

Luteal Phase Support: Why, When and How

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ABSTRACT

Luteal phase support (LPS) is a known intervention for preventing the pregnancy loss. It is most commonly used in the artificial reproduction cycles. Most common agent used for the luteal phase support is progesterone. Current review discusses the reasons of luteal phase defects in stimulated and unstimulated cycles and also analyses the utility of various drugs in the treatment of the same.

Keywords: Corpus luteum, luteal phase support, progesterone, artificial reproduction cycle.

INTRODUCTION

Luteal phase support (LPS) is a known intervention for preventing the pregnancy loss for last many decades and is a common practice among obstetricians. This is more evident in the field of infertility, recurrent pregnancy loss and preterm labour. This review has been done with the intend of finding the evidences and reasons use of various agents for luteal phase support. Reviews, original articles, guidelines have been searched in PUBMED from 1995-2018 using the key words 'luteal phase support', 'recurrent pregnancy loss', 'progesterone', 'infertility' and 'threatened miscarriage'.

To understand the concept of LPS, one must understand the physiology of the luteal phase

NORMAL PHYSIOLOGY OF LUTEAL PHASE

Natural menstrual cycle is divided into follicular phase (proliferative phase) and Luteal phase (secretory phase). Follicular phase starts from menstruation and ends with ovulation. Luteal phase extends from ovulation to the establishment of pregnancy or start of menses. This phase is governed by corpus luteum which secretes progesterone and estradiol. If the patient conceives, embryo implantation occurs on around 6th day. This embryo implantation process is complicated and largely depends on the local environment supported by progesterone mainly and the human chorionic gonadotropin (HCG) hormone secreted by the developing blastocyst to maintain the corpus luteum.

Progesterone levels at conception have been found linearly associated with miscarriage, preterm birth, intrauterine growth retardation, and eutrophic term birth.¹

For the adequate secretion of progesterone, the corpus luteum requires continuous stimulation by luteinizing hormone (LH) which has a pulsatile secretion from the pituitary under the influence of HCG. Basically, HCG is secreted from developing syncytio-trophoblasts of placenta from week 2 of implantation. It also interacts with L-HCG receptor of the ovary to maintain the corpus luteum so that corpus luteum continues to secrete the progesterone for the support of pregnancy in the first trimester. Corpus luteal cells develop from the follicular cells surrounding the ovarian follicle. These follicular cells are either theca cells or luteal cells. After ovulation theca cells luteinize into small luteal cells and granulosa cells luteinize into large luteal cells. Both these cells secrete progesterone but the small luteal cells synthesize androgens besides progesterone due to the lack of aromatase enzyme whereas large luteal cells secrete estrogen and inhibin A besides progesterone. The studies have shown that although the progesterone is most important component for the luteal support but the estrogen should also be given importance as evidenced by the studies^{1,2} where the better results have been obtained on stimulating the follicular phase only to optimize the luteal phase producing higher estrogen and progesterone. Estradiol metabolites from corpus luteum may play role in angiogenesis and its lifespan and regression.²

It is important to remember that corpus luteum requires continuous LH stimulation for adequate steroidogenic activity (progesterone secretion) and in the event of LH withdrawal, premature luteolysis occurs. It has been observed that if corpus luteum is removed prior to 7 weeks of gestation, it leads to pregnancy loss. This pregnancy can be supported by high dose of progesterone supplementation.

LUTEAL PHASE DEFECT (LPD)

Any problems with the progesterone secretion during the secretory phase leads to defective luteal phase which is clinically observed by the early menses in a stimulated cycle. LPD is usually observed in cases of polycystic ovarian disease, recurrent pregnancy loss and stimulated/in vitro fertilization (IVF) cycles. LPD has also been observed around 8% of normo-ovulatory patients who present with infertility.³

It is said the half of the LPD occurs due to the defect in gonadotropin releasing hormone (GnRH) pulse generation. With the more understanding of the corpus luteum function the subclassification of the LPD of ovarian origin has given according to the dysfunction of small/large luteal cells.⁴ As the small luteal cells are LH responsive, if there is improper development of these cells, these cells will not secrete progesterone under the influence of normal LH pulses this is known as small luteal cell defect. Large cell luteal defect results in decrease in basal level of progesterone levels in presence of normally secreted progesterone under the influence of LH. This subclassification is important as the treatment varies in different defects. In case of LH responsive large cells corpus luteum defect HCG and GnRH pulses will be beneficial but in case of LH unresponsive small cell defect, progesterone supplementation is needed.

It is well proven that IVF cycles are almost always associated with LPD because of varied reason as discussed below^{5,6}

1. It is said that the removal large amount of granulosa cells during oocyte retrieval diminishes the source of progesterone.
2. Multifollicular development in the IVF cycle leads to Supraphysiological levels of steroids due to high number of corpora lutea. This directly inhibits the LH release via pituitary through negative feedback leading to LPD.⁷

3. GnRH agonist supplementation to prevent spontaneous LH rise may also delay the pituitary recovery to stimulate the corpus luteum.
4. Another reason of LPD in IVF cycles is the suppression of LH production in the final stages of oocyte maturation because of HCG administration
5. In the GnRH antagonist treated IVF cycles, premature luteolysis causes LPD and decreases the chances of pregnancy.

In ART cycles, depending upon the type of stimulation, LPD can be of 4 types

- **Luteal phase of monofollicular cycle:** There is less impairment of luteal phase because of milder stimulation.
- **Luteal phase after controlled ovarian hyperstimulation (COH) in which GnRH analogs have been used:** Intense ovarian stimulation protocols need high progesterone support for reasons discussed above.
- **Luteal phase where GnRH antagonists have been used with GnRH agonist used as trigger leading to premature luteolysis:** Here stimulation is intense stimulation intense but lesser than above and needs LP support.
- **Artificial cycle where ovulation is suppressed and thawed embryo has been implanted:** Due to the absence of corpus luteum, endometrial receptivity is totally dependent on exogenously supported sex steroids. These cycles have also helped us to understand the efficacy of different luteal phase support preparations, doses, regimens, and routes of administration.⁸

TREATMENT FOR LUTEAL PHASE DEFECT

Progesterone is the main stay of the treatment but there is still controversy regarding the type and route of progesterone preparations. Most common progesterone used is micronized progesterone followed by dydrogesterone. Former can be given by various routes but the latter can be used by oral route only.

Role of Progesterone

Besides maintenance of pregnancy,

1. It also improves the endometrial receptivity in adequately estrogenized endometrium.

2. It stabilizes lysosomal membranes leading to quiescent uterus.
3. It blocks the chemokines - transcription factor, NF-KB leading to inhibition of prostaglandin synthesis causing uterine relaxation. This is also supported by the reduced intracellular calcium concentration and lowered amount of phosphorylated myosin.
4. It causes uterine relaxation by causing nitric oxide synthesis.
5. It increases endometrial vascularity and promotes secretory transformation of endometrium.
6. Progesterone along with HCG and cortisol inhibits the tissue rejection and protect the conceptus by its immunomodulatory action.
7. Progesterone positively regulates 'Progesterone Induced Blocking Factor', 'Natural Killer cells', HOX-10, trophoblast HLA gene leading to positive shift towards Th2 type.⁹

Various Routes of Progesterone Supplementation and Doses

Currently available formulations of progesterone include oral, vaginal, rectal and intramuscular. There is still a controversy regarding the optimal route of progesterone administration for luteal phase support in ART cycles.¹⁰ Literature is full of studies which shows no difference in efficacy between intramuscular/vaginal/oral route of progesterone supplementation but the compliance with oral sustained release preparations have been found to be better.^{11,12}

Oral Progesterone Preparations

The two oral progesterone preparations available with us are Dydrogesterone and Natural Micronized Progesterone (NMP). These preparations are known to undergo first pass prehepatic and hepatic metabolism which results in progesterone degradation and this reduces their bioavailability. Thus oral drugs require more doses but these are the easiest and acceptable routes.

Dydrogesterone: This is a retroprogesterone and is a biologically active metabolite of progesterone, thus having a good oral bioavailability. It induces secretory transformation of the endometrium through its antioestrogenic effect. It has also been shown in the studies that dydrogesterone has immunological effects which are associated with higher rates of pregnancy.¹³

Natural micronized progesterone (NMP)^{14,15:} The problem of lesser bioavailability have been overcome by the invent of sustained released preparations of the NMP in last decade. This preparation is provided in a methylcellulose base which hydrates in the gastrointestinal tract causing a slow release of progesterone. Oral NMP have high protein binding with long half-life (18 hours) leading to once a dosage benefit. The 'Smooth' release pattern of the drug helps in maintenance of the steady drug levels in blood because of decreased hepatic metabolism.

Both dydrogesterone and NMP are associated with similar rates of successful pregnancies (24.1% versus 22.8% respectively).^{16,17}

Vaginal Preparations of the Progesterones

These are available in the form of the gel and pessaries. The advantage of vaginally progesterone is that they have first uterine pass effect and a better bioavailability in the uterus. This causes adequate secretory endometrial transformation despite lower serum progesterone concentrations.^{18,19} The side effects of oral absorption are also minimal. Studies have shown similar clinical pregnancy rates with significantly higher implantation rate in the vaginal progesterone groups in ART cycles. It has also been recommended by authors that low dose vaginal micronized progesterone administration is simple, easy and well tolerated, so it can be the method of choice for LPS especially for high responder patients at risk of OHSS.^{6,20} Studies have clearly shown that vaginal micronized progesterone is significantly more effective in creating an 'in phase' secretory endometrium than oral dydrogesterone.^{18,19}

Patient compliance with vaginal progesterone is poor because of side effects like vaginal discharge, pruritus, vaginal messiness and irritation.

Injectable Preparations of Progesterone

This comes in the form of oil based intramuscular injections and aqueous solution subcutaneous injections. Subcutaneous administration avoids the concerns regarding vaginal administration and, unlike IM injections that are known to cause significant adverse reactions, the subcutaneous injections in the studies have been well tolerated. The doses of injectable progesterone used for LPS may vary between 25 and 100 mg per day without any significant difference concerning the outcome.

Side effects of injectable progestones are pain and rashes at the injection site which are more commonly observed with intramuscular preparations.

Proesterone + Estrogen

As discussed above the corpus luteum secretes not only progesterone, but also estrogens and other steroid hormones, thus authors debated the need of adding estrogen to progesterone for LPD²¹ and suggested that it would improve the implantation rates.^{22,23} However, in a meta-analysis it has been shown that routine use of oestrogen is not justified in progesterone supported luteal phase in IVF cycles.²⁴

HCG

Increased hyperstimulation rates have been observed when the HCG is being used for luteal support.²⁵ Luteal support with HCG should be avoided if oestradiol concentrations are above 2500–2700 pg/ml on the day of HCG administration in IVF cycles or if there are more than 10 follicles.^{26,27} Cochrane review clearly states that HCG with or without progesterone is associated with higher risk of ovarian hyperstimulation syndrome, therefore should be avoided^{28,29}.

GnRH Agonist

GnRH agonists have been suggested as a novel LPS that act at three levels i.e. pituitary, endometrium and the embryo itself.³⁰ It may also support the corpus luteum by stimulating the secretion of LH by pituitary or act directly on the endometrium through the locally expressed GnRH receptors.³¹ Prospective trials have shown opposing effects of GnRH agonist with low quality of evidence in its support.³²

Duration of Luteal Phase Support

As far as opinion regarding the progesterone initiation, dose and duration of treatment is concerned, there is still no consensus in the literature. This might be due to the fact that the timing and duration of implantation is not precisely known. Some have recommended the start of progesterone dose from the day of retrieval, others the day after retrieval or 2 days after retrieval. But so far no impact on treatment effect has been known.³³ There are differing reports regarding the duration of support but it has been suggested that LPD support

can be stopped any time after positive pregnancy test or ultrasound detection of pregnancy.³² The withdrawal of support after the confirmation of pregnancy has been suggested by the studies on pregnancies where the conception has occurred after donor oocyte.³²

CONCLUSION

The embryo implantation and the luteal phase support is a complicated event. Whatever may be the reason, the progesterone is the mainstay of the treatment for the LPD. All the routes of progesterone administration has almost equal efficacy and it remains the woman's choice to choose the type and route of administration.

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