Luteal Phase Support

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luteal phase

- The time between ovulation and pregnancy or the onset of menses, which occurs 2 weeks later.
- Corpus luteum is a unique endocrine gland important role in the regulation of menstrual cycle and early pregnancy.
- Corpus luteum secretes estrogen and progesterone (which support the implantation process).

After ovulation continuous production of progesterone from corpus luteum is essential to maintain a viable intrauterine pregnancy until luteo-placental shift occurs

Placenta begins to produce adequate progesterone (8–10 weeks).

Inadequate ovarian production of progesterone may lead to early pregnancy loss or infertility.

Luteal phase

- Successful implantation the growing blastocyst secretes hCG, the corpus luteum and its secretions until luteo placental shift occurs
- Luteal vascularity, peaks at around 7 days following ovulation, which correlates with peak serum progesterone levels.

Timing of the Luteal-Placental Shift

- During the first 6 weeks of pregnancy, 17α-hydroxyprogesterone is also elevated in the maternal circulation at levels comparable to those of progesterone.
- After 6 weeks of gestation,17α-hydroxyprogesterone levels decrease progressively, whereas progesterone levels fall transiently between 8 and 10 weeks of gestation.
- The secretion of 17α-hydroxyprogesterone during the last third of pregnancy occurs largely from the fetoplacental unit.

LUTEAL PHASE DEFECT (LPD)

- Failure to develop a receptive secretory endometrium due to disruption in the function of corpus luteum.
- Failure folliculogenesis results in defective neo angiogenesis leading to inadequate production of progesterone.
- Progesterone plays a pivotal role in the maintenance of endometrial integrity and implantation.
- LPD presents clinically as short menstrual cycles ,RIF recurrent implantation failure or recurrent pregnancy loss RPL

LPD

- Insufficient endogenous progesterone
- Dyfunctional secretory endometrium
- Abnormal embryo implantation and growth is termed as luteal phase defect .

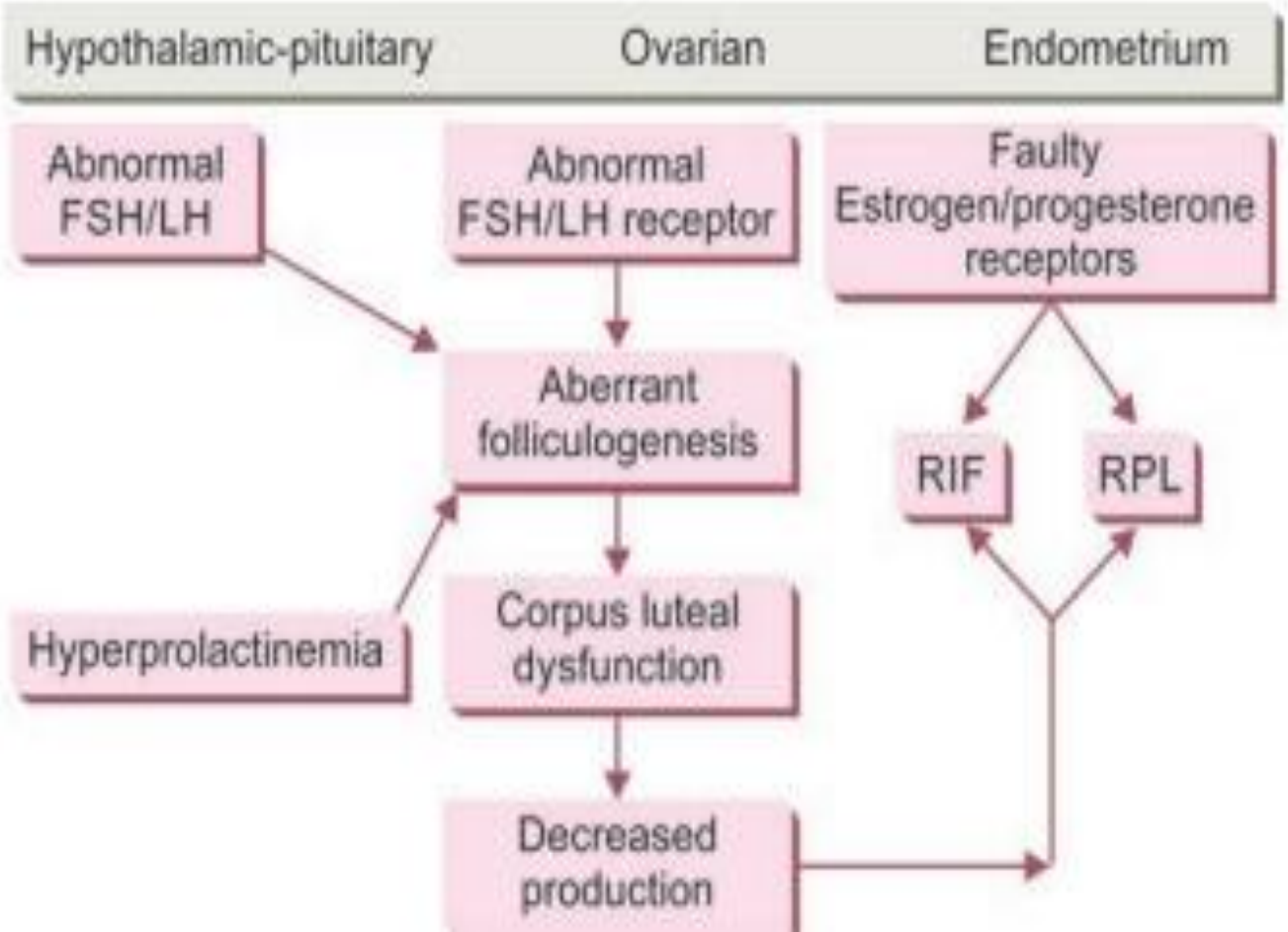
Pathophysiology of Luteal Phase Defect

A normal hypothalamic pituitary ovarian (HPO) axis

and complex between GnRH pulsatile patterns, release of FSH, and 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.

Flowchart 2: Pathophysiology of luteal phase defect.



Risk factors for LPD

- Thyroid disorders, hyperprolactinemia, obesity, pcos, endometriosis, ageing, stress, anorexia nervosa and other eating disorders, excessive exercise, weight loss, ovulation induction with or without (GnRH) agonist, (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.

IVF/ICSI cycles, luteal phase may abnormal?

- Disruption of granulosa cells during oocyte retrieval
- Gonadotropin-releasing hormone (GnRH) agonist and antagonists
- Excessive levels of E2 induced by COS
- The replacement of the LH surge by a triggering dose of hCG

- The mid-cycle LH surge or a triggering dose of human chorionic gonadotropin (hCG; 5000–10,000 IU), luteinized granulosa cells forming the Corpus Luteam start producing estradiol and progesterone.
- The hormonal activity of CL is tightly controlled by the pulsatile production of LH by the anterior pituitary.

LUTEAL PHASE SUPPORT IN ART: WHY IS IT NEEDED?

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.

Indications of Luteal Phase Support

- Recurrent pregnancy loss
- Controlled ovarian stimulation in IVF or intracytoplasmic sperm injection (ICSI) cycle
- Frozen embryo transfer (FET) cycles and donor oocyte cycles
- Ovulation induction with gonadotropins in (IUI) cycle.
- Luteal phase defect in cases of hyperprolactinemia, hypothyroidism, obesity, autoimmune disorders causing disruption of HPO axis.

LUTEAL PHASE SUPPORT

Luteal phase support may be defined as administration of pharmacological agents aimed at supporting implantation process to enhance the probability of pregnancy with a successful outcome.

Agents Used for Luteal Phase Support

- Progesterone after adequate estrogen priming, causes secretory changes in the endometrium, which improves endometrial receptivity where in endometrium acquires a blastocyst adhesion.
- The endometrial glands become tortuous and secretory, and stromal vascularity increases which enhance the endometrial receptivity.
- Progesterone induces nitric oxide synthesis in the decidua, which helps in promoting local vasodilatation and uterine musculature quiescence. Excessive uterine contractility has been found to play a role in causing ectopic pregnancies and miscarriages.

Progesterone

Directly on endometrium help secretory transformation of endometrium for implantation and early development of fertilized ovum.

- Oral
- Vaginal
- Rectal
- Parenteral preparations

ORAL

- Poor bioavailability (as less as 10%), owing to high first-pass hepatic metabolism. higher doses are required to reach an effective serum level, which causes sedative and anxiolytic central nervous system (CNS) side effects.
- Progesterone metabolites bind to (GABA), a receptor complex in CNS and cause headache, vertigo, and postural hypotension.
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Micronized progesterone

- 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. poor bioavailability (as less as 10%), owing to high first-pass hepatic metabolism. higher doses are required to reach an effective serum level, which causes sedative and anxiolytic central nervous system (CNS) side effects.

Synthetic progesterone

- Dydrogesterone was introduced to overcome the side effects of natural oral micronized progesterone and its less bioavailability.
- Its structure is closely related to progesterone and has a highly selective action on progesterone receptors.
- It lacks androgenic, estrogenic, and corticoid properties.
- It is available as 10 mg oral preparation.

Dydrogestrone

- dydrogesterone as LPS and found high oral bioavailability and specificity for P receptors suggesting higher efficacy than micronized progesterone.
- Decreased incidence of preeclampsia has been found in this study after use of dydrogesterone in natural and IUI cycles.

Transdermal

- Transdermal Administration of progesterone through this route is not possible due to presence of an enzyme in the skin, 5α-reductase, which inactivates progesterone.

Intramuscular

- Various side effects such as injection site pain, skin irritation, inflammatory reactions, and rarely abscess formation as these are oil-based preparations.
- Single daily dosing of 50 mg progesterone in oil produces physiological serum progesterone levels of 25 ng/24 hours.
- Intramuscular progesterone has been associated with highest serum levels compared to other routes.
- Intramuscular injections are oil based, achieve highest serum levels but very painful to administer daily.

Vaginal

- Vaginal route leads to highest concentration (uterus and endometrium)
- Avoids first pass hepatic metabolism
- Associated with minimal side effects with good patient compliance.
- Few patients report distress due to unavoidable vaginal discharge caused by these preparations.
- Progesterone can be administered vaginally in various forms as tablet, suppository, 8% gel preparation, and vaginal spray.

Intramuscular progesterone

- Intramuscular progesterone has been found to have more beneficial than vaginal progesterone in FET cycles.
- The reason behind this was explained by Casper 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.

Comparing the IM route of progesterone and vaginal route

- A meta-analysis of such studies done in 2009 showed comparable results in terms of clinical pregnancy rates and ongoing pregnancy rates between vaginal and intramuscular preparations.
- A Cochrane review published in 2011 showed no difference in clinical pregnancy rate or live birth rate between intramuscular and vaginal route progesterone; however, it did find a difference favoring intramuscular progesterone in ongoing pregnancy rate.
- Although more randomized controlled trials (RCTs) are needed to confirm these findings

Subcutaneous

- To avoid the painful intramuscular progesterone in oil injection, aqueous progesterone preparation was introduced.
- It is made by encapsulating progesterone in a starch residue called cyclodextrin, thus making it water soluble.
- The aqueous form comes as 25 mg and 50 mg/ day preparation, both found to reach serum progesterone levels resembling pulsatile progesterone levels in the luteal phase of menstrual cycle.

Progestrone treatmaent

- Early onset of LPS in ART on the evening of oocyte retrieval or the day after
- This is in part motivated by the fact that the uterus-relaxing properties of progesterone tend to reduce uterine contractions (UCs) at the time of ET.

Human Chorionic Gonadotropin

- Human chorionic gonadotropin is similar to LH in its molecular structure, mode of action, and physiological effects.
- However, hCG has a longer half-life and potency owing to the presence of higher sialic acid residues.
- Two types of hCG have been in use:
- Intramuscular
- Subcutaneous—recombinant form

Comparing the efficacy of hCG with traditional progesterone

- HCG has a similar efficacy to luteal progesterone in terms of pregnancy outcomes
- HCG has been associated with increased rates of ovarian hyperstimulation syndrome (OHSS)
- According to a Cochrane review published in 2015, it was shown that there was no significant difference between the two groups in terms of live births and ongoing pregnancy rates. However, use of progesterone alone was associated with lower incidence of OHSS

Gonadotropin-releasing Hormone Agonist

- Increase LH secretion from the anterior pituitary, thereby supporting the corpus luteum.
- It was also hypothesized that it may have effects on the endometrial GnRH receptors or direct effects on the embryo.
- It is available in three forms—subcutaneous, intramuscular, and intranasal.

GNRH

- It has been used as either a single dose subcutaneous injection decapeptyl 0.1 mg on day 5 or day 6 of oocyte retrieval, or intranasal form with nafarelin 200 mg twice daily initiated on the evening after oocyte retrieval.
- Cochrane review by van der et al. published in 2015, it was found that there was an increased live birth rate and ongoing pregnancy rate with the use of GnRH agonist along with progesterone in the luteal phase, compared to using progesterone alone.

Estrogen

- Estrogen pre treatment has a role in priming the endometrium in FET cycles, especially in donor egg recipients.
- Due to lack of endogenous estrogen production, there is inadequate endometrial priming, which hampers embryo implantation.
- It is available in various forms such as oral, transdermal, and intramuscular.

Role of estrogen

- The role of estrogen in the luteal phase for the preparation of a favorable endometrium is also unclear.
- Earlier studies showed that a drop in estradiol and progesterone levels in the luteal phase of IVF cycles was associated with reduced pregnancy and implantation rates.
- Subsequently, some investigators reported that luteal phase support with estradiol and progesterone was associated with higher pregnancy rates per embryo transfer

Oral dose of Estradiol valerate

- Oral dose of estradiol valerate is 4–8 mg/day, It has a high first liver-pass effect, it should be caution in patients at risk for venous thromboembolism.
- Transdermal gel or patch preparation should be considered in such patients. Transdermal preparations have been found to be less effective in hot and humid weather, and obese patients due to reduced absorption.
- There has been no fixed protocol regarding dose and duration of estrogen administration in LPS.

LPS

- Currently, there is no evidence that LPS is beneficial in natural, unstimulated cycles.
- LPS has not been found to be effective in women undergoing IO with clomiphene citrate with gonadotropins.
- On the contrary, progesterone LPS is beneficial in women undergoing IO with gonadotrophins followed by IUI.

Optimal Timing of Luteal Phase Support in ART

- In ART cycles, there is substantial endogenous production of progesterone starting after the hCG trigger
- Although it is important to give LPS in IVF cycles, it is equally important to time it correctly.
- LPS, if given early might advance the endometrial maturation making it out of sync with the growing embryo, thus, hampering the implantation process.

Timing of onset of start of LPS in patient undergoing IVF cycles

- According to an RCT, comparing the timing of onset of start of LPS in patient undergoing IVF cycles, there was no significant difference in the ongoing pregnancy rates between the three arms:
- Starting LPS on the day of hCG administration
- The day of oocyte retrieval
- The day of embryo transfer
- It may be concluded from the published data that there is an acceptable window of 24–48 hours of starting LPS after oocyte retrieval for optimum cycle results.

Aspirin

- (Aspirin) is a non-steroidal anti-inflammatory agent that works by inhibition of cyclooxygenase enzyme in platelets and reduction of prostaglandin synthesis.
- The research studies observed that daily administration of aspirin caused a shift from thromboxane A2 to prostacyclin, thereby leading to vasodilation and increased peripheral blood flow.
- Aspirin increases uterine blood flow that in turn may enhance endometrial receptivity and improve implantation rates.

Aspirin

- Beneficial effect in women :
- Anti-phospholipid (APL) syndrome
- Recurrent miscarriage
- Prevention of pre-eclampsia
- Supporting its use in women undergoing IVF cycles is controversial.
- Various studies and seven meta-analysis have provided conflicting evidence. A Cochrane review (Siristatidis et al. 2011) concluded that the use of aspirin in IVF does not improve pregnancy rates.
- A subsequent meta-analysis of 268 pregnancies from four studies showed that pre-conception administration of low-dose aspirin in IVF does not confer benefits in sustaining pregnancy.

- Doses of aspirin used in the studies varied between 75 mg daily, 80 mg daily or 100 mg daily and aspirin was continued until hCG administration for final oocyte maturation, 12 weeks of pregnancy or until delivery.
- The existing evidence suggests that adjuvant aspirin before and/ or during controlled ovarian stimulation does not improve ovarian response in terms of number of oocytes retrieved and clinical outcomes of clinical or ongoing pregnancy, or live birth rates following IVF treatment.

Luteal Phase Support in IUI Cycle

- Progesterone supplementation improves clinical pregnancy and live birth in gonadotropin ovulation induction–IUI (OI–IUI) cycles.
- There does not to be a benefit of exogenous progesterone in Clomiphene Citrate OI–IUI cycles.
- There is insufficient evidence that progesterone support improves outcomes in OI–IUI cycles using letrozole or clomiphene citrate plus gonadotropins

Luteal Phase Support in Using GnRH Agonist as Trigger

- GnRH antagonist protocol to prevent premature LH surge in COS cycles, it became possible to use GnRH agonist as a trigger, thus reducing the risk of OHSS.
- Effect on the luteal phase of the IVF cycle compared to that of a natural cycle.
- There is a significant difference in the luteal phase of GnRH agonist trigger cycle compared to hCG trigger cycle owing to the shorter half-life of endogenous LH (~60 minutes) compared to that of hCG (>24 hours).
- This leads to low circulatory levels of estrogen and progesterone throughout early or mid-luteal phase, causing premature luteolysis and implantation failure

Modified Luteal Phase Support after GnRH Triggering

- Earlier RCTs have shown high incidence of early pregnancy loss with the use of standard LPS with vaginal progesterone and oral estrogen in cycles where GnRH agonist was used as a trigger for final oocyte maturation.
- This necessitated the use of modified LPS in such cycles

HCG bolus after GnRH agonist trigger

- HCG when used in small bolus (1,500 IU) after GnRH agonist trigger gives similar ongoing pregnancy rates and clinical pregnancy rates as compared to hCG triggered cycles, without increasing the risk of OHSS, thus allowing fresh embryo transfer.
- Women undergoing IVF or ICSI treatment with GnRH agonist trigger. The women were supplemented by two bolus doses of hCG (1,500 on the day of ovum pick up and second dose 4 days later, with no exogenous progesterone support.
- The study reported an ongoing pregnancy rate of 47% with no incidence of OHSS.
- Small dose of hCG rescues the luteal phase in GnRH agonist triggered cycles, however, more studies are needed to establish a protocol.

Recombinant LH (rLH)

- Similar reproductive outcomes were obtained using rLH as LPS in GnRH triggered cycles compared to hCG triggered cycles.
- rLH was used in doses of 300 IU on alternate days starting from the oocyte retrieval day along with daily vaginal progesterone.
- Larger studies are needed to establish the safety and efficacy of this protocol. Another drawback is the high cost associated with it.

Intensive progesterone and estrogen support

- Various studies have been performed using intensive LPS protocol consisting of estrogen and progesterone only, for GnRH agonist triggered cycles compared to cycles using hCG trigger.
- While some studies favored this protocol, others discouraged its use reporting a low reproductive outcome.
- There seems to be a need for larger RCTs to justify the use of intensive LPS.
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Luteal Phase Support in Natural AND FET Cycles

- Progesterone supplementation improves implantation rates in fresh embryo transfer cycles.
- It has also been observed that there is a positive role of luteal support in hormonally controlled frozen- ET cycles.
- Endogenous production of progesterone is sufficient to support implantation in a natural ovulation cycle in a fertile female.

when to start, route, and duration of progesterone in luteal phase

- Di Guardo47 et al. developed a web based questionnaire for 1,480 clinicians on when to start, route, and duration of progesterone in luteal phase supplementation.
- It was concluded that most common practice is to start progesterone on day of oocyte retrieval via vaginal/intramuscular route and continue until 12 weeks gestation.
- Survey has shown gradual increase in use of vaginal progesterone for LPS instead of intramuscular or oral route

prolongation of progesterone supplementation

- In a prospective study, it was shown that prolongation of progesterone supplementation beyond positive betahCG test had no effect on miscarriage rate or delivery rate.
- Another study randomized IVF patients into two groups comparing the impact of progesterone supplementation, beyond first ultrasound showing viable pregnancy. It concluded that there was no significant difference in miscarriage rates or bleeding in early pregnancy between the two groups
- From the current available evidence, it has been found that continuation of progesterone supplementation beyond first viability ultrasound in patients undergoing IVF treatment is generally unnecessary

Endometrial receptivity

- Endometrial receptivity is considered critical for successful implantation.
- Endometrial immune hostility
- Suboptimal uterine perfusion
- Inadequate LPS
- Increased myometrial contractility

Adjuvants in Luteal Phase Support

- Adjuvant therapies have been used in IVF cycles in order to counteract the reasons for recurrent implantation failure, and to optimize IVF outcomes.

TABLE 1: Adjuvants in luteal phase support.

	Adjuvant	*Rationale*	*Evidence*
1.	Intravenous immunoglobulin	Inhibiting (NK) cell production and/or activity correcting abnormal Th1:Th2 ratio	No convincing evidence for the use and safety of IVIg
2.	Anti-TNF alpha agents	Increased TNF-alpha:interleukin-4 ratio-role in RIF	Lack of evidence to support its use owing to adverse effects like lymphoma
3.	Intravenous lipids	Inhibits Th1 cytokines and reduces the cytotoxic effect of NK cells	Routine use not recommended
4.	Corticosteroids	• Anti-inflammatory and immunosuppressive activity • Improves intraendometrial milie	Limited evidence to improve pregnancy rate (PR) in women undergoing conventional IVF and in those with autoimmune disorders and unexplained RIF
5	Low-dose aspirin	Increases uterine blood flow, enhances endometrial receptivity and improves implantation rates	• Lack of evidence supporting routine use • Limited evidence to support use in RPL
6.	LMWH (Low molecular weight heparin)	• Anti-thrombotic effect • There is increased incidence of thrombophilia in women with RIF. LMWH reduces formation of microthrombi at implantation site	• Routine use not warranted • Should be considered in women with thrombophilia and RIF
7.	Metformin	Modulation of insulin like growth factors	Beneficial effects in PCOS patients undergoing IVF by reducing risk of OHSS and improving CPR
8.	Myo-Inositol[51]	Acts on insulin, FSH, and LH receptors	Pivotal role in the development of oocytes and embryos
9.	Probiotics[52]	Reduces IL-6 and hs-CRP and increases IL-10 level	Beneficial effects in PCOS patients undergoing IVF by improving CPR
10.	L-Arginine[53,54]	Activates immune system and increases uterine vascular flow	Role in patients with recurrent thin endometrium

(CPR: clinical pregnancy rate; FSH: follicle-stimulating hormone; IVF: in vitro fertilization; IVIg: intravenous immunoglobulin; LH: luteinizing hormone; OHSS: ovarian hyperstimulation syndrome; PCOS: polycystic ovary syndrome; RIF: recurrent implantation failure; RPL: recurrent pregnancy loss; NK: natural killer; IL: interleukins; hs: high sensitivity)

KEY POINTS

- Luteal phase support is mandatory in assisted reproductive technology (ART) cycles to optimize reproductive outcomes.
- Progesterone and hCG use in the luteal phase confers benefit to infertile women undergoing (IVF) treatment.
- Use of hCG for trigger is associated with greater risk of ovarian hyperstimulation syndrome (OHSS).

- Natural micronized progesterone as a luteal phase agent is not effective if taken orally
- Vaginal and injectable progesterone have similar implantation and clinical pregnancy rates.
- Synthetic progesterone, dydrogesterone, has been found to be equally effective as vaginal micronized progesterone for (LPS) in ART cycles.
- Use of estrogen with progesterone does not seem to enhance the probability of implantation and pregnancy rates.

- Optimal timing of LPS is important, the window of starting LPS being within 24–48 hours from the oocyte retrieval.
- According to the literature available, there is no role of continuation of LPS beyond first positive beta hCG or first ultrasound showing viability.
- Although, the common practice by clinicians is to continue LPS till 12 weeks.
- Modified LPS in GnRH agonist triggered cycles in the form of hCG bolus and rLH has shown positive effect on pregnancy outcomes, but more studies are needed to support its use.
- Despite widespread use of adjuvants in LPS, current evidence does not recommend their routine use in all IVF cycles


Thank you for your
attention