH-dependent process.[15] The process determining luteal phase length and degradation of the CL is still incompletely understood.

The CL can be rescued from luteolysis and continue progesterone production by rapidly rising HCG produced by the trophoblast of early pregnancy. Blastocysts grown in culture have been shown to produce HCG 7 to 8 days after fertilization.[16] Although an early pregnancy is essential to the survival of the CL, a functioning CL is also essential to early pregnancy survival. The latter is evident in a classic series of studies by Csapo and colleagues[17] who performed luteectomy in pregnant subjects. Luteectomy uniformly resulted in abortion if performed before 7 weeks gestation. If luteectomy was performed between 7 to 9 weeks, abortion was sometimes seen. Luteectomy after 9 weeks resulted uniformly in pregnancy survival. Additionally, pregnancy could be salvaged by progesterone supplementation after luteectomy. These findings dramatically illustrate the transition from the embryo's dependence on the CL to the placental trophoblast for support and emphasize the absolute requirement for progesterone.[18]

The studies described above, as well as many others, highlight the essential role of luteal progesterone in pregnancy establishment and maintenance. Given this essential role, it is undeniable that there must be a progesterone threshold below which pregnancy establishment and/or maintenance is impaired or prevented. Thus, it is critical for the clinician to understand and recognize an abnormal luteal phase and understand the available therapies in both ART and non-ART cycles.

LUTEAL PHASE DEFICIENCY

Luteal phase deficiency (LPD) is a condition of insufficient progesterone exposure to maintain a normal secretory endometrium and allow for normal embryo implantation and growth.[19] The condition was first described as a possible cause of infertility by Georgiana Seegar Jones[20] in 1949. This early, elegant study investigated the luteal phase of 206 ovulatory women with primary or secondary infertility. Some of these women were found to have a blunted rise in basal body temperature, decreased 48-hour urinary pregnanediol excretion, and/or endometrial biopsies with inadequate secretory changes, and labeled with LPD. Despite this early description and 65 further years of research, the understanding of LPD is still incomplete and controversy continues to surround its pathogenesis and diagnosis.[21]

LPD is sometimes clinically manifest by a shortened luteal phase lasting less than 9 days, from the day of ovulation to menstrual bleeding.[20,22,23] LPD is also suspected when spotting begins many days before mensuration without a structural or infectious cause. LPD has been implicated as a cause of irregular menstrual bleeding,[24] infertility,[25,26] and recurrent pregnancy loss.[23,27,28] However, despite the repeated association, a 2012 American Society for Reproductive Medicine (ASRM) committee opinion reminds readers that LPD has yet to be proven as a cause of infertility.[19]

The Dilemma of Diagnosing Luteal Phase Deficiency

Confusion surrounding LPD is the result of inconsistent and unreliable diagnostic criteria. In the initial description, Jones[20] provided clinical (shortened luteal phase), laboratory (decreased urinary pregnanediol), and histologic (endometrial biopsy) criteria for the diagnosis. Much of the research conducted since this initial description has used these methods singularly or in combination to identify affected individuals.

The normal luteal phase length from ovulation to menses ranges from 11 to 17 days with most luteal phases lasting 12 to 14 days. One proposed diagnostic criteria for LPD is a shortened luteal phase of less than 9 days.[29] However, a short luteal phase can occur in up to 5% of healthy fertile women with no significant increase in short luteal phase seen in the infertile population.[13,30]

Use of low luteal phase serum progesterone as a diagnostic tool for LPD is plagued by the pulsatile release of progesterone from the CL, echoing the pulsatile release of LH from the pituitary. Serum progesterone levels can fluctuate 8-fold in a 90-minute period during the midluteal phase and range from 2.3 to 40.1 pg/mL during a 24-hour period in the same healthy subject.[11] Because this rapid fluctuation traverses almost the entire range of luteal values, there can be no standard for appropriate luteal phase progesterone in fertile women[31] and, therefore, a single value can neither diagnose nor exclude LPD in patients. It is suggested that the sensitivity and specificity of the test can be improved by evaluating pooled samples from three separate blood draws in the midluteal phase.[31] However, the frequency and amplitude of progesterone pulses preclude sufficient precision. In the original description of LPD by Jones,[20] daily luteal progesterone was offered as the most accurate, yet clinically impractical, diagnostic test. Other investigators have suggested a 24-hour or 48-hour urinary pregnanediol glucuronide level to minimize progesterone fluctuations.[32] Remarkably, despite the clearly established barriers to its use, isolated serum progesterone concentrations are still used in the published literature to define biochemical LPD.[23]

The luteal phase biopsy, once considered the gold standard[33] for LPD diagnosis, has also been shown to be too imprecise to be clinically useful for most patients. The goal of this test, previously considered by many clinicians to be a standard component of the fertility evaluation, was to detect histologic changes in the endometrium that were out of phase with the cycle in regard to days after ovulation.[34] If the morphologic characteristics lagged more than 2 days behind the known luteal day, then LPD was presumed. In a study investigating histologic endometrial dating in healthy fertile volunteers, there was poor correlation between the actual cycle-day based on urinary detection of LH surge and histology report.[35] The study demonstrated a poorer precision in the timing of histologic features than had been described in previous studies using less rigorously timed biopsies. A large, multicenter, randomized trial designed to assess an association between and abnormal luteal phase biopsy and fertility failed to show usefulness. In this trial, 332 fertile women and 287 infertile women underwent endometrial biopsy in the midluteal to late luteal phase. Contrary to expectations, out-of-phase biopsies were more common in the fertile women compared with their infertile counterparts (42.2% vs 32.7%, $P<.05$).[36] Taken together, these studies provide strong evidence that histologic evaluation of the luteal phase biopsy to determine

luteal phase adequacy is imprecise and cannot distinguish between infertile subjects and fertile controls.

The ASRM committee opinion sums up these issues succinctly, “There is no reproducible, physiologically relevant, and clinically practical standard to diagnose LPD or distinguish fertile from infertile women.”[19] The poor performance of the diagnostic tools used significantly complicates the interpretation of 65 years of research based on these tools. It is important to point out, however, that a test that is too imprecise to determine a disorder in an individual, may allow enrichment of groups with and without a disorder when applied to a larger population. However, the uncertainty is clearly driving research toward molecular biomarkers that may be a more specific tool for the evaluation of inadequate progesterone action.[37]

Pathophysiologic theories of luteal phase deficiency

Two mechanisms have been proposed as causes of clinical LPD. The first and likely more common cause relates to the impaired function of the CL resulting in insufficient progesterone and estradiol secretion.[38] Impaired function can be the result of improper development of the dominant follicle destined to become the CL or aberrant stimulation of a normally developed follicle. Both mechanisms result in a CL with deficiencies in progesterone production. The second theory suggests an inability of the endometrium to mount a proper response to appropriate estradiol and progesterone exposure.[39]

Because the CL originates from the dominant follicles, it is logical to infer that abnormal development of the dominant follicle could result in an abnormal CL. Multiple studies have found a correlation between low follicular follicle-stimulating hormone (FSH) and LPD as defined by luteal phase progesterone secretion or luteal phase biopsy.[40,41] However, other investigators have reported a normal FSH profile in the setting of luteal phase defect.[42] Abnormal LH pulsatility has also been implicated as a potential cause of LPD. Experiments by Soules and colleagues[43] found some women with LPD have a fixed and increased LH pulse frequency throughout the early follicular phase compared with women with normal luteal function who have an accelerating LH pulse frequency approaching ovulation. It is suggested that an earlier increase in LH pulse frequency in the early follicular phase leads to decreased LH bioactivity in the luteal phase, decreasing progesterone secretion.[44] The importance of pulsatile LH and FSH is further evidenced by patients receiving GnRH agonists or antagonists during ART cycles. These medications can cause suppression of pituitary LH secretion for 2 to 3 weeks after discontinuation, resulting in decreased CL progesterone production and necessitating progesterone supplementation for optimal outcomes.[45]

Another potential form of LPD is an abnormal endometrial response to adequate levels of progesterone exposure. Usadi and colleagues[39] investigated normal, young research subjects who underwent modeled cycles, highly similar to endometrial preparation for donor oocyte recipience, except that progesterone levels were reduced to simulate LPD. These subjects underwent pituitary downregulation with a GnRH agonist and were supplemented with estradiol, to mimic the follicular phase, followed by estradiol and varying doses of progesterone to mimic the effects of the luteal phase on the endometrium. These

investigators found that unequivocally low levels of progesterone produced a completely normal appearing endometrium on histologic evaluation. The findings suggest that lower levels of progesterone might not be the sole culprit in LPD and there may be other molecular mechanisms affecting abnormal responses to progesterone and, therefore, abnormal endometrial development and receptivity.

Treatment of luteal phase deficiency

Due to the incomplete understanding of the pathophysiology and lack of an accurate method to diagnose LPD, empiric treatment of suspected LPD cannot be completely evidence-based. Clinical studies of treatment regiments are faced with a catch-22: how to evaluate treatment in a disease that cannot be accurately diagnosed. Most studies have used improvements in surrogate markers, such as endometrial biopsy and progesterone level, to show treatment effect. Unfortunately all attempts to link these surrogate outcomes to fertility outcomes have been unsuccessful.[19] Although these limitations preclude effective study of treatment regiments, they do not designate treatment attempts as nonsensical. Instead, this is an area in which many treating physicians believe that the art of medicine plays a role and they continue to treat patients they suspect to be affected by a LPD. In this scenario, the risk of the treatment must be exceptionally small.

Before considering treatment of LPD, it is important to evaluate and treat underlying conditions, such as hypothyroidism and hyperprolactinemia, which can alter the hypothalamic-pituitary-ovary axis function, causing abnormalities in hormone production. If clinical suspicion over multiple cycles points to LPD as a cause of infertility or miscarriage, it is reasonable to consider empiric treatment to correct LPD. Two strategies, improving the follicular development and supplementing progesterone, have been used to correct suspected LPD and treat infertility or recurrent miscarriage.

Extrapolating from studies showing impaired luteal progesterone secretion with lower gonadotropins in the follicular phase, it is inferred that more robust or numerous mature follicles will improve luteal progesterone secretion from the CL, correcting LPD. Therefore, many clinicians treat suspected LPD by attempting to optimize follicular development and number using ovulation induction agents, including clomiphene citrate (CC), letrozole, or injectable gonadotropins. To the authors' knowledge, only one small study has investigated the effect of clomiphene in subjects with LPD (diagnosed by out-of-phase endometrial biopsy).[46] In this study, designed to determine if the number of mature follicles after 100 mg of CC on cycle days 5 to 9 had an effect on endometrial biopsy, 10 out of 18 subjects with previously out-of-phase biopsies had an in-phase biopsy after receiving 100 mg of CC. However, how many would have had the same without CC cannot be determined. In a small retrospective study of 23 women investigating the use of injectable gonadotropins in women with presumed LPD and recurrent pregnancy loss, a significantly lower miscarriage rate was seen in those using gonadotropins versus controls (15% vs 58%).[47] To date, there are no published studies evaluating the effectiveness of ovulation induction with letrozole in women with LPD.

Progesterone supplementation is suggested as a treatment of LPD. Although frequently used, there is no published evidence that it improves pregnancy outcomes in natural cycles.[19]

Progesterone may be supplied as micronized progesterone or synthetic progestins. Given reports of teratogenicity associated with synthetic progestins[48] (that have since been disproven[49]), natural micronized progesterone has been the treatment of choice. Micronized progesterone can be potentially supplied orally, sublingually, rectally, as an oil-based vaginal suppository, an aqueous vaginal cream, or intramuscularly (see later discussion).

A retrospective study comparing the CC treatment to progesterone vaginal suppositories in patient with presumed LPD based on endometrial biopsy showed a 100% pregnancy rate in those treated with progesterone and an 81% pregnancy rate in those treated with CC after 1 year.[50] These groups were compared with a historical population control with a pregnancy rate of 93%, suggesting effectiveness of treatment of LPD. A meta-analysis evaluated 3 underpowered controlled trails that failed to show a positive effect of progesterone treatment of recurrent pregnancy loss in patients with LPD.[51] When the studies were pooled, the odds ratio (OR) for ongoing pregnancy after treatment with progesterone was 3.09 (95% CI 1.28–7.42), suggesting a beneficial effect of progesterone. Well-designed randomized trials are needed to definitively answer whether ovulation induction or luteal progesterone supplementation is beneficial for patients with LPD.

It is the authors' clinic practice to consider treatment in patients with a clinical suggestion of LPD, including infertility or recurrent miscarriage in women with a short luteal phase or intermenstrual spotting without an identifiable cause. We typically treat with ovulation induction agents (50 mg CC or 2.5 mg letrozole on cycle day 5–9) and/or 200 mg micronized progesterone in oil suppositories beginning 3 to 4 days after LH surge. In patients with recurrent loss, the progesterone supplementation is often given after the first positive pregnancy test. We do not treat suspected LPD with injectable gonadotropins, given the high cost and unacceptable risk of twins or higher order multiples. We acknowledge these treatments are not based on strong evidence; however, they are based on clinical interpretation of underlying physiology and come with few risks.

LUTEAL PHASE SUPPORT DURING ASSISTED REPRODUCTION

Treatments that encompass ART include IVF, intracytoplasmic sperm injection (ICSI), and frozen embryo transfer (FET). These treatments frequently result in either the transfer of an embryo into a woman who has undergone controlled ovarian hyperstimulation with subsequent oocyte retrieval or a woman receiving an embryo in a nonovulatory cycle (FET or fresh embryo transfer of embryos from donor eggs into a recipient). In both situations, there is an effective LPD. In the patients who are receiving embryos in nonovulatory cycles, the need for progesterone supplementation is easy to understand given the absent CL. These are cycles in which the natural cyclicity is absent or suppressed, and the endometrial effects of the follicular phase are mimicked with estradiol supplementation to cause a proliferative endometrium. To prepare the endometrium for implantation of the embryo, the luteal phase is mimicked by exposing the endometrium to progesterone. Timing the transfer of an embryo to the appropriate duration of progesterone exposure allows for successful implantation. It is also clear that the luteal phase following controlled ovarian hyperstimulation and oocyte aspiration is dysfunctional, a fact that has been recognized since the infancy of IVF.[52] However, the reason for this deficiency is still controversial.[53]

Multiple explanations for this phenomenon have been reported and subsequently disputed. It was initially assumed that the LPD after IVF resulted from destruction of granulosa cells destined to become the CL during oocyte aspiration. This theory was questioned after no changes in progesterone levels or luteal phase length were seen after aspiration of the single mature follicle in a natural, unstimulated cycle.[54] The administration of HCG to mimic the LH surge in IVF has been implicated as a cause of LPD by inhibition endogenous LH secretion from the pituitary.[55] However, normal luteal phase length and pregnancy rates are routinely seen in women receiving HCG triggers in natural cycles or while undergoing superovulation and intrauterine insemination. Other investigators have posited that the LPD is the result of GnRH agonist used to downregulate pituitary LH secretion, suppressing LH secretion well into the luteal phase.[45] With the advent of GnRH antagonists, which clear quickly and do not cause long-term pituitary LH suppression, premature luteolysis and poor pregnancy rates were seen when used during IVF cycles without progesterone support,[56] illustrating prolonged GnRH agonist pituitary suppression cannot be the sole cause of LPD in women undergoing IVF. Currently, the most widely accepted theory of LPD after IVF states the supraphysiologic steroid hormones secreted by the multiple CL in the early luteal phase of an IVF cycle causes direct inhibition of LH secretion via negative feedback on the hypothalamic-pituitary axis.[56–58]

The optimization of ART success rates relies not only on the creation of high-quality embryos but also on the establishment of a receptive endometrium. During the past 35 years, since the first IVF pregnancy and subsequent first pregnancy from frozen embryos, significant research has been directed toward establishing the optimum supplementation of the luteal phase in both IVF and FET cycles, with a goal to maximize live births while minimizing patient discomfort and inconvenience.

Luteal Phase Support in In Vitro Fertilization

Multiple treatments options, including progesterone, HCG, and GnRH agonist, have been tested in luteal phase supplementation after IVF. A recent Cochrane systematic review has evaluated many of these options and will be referred to in the remainder of this article.[53] In a recent survey of ART providers by Vaisbuch and colleagues,[59] all of the 408 centers across 82 countries used some form of progesterone for luteal phase support, with none of the surveyed centers using solely HCG, a historical treatment option. This is a change from a similar survey conducted 3 years earlier in which 5% of the IVF clinics were using HCG as the sole agent for luteal support.[60] Although luteal HCG has a similar effectiveness to luteal progesterone in terms of pregnancy outcomes, the avoidance of luteal HCG is due to the increased risk of ovarian hyper-stimulation syndrome with this medication.[53,61,62] Given the paucity of use, luteal support with HCG is not further considered in this article.

Progesterone supplementation is available in multiple preparations, including intramuscular, vaginal, oral, or in a newly developed subcutaneous preparation. In a 2014 survey of 284,600 IVF cycles in 82 separate centers, 77% of the cycles were performed with vaginal progesterone only and an additional 17% used vaginal progesterone in combination with oral or intramuscular progesterone. Just 5% used only intramuscular progesterone and 0.5% used only oral progesterone.[59] However, there were regional differences in the choice of

progesterone preparation with 57% of North American cycles choosing intramuscular progesterone. Subcutaneous progesterone is still in the trial phase.

Oral micronized progesterone was the luteal support progesterone of choice in the 1980s; however, it has since proven to be a poor treatment option. Although the most convenient form of progesterone, micronized progesterone, has poor and inconsistent bioavailability. After ingestion, it is absorbed by the intestines, undergoes a first-pass metabolism by the liver, and is excreted by the kidneys, resulting in a bioavailability that is only 10% of intramuscular preparations.[63] Serum levels reach maximum in 2 to 4 hours and remain significantly elevated for only 6 to 7 hours,[64] requiring more frequent dosing. In a randomized, controlled trial, users of oral micronized progesterone had a significantly decreased implantation rate compared with users of intramuscular progesterone (18.1 vs 40.9%, $P = .004$).[65] In a second trial, when compared against vaginal micronized progesterone, the oral route once again resulted in a lower implantation rate (10.7 vs 30.7%, $P \leq .01$).[66]

Given the allure of an oral agent for luteal support, other oral agents have been studied to replace oral micronized progesterone. Dydrogestrone, is an oral progestin with improved bioavailability compared with oral micronized progesterone.[67] In one randomized, controlled trial, pregnancy rates were higher in women undergoing IVF using oral dydrogesterone for luteal support versus vaginal micronized progesterone (41.0 vs 29.4%, $P \leq .01$).[68] A second trial comparing the same agents showed similar pregnancy rates.[69] Another randomized, controlled trial compared oral dydrogesterone to micronized progesterone vaginal gel (Crinone 8%) and found similar pregnancy rates (28.7 vs 28.6%).[70] Another synthetic progesterone, chlormadinone acetate, was compared with intramuscular progesterone with no changes in pregnancy rates or implantation rates.[71] In the 2011 Cochrane review, analysis favored the use of synthetic progesterone compared with micronized progesterone for clinical pregnancy (OR, micronized progesterone use: 0.79, 95% CI 0.65–0.96).[53]

Intramuscular progesterone was first described as a form of luteal supplementation during IVF in 1985.[72] The use of intramuscular progesterone is associated with injection site pain, skin irritation, inflammatory reactions, and rare abscess formation.[73] Early randomized trials comparing intramuscular progesterone to vaginal progesterone showed superior pregnancy rates in the intramuscular group.[73,74] However, since this time, multiple other randomized trials using newer progesterone preparations have been conducted and a 2009 meta-analysis showed no difference between the 2 groups in pregnancy rates and ongoing pregnancy rates.[75] A 2011 Cochrane review showed no difference in pregnancy or live birth rate; however, it did find a difference favoring intramuscular progesterone in ongoing pregnancy rates.[53] Intramuscular and vaginal administration of luteal progesterone are now considered by most investigators as equivalent in terms of IVF pregnancy outcomes.

Vaginal preparations of progesterone have become the mainstay of luteal supplementation during IVF because of their relative ease of use and equivalence to intramuscular progesterone. Vaginal progesterone is typically available as a tablet, suppository, or 8% gel. Vaginal progesterone benefits from a first-pass uterine effect in which endometrial tissue

concentrations are typically much greater than would be expected based on serum levels.[76] Pharmacy-compounded vaginal suppositories are typically discouraged in IVF cycles due to unreliable and variable progesterone levels.[77] In a large, multicenter, randomized, controlled trial, progesterone tablets (Endometrin 100 mg twice a day or 3 times a day) were compared with 8% progesterone gel (Crinone 8% gel) with similar pregnancy and live birth rates between the 3 groups (live birth rate, Endometrin twice a day 35%, Endometrin 3 times a day 38%, Crinone gel 38%, normal saline).[78] Vaginal progesterone is well tolerated by most patients although some dislike this medication because of higher cost than injectable forms, difficulty with administration, and/or vaginal discharge.

Recently, a water-soluble injectable progesterone complex (Prolutex) has been developed for subcutaneous administration.[79] A pharmacokinetic study of this compound demonstrated sufficient serum progesterone levels to allow clinical use in ART.[80] To date, 2 randomized noninferiority trials have been conducted. The first compared subcutaneous progesterone (Prolutex) to 8% progesterone gel (Crinone) as luteal phase supplementation during IVF with no difference in ongoing pregnancy rate (27.7 vs 30.5%, P = NS).[81] A second randomized trial compared subcutaneous progesterone (Prolutex) to vaginal progesterone tablets (Endometrin) with no change in ongoing pregnancy rate (40.8 vs 43.3%).[82] Common side effects related to the subcutaneous injection include injection site pain, bruising, inflammation, and edema.

There is currently no consensus on when to begin progesterone supplementation during an IVF cycle. The first dose of progesterone is typically administered between the between the day of retrieval to 2 days after retrieval with no obvious changes in pregnancy rates.[83,84] Insight into the timing of embryo transfer in relation to progesterone exposure can be gathered from an experiment by Prapas and colleagues.[85] Vaginal or intramuscular progesterone exposure before transfer of fresh embryos from donor oocytes was varied from 2 to 6 days and implantation and clinical pregnancy rates were highest in a narrow window of progesterone exposure (Fig. 1). Most surveyed clinics (80.1%) begin progesterone supplementation on the day of egg retrieval.[59] In addition there is no consensus on the duration of progesterone use. A recent meta-analysis of 6 eligible studies and 1201 randomized subjects concluded there may be no additional benefit of progesterone supplementation beyond the first positive HCG value, showing no difference in live birth (risk ratio [RR]: 0.95, CI 0.86–1.05), ongoing pregnancy (RR: 0.97, CI 0.90–1.05), or miscarriage (RR: 1.01, CI 0.74–1.38).[86] Despite these data, most surveyed clinics (72%) continue progesterone until 8 weeks or more of pregnancy and only 15% discontinue progesterone after detection of beta HCG.[59]

Adjuvants to progesterone supplementation to increase IVF pregnancy rates have been widely discussed in the literature. The CL is not only a source of progesterone but also produces estradiol, along with many nonsteroidal hormones. Therefore, it has been suggested luteal support should include estradiol supplementation.[87] A 2008 meta-analysis identified 4 randomized studies evaluating estradiol supplementation in the luteal phase and found no difference between clinical pregnancy (587 subjects, RR: 0.94, CI 0.78–1.13) and live birth (527 subjects, RR: 0.96, CI 0.77–1.21).[88] In the 2011 Cochrane review, progesterone plus estradiol did not perform any better than progesterone in terms of

biochemical pregnancy, clinical pregnancy, or live birth. However, when a subgroup analysis of clinical pregnancy was performed, progesterone alone performed worse then progesterone plus transdermal estradiol (OR: 0.50, CI 0.31–0.82), suggesting route of estradiol administration may play a role.[53]

Another suggested adjuvant to progesterone supplementation is a single dose of GnRH agonist 5 to 6 days after oocyte retrieval. It is hypothesized the GnRH agonist may support the CL by stimulating LH secretion for the pituitary but also may have effects on the endometrial GnRH receptors or direct effects on the embryo.[89] A 2010 meta-analysis[90] evaluated 5 randomized, controlled trials investigating luteal phase GnRH agonist[91–95] in both long and GnRH-antagonist protocols. When data were pooled, there was an increased pregnancy rate in cycles in which a single dose of luteal GnRH agonist was given 5 to 6 days after oocyte retrieval (42.4 vs 35.7%, OR: 1.33, 95% CI 1.08–1.64). A subgroup analysis was performed and pregnancy rate was significantly higher with luteal GnRH agonist used in a GnRH antagonist stimulation compared with the long protocol. Similarly, the recent Cochrane review showed increased pregnancy, ongoing-pregnancy, and live birth rates in subjects receiving luteal GnRH agonists.[53] Despite promising early evidence, additional study is needed given the lack of clear biologic mechanism before wide acceptance of this practice.

Luteal Phase Progesterone During Frozen Embryo Transfer and Donor or Recipient Cycles

Data from IVF cycles should not be extrapolated to FET or donor or recipient cycles because, unlike IVF cycles, there is no formed CL, thus no endogenous source of progesterone. In these cycles, exogenous estradiol is typically used to proliferate the endometrium, then exogenous progesterone is added to induce secretory changes in preparation for implantation. Intramuscular progesterone is typically used for this purpose in the United States, whereas in Europe vaginal progesterone is preferred.[96] Unfortunately, there are a paucity of data on this topic and, therefore, treatment decisions are based on limited information. Two small, prospective, randomized trials from the same group showed no difference in ongoing pregnancy rate when comparing intramuscular progesterone to vaginal progesterone in recipients of donor oocytes.[97,98] In addition, a retrospective study of donor oocyte recipients[99] and another retrospective study of subjects receiving donor and autologous frozen blastocysts[100] showed no difference in implantation, clinical pregnancy, or live birth rates. However, 2 other retrospective studies of women undergoing FET illustrated a deceased live birth rate in subjects receiving vaginal progesterone (24.4 vs 39.1%)[101] and (22.8 vs 34.5%).[102] The timing of progesterone exposure in FET and donor cycles has not been fully studied; however, a review of luteal progesterone during FET cycles was performed by Nawroth and Ludwig[103] and concluded cleavage-stage embryos should not be transferred before 3 to 4 days of progesterone treatment. In the clinical studies mentioned above,[97–102] cleavage-stage embryos were transferred on the fourth day of progesterone exposure and blastocyst were transferred on the sixth day of progesterone exposure.

SUMMARY

Progesterone production from the CL is critical for natural reproduction and progesterone supplementation seems to be an important aspect of any ART treatment. LPD in natural cycles is a plausible cause of infertility and pregnancy loss, although there is no adequate diagnostic test. Future research should concentrate on establishing thresholds of progesterone dose and timing for fertile and infertile women, as well as on a precise and accurate diagnostic test.

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KEY POINTS

- Luteal phase deficiency is a disease without a reliable diagnostic test, impairing clinical research and patient care.
- Exogenous progesterone is the primary agent for luteal support during assisted reproductive technology treatment; however, the best delivery method, protocol, and formulation are not yet known.
- Vaginal or intramuscular progesterone seem to be equivalent in terms of pregnancy outcomes after in vitro fertilization.
- The best route of progesterone supplementation after frozen embryo transfer is not yet established.

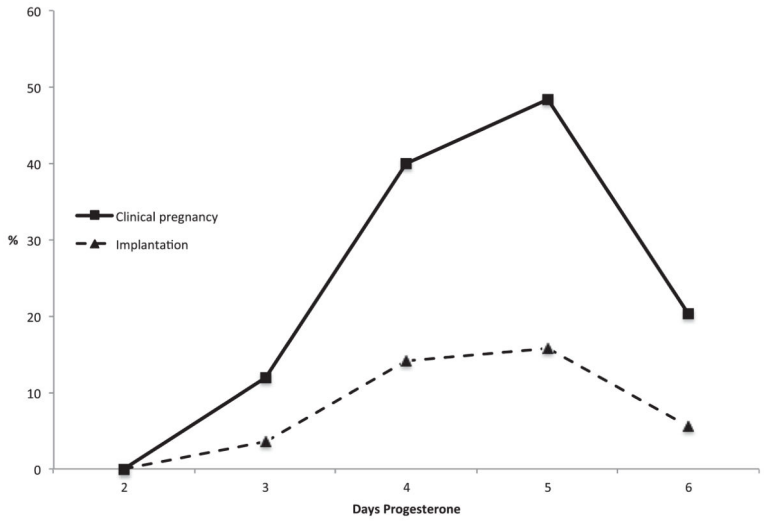

Fig. 1.

Effect of days of progesterone exposure on implantation and pregnancy rates after cleavage-stage embryo transfer from donor oocytes. (*Data from* Prapas Y, Prapas N, Jones EE, et al. The window for embryo transfer in oocyte donation cycles depends on the duration of progesterone therapy. Hum Reprod 1998;13(3):720–3.)