Original Article

Comparing Progesterone Primed Ovarian Stimulation (PPOS) to GnRH Antagonist Protocol in Oocyte Donation Cycles

Rupali Khaparde Khurana, Vyshnavi Rao, Chaitra Nayak, Gautham T Pranesh, Kamini A. Rao

Department of Reproductive Medicine, Milann Fertility Centre, Bengaluru, Karnataka, India

Abstract

Background: Progesterone-primed ovarian stimulation (PPOS) protocol is based on the principle of preventing pre-mature luteinising hormone surge during ovarian stimulation using progesterone. **Aims:** In this study, we aimed to compare the cost-effectiveness of PPOS over GnRH antagonist cycles in oocyte donor cycles where freeze all is a norm. **Settings and Design:** It is a prospective cohort study with 130 participants. **Materials and Methods:** We included all women undergoing oocyte donation using PPOS protocol and antagonist protocol at our centre. Fifty-seven belonged to the PPOS group and were given medroxyprogesterone acetate (MPA) and 73 belonged to the GnRH antagonist group who received cetrorelix. The primary outcome was the number of mature oocyte retrieved at OPU and the cost involved per stimulation cycle. **Statistical Analysis Used:** For normally distributed observations, we used *t*-test, and for the variables of non-normal distribution, Mann–Whitney *U*-test was used. The significance was accepted for $P < 0.05$. **Results:** The baseline clinical characteristics of the donors were comparable with a mean age of 25.42 ± 2.90 years, body mass index of 24.00 ± 4.00 kg/m^2 and antral follicle count of 18.63 ± 5.23. The duration of stimulation was similar in both the groups as well as the total gonadotropin dose required was not significantly different. The number of mature oocytes retrieved was same in both the groups (10.41 ± 4.04 with antagonist and 10.25 ± 3.23 with PPOS, $P = 0.964$). There were no reported cases of severe ovarian hyperstimulation syndrome (OHSS) in any of the groups. The incidence of mild-to-moderate OHSS in the antagonist group was 5.4% and in the PPOS group was 3.6%, and the difference was not significant ($P = 0.69$). The cost per mature oocyte (M2) was significantly higher in the antagonist protocol in comparison to the PPOS protocol (INR 9485.69 ± 5751.11 vs. Rs. 5945.86 ± 2848.59, respectively, $P < 0.001$). **Conclusion:** Our study identifies PPOS protocol using MPA to be more cost-effective and patient-friendly than conventional GnRH antagonist protocol in oocyte donor cycles.

Keywords: *Cetrorelix, controlled ovarian stimulation, cost-effective analysis, mature oocytes, medroxyprogesterone acetate, oocyte donation, PPOS*

Introduction

High levels of oestrogen can cause the pre-mature rise of luteinising hormone (LH) in *in vitro* fertilisation cycles. The drugs used to prevent the LH surge have progressed from GnRH agonists to GnRH antagonists, which offer benefits in terms of a later starting point for dosing, shorter duration of stimulation, a lesser dose of gonadotropins and safety in terms of prevention of

Address for correspondence: Dr. Rupali Khaparde Khurana, 18A/6C, Vibhav Nagar Road, Agra - 282 001, Uttar Pradesh, India.
E-mail: drrup_2222@gmail.com

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ovarian hyperstimulation syndrome (OHSS).[1] GnRH antagonist protocol is the most commonly used protocol presently, but it is associated with disadvantages such as the discomfort of taking daily injections, maintenance of the cold chain and the high cost.[2,3] In recent times, there has been a resurgence in interest in low-cost, patient-friendly protocols with similar or better efficacy and safety than the GnRH antagonist protocol.

Progesterone is an effective agent to prevent LH surge and has no impact on the number of oocytes collected or the quality of the embryos obtained.[4] A few studies have compared GnRH antagonist protocols to newer progesterone-primed stimulation (PPOS) protocols. The downside of using PPOS protocol is the requirement for a frozen transfer cycle as the endometrium becomes out of phase. This makes it a protocol of choice in cycles where a freeze-all strategy is adopted, like in oocyte donor cycles, fertility preservation, PGT cycles, pooling cycles and in women at risk of OHSS.[5]

In this study, we aimed to find the cost-effectiveness of PPOS over GnRH antagonist cycles in oocyte donor cycles where freeze all is a norm.

Materials and Methods

It was a prospective cohort study. The study was designed as a pilot study. The study was based on calculation that a sample size of approximately 55 subjects per group would be required to estimate a mean difference of 1 mature (M2) oocyte assuming a population variance of 3.5 with a power of 80%. $P < 0.05$ was deemed to be statistically significant.

It was performed between January 2020 and June 2021 in a tertiary care fertility centre. The study adheres to the principles of the Helsinki Declaration (2013) and is approved by the institutional ethics committee (081/I/21/05). Written informed consent was obtained from all subjects before starting the ovarian stimulation. All participants have provided consent for the use of anonymised data for research or educational purposes.

Screening of voluntary oocyte donors found eligible to donate eggs according to the national guidelines was done based on age, medical history, transvaginal ultrasound and hormonal levels of follicle-stimulating hormone (FSH), LH, oestrogen and progesterone on the 2nd day of their periods.

Women between 18 and 35 years, with normal-appearing ovaries and antral follicle count (AFC) of more than 10, were enrolled. Cycles with a suboptimal response or cancelled due to other reasons before egg pickup were excluded. Ovarian stimulation was started on the 2nd day of menses with recombinant FSH (Gonal-F, Merck). The initial dose was decided based on age, AFC and body mass index (BMI). In the PPOS group, tablet medroxyprogesterone acetate (MPA) (Meprate, Serum Institute of India) 10 mg once daily was started from the 2nd day of menses and continued till the day of ovulation trigger. In the GnRH antagonist group, injection cetrotide 0.25 mg (Merck Serono, Germany) subcutaneously was administered once subcutaneously daily from the day when the leading follicle is of 12–13 mm or E2 level of more than 300 pg/mL (flexible antagonist) till the day of the ovulation trigger.

The cycle was monitored with transvaginal ultrasonography and serum oestradiol levels according to the response. On the day of trigger, peak serum oestradiol, LH and progesterone were measured. In all the cycles, GnRH agonist trigger 0.2 mg (Decapeptyl, Ferring, Germany) subcutaneously was used and after 35 h ovum pickup was performed.

The primary outcome of this study was the cost-effectiveness of the two protocols which was calculated by taking into account the cost of medication involved per mature oocyte in each group. The secondary outcomes were the total number of days of stimulation, the total dose of gonadotropins, the total dose of antagonist, the total number of dominant follicles on the day of trigger and incidence of OHSS.

Statistical analysis

For the continuous outcomes, we used a *t*-test of the observations in each group that were normally distributed. Wilcoxon–Mann–Whitney *U*-test was used for the variables of non-normal distribution such as hormone levels. The significance was accepted for $P < 0.05$. All data were analysed using the SPSS (v25.0, IBM Corp. Released 2017.Armonk, NY).

Results

Study groups and baseline characteristics

Between January 2020 and June 2021, 130 donor participants were enrolled, of which 57 underwent ovulation stimulation using PPOS protocol and 73 via antagonist protocol. The cohort consisted of young women having normal BMI and AFC [Table 1]. The baseline clinical characteristics in both the groups were comparable [Table 2]. Age, BMI, AFC and basal endocrine parameters were similar in both the groups ($P > 0.05$).

Stimulation characteristics

The starting dose of gonadotropin, duration of stimulation and the levels of oestrogen, LH and progesterone on the day of the trigger were comparable in both the

groups [Table 3]. Peak LH and peak progesterone values were not significantly different between the antagonist and the PPOS groups (1.66 ± 1.35 vs. 1.82 ± 1.68, $P = 0.906$, and 1.15 ± 0.78 vs. 1.29 ± 1.22, $P = 0.601$).

Outcome

There were no significant differences between the antagonist and PPOS groups in the number of follicles >16 mm on the trigger day (16.24 ± 5.80 vs. 14.62 ± 4.84, respectively, $P = 0.184$). The numbers of total oocytes and mature oocytes were similar in the antagonist and PPOS groups (15.00 ± 6.47 vs. 13.11 ± 4.66, respectively, $P = 0.107$, and 10.41 ± 4.04 vs. 10.25 ± 3.23, respectively, $P = 0.964$) [Table 4].

There were no reported cases of severe OHSS in both the groups. The incidence of mild-to-moderate OHSS was 5.4% in the antagonist group and 3.6% in the PPOS group ($P = 0.69$), and the difference was not found to be significant [Table 5].

Cost-effective analysis

The total cost of gonadotropin used in the antagonist was higher (INR 64824.58 ± 33856.89) than PPOS protocol (INR 54,900.09 ± 15,532.43), but the difference was not statistically significant ($P = 0.125$). Considering the additional cost of antagonist (INR 18,044.61 ± 3933.95) and MPA (INR 59.79 ± 7.05) in respective protocols, the total cost of the cycle in the antagonist protocol was significantly higher than the PPOS protocol (INR 84,062.05 ± 35135.04 vs. Rs. 54,958.91 ± 15,534.28, respectively, $P < 0.001$) [Table 6].

The cost per mature oocyte was higher in the antagonist protocol group in comparison to the PPOS protocol (INR 9485.69 ± 5751.11 vs. Rs. 5945.86 ± 2848.59, respectively, $P < 0.001$).

Discussion

The demand for oocyte donation has been increasing, owing to its use in treating age-related diminished reserve.[6,7] An ideal donor stimulation cycle should be cost-effective and safe as the donors have an increased risk of ovarian hyperstimulation. The result of our study indicates that PPOS is as safe and effective as antagonist protocol in donor cycles with the added benefit of oral administration at a lower cost. The safety of the PPOS protocol lies in the fact that the GnRH agonist trigger can be used along with the freeze-all strategy. Progesterone acts at the level of the hypothalamus; therefore, the GnRH agonist can act as a trigger at the pituitary level.[8]

The rationale of PPOS is based on the fact that progesterone (P4) regulates GnRH secretion by acting directly at the level of hypothalamus, but there is a lack of progesterone receptors on GnRH neurons.[9] P4 acts through its receptors present on KNDY neurons which are responsible to integrate the steroid action to modulate GnRH secretion.[10] The timing of P4 administration in relation to oestradiol (E2) priming decides its effect on LH surge. If P4 is administered before or concurrent with E2, then it inhibits pre-ovulatory LH surge, and this

Table 1: Baseline parameters

	Mean±SD
Age (years)	25.42±2.90
BMI (kg/m^2)	24.00±4.00
AFC	18.63±5.23

BMI=Body mass index, AFC=Antral follicle count, SD=Standard deviation

Table 2: Comparison of baseline parameters amongst the two protocols

Parameters	Protocol		*P*
	Antagonist (*n*=74)	PPOS (*n*=56)	
Age (years)	25.61±3.02	25.16±2.75	0.380[a]
BMI (kg/m^2)	24.26±4.75	23.65±2.70	0.359[a]
AFC	17.86±5.32	19.64±4.97	0.083[b]
FSH	5.67±1.62	6.15±1.50	0.081[a]
LH	6.54±3.20	6.68±2.42	0.550[b]
E2	35.02±14.55	37.80±10.12	0.091[b]

[a]*t*-test, [b]Wilcoxon–Mann–Whitney *U*-test. BMI=Body mass index, AFC=Antral follicle count, FSH=Follicle-stimulating hormone, E2=Oestradiol, LH=Luteinising hormone

Table 3: Comparison of stimulation characteristics amongst the two protocols

Parameters	Protocol		*P*
	Antagonist (*n*=74)	PPOS (*n*=56)	
Start dose	227.03±51.23	240.85±67.61	0.231[b]
Days of stimulation	9.97±0.95	9.96±1.17	0.849[b]
Visits for USG	4.24±0.52	4.34±0.58	0.276[b]
Number of blood test	8.24±0.52	8.34±0.58	0.276[b]
Total dose gonadotrophin	2674.84±692.97	2612.59±738.62	0.694[b]
Peak E2	4681.32±2733.41	4369.89±2596.80	0.378[b]
Peak LH	1.66±1.35	1.82±1.68	0.906[b]
Peak P4	1.15±0.78	1.29±1.22	0.601[b]

[b]Wilcoxon–Mann–Whitney *U*-test. USG=Ultrasonography, E2=Oestradiol, P4=Progesterone, LH=Luteinising hormone

Table 4: Association between protocol and outcome

Parameters	Protocol		*P*
	Antagonist (*n*=74)	PPOS (*n*=56)	
Follicle	16.24±5.80	14.62±4.84	0.184[b]
Oocyte	15.00±6.47	13.11±4.66	0.107[b]
M2	10.41±4.04	10.25±3.23	0.964[b]

[b]Wilcoxon–Mann–Whitney *U*-test. M2=Mature

action is utilised in a PPOS protocol.[11] The previous studies have used different types of progesterone in the PPOS protocol, such as medroxyprogesterone (MPA), utrogestan, dydrogesterone and desogestrel. The pregnancy rate and live birth rate were found to be comparable amongst them.[12-14] In our study, we have used MPA as the progesterone due to its low cost, once-a-day dosing, good bioavailability and no interference with the monitoring of endogenous progesterone levels.[7] There is a concern regarding MPA being teratogenic in animals, but as frozen embryo transfer is performed in all cycles, there is no exposure to the embryo because the therapeutic window is around 4 weeks and the biological half-life is only 40–60 h.[4,15]

Both the doses of MPA, 4 and 10 mg per day, were comparable in terms of the number of oocytes retrieved and pregnancy outcome.[16] We have used MPA at 10 mg per day because of its ease of availability.

We found similar stimulation characteristics in both the groups. There was no difference in terms of the total dose of gonadotrophin and duration of stimulation with similar findings being reported by other studies.[13,17-19]

The outcome of our study shows a comparable number of dominant follicles on the day of trigger, the total number of oocytes and the number of mature oocytes obtained. Similar findings were asserted by Beguería *et al*., Giles *et al*. and Guan *et al*. in their respective randomised controlled trials (RCTs) and meta-analysis and Martinez *et al.* (2019) in their retrospective study.[13,17-19] The retrospective study by Yildiz *et al*. had reported more total number of oocytes and several mature oocytes in the PPOS group.[20] This finding has been explained by the fact that flexible PPOS protocol was used in their study, so there was an absence of pituitary suppression in the early follicular phase.

The PPOS protocol was as safe as antagonist protocol in terms of OHSS similar to other studies.[13,20]

There were no differences in terms of the total number of visits for USG, number of hormonal tests done, duration of stimulation and total dose of gonadotropin used between the two groups. The only difference was the use of cetrorelix injection in the antagonist group and tablet MPA in the PPOS arm which resulted in the difference in the cost of the cycle. All the cycles being donor cycles, where freeze all is a norm, the cost of freezing was not taken into account while calculating the cost difference in two protocols. To incorporate the cost-effectiveness, the cost per mature oocyte was calculated and it was still significantly higher in antagonist protocol in comparison to the PPOS protocol. Hence, PPOS is found to be a highly cost-effective method in a donor stimulation cycle. Evans *et al*. had also confirmed progestins to be more cost-effective per live birth compared with antagonist cycles in planned freeze-all cycles.[21]

The strength of our study lies in the prospective design with the use of the donor population, who are fertile women, so can be considered the gold standard for comparing stimulation protocol. This is the first study using PPOS protocol in donor cycles in the Indian population.

The limitations of our study are that we have compared the number of mature oocytes as the outcome and have not extended the outcome up to live birth. The reason was the deferment of a majority of the embryo transfer cycle because of the ongoing COVID-19 pandemic during most of the study period. The second limitation is the non-randomised design and small sample size of the study.

The majority of studies have proven that the live birth rate of PPOS and the antagonist protocol were comparable.[7,18,20,22] One of the RCTs by Beguería *et al*. reported a lower clinical pregnancy rate with PPOS protocol as compared with the GnRH antagonist cycle, but still, there was no statistical difference in

Table 5: Comparison of incidence of ovarian hyperstimulation syndrome amongst two protocols

Parameters	Protocol		*P*
	Antagonist (*n*=74), *n* (%)	PPOS (*n*=56), *n* (%)	
Mild/moderate OHSS	4 (5.4)	2 (3.6)	0.699[c]

[c]Fisher's exact test. OHSS=Ovarian hyperstimulation syndrome

Table 6: Comparison of cost-effectiveness of the two protocols

Parameters	Protocol		*P*
	Antagonist (*n*=74)	PPOS (*n*=56)	
Cost of gonadotropin	64,824.58±33,856.89	54,900.09±15,532.43	0.125[b]
Antagonist	18,044.61±3933.95	-	-
MPA	-	59.79±7.05	-
Total cost***	84,062.05±35,135.04	54,958.91±15,534.28	<0.001[b]
Total cost/M2 oocyte***	9485.69±5751.11	5945.86±2848.59	<0.001[b]

***Significant at $P<0.05$, [b]Wilcoxon–Mann–Whitney *U*-test. M2=Mature, MPA=Medroxyprogesterone acetate

the live birth rate between the groups.[17] La Marca *et al*. confirmed a similar rate of euploid blastocyst formation in both the PPOS and antagonist protocols.[23] The meta-analysis by Zolfaroli *et al*. asserted that both the groups had agonist protocol with similar rates of congenital malformations and low birth weight but with low quality of evidence.[24] As PPOS is a newer protocol, further evidence regarding live birth and neonatal outcome is still weak and further studies are required.

Conclusion

Our study finds PPOS protocol using MPA to be more cost-effective and patient-friendly with similar outcomes in terms of mature oocytes and incidence of OHSS in oocyte donor cycles. However, further research is needed for live birth rate and neonatal outcomes.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Data availability statement

The data set used in the current study is available on request.

References

1. Homburg R. Ovulation Induction and Controlled Ovarian Stimulation: A Practical Guide 1st ed. London: CRC Press; 2005. p. 85.
2. Huirne JA, Homburg R, Lambalk CB. Are GnRH antagonists comparable to agonists for use in IVF? Hum Reprod 2007;22:2805-13.
3. Wang R, Lin S, Wang Y, Qian W, Zhou L. Comparisons of GnRH antagonist protocol versus GnRH agonist long protocol in patients with normal ovarian reserve: A systematic review and meta-analysis. PLoS One 2017;12:e0175985.
4. Massin N. New stimulation regimens: Endogenous and exogenous progesterone use to block the LH surge during ovarian stimulation for IVF. Hum Reprod Update 2017;23:211-20.
5. La Marca A, Capuzzo M. Use of progestins to inhibit spontaneous ovulation during ovarian stimulation: The beginning of a new era? Reprod Biomed Online 2019;39:321-31.
6. Kawwass JF, Monsour M, Crawford S, Kissin DM, Session DR, Kulkarni AD, *et al.* Trends and outcomes for donor oocyte cycles in the United States, 2000-2010. JAMA 2013;310:2426-34.
7. Martinez F, Racca A, Rodríguez I, Polyzos NP. Ovarian stimulation for oocyte donation: A systematic review and meta-analysis. Hum Reprod Update 2021;27:673-96.
8. Harris TG, Dye S, Robinson JE, Skinner DC, Evans NP. Progesterone can block transmission of the estradiol-induced signal for luteinizing hormone surge generation during a specific period of time immediately after activation of the gonadotropin-releasing hormone surge-generating system. Endocrinology 1999;140:827-34.
9. Le WW, Attardi B, Berghorn KA, Blaustein J, Hoffman GE. Progesterone blockade of a luteinizing hormone surge blocks luteinizing hormone-releasing hormone Fos activation and activation of its preoptic area afferents. Brain Res 1997;778:272-80.
10. Wakabayashi Y, Nakada T, Murata K, Ohkura S, Mogi K, Navarro VM, *et al.* Neurokinin B and dynorphin a in kisspeptin neurons of the arcuate nucleus participate in generation of periodic oscillation of neural activity driving pulsatile gonadotropin-releasing hormone secretion in the goat. J Neurosci 2010;30:3124-32.
11. He W, Li X, Adekunbi D, Liu Y, Long H, Wang L, *et al.* Hypothalamic effects of progesterone on regulation of the pulsatile and surge release of luteinising hormone in female rats. Sci Rep 2017;7:8096.
12. Guo H, Li J, Shen X, Cong Y, Wang Y, Wu L, *et al.* Efficacy of different progestins in women with advanced endometriosis undergoing controlled ovarian hyperstimulation for *in vitro* fertilization-a single-center non-inferiority randomized controlled trial. Front Endocrinol (Lausanne) 2020;11:129.
13. Martínez F, Rodriguez-Purata J, Clua E, Garcia S, Coroleu B, Polyzos N. Ovarian response in oocyte donation cycles under LH suppression with GnRH antagonist or desogestrel progestin: Retrospective and comparative study. Gynecol Endocrinol 2019;35:884-9.
14. Yu S, Long H, Chang HY, Liu Y, Gao H, Zhu J, *et al.* New application of dydrogesterone as a part of a progestin-primed ovarian stimulation protocol for IVF: A randomized controlled trial including 516 first IVF/ICSI cycles. Hum Reprod 2018;33:229-37.
15. Johansson ED, Johansen PB, Rasmussen SN. Medroxyprogesterone acetate pharmacokinetics following oral high-dose administration in humans: A bioavailability evaluation of a new MPA tablet formulation. Acta Pharmacol Toxicol (Copenh) 1986;58:311-7.
16. Dong J, Wang Y, Chai WR, Hong QQ, Wang NL, Sun LH, *et al.* The pregnancy outcome of progestin-primed ovarian stimulation using 4 versus 10 mg of medroxyprogesterone acetate per day in infertile women undergoing *in vitro* fertilisation: A randomised controlled trial. BJOG 2017;124:1048-55.
17. Beguería R, García D, Vassena R, Rodríguez A. Medroxyprogesterone acetate versus ganirelix in oocyte donation: A randomized controlled trial. Hum Reprod 2019;34:872-80.
18. Giles J, Alama P, Gamiz P, Vidal C, Badia P, Pellicer A, *et al.* Medroxyprogesterone acetate is a useful alternative to a gonadotropin-releasing hormone antagonist in oocyte donation: A randomized, controlled trial. Fertil Steril 2021;116:404-12.
19. Guan S, Feng Y, Huang Y, Huang J. Progestin-Primed ovarian stimulation protocol for patients in assisted reproductive technology: A meta-analysis of randomized controlled trials. Front Endocrinol (Lausanne) 2021;12:702558.
20. Yildiz S, Turkgeldi E, Angun B, Eraslan A, Urman B, Ata B. Comparison of a novel flexible progestin primed ovarian stimulation protocol and the flexible gonadotropin-releasing hormone antagonist protocol for assisted reproductive technology. Fertil Steril 2019;112:677-83.
21. Evans MB, Parikh T, DeCherney AH, Csokmay JM, Healy MW, Hill MJ. Evaluation of the cost-effectiveness of ovulation suppression with progestins compared with GnRH analogs in assisted reproduction cycles. Reprod Biomed Online 2019;38:691-8.
22. Kuang Y, Chen Q, Fu Y, Wang Y, Hong Q, Lyu Q, *et al.* Medroxyprogesterone acetate is an effective oral alternative for preventing premature luteinizing hormone surges in women

undergoing controlled ovarian hyperstimulation for *in vitro* fertilization. Fertil Steril 2015;104:62-70.

23. La Marca A, Capuzzo M, Sacchi S, Imbrogno MG, Spinella F, Varricchio MT, *et al.* Comparison of euploidy rates of blastocysts in women treated with progestins or GnRH antagonist to prevent the luteinizing hormone surge during ovarian stimulation. Hum Reprod 2020;35:1325-31.
24. Zolfaroli I, Ferriol GA, Mora JH, Cano A. Impact of progestin ovarian stimulation on newborn outcomes: A meta-analysis. J Assist Reprod Genet 2020;37:1203-12.