Review Article

Luteal phase support in assisted reproductive technologies: a comprehensive review

Kaberi Banerjee[1], Kavita Khoiwal[2], Bhavana Singla[1]

[1]Advance Fertility and Gynae Centre, New Delhi, India
[2]Department of Obstetrics & Gynaecology, AIIMS, Rishikesh, Uttarakhand, India

Abstract

Luteal phase defect (LPD) is a condition with insufficient endogenous progesterone for maintenance of functional secretory endometrium, normal embryo implantation, and growth. In today's era, there is a lot of complex research with wide diversity with respect to LPD and its treatment. With such diversity and complexity of research data, we hereby did this review to address the pathophysiology of LPD and the role of luteal phase support in assisted reproductive cycles based on available scientific evidence in a simplified manner. An electronic search of Pubmed, Scopus, Embase, and Google Scholar was performed for LPD, luteal phase support, and assisted reproductive technologies. There is no valid diagnostic test for LPD. Prompt identification and treatment of underlying factors is the preferred approach. In assisted reproductive cycles, the luteal phase is usually abnormal and luteal phase support in form of exogenous progesterone with or without estrogen or hCG and GnRH agonists, which enhance endogenous progesterone release have a significant effect on successful reproductive outcomes. The choice of drug is dependent upon the patient's characteristics and type of ongoing treatment. It should be started on the day of oocyte retrieval or till the day 3 postretrieval and to be continued till a positive pregnancy test at least.

Keywords: Luteal phase support, luteal phase defect, assisted reproductive cycles, progesterone, hCG, GnRH agonist

Address for correspondence: Dr. Kavita Khoiwal, MD OBG, Assistant Professor, Department of Obstetric & Gynaecology, AIIMS, Rishikesh, Uttarakhand-249201, India.
E-mail: kavita.kh27@gmail.com
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Key messages

Luteal phase support is beneficial in assisted reproductive cycles to improve fertility outcomes. Most commonly used drug is vaginal progesterone which is safe, efficacious, and feasible followed by intramuscular and aqueous progesterone. Newer alternatives are low dose hCG and GnRH agonist particularly by intranasal route seems to be promising as they will support corpus luteum to produce endogenous progesterone which is more physiological.

INTRODUCTION

Luteal phase is the period between ovulation and establishment of a pregnancy or onset of menses. After ovulation continuous production of progesterone from corpus luteum is essential to maintain a viable intrauterine pregnancy until luteo-placental shift occurs, placenta

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begins to produce adequate progesterone (8–10 weeks). Inadequate ovarian production of progesterone may lead to early pregnancy loss or infertility. The condition with insufficient endogenous progesterone for maintenance of functional secretory endometrium, normal embryo implantation, and growth is termed as luteal phase defect (LPD).[1]

Risk factors for LPD are thyroid disorders, hyperprolactinemia, obesity, polycystic ovary syndrome, endometriosis, ageing, stress, anorexia nervosa and other eating disorders, excessive exercise, weight loss, ovulation induction with or without gonadotropin-releasing hormone (GnRH) agonist, and assisted reproductive technologies (ART). ART has a wide variety, commonly performed procedures are in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI), frozen embryo transfer, or donor oocyte cycle.

Pathophysiology of LPD in ART cycles

A normal hypothalamic pituitary ovarian (HPO) axis and complex interplay between GnRH pulsatile patterns, release of follicle-stimulating hormone (FSH), and luteinizing hormone (LH) followed by estrogen and progesterone, and feedback mechanisms result in normal menstruation and conception. Any abnormality in HPO axis will abate LH pulsatility and eventually lead to abnormal luteal estrogen and progesterone secretion, which can affect endometrial development and implantation.

In IVF/ICSI cycles, luteal phase may be abnormal because of mechanical disruption of granulosa cells destined to become corpus luteum during oocyte retrieval, supra physiological concentrations of steroids secreted by high number of corpus luteum during early luteal phase and direct inhibition of LH release via negative feedback actions at HP axis level in case of multi follicular development. IVF cycles with both GnRH agonist and antagonist protocol are associated with LPD. GnRH agonist leads to deficient luteal phase by prolonged suppression of pituitary LH secretion after 3 weeks of down regulation.[2,3] Moreover, hCG administration to mimic the LH surge inhibit endogenous LH secretion further contribute to LPD. GnRH antagonist directly acts on receptors and reduce secretions of pituitary LH. Though the recovery of LH production from the pituitary is quite rapid following cessation, still it significantly reduces pregnancy rates.[4] Inadequate LH stimulation of the corpus luteum eventually curtails secretion of progesterone and premature luteolysis.[5]

Hypothyroidism and hyperprolactinemia also inhibits GnRH secretion. In morbidly obese women, altered LH pulsatility and reduction in pulse amplitude has been reported.[6] Therefore, obesity has been considered one of the associating factors in infertility and early pregnancy loss.[7] Advanced maternal age is also associated with luteal phase abnormalities as these women found to have decreased luteal phase estrogen and progesterone than younger age women.[8] In addition, altered luteal progesterone levels have been reported in lactating women and with renal transplantation.[9]

Clinical presentation of LPD may include frequent menstrual cycles, premenstrual spotting, early pregnancy loss, and difficulty to conceive.

Luteal phase support in ART

The foremost approach to treat LPD is to correct underlying pathology, will automatically correct abnormal luteal estrogen and progesterone secretion. Empirical treatment can be given if no underlying pathology identified in cases of infertility, recurrent pregnancy loss, and women undergoing ART to strengthen endometrial maturation and receptivity, and to aid implantation and early development of fertilized ovum. Luteal phase support (LPS) can be given in various forms include progesterone with or without estrogen, hCG (Human Chorionic Gonadotropin) and GnRH agonist.

Women undergoing ART are the most appropriate candidates of LPS. Cochrane 2015 recommends LPS in IVF and ICSI cycles to improve implantation and pregnancy rates.[10] It can be achieved by either progesterone or GnRH agonist/ hCG to support corpus luteum to produce adequate progesterone.[10,11]

LPS is essential in Frozen Embryo Transfer (FET) or donor oocyte cycles till placenta begins to produce adequate progesterone to support pregnancy [12] as corpus luteum is not present in these women. Intramuscular progesterone has been found to have more beneficial than vaginal progesterone in FET cycles. The reason behind this was explained by Casper [13] who noticed excessive uterine waves on ultrasound in women receiving vaginal progesterone and reduced significantly to one wave per minute within 1 day of oil-based progesterone injection.

Currently, there is no evidence that LPS is beneficial in natural, unstimulated cycles.[1] LPS has not been found to be effective in women undergoing OVI with clomiphene

citrate with or without gonadotropins. On the contrary, progesterone LPS is beneficial in women undergoing OVI with gonadotrophins followed by intrauterine insemination.[14]

Progesterone LPS both micronized progesterone and dydrogestrone have been found beneficial in patients with threatened abortion. Cochrane 2011 states 47% of relative risk reduction with the use of progesterone in threatened abortion.[15]

Medications for LPS

Medications for LPS include both which supplements corpus luteum (progesterone and estrogen) and which supports corpus luteum (hCG and GnRH agonist).

Progesterone

Acts directly on endometrium help secretory transformation of endometrium for implantation and early development of fertilized ovum. Progesterone should be given till luteo-placental shift occurs. It is available in various forms as tablet, capsule, pessary, vaginal gel, and injection. Different routes of progesterone supplementation are described in literature, which include oral, vaginal, rectal, intramuscular, and subcutaneous route. Oral route is easiest but not very effective as only 10% of the total dose absorbed by gastrointestinal tract and associated with side effects such as sedation and hypnosis. Intramuscular injections are oil based, achieve highest serum levels but very painful to administer daily. Vaginal route leads to highest target tissue concentration (uterus and endometrium), avoids first pass hepatic metabolism,[16] associated with minimal side effects with good patient compliance. Lower pregnancy rates were reported with oral route than intramuscular or vaginal route in ART cycles.[17,18] Efficacy and safety of vaginal progesterone is comparable in different doses, preparations and schedules of administration in ART cycles.[19] Intramuscular progesterone optimizes outcome after GnRH agonist trigger but the efficacy is similar to vaginal progesterone after hCG trigger.[20]

Aqueous progesterone is the latest addition in progesterone family. It has properties of water solubility, subcutaneous route of administration and very less pain, can be self-injected [21] and similar pregnancy rates to vaginal progesterone.[22,23]

Cochrane 2015 states progesterone as LPS is associated with high-live birth rate or ongoing pregnancy rate. Live birth rate, ongoing pregnancy rate, and miscarriage rate have been found similar with all routes of progesterone administration.[10]

European society of human reproduction and embryology (ESHRE) 2019[24] strongly recommends progesterone use for LPS in ART cycles. It should be started between the day of oocyte retrieval to day 3 postoocyte retrieval and to be continued till the day of pregnancy test at least.

Micronized progesterone and dydrogesterone can be used for LPS as both of them are similar to endogenous progesterone with respect to molecular structure and pharmacological effects. The dosing of natural progesterone has evolved empirically, usually dosages used include: 50 to 100 mg daily for intramuscular progesterone, 25 mg daily for subcutaneous progesterone, 90 mg daily for vaginal progesterone gel, and 600 mg daily at least for vaginal progesterone capsules.[24]

The adverse effects of oral progesterones include breast tenderness, bloating, headache, constipation/diarrhea, itching/urticarial rash, fatigue, irritability, anxiety/, and somnolence. Intramuscular progesterone may cause pain, redness at injection site. While vaginal discharge, irritation may happen in some patients with vaginal progesterone. It should be used with caution in patients with cardiovascular diseases and impaired liver function test.

Recently, Griesinger *et al.*[25] reported dydrogestrone (30 mg) is a potential alternative to micronized vaginal progesterone gel () in fresh ART cycles as it is equally efficacious and tolerable. Despite of comparable efficiency and ease of oral administration, it is still not being regularly used in ART cycles.

Estrogen

Exogenous estrogen has a role for LPS in donor oocyte and FET cycles as there is no corpus luteum. Additionally, estrogen along with progesterone may be given in ART cycles where GnRH agonist was used to trigger ovulation instead of hCG.[21]

hCG

Exogenous administration of hCG stimulates corpus luteum to boost production of endogenous progesterone and estradiol. Earlier high doses of hCG used to be given, led 5 to 10 times higher concentration than normal cycle which was more than adequate and associated with very high chances of ovarian hyper stimulation syndrome (OHSS).[21] Cochrane 2015 states

hCG as LPS is associated with high-live birth rate or ongoing pregnancy rate but has high risk of OHSS with or without progesterone than progesterone alone.[10] Later on, newer hCG regimens have shown up with 'low dose or micro dose' along with the concept that stimulation of endogenous progesterone production is more physiological than exogenous supplemental of progesterone. To avoid high hCG supplementation, GnRH agonist trigger was given in place of hCG. But studies suggest requirement of additional dose of 1500 IU hCG at oocyte retrieval to produce adequate endogenous progesterone.[26] Recently, a newer concept was reported for LPS with daily micro doses of hCG (100–150 IU) throughout the luteal phase without exogenous progesterone in GnRH agonist triggered IVF cycles.[27] Some ART centers prefer micro dose hCG over exogenous progesterone supplementation but the difficult administration of such small dose is one of the limiting factor.[21]

GnRH agonist

GnRH agonist stimulates secretion of LH from pituitary gonadotroph cells, further supports corpus luteum to produce endogenous progesterone and acts directly on endometrium through locally expressed GnRH receptors. The role of GnRH agonist to support luteal phase along with progesterone is not well defined. Some benefit was described in a meta-analysis supported by low-quality evidence.[28] Furthermore, studies were done by using solely GnRH agonist as LPS in antagonist stimulation cycles.[29,30] Administration of GnRH agonist by intranasal route has been found to be associated with significantly high ongoing pregnancy rates.[29] ASRM also proposes repeated GnRH agonist particularly nasally administered as an alternative to common forms of LPS in antagonist stimulation cycles.[21]

Cochrane 2015[10] reported addition of GnRH agonist to progesterone further improve outcomes.

ASRM recommends LPS should be started on the day or day after oocyte retrieval.[1] The rationale behind is to suppress uterine contractions due to high estradiol level. ESHRE 2019 [24] also recommends LPS to be started between the day of oocyte retrieval to day 3 postoocyte retrieval.

It has been a common practice to continue LPS till approximately 10th week of gestation, when luteoplacental shift is ascertained. ESHRE recommends LPS till the day of pregnancy test at least.[24] ASRM also supports that LPS is not essential once a positive pregnancy test is achieved. As after that corpus luteum will be supported by embryonic hCG and produce endogenous progesterone.[1] On the contrary, in FET or donor oocyte cycles, LPS has to be continued till placenta begins to produce adequate progesterone to support pregnancy as there is no corpus luteum.[1]

An updated website-based survey was performed to assess real life practices worldwide about LPS in ART cycles.[31]. almost 80.1% start LPS on the day of oocyte retrieval, 15.4% on day of embryo transfer, and 3.2% on day of hCG trigger. Most of them (77%) preferred vaginal progesterone and 17.3% used combined (vaginal + intramuscular) progesterone. LPS was continued till 8 to 10 weeks by 44%, 12 weeks or more by 28% followed by 15% and 13% until positive βhCG and fetal heart sound on USG, respectively.

Other commonly used medications in luteal phase to aid implantation process in ART are aspirin, heparin, prednisolone, and sildenafil.

Aspirin improves tissue perfusion by increasing uterine and ovarian blood flow. It acts by inhibiting cyclo-oxygenase enzyme in platelets and prevents thromboxane A2 synthesis, which is a potent vasoconstrictor and platelet aggregation enhancer. However, Cochrane 2016 clearly suggested no benefit of routine use of aspirin in general IVF population to improve pregnancy rates. [32]

Heparin is an anticoagulant and has immunomodulatory and anti-inflammatory properties, which may help in adhesion of blastocyst to endometrial epithelium and subsequent invasion. Both unfractionated heparin 5000 IU every alternate day or low-molecular weight heparin (LMWH) 40 mg daily/every alternate day by subcutaneous route can be given. Cochrane 2013[33] did not favor the use of heparin outside well-conducted research trials. However, Potdar *et al.* [34] reported improved live birth rate by 79% with adjunct LMWH in women with ≥ three recurrent implantation failures. Simultaneously, they called for adequately powered multicentered randomized controlled trials to recommend LMWH in routine clinical use. Prednisolone improves implantation rate by suppressing uterine natural killer cells, cytokines and endometrial inflammation. It has been used world widely in the doses of 10 mg once daily. Its use is based on individualized decision as evidence is lacking in literature. Standard use of corticosteroids has not been found to improve reproductive outcomes.[35]

Sildenafil is a phosphodiesterase inhibitor, enhance vasodilatory effects of nitric oxide, uterine blood flow, and improve endometrial thickness. Usually, used as vaginal tablet 25 to 75 mg once daily for this purpose. Luteal supplementation of vaginal sildenafil has been found beneficial to improve uterine receptivity.[36]

CONCLUSION

Luteal phase support is beneficial in ART cycles to improve fertility outcomes. LPS can be given in various forms include progesterone with or without estrogen, hCG and GnRH agonist. The choice of drug is dependent upon the patient characteristics and type of ongoing treatment. Most commonly used drug for LPS is vaginal progesterone which is safe, efficacious, and feasible followed by intramuscular and aqueous progesterone. Newer alternatives are low dose hCG and GnRH agonist particularly by intranasal route seems to be promising as they will support corpus luteum to produce endogenous progesterone which is more physiological. LPS should be started on the day of oocyte retrieval or till the day 3 postretrieval and to be continued till positive pregnancy test at least.

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Conflicts of interest
There are no conflicts of interest.

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