International Journal of Reproduction, Contraception, Obstetrics and Gynecology
*Mishra VV et al. Int J Reprod Contracept Obstet Gynecol. 2023 Nov;12(11):3252-3256*
www.ijrcog.org
pISSN 2320-1770 | eISSN 2320-1789

DOI: https://dx.doi.org/10.18203/2320-1770.ijrcog20233289

**Original Research Article**

# Role of cetrorelix in the prevention and treatment of ovarian hyperstimulation syndrome: a prospective case control study

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**Received:** 21 September 2023
**Accepted:** 10 October 2023

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## ABSTRACT

**Background:** Ovarian hyperstimulation syndrome (OHSS) has intrigued clinicians for many years because of its devastating consequences. As an iatrogenic condition resulting from elective ovarian stimulation in the quest for pregnancy, the need to completely prevent the syndrome is evident. Gonadotropin releasing hormone (GnRH) antagonist Cetrorelix has found to be effective in treatment of OHSS and some studies have found it to be helpful in prevention of this condition. Hence, we designed a hospital-based study to investigate the effect of Cetrorelix in preventing and treating OHSS in in-vitro fertilization – embryo transfer (IVF–ET) patients at risk of OHSS undergoing long and short protocol.
**Methods:** The study includes total 102 patients undergoing controlled ovarian stimulation COS for IVF/ICSI. All cases were stimulated using long and short protocol. Depending on whether a GnRH antagonist was given after ovum pick-up (OPU) the patients were divided in two groups: Cetrorelix (antagonist) group (n=51) and control group (n=51). The study group was treated with Cetrorelix 0.25 mg for 5 days commencing on the day of ovum pick up.
**Results:** Incidence of mild OHSS was significantly higher (p=0.01) whereas moderate to severe OHSS was significantly lower in the antagonist group (p<0.05). None of the patients had critical OHSS.
**Conclusions:** GnRH antagonist Cetrorelix administration in early luteal phase in patients undergoing long or short protocol is effective in prevention and treatment of OHSS.

**Keywords:** Cetrorelix, Gonadotropin releasing hormone antagonist, Ovarian hyperstimulation syndrome

## INTRODUCTION

The gravest complication of controlled ovarian-stimulation is ovarian hyper stimulation syndrome (OHSS).[1] In the IVF cycles the incidence of moderate to severe OHSS is 3-6% and 0.1-2% respectively.[2] OHSS includes two distinct disease entities: early OHSS that occurs 3-7 days after HCG triggering and Late OHSS that occurs more than 10 days after hCG triggering.[3-5] In early OHSS the exogenously injected HCG drives the granulosa cells directly to secrete sufficient vasoactive substances to produce the syndrome within three to seven days, while in late OHSS, early pregnancy is responsible for the granulosa cell hyperactivity, as the implanting trophoblast produces increasing levels of endogenous hCG.

In spite of embryo freezing, early OHSS still occurs in long stimulation protocol. Therefore, prevention of OHSS remains an issue to be addressed in clinical practice of assisted reproduction. Some studies have shown that the GnRH antagonist protocol is a safe and effective way of preventing OHSS for women undergoing in vitro fertilization.[6-9] Lainas et al reported that 3 cases of severe OHSS happened in patients with polycystic ovary syndrome (PCOS) on day 6 after ovum pickup and were improved considerably after 3 days of GnRH antagonist

administration.[10] The authors concluded that administration of GnRH antagonists in the luteal phase could treat early OHSS effectively.

Prediction of OHSS is the cornerstone of prevention which is based on identifying the risk factors of patients who would be high responder based on ultrasound and estradiol levels. High risk factors associated with OHSS are young patients (<35 years of age), polycystic appearing ovaries, asthenic habitus, multiple stimulated follicles, high serum estradiol, necklace sign, pregnancy, hCG luteal supplementation, GnRH agonist down regulatory protocol, high serum anti Mullerian hormone.[11] In the present study we investigated the treatment effect of gonadotropin releasing hormone (GnRH) antagonist in the early luteal phase on ovarian hyperstimulation syndrome (OHSS) for in vitro fertilization – embryo transfer (IVF-ET).

## METHODS

This was a prospective case control study conducted at IKDRC, Ahmedabad Gujarat India. The present study included a total of 102 patients undergoing controlled ovarian stimulation (COS) for IVF/ICSI (in-vitro fertilization/ Intra cytoplasmic sperm injection). Depending on whether GnRH antagonist Cetrorelix was given after ovum pick-up (OPU) the patients were divided in two groups: antagonist group (Cetrorelix, n=51) and control group (n=51). The study was explained to the patients and written and informed consent for participation was obtained in English/ Hindi/Gujarati consent forms.

### *Inclusion criteria*

We included patients who met the following criteria: age between 25 and 45 years, BMI not more than 35, patients on long and short protocol, more than 10 oocytes retrieved, high responder patients and good antral follicle count, PCOS patients, who are at risk of OHSS, women who gave consent for the study.

### *Exclusion criteria*

We excluded the following patients with: endometriosis, previous ovarian surgery, those with low antral follicle counts, AMH less than 1.5, women who refused to give consent.

Detailed history and examination of patients was done. Prior to recruitment patients had undergone routine blood investigations, day 2 hormonal profile, abdominal, pelvic examination and basal ultrasound examination to rule out exclusion criteria. Follicular monitoring was done by using ultrasound examination (Voluson E8 GE) who underwent stimulation protocol. All cases were stimulated using long or short protocols depending upon the different parameters like age, antral follicle count, hormonal profile.

In long protocol (gonadotropin) injection (inj.) Leupride 0.5 mg started from day 21 of previous cycle and after complete desensitization, ovarian stimulation using recombinant follicle stimulating hormone (FSH) 200-225IU from day 2 of the stimulation cycle. In short protocol inj. Leupride and recombinant FSH started from day 2 of stimulation cycle. Transvaginal ultrasound was done every 3-5 days for examination of follicular development. When at least two or more follicles with diameter of at least 17 mm were observed, oocyte retrieval was performed 34-36 hours. after administration of 500 mcg of recombinant hCG. The study group was prophylactically administered GnRH antagonist Cetrorelix 0.25 mg for 5 days commencing on the day of ovum pick up. In the control group the standard conservative and supportive management for OHSS was employed. All OHSS patients were diagnosed according to standard definition.

The standard classification categorizes the disease based on its severity to mild, moderate, severe and critical OHSS according to Navot et al classification as shown in Table 1.[12]

**Table 1: Classification of OHSS.**

| Mild | Moderate | Severe | Critical |
|---|---|---|---|
| **Bloating** | Vomiting | Massive ascites | Tense ascites |
| **Nausea** | Abdominal pain | Hydrothorax | Hypoxemia |
| **Abdominal distension** | USG evidence of ascites | Hematocrit >45% | Pericardial effusion |
| **Ovaries ≤5 cm** | Hematocrit >41% | WBC count >15000/mm$^3$ | Hematocrit >55% |
| | WBC count >10000/mm$^3$ | Oliguria | WBC count > 25000/mm$^3$ |
| | Ovaries >5 cm | Creatinine 1-1.5 mg/dl | Oliguria/anuria |
| | | Creatinine clearance ≥50 ml/min | Creatinine >1.5 mg/dl |
| | | Hepatic dysfunction | Creatinine clearance <50 ml/min |
| | | Anasarca | Renal failure |
| | | Ovaries variably enlarged | Thromboembolic phenomena |
| | | | Ovaries variably enlarged |
| | | | Acute respiratory distress syndrome (ARDS) |

WBC – White blood count, USG – ultrasound

Patients were followed on 1st, 3rd, 5th and 7th day to find out any signs and symptoms of OHSS. Hematocrit, albumin, presence of ascites, measuring the free fluid in the pouch of Douglas, size of ovary, urine output, oral and intravenous fluid intake, bodyweight, abdominal girth and serum electrolytes were the parameters measured. If symptoms of OHSS develop standard treatment was given in both the groups in the form of IV fluids, albumin and paracentesis. Predesigned proforma was filled up which included questionnaires, clinical, laboratory and ultrasound reports. Data was filled in Microsoft excel sheet. Age, BMI, number of retrieved oocytes, hormonal profile, protocol used were recorded. According to the quality of embryo and endometrial thickness fresh embryo transfer was done and others were freezed. For fresh embryo transfer chemical pregnancy was detected by the measurement of serum β hCG 14 days after embryo transfer and existence of clinical pregnancy was confirmed using transvaginal ultrasound scan 2-3 weeks later for confirming gestational sac and cardiac activity. On each clinical visit all the patients were checked for drug complication or side effects of Cetrorelix which are nausea, headache and local injection site reaction, however, none of them reported any side effects.

### *Statistical analysis*

Quantitative data are presented as mean±SD. Quantitative and qualitative data were analyzed using IBM statistical package for the social sciences (SPSS) version 20.0. Mann-Whitney U test and independent t test have been performed to carry out results. P<0.05 was considered statistically significant.

## RESULTS

Demographic data were compared in both the groups. As shown in Table 2, there was no statistical difference between these two groups in age, BMI, duration of infertility, type of infertility, basic follicle stimulating hormone FSH, basic luteinizing hormone LH, polycystic ovary (PCOS) patients. There is no statistical difference in cause of infertility except ovarian cause which shows statistically significant with p value 0.03.

**Table 2: Demographic data.**

| Variable name | Control group (N=51) | Antagonist group (N=51) | P value |
|---|---|---|---|
| **Age (year)** | 32.39±5.48 | 28.27±3.66 | 0.23 (NS) |
| **BMI (kg/m$^2$)** | 24.69±2.40 | 22.76±2.61 | 0.46 (NS) |
| **Infertility – primary** | 36 | 37 | 0.82 (NS) |
| **Secondary** | 15 | 14 | |
| **Duration (year)** | 6.69±2.89 | 7.24±3.17 | 0.36 (NS) |
| **Cause – tubal** | 16 | 10 | 0.17 (NS) |
| **Ovarian** | 16 | 27 | 0.03* |
| **Male** | 9 | 6 | 0.40 (NS) |
| **Unexplained** | 10 | 8 | 0.60 (NS) |
| **FSH (mIU/ml)** | 6.06±1.38 | 5.76±1.38 | 0.27 (NS) |
| **LH (mIU/ml)** | 5.27±1.79 | 4.98±1.66 | 0.40 (NS) |
| **PCO (no. of patients)** | 18 | 24 | 0.31 (NS) |
| **Long protocol** | 22 | 24 | |
| **Short protocol** | 29 | 27 | |

**Table 3: Clinical outcome of the OHSS.**

| Final diagnosis | Control group | Antagonist group | P value |
|---|---|---|---|
| **Mild** | 23 | 42 | 0.01* |
| **Moderate** | 18 | 08 | 0.03* |
| **Severe** | 10 | 01 | 0.01* |
| **Critical** | 0 | 0 | |

Clinical outcomes of OHSS were recorded according to classification of OHSS (Table 3). Incidence of severe OHSS was significantly lower in the antagonist group than in the control group (p value=0.01). Incidence of mild OHSS was significantly higher in the antagonist group than in the control group (p value=0.01). Also, incidence of moderate OHSS was lower in the antagonist group than in the control group (p value=0.03). In the present study none of the group patients had critical OHSS. As shown in Table 4, chemical and clinical pregnancy rate was statistically higher in the antagonist group than in the control group.

**Table 4: Pregnancy rate.**

| Variable | Control group | Antagonist group | P value |
|---|---|---|---|
| **Pregnancy rate (chemical and clinical)** | 13 | 24 | 0.02* |

## DISCUSSION

Study done by Chen et al which is similar to our study, was a retrospective study that showed administration of

Cetrorelix in the early luteal phase can reduce occurrence of OHSS, lower the incidence of moderate and severe OHSS.[13] In the study Cetrorelix was given 0.25 mg for 3 days and in long agonist protocol. In our prospective study Cetrorelix was given for 5 days and in both long and short protocols. In the previous study the incidence of mild forms are more and severe forms are less in antagonist groups which is same result as our study. Dose and duration of Cetrorelix used in our study helps to prevent and treat OHSS. Our study shows exclusive critical criteria in which none of the patients were found. Lainas et al study reported that Ganirelix was used after development of severe early OHSS who underwent antagonist protocol for PCOS patients.[10] In our study long and short protocols were used and Cetrorelix was given from the day of ovum pickup in high risk patients of OHSS. As mild forms of OHSS were significantly higher in antagonist group, thus Cetrorelix prevents and treats OHSS.

In a previous study which showed 40 patients diagnosed with severe OHSS on day 5 after OPU received GnRH antagonist administration from day 5 to 8 after OPU have reduced OHSS.[14] Another study by Wang et al showed 7 day administration of GnRH antagonist from day of OPU effectively prevented the progression of mild to moderate and severe OHSS.[15] In our study incidence of severe OHSS is only one patient in antagonist group which shows that Cetrorelix has prevented mild to moderate and severe OHSS. OHSS exists in a clinical spectrum. Some patients, at one end of spectrum, exhibit mild symptoms and at other extreme require intensive management and may be at risk of death from the disease.[16-20] Vascular endothelial growth factor (VEGF) is responsible for increased vascular permeability causing OHSS. VEGF is secreted by granulosa and theca cells during late follicular phase. OHSS is the result of increased vascular permeability induced by VEGF over secretion. The severity of OHSS is related to level of free VEGF. The improvement of vascular permeability is caused by inhibition of VEGF.[21,22] GnRH antagonist Cetrorelix which is used in the study is known to lower VEGF secretions in human granulosa lutein cell cultures, as well as expression of VEGF-R in hyperstimulated ovaries.[23] Similarly, GnRH antagonist treatment reduced expression of VEGF and VEGF receptor at mRNA and protein levels in ovaries of hyper-stimulated rats.[24] GnRH antagonist is reported to have a luteolytic effect, which is a way to reduce the excess production of vasoactive cytokines from the corpora lutea responsible for OHSS development.[10,25]

In a previous study by Bosch et al, GnRH antagonist administration during peri implantation period may cause concern about potential adverse effects of GnRH antagonist on pregnancy and neonatal outcomes.[26] Lainas et al in a prospective cohort study on 192 IVF patients who were at risk of OHSS showed pregnancy and neonatal outcomes did not decrease after luteal GnRH antagonist administration.[14] Some studies have shown that GnRH antagonist is not associated with pregnancy or congenital adverse effects.[10,14,25,27,28] In a previous study luteal phase GnRH antagonist administration does not influence the chance of pregnancy.[29] In our study bio-chemical and clinical pregnancy rates are higher in antagonist group. In a previous study by Papanikolaou et al it has to be noted that significantly higher biochemical pregnancy rates were previously shown in women with early OHSS compared with non OHSS patients.[30]

***Limitations***

Our study was a single center study therefore multicenter clinical trials should be done.

## CONCLUSION

Administration of Cetrorelix, GnRH antagonist in the early luteal phase during the ovulation stimulation cycle in IVF, undergoing long and short protocols, can reduce the incidence of moderate and severe OHSS and is safe and effective drug to prevent and treat OHSS.

## ACKNOWLEDGMENTS

Authors would like to thank the patients who took part in the study.

*Funding: No funding sources*
*Conflict of interest: None declared*
*Ethical approval: The study was approved by the Institutional Ethics Committee*

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**Cite this article as:** Mishra VV, Rane PH, Aggarwal RS, Choudhary S, Chhetry M, Solanki SB. Role of cetrorelix in the prevention and treatment of ovarian hyperstimulation syndrome: a prospective case control study. Int J Reprod Contracept Obstet Gynecol 2023;12:3252-6.