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Comparison of outcomes in terms of number and quality of oocytes, embryos, and pregnancy rate in pretreatment and non-pretreatment groups in GNRH antagonist protocol in IVF – A cohort study.

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Abstract

Background
The GnRH antagonist protocol in IVF offers a patient-friendly approach with reduced treatment duration. However, follicular asynchrony remains a concern due to the inherent FSH sensitivity during the late luteal phase, potentially affecting IVF outcomes.
Aim: To compare the outcomes of pre-treatment versus non-pre-treatment groups in GnRH antagonist IVF cycles in terms of gonadotropin consumption, oocyte and embryo quality, and pregnancy rates.

Materials and methods
This prospective observational study included 130 subfertile women undergoing IVF at IGIMS, Patna, randomized into pre-treatment (n=65) and non-pre-treatment (n=65) groups. Synthetic progestogens were administered in the pre-treatment group. Controlled ovarian hyperstimulation was conducted using recombinant FSH, with GnRH antagonist initiated when follicles reached 14 mm.

Results
This prospective observational study assessed IVF outcomes in a pre-treatment group (n = 65) and a non-pre-treatment group (n = 65) undergoing GnRH antagonist protocols. The majority of participants were 28–33 years old (55.38% in non-pre-treatment and 40% in pre-treatment), with mean ages of 30.98 ± 4.15 and 31.57 ± 4.48 years, respectively. There were no significant differences in ovarian reserve, oocytes retrieved (5.87 vs. 6.13), 2PN (4.63 vs. 5.06), good quality embryos (1.30 vs. 2.12), or pregnancy rates (44.62% vs. 46.15%) between groups ($p > 0.05$). The findings suggest that pre-treatment with synthetic progestogens does not improve IVF outcomes in these women.

Conclusion
Pre-treatment with progestogens in GnRH antagonist IVF protocols does not improve clinical outcomes, suggesting that routine pre-treatment may not be necessary in normal responders.

Recommendation
A larger cohort would allow for more robust statistical analysis and might uncover additional nuances in the relationships between laboratory parameters and clinical outcomes.

Keywords: *In Vitro Fertilization, Gonadotropin-release Hormone Antagonist, Pre-treatment, Oocyte quality*
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Introduction

Due to its shorter treatment duration and lower gonadotropin consumption, the gonadotropin-releasing hormone (GnRH) antagonist protocol has become a patient-friendly method for in vitro fertilisation (IVF) [1]. The lack of synchronization among the ovarian follicular cohort before stimulation remains a key challenge in GnRH antagonist cycles. Because of their innate sensitivity to follicle-stimulating hormone (FSH), certain early antral follicles start to react to slight increases in FSH during the late luteal phase of a normal menstrual cycle [2,3]. Consequently, while the next cycle begins, a diverse follicular population of different sizes manifests. When controlled ovarian hyperstimulation (COH) is initiated, this follicular asynchrony may intensify further during the stimulation process, which may affect the quality of the embryo, oocyte retrieval, and pregnancy outcomes in IVF cycles [4]. Oral contraceptive pills (OCPs), progestins, estradiol, and GnRH antagonists are among the pre-treatment techniques that have been suggested to improve follicular synchronisation to solve this problem. To synchronise follicular development before COH, these agents are started during the late luteal phase of the previous cycle, which is marked by increased FSH levels that encourage follicular recruitment [5].

Comparing the results of the GnRH antagonist IVF regimen between pre-treatment and non-pre-treatment groups was the main goal of this study. The goals included assessing the quantity and quality of mature oocytes recovered, the quality of the embryos, the length and dosages of gonadotropins needed, and the overall pregnancy rates [6]. The study's objective was to evaluate these factors to ascertain whether pre-treatment tactics considerably enhance clinical results in IVF cycles that employ the GnRH antagonist regimen.

Materials and methods

Study design

This was a prospective observational cohort study conducted in the Department of Reproductive Medicine at Indira Gandhi Institute of Medical Sciences (IGIMS), Patna.

Study setting

The study was carried out at IGIMS, Patna — a tertiary care, teaching hospital with specialized facilities for assisted reproduction — between February 2022 and January 2024. Participant recruitment, follow-up, and data collection were performed during this period.

Study population

A total of 130 subfertile women, classified as normal responders with similar baseline characteristics, undergoing their first or second IVF-ICSI cycle, were enrolled.

Participants were randomly assigned to two groups:

- Pre-treatment group (case group): 65 women
- Non-pre-treatment group (control group): 65 women

Inclusion criteria

- Women aged 21-39 years
- Basal FSH levels ≤15 mIU/mL (measured on day 2 or 3 of the menstrual cycle)
- Regular menstrual cycles (25–35 days) for at least 3 months before treatment initiation

Exclusion criteria

- Severe endometriosis (Stage III-IV)
- Severe male factor infertility
- Elevated day-3 FSH levels (>15 mIU/mL)
- Uterine or ovarian disorders

Pre-treatment Protocol: In the pre-treatment group, synthetic progestogens were administered starting on day 21 of the preceding menstrual cycle for 5 days. Participants reported on day 2 of the subsequent menstrual period for a baseline transvaginal scan assessing antral follicle count and ruling out ovarian cysts or dominant follicles.

Controlled Ovarian Hyperstimulation (COH)

- Initiation of recombinant FSH (r-FSH) on day 2 of the menstrual cycle
- Monitoring with transvaginal ultrasound on day 6 of gonadotropin stimulation
- Gonadotropin doses were individualized based on ovarian response

GnRH antagonist administration

A GnRH antagonist (cetrorelix 0.25 mg subcutaneously daily) was introduced when at least one follicle reached 14 mm in diameter and continued until the trigger.

Trigger and Ovum Pickup

- The final oocyte maturation trigger was administered when three dominant follicles reached ≥17 mm

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- Ovum pickup (OPU) was performed 36-38 hours post-trigger

Measurement of FSH levels

Serum FSH was measured by chemiluminescence immunoassays (CLIA) (using a fully automated analyzer) on day 2 or 3 of the cycle. The assay has a sensitivity of 0.05 mIU/mL and an analytical variability of < 10%.

Efforts to reduce bias

To minimize bias, allocation to groups followed predefined criteria (those willing to undergo progestogen were placed in the pre-treatment group; controls were those proceeding directly to COH). Furthermore, clinical and ultrasound assessments were performed by the same team of experienced practitioners, blinded to group assignment. Serum assays were processed in a single laboratory to avoid inter-assay variability. Standardized protocols were used for ovarian stimulation and oocyte retrieval across all participants.

Ethical approval

The study was approved by the IGIMS Ethics Committee (Approval no IGIMS/IEC/2023/45, dated 10th January 2023).
Written informed consent was obtained from all participants before their enrollment in the study.

Results

The study population consisted of 130 women undergoing IVF-ICSI treatment. The majority of participants fell within the 28–33 years age group (55.38% in the non-pre-treatment and 40% in the pre-treatment group). The mean age of the pre-treatment group was 31.57 ± 4.48 years, while that of the non-pre-treatment group was 30.98 ± 4.15 years. There was no significant difference in age distribution between the two groups (p = 0.445).
In this prospective observational study comparing pre-treatment and non-pre-treatment groups in the GnRH antagonist IVF protocol, no statistically significant differences were observed between the two groups across key outcome parameters.

- Age, Anti-Müllerian Hormone (AMH) levels, Antral Follicle Count (AFC), duration of stimulation, number of mature oocytes retrieved, 2PN (two-pronuclear) stage oocytes, good-quality embryos, and pregnancy rates were comparable between the pre-treatment and non-pre-treatment groups.

These findings suggest that pre-treatment with synthetic progestogens did not confer any additional benefit in terms of improving ovarian response, oocyte yield, embryo quality, or pregnancy outcomes in IVF cycles using the GnRH antagonist protocol.
Supporting studies also align with these findings:

- Cedrin-Durnelin et al. reported similar IVF outcomes between estradiol pre-treatment and no pre-treatment groups.
- P.G. Wardle et al. evaluated the use of norethisterone as a pre-treatment in 181 patients and found no significant impact on IVF outcomes compared to controls.

Thus, the study concluded that while pre-treatment options may assist in scheduling and follicular synchronization, they do not significantly improve clinical outcomes in IVF cycles employing GnRH antagonist protocols.

The majority of participants in both groups were aged between 28-33 years. Statistical analysis revealed no significant difference in age distribution between the groups (p = 0.445), with the mean age of the pre-treatment group being 31.57 years and that of the non-pre-treatment group being 30.98 years.

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Table 1: Comparison of age

Age	Non-Pre-Treatment Group		Pre-Treatment Group		P Value
	Number	%	Number	%	
22-27	11	16.92%	13	20%	
28-33	36	55.38%	26	40%	**0.445**
34-39	17	26.15%	24	36.92%	
>39	1	2.86%	2	3.08%	
Total	65	100%	65	100%	
Mean±SD	30.98±4.15		31.57±4.48		

Table 2: Comparison of Ovarian Reserve and other parameters in both groups

Variables	Non-Pre-Treatment Group	Pre-Treatment Group	P value
AFC	16.10±4.98	15.70±5.01	0.667
AMH	3.44±2.97	2.70±1.66	0.094
Days of Stimulation	10.451±1.99	11.06±1.53	0.416
Number of Mature Oocytes	6.63±4.36	7.04±2.30	0.478
Oocytes Retrieved	5.87±1.49	6.13±1.57	0.256
2 PN Stage	4.63±2.10	5.06±1.42	0.152
Good Quality Embryos	1.30±2.11	2.12±2.25	0.139
Total Dose of Gonadotropins used	2636.15±696.98	2693.07±497.62	0.569

Table 2 compares key ovarian reserve parameters between the two groups. The average Antral Follicle Count (AFC) in the non-pre-treatment group was 16.10 ± 4.98, while the pre-treatment group had an AFC of 15.70 ± 5.01. The difference between the two groups was not statistically significant ($p = 0.667$). Similarly, Anti-Müllerian Hormone (AMH) levels, gonadotropin dose, stimulation duration, and number of mature oocytes retrieved showed no significant differences between the groups. The number of 2PN (two-pronuclear) stage oocytes and the number of good-quality embryos were also comparable ($p = 0.152$ and $p = 0.139$, respectively).

Table 3: Pregnancy outcome of the two groups.

PREGNANCY	Pre-treatment Group		Non-Pretreatment Group		P value
	Number	%	Number	%	
Yes	**30**	**46.15 %**	**29**	**44.62%**	
No	**35**	**53.85.38%**	**36**	**55.38%**	**1.000**
Total	**65**	**100%**	**65**	**100%**	
Mean±SD	**31.50±4.94**		**32.50±3.53**		

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The pregnancy rate in the pre-treatment group was 46.15%, compared to 44.62% in the non-pre-treatment group. This difference was not statistically significant (p = 1.000), indicating that pre-treatment did not lead to improved pregnancy rates.

Discussion

The present study demonstrates that pre-treatment with synthetic progestogens before ovarian stimulation in a GnRH antagonist IVF-ICSI cycle does not confer any additional benefits in ovarian response or pregnancy outcomes. The two groups were well-matched at baseline in age, ovarian reserve, and other key parameters, reflecting homogeneity and comparability at the outset. Furthermore, there were no significant differences in the number of oocytes retrieved, 2-pronuclear (2PN) oocytes, good quality embryos, total gonadotropin dose, or clinical pregnancy rates between the pre-treatment and non-pre-treatment groups. Importantly, these findings align with previous reports by Cedrin-Durnelin et al. and P.G. Wardle et al., which also observed no improvement in ovarian or clinical outcomes following progestogen or estradiol pre-treatments in GnRH antagonist cycles.

Recent research has extensively investigated the role of pre-treatment in IVF protocols, yielding varied outcomes depending on patient subgroup and treatment strategies. Moini et al. found no significant benefits of OCP or estradiol valerate pre-treatments on oocyte maturity, embryo quality, or pregnancy rates, although the pregnancy rate was slightly, but not significantly, higher with estradiol [8]. Furthermore, Wang et al. demonstrated selective benefits of OCP in young women with poor ovarian response (POSEIDON group 1), where OCP resulted in greater oocyte retrieval and improved embryo quality — a subgroup-specific phenomenon not observed in their other patient groups [9]. Zhang et al. reported improved oocyte maturity with a short GnRH antagonist pre-treatment. However, this came at the cost of higher gonadotropin usage, reflecting a potential trade-off between efficacy and medication burden [10]. Li et al.'s trial, however, did not find a clear advantage in adding a short antagonist pre-treatment [11]. Di Guardo et al.'s retrospective analysis suggested only a modest rise in oocytes retrieved without improvement in pregnancy rates. At the same time, Xu et al. documented a context-specific improvement in live birth rate with a long-acting GnRH agonist pre-treatment in frozen-thawed cycles, reflecting the influence of treatment context on outcomes [13]. Furthermore, systematic reviews, including Al-Inany et al.'s, broadly indicate that pre-treatment is not universally required and should be tailored to individual patient profiles [14]. Taken together, these findings underscore the necessity for individualized approaches in choosing whether or not to apply pre-treatments, a view supported by the present study's results, which show no universal benefit of progestogen pre-treatments in women with normal ovarian reserve undergoing IVF-ICSI with a GnRH antagonist regimen. Future research should aim to identify predictive factors that may guide the use of pre-treatments, and consider their cost-effectiveness and patient preferences to help personalize assisted reproduction protocols [15].

Conclusion

This study found that pre-treatment with synthetic progestogens in GnRH antagonist IVF cycles does not affect key clinical outcomes like mature oocyte count, embryo quality, or pregnancy rates. Pre-treatment may help synchronise follicles and schedule cycles, but it does not increase reproductive outcomes. These findings support earlier research showing that the GnRH antagonist regimen for regulated ovarian stimulation in IVF is efficacious, patient-friendly, and efficient without pre-treatment. In typical responders, pre-treatment techniques may not be necessary, simplifying treatment processes and minimising patient stress. More large-scale randomised trials may uncover patient subgroups that benefit from individualised pre-treatment.

Limitations

Small sample size and single-center study may limit the generalizability of results.

Recommendation

A larger cohort would allow for more robust statistical analysis and might uncover additional nuances in the relationships between laboratory parameters and clinical outcomes.

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List of abbreviations

IVF – In Vitro Fertilization
ICSI – Intracytoplasmic Sperm Injection
GnRH – Gonadotropin-release Hormone
AMH – Anti-Müllerian Hormone
AFC – Antral Follicle Count
2PN – 2 Pronuclei

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Conflict of interest

The authors declare no conflict of interest.

Author contributions

All authors contributed to the study design, data collection, analysis, and manuscript preparation.

Author biography

All authors are members of the Department of Reproductive Medicine at IGIMS, Patna, with expertise in assisted reproduction and gynecology.

Data availability

The data generated during this study are available from the corresponding author upon reasonable request.

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