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Review Article

Luteal Phase Defect (LPD): A necessary tool in assisted reproductive techniques

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ABSTRACT

In Luteal Phase Defect (LPD), endogenous progesterone is insufficient to maintain a functional secretory endometrium and also inhibit embryo growth and implant. In 1960, it was estimated that 20 million pregnancies were exposed to Dydrogesterone in utero. LOTUS I and LOTUS II two major multicenter Phase III studies were conducted on patients who were planning to undergo *In Vitro* Fertilization (IVF) with or without Intracytoplasmic Sperm Injection (ICSI). The result of both studies shows that Dydrogesterone was non-inferior to micronized vaginal progesterone, which was the presence of fetal heartbeats at 12 weeks of gestation. Progesterone which can be administered either by oral preparation, vaginal administration along with optimal use of estrogen and Gonadotropin-Releasing Hormon (GnRH) agonist drugs is used in the treatment of LPD. Studies have suggested the use of Dydrogesterone in fresh IVF cycles and Luteal Phase Support (LPS) is continued till 10–12 weeks. However, it may be stopped at the time of β-hCG becoming positive or visualization of a fetal heartbeat.

1. Introduction

The normal menstrual cycle is 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) produces progesterone, which inhibits endometrial proliferation and determines endometrial receptivity. Post-operation progesterone is secreted by the CL. If no fertilization occurs the CL degrades, progesterone levels fall and menstrual bleeding occurs. However, if the fertilization is there then CL is stimulated by the Human Chorionic Gonadotropin (hCG) and it continues to produce progesterone and ultimately once the pregnancy is there and there is a luteal placental shift in 6—7 weeks of pregnancy then the rest of the progesterone is taken over by the CL and ultimately the placenta. Progesterone is required for several processes in early pregnancy stages: preparation of the endometrium for the implantation, decreasing the contractility of the uterine smooth muscle, regulation of cellular immunity, and also mediate uterine blood flow, uterine endothelial adaptation to pregnancy by increasing the nitrous oxide production.

2. Luteal Phase Defect

LPD was first described in 1949 by Georgiana Seegar Jones. It is the condition in which endogenous progesterone is

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insufficient to maintain a functional secretory endometrium and does not allow normal embryo implantation and growth.[1]

3. Diagnosis of LPD

Biopsy is the method for diagnosis of LPD. It is performed two days prior to expect period and if there is an out-of-sync by 2 days then it is a LPD. Normally biopsy cannot be performed on the basis of symptoms or by serum progesterone on day 21 of the cycle. If the progesterone level is less than 20, then it is the static progesterone level.

In *In Vitro* Fertilization (IVF) and Assisted Reproductive Technologies (ART), there is a deficiency of the luteal phase. Many a time after aspiration there is supraphysiological estradiol level caused by overstimulation. Due to the high Estradiol (E2) level, there is a negative feedback of the pituitary which naturally promotes luteolysis and low progesterone level during the luteal phase. Thus, there is a major luteal phase deficiency in ART. Progesterone overcomes this deficiency as it can be seen in all kinds of IVF protocol whether it is the non-agonist protocol which is not in much use nowadays, short agonist protocol, or antagonist protocol, in all the protocols luteal support is needed.

4. Various Available Options for Luteal Support in ART

Human chorionic gonadotropin: hCG stimulates the ovaries to induce the production of endogenous progesterone and estradiol in Gonadotropin-Releasing Hormone (GnRH) agonist and antagonist cycles. Various routes for administration are available: vaginal, tablets, gels, suppositories, intramuscular, and also subcutaneous. The problem with hCG is the risk of hyperstimulation. GnRH injection on the sixth day was an established option for luteal support in ART. Estrogen is widely practiced to induce the supplement of progesterone.

Supplementation with exogenous progesterone has been shown to improve the ART outcomes in GnRH agonist and antagonist stimulation cycles. Various products are available: natural progesterone, synthetic progesterone, micronized progesterone, and the retro progesterone namely Dydrogesterone which can be given vaginally, intramuscularly, subcutaneously, and by various other routes. Progesterone improves IVF and ART outcomes and is usually given from the day of Oocyte retrieval and often till 12 weeks. The standard protocol is to start on the day of hCG.

5. Conditions Related to Progesterone Insufficiency

It was estimated that cumulative exposure for all indications is more than 113 million patients in the 1960s and of those, it is estimated that more than 20 million pregnancies have been exposed to Dydrogesterone in utero. Dydrogesterone has been used for many years but there is no definite use in ART cycles and thus two major studies: THE LOTUS I and THE LOTUS II studies were conducted.

The LOTUS I study was a randomized, double-blind, double-dummy, multicenter Phase III RCT study. Patients with infertility who were planning to undergo IVF with or without Intracytoplasmic Sperm Injection (ICSI) were screened for possible study inclusion and enrolled prior to oocyte retrieval. The embryo transfer was either single transfer or double transfer. Only the fresh cycles were studied not frozen cycles. The intervention of this study was to compare 30 mg of Dydrogesterone *vs.* 600 mg of vaginal micronized progesterone and was started from the day of OPU. Subjects were randomized to receive either oral Dydrogesterone 10 mg tablets three times daily (TID) (Group 1), or MVP 200 mg capsules with oral placebo tablets TID (Group 2). There were 511 patients and the end of the 14 days. Luteal support was started on the day of oocyte retrieval (Day 1) and continued until 12 weeks of gestation (Week 10). The conclusion of The Lotus I study demonstrated that oral Dydrogesterone was non inferior to MVP for the primary objective, which was the presence of fetal heartbeats at 12 weeks of gestation. It also met the secondary objective which was the rate of live births and newborn assessment was similar between the two treatment groups. It is also safe and tolerable, oral Dydrogesterone had similar safety profile to micronized vaginal progesterone with more new safety concern identified in the study and the implication were the oral Dydrogesterone may replace micronized vaginal progesterone as the standard of care for luteal support in IVF, owing to the ease of oral. Because oral has the ease, only thing till now was that micronized could not be taken orally as micronized has sleepiness very high which is the big disadvantage of micronized vaginal progesterone.[2]

The LOTUS II was a randomized, open-label, multicenter, Phase III, non-inferiority study. Premenopausal women (>18 to <42 years of age) with a documented history of infertility who were planning to undergo IVF with or without ICSI, were enrolled in the study. Only fresh cycles were used. The objective was to establish oral Dydrogesterone 30 mg daily non-inferior to 8% Micronized Vaginal Progesterone (MVP) gel 90 mg daily for Luteal Phase Support (LPS). The structure of the study was same as LOTUS 1 study, again the 2 arms were there and the first arm has oral Dydrogesterone and the second arm was gel. At the end of 14 days, β-hCG was done and they were followed up for nearly 12 weeks and 4 outcomes were studied. The LOTUS II demonstrated that oral Dydrogesterone was non-inferior to micronized vaginal gel in the presence of fetal heartbeat and 12 weeks of gestation. Then the secondary objective was also met: positive pregnancy test, clinical pregnancy, live birth and

new born were equivalent. Third objective was safety, which was very good and the implications were that it may replace gel as the standard of care for luteal support in IVF, which is again because of the ease of oral administration.[3]

Barbosa *et al.* in 2016, studied 8 RCTs & compared oral Dydrogesterone with progesterone by the administration through any route in women undergoing ART. Results suggest that there was no relevant difference between oral Dydrogesterone and vaginal progesterone for LPS with respect to the rate of ongoing pregnancy or clinical pregnancy or miscarriage rate, so, this is a good study.[4]

However Van der Linden M in 2015, studied 94 RCTs of luteal support using progesterone hCG or GnRH agonist supplementation in ART cycles that fulfill the criteria of meta-analysis and the results state that hCG or progesterone given during the luteal phase may be associated with higher rates of live birth rate or ongoing pregnancy than placebo.

On comparing synthetic progesterone with micronized progesterone using two different studies, both synthetic and micronized give the same outcome and evidence suggests that synthetic progesterone is associated with higher clinical pregnancy. Dydrogesterone is one of the synthetic progesterone and it is presented with higher clinical pregnancy rate than micronized progesterone.

6. Physiology of CL Function and Disruption

1. The human CL is a temporary endocrine gland derived from the ovulated follicle and is composed of stereogenic (theca and granulosa luteal cells) and non-steroidogenic (endothelial, immune, and fibroblast) cells which are critical for luteal steroid biosynthesis.[5]
2. After ovulation is induced by the mid-cycle Luteinizing Hormone (LH) surge, the luteinized granulosa cells collectively form corpus luteum start producing estrogen (E_2) and progesterone.[6,7]
3. The hormonal activity of CL is tightly controlled by the pulsatile production of LH by the anterior pituitary.
4. Numerous hormonal changes caused by the Controlled Stimulation (COS), interferes with the normal function of the anterior pituitary, causing the disruption of CL and progesterone secretion.
5. In ART, the factors interfering with the normal support of CL function by the anterior pituitary notably are:[7"]
   a. Excessive levels of E2 induced by COS leading to negative feedback to the hypothalamus-pituitary axis and suppression of LH pulsatile secretion.
   b. Damage to the granulosa cell apparatus.
6. ART outcomes, pregnancy rates and live birth rates are improved by LPS.[8]

7. Drugs used for LPS

1. Drugs used for LPS are progesterone, estrogens, GnRH agonist, and hCG.[9]
2. Inadequate progesterone ultimately going to act upon the endometrium and make it imperfect. Decrease progesterone impacts the endometrium receptivity.[10]
3. LPS can be accomplished by either an intermittent administration of hCG or daily progesterone replacement via oral, intramuscular, subcutaneous, and vaginal routes.[11]
4. Some studies have used added estrogen to progesterone, but benefit observed in the clinical pregnancy.[12]
5. The hCG has been abandoned due a several-fold increase in the risk of ovarian hyperstimulation syndrome and a lack of demonstrated superiority over simple progesterone supplementation.[7]

8. Progesterone

It can be administered orally, intramuscularly, vaginally or, rectally with similar efficacy for each route of administration. However, oral progesterone is subjected to substantial first pass metabolism, resulting in a bioavailability of <10%. Intramuscular progesterone is associated with the highest serum levels, and vaginal progesterone increases endometrial tissue levels. The main disadvantages with intramuscular progesterone is pain caused by daily injection, inflammatory response, and local abscesses. The vaginal route are associated with irritation, discharge, bleeding, and interference with coitus.[12,13]

8.1. Dydrogesterone

1. Dydrogesterone is synthetic progesterone with enhanced bioavailability, effective in treating reproductive disorders such as threatened and recurrent miscarriage.
2. It has a greater affinity for the progesterone receptors and can be used at lower doses to promote endometrial proliferation owing to its better bioavailability and the progestogenic activity of its metabolites when compared with progesterone.
3. Dydrogesterone shows no affinity for androgenic, estrogenic, glucocorticoid, or mineralocorticoid receptors.
4. Dydrogesterone is safe and tolerable therefore favorable in pregnancy profile.[2]

8.2. Estrogens

Estrogen supplementation is important particularly in older women with poor responders. Estrogen administration in the follicular phase can improve endometrium preparation.

Not all products may be available. With high dose estrogens, it may be suggested to add a low dose Aspirin and/or Low-Molecular-Weight Heparin (LMWH).[14]

Table 1:

Drug Preparation	Dose	Benefits
1. Oral		Better bioavailability
Dydrogesterone	30 mg/day (10 mg TID) till 12 weeks of gestation	10–20 times more potent Lesser side effects Comparable live birth Oral compliance No estrogenic, androgenic, glucocorticoid activities Better progestational and immunomodulatory activity
2. Vaginal Progesterone		
Micronized progesterone capsules	600 mg/day (200 mg TID)	Bypassing first-pass metabolism Higher concentration in uterine circulation
Micronized progesterone (Gel)	90 mg/day	Same as above
3. Injectable		
Micronized progesterone (Oil-based)	100 mg/day	High plasma concentration
Micronized progesterone* (Water-based)	50 mg/day (25 mg twice a day)	No pain at injection site

*In some countries oral sustained release micronized progesterone is available and the main side effect is drowsiness

Table 2:

Drug Preparation	Dose	Benefits	Side Effects
1. Oral			1. Nausea 2. Vomiting 3. Deep vein thrombosis (DVT) 4. Breast tenderness 5. Loss of appetite 6. Migraine, headache, dizziness 7. Bloating 8. Venous thromboembolism (VTE)
Estradiol valerate 2 mg	6–12 g	Better compliance	
Estradiol hemihydrates 2 mg	6 mg	Better compliance	
2. Transdermal			
17-β estradiol	6 mg	Decreases chance of DVT and VTE in post menopausal women or older women	
3. Vaginal			
Estradiol valerate 2 mg	6–12 mg	Increases clinical pregnancy rate but no other parameters	

8.3. Agonist

0.1 mg of agonist on day 6 of Oocyte Pick-Up (OPU).

8.4. Onset of treatment[6]

1. In ART, cycles initiate from the evening of oocyte retrieval or the day after. The relaxing properties of progesterone tend to reduce the Uterine Contraction (UCs) at the time of Embryo Transfer (ET).
2. Frozen Embryo Transfer (FET) cycle - endometrium – more than 7 mm, triple layer pattern with adequate blood flow.
3. Intrauterine Insemination (IUI) cycles: Day of IUI, if Controlled Ovarian Hyperstimulation (COH) with gonadotropin has been done.

9. How to Choose Progesterone? [15–18]

Choice of progesterone depends upon the following four factors:

1. Bioavailability
2. Side effects
3. Ease of use
4. Clinical outcome

10. Conclusion

Luteal Phase Defect (LPD) has been proven to be necessary for assisted reproductive technique. Progesterone with optional use of estrogen and GnRH agonist drugs are used in the treatment of LPD. The drug can be administered either by the oral preparation, vaginal administration or by injectable route. Dydrogesterone has been routinely used for LPD in IUI cycles. Studies have suggested the use of Dydrogesterone in fresh IVF cycles and Luteal Phase Support (LPS) is continued till 10–12 weeks. However, it may be stopped at the time of β-hCG becoming positive or visualization of a fetal heartbeat.

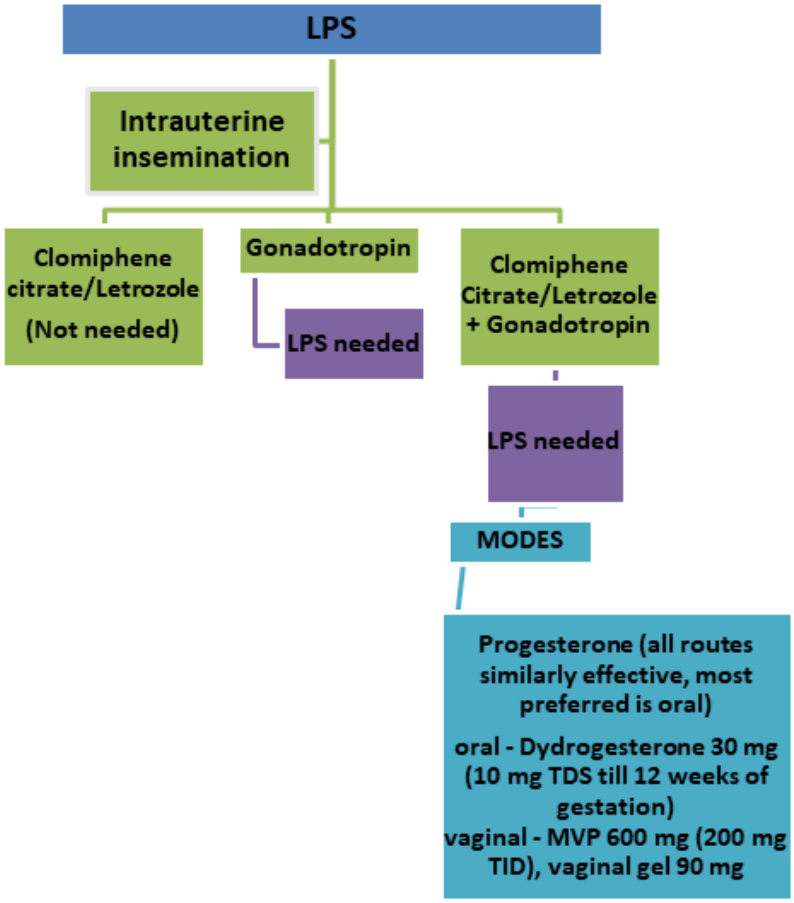

Fig. 1: Algorithm for LPS in Controlled Ovarian Stimulation (COS) cycles with timed intercourse or Intrauterine Insemination (IUI). LPS: Luteal Phase Support; MVP: Micronized Vaginal Progesterone; OD: Once Daily; TDS/TID: Thrice Daily

Table 3:

Route and Type of Progesterone	Advantages	Disadvantages
Oral Dydrogesterone	Well tolerated Oral compliance Lesser side effects Better bio-availability More potent Comparable live birth rate Less estrogenic, androgenic glucocorticoid activities Better progesterone and immunomodulatory activity	
Vaginal (MVP)	Good bioavailability	Vaginal irritation Discharge and bleeding Messy to use
Intramuscular	Good bioavailability	Pain at the injection site Local abscess Lacks compliance
Subcutaneous	Good bioavailability	Low compliance Daily injections

Oral Dydrogesterone may replace MVP as a standard of care in ART due to comparable efficacy, better bioavailability, well tolerated oral compliance, and fewer side effects. [19]

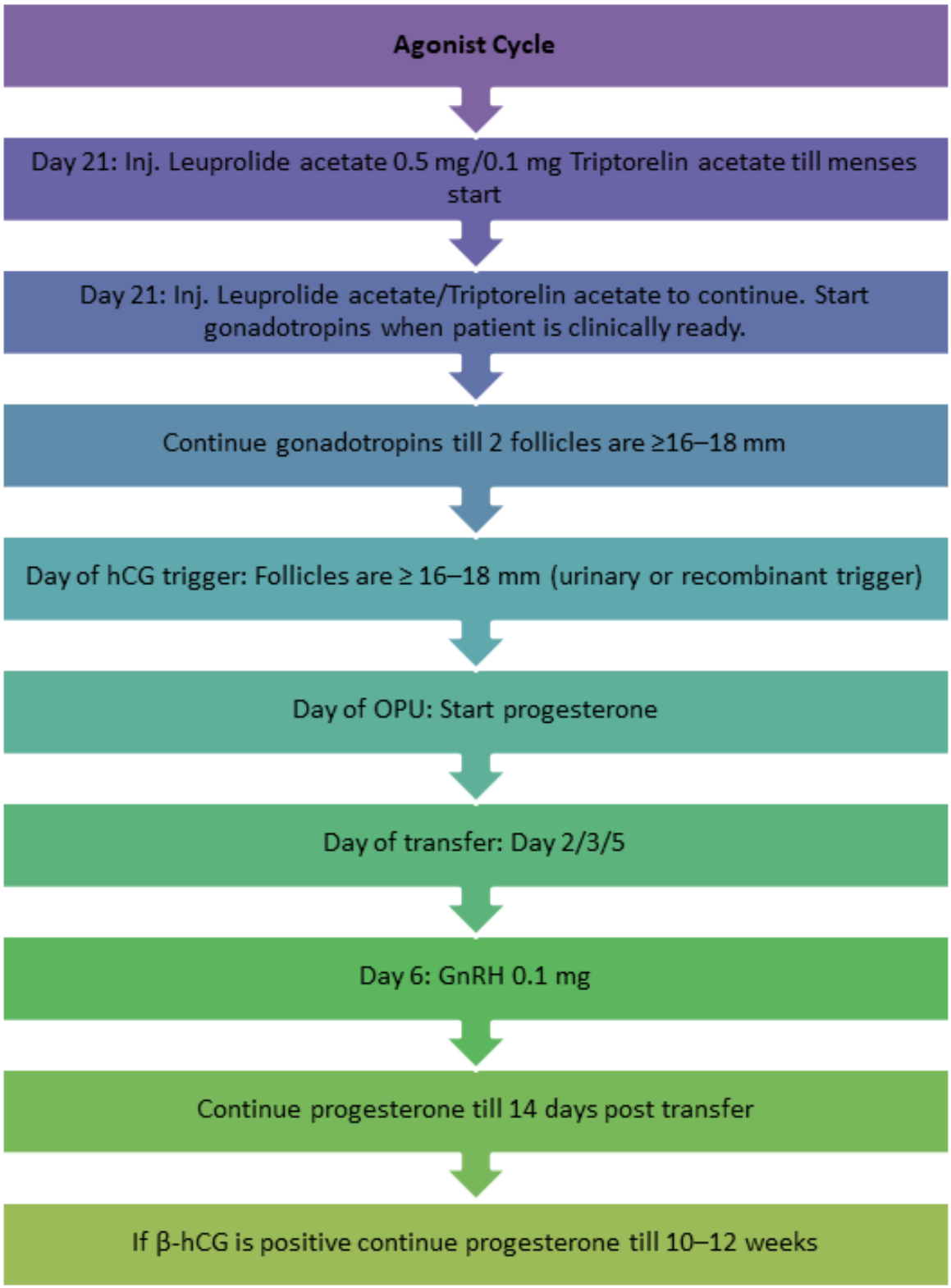

Fig. 2: Algorithm of LPS in ART using agonist protocol
OPU: Ovum Pick-Up; hCG: Human Chorionic Gonadotropin; GnRH: Gonadotropin-Releasing Hormone

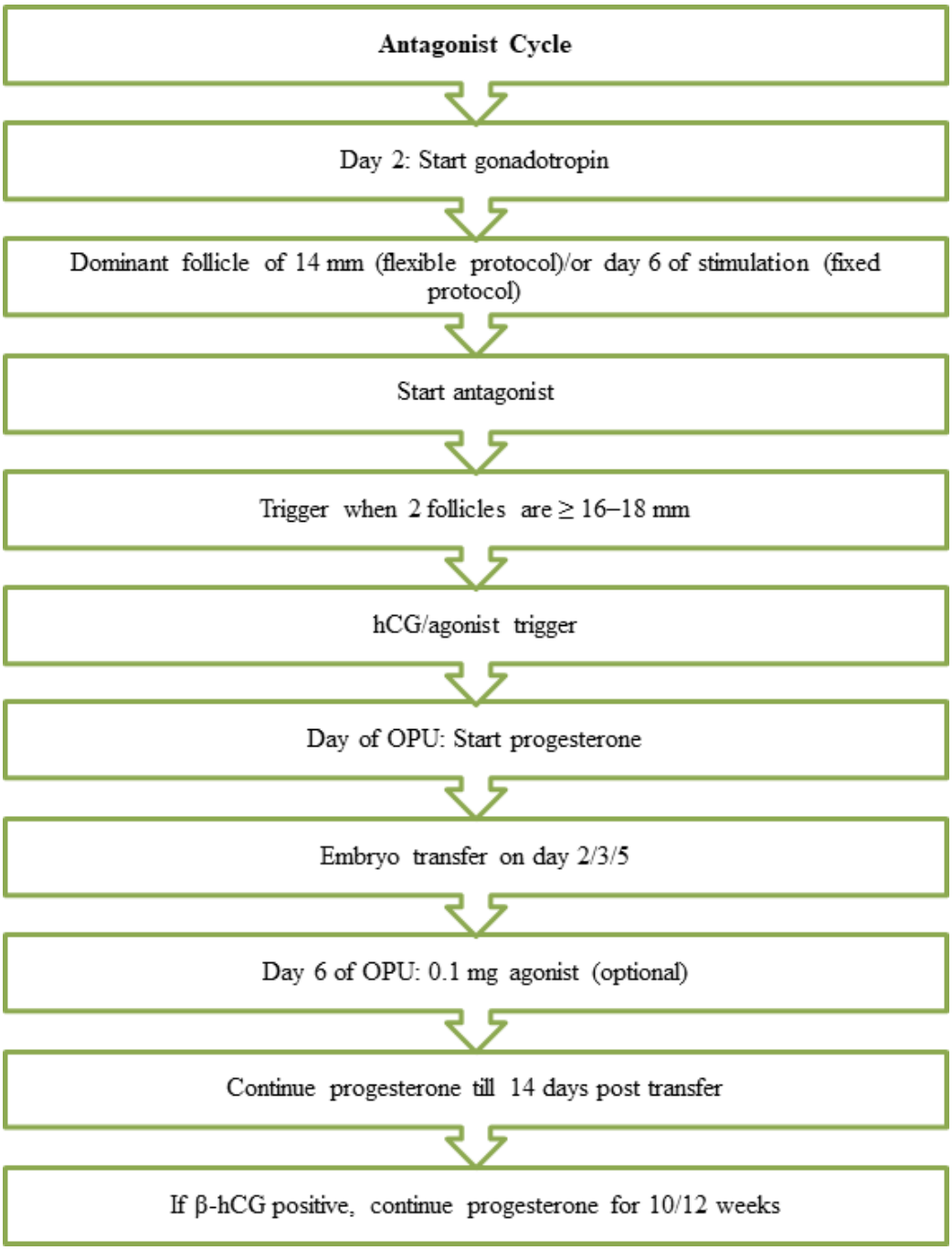

Fig. 3: Algorithm of LPS in antagonist cycle

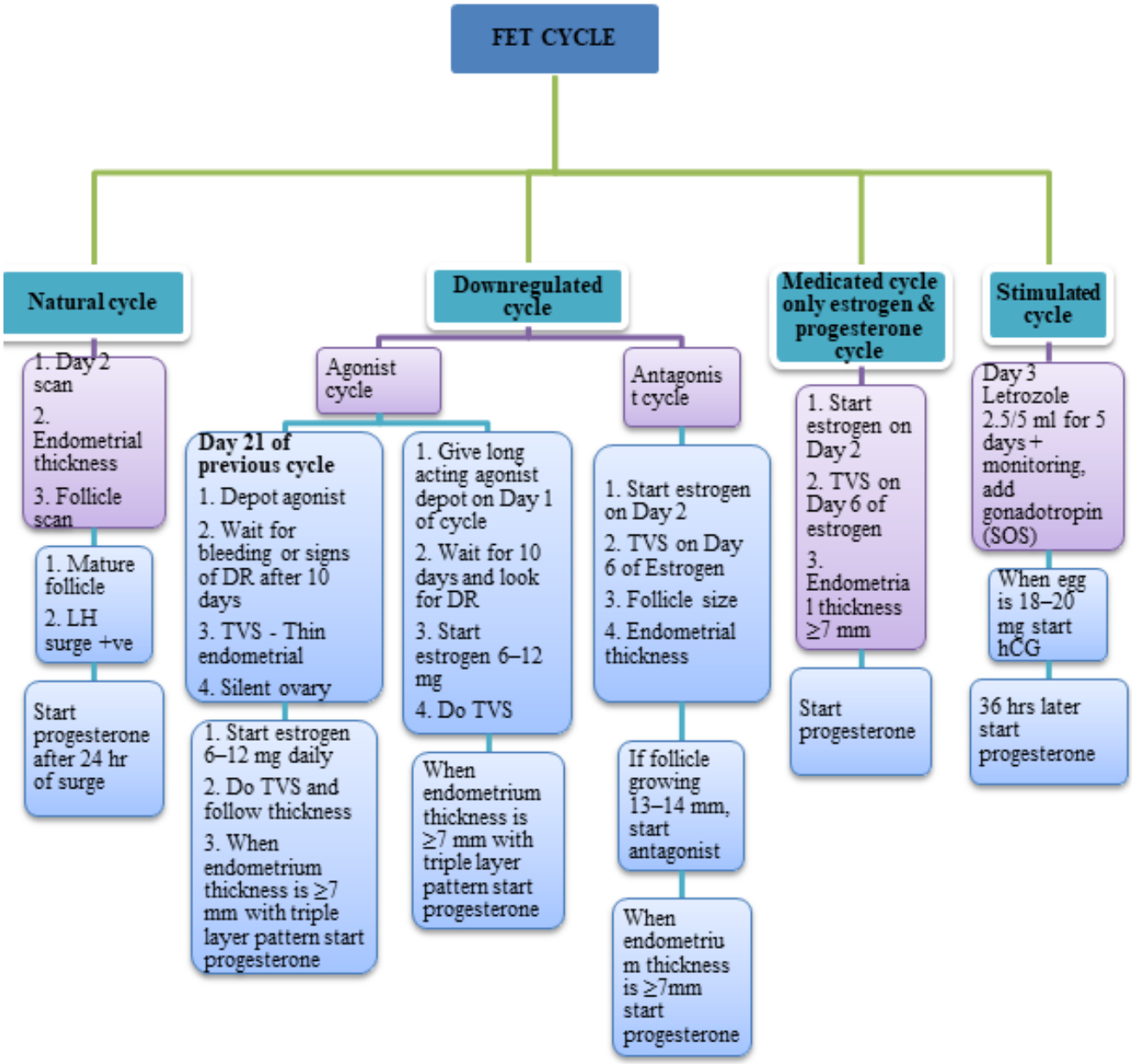

Fig. 4: Continue estrogen and progesterone till 10 weeks of pregnancy
DR: Downregulation; ET: Embryo Transfer; FET: Frozen Embryo Transfer; LH: Luteinizing Hormone; TVS: Transvaginal sonography

11. Source of Funding

None.

12. Conflict of Interest

None.

References

1. Mesen TB, Young SL. Progesterone and the Luteal Phase. *Obstet Gynecol Clin North Am*. 2015;42(1):135–51.
2. Tournaye H, Sukhikh GT, Kahler E, Griesinger G. A Phase III randomized controlled trial comparing the efficacy, safety and tolerability of oral dydrogesterone versus micronized vaginal progesterone for luteal support in in vitro fertilization. *Hum Reprod*. 2017;32(5):1019–27.
3. Griesinger G, Blockeel C, Sukhikh GT, Patki A, Dhorepatil B, Yang DZ, et al. Oral dydrogesterone versus intravaginal micronized progesterone gel for luteal phase support in IVF: A randomized clinical trial. *Hum Reprod*. 2018;33(12):2212–21.
4. Barbosa MW, Silva LR, Navarro PA, Ferriani RA, Nastri CO, Martins WP. Dydrogesterone vs progesterone for luteal-phase support: Aystematic review and meta-analysis of randomized controlled trials. *Ultrasound Obstet Gynecol*. 2016;48(2):161–70.

5. Devoto L, Kohen P, Muñoz A, Strauss JF. Human corpus luteum physiology and the luteal-phase dysfunction associated with ovarian stimulation. *Reprod Biomed Online*. 2009;18(Suppl 2):S19–S24.
6. Kumar P, Sait SF. Luteinizing hormone and its dilemma in ovulation induction. *J Hum Reprod Sci*. 2011;4(1):2–7.
7. Stephens SM, Pau FKY, Yalcinkaya TM, May MC, Berga SL, Post MD, et al. Assessing the pulsatility of luteinizing hormone in female vervet monkeys (Chlorocebus aethiops sabaeus). *Comp Med*. 2013;63(5):432–8.
8. Nadarajah R, Rajesh H, Wong KY, Faisal F, Yu SL. Live birth rates and safety profile using dydrogesterone for luteal phase support in assisted reproductive techniques. *Singapore Med J*. 2017;58(6):294–7.
9. Gardner DK, Weissman A, Howles CM. Textbook of Assisted Reproductive Techniques. 5th ed. CRC Press; 2018.
10. Liang YX, Liu L, Jin ZY, Liang XH, Fu YS, Gu XW, et al. The high concentration of progesterone is harmful for endometrial receptivity and decidualization. *Sci Rep*. 2018;8(1):712.
11. Palomba S, Santagni S, Sala GL. Progesterone administration for luteal phase deficiency in human reproduction: an old or new issue? *J Ovarian Res*. 2015;8:77.
12. de Ziegler D, Pirtea P, Andersen CY, Ayoubi JM. Role of gonadotropin-releasing hormone agonists, human chorionic gonadotropin (hCG), progesterone, and estrogen in luteal phase support after hCG triggering, and when in pregnancy hormonal support can be stopped. *Fertil Steril*. 2018;109(5):749–55.
13. Practice Committee of the American Society for Reproductive Medicine. The clinical relevance of luteal phase deficiency: a committee opinion. *Fertil Steril*. 2012;98(5):1112–7.
14. Jilma B, Kamath S, Lip GY. Antithrombotic therapy in special circumstances. I-pregnancy and cancer. *Bmj*. 2003;326(7379):37–40.
15. Zafardoust S, Jeddi-Tehrani M, Akhondi MM. Effect of administration of single dose GnRH agonist in luteal phase on outcome of ICSI-ET cycles in women with previous history of IVF/ICSI failure: A randomized controlled trial. *J Reprod Infertil*. 2015;16(2):96–101.
16. Ludwig M, Schwartz P, Babahan B, Katalinic A, Weiss JM, Felberbaum R, et al. Luteal phase support using either Crinone® 8% or Utrogest®: Results of a prospective, randomized study. *Eur J Obstet Gynecol Reprod Biolol*. 2002;103(1):48–52.
17. Shapiro D, Boostanfar R, Silverberg K, Yanushpolsky EH. Examining the evidence: progesterone supplementation during fresh and frozen embryo transfer. *Reprod Biomed Online*. 2014;29(Suppl 1):S1–14 quiz S15–S6.
18. Tournaye H, Sukhikh GT, Kahler E, Griesinger G. A Phase III randomized controlled trial comparing the efficacy, safety and tolerability of oral dydrogesterone versus micronized vaginal progesterone for luteal support in in vitro fertilization. *Hum Reprod*. 2017;32(5):1019–27.
19. Salehpour S, Tamimi M, Saharkhiz N. Comparison of oral dydrogesterone with suppository vaginal progesterone for luteal-phase support in in vitro fertilization (IVF): A randomized clinical trial. *Iran J Reprod Med*. 2013;11(11):913–8.

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