



## GnRH Agonist Versus GNRH Antagonist in IVF: A Comparison of Ovarian Hyperstimulation Syndrome in Infertile Females

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### ABSTRACT

**Background:** Gonadotropin-releasing hormone (GnRH) antagonists and agonists are a major part of in vitro fertilization as they control ovulation and egg development. But there are conflicting results regarding the effectiveness of GnRH agonists and antagonists and the development of OHSS in the literature. This study was conducted to compare the frequency of ovarian hyperstimulation syndrome in infertile females with GnRH agonists versus GnRH antagonists seeking in vitro fertilization.

**Methods:** A prospective cohort study was conducted at the Obstetrics and Gynecology Department of Hameed Latif Hospital, Lahore, from 4th January 2024 to 4th January 2025. A total of 60 infertile women aged 20-40 years referred for the first IVF/ ICSI were selected for the study, using non-probability, consecutive sampling. Patients in Group A were 30 women administered 500 µg GnRH agonist (Buserelin) subcutaneously every day since the 21st day of the menstrual cycle. Patients in Group B were 30 women administered 0.25 mg GnRH antagonist

(Cetrotide) subcutaneously. An estradiol >3000 pg/ml in more than three follicles at 3 months and 6 months was described as OHSS, which was managed by standard procedure. Data analysis was done by SPSS version 25.

**Results:** The frequency of primary infertility patients in Group A was 16 (53.3%), and secondary infertility was 14(46.7%). The frequency of primary infertility patients in Group B was 19(63.3%), and secondary infertility was 11(36.7%). The mean number of mature follicles of patients in Group A was 14.4±1.27 (1-35). The mean number of mature follicles of patients in Group B was 13.6±1.24 (2-27). The mean E2 level in patients of Group A was 3261.8±134.7 (Range: 1008-4215), and the mean E2 level in patients of Group B was 3500±167.4 (Range: 1000-4890). The frequency of patients with ovarian hyperstimulation syndrome in Group A was 2 (6.7%) and in Group B was 8 (26.7%).

**Conclusion:** GnRH agonist is more effective than GnRH antagonist in terms of frequency of ovarian hyperstimulation syndrome in infertile women seeking in vitro fertilization.

**Keywords:** Fertilization, Gonadotrophins, Infertility.

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## INTRODUCTION

External fertilization involves the mating of specially selected embryos, oocytes, and sperm outside the body for desired results. Since embryo selection cannot be altered after fertilization due to religious, legal and ethical reasons, this step must be done with consideration. The subjective evaluation of the morphology of the oocyte is essential to check its eligibility and potential for development. Gonadotropin-releasing hormone (GnRH) antagonists and agonists are a major part of in vitro fertilization as they control ovulation and egg development<sup>1,2</sup>.

However, GnRH agonists have some drawbacks like the risk of ovarian hyperstimulation syndrome, a lengthy process until desensitization, and side effects such as cysts, headache, haemorrhage, and hot flushes<sup>3,4</sup>. Additionally, replacing it with the antagonist after ovarian stimulation can also impact the embryo donation cycle<sup>5,6</sup>. A study reported that the administration of antagonists for more than 3 days leads to decreased estrogen levels, reducing the chances of pregnancy<sup>7,8</sup>. In addition, while comparing the incidence of OHSS, it was reported as 0% vs 30.4% for agonist and antagonist, respectively<sup>9</sup>. However, another study reported that the OHSS was reported in 1.1% with GnRH antagonists and 0.36% with GnRH agonists ( $p>0.05$ )<sup>10</sup>.

The rationale of this study was to compare the frequency of OHSS in infertile females with GnRH agonists versus GnRH antagonists seeking in vitro fertilization. Through literature, conflicting results were observed regarding the effectiveness of GnRH agonists and antagonists and the development of OHSS. Also, there is a lack of local evidence, and in routine, both drugs are prescribed. Therefore, we planned to conduct this study to get evidence for local settings and improve our practice. This will also help us to get evidence for the local population, and in the future, we will implement more beneficial drugs for in vitro fertilization.

The objective of this study was to compare the frequency of ovarian hyperstimulation syndrome in infertile females with GnRH agonists versus GnRH antagonists seeking in vitro fertilization.

## METHODS

A prospective cohort study was conducted at the Obstetrics and Gynecology Department of Hameed Latif Hospital, Lahore, from 4th January 2024 to 4th January 2025. A total of 60 infertile women aged 20-40 years referred for the first IVF/ ICSI were selected for the study, using non-probability, consecutive sampling. The sample size was calculated with 90% power of the study, 5% significance level, and predicted OHSS incidence of 0% with GnRH agonist and 30.4% with GnRH antagonist.<sup>11</sup> Females with uterine malformations (on ultrasound), previous IVF/ICSI, hypertension

(BP $\geq$ 140/90mmHg), and diabetes were excluded. Informed consent was obtained. Ethical approval was obtained to proceed with the study by Ref/HLHL/13-78 dated 17-11-2023.

The patient's age, body mass index, and type and duration of infertility were obtained from medical records. Women were divided into two groups: Group A and Group B. Patients in Group A were 30 women administered 500 $\mu$ g GnRH agonist (Buserelin) subcutaneously every day since the 21<sup>st</sup> day of the menstrual cycle. The dose was reduced by 300  $\mu$ g on the 2<sup>nd</sup> day of the cycle after pituitary suppression, and 150  $\mu$ g gonadotropin was added to the regimen. Patients in Group B were 30 women administered 0.25 mg GnRH antagonist (Cetrotide) subcutaneously on the second day of the cycle, and the level of gonadotropin and ovarian hormones was measured. 150 IU Pregonal was administered intramuscularly from the third day. Once the follicle size reached larger than 12mm, Cetrotide was restarted till the HCG injection to prevent premature ovulation. Ultrasonographic assessment was done every day. When the size of at least three follicles reached 18 mm or larger, a 10000 IU HCG injection was administered for egg maturation. After 36-40 hours, follicular aspiration was done to retrieve eggs from the ovaries. If more than three follicles had estradiol greater than 3000 pg/ml at 3 months and 6 months, it was described as OHSS, which was managed by standard procedure.

Data analysis was done by SPSS version 25. Mean  $\pm$  SD was used to present numeric variables like age, BMI, duration of infertility and E2 level. Percentage was used to present categorical variables like type of infertility, smoking, and ovarian hyperstimulation syndrome. Independent t-tests were performed to compare quantitative variables like mean age, BMI, E2 level and duration of fertility between both groups. Data normalcy for continuous variables was checked by the Shapiro-Wilk test. The incidence of OHSS in both groups before and after stratification was compared by the Chi-squared test or Fisher's exact test, where appropriate. Data stratification was done for demographic factors. Statistical significance was determined at p-value  $\leq$  0.05.

## RESULTS

**Table 1. Patient's Demographic Variables**

Variables	Group A	Group B	P-value
Mean age	31.16 $\pm$ 0.76	30.7 $\pm$ 4.95	0.62
18-28 years	9 (30%)	8 (26.7%)	
29-39 years	21 (70%)	22 (73.3%)	

<b>Mean BMI</b>	27.06 ± 2.71	26.5 ± 3.47	0.58
<b>Normal</b>	1 (3.3%)	7 (23.3%)	
<b>Overweight</b>	22 (73.3%)	18 (60%)	
<b>Obese</b>	7 (23.3%)	5 (16.7%)	
<b>Mean infertility duration</b>	4.36 ± 0.51	5.51 ± 0.58	0.08
<b>1-6 years</b>	25 (83.3%)	19 (63.3%)	
<b>6-12 years</b>	5 (16.7%)	11 (36.6%)	
<b>Types of infertility</b>			0.43
<b>Primary</b>	16(53.3%)	19(63.3%)	
<b>Secondary</b>	14(46.7%)	11(36.7%)	
<b>Number of mature follicles</b>	14.4 ± 1.27	13.6 ± 1.34	0.41
<b>E2 level</b>	3261.8 ± 134.7	3500 ± 167.4	0.07

The mean age of patients in Group A was 31.16±0.76 (23-39 years), while in Group B the mean age was 30.7±4.95 (18-38 years). The mean BMI of patients in Group A was 27.06±2.71 (21-33 kg/m<sup>2</sup>), while in Group B, the mean BMI was 26.59±3.47 (21-36kg/m<sup>2</sup>). The mean duration of infertility of patients in Group A was 4.36±0.51 years (1-10 years), while in Group B, the mean duration of infertility was 5.51±0.58 years (1-12 years). The frequency of primary infertility patients in Group A was 16 (53.3%), and secondary infertility was 14(46.7%). The frequency of primary infertility patients in Group B was 19(63.3%), and secondary infertility was 11(36.7%). The mean number of mature follicles of patients in Group A was 14.4±1.27 (1-35). The mean number of mature follicles of patients in Group B was 13.6±1.24 (2-27). The mean E2 level in patients of Group A was 3261.8±134.7 (Range: 1008-4215), and the mean E2 level in patients of Group B was 3500±167.4 (Range: 1000-4890) (**Table 1**).

**Table 2. Incidence of Ovarian Hyperstimulation Syndrome and Stratification with Respect to Demographics**

Variables	Group A	Group B	P-value
<b>OHSS</b>	2(6.7%)	8(26.7%)	0.037

<b>Age Groups</b>			
<b>18-28 years</b>	0(0%)	3(37.5%)	0.043
<b>29-39 years</b>	2(100%)	5(62.5%)	0.241
<b>BMI</b>			
<b>Normal</b>	0(0%)	1(12.5%)	0.68
<b>Overweight</b>	1(50%)	5(62.5%)	0.041
<b>Obese</b>	1(50%)	2(25%)	0.310
<b>Duration of Infertility</b>			
<b>1-6 years</b>	1(4%)	4(21.1%)	0.077
<b>6-12 years</b>	1(20%)	4(36.4%)	0.513
<b>Type of Infertility</b>			
<b>Primary</b>	2(12.5%)	6(31.6%)	0.18
<b>Secondary</b>	0(0.0%)	2(18.2%)	0.096

The frequency of patients with ovarian hyperstimulation syndrome in Group A was 2 (6.7%) and in Group B was 8(26.7%). All patients with OHSS in Group A were aged 29-39 years, and in Group B, 3 (37.5%) were aged 18-28 years, and 5 (62.5%) were aged 29-39 years. The frequency of overweight patients with ovarian hyperstimulation syndrome in Group A was 1(4.5%), while in Group B it was 5(27.8%) ( $p=0.041$ ). While normal weight (Group A: 0% vs. Group B: 14.3%) and obese (Group A: 14.3% vs. Group B: 40%) patients showed insignificant results ( $p=0.68$  and  $p=0.310$ , respectively). Frequency of primary infertility (Group A: 12.5% vs. Group B: 31.6%) patients with OHSS and secondary infertility (Group A: 0% vs. Group B: 18.2%) showed insignificant results ( $p= 0.18$  and  $p= 0.096$ , respectively) (**Table 2**).

## DISCUSSION

In this study, we compared the frequency of ovarian hyperstimulation syndrome in infertile females administered GnRH agonists versus GnRH antagonists seeking in vitro fertilization. Results showed that patients with GnRH antagonists had a higher frequency of ovarian hyperstimulation syndrome as compared to GnRH agonists. i.e., 6.7% vs.26.7% ( $p=0.037$ ). Similar findings were reported, in which OHSS was reported in 0% with GnRH agonist, while 30.4% with GnRH antagonist ( $p$ -value $<0.05$ )<sup>12</sup>. Other related studies backed these results.<sup>13, 14, 15</sup>

Contrary to this, a study reported that the OHSS was reported in 1.1% with GnRH agonists and 0.36% with GnRH antagonist ( $p\text{-value}>0.05$ )<sup>16</sup>. Although the frequency of OHSS was quite lower when compared with this study. This was due to the difference in the sample size. The study has used a larger sample size as compared to this study.

A Chinese study reported no significant difference for OHSS with agonist protocol as compared to GnRH antagonist protocol. i.e. 3.58% vs 3.06%,  $p\text{-value}=0.595$ <sup>17</sup>. In this study, the frequency of OHSS with GnRH antagonist was quite high when compared with the frequency in a previous study.<sup>18</sup>This may be due to differences in methodology as well as due to differences in sample size.

A recently published study reported the severe and moderate OHSS with GnRH-antagonist as 10% and 25% respectively<sup>19</sup>. The results of the present study are not in line with the other findings because we did not assess the severity of OHSS as was done previously<sup>20, 21, 22</sup>.

## CONCLUSION

GnRH agonist is more effective than GnRH antagonist in terms of frequency of ovarian hyperstimulation syndrome in infertile women seeking invitro fertilization.

## LIST OF ABBREVIATIONS

**GnRH** Gonadotropin Releasing Hormone

**OHSS** Ovarian Hyperstimulation Syndrome

**IVF** In vitro Fertilization

**ICSI** Intracytoplasmic Sperm Injection

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## FUNDING

None.

## CONFLICT OF INTEREST

None.

## ETHICAL APPROVAL

Ethical approval was obtained from Hameed Latif Hospital, Lahore Ref/HLHL/13-78 (dated 17-11-2023).

### AUTHORS' CONTRIBUTION

**ZI:** writing, design, **SA:** Review, **SH:** Data collection, Analysis, **ZA:** Interpretation, **BY:** collection and study design, **HT:** conceived and analysis

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