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A retrospective observational study to see the effect of dual trigger on IVF outcomes in poor ovarian responders

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Abstract
Background: Poor Responders Patients undergoing IVF treatment were given Dual Trigger for final oocyte maturation. Poor responders are the patients in whom, less number of egg were retrieved. Typically, they were with advanced maternal age and poor ovarian reserve (AFC <5-7 follicle or AMH < 1.2ng/ml) or with a history of previous Poor ovarian reserve (≤3 oocytes) with Controlled ovarian stimulation. This study aimed to examine the effectiveness of dual trigger for final oocyte maturation in poor responder patients based on Bologna criteria (2011).
Methods: A total of 30 IVF cycles of poor responder patients were retrospectively analyzed. The study group (15 patients) was given dual triggers (HCG and GnRH agonist) for final oocyte maturation whereas in control group final oocyte maturation was performed with HCG only. GnRH antagonist Protocol was used in both the groups.
Baseline characteristics, number of oocyte retrieved, the number of M-2 and the quality of embryo of both groups were compared.
Results: Both the groups were comparable in baseline characteristics. In our study, there was not much difference in number of oocyte retrieved, but there was higher number of M2 and top quality embryo, compared to control group.
Conclusion: Dual trigger might be a superior option for final oocyte maturation as compared to hCG trigger alone in terms of IVF cycles outcomes in poor responders and further large scale randomized prospective studies needed to validate our results.

Keywords: Dual trigger, human chorionic gonadotrophin, IVF, poor ovarian responders

Introduction
In normal menstrual cycle, for final oocyte maturation there is an endogenous LH surge and a smaller follicle stimulating hormone (FSH) surge too. Over the past few decades, HCG has been the choice of trigger for final oocyte maturation in IVF cycles due to its molecular similarity with LH [1]. However, its half-life is much longer than LH which facilitates the development of ovarian hyper stimulation syndrome (OHSS) in high responders [2]. Moreover, HCG lacks FSH activity which play a vital role in oocyte nuclear maturation and release [3].
Gonen *et al* in 1990 [4] first suggested the use of GnRH agonists for final oocyte maturation as it can trigger the endogenous surge of both FSH and LH [4]. With a shorter duration of LH surge of about 34 hrs, it mimics the natural cycle surge duration of 48 hrs and thereby reducing the risk of OHSS in high responders [5, 6, 7]. However, there was increased risk of empty follicle syndrome following isolated GnRH agonist trigger due to suboptimal surge of LH [8]. In cases of poor response to GnRH agonist which is seen in about 2.71% of the study population in the respective studies, the HCG injection of the dual trigger could act as a safeguard against empty follicular syndrome [9, 10].
Ever since, the concept of dual trigger came into effect, various studies have shown the advantage of using it for final oocyte maturation in normal responders [9, 11] including an improvement in the total number of oocytes retrieved, M-2 oocytes, quality of embryos, etc. These benefits have been attributed to GnRH-induced FSH surge. Also it was seen that GnRH receptors are present in several sites such as the endometrium, fallopian tube, myometrium, ovaries, placenta, and pre-implanting embryo and has multiple roles thereby improving the endometrial receptivity and embryo implantation.

However, for poor ovarian responders who have a low reserve, thereby resulting in poor IVF outcomes poses a challenging situation to clinicians regarding strategies to improve outcomes [12]. Various criteria were proposed for the definition of Poor ovarian reserve [13], but none was regarded as the international standard to define POR until Bologna criteria came in 2011[14] by The European Society of Human Reproduction and Embryology Women with POR (Bologna criteria) manifest a very low follicular response to controlled ovarian stimulation irrespective of the stimulation protocol utilized.

At least two of the following three criteria must be present for definition of POR:

1. Maternal age>40 years or any other risk factor for POR
2. Abnormal ovarian reserve test (AFC<5-7 or AMH< 1.2ng/ml)
3. A previous POR reserve (<=3oocytes) with Controlled ovarian stimulation.

Based on the existing data of enhanced reproductive outcomes in normal responders, and the logical advantage of a more physiological trigger simultaneously, we hypothesized that similar benefits can be gained using a dual trigger in poor responders. So our aim was to show whether the co-administration of GnRH agonist and HCG for final oocyte maturation improve oocyte collection, maturation rate and the quality of embryo in poor responders.

Materials and Methods

The present study was undertaken at RISAA IVF for a period of three months from 1st May 2022 to 31st July 2022. It was a retrospective observational study in which data of total 30 poor responder patients who underwent IVF in our centre were taken. The details were obtained from clinical case records and maintained database:

Inclusion criteria

Patients were taken based on BOLOGNA CRITERIA

1. Maternal age > 40 years or any other risk factor for POR.
2. Abnormal ovarian reserve test (AFC < 5-7 or AMH < 1.2ng/ml) irrespective of age
3. A previous POR reserve (<=3 oocytes) with Controlled ovarian stimulation irrespective of age.

If the patients met any two of the above three criteria, they were taken in our study.

Exclusion criteria

1. Abnormal uterine cavity
2. FSH > 25 (premature ovarian failure)
3. Cancer patients with chemotherapy
4. Patients who have not received GnRH antagonist protocol.
5. Previous surgical history involving ovaries (eg. Cystectomy, partial oophorectomy)
6. Severe Male factor infertility were surgical procedure was required for sperm extraction (as they may affect the quality of embryo)

Treatment protocol

All poor ovarian responder patients who fulfilled the inclusion and exclusion criteria underwent GnRH antagonist controlled ovarian hyper stimulation protocols in ART cycles. A baseline hormone level and transvaginal sonography for AFC was done. Gonadotropins (with fresh or with HP-HMG) were started on day 2 or day 3 of the menstrual cycle.

The initial dose of gonadotropin was individualized for each infertile patient according to age, BMI, AFC, AMH level and previous response to ovarian stimulation. Patient response was monitored with serial transvaginal scans. Dosages were adjusted according to the follicular response to gonadotropins. Daily GnRH antagonist injections (cetrimide 0.25mg) were added from day 6-7 when the mean diameter of dominant follicles reached upto 14mm in diameter and continued till the date of triggering. The patient then either received a dual trigger with recombinant HCG with GnRH agonist or recombinant HCG alone. The trigger was given when at least 1 leading follicle measures ≥18mm.

Outcomes

Retrieval of oocytes was done after 36 hours of triggering under TVS guidance. The retrieved oocytes were kept in incubation in the cultured medium and oocytes were denuded by gentle pipetting after a short incubation in 80 IU/ML hyaluronidase.

Then oocytes were scanned for their maturation level and oocyte with extruded first polar body i.e. metaphase 2 stage were considered to have matured and were used for the Intra Cytoplasmic sperm injection (ICSI) procedure. Day 3 embryo quality was assessed by using Cummin criteria [15].

1. Grade 1 (embryos with 8 blastomeres with cell regularity and size equality without necrosis and fragmentation)
2. Grade 2 (embryos 1–20% fragmentation)
3. Grade 3 (21–50% fragmentation)
4. Grade 4 (fragmentation greater than 50%)

Grade 1 was considered to be good quality; Grade2 average quality and grade 3 & 4 were considered as poor quality. Day 5 embryo were assessed by considering the following three parameters (Gardner's classification)

1. Size of cavity
2. Inner cell mass
3. Trophoectoderm

Embryos with grade AA, BA were considered to be good quality while AB, BB was considered to be average. The number of total retrieved oocytes, number of mature oocytes and number of embryos with good quality were recorded.

Statistical analysis

The statistical analyses were performed using SPSS software package version 25. All categorical data was analysed using Chi-square test or Fischer exact test. The data was considered significant when P value < 0.05.

Results

A total of 30 patients were randomly assigned into two groups, of which 15 were in the HCG trigger group (control group) and 15 were in the dual trigger group. The mean age of participants in the dual trigger group was 35.4±2.75years and 34.6±3.02 years in the control group. There was no statistically significant difference in baseline characteristics between the two groups (Table 1).

Table 1: Baseline characteristics of the Participants in mean (standard deviation)

Variables	Dual group	Control group	P-value

Age (Years)	35.4 ± 2.75	34.6 ± 3.02	0.958
Infertility duration(years)	7.3 ± 2.1	6.4 ± 1.8	0.84
Day 2 FSH	7.2 ± 2.2	8.5 ± 2.3	0.79
Number of previous failed transfers	0.80 ± 0.41	0.66 ± 0.88	0.91
AMH	0.83 ± 0.41	0.78 ± 0.43	0.97
AFC	3.93 ± 1.2	4.13 ± 0.9	0.95

Key: (FSH: follicle-stimulating hormone; AMH: anti-mularian hormone, AFC- Natral follicular count)

The number of oocytes retrieved among the dual group was higher than the control group, but the difference was statistically insignificant (Table 2).

Table 2: Characteristics of the ovarian stimulation in the two studied groups.

Variables	Dual group	Control group	P value
Duration of stimulation (Average)	10.33	10.27	0.99
Duration of GnRH antagonist (Average)	5.26	5.33	0.985
Total number of oocyte retrieved in 15 patients	69	60	0.985

Though there was a higher number of metaphase 2 oocyte in the dual trigger compared to control, the difference was not statistically significant. However the number of good quality embryo was significantly higher in the dual trigger group (Table-3).

Table 3: Characteristics of IVF cycle in the two studied groups.

Variables	Dual trigger group (n=15)	Control group (n=15)	P value
Total number of MII oocyte	51	39	0.525
Total number of embryo	46	37	0.609
Total number of good quality embryo Good quality embryo (%)	30, 65.2	9, 25	0.02

Discussion

Dual trigger was used initially in high responders (such as PCOS) to minimize the risk of OHSS. This was accompanied with better ART treatment outcomes. Dual trigger was also used in normal responders and study showed significant increases increase in the number of mature oocytes and number of zygotes too, thereby improving the outcome of the IVF cycle. [16, 17, 18]

Griffin and colleagues showed that the dual trigger (HCG plus GnRH agonist) can improve number of mature oocytes although pregnancy rates were not improved in their study. We also found significantly good-quality embryos in the dual trigger group compared to HCG alone. One of the reasons attributed to good quality embryos may be due to total number of retrieved oocytes and their metaphase II being more in the dual trigger group [19].

Zilberberg *et al*. showed that by using dual triggering in patients with low proportion of mature oocytes, there was a significant higher number of mature oocytes (MII), number of embryos transferred, higher proportions of MII oocytes per number of oocytes retrieved and a higher number of top quality embryos and more clinical pregnancy, as compared to hCG-only trigger [20].

The aim of present study was to evaluate whether the "Dual trigger, can improve oocyte maturation in poor responder patients based on Bologna criteria and their ART out comes. Our study found an increase in the number of good quality embryos in cycles triggered by GnRH agonist and hCG trigger (dual trigger) in antagonist cycles. Also, in dual trigger group, empty follicle syndrome were not seen, while one case reported empty follicle syndrome in HCG trigger group. The number of oocyte retrieved and M 2 number were not significantly different between the two groups, the reason being the small sample size which was a major limitation of our study.

Before introducing the dual trigger as a routine practice further large prospective studies should be done to evaluate the role of dual triggers in poor ovarian responders in GnRH-antagonist protocols. Dual trigger should be advocated as a safe approach to optimizing clinical outcome without cycle cancellation in poor ovarian responders of GnRH-antagonist protocols.

Conclusion

In our study, there were a significant higher number of good-quality embryos in the dual trigger group compared to the HCG group. However, there was no significant difference in the oocyte retrieved metaphase II number and further large scale clinical trials are needed

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Not available

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