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Original Research Article

A randomized study comparing flexible PPOS with flexible GnRH antagonist protocol in IVF outcomes

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ABSTRACT

Background: To compare clinical efficacy of flexible PPOS and flexible GnRH antagonist protocol in ART.
Methods: A prospective randomized controlled study was conducted at RIDGE IVF Centre, Delhi, from July 2024 to June 2025. 100 women with normal ovarian reserve, aged 21–40 years, undergoing IVF/ICSI were randomly assigned to Group A (fPPOS, n=50) or Group B (flexible GnRH antagonist, n=50). Primary outcomes were number of oocytes retrieved, mature oocytes (MII), embryo formation, embryo quality on day 3 and day 5. Gonadotropin dosage, stimulation duration and clinical pregnancy rates were secondary outcomes.
Results: The two groups shared comparable baseline characteristics, including age, BMI, type of infertility and infertility duration. Although day 2 FSH levels were lower in Group A, serum AMH and AFC levels were comparable in both groups. The number of oocytes retrieved, MII oocytes and embryos formed were comparable ($p>0.05$). In either protocol, there were no instances of premature luteinization. On day 3 and day 5, neither the quality/distribution of the embryos differed significantly ($p>0.05$). Both groups had comparable clinical pregnancy rates ($p=1.0$) and β-hCG positivity rates (50 percent vs. 42 percent, $p=0.42$). There were no significant differences in duration of stimulation or total dose of gonadotropin used. No cases of OHSS were reported.
Conclusions: In IVF cycles, flexible PPOS and flexible GnRH antagonist protocols have comparable clinical and embryological outcomes. Flexible PPOS is a viable, patient-friendly alternative for frozen- embryo transfer cycles.

Keywords: ART, Flexible PPOS, Flexible GnRH antagonist, Normoresponders

INTRODUCTION

Protocols for ovarian stimulation are an essential component to in-vitro fertilization (IVF), with the goal of maximising the number of oocytes extracted in order to raise clinical success rates. Because of its shorter duration, convenience of administration and decreased risk of ovarian hyperstimulation syndrome (OHSS), the GnRH antagonist strategy has become a widely used protocol.[1] Progesterone-primed ovarian stimulation or PPOS, has been gaining popularity recently as a substitute for traditional procedures. PPOS removes the requirement for GnRH analogs by suppressing premature luteinizing hormone (LH) surges during the follicular period with exogenous progesterone. Because of this, PPOS is a more patient-friendly and economical approach than traditional protocols.[1] Traditional PPOS follows a fixed initiation schedule for progesterone administration (e.g. from cycle day 1 or 2). In contrast, flexible PPOS, in which progesterone is initiated based on follicular size (~14 mm) or serum estradiol thresholds (>200 pg/ml), enables more individualized timing and milder pituitary suppression paralleling the individualized approach of flexible GnRH antagonist protocols where antagonist start is similarly linked to follicular development or hormone level.[2] In women with diminished ovarian reserve (DOR), flexible PPOS (fPPOS) has been shown to yield a median of 4 cumulus–oocyte complexes (COCs) versus 5.5 in matched

flexible antagonist cycles, with comparable numbers of MII oocytes and maturation rates—and no increase in premature ovulation.[2] Similarly, overall oocyte yield and mature oocyte count were comparable in propensity-matched cohorts of DOR patients aged ≥35 years receiving PPOS versus antagonist protocols.[3] Among poor responders, a retrospective comparison showed no significant differences between PPOS and GnRH antagonist protocols in clinical pregnancy, live birth, abortion or cycle cancellation rates but PPOS resulted in a higher proportion of high-quality embryos (50 % vs. 42.9 %, p=0.045).[4] In oocyte donor cycles and PCOS populations, PPOS protocols (often fixed-start regimens) demonstrated similar numbers of retrieved oocytes, fertilization rates and top-quality embryos compared to flexible antagonist protocols, with a notably lower incidence of OHSS (6 vs. 0 cases in one study).[5]

Long-term safety data from a large retrospective propensity-matched cohort of singleton births (457 PPOS vs. 457 antagonist) reported no significant differences in neonatal outcomes including preterm birth, low birth weight, small or large for gestational age or congenital malformations. However, the PPOS group used a significantly higher total gonadotropin dose.[6] Systematic review and meta-analysis of PPOS versus antagonist protocols across diverse patient populations including PCOS, DOR, young donors and advanced-age women showed generally comparable mature oocyte yield, clinical pregnancy and live birth rates, albeit PPOS often required higher gonadotropin exposure and evidence quality remains moderate.[7] Given these findings, comparing flexible PPOS and flexible GnRH antagonist protocols in a controlled side-by-side manner evaluating ovarian response, hormonal dynamics, embryological parameters, pregnancy outcomes and OHSS incidence is essential to guide individualized protocol selection in routine IVF practice.

METHODS

This prospective, randomized controlled study was conducted at the Department of Assisted Reproduction, RIDGE IVF Centre, Delhi, between 1st July 2024 and 30th June 2025. Women aged 21 to 40 years attending the ART clinic and eligible for IVF/ICSI during the study period were considered for inclusion. A total of 100 participants were recruited based on predefined eligibility criteria and randomly allocated into two equal groups (n=50 each).

Group A: Flexible progestin-primed ovarian stimulation (fPPOS) protocol. Group B: Flexible GnRH antagonist protocol.

Inclusion criteria

It includes female patients aged 21–40 years, anti-müllerian hormone (AMH) level>1 ng/ml. Only grade A or B embryos were considered for transfer.

Exclusion criteria

Uterine factor infertility, endometriosis, adenomyosis, fibroid uterus, couples with male factor infertility.

Randomization and sample size

Randomization was performed using computer-generated random numbers. Sample size was determined based on a time-bound design and availability of eligible participants within the study period. A total of 100 patients meeting the inclusion criteria and providing informed consent were included (50 in each group).

Primary outcome measures

Number of oocytes retrieved, number of mature oocytes (MII), number of embryos formed, number of day 3 and day 5 embryos, embryo grading on day 3 and day 5.

Secondary outcome measures

Hormonal profile (S.FSH, S.LH, S.E2, S.AMH), duration of ovarian stimulation, total dose of gonadotropins used, clinical pregnancy rate.

Ethical considerations

The study protocol was reviewed and approved by the Ethical and Scientific Committee of RIDGE IVF Centre (Approval Number: RIDGE/HEC/001/2025). Informed written consent was obtained from all participants after detailed explanation of the study objectives and procedures.

This study utilized two ovarian stimulation protocols the fPPOS protocol (Group A) and the GnRH antagonist protocol (Group B).

For both protocols, all patients underwent a baseline transvaginal ultrasound scan on Day 2 of the menstrual cycle to rule out ovarian cysts, assess for any follicles >12 mm in diameter and evaluate endometrial thickness. Baseline serum levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH) and estradiol (E2) were also measured.

Controlled ovarian stimulation was initiated with either highly purified human menopausal gonadotropin (HMG) or recombinant FSH at a daily dose of 225–300 IU, individualized based on patient characteristics. Transvaginal ultrasound was used to monitor the follicular development along with serum estradiol levels. Gonadotropin dose was adjusted based on follicular response and hormonal levels.

In the fPPOS protocol, oral medroxyprogesterone acetate (MPA) 10 mg/day was initiated either on stimulation Day 7 or when the leading follicle reached ≥13 mm and serum estradiol exceeded 500 pg/ml, whichever occurred earlier.

Final oocyte maturation was triggered when at least two follicles reached ≥18 mm in diameter. Oocyte retrieval was done 34–36 hours post-trigger.

In the GnRH antagonist protocol, Cetrorelix 0.25 mg/day was introduced once the leading follicle measured ≥13 mm with serum estradiol >500 pg/ml, following a flexible initiation approach. The trigger and oocyte retrieval were timed similar to the fPPOS protocol.

RESULTS

The baseline characteristics of the participants were comparable between Group A and Group B. There were no statistically significant differences in mean age (30.72±3.70 vs. 31.96±4.24 years, p=0.12), BMI (26.64±4.24 vs. 26.79±4.34, p=0.85), duration of married life (6.11±2.34 vs. 6.14±3.15 years, p=0.67) or duration of infertility (3.65±1.86 vs. 3.89±2.51 years, p=0.95). The distribution of primary and secondary infertility was similar across both groups (p=0.36). The causes of infertility were broadly comparable. PCOS and tubal factors were the most common causes in both groups. Uncommon causes such as advanced maternal age, BOH and TB were noted only in Group B, while hypothyroidism was observed in one case in Group A. Serum AMH levels (4.52±1.66 vs. 4.61±2.40 ng/ml, p=0.68) and AFC (15.46±5.80 vs. 13.06±3.31, p=0.08) did not differ significantly between the groups. Among hormonal parameters, only day 2 serum FSH was significantly lower in group A (6.26±1.69 mIU/ml) compared to Group B (7.69±1.79 mIU/ml; p<0.01). No significant differences were observed in day 2 LH (p=0.32) or E2 levels (p=0.26).

The dose and duration of gonadotropin stimulation were similar in both groups. Group A required slightly less gonadotropin (2735.0±519.41 IU vs. 2989.12±748.55 IU), though not statistically significant (p=0.07). Duration of stimulation was nearly identical (10.50±1.89 vs. 10.60±1.12 days; p=0.99). The number of oocytes retrieved, M2 oocytes and embryos formed were comparable (all p>0.05), with no significant differences in day 3 or day 5 embryo counts. In Group A, the mean cumulative dose of progesterone used was 49.00±9.74 mg, with a minimum of 30 mg and a maximum of 70 mg administered. The average duration of progesterone use was 4.90±0.97 days. In contrast, Group B participants received a mean cumulative antagonist dose of 1.28±0.22 mg, with a range from 0.50 to 1.75 mg, over an average of 5.12±0.91 days. These values indicate that both groups had similar durations of medication use, though the type and amount of medication varied based on the protocol.

Embryo quality was assessed through grading on Day 3 and Day 5. On Day 3, Group A produced 247 embryos, of which 167 (67.6%) were Grade A and 80 (32.4%) were Grade B, with no Grade C embryos. Group B produced 260 embryos, with 185 (71.2%) classified as Grade A and 75 (28.8%) as Grade B and no Grade C embryo. The p-value of 0.38 suggests no significant difference in day 3 embryo grading between the groups. Similarly, day 5 embryo grading revealed that in Group A, out of 165 embryos, 16 (9.69%) were Grade AA, 136 (82.42%) were AB and 13 (7.87%) were BB. In Group B, among 136 embryos, 9 (6.61%) were AA, 118 (83.08%) were AB and 9 (6.61%) were BB. The p-value of 0.55 again indicated no statistically significant difference in embryo quality between the groups at the blastocyst stage.

Embryo transfer quality was also assessed. On day 3, 75 embryos were transferred in Group A, with 67 (89.33%) being Grade A and 8 (10.66%) Grade B. Group B had 70 embryos transferred, of which 62 (88.57%) were Grade A and 8 (11.42%) were Grade B. The similarity in proportions and a p-value of 0.88 confirm that there was no significant difference between the groups. On Day 5, Group A transferred 45 embryos: 12 (26.66%) Grade AA, 26 (57.77%) Grade AB and 7 (15.55%) Grade BB. In Group B, 39 embryos were transferred, including 10 (25.64%) Grade AA, 28 (71.79%) Grade AB and only 1 (2.56%) Grade BB. Although there was a numerical difference in the number of BB grade embryos transferred, the p-value of 0.11 shows that this difference was not statistically significant.

Table 1: Data comparing various parameters related to fertility treatment between Group A and Group B.

	Group A (n=50)		Group B (n=50)		P value
	Mean±SD	Median (IQR)	Mean±SD	Median (IQR)	
DAY 2 S.FSH (miu/ml)	6.26±1.69	6.34 (5.22-7.51)	7.69±1.79	7.43 (6.30-8.61)	<0.01
DAY 2 LH (miu/ml)	6.34±8.06	5.19 (3.60-6.71)	4.85±2.03	4.38 (3.16-5.91)	0.32
DAY 2 S.E2 (pg/ml)	47.59±15.94	45.5 (36.55-58.31)	44.14±18.43	44.66 (34.56-50.18)	0.26
Days of GN	10.50±1.89	11 (10-11)	10.60±1.12	11 (10-11)	0.99
Dose of GN	2735.0±519.41	2700 (2306.25-3056.25)	2989.12±748.55	2925 (2475-3187.5)	0.07
No of oocytes	16.96±6.56	16 (12.75-21.25)	16.66±6.20	17 (11.75-21.25)	0.97
No of M2	14.24±5.93	14.5 (10-17.25)	13.98±5.35	14 (9.75-17)	0.90
Total embryos	8.34±3.78	8 (5-11)	8.0±3.44	7.5 (5.75-10)	0.63
No of day 5 embryos	3.40±2.64	3 (1-5)	2.76±1.94	3 (1-4)	0.38
No of day 3 embryos	4.94±3.02	5 (3-6)	5.20±2.53	5 (3.75-6)	0.40

Table 2: Data comparing S.β HCG levels between Group A and Group B.

β HCG levels	Group A (n=50)	Group B (n=50)	P value
Negative	25 (50.0%)	29 (58.0%)	0.42
Positive	25 (50.0%)	21 (42.0%)	

Table 3: Data comparing Clinical pregnancy between Group A and Group B.

Clinical pregnancy	Group A (n=50)	Group B (n=50)	P value
No	32 (64.0%)	32 (64.0%)	1.0
Yes	18 (36.0%)	18 (36.0%)	

Regarding pregnancy outcomes, the serum β-hCG positivity rate was 50.0% in Group A (25 out of 50 participants) and 42.0% in Group B (21 out of 50 participants). Despite this numerical difference, the p-value of 0.42 indicates that there was no statistically significant difference in biochemical pregnancy rates between the two groups. Similarly, clinical pregnancy rates were the same across both groups, with 18 participants (36.0%) achieving clinical pregnancy in each. The p value of 1.0 confirms that the clinical outcomes were statistically comparable between the two protocols. In summary, both progesterone and antagonist protocols demonstrated comparable results in terms of medication usage, pregnancy outcomes, embryo quality and embryo transfer characteristics. No statistically significant differences were observed across any of the assessed parameters, indicating that both stimulation protocols are equally effective and can be considered viable options in assisted reproductive treatments.

DISCUSSION

This randomized controlled trial comparing fPPOS with the flexible GnRH antagonist protocol demonstrated that both protocols demonstrated comparable outcomes in terms of oocyte retrieval, embryo development and clinical pregnancy rates suggesting the non-inferiority of flexible PPOS protocol.

The number of oocytes retrieved, mature (MII) oocytes and embryos formed were statistically similar in both the groups. This supports prior studies indicating that PPOS does not adversely affect oocyte competence or embryo development. Wang et al similarly reported no significant differences in oocyte yield or fertilization rates when comparing PPOS with GnRH antagonist protocols in normal responders.[8] Embryo grading done on Day 3 and Day 5 revealed equivalent quality across both groups. No significant differences were noted in the distribution of Grade A or top-quality blastocysts. This is consistent with findings from Kuang et al who showed that progesterone used during the follicular phase does not negatively influence embryo quality or blastocyst formation.[9] Additionally, Turgut et al concluded that the PPOS protocol leads to embryo quality outcomes comparable to those of antagonist cycles, further supporting our findings.[10] Clinical pregnancy rates were similar in both groups, reinforcing the viability of fPPOS as an effective stimulation strategy. The β-hCG positivity rate was marginally higher in the fPPOS group (50% vs. 42%), though this difference was not statistically significant. Similar pregnancy outcomes between PPOS and antagonist protocols have been documented by Turgut et al, which concluded that PPOS is a safe and effective alternative to conventional antagonist protocols in terms of pregnancy outcomes.[10]

A key advantage of the fPPOS protocol is its patient-centric design. By allowing oral administration of progestins instead of injectable antagonists, the protocol enhances patient compliance and comfort. Moreover, the flexible initiation of progestin based on follicular development as employed in this study introduces greater individualization. Cai et al emphasized that tailoring progesterone initiation may improve the efficiency of ovarian stimulation without compromising results.[11]

Another important observation is the complete absence of OHSS in both groups. The use of progestins, like medroxyprogesterone acetate, effectively suppresses premature LH surge and reduces the likelihood of OHSS, especially when combined with a freeze-all strategy. This aligns with findings from Qi et al who noted a markedly reduced OHSS risk in PPOS cycles.[12] The study also noted a significantly lower baseline Day 2 FSH in the fPPOS group. While the clinical significance of this difference is uncertain, it might reflect mild variability in ovarian reserve between the groups, although AMH and AFC were statistically similar. The cumulative gonadotropin dose and duration of stimulation were slightly lower in the fPPOS group, although not statistically significant. Our study suggests potential cost-effectiveness of fPPOS, especially in resource-limited settings a point also highlighted by Alabi et al in their economic analysis between progestin-primed and antagonist ovarian stimulation protocol.[13]

Strengths

A strength of our study is its randomized prospective design and comprehensive assessment of embryo quality,

hormonal dynamics and clinical pregnancy. Given the flexibility in both protocols, our findings are applicable to real-world IVF practice.

Limitations of this study include the single-center design and relatively small sample size. Additionally, only fresh biochemical and clinical pregnancy rates were assessed. Ongoing follow-up for live birth outcomes and neonatal health would provide a more comprehensive understanding of the safety and efficacy of these protocols. As in other PPOS research, freeze-all cycles were necessary thus fresh embryo transfer outcomes could not be assessed.

CONCLUSION

The findings of this study reinforce the clinical utility of flexible PPOS as a safe, effective and patient-friendly alternative to flexible GnRH antagonist protocols in IVF. Comparable outcomes in oocyte yield, embryo quality and pregnancy rates, along with a reduced injection burden and potential cost savings, support its broader implementation in clinical practice.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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