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Progestin as an Inhibitor of Premature Ovulation through LH Suppression in IVF

Joydeep Das, Banani Bindhani* and Sneha Maity

Department of Zoology, Dinabandhu Andrews College, Kolkata - 700084, West Bengal, India; bindhanibanani@gmail.com

Abstract

Progestin is a synthetic form of progesterone hormone. Progestin is used as a contraceptive pill. Progestin can suppress endogenous Luteinizing Hormone (LH) secretion from the pituitary. Premature ovulation in Assisted Reproductive Technology (ART)can be prevented by taking progestin. Progestin–Primed Ovarian Stimulation (PPOS) is now widely used for the treatment of infertility through IVF. Progestin pills are more effective than GnRH analogue for patients. Progestins are an excellent alternative to antagonists. PPOS is slightly more advantageous than the Controlled Ovarian Stimulation (COS) protocol. Progesterone regulates follicular growth through PI3K/AKT and MAPK signaling pathway.

Keywords: GnRH Analogue, IVF, Progestin, PPOS

1. Introduction

IVF is now the most common technique for the treatment of . Controlled Ovarian Stimulation (COS), using GnRH analogues, is practiced in the case of IVF. Progestin is a synthetic form of progesterone used in IVF as Progestin-Primed Ovarian Stimulation (PPOS) protocol. Induction of withdrawal bleeding is facilitated by progestin before infertility . Women with Polycystic Ovarian Syndrome (PCOS) have fertility-related problem and so they undergo IVF procedure. Excess LH secretion from pituitary causes multifollicle growth and premature. Premature ovulation gets crammed due to the use of progestin by way of suppression of luteinizing hormone (LH) from the pituitary. This is very important for successful outcomes of *in vitro* Fertilization (IVF) cycles for infertility treatment. In poor responders, PPOS exhibits better control in preventing LH surge than COS using GnRH antagonist. Use of GnRH analogues increase the risk of Ovarian Hyperstimulation Syndrome (OHSS) and formation of ovarian .

The complication in IVF is low but there are some problems associated with ovarian stimulation regimens, high estrogen levels, and Ovarian Hyperstimulation Syndrome. ThePPOS protocol was introduced in place of COS. PPOS protocol is slightly more advantageous than COS protocol. During ovarian stimulation, progesterone inhibits growth of the follicle.

2. Objective

2.1 Progestin as Oral Contraceptive Pill

In PCOS patients, menstrual bleeding occurs in an unregulated fashion. Administration of progestin regulates menses and helps to start the IVF cycle in proper way. Progestin or any oral contraceptive is used for pretreatment in PCOS patients. The progestin that was used for this pretreatment was either micronized progestin (200 mg/d) or dydrogesterone (20 mg/d). This progestin was taken for 6-10 days. Women having progestin-induced menses have higher level of estradiol and . Progestin-based ovarian stimulation protocol is highly successful in PCOS patients because progestin is an effective inhibitor of premature LH surge and it reduces

*Author for correspondence

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Oral contraceptive pills help to synchronize the follicles, induce oocyte retrieval and prevent LH surge. These pills are taken before gonadotropin stimulation in an IVF Birth control pills like progestin allows better response of ovary in IVF cycle. Progesterone soft capsule like utrogestan contains natural micronized progestin. This capsule induces luteal development during pregnancy. Taking utrogestan reduces the risk of congenital .

2.2 Progestin as an Inhibitor of Premature Ovulation

Progestin is synthetic form of progesterone. Progestin has progestogenic effect, and induces changes in estrogen secretion in the endometrium. These changes differ between different compounds and their different doses. Transformation dose is a dose for transformation of Progestin has also an antigonadotropic effect to inhibit premature ovulation. Table 1 shows ovulation inhibition dose and transformation dose of different .

2.3 Mechanism of Prevention of Premature Ovulation by Progestin

Premature LH surge causes premature ovulation which results in the ultimate rejection of that IVF , So it is necessary to prevent premature LH surge.

Progesterone has a stimulatory effect on gonadotropin secretion. High estradiol in late follicular phase induces LH surge. Progesterone may act as anantagonist to estrogen depending on hormone ratio and exposure. The interaction between progesterone and estradiol facilitates LH surge. Progestin stimulates progesterone receptors. When progesterone is released in higher amounts, it causes LH suppression and inhibits growth of Prolonged suppression of LH prevents premature ovulation. Progesterone has two receptors: A and B. Progesterone receptor A engages in inhibitory activity whereas progesterone receptor B engages in stimulatory . Figure 1engages the effects of normal and high progesterone levels on hypothalamo-pituitary-ovarian axis (HPO .

3. Comparison between PPOS Protocol and COS Protocol

Progestin-primed ovarian stimulation (PPOS) is a protocol in which progestin is used as a substitute form of GnRH analogue to facilitate LH suppression.

In COS protocol where GnRH antagonists are used, LH suppression is made transiently by competitive blocking of GnRH In the hypothalamus, inhibition of GnRH secretion is facilitated by progestin, if progestin is taken before estrogen-priming in PPOS In poor responders, PPOS exhibits better control in preventing LH surge than COS using GnRH PPOS protocol consumes high gonadotropin (462 IU) than PPOS protocol uses a freeze all strategy. Figure 2 depicts the difference between COS and PPOS .

3.1 Controlled Ovarian Stimulation (COS) or GnRH Agonist Long Protocol

In long GnRH agonist protocol during the menstrual cycle of women GnRH analogues are introduced into the women to desensitize pituitary secretion. On the grounds of antral follicle count (AFC), human Menopausal Gonadotropin (hMG) or FSH is injected intramuscularly or subcutaneously into women at 150-225 IU/day. For maturation of oocytes, human Chorionic Gonadotropin (hCG) is also injected into patient's body. Oocyte retrieval or Oocyte Pick Up (OPU)

Table 1. Ovulation inhibition dose and transformation dose of different progestin

Progestin	Ovulation inhibition dose (mg/day)	Transformation dose (mg/day)
Progesterone	300	200-300
Dydrogesterone	>30	10–20
Medroxyprogesterone acetate	10	5–10
Cyproterone acetate	1	1.0
Nomegestrol acetate	5.0	5.0
Norethisterone acetate	0.5	0
Levonorgestrel	0.05	0.15
Drospirenone	2.0	4-6

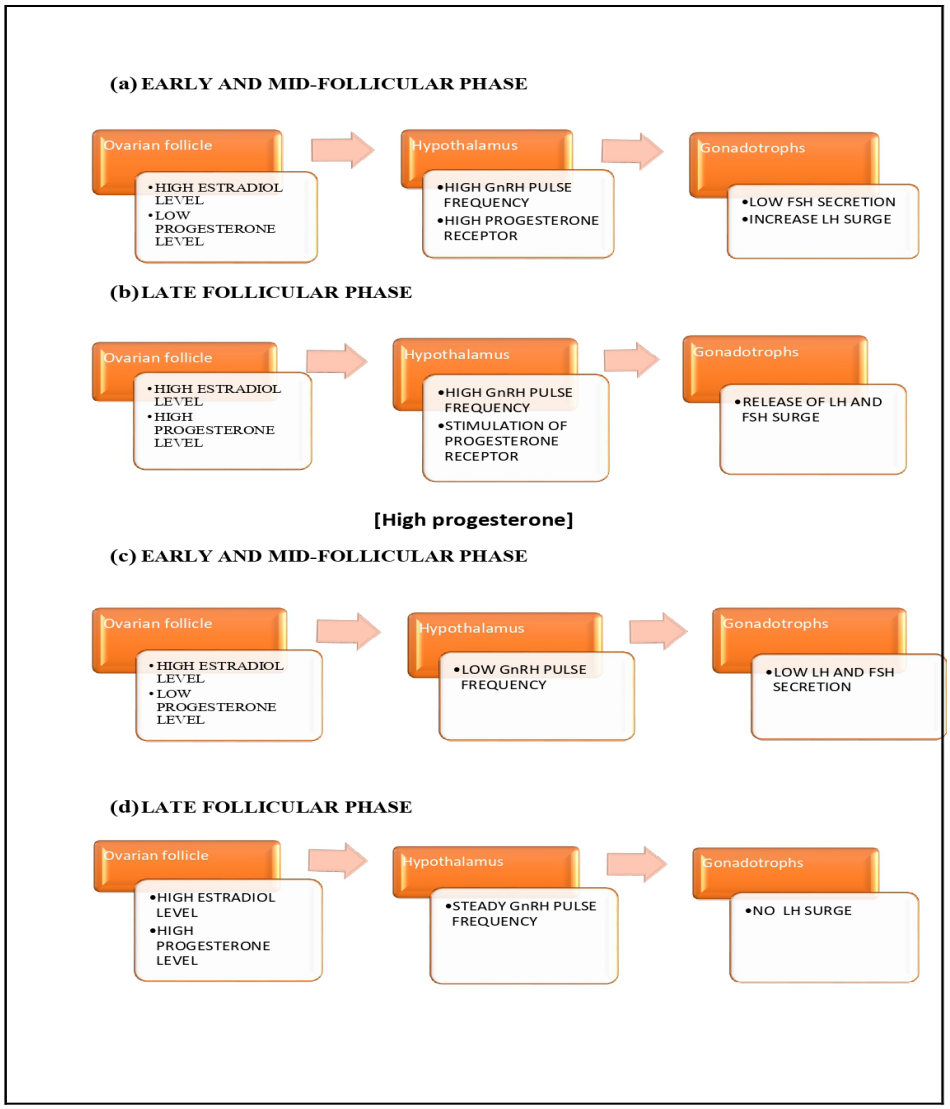

Figure 1. Effect of progesterone on hypothalamo-pituitary-ovarian axis.

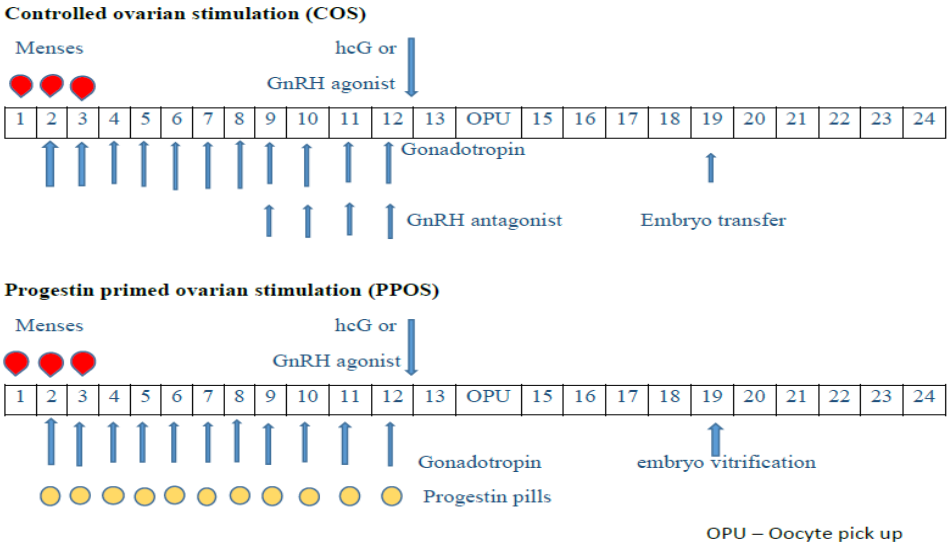

Figure 2. Comparison ofcontrolled ovarian stimulation (COS) and progestin-primed ovarian stimulation (PPOS).

is performed on day 14 of the cycle. Then, through ICSI (Intracytoplasmic sperm injection) or in a conventional way the oocytes are fertilized. Now embryos are graded as top quality embryos having good quality and containing 6-8 cells and some non-top quality embryos. The oocyte quality is determined by the presence of clear polar body 1 and the attachment level of cumulus cells. After incubation, top quality embryos are transferred to the uterus of women on day 19 for proper implantation. Thereafter, pregnancy confirmation of that women will be .

3.2 Progestin-Primed Ovarian Stimulation (PPOS) Protocol

During ovarian stimulation through PPOS, progestin, say Medroxy Progesterone Acetate (MPA) is administered through oral route at 10mg/day dose. Ovarian response is monitored through transvaginal ultrasound examination.

Human Menopausal Gonadotropin (hMG) is also given but in a higher dose than COS, 462 IU/ day. Like previous protocol, here also hCG is given to activate maturation of oocytes. Hereafter, oocyte retrieval occurs on day 14 day. The oocytes are fertilized through IVF or ICSI. The top-quality embryos are then cryopreserved with liquid nitrogen or subjected to vitrification. These embryos are frozen using ethylene glycol, propylene glycol, or sucrose as cryoprotectant. After vitrification, the thawing/warming is done. Then these frozen embryos are transferred to the uterus of women in the next .

4. Effect of PPOS on Cumulative Birth Rate

GnRH analogues can also prevent LH surge as well as premature ovulation in IVF. But sometimes inadequate LH suppression by GnRH analogues causes premature ovulation and results in poor oocyte quality and so lower rate of pregnancy. Also, these drugs are very expensive and even it makes IVF process more complicated. Use of GnRH analogues increases the risk of Ovarian Hyperstimulation Syndrome (OHSS) in .

On the other side, progestin is especially useful, more effective and less expensive than GnRH analogues. Progestin results in increased pregnancy rates compared to GnRH analogues. Progestin-Primed Ovarian Stimulation (PPOS) causes low cumulative birth rates and increased pregnancy time compared to GnRH agonist in women with normal ovarian reserve. PPOS can be helpful for high responders and not for them who have a high probability of getting OHSS. PPOS protocol is very efficient in newborn outcome than GnRH .

5. Using of Dydrogesterone in Flexible PPOS Protocol

Dydrogesterone is used in PPOS protocol and it is very effective in suppressing LH surge. In the beginning of PPOS protocol with dydrogesterone, administration

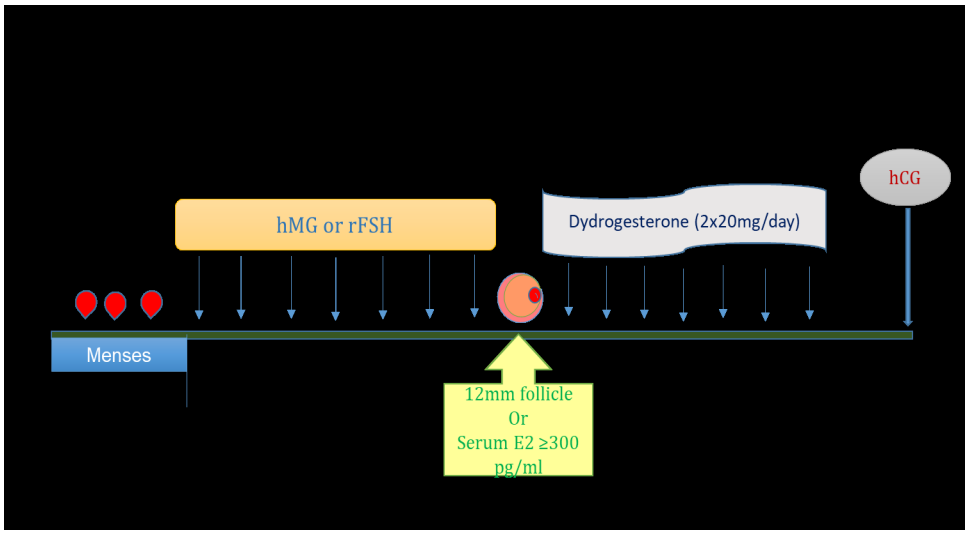

Figure 3. Flexible PPOS protocol with dydrogesterone.

of gonadotropin (150-225 IU) ie., human Menopausal Gonadotropin (hMG) or recombinant follicle stimulating hormone (rFSH) is done. After that, when dominant follicle reaches 12mm diameter or serum estradiol level goes above 300pg /mL, then dydrogesterone is administered at the dose of 2x20 mg/day.

Oocyte maturation is kicked to start with choriogonadotropin alpha (250 µg) and GnRH antagonist when two other follicles reach 18mm diameter. After 36 hours, oocyte retrieval is performed. Then, through vitrification, oocytes are cryopreserved. Figure 3 depicts the flexible PPOS protocol with . Dydrogesterone in flexible PPOS protocol gives almost same results as GnRH antagonist protocol. Dydrogesterone effectively suppresses pituitary for longer .

6. Progestin Advantage Over GnRH Antagonist

The Controlled Ovarian Stimulation (COS) protocol makes use of GnRH antagonist along with GnRH agonist. Either of them also prevents LH surge as well as premature ovulation. But these drugs are cost-intensive for the patients and produce side effects such as hot flashes, headache, insomnia, vaginal dryness, etc. The route of administration of such drugs also causes someIn case of ART, embryo freezing is a common procedure to practice. At the present progestin is remarkably effective in ART. Progestin is easily administered through oral route. The lower cost of progestin makes it affordable for and it is more flexible than initiating an ultrasound**.** Medroxyprogesterone 17-acetate (MPA) is a type of progestin having high progestational activity and antigonadotropic activity.

Medroxyprogesterone 17-acetate (MPA) at10 mg MPA/ day is sufficient to inhibit premature ovulation. MPA is effective in ovarian stimulation and lowers the risk of Ovarian Hyperstimulation Syndrome (OHSS) in .

Ganirelix is a GnRH antagonist used in ART to control ovulation. Administration of ganirelix is done by injection of 250 µg per day. Ganirelix has a negative effect on child. It increases the chance of congenital malformation (birth defect of a babylike hydrocephalus, Beckwith-Wiedemann syndrome, asymmetric skull and supernumerary digit/finger.

7. Effect of Progesterone on Follicle Growth through PI3K/ AKT and MAPK Signaling Pathway

During ovarian stimulation, progesterone inhibits growth of follicles. On the other side, FSH induces multiple follicular growth. In the presence of FSH, progesterone regulates follicular growth through PI3K/ AKT and MAPK signalling. In PPOS protocol, the number of follicles and mature oocytes would be decreased, but administration of hMGat a high dose can restore follicle .

7.1 PI3K/AKT Signaling Pathway

FSH stimulates PI3K/AKT signalling pathway. FOXO (Forkhead box) is a transcription factor and a negative regulator of PI3K/AKT signaling pathway. Activated (CDKI /Cyclin dependent kinase inhibitor) inhibits CDK complexes and thus helps FSH to become unphosphorylated, thereby ceasing cell .

FSH phosphorylates AKT and FOXO, which further causes inactivation of and so granular cells can There is a possibility that the presence of progesterone inhibits this signalling pathway through suppression in phosphorylated AKT and CDK and that ultimately induces activation of Therefore, proliferation of granular cells Figure 4 represents the action of progesterone on PI3K/AKT signaling .

7.2 MAPK Signalling Pathway

Down-regulation of Protein Kinase C (PKC) alpha, Raf1, and its substrate MEK1occursin presence of progesterone. Phosphorylation of the downstream target genes or transcription factors such as serum response factor (SRF) and Mycare significantly reduced**.** Thus, progesterone inhibits follicle growth through MAPKAlthough FSH stimulates MAPK signalling cascade and, therefore, induces granular cell proliferation and, ultimately, follicle growth. Figure 5 shows the action of progesterone on MAPK signalling.

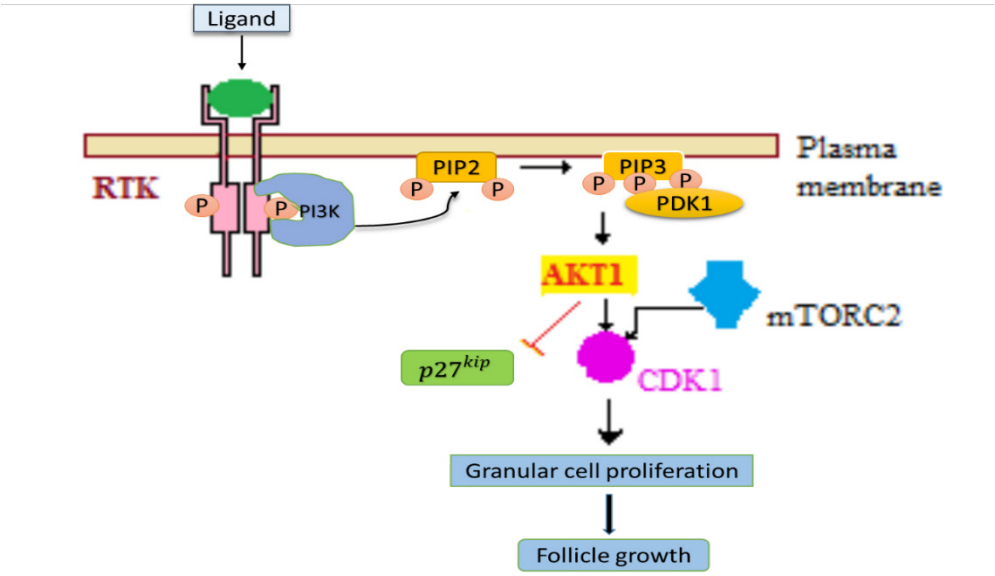

Figure 4. Regulation of follicle growth by action of progesterone and FSH through PI3K/AKT signalling pathway. [RTK- Receptor tyrosine kinase; PI3K – Phosphoinositide 3-kinase ; PIP2 – Phosphatidyl inositol 3,4- bisphosphate; PIP3 – Phosphatidyl inositol 3,4,5 – triphosphate; PDK1 – Phosphoinositide - dependent protein kinase 1 and mTORC2 – Mammalian target of rapamycin complex 2].

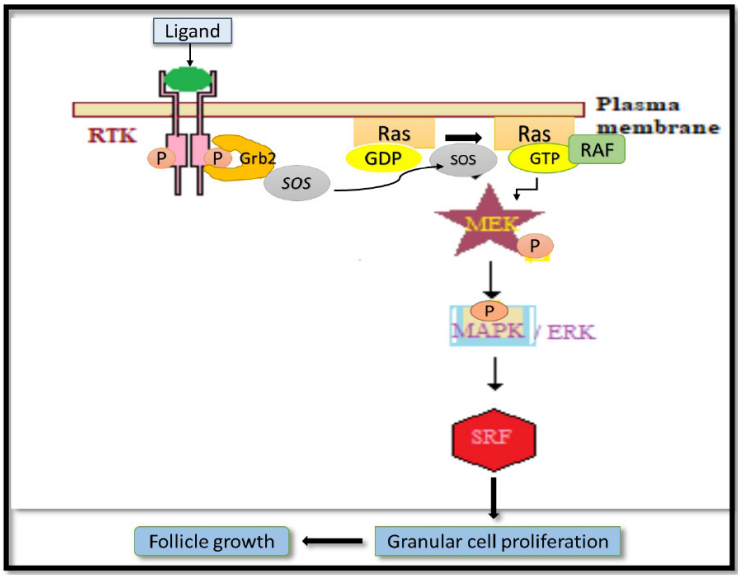

Figure 5. Regulation of follicle growth by action of progesterone and FSH through MAPK signaling pathway. [RTK- Receptor tyrosine kinase; MAPK – Mitogen activated protein kinase; RAF (MAP-kinase-kinase-kinase); MEK (MAP-kinase-kinase); ERK – (MAP kinase)].

7.3 Application of PPOS in Fertility Preservation

PPOS is particularly useful in fertility preservation cases. During the ovarian stimulation, patients with thrombocytopenia (uterine bleeding) and even without thrombocytopenia also, undergo random-start PPOS because this process cannot be disrupted by menstruation. In breast cancer, fertility preservation is made by Menopausal hormone replacement therapy contains some progestins like levonorgestrel, levonorethisterone acetate and medroxyprogesterone acetate which increase the chances of inducing breast cancer. Letrozole, an

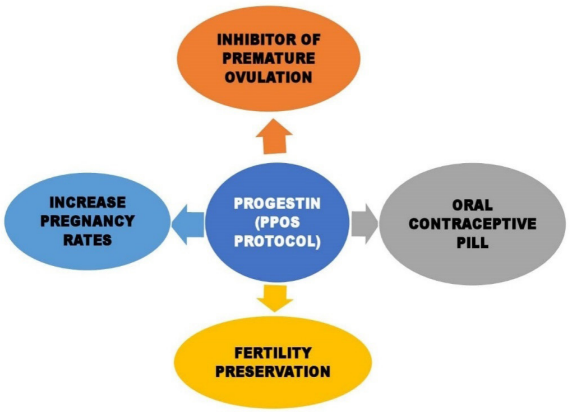

Figure 6. Schematic representation of future perspective of progestin.

aromatase inhibitor, is effective in estrogen receptor-positive breast But Progestin like dydrogesterone is very safe in the context of breast cancer. In case of breast cancer, the dosage of dydrogesterone would be decreased to 10mg/d if the level of LH is suppressed below 1.0 mIU/.

8. Conclusion

Progestin is a potent inhibitor of premature ovulation. It is more effective than GnRH antagonist. Progestin is safer for patients than GnRH antagonist. Progestin-Primed Ovarian Stimulation protocol (PPOS) can be a very good option for the future. Random-start PPOS is safe and more effective than random-start GnRH antagonist, and the use of PPOS protocol can make IVF cycle more successful. PPOS protocol undergoes freeze-all strategy. Embryo freezing gives better success rates in IVF. Progestin like Medroxyprogesterone 17-acetate (MPA)is effective in suppressing LH surge. Use of progestin in IVF cycle increases the pregnancy rate.

Figure 6 highlights the future perspective of progestin.

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