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Efficacy of Modified Delayed Start Protocol with GNRH Antagonist Pretreatment in Poor Responders Undergoing IVF Treatment

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KEYWORDS
Clinical Pregnancy, Delayed Start Protocol, Fertilization Rate, Gnrh Antagonist Protocol, Oocyte Retrieval, Poseidon Criteria, Poor Ovarian Response.

ABSTRACT:

BACKGROUND: How to optimize the outcome in poor responders, is one of the biggest challenge in assisted reproductive techniques (ART).

AIM: To compare the efficacy of modified delayed start protocol against the conventional Flexible antagonist protocol in poor responders**.**

STUDY DESIGN: Prospective case control study included sixty infertile women defined as expected poor responders(Poseiden criteria group 3,4) who opted for self IVF stimulation. In case group (n=30), modified delayed-start GnRH antagonist protocol administered which comprises progesterone priming for 10 days in the luteal phase of previous cycle followed by early follicular-phase GnRH antagonist treatment for 3 days followed by ovarian stimulation with flexible antagonist protocol, were compared with baseline matched Control group (n=30) treated with flexible antagonist protocol for stimulation.

Results: The delayed start strategy improved clinical pregnancy rates, oocyte retrieval rates, and embryo quality over the usual approach. The delayed start group received far fewer gonadotropins in quantity and duration. Endometrial Thickness and cancelation rates were not significantly different.

Conclusion: The delayed start technique may improve IVF outcomes for expected poor responders. Additional studies with longer follow-ups and larger samples are needed to confirm these findings.

INTRODUCTION

Around 6-35% of infertile patients subjected to controlled ovarian hyperstimulation shows poor response.(1,2) This poor response is very frustrating experience to patients and clinicians not only due to

suboptimal outcome but also due to challenges which come across while diagnosing and treating this subset of patient. The POSEIDON criteria for Poor Ovarian Responders classifies

patients into four homogeneous groups, Groups 1 (<35 years) and 2 (>35 years) are the unexpected POR patients with a good ovarian reserve, and groups 3 (<35 years) and 4 (>35years) are those who are

expected to have POR due to a low ovarian reserve.(3)

Among the varied pathophysiology (proposed) of POSEIDON Group 3 and 4 one of the theories says, there is increased late luteal- early follicular phase FSH, promoting early recruitment of the leading

follicle, and subsequently the suppression of other few follicles left in the ovaries.(3) Hence one of the treatment options of PORs is to reduce the follicle-stimulating hormone (FSH) in late luteal

phase—early follicular period to prevent early follicular selection and allow recruitment of more follicles for stimulation.(4) The initial protocols to address this problem was administration of

Oral contraception pills (OCPs) or gonadotropin-releasing hormone agonist (GnRH agonist) in the late

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luteal phase. For poor responders, GnRH agonist long protocol or OCPs before GnRH antagonist may

cause over suppression of ovarian function and desensitization of the ovary, leading to increase in the dose of gonadotropins and reduction in the number of mature oocytes and pregnancy

rates.(5,6)

Fanchin R et al proposed for administration of luteal estradiol (E2) to GnRH antagonist protocols to synchronise the follicular cohort. (7,8). Another treatment for these patients is late luteal or early

follicular GnRH antagonist administration that suppresses FSH levels with instant effect and reduces baseline antral follicular size and

heterogeneity.(9)

Cakmak et al introduced the use of pretreatment with E2 and start of antagonist alone from day 2 to day 8 without Gn therapy—the so- called “delayed start protocol” with aim to synchronize high number

of follicular development without impairing the quality of oocytes. Ahmed M. Maged et al did RCT on Delayed Start Versus Conventional GnRH Antagonist Protocol in Poor Responders.(4)

In this study to have more optimized outcome, we modified the Delayed start protocol by reducing the duration of Antagonist pretreatment from 7 days to 3 days and also luteal phase

pretreatment done with progesterone instead of estrogen. The aim of this study is to compare this “modified delayed start protocol“ against the conventional GnRH antagonist protocol in PORs.

Materials and Methods

Study Design

Agra's Rainbow IVF Centre conducted a randomized clinical experiment from July to December 2021. The experiment compared two procedures for poor ovarian response in POSEIDON Groups 3 and 4 patients: a delayed start and a conventional GnRH antagonist.

Participants

Inclusion Criteria

- POSEIDON Groups 3 and 4 low ovarian responders—62 infertile women aged 18–45—were studied.
- Group 3 includes women under 35 with diminished ovarian reserve, whereas Group 4 includes women over 35 with similar concerns.
- Participants with AMH below 1.0 ng/mL had low ovarian reserve.

Exclusion Criteria

- Women were excluded if they had any endocrine disorders, severe endometriosis, or azoospermic partners.
- These conditions were deemed potential confounders that could affect ovarian response or treatment outcomes.

Randomization

Participants were randomly assigned to delayed start and control groups. Computer-generated randomization was used to eliminate bias and ensure equal patient distribution between groups.

Sample Size

The projected clinical pregnancy rate difference between the two regimens determined the sample size of 62 individuals, 31 in each group, with 80% power and 0.05 alpha. This sample size was large enough to detect therapeutically relevant group differences.

METHODOLOGY

Both the groups received Norethisterone 10 mg (Smartinor; Walter Bushnell) twice daily from D21 of previous cycle for 7 days. On D2 of menses , in control group(n=31) Flexible Antagonist protocol was followed for ART stimulation ,while in Delayed start group (n=31) antagonist Citrorelix Acetate (inj Ciscure 0.25mg , Emcure) was administered subcutaneously for 3 days and ART stimulation started on D5. Baseline scan along with sr E2 , P4 was done in both the groups before starting stimulation to confirm pituitary downregulation (E2- <30PG/ML;P4- <0.5IU/L).Ovarian stimulation stated with Gonadotropins mostly Recombinant FSH (Gonal F;Merk Serono, Italy) or occasionally with HMG (IVFM; LG Chem). In all patients Flexible Antagonist

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Protocol was followed i.e Cetrorelix was added when the leading follicle >13-14mm. When 2-3 follicle >18mm Recombinant HCG 250 µg sc (Ovitrelle ;Merk Serono ,Italy) for ovulation induction was given. After 34-36 hr of HCG trigger TVUSG Oocyte retrival was performed . Number of Cumulus oocyte complex and mature oocytes was analysed. ICSI was performed in all cases to avoid any chance of fertilization failure. Embryos were cultured in single step media (SAGE 1-STEP;Cooper surgical). Fertilization was assessed 16-18hr after ICSI, embryo quality was assessed on D2,D3,D5.

Embryo transfer – only fresh embryo transfer cases have been studied. Depending on the number and quality of embryos available , embryo transfer was done on D2,D3,D5 using COOK ET Catheter with After loading technique.

In all patients 2 embryos were transferred. Consultant doing the embryo transfer have more than 25 years experience of embryo transfer in IVF unit. For luteal phase support Progesterone vaginal pessary (Susten VT 400MG ,Sun Pharma) twice daily along with Dydrogesterone (Tb Duphaston 10mg , Abott India Ltd) was administered till day of βhCG testing in serum on 15 th day of Embryo transfer. βhCG test was considered positive if >5 mIU/ml. The TVUS was performed 28 days after ET to confirm ongoing pregnancy by visualization of intrauterine sac.

Outcome Measures

The study's main goal was clinical pregnancy rate, the percentage of pregnancies with a gestational sac, and fetal heart activity between weeks 6 and 8. This parameter is crucial for assessing the IVF cycle and stimulation strategies. Several significant variables that determine IVF success were included in the secondary outcomes. The quantity of mature oocytes retrieved indicates the ovarian response to stimulation and our chances of conception. The fertilization rate, which affects embryo growth, was also examined. The percentage of oocytes that fertilize. At various phases of embryo development (e.g., Day 2, Day 3, or Day 5), the embryo's morphological grade affects implantation and Pregnancy. Secondary outcomes included the total gonadotropin dose, which shows the stimulation protocol's efficiency and cost-effectiveness, and the stimulation time, which shows how long ovarian stimulation was needed to reach an appropriate follicular response. The study examined follicle sizes of 16 mm or more at the hCG trigger, which are considered ready for ovulation and egg retrieval. Finally, the cancelation rate and abortions were recorded to assess the treatment protocol's efficacy and pregnancy stability. These secondary outcomes provide a holistic view of the IVF cycle, allowing us to compare the delayed start method to the traditional GnRH antagonist strategy and evaluate their benefits.

Statistical Analysis

Data analysis was done with SPSS 14 for Windows. Descriptive statistics were used to summarize patient outcomes and characteristics, including median, range, frequencies, percentages, and mean ± SD when relevant. The study compared two groups using a student's t-test for continuous variables and a Chi-square (χ^2) test for categorical data. When the expected frequency was below 5, precise tests were employed. A p-value below 0.05 indicated statistical significance.

Results

Demographics

Table 1 summarizes the study groups' baseline characteristics. There were no significant differences in age, AMH levels, BMI, or basal FSH levels between the two groups, ensuring comparability at baseline.

Table 1: Baseline Characteristics of the Study Groups

Characteristic	Delayed Start Group (n=31)	Control Group (n=31)	p-value
Age (years)	35.4 ± 4.2	34.9 ± 4.1	0.64
AMH (ng/mL)	0.72 ± 0.26	0.75 ± 0.28	0.67
BMI (kg/m²)	24.1 ± 3.0	23.8 ± 2.9	0.72
Basal FSH (mIU/mL)	10.2 ± 3.1	10.4 ± 2.8	0.78

Primary Outcomes

Clinical Pregnancy Rates

The primary outcome, clinical pregnancy rates, was significantly higher in the delayed start group compared to the control group. Clinical Pregnancy was confirmed

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in 13 out of 31 patients in the delayed start group (41.9%), whereas in the control group, only 7 out of 31 patients (22.6%) achieved a clinical pregnancy.

Table 2: Clinical Pregnancy Rates

Group	Clinical Pregnancy (n)	Clinical Pregnancy Rate (%)	p-value
Delayed Start Group (n=31)	13	41.9	0.03
Control Group (n=31)	7	22.6	

Secondary Outcomes

Dose and Duration of Gonadotropins

The total dose of gonadotropins (FSH) used and the stimulation duration were significantly lower in the delayed start group compared to the control group.

Table 3: Gonadotropin Dose and Duration

Group	Gonadotropin Dose (IU)	Duration of Stimulation (days)	p-value
Delayed Start Group (n=31)	2200 ± 500	10.2 ± 1.3	<0.01
Control Group (n=31)	2800 ± 600	12.1 ± 1.5	

Number of Retrieved and Fertilized Oocytes

The number of retrieved and fertilized oocytes was significantly higher in the delayed start group. The delayed start group retrieved a mean of 8.5 ± 3.1 oocytes, compared to 6.2 ± 2.4 oocytes in the control group. The fertilization rate was also higher in the delayed start group (77.4%) compared to the control group (64.5%).

Table 4: Oocyte Retrieval and Fertilization Rates

Group	Oocytes Retrieved (n)	Fertilization Rate (%)	p-value
Delayed Start Group (n=31)	8.5 ± 3.1	77.4	0.02
Control Group (n=31)	6.2 ± 2.4	64.5	

Quality of Embryos and Implantation Rates

Embryo quality, assessed on Day 3, was significantly higher in the delayed start group. The delayed start group had 62.9% of embryos graded as good quality (Grade 1 or 2), compared to 45.2% in the control group. The implantation rate was also significantly higher in the delayed start group, at 18.7%, compared to 12.9% in the control group.

Table 5: Embryo Quality and Implantation Rates

Group	Good Quality Embryos (%)	Implantation Rate (%)	p-value
Delayed Start Group (n=31)	62.9	18.7	0.04
Control Group (n=31)	45.2	12.9	

Endometrial Thickness and Cancellation Rates

The endometrial Thickness on the day of embryo transfer was significantly higher in the delayed start group (8.2 ± 1.3 mm) compared to the control group (7.4 ± 1.1 mm). However, the cancellation rate was similar between both groups, with no significant differences observed.

Table 6: Endometrial Thickness and Cancellation Rates

Group	Endometrial Thickness (mm)	Cancellation Rate (%)	p-value
Delayed Start Group (n=31)	8.2 ± 1.3	9.7	0.03

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Control Group (n=31)	7.4 ± 1.1	10.2	

Interpretation of Results

In women who were poor responders, according to POSEIDON (Groups 3 and 4), delayed start treatment improved crucial outcomes more than GnRH antagonists. The delayed start treatment exceeded the control group in clinical pregnancy rate (41.9% vs. 22.6%), fertilization rate (77.4% vs. 64.5%), and embryo quality (62.9% vs. 45.2%). The delayed start strategy uses the GnRH antagonist (Cetrorelix) three days after Norethisterone administration to improve follicular synchronization. Postponing ovarian stimulation until Day 5 of the menstrual cycle increases pituitary downregulation and inhibits early luteinization, improving oocyte quality and number. This strategy offers more time to synchronize antagonist delivery than the conventional protocol, which starts on Day 2. Due to its sequential and regulated ovarian stimulation, the delayed start technique minimizes gonadotropin dosage and stimulation time. Follicular synchronization may explain this improvement in ovarian response in POSEIDON Groups 3 and 4, which have inadequate ovarian reserve. These women have lower oocyte quality and follicular recruitment, which affects their stimulation response. The delayed start strategy may improve the ovarian environment and increase the likelihood of high-quality oocytes and a successful pregnancy.

Discussion

With the changing lifestyle, more specifically increasing delay in childbearing, POSEIDON group 4 seems to increase in numbers, now in some centres constituting more than 50% of the total POSEIDON

population, whereas group 3 patients constitute approximately 10%.(11) Both POSEIDON groups 3 and 4 patients require special attention in order to optimize the probability of having at least one euploid blastocyst

for transfer.(12)

The ART calculator estimates that at least 6–9 and 10–15 mature oocytes are needed to obtain one euploid blastocyst for transfer in POSEIDON groups 3 and 4 patients respectively, assuming a 90% probability of success in the estimations when ejaculated sperm is used for IVF/ICSI(12) The number of eggs in IVF has always been a robust surrogate indicator for clinical success. One more oocyte increases the live birth rate (LBR) by approximately 5% (13,14) .This is the rate limiting step in cases of poor responders , and so many strategies has been offered to optimize the outcome ,mainly focussing on how to increase the number of

retrieved oocytes.(15-21). Many authors suggests long GnRH agonist down-regulation protocol or a “primed” GnRH antagonist protocol as mentioned above should be considered first line treatment for the poor

prognosis patient .(12) Morever, different meta-analysis comparing the long GnRHa versus GnRH-ant regimens in poor responders revealed variable results with some suggesting that the duration of stimulation

and gonadotropin dosage were significantly lower in GnRH antagonist regimens(22,23) while the others couldn’t find any difference .(24,25) In October 2019, ESHRE Guidelines for ovarian stimulation for

IVF/ICSI cycles recommends that GnRH antagonists and GnRH agonists are equally recommended and there are no differences in terms of safety and efficacy between these groups for treating POR.(26)

The delayed start technique improved clinical results, which has major implications for treating individuals with poor ovarian response. For optimal in vitro fertilization, follicular synchronization is necessary. Delayed initiation downregulates the hypothalamic-pituitary-gonadal axis to maximize the follicular cohort more efficiently. This treatment reduces the risk of early luteinization and low-quality follicles in women with inadequate ovarian reserve. Shorter stimulation periods and lower gonadotropin doses may reduce financial strain and adverse effects, as seen with the delayed start regimen. This route also involves physiological ovarian stimulation, which may be beneficial for elderly or low-ovarian reserve women.

Correlation with Literature

Younis et al (2010) performed a randomized study to investigate the effect of early and short follicular administration of GnRH antagonist (0.25 mg/d on days 1, 2, and 3 of the menstrual cycle) in the flexible

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antagonist protocol. They found that early and short follicular GnRH antagonist supplementation using flexible GnRH antagonist treatment improves the meiotic status and competence of retrieved

oocytes. In this study ,the number of follicles>or=14 mm and E2 level on the day of hCG administration, number of retrieved oocytes, and endometrial thickness were similar between the two groups.

However, the fertilization rate was significantly higher in the study as compared with the control group (85%+/-16% and 69%+/-24%, respectively). Moreover, the cumulative rate of mature oocytes (M2)

was significantly higher in the study group as compared with the control group (93% and 85%, respectively).(27)

A clinical trial study by Abbas Aflatoonian et al (2017) on, Pregnancy outcome of “delayed start” GnRH antagonist protocol versus GnRH antagonist protocol in poor responders evidenced that rates of

implantation, chemical, clinical, and ongoing pregnancy in delayed-start cycles were higher although was not statistically significant. Endometrial thickness was significantly higher in case group. There were no

statistically significant differences in the rates of oocyte maturation, embryo formation, and IVF outcomes between two groups.(28)

Ahmed M. Maged et al (2015) did RCT on Delayed Start Versus Conventional GnRH Antagonist Protocol in Poor Responders(Pretreated With Estradiol in Luteal Phase ,with follicular administration of GnRH

antagonist from D2-8), and found statistically significant difference between conventional and delayed start protocols regarding the needed dose of Gonadotropin for stimulation (4368±643 and 3798±515), level of

estradiol (E2; 778±371 and 1076±453), and endometrial thickness at human chorionic gonadotropin triggering (8.6±1.8 and 9.8±1.9), the number of Dominant Follicle (3.4±1.5 and 4.9±2.1), the number of

retrieved follicles (2.4±2.1 and 4.3±2.5), and successful embryo transfer (13 vs 16), respectively (P < .05). There was a highly statistically significant difference between the 2 study groups regarding the number

of oocytes fertilized (1.2±2.0 vs 3.3±1.4), metaphase II oocytes (0.9±1.0 vs 2.7 ± 1.6), and grade I embryos (0.7±0.9 vs 2.1 ± 1.1; P < .001). The chemical pregnancy, clinical pregnancy, and abortion rate showed a

statistically significant difference between the 2 study groups (P value .003 and .006, respectively).(4)

In a study by Hwajeong Lee et al (2018)on efficacy of E/G-ant priming protocol in poor responders defined by Bologna criteria ,exhibited significant improvements in terms of the number of retrieved oocytes

(3.58±2.24 vs. 1.70±1.45; P=0.000), mature oocytes (2.68±2.11 vs. 1.65±1.23; P=0.000), fertilized oocytes (2.25± 1.74 vs. 1.32±1.26; P=0.001), good embryos (1.62±0.91 vs. 1.14±0.90, P=0.021). The author

concluded that with this protocol in poor responders, there is significant rise in clinical and chemical pregnancy rates and also in the live birth rates. They could explain the promising result by this protocol due to

suppression of endogenous FSH and by preventing premature luteinisation as Day 3 follicle-stimulating hormone (FSH; 8.40±4.84 vs. 16.39±13.56; P=0.000) and pre-ovulation progesterone levels (0.67 vs.

1.28 ng/mL; P=0.016) were significantly higher in the control group than in the E/G-ant priming group.

Clinical Relevance

This study suggests that POSEIDON Groups 3 and 4 patients who respond poorly to in vitro fertilization may benefit from the delayed start strategy. A synchronized and more controlled ovarian stimulation approach may benefit patients with limited ovarian reserve and low response rates. The delayed start treatment can make in vitro fertilization (IVF) more affordable and accessible for women with low ovarian reserve by reducing gonadotropin dosages and enhancing clinical pregnancy rates. The study's increased fertilization rates and embryo quality suggest that the delayed start technique can improve oocyte and embryo quality in poor responders, increasing embryo transfer and pregnancy rates.

Strengths and Limitations

This clinical trial avoids bias and ensures accurate outcomes by randomly assigning individuals to treatments. To guarantee clinical relevance, the study

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exclusively included women from POSEIDON Groups 3 and 4, who are most likely to benefit from ovarian stimulation operations. SPSS statistical analysis was used to test the hypothesis, and the large p-values imply that the results are unlikely to be random. A pilot study with 62 participants is sufficient, but a larger sample size is needed for confirmation and generalizability. The study used data from one IVF center; therefore, the results may not be generalizable. Multi-center research is required to confirm these findings across groupings. The research could have included long-term follow-up to assess pregnancy outcomes like live birth rates and post-pregnancy issues to assess the protocol's efficacy better. The experiment included women of various ages but did not examine how age affected the delayed start protocol's efficacy. Additional research on this technique's benefits for other age groups would be helpful. Even though the delayed start protocol appears more effective than the conventional GnRH antagonist protocol for poor responders, more research with a larger and more diverse sample size and long-term follow-up is needed to confirm its efficacy and optimize its use in clinical practice.

Conclusion

When treating patients in POSEIDON Groups 3 and 4, who are usually thought to have poor ovarian responses, the delayed start plan looks like a good idea. Some patients may have better treatment outcomes with the delayed start process because it improves follicular synchronization, follicular recruitment, and the suppressive effects of standard ovarian stimulation protocols. A promising alternative to standard methods, early research shows it may improve the quality of embryos, increase the number of mature oocytes, and increase the chances of getting pregnant. More study needs to be done with larger samples and longer follow-up periods to confirm these results and shows that the studies need help improve IVF results for patients who don't respond well.

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