RESEARCH ARTICLE

A Prospective Cohort Study on the Impact of Delaying Ovulation Trigger on Assisted Reproductive Technology Outcomes

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Abstract

Aims and background: The optimal size of the leading follicle at which ovulation trigger should be given in the gonadotropin-releasing hormone (GnRH) antagonist protocol has not been validated yet. We carried out this study to assess the role of delaying ovulation triggering, with the leading follicle beyond 20 mm, in enabling the maturation of medium-sized follicles during controlled ovarian stimulation (COS).

Materials and methods: A total of 427 infertile women between the age-group 21 and 45 years, undergoing COS with flexible GnRH antagonist protocol were included, and before stimulation, they were categorized into three groups, namely predicted poor (group I), normal (group II), and hyper (group III) responders. On the day of the trigger, all three groups were further split into two subgroups based on the leading follicle diameter (subgroup A: <20 mm and subgroup B: ≥20 mm), and assisted reproductive technology (ART) outcomes were analyzed between the subgroups.

Results: The number of oocytes retrieved [6.8 ± 3.9 vs 4.0 ± 2.7, 95% confidence interval (CI): 1.10–4.44; $p = 0.001$], the number of metaphase II oocytes among them (4.6 ± 3.1 vs 2.8 ± 1.9; 95% CI: 0.48–3.06; $p = 0.008$) and the resultant total number of embryos available for freezing (3.5 ± 2.6 vs 2.2 ± 1.7; 95% CI: 0.17–2.41; $p = 0.024$) and the number of grade I embryos (2.0 ± 1.9 vs 1.1 ± 1.4; 95% CI: 0.15–1.77; $p = 0.021$) were significantly increased in group IB when compared to group IA. The cycle outcomes were marginally improved, though not significant, in subgroups IIB and IIIB when compared to subgroups IIA and IIIA, respectively. Oocyte maturation rate and fertilization rate were comparable between the subgroups.

Conclusion: Delaying the trigger for oocyte maturation has a role in improving the outcomes in poor responders.

Clinical significance: Delaying the ovulation trigger in enabling the maturation of medium-sized follicles leads to clinically better yield of oocytes and good quality embryos in predicted poor responders.

Keywords: Assisted reproductive technology outcome, Follicle size, Oocyte maturation, Ovulation trigger.

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Introduction

In assisted reproductive technology (ART), women undergo controlled ovarian stimulation (COS), which gives rise to a heterogeneous cohort of follicles that may contain oocytes of varying competency and maturity. The size of the follicle and oocyte competence are positively correlated.[1] Various studies from the literature have shown that bigger follicles presumably have mature oocytes, which potentially develop into good-quality embryos.[2–11] A recent study also showed that oocytes obtained from follicles measuring 19–24.5 mm in diameter during retrieval resulted in the formation of good-quality blastocysts.[12]

The optimal size of the leading follicle at which ovulation trigger should be given in the gonadotropin-releasing hormone (GnRH) antagonist protocol has not been validated yet. With this background, we carried out a study to assess the role of delaying ovulation triggering, with the leading follicle beyond 20 mm, in enabling the maturation of medium-sized follicles during COS. We assessed the total number of oocytes collected, oocyte maturation rate, and the number of metaphase II oocytes as primary objectives, and the resulting total number of embryos available for freezing, fertilization rate, and the number of grade I embryos were considered as secondary objectives.

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Materials and Methods

We conducted a prospective cohort study between June 2021 and February 2023 at the Department of Reproductive Medicine and

Surgery in a tertiary medical center. All infertile women between the age-group 21 and 45 years undergoing COS with GnRH antagonist protocol were included. Women undergoing other stimulation protocols, those who had ovarian cysts at the start of stimulation, and those cycles that were canceled or converted to intrauterine insemination were excluded from the study. Institutional Ethical Committee approval (reference number: CSP-MED/21/JUN/69/89) was obtained, and all study participants signed a written informed consent.

A total of 427 women satisfying the selection criteria were enrolled. The demographic details, gynecological and obstetric history, medical and surgical history, past infertility treatments, and cause and evaluation of infertility were recorded from the study participants.

Study participants were categorized into three groups based on the ovarian reserve before starting the stimulation.

Group I: Predicted poor responders—serum anti-Müllerian hormone (AMH) <1.2 ng/mL and/or antral follicle count (AFC) ≤7.[13]

Group II: Predicted normal responders—serum AMH 1.2–3.5 ng/mL and AFC of 8–16.

Group III: Predicted hyperresponders—serum AMH >3.5 ng/mL and/or AFC >16, known case of polycystic ovary syndrome, history of ovarian hyperstimulation syndrome (OHSS).[13]

Controlled Ovarian Stimulation (COS)

Women underwent COS with a flexible antagonist protocol, either directly or after pretreatment suppression with combined oral contraceptive pills for 10–15 days, according to department protocol. On day 2 or 3 of the cycle or following a pill-free period of 5 days, transvaginal ultrasound (TVS) was performed in a GE Voluson S8 Pro ultrasound machine with a 3.8–9.3 MHz bandwidth probe to assess the thickness of the endometrium and AFC. Recombinant follicle stimulating hormone (Gonal F®, Merck Serono SA, Switzerland) with or without human menopausal gonadotropin (Gynogen® HP 150, Sanzyme (P) Ltd, India) was started on the same day. The dose and type of gonadotropins were individualized considering the age, AMH, AFC, body mass index (BMI), and prior response to stimulation. The starting dose varied from 150 to 300 IU/day. TVS was performed on day 5 or 6 of stimulation, and the dose of gonadotropins was calibrated by the response. When a minimum of one follicle attained 14 mm diameter, or when multiple follicles of size 12–13 mm were present, GnRH antagonist, injection (inj) cetrorelix 250 µg (Asporelix™ 0.25 mg, Bharat Serum and Vaccines Limited, India) was added and was continued until the day of trigger. Follicular monitoring was continued daily or alternate days based on the response to stimulation.

When the leading follicle of the cohort attained ≥18–20 mm diameter and intermediary follicles were around 14–17 mm, the ovulation trigger was administered according to the department protocol. Patients received either of the following triggers: urinary human chorionic gonadotropin (uhCG) 10000 IU intramuscularly (HUCOG®–10000 HP, Bharat Serum and Vaccines Limited, India), recombinant human chorionic gonadotropin (rhCG) 250 µg subcutaneously (Ovitrelle®, Merck Serono SA, Switzerland), GnRH agonist trigger–inj triptorelin (Decapeptyl®, Ferring Pharmaceuticals, Germany) 0.2 mg subcutaneously, followed by a second dose of 0.1 mg subcutaneously 12 hours apart,[14] or dual trigger with uhCG 10000 IU intramuscularly and inj triptorelin 0.2 mg subcutaneously.

On the day of the trigger, all three groups were divided into two subgroups based on the diameter of the leading follicle.

Subgroup A: <20 mm

Subgroup B: ≥20 mm

Once the ovulation trigger was given, retrieval of oocytes was performed under TVS guidance 34–36 hours later. Oocyte maturation was assessed after denudation of cumulus-oocyte complexes 2 hours post retrieval, and intracytoplasmic sperm injection (ICSI) was performed for all mature oocytes. A fertilization check was done 18 hours postinsemination. On day 3, embryos were graded according to the Istanbul Consensus 2011.[15]

Statistical Analysis

Statistics were carried out with the help of IBM Statistical Package for the Social Sciences Statistics software for Windows, version 29.0. (Armonk, New York, United States of America: IBM Corp). The descriptive statistics of categorical variables were done using frequency and percentage analysis, and the Chi-squared test was applied to calculate the significant difference between them. Mean and standard deviation were used to describe continuous variables. To compare the bivariate samples in independent groups, we used the independent sample *t*-test. In all the above analyses, the probability value (*p*-value) of <0.05 was regarded as significant.

Results

A total of 427 women who enrolled in the study were analyzed. Groups I, II, and III had 100 (23.4%), 84 (19.7%), and 243 (56.9%) women, respectively. Baseline characteristics were comparable between the subgroups as depicted in Table 1.

Controlled ovarian stimulation (COS) cycle characteristics of each subgroup are listed in Table 2. The primary and secondary outcomes are listed in Table 3.

Discussion

Around two to three major/minor waves of recruitment of antral follicles within one interovulatory interval or menstrual cycle have been described in the literature.[16] Delaying the ovulation trigger in ART cycles until the lead follicle reaches ≥20 mm diameter may help in the maturation of intermediary follicles, measuring 12–15 mm, which would have been recruited in the subsequent wave, ultimately leading to increased yield of mature oocytes. This study differs from others in the fact that the effect of delaying ovulation trigger was assessed individually in predicted poor, normal, and hyper responders.

In our study, the number of oocytes retrieved [6.8 ± 3.9 vs 4.0 ± 2.7, 95% confidence interval (CI): 1.10–4.44; $p = 0.001$], the number of metaphase II oocytes among them (4.6 ± 3.1 vs 2.8 ± 1.9; 95% CI: 0.48–3.06; $p = 0.008$) and the resultant total number of embryos available for freezing (3.5 ± 2.6 vs 2.2 ± 1.7; 95% CI: 0.17–2.41; $p = 0.024$), and the number of grade I embryos (2.0 ± 1.9 vs 1.1 ± 1.4; 95% CI: 0.15–1.77; $p = 0.021$) were significantly increased when ovulation trigger was delayed until leading follicle reaches ≥20 mm, in the predicted poor responders' group. Women in group IB had an average of 2.8 oocytes more than those in group IA. Its significance lies in the fact that the number of oocytes retrieved is crucial in increasing the predicted live birth rate (LBR); that is, retrieval of three instead of two oocytes increases the predicted LBR from 16 to 22% in the women age-group of 18–34 years, and from 14 to 19% in the women age-group of 35–37 years.[17] Thus, there was a relative increase in LBR in suboptimal responders, who obtained five to nine oocytes, when compared to the poor responders who obtained more than five oocytes. This was also supported by a national registry-based retrospective study from Switzerland.[18] As

Table 1: Baseline characteristics

	Group I (n = 100)			*Group II (n = 84)*			*Group III (n = 243)*		
Parameters	*Subgroup A (n = 25)*	*Subgroup B (n = 75)*	*p-value*	*Subgroup A (n = 16)*	*Subgroup B (n = 64)*	*p-value*	*Subgroup A (n = 41)*	*Subgroup B (n = 202)*	*p-value*
Age (years)	33.6 ± 4.4	33.0 ± 4.8	0.558[a]	32.9 ± 4.9	32.0 ± 4.6	0.499[a]	29.8 ± 3.3	29.7± 4.2	0.855[a]
Type of infertility									
Primary	64%	73.3%	0.373[a]	68.8%	76.5%	0.521[a]	68.3%	79.2%	0.128[a]
Secondary	36%	26.7%		31.3%	23.5%		31.7%	20.8%	
Cause of infertility									
Female	52%	56%	0.811[a]	31.3%	36.8%	0.940[a]	34.1%	40.6%	0.566[a]
Male	8%	8%		25%	27.9%		29.3%	20.8%	
Combined	40%	33.3%		31.3%	25%		31.7%	30.2%	
Unexplained	0%	2.7%		12.5%	10.3%		4.9%	8.4%	
Duration of infertility (years)	8.5 ± 4.6	6.8 ± 4.7	0.114[a]	7.0 ± 4.7	6.2 ± 3.9	0.491[a]	5.9± 3.0	5.7± 3.4	0.704[a]
BMI (kg/m^2)	26.9 ± 3.5	26.7 ± 5.2	0.885[a]	25.4 ± 4.4	26.1 ± 5.1	0.616[a]	29.8 ± 3.3	26.8 ± 4.6	0.844[a]
Serum AMH (ng/mL)	0.9 ± 0.4	0.9 ± 0.5	0.967[a]	2.1 ± 0.6	2.1 ± 0.6	0.949[a]	4.7 ± 2.6	5.1 ± 2.6	0.410[a]
AFC	7.5 ± 3.1	8.9 ± 4.3	0.138[a]	13.1 ± 1.7	12.0 ± 2.5	0.087[a]	26.0 ± 11.7	25.3± 9.1	0.660[a]

[a]Statistically not significant

Table 2: Cycle characteristics

	Group I (n = 100)			*Group II (n = 84)*			*Group III (n = 243)*		
Parameters	*Subgroup A (n = 25)*	*Subgroup B (n = 75)*	*p-value*	*Subgroup A (n = 16)*	*Subgroup B (n = 64)*	*p-value*	*Subgroup A (n = 41)*	*Subgroup B (n = 202)*	*p-value*
Total dose of gonadotropins (IU)	4730.0 ± 2245.4	4730.3 ± 1583.5	0.999[a]	3918.8 ± 1662.8	4301.5 ± 1577.4	0.390[a]	2622.0 ± 1073.5	2952.9 ± 1129.0	0.086[a]
Total days of antagonist	4.3 ± 2.1	5.0 ± 1.6	0.101[a]	4.4 ± 1.4	4.9 ± 1.4	0.274[a]	4.0 ± 1.4	4.5 ± 1.3	0.015[b]
Days of stimulation	10.4 ± 2.8	10.8 ± 2.2	0.681 [a]	10.3 ± 1.7	10.5 ± 1.8	0.623 [a]	9.6 ± 1.7	9.9 ± 1.6	0.442[a]
Type of trigger									
Agonist	0%	2.7%	0.369[a]	6.3%	8.8%	0.011[b]	34.1%	41.6%	0.008[b]
rHCG	12%	20%		25%	2.9%		19.5%	4.0%	
uHCG	16%	6.7%		25%	16.2%		4.9%	8.4%	
Dual trigger	72%	70.7%		43.8%	72.1%		41.5%	46.0%	
Number of intermediary follicles (12–15 mm) on the day of trigger	2.5 ± 2.0	2.8 ± 2.5	0.617[a]	3.4 ± 2.0	5.2 ± 2.5	0.008[b]	9.5 ± 6.7	8.9 ± 4.8	0.507[a]
Number of preovulatory follicles on the day of trigger (≥16 mm)	3.1 ± 1.5	4.1 ± 2.0	0.023[b]	4.6 ± 2.1	5.9 ± 2.7	0.080[a]	7.7 ± 3.5	10.2 ± 4.3	0.0004[b]

[a]Statistically not significant; [b]statistically significant

Table 3: Cycle outcomes

	Group I (n = 100)			*Group II (n = 84)*			*Group III (n = 243)*		
Parameters	*Subgroup A (n = 25)*	*Subgroup B (n = 75)*	*p-value*	*Subgroup A (n = 16)*	*Subgroup B (n = 64)*	*p-value*	*Subgroup A (n = 41)*	*Subgroup B (n = 202)*	*p-value*
Number of oocytes retrieved	4.0 ± 2.7	6.8 ± 3.9	0.001[b]	8.6 ± 3.3	10.6 ± 5.0	0.113[a]	15.5 ± 7.5	18.8 ± 10.2	0.053[a]
Number of metaphase II oocytes	2.8 ± 1.9	4.6 ± 3.1	0.008[b]	6.5 ± 3.1	6.9 ± 3.6	0.655[a]	11.0 ± 5.8	13.6 ± 8.5	0.063[a]
Maturation rate	72.2 ± 24.7	66.9 ± 27.4	0.387[a]	74.4 ± 20.2	65.7 ± 18.2	0.096 [a]	72.1 ± 19.7	71.4 ± 20.0	0.829[a]
Total number of embryos available for freezing	2.2 ± 1.7	3.5 ± 2.6	0.024[b]	5.1 ± 3.0	4.9 ± 3.0	0.871[a]	8.4 ± 4.6	9.9 ± 6.4	0.166[a]
Fertilization rate	67.8 ± 35.6	69.8 ± 32.4	0.792[a]	75.5 ± 20.8	71.3 ± 20.4	0.471[a]	79.2 ± 19.2	74.4 ± 20.6	0.165[a]
Number of grade I embryos	1.1 ± 1.4	2.0 ± 1.9	0.021[b]	3.2 ± 2.5	2.7 ± 2.3	0.415[a]	5.5 ± 3.9	6.2 ± 5.2	0.410[a]

[a]Statistically not significant; [b]statistically significant

previously studied, the more the number of oocytes obtained, the more the number of embryos that are euploid, and they can be used for fresh embryo transfer as well as cryopreserved for subsequent frozen embryo transfer cycles.[19,20] This also increases the overall cumulative LBR.[21]

Cycle outcomes were clinically better in subgroup B of predicted normal and hyper responders, although appreciable statistical significance was not made out. There was no adverse effect on the oocyte maturation rate as well as the fertilization rate by delaying the trigger in any of the groups.

The above findings were also supported by a randomized controlled trial (RCT),[22] which suggested that delaying the ovulation trigger by 24 hours in those with more than or equal to three follicles ≥18 mm diameter and serum progesterone level ≤1 ng/mL yields a greater number of mature oocytes.

In another RCT which included 190 women,[23] better ongoing pregnancy rates were observed when oocyte retrieval was delayed until the leading follicle reached 22 mm, when compared to 18 mm (38 vs 24%, relative risk, 1.6, 95% CI: 1.03–2.5), even though LBRs were comparable. Morley et al. conducted an RCT[24] in which 125 women undergoing in vitro fertilization (IVF)/ICSI cycles were categorized into three groups. Group I included women in whom the hCG trigger was administered when more than or equal to three follicles reached ≥17 mm, group II included women in whom the trigger was delayed by 1 day, and group III included women in whom the trigger was delayed by 3 days. The later two groups had more mature follicles without significant differences in clinical outcomes.

Chen et al. carried out a systematic review and meta-analysis, which suggested that delaying the ovulation trigger by 1–2 days may help in retrieving significantly more oocytes, while LBR and ongoing pregnancy rate were unaffected by the same.[25]

The optimal timing of ovulation trigger during COS cycles is always controversial. When comparing GnRH antagonists with agonist stimulation protocols, there are significant differences in the follicular recruitment and endocrine characteristics, and hence, the triggering criteria need modification.

The decision regarding when to administer the ovulation trigger depends on multiple factors. It should be individualized among the patients, considering the size of the leading follicle along with the growing intermediary follicular cohort, serum estradiol levels, duration of stimulation, the financial burden to the patient, previous response to the COS cycle, and organizational factors for the hospital.

As mentioned earlier, the follicles measuring 19–24.5 mm at the time of ovum pickup gave rise to the highest number of good-quality blastocysts, and in follicles >25 mm, the blastocyst yield was not significantly less.[12] This suggests that in patients with asynchrony of the follicular cohort, continuing the stimulation to allow the maturation of medium-sized follicles could be possible without affecting the quality of bigger follicles. Hence, from the above-mentioned studies, we suggest that the ovulation trigger can be modestly delayed by 1–2 days to retrieve more mature oocytes without affecting the implantation and clinical pregnancy rates in GnRH antagonist cycles.[26] However, if the trigger is delayed for >2 days due to endometrial advancement, there might be decreased clinical pregnancy rates during fresh transfer cycles. Hence, prolonging the follicular phase can be considered particularly in freeze-all cycles, and it can also help in increasing the flexibility of scheduling oocyte retrieval.[27]

There were no moderate and severe OHSS cases in our study, even though there was an increased number of intermediary follicles in subgroups IB, IIB, and IIIB. The risk of early onset OHSS due to prolonged stimulation can be eliminated by GnRH agonist trigger without affecting the clinical outcomes, particularly in freeze-all cycles.[26] Hence, there were significant differences in the type of trigger used between the subgroups of predicted normal and hyper-responders. However, it did not influence the cycle outcomes, as shown in Table 3. A study by Mohr-Sasson et al. also inferred that the mode of triggering does not influence the oocyte recovery rate.[11]

The strength of the study is that it is conducted by a consistent professional team in a single tertiary care hospital.

The limitations of the study lie in the fact that it is observational, lacks randomization, and limited sample size. We have not assessed the clinical pregnancy rates and LBRs in our study population.

To summarize, in poor responders, delaying the trigger till the leading follicle is ≥20 mm significantly improved the oocyte yield, mature oocytes, and the number of grade I embryos for freezing without affecting the maturation rate and fertilization rate. However, this was not significant in normal or hyper responders, even though there was a marginal increase in the cycle outcomes.

Conclusion

Delaying the trigger for oocyte maturation has a role in improving the outcomes in poor responders.

Clinical Significance

Delaying ovulation triggers in enabling the maturation of medium-sized follicles leads to clinically better yield of oocytes and good quality embryos in predicted poor responders.

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