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Optimizing *in vitro* fertilization outcomes: Long-acting gonadotrophin releasing hormone agonist versus gonadotrophin releasing hormone antagonist protocol in Poseidon groups 3 and 4

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Abstract
Background: Infertility is a disease with profound consequences on the quality of life of both men and women. In modern times as women tend for bearing children at older age, the average age of first-time mothers is increasing in many countries. Poor ovarian reserve (POR) is an important limiting factor for the success of any treatment modality for childbearing and infertility. Low AMH or low AFC is defined as diminished ovarian reserve (DOR) which suggests that only few oocytes will be retrieved from these patients in a single stimulation cycle. It is dilemma in clinical practice for clinicians which protocol to be consider with agonist or antagonist in patients with low ovarian reserve to achieve multiple follicle development and clinical pregnancy. Till now there are not many studies which discuss this valid point. The hypothesis of this study is to discover a perfect protocol in patients with poor ovarian reserve and optimize reproductive outcomes.
Material and Methods: A prospective, randomised controlled study was conducted in a period of one year from 1st July, 2023- 30th June, 2024 at Ridge IVF centre, Delhi. Women of all ages (25-40 years) attending the ART clinic eligible for IVF/ICSI at our centre were randomized using computer generated sequence and assigned in 2 groups: Group A, which follows the long-acting GnRH agonist protocol, and Group B, which follows the GnRH antagonist protocol. Women with age <35 years and S.AMH ≤ 1.2 ng/ml and AFC< 5 (POSEIDON 3) and Age >35 years and S.AMH ≤1.2ng/ml and AFC< 5 (POSEIDON 4) were included. Only Grade A/B embryos of Day 3 and Day 5 were transferred in patients.
Results: The study showed that that no. of oocytes retrieved, no. of M2 oocytes, no. of total embryos formed, no. of day5 (blastocyst) embryos and no. of day3 embryos formed were similar with statistically no significant difference (p>0.005) in both protocol groups. The duration of stimulation was similar in both groups, but the total dose of gonadotrophins used was higher in Long- acting GnRH agonist protocol (p<0.001) as compared to GnRH antagonist protocol. The study also showed that the good quality embryos (Grade A/B) formed at day3 were higher in agonist group with no statistical significance (p>0.005) while the blastocyst grading (AA/AB/BB) was comparable in both groups. The clinical pregnancy rate was higher in agonist group, but the difference was not statistically significant (p=0.545).
Conclusion: The present study demonstrated that Long-acting GnRH agonist and GnRH antagonist protocols are equally efficient in POR. Due to reduced quality and quantity of oocytes in POR patients, a perfect protocol is still yet to be discovered.

Keywords: POR, GnRH agonist, GnRH antagonist, controlled ovarian stimulation (COS)

Introduction
Infertility is a disease with profound consequences on the quality of life of both men and women. In modern times as women tend for bearing children at older age, the average age of first-time mothers is increasing in many countries. Poor ovarian reserve (POR) is an important limiting factor for the success of any treatment modality for childbearing and infertility. Low AMH or low AFC is defined as diminished ovarian reserve (DOR) which suggests that only few oocytes will be retrieved from these patients in a single stimulation cycle. It is dilemma in clinical practice for clinicians which protocol to be consider either agonist or antagonist in patients with low ovarian reserve to achieve multiple follicle development and clinical pregnancy and live birth. It is believed that approximately 10% of women undergoing IVF will present as poor response to gonadotrophins stimulation [1-3]. Till now there are not many studies which discuss this valid point. The hypothesis of this study is to discover a perfect protocol in

patients with poor ovarian reserve and optimize reproductive outcomes.

Over the past few years, many tests have been developed to predict the ovarian reserve and ovarian responsiveness to controlled ovarian stimulation (COS). Variables such as age, body mass index (BMI), basal oestradiol, inhibin B and follicle stimulating hormone (FSH) are indirect and less reliable markers of ovarian reserve. Antimullerian hormone (AMH) and antral follicle count (AFC) are the most reliable markers for predicting the ovarian response in controlled ovarian stimulation (COS).

The POSEIDON (Patient-Oriented Strategies Encompassing IndividualizeD Oocyte Number) classification system, introduced in recent years, has contributed significantly to our understanding of the heterogeneity among IVF patients [4]. It allows better stratification of the women with a low prognosis based on age, AFC and S.AMH levels. Group 3 of the POSEIDON classification comprises those with poor ovarian response, characterized by a diminished ovarian reserve and reduced follicular recruitment. Group 4, on the other hand, includes a subset of women facing an even more formidable challenge with an extremely poor ovarian response. Both groups pose unique clinical dilemmas, demanding innovative and personalized approaches to enhance IVF success rates.

The Long-Acting GnRH Agonist Protocol involves down-regulating the pituitary gland to suppress the release of Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH) [5]. This approach is designed to optimize the ovarian milieu and potentially improve oocytes maturation. This may also increase the endometrial receptivity of women undergoing IVF treatment leading to better reproductive outcomes [6-8]. A systematic review and meta-analysis emphasize the long-acting GnRH agonist protocol as the first-choice treatment with increased ongoing pregnancy rate compared with the GnRH antagonist protocol [9]. A study by Van den Wijngaard *et al*. evaluating patients' preferences using discrete choice analysis showed that many patients preferred a long-acting GnRH agonist protocol as it shorten time to live birth in fresh transfer cycle relative to frozen transfer cycle [10]. A Cochrane review by Albuquerque *et al*. highlights the advantages of the long-acting GnRH agonist protocol among the other types of GnRH agonist ovarian-stimulating protocols [11].

Introduction of the GnRH antagonist in the field of assisted reproductive techniques is quite recent compared with the GnRH agonist, which has been in use in IVF cycles since the 1980s [12]. This protocol entails the administration of GnRH antagonist to prevent premature ovulation and manage the LH surge during controlled ovarian stimulation. A meta- analysis conducted by Polyzos *et al*. compared different ovarian stimulation protocols, including the GnRH agonist long protocol and GnRH antagonist protocol, in women with poor ovarian response. They found that the GnRH antagonist protocol was associated with higher ongoing pregnancy rates compared to the long agonist protocol [13]. This protocol is associated with shorter duration and lower risk of OHSS and reduced total dose of gonadotropins. While both protocols have been widely employed in IVF practice, their comparative effectiveness and outcomes in women belonging to the challenging POSEIDON groups 3 and 4 remain underexplored.

Material and Methods

Study population

A Prospective, Randomized controlled study was conducted at the department of Assisted Reproduction at RIDGE IVF CENTRE, Delhi from 1st July, 2023- 30th June, 2024.Women of all ages (25-40 years) attending the ART clinic were screened for eligibility. The patients were randomized using a computer-generated sequence of random numbers to 2 groups: Group A, which follows the long-acting GnRH agonist protocol, and Group B, which follows the GnRH antagonist protocol. The inclusion criteria in the study were women coming to ART clinic with age <35 years and AMH ≦ 1.2 ng/ml and AFC< 5 (POSEIDON 3). Women of age >35 years and AMH ≦ 1.2ng/ml and AFC< 5(POSEIDON 4). Only Grade A/B embryos are transferred of Day 3 and Day 5. Women with uterine factor infertility, endometriosis, endocrine abnormalities, cycles for PGT for aneuploidy and male factor infertility were excluded from the study. Ethics committee approval was obtained prior the commencement to the study and written informed consent was taken from all patients selected in the study.

The study assessed the primary outcomes as the number of retrieved oocytes, number of mature oocytes (M2), the number of embryos formed, the number of Day 3 and Day 5 embryos formed. Additionally, the grading of embryos on Day 3 and Day 5 was evaluated. The secondary outcomes measured as Hormonal profiles (S.FSH, S. LH, S.E2, S. AMH), duration of treatment (Days of stimulation), total dose of gonadotrophins and clinical pregnancy rate. Sample size was calculated by using sample size calculator. 100 patients were recruited for this single centre study according to the inclusion criteria.

Ovarian stimulation protocols

Long GnRH agonist protocol

On day 2 of the previous cycle, a baseline transvaginal ultrasound was done to measure endometrial thickness and AFC. Daily subcutaneous injection of 0.5mg of leupride acetate was started in the mid luteal phase (day 20) of their previous cycle. The dose is reduced to 0.3mg once pituitary downregulation on day 2 is confirmed and continued till the day of the trigger. Patients were reviewed on day 2 of the cycle to ascertain pituitary downregulation (Endometrial thickness <5mm, follicle <10mm, no ovarian cyst) and baseline S.FSH, S. LH, Oestradiol were sent. The ovarian stimulation with 225IU of Human Menopausal Gonadotrophins (hMG) was started on day 3. The ovarian response was monitored through serial ultrasonography and evaluation of serum oestradiol levels. The trigger was given with recombinant hCG (250µg Ovitrelle, Merck Serono) when at least two leading follicles are ≧18mm. Ovum retrieval was done after 34-36 hours

GnRH antagonist protocol

On day 2, baseline transvaginal scan was done to rule out ovarian cyst and assess the endometrium. Baseline S.FSH, S. LH and S. Oestradiol were sent. HMG at a dose of 225IU was started daily from day 3. A transvaginal scan was done on day 6 to assess follicular growth and endometrial thickness and repeated daily till the leading follicle is ≧14mm in size and serum oestradiol >400 pg/ml when the GnRH antagonist, Cetrorelix (0.25mg/day of cetrorelix: Cetrotide: Merek Seono, Aubonne Switzerland) was added (Flexible protocol). The trigger recombinant hCG (250 µg Ovitrelle, Merck Serono) was added when at least two leading follicles are≧ 18mm. Ovum retrieval was done after 34-36 hours.

Oocyte retrieval

Oocyte retrieval was done after 34-36 hours of trigger. The retrieved oocytes were washed in G-MOPS solution and incubated for 2-3 hours in a G-IVF Plus solution in an incubator at 6% CO_2 at 37 ºC before proceeding to denudation of oocyte.

ICSI was done with husband sperm on mature (M2) oocytes.
Embryo transfer was done on day 3 at the 8-cell stage or Day 5 (Blastocyst stage). Not more than 3 Grade A/B Day 3 embryos and not more than 2 Day 5 embryos were transferred. Luteal phase support was given with micronized progesterone and oral dydrogesterone 10 mg BD. Pregnancy confirmation was done by estimating the S.ßhcg concentration (≧80 mIU/L) in the blood 14 days after embryo transfer and doubling of the S.ßhcg after 48 hours. The clinical pregnancy was established by the presence of gestational sac by ultrasonography performed at 6-7 weeks of pregnancy.

Statistical Analysis

Statistical analysis was conducted using the Statistical Package for the Social Sciences (SPSS) version 28.0. Continuous variables were presented as mean± SD or median (IQR) for normally distributed data. Categorical variables were expressed as frequencies and percentages. The comparison of normally distributed continuous variables between the groups was performed using Student's t-test. Nominal categorical data between the groups were compared using the Chi-squared test or Fisher's exact test as appropriate. Non-normally distributed continuous variables were compared using the Mann-Whitney U test. For all statistical tests, a p-value less than 0.05 was taken to indicate a significant difference.

Results

In our study, baseline characteristics of patients such as age, BMI, type of infertility, S.AMH, AFC, were not statistically significantly different between the two protocols as presented in Table 1 and 2. Similarly Day 2 S.FSH, S. LH, S.E2 were also similar in both the protocols in this study.
In this study, the duration of stimulation was same in both the groups, with no statistically significant difference (p=0.949). The median total dose of gonadotrophins used was higher in Long-acting GnRH agonist protocol (3500 IU IQR 2625.00 - 4125.00) and was statistically significant (p<0.001) as compared to antagonist protocol (2512.50 IU, IQR 2025.00 - 3037.50) (Table 3).
The no of oocytes retrieved, no. of M2 retrieved, no. of total embryos formed, no. of Day 3 and Day 5 embryos formed were similar with statistically no significant difference (p>0.005) between both the stimulation protocol (Table 3). The clinical efficacy of both the stimulation protocols were found to be similar in patients with POR in our study.
Out of the 50 patients on long agonist protocol, 23 had a positive pregnancy and out of 50 patients on antagonist protocol, 21 had positive pregnancy rate, with no statistical significance (Table 4). The good quality embryos formed for day 3 were higher in Long GnRH agonist group with no statistical significance while blastocyst rate was less in both protocol group due to less no of oocytes retrieved in POR. The embryos formed at day 5 was comparable with no statistical significance. Cleavage stage embryo transfer was done in 41 patients out of 50 in long agonist protocol versus 38 patients out of 50 in antagonist protocol. Blastocyst stage transfer was done in 6 patients in agonist group versus 9 patients in antagonist group. When the positive pregnancy rate with day 3 and day 5 embryos transferred was compared between both groups, it was found that long agonist group was better in achieving pregnancy than antagonist group.
Out of 50 cases in Long GnRH agonist group, 3 patients did not undergo embryo transfer due to poor quality of oocyte retrieved and poor grade embryo formed. Similarly, in GnRH antagonist group, out of 50 cases, 3 patients did not go for embryo transfer due to poor grade embryos formed.

Table 1: Demographic Characteristics of Women Group A and Group B

Demographic Characteristics of Women		Group A Long agonist (n = 50)	Group B Antagonist (n = 50)	p value
Wife's Age		32.54±4.25	32.16±3.67	0.317
Husband's Age		35.42±4.01	34.30±4.27	0.090
BMI		25.61±4.54	26.89±6.52	0.128
Married Life (years)		6.02±3.622	3.65±3.031	< 0.001
Duration of infertility (years)		3.92±2.381	2.47±2.375	< 0.001
Type of infertility (%)	Primary	35 (70%)	39 (78%)	0.362
	Secondary	15 (30%)	11 (22%)	
Cycle regularity (%)	Regular	46 (92%)	44 (88%)	0.741
	Irregular	4 (8%)	6 (12%)	
S. AMH (ng/ml)		0.99±0.235	1.06±0.215	0.075

*Statistical significance at p value <0.05

Table 2: Data comparing the Antral follicle count (AFC) between Group A and Group B

AFC	Group A		Group B		p value
	N	%	N	%	
1 – 2	2	4	3	6	0.230
2 – 3	12	24	6	12	
3 – 4	25	50	21	42	
3 – 5	1	2	0	0	
4 – 5	9	18	18	36	
5 – 6	1	2	2	4	
Total	50	100	50	100	

Table 3: Data comparing various parameters related to fertility treatment between Group A and Group B

	Group A		Group B		p value
	Mean±SD	Median (IQR)	Mean±SD	Median (IQR)	
DAY 2 S.FSH (mIU/ml)	8.34±3.62	8.50 (6.12 - 9.77)	7.83±4.11	7.27 (5.22 - 9.37)	0.217
S. LH (Miu/l)	4.32±1.96	4.41 (2.52 - 5.76)	4.31±2.58	3.86 (2.75 - 5.37)	0.553

S. E2 (pg/ml)	32.85±11.55	32.45 (23.91 - 41.71)	38.74±13.66	39.84(29.04 - 49.14)	0.030*
DAYS OF GN	10.70±1.04	11.00 (10.00 - 11.00)	10.64±1.66	11.00 (9.75 - 12.00)	0.949
DOSE OF GN (IU)	3381.84±1030.32	3500.00 (2625.00 - 4125.00)	2561.64±644.95	2512.50 (2025.00 - 3037.50)	<0.001**
No. Of oocytes	7.02±2.46	8.00 (5.75 - 9.00)	6.76±2.46	7.50 (5.00 - 9.00)	0.575
No. Of M2 Oocytes	5.80±2.55	6.00 (4.00 - 8.00)	5.62±2.31	6.0 (4.00 - 7.25)	0.544
No. Of embryos formed	4.22±2.05	4.00 (3.00 - 6.00)	4.66±2.46	4.00 (3.00 - 7.00)	0.335
No. Of D5 Embryos	0.48±0.84	0.00 (0.00 - 1.00)	0.38±0.80	0.00 (0.00 - 0.00)	0.495
No. Of Day3 Embryos	3.58±1.84	4.00 (3.00 - 5.00)	4.18±2.41	4.00 (2.75 - 6.00)	0.266

Table 4: Reproductive outcome characteristics of agonist/antagonist protocol

	Group A (Agonist) n = 50	Group B (Antagonist) n = 50	p value
Positive pregnancy rate	23 (46%)	21 (42%)	0.918
Clinical pregnancy rate	23 (46%)	21 (42%)	0.545
No et	3 (6%)	3 (6%)	

Table 5: Data comparing the grading of embryos at Day 3 between Group A and Group B

Embryos Graded at D3	Group A (n=50)		Group B (n=50)		p value
	N	%	N	%	
Grade A	43	86.0%	39	78.0%	0.435
Grade B	36	72.0%	34	68.0%	0.827

Table 6: Data comparing the grading of embryos at Day 5 between Group A and Group B

Embryos Graded at D5	Group A (n=50)		Group B (n=50)		p value
	N	%	N	%	
AA	3	6.0%	4	8.0%	1.000
BB	4	8.0%	4	8.0%	1.000
AB	7	14.0%	5	10.0%	0.758

Table 7: Data comparing Clinical Pregnancy Rate with Day 3 Embryos between Group A and Group B

Embryo transfer (Day 3)	Group A (Agonist) N=41	Group B (Antagonist) N=38	P Value
Positive pregnancy rate	20 (48.7%)	16 (42.1%)	0.01

Table 8: Data comparing Clinical Pregnancy Rate with Day 5 Embryos between Group A and Group B

Embryo transfer (Day 5)	Group A (Agonist) N=6	Group B (Antagonist) N=9	p Value
Positive pregnancy rate	3 (50%)	5 (55.5%)	0.005

Discussion

A good stimulation protocol should assist the development and retrieval of an adequate number of mature oocytes. The number of retrieved oocytes and mature oocytes in response to COH is an independent predictor of success of the cycle. Patients with POR are a challenge as the number of retrieved oocytes is very low in such cases, decreasing the overall chances of success and leading to the repeated cancellation of a cycle. As age advances, reproductive and ovarian ageing occurs with depletion of the number of oocytes or ovarian reserve. AMH and AFC can POR. The ideal protocol for poor responders should be the one that results in the yield of a maximum number of mature oocytes with minimum cycle cancellation and subsequently clinical pregnancy and live birth. In this study, we are comparing efficacy of long agonist and antagonist in patients with S. AMH of ≤1.2ng/ml and AFC ≤ 5 as POR and evaluate an ideal protocol in these patients.

The current study suggests that the S.beta hcg positivity and clinical pregnancy rates in women under POSEIDON 3 and 4 showed no significant difference following the use of Long acting GnRH agonist protocol versus the GnRH antagonist protocol with similar days of stimulation while the total dose of gonadotropin required was lower in antagonist protocol with a statistical difference and was supported by a similar study by Drakopoulos *et al*. (2016) which compared the GnRH agonist and antagonist protocols in women with POSEIDON group 4 and found that the GnRH antagonist protocol was associated with similar outcomes in terms of clinical pregnancy rates and live birth rates, but with a shorter duration of stimulation and lower total gonadotropin dose [14]. Other studies on POR have also reported similar results [15].

An RCT by Sunkara *et al*. (2011) compared long GnRH agonist, short agonist, and antagonist regimens in poor responders undergoing IVF. This study found no significant differences in clinical pregnancy rates between the three protocols but noted that the antagonist protocol was associated with a shorter duration of treatment and lower total gonadotropin dose [16].

In our study, good quality embryos formed for day 3 were higher in Long GnRH agonist group with no statistical significance while the blastulation rate was comparable with no statistical significance while a study by Yannis papras *et al*. showed that the mean embryo quality was significantly higher in the agonist group (p<.001) but there was no statistically significant difference between the two groups concerning fertilization rates [17]. Cycle cancellation rates were similar in both groups in our study and similar results were also observed in other study [15].

Conclusion

Nowadays, the number of patients with low ovarian reserve has substantially increased due to late marriage and delayed childbearing. Despite, extensive research, multiple stimulation protocols, and the addition of adjuncts, the treatment of patients with POR remains challenging to treat. The present study suggests that clinical pregnancy rate is higher in long GnRH agonist protocol compared to GnRH antagonist protocol, but the difference was not statistically different. However, there is a need for RCT to investigate further the current study findings in the POSEIDON 3 and 4 groups. It is also important to include LBR as the main outcome for future studies.

Conflict of Interest: Not available

Financial Support: Not available

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