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Research Article

Gnrhagonist versus GNRH Antagonist in IVF: A Comparison of Ovarian Hyperstimulation Syndrome in Infertile Females

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ABSTRACT
Objective: To compare the frequency of ovarian hyperstimulation syndrome in infertile females with GnRH agonists versus GnRH antagonists seeking invitro fertilization
Study design: A prospective cohort study
Settings and duration: At Obstetrics and Gynecology Department of Arif Memorial Teaching Hospital Lahore, from 14th March 2024 to 14th March 2025.
Methods: 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.Women were divided into two groups: Group A and Group B. Patients in Group A were 30 women administered 500 µg GnRH agonist (Buserelin) subcutaneously every day since the 21st day of the menstrual cycle. The dose was reduced by 300 µg on the 2nd day of the cycle after pituitary suppression, and 150 µg gonadotropin was added to the regimen. Patients in Group B were 30 women administered 0.25 mg GnRH antagonist (Cetrotide) subcutaneously. 150 IU Pregonal was administered intramuscularly from the third day.After ovum retrieval,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
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 GroupB was 19(63.3%), and secondary infertility was 11(36.7%). The mean number of mature follicles of patients in GroupA was 14.4±1.27 (1-35). The mean number of mature follicles of patients in GroupB was 13.6±1.24 (2-27). The mean E2 level in patients of GroupA was 3261.8±134.7 (Range: 1008-4215) and the mean E2 level in patients of GroupB was 3500±167.4 (Range: 1000-4890). The frequency of patients with ovarian hyperstimulation syndrome in GroupA was 2 (6.7%) and in GroupB 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 invitro fertilization.

Keywords: Fertilization, Gonadotrophins, Infertility.

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.[1, 2]

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.[3]Additionally, replacing it with the

antagonist after ovarian stimulation can also impact the embryo donation cycle.[4]A study reported that the administration of antagonists for more than 3 days leads to decreased estrogen levels, reducing the chances of pregnancy.[5]In addition, while comparing the incidence of OHSS, it was reported as 0% vs 30.4% for agonist and antagonist, respectively.[6]However, another study reported that the OHSS was reported in 1.1% with GnRHantagonistsand 0.36% with GnRH antagonists ($p>0.05$).[7]

The rationale of this study is to compare the frequency of OHSS in infertile females with GnRH agonists versus GnRH antagonists seeking invitro fertilization. Through literature, we observed conflicting results 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 future, we will implement more beneficial drugs for invitro fertilization.

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

METHODOLOGY

A prospective cohort study was conducted at the Obstetrics and Gynecology Department of Arif Memorial Teaching Hospital, Lahore, from 14th March 2024 to 14th March 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% powerofthe study, 5% significance level and predicted OHSS incidence of 0% with GnRH agonist and 30.4% with GnRH antagonist. Females with uterine malformations (on ultrasound), previous IVF/ICSI, hypertension (BP≥140/90mmHg) and diabetes were excluded. Informed consentwas obtained.

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 500µg GnRH agonist (Buserelin) subcutaneously every day since the 21st day of the menstrual cycle. The dose was reduced by 300 µg on the 2nd day of the cycle after pituitary suppression, and 150 µg 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 ± SD was used to present numeric variableslike 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 ≤ 0.05.

RESULTS

The mean age of patients in GroupA 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 GroupA was 27.06±2.71 (21-33 kg/m^2), while in Group B, the mean BMI was 26.59±3.47 (21-36kg/m^2). The mean duration of infertility of patients in GroupA was 4.36±0.51 years (1-10 years), while in Group B, the mean duration of infertility was 5.51±0.58years(1-12 years). The frequency of primary infertility patients in GroupA was 16 (53.3%), and secondary infertility was 14(46.7%). The frequency of primary infertility patients in GroupB 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 GroupA was 3261.8±134.7 (Range: 1008-4215) and the mean E2 level in patients of GroupB was 3500±167.4 (Range: 1000-4890) (Table I).

The frequency of patients with ovarian hyperstimulation syndrome in GroupA was 2 (6.7%) and in GroupB 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 GroupA was 1(4.5%), while in GroupBit was 5(27.8%) (p=0.041). While normal weight (GroupA: 0% vs. GroupB: 14.3%) and obese (GroupA: 14.3% vs. GroupB: 40%) patients showed insignificant results (p=0.68 and p=0.310, respectively). Frequency of primary infertility (GroupA: 12.5% vs. GroupB: 31.6%) patients with OHSS and secondary infertility (GroupA: 0% vs. GroupB: 18.2%) showed insignificant results (p= 0.18 and p= 0.096, respectively) (Table II).

Table I: Patient's Demographic Variables

Variables	Group A	Group B	P value
Mean age	31.16 ± 0.76	30.7 ± 4.95	0.62
18-28 years	9 (30%)	8 (26.7%)	
29-39 years	21 (70%)	22 (73.3%)	
Mean BMI	27.06 ± 2.71	26.5 ± 3.47	0.58
Normal	1 (3.3%)	7 (23.3%)	
Overweight	22 (73.3%)	18 (60%)	
Obese	7 (23.3%)	5 (16.7%)	
Mean infertility duration	4.36 ± 0.51	5.51 ± 0.58	0.08
1-6 years	25 (83.3%)	19 (63.3%)	
6-12 years	5 (16.7%)	11 (36.6%)	
Types of infertility			0.43
Primary	16(53.3%)	19(63.3%)	
Secondary	14(46.7%)	11(36.7%)	
Number of mature follicles	14.4 ± 1.27	13.6 ± 1.34	0.41
E2 level	3261.8 ± 134.7	3500 ± 167.4	0.07

Table II: Incidence of Ovarian Hyperstimulation Syndrome and Stratification with Respect To Demographics

Variables	Group A	Group B	P
OHSS	2(6.7%)	8(26.7%)	0.037
Age Groups			
18-28 years	0(0%)	3(37.5%)	0.043
29-39 years	2(100%)	5(62.5%)	0.241
BMI			
Normal	0(0%)	1(12.5%)	0.68
Overweight	1(50%)	5(62.5%)	0.041
Obese	1(50%)	2(25%)	0.310
Duration of infertility			
1-6 years	1(4%)	4(21.1%)	0.077
6-12 years	1(20%)	4(36.4%)	0.513
Type of infertility			
Primary	2(12.5%)	6(31.6%)	0.18
Secondary	0(0.0%)	2(18.2%)	0.096

DISCUSSION

In this study, we compared the frequency of ovarian hyperstimulation syndrome in infertile females administered GnRH agonists versus GnRH antagonists seeking invitro 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 by Yang et al,inwhich OHSS was reported in 0% with GnRH agonist, while 30.4% with GnRH antagonist (p-value<0.05).[8] Other related studies backed these results.[9, 10, 11]

Contrary to this,a study reported that the OHSS was reported in 1.1% with GnRH agonistsand 0.36% with GnRH antagonist (p-value>0.05).[12] 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.

Geng et al in the study reported no significant difference for OHSS with agonist protocol as compared to GnRH antagonist protocol. i.e. 3.58% vs 3.06%, p-value=0.595.[13] In this study, the frequency of OHSS with GnRH antagonist was quite high when compared with the frequency reported by Zhang et al.[14] This may be due to differences in methodology as well as due to differences in sample size.

A recently published study by Mills and Dahan reported the severe and moderate OHSS with GnRH-antagonist as 10% and 25% respectively.[15]The results of the present study are not in line with the findings of Ginevra Mills because we did not assess the severity of OHSS as was done by Ginevra Mills in his study.

CONCLUSION

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

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