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KEY PRACTICE POINTS 2024
INDIAN PERSPECTIVE

The current practice of **luteal phase support**

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THE CURRENT PRACTICE OF LUTEAL PHASE SUPPORT: KEY PRACTICE POINTS

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Background

The luteal phase refers to the time between ovulation and the onset of menstruation two weeks later or the start of a pregnancy. This phase is critical in the development of pregnancy by preparing the endometrium for blastocyst implantation.[1] As per the American Society for Reproductive Medicine (ASRM), the typical length of the luteal phase is relatively consistent at 12–14 days, although it may vary, ranging from 11–17 days.[2] Luteal phase deficiency (LPD) can be due to inadequate progesterone production, defective corpus luteum and/or defective progesterone receptor response.[3] Clinically diagnosed LPD as per the ASRM is defined as a luteal phase of ≤10 days; however, other definitions consider durations of <11 days or ≤9 days.[2] In addition to recurrent pregnancy loss (RPL), luteal phase defects have been linked to fertility and subfertility, first-trimester pregnancy loss, shorter menstrual cycles, and premenstrual spotting.[2] Notably, it can occur in 8.9% of cycles in normally menstruating women.[2,4] Luteal-phase support (LPS) is used in nearly all stimulated assisted reproductive technology (ART) cycles.[5] However, there are no clear consensus about the formulation and route of administration, as well as the timing and duration of treatment.[6]

Objective

The aim of this key practice points is to develop validated LPS treatment approach suitable for daily clinical practice.

Methodology

The task force comprised of six experts from the field of Obstetrics and Gynaecology formed. Task force reviewed the existing literature and developed the consensus statement based on published literature,

their individual clinical experience and focused discussion within task force. The task force members followed a well-defined grading system (Table 1) for the critical appraisal of evidence and grading strength of consensus statements. The consensus statements developed by task force were presented to larger group consisting 39 experts in the field of Obstetrics and Gynaecology. There was deliberation on each consensus point and later accepted, modified, or deleted. Thus, this document provides much-required insights and useful, practical, and accurate feasible guidance that aids a practicing clinician across the country.

Table 1. Level of evidence and grading strength of recommendations

Grades of recommendation	Level of evidence	Type of study
A	1a	Systematic review of (homogenous) randomized controlled trials
A	1b	Individual randomized controlled trials (with narrow confidence intervals)
B	2a	Systematic review of (homogenous) cohort studies of "exposed" and "unexposed" subjects
B	2b	Individual cohort study/low-quality randomized control studies
B	3a	Systematic review of (homogenous) case-control studies
B	3b	Individual case-control studies
C	4	Case series, low-quality cohort, or case-control studies
D	5	Expert opinions based on non-systematic reviews of results or mechanistic studies

LPS and its role in establishing and maintaining pregnancy

Optimal luteal function is a crucial factor in maintaining pregnancy.[7] The corpus luteum can produce adequate progesterone following ovulation in natural ovulatory cycles, until the placental function begins at seven weeks gestation. Any disruptions in progesterone secretion during the secretory phase can lead to an impaired luteal phase.[2]

Since low progesterone levels can decrease the possibility of implantation, it is essential to provide support during the luteal phase.[8] Luteal phase support aims to increase progesterone levels following ovulation, potentially improving pregnancy outcomes.[9]

A review has suggested that patients at low risk of developing ovarian hyperstimulation syndrome (OHSS), who are undergoing fresh embryo transfer and GnRHa trigger can be provided with a virtually OHSS-free treatment with non-inferior reproductive outcomes. This can be achieved with use of a modified LPS, which involves the administration of small boluses of hCG, daily recombinant LH (rLH), or GnRHa.[10] The European Society of Human Reproduction and Embryology (ESHRE) guideline does not recommend GnRH agonist with conventional luteal support and fresh transfer for the general IVF/ICSI population (Strength- Strong).[11]

PRACTICE POINT

For establishing and maintaining pregnancy

Luteal phase support with administration of progesterone and low dose hCG (1500 IU) in case on GnRH agonist as a trigger in fresh embryo transfer cycle can have positive effects on pregnancy outcomes. Individualized LPS for infertile women can be suggested based on the patient's specific characteristics, desires and the treatment protocol. (Grade A/Level 1a)

Choosing a LPS regimen

Progesterone supplementation or hCG is frequently administered for LPS, with hCG linked to a higher risk of OHSS compared to progesterone.[12] Progesterone supplementation for LPS is available in synthetic and natural formulations.[5] Progesterone should be administered until the luteo-placental shift.[13]

The European Society of Human Reproduction and Embryology (ESHRE) guideline recommends progesterone for LPS following IVF/ICSI (Strength-Strong).[11] The FOGSI position statement on the use of progestogens recommends the use of progesterone supplementation for LPS in ART.[14]

Dydrogesterone for LPS

Dydrogesterone is an established oral retroprogesterone, which exhibits a higher affinity for progesterone receptors than natural progesterone and has a reduced affinity for androgen and glucocorticoid receptors.[12,15] The ESHRE guidelines recommend dydrogesterone can be used for LPS (Strength- Conditional).[11]

Reports from several small-scale clinical trials and meta-analyses suggest that dydrogesterone is as

effective as micronized vaginal progesterone (MVP) for LPS.[15] Findings from both Lotus I and Lotus II studies establish that oral dydrogesterone was non-inferior to (non-inferiority margin of 10%) MVP (capsules or gel) for LPS in fresh-cycle IVF, demonstrating a comparable safety profile within the conducted studies. Due to its convenient oral administration, dydrogesterone holds the potential to bring about a paradigm shift for LPS in women undergoing IVF.[15]

In the meta-analysis of individual patient data (IPD), oral dydrogesterone showed a significantly higher likelihood of ongoing pregnancy at 12 weeks of gestation (odds ratio [OR]: 1.32; 95% confidence interval [CI]: 1.08 to 1.61; p = 0.0075) and live birth (OR: 1.28; 95% CI: 1.04 to 1.57; p = 0.0214) when compared to MVP. Furthermore, this meta-analysis combining IPD and aggregate data from all nine studies also revealed a statistically significant difference in ongoing pregnancy rate (OR: 1.16; 95% CI: 1.01 to 1.34; p = 0.04) and live birth rate (OR: 1.19; 95% CI: 1.03 to 1.38; p = 0.02) between oral dydrogesterone and MVP. This study indicates that oral dydrogesterone may be associated with a higher pregnancy rate and live birth rate than MVP.[16]

A study has shown that dydrogesterone and micronized progesterone showed comparable rates of ongoing pregnancies, but 10.5% of patients who received micronized progesterone reported vaginal discharge or irritation. Significantly more patients treated with dydrogesterone were satisfied with the treatment vs. micronized progesterone ($p < 0.05$).[17]

Research has shown that the ongoing pregnancy rates with oral dydrogesterone and MVP gel were similar. However, a significantly higher patient tolerability score was reported in patients treated with dydrogesterone.[18] Oral dydrogesterone when compared with vaginal and intramuscular progesterone for LPS in frozen-thawed embryo transfer (FET) artificial cycles showed comparable pregnancy (p=0.466), live birth rates (p=0.367), and miscarriage rates (p=0.487).[19]

A study was conducted to assess the role of dydrogesterone for LPS in ART cycles and to compare its efficacy with MVP. During phase I, 498 patients were categorized into three groups, and patients received MVP 600 mg/day. These patients were randomly assigned to receive either dydrogesterone 20 mg/day (n=218) or placebo (n=280). The pregnancy rate was higher with dydrogesterone compared to placebo in all groups: long protocol and not at risk of OHSS (33.0% vs. 23.6%), long protocol with a risk of OHSS (36.8% vs. 28.1%), and patients in a donor oocyte program (42.9% vs. 15.6%; p<0.001). In phase II, 675 patients were categorized into the same corresponding three groups and were randomly assigned to receive either dydrogesterone 30 mg/day (n=366) or micronized progesterone 600 mg/day (n=309). The pregnancy rate was significantly higher with dydrogesterone compared to progesterone in all groups.[20]

A study showed that dydrogesterone was equally effective as MVP as LPS in ART cycles. Moreover, advantages of dydrogesterone include its oral administration and lack of side effects, making it more favorable and acceptable to patients.[21]

The PROMISE (PROgesterone in recurrent MIScarriagE) and PRISM (PRogesterone In Spontaneous Miscarriage) trials were conducted to establish comprehensive evidence regarding the efficacy of progesterone therapy in preventing miscarriage and enhancing live

PRACTICE POINTS

For choosing a LPS regimen

- Progesterone is recommended for LPS following IVF/ICSI (Grade B/Level 2a).
- Dydrogesterone is non inferior in terms of pregnancy rates and live birth rates than MVP, therefore a potential option for LPS (Grade A/ Level 1b).
- Dyrdogesterone is associated with higher patient satisfaction rates, due to better tolerance, higher compliance, and negligible side effects (Grade A/ Level 1b) .
- Progesterone supplementation, with either oral dydrogesterone or MVP is beneficial and can be recommended in HRT frozen embryo transfer cycle (Grade A/Level 1b) .

birth rates.[22] Both of these trials did not support the role of progesterone therapy for LPS.[23, 24]

The MIDRONE study assessed the effectiveness of combining MVP with oral dydrogesterone versus MVP alone as LPS during FET cycles in infertile women undergoing IVF. The study showed that addition of oral dydrogesterone to vaginal progesterone for LPS resulted in a higher live birth rate and a lower miscarriage rate than with vaginal progesterone alone.[25]

Timing of initiation of LPS

Administration of early progesterone may benefit embryo transfer due to the uterine smooth muscle relaxing effects of progesterone.[26] Premature administration of progesterone before oocyte retrieval may lead to endometrial progression and embryo-endometrial asynchrony. Conversely, delayed administration beyond 72 hours may be inadequate to support endometrial development, potentially interfering with endometrial receptivity.[5]

According to a study, a lower clinical pregnancy rate was reported when progesterone was initiated before oocyte retrieval compared to starting it after oocyte retrieval (12.9 % vs. 24.6 %).[27] Patients who were administered progesterone as LPS starting on day 6 after retrieval exhibited a significantly lower clinical pregnancy rate per transfer compared to those starting support on day 3 after retrieval (44.8% vs. 61.0%, respectively, p=0.05). Initiating support on day 6 also led to a significant decrease in implantation rates (21.0% vs. 34.0% for day 6 vs. day 3, respectively, p=0.02).[28]

The ESHRE guideline recommends initiating LPS with progesterone in the window between the evening of day of oocyte retrieval and day 3 after oocyte retrieval (Strength- Good practice point [GPP]).[11] The FOGSI position statement on the use of progestogens recommends initiating progesterone supplementation from the day of oocyte retrieval.[14]

A systematic review has suggested that embryo transfer for cleavage stage embryo should be done after 3 days of progesterone (4th day of progesterone) and blastocyst stage embryo can be transferred after 5 days of progesterone (6th day of progesterone).[29]

In hormone replacement therapy (HRT)-FET cycles, the primary factor influencing the endometrial implantation window is the timing of progesterone administration. Progesterone should be administered upon reaching an endometrial thickness of 8 mm, typically occurring around day 12 to day 20 of the cycle. The optimal live birth rate would be achieved when the endometrial thickness falls within the range of 8.7–14.5 mm.[30]

PRACTICE POINTS

For ideal timing of initiation of LPS

- Progesterone should be started from the day of oocyte retrieval or within 72 hours after oocyte retrieval (Grade D/Level 5).
- In HRT-frozen ET cycles progesterone should be started after adequate endometrial preparation (endometrial thickness at least > 8 mm) (Grade B/Level 2b).
- Embryo transfer for cleavage stage embryo should be done after 3 days of progesterone (4th day of progesterone) and blastocyst stage embryo can be transferred after 5 days of progesterone (6th day of progesterone) (Grade A/Level 1a).

Duration of administration of progesterone for LPS

The use of progesterone supplementation following oocyte retrieval is nearly universal; however, the optimal duration of administration remains controversial.

PRACTICE POINTS

For the optimal duration of administration of progesterone for LPS

- LPS should be continued until a positive pregnancy test is confirmed (Grade A/Level 1a).
- LPS is commonly used by many clinicians until the 10th week of gestation when the luteal placental shift is completed (Grade D/level 5).

A meta-analysis of RCTs involving 1,201 women undergoing IVF/ICSI showed no statistically significant differences in live birth rate, miscarriage rate, or ongoing pregnancy rate between patients who underwent early cessation of progesterone and those who continued progesterone for LPS.[31]

A systematic review and meta-analysis evaluating the effects of extended progesterone support on pregnancy outcomes in women undergoing IVF/ICSI found no significant differences in live birth rate, miscarriage rate, or ongoing pregnancy rate between early cessation of progesterone and its continuation.[32]

The ESHRE guidelines recommend that progesterone administration for LPS should be continued at least until the day of the pregnancy test (Strength- GPP).[11]

Route of administration and dosage for LPS

Luteal phase support with progesterone can be administered via oral, intramuscular, vaginal, rectal, and subcutaneous routes, each route having distinct bioavailability and tolerability profiles.[15] However, patient compliance with vaginal progesterone is often poor due to side effects such as vaginal discharge and irritation.[33] Subcutaneous progesterone injection is associated with lower injection site reactions, including less pain and irritation, compared to the IM route.[34]

Dydrogesterone, a retroprogesterone, serves as a biologically active metabolite of progesterone. It has good oral bioavailability, which may address the challenge posed by the extensive metabolism of oral micronized progesterone.[6] A systematic review and meta-analysis of RCTs showed no significant differences in clinical and ongoing pregnancies between vaginal progesterone and IM progesterone. Compared to IM progesterone, vaginal progesterone was significantly associated with higher satisfaction.[35]

Subcutaneous progesterone had similar efficacy as that of vaginal progesterone on the likelihood of ongoing pregnancy, live birth, and the risk of OHSS in providing LPS during IVF. The study findings showed no statistically significant or clinically significant differences between the subcutaneous and vaginal progesterone for LPS.[36]

The findings from the Lotus I and Lotus II studies show that oral dydrogesterone is non-inferior than MVP (capsules or gel) for LPS in fresh IVF cycle, demonstrating a comparable safety profile within the studies.[14]

Good-quality evidence from RCTs indicate that oral dydrogesterone yields reproductive outcomes at least comparable to vaginal progesterone capsules when used for LPS in women undergoing embryo transfers. Oral dydrogesterone is considered as a viable option for LPS.[12,37]

A study has shown that dydrogesterone was well tolerated and can be applied for LPS in frozen embryo transfer cycles.[38] The MIDRONE study indicated that in LPS for FET cycle, the addition of oral dydrogesterone with MVP was associated with a non-significantly higher birth rate but a significantly lower miscarriage rate.[24]

PRACTICE POINTS

For the optimal route of administration and dosage for LPS

- The route of administration of progesterone should be individualized according to patient preferences, efficacy, and potential side effects, although the oral route has been proven to improve patient compliance and enhance treatment adherence, which can increase success of LPS management. (Grade A/level 1b).
- Dydrogesterone is well-tolerated, has higher bioavailability with minimal side effects profile; thus, oral dydrogestrone appears to be the first choice for LPS in comparison with vaginal, IM, and subcutaneous routes of progesterone (Grade A/Level 1b).
- Dydrogesterone is associated with higher live birth rate and significant reduction in miscarriage rates so one may consider combination of dydrogesterone with MVP for LPS (Grade A/ Level 1b).
- Oral dydrogesterone is recommended in 30 mg daily dosage in 3 divided doses for optimal LPS (Grade A/Level 1b).

The standard dosage of oral dydrogesterone ranges typically from 10 to 40 mg daily. This dosage should be divided into 3 doses daily as the half-life is 5–7 hours, to maintain stable progesterone levels throughout the luteal phase.[39,40,41]

In women undergoing programmed FET cycles, steady state of dydrogesterone and dihydrodydrogesterone levels, its active metabolite was achieved by day 3 of dydrogesterone administration. On the day of embryo transfer, the 25th percentile for dydrogesterone level was 0.71 ng/ml, and for dihydrodydrogesterone level, it was 20.675 ng/ml. A significantly higher ongoing pregnancy rate was achieved when plasma dydrogesterone and dihydrodydrogesterone levels were above 25th percentile.[42]

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