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Original Research Article

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

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ABSTRACT

Background: Because of its terrible effects, ovarian hyperstimulation syndrome (OHSS) has long piqued the interest of medical professionals. Since the syndrome is an iatrogenic condition brought on by elective ovarian stimulation in the pursuit of pregnancy, its complete prevention is imperative. The gonadotropin releasing hormone (GnRH) antagonist Cetrorelix has been shown in some studies to be beneficial in the prevention of OHSS as well as an effective treatment for the condition. Therefore, we created a study at a hospital to find out how Cetrorelix works to prevent and treat OHSS in patients undergoing long and short protocols for those undergoing embryo transfer and in-vitro fertilization (IVF–ET) who are susceptible to the illness.

Materials and Methods: The study includes 102 patients undergoing COS for IVF in total. To stimulate each case, a long and a short protocol were employed. Depending on whether a GnRH antagonist was administered following ovum pick-up (OPU), the patients were split into two groups: the control group (n = 51) and the Cetrorelix (antagonist) group (n = 51). Beginning on the day of ovum pickup, the study group received five days' worth of Cetrorelix 0.25 mg.

Results: While the antagonist group had a significantly higher moderate OHSS incidence (p=0.01), the incidence between mild and severe OHSS was considerably reduced($p<0.05$). Not a single patient experienced critical OHSS.

Conclusion: OHSS can be prevented and treated effectively by administering the GnRH antagonist Cetrorelix to patients undergoing either a long- or short-term protocol during the early luteal phase.

1. Introduction

The most dangerous adverse effect of regulated ovarian stimulation is ovarian hyperstimulation syndrome (OHSS).[1,2] 3.6% and 0.1-2%, respectively, of IVF cycles result in moderate to severe OHSS. In OHSS there are two separate disease entities: early OHSS, which manifests 3-6 days following HCG triggering, and late OHSS, which manifests more than 10 days following HCG triggering.[3–9] Early OHSS is caused by exogenously administered HCG, which causes the granulosa cells to generate a sufficient amount of vasoactive chemicals over the course of three to seven days. Granulosa cell hyperactivity in late OHSS is caused by early pregnancy, as the implanting trophoblast releases more endogenous hCG.

The foundation of prevention *is the prediction of OHSS*, which is predicated on identifying risk factors for those who would be high responders based on ultrasonography and estradiol levels. Many stimulated follicles, asthenic habitus, many stimulated follicles, high serum estradiol, necklace sign, pregnancy, hCG luteal supplementation, GnRH agonist downregulating process, and high serum anti Mullerian hormone are high risk factors associated with OHSS.[10] In this study, we examined how patients

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undergoing early luteal phase IVF-ET responded to therapy with gonadotropin releasing hormone (GnRH) antagonists for ovarian hyperstimulation syndrome (OHSS).

2. Materials and Methods

In Indore, Madhya Pradesh, India, at the Index Medical College, Hospital & Research Center, a prospective case-control research was carried out. The study concentrated on 102 patients receiving controlled ovarian stimulation (COS) or in-vitro fertilization (IVF). The patients were divided into two groups based on whether they received the GnRH antagonist Cetrorelix after ovum pick-up (OPU): the antagonist group (n=51) and the control group (n=51). Patients were given thorough descriptions of the study, and consent forms in English, Hindi, and written and informed consent were used to get signed for participation. [11]

2.1. Inclusion criteria

Patients who satisfied certain requirements were included in the study: they had to be between the ages of 25 and 45, have a BMI of no more than 35, be on both long- and short-term protocols, have had participants must be female, have PCOS and be at risk of OHSS, have a decent antral follicle count and be high responder patients with more than 10 retrieved oocytes.

2.2. Exclusion criteria

Exclusions from the trial were poor counts of antral follicles, AMH < 1.5, endometriosis, prior ovarian surgery, and refusal to provide permission.

Patients had thorough examinations and history. In order to rule out exclusion criteria, patients had regular blood tests, day 2 hormonal profiles, pelvic and abdominal examination, and basal ultrasound examinations performed prior to recruitment. Follicular monitoring was carried out for individuals undertaking the stimulation regimen by means of ultrasonography examination (Phillips ClearVue 350). Using lengthy or brief procedures determined by many factors such age, the number of antral follicles, and the hormonal profile, all cases were stimulated.

Leupride 0.5 mg gonadotropin injection (inj.) was begun on day 21 of the preceding cycle in the lengthy protocol. Following total desensitization, recombinant follicle-stimulating hormone (FSH) was administered at 200–225 IU on day 2 of the stimulation cycle to start ovarian stimulation. Recombinant FSH and injectable Leupride were included into the short regimen on the second day of the stimulation cycle. Every three to five days, transvaginal ultrasonography was carried out to monitor follicular growth. After receiving 500 mcg of recombinant hCG, and after seeing two or more follicles with a diameter of at least 17 mm, oocyte retrieval was carried out 34–36 hours later.

Starting on the day of ovum pick-up, the study group was administered Cetrorelix 0.25 mg as a preventive measure for five days. Standard cautious and supportive OHSS management was given to the control group. As indicated in Table 1. [12], all OHSS patients had their diagnosis made in accordance with the usual categorization, which divided the condition into four categories: mild, moderate, severe, and critical OHSS.

2.3. Statistical analysis

The format for quantitative data is mean±SD. Version 20.0 of the IBM statistical program for the social sciences (SPSS) was used to analyze both quantitative and qualitative data. The data were analyzed using the independent t test and the Mann-Whitney U test. The threshold for statistical significance was set at P<0.05.

3. Results

llustrates the classification of OHSS severity, with the antagonist group exhibiting a significantly higher prevalence of mild cases (42 vs. 23, p=0.01*). Demographic data in Table 2 shows no significant differences between the control and antagonist groups in age, BMI, infertility type, duration, or hormonal levels. However, the antagonist group had a higher incidence of ovarian causes of infertility (27 vs. 16, p=0.03*). Table 3 reveals a notable difference in the clinical outcome of OHSS, with the antagonist group demonstrating fewer cases of moderate and severe OHSS (p=0.03* and p=0.01*, respectively). In Table 4, the antagonist group exhibits a higher pregnancy rate compared to the control group (24 vs. 13, p=0.02*). Overall, GnRH antagonist administration post-OPU shows promise in mitigating OHSS severity and improving pregnancy outcomes. [11–15]

4. Discussion

Similar to our work, Chen et al.'s retrospective investigation demonstrated that administering Cetrorelix in the early luteal phase can decrease the incidence of moderate and severe OHSS as well as the occurrence of OHSS. Thirteen Cetrorelix was administered 0.25 mg for three days as part of a lengthy agonist protocol in the trial. Cetrorelix was administered for five days in both long and short protocols as part of our prospective trial. Similar to our analysis, the prior research found that antagonist groups had a higher incidence of moderate forms and a lower incidence of severe forms. The Cetrorelix dosage and duration utilized in our study aid in the treatment and prevention of OHSS. Our research demonstrates unique crucial standards that none of the patients meet.

According to a Lainas et al. study, Ganirelix was administered to PCOS patients who had undergone an antagonist protocol but had developed severe early on

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/mm3	Hematocrit >55%
WBC count >10000/mm3		Oliguria	WBC count > 25000/mm3
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)			

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/m2)	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 d iagnosis	Control group	Antagonist group	P value
Mild	23	42	0.01*
Moderate	18	08	0.03*
Severe	10	01	0.01*
Critical	0		0

Table 4: Pregnancy rate

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

hand symptoms of OHSS.10 In our study, high-risk OHSS patients received Cetrorelix beginning on the day of ovum collection, using both lengthy and short regimens. Cetrorelix prevents and cures OHSS since the antagonist group had a noticeably greater frequency of moderate manifestations of the condition.

In a prior study, it was observed that 40 patients who were diagnosed with severe OHSS on day 5 following OPU and who were administered GnRH antagonists from day 5 to day 8 following OPU had decreased OHSS.[16] Wang et al. conducted a study which demonstrated that administering a GnRH antagonist for seven days starting on the day of OPU effectively prevented the progression of mild to moderate and severe OHSS.[17] Only one patient in the antagonist group experienced severe OHSS in our study, indicating that cetrorelix has prevented mild to moderate and severe OHSS. There is a clinical spectrum for OHSS. On one end of the spectrum, some patients have minor symptoms, while others need intensive care and may even be at risk of dying from the illness.[18–22]

OHSS is brought on by increased vascular permeability, which is caused by vascular endothelial growth factor, or VEGF. Theca and granulosa cells secrete VEGF in the late follicular phase. Increased vascular permeability brought on by VEGF oversecretion is the cause of OHSS. The amount of free VEGF is correlated with the severity of OHSS. The suppression of VEGF is the reason for the increase in vascular permeability.[23,24] The GnRH antagonist Cetrorelix, which is employed in this investigation, has been shown to reduce VEGF expression in hyperstimulated ovaries and VEGF secretions in human granulosa lutein cell cultures.[25] In the ovaries of hyperstimulated rats, GnRH antagonist treatment also decreased VEGF and VEGF receptor expression at the mRNA and protein levels.[26] A luteolytic effect—a method of lessening the excessive synthesis of vasoactive cytokines from the corpora lutea that contributes to the development of OHSS—is reported to be present in GnRH antagonists.[9,27]

The administration of GnRH antagonists during the peri-implantation period may raise concerns regarding potential negative effects on pregnancy and neonatal outcomes, according to a previous study by Bosch et al.[28] In a prospective cohort study involving 192 IVF patients who were at risk of OHSS, Lainas et al. found that luteal GnRH antagonist administration had no negative effects on pregnancy or neonatal outcomes.[16] According to certain research, there is no connection between GnRH antagonists and pregnancy or unfavorable birth outcomes.[9,16,27,29,30] Administration of GnRH antagonists during the luteal phase did not affect the likelihood of pregnancy in a prior study.[29] The antagonist group in our study had higher biochemical and clinical pregnancy rates. It should be mentioned that women with early OHSS had much higher biochemical pregnancy rates than non-OHSS patients in a prior study by Papanikolaou et al.[31]

5. Conclusion

Cetrorelix, which is given during the early luteal phase of the ovulation stimulation cycle in IVF, under long and short protocols, is a safe and effective medicine to prevent and cure OHSS. The frequency of moderate and severe OHSS may decrease as a result.

6. Source of Funding

None.

7. Conflict of Interest

None.

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