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Assessment of the Role of Luteal Phase Antagonist in Women at High-risk of Developing Ovarian Hyper-Stimulation Syndrome (OHSS) Receiving GnRH Agonist Trigger

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ABSTRACT

Background: Ovarian hyperstimulation (OHSS) is a serious complication of assisted reproductive technology (ART). This paper aims to assess the effectiveness of luteal phase cetrotide, administered for 3 days starting on the day of oocyte retrieval, on the incidence of mild and moderate ovarian hyperstimulation syndrome (OHSS) and vascular endothelial growth factor (VEGF) levels in females at high risk for the development of OHSS who receive the GnRH antagonist induction protocol.

Patients and methods: The study included 110 infertile women candidates for IVF at high risk for OHSS, randomized into two cohorts: the cetrotide cohort (n=55) and the control (no-cetrotide) cohort (n=55). All participants received the conventional antagonist protocol, followed by the freeze policy. The control cohort received traditional symptomatic treatment. In addition to symptomatic treatment, the study cohort received a subcutaneous injection of cetrorelix acetate; all patients underwent clinical evaluation on days 0, 3, and 5. Then, on day 5 after oocyte retrieval, all patients underwent ultrasound scanning for ascites grading and maximum ovarian diameter (MOD). We took blood samples to determine the level of VEGF.

Results: The results indicated that patients in both groups exhibited non-significant differences in terms of age, BMI, ovarian serum E2 on the day of trigger, and number of oocytes retrieved ($P > 0.05$). Day 3 VAS pain scores were significantly lower in both groups than the Day 0 scores ($P = 0.000$). On day 5, we found a statistically significant difference in MOD ($P=0.000$). Additionally, serum vascular endothelial growth factor levels on day -5 showed a statistically significant difference between the two groups ($P = 0.000$). The incidence of mild and moderate OHSS syndrome was significantly lower in the cetrotide cohort than in the control cohort (9.1% and 32.7%, respectively; $P = 0.005$).

Conclusion: Administering the GnRH antagonist (cetrotide) during the luteal phase decreased the severity and frequency of early ovarian hyperstimulation syndrome symptoms in high-risk females with all embryos cryopreserved. Cetrotide may work by directly affecting the ovary, which could lead to lower levels of a substance called serum vascular endothelial growth factor.

Keywords: *ovarian hyperstimulation syndrome, cetrotide therapy, embryo freezing, and VGEF*

1. INTRODUCTION

Controlled ovarian hyperstimulation (COH) is a crucial component of in vitro fertilization (IVF), and it has been utilized since its beginnings in the 1970s (1). The discovery of gonadotropin-releasing hormone (GnRH) agonists and antagonists of natural steroid hormone (estradiol) has provided a variety of choices for assisted reproduction and has enhanced the success rates of in vitro fertilization (IVF) (2). IVF procedures are categorized as GnRH antagonists or agonist procedures based on the use of a GnRH agonist or antagonist (3). Minimal stimulation protocol is another approach that applies clomiphene citrate (CC) when combined with follicle-stimulating hormone (FSH) or gonadotropin mixtures (Gn) (4).

GnRH agonist and antagonist regimens employ agonistic or antagonistic analogs of GnRH. GnRH analogs are decapeptides modeled after human GnRH to engage with GnRH receptors. These analogs possess specific amino acid changes in the gonadotropin sequence that enhance their half-lives and efficacy relative to natural hormones (5,6). GnRH agonists facilitate prolonged stimulation of gonadotropin production, whereas GnRH antagonists function as agents of chemical hypophysectomy (7). Both analogs are extensively utilized in IVF to stimulate folliculogenesis by inhibiting the natural LH surge and facilitating scheduled oocyte retrieval (8,9). Multiple agonistic analogs (triptorelin, leuprorelin, deslorelin, goserelin, and nafarelin) and a few antagonistic analogs (cetrorelix and ganirelix) have been incorporated into clinical practice (4). Among the many GnRH agonist long protocols, specifically ultra-short, short, and long, the long GnRH agonist protocol has been established as the gold standard in IVF since its inception in the 1980s (9–11). The recent advancement of GnRH antagonists has provided an alternate strategy in IVF therapy.

Ovarian hyperstimulation syndrome (OHSS) is a potentially fatal iatrogenic condition occurring during the early luteal phase or early pregnancy following ovulation induction (OI) or ovarian stimulation (OS). Mild OHSS manifests in 32% of IVF cycles, whereas 10–15% of IVF patients experience moderate OHSS, and 5–8% are diagnosed with severe OHSS (12). Compared to the GnRH agonist protocol, the risk of severe OHSS is diminished by 50% when utilising GnRH antagonists for co-treatment during controlled ovarian stimulation (COS) prior to IVF or intra-cytoplasmic sperm injection (ICSI); notably, both protocols yield equivalent efficacy regarding reproductive outcomes. However, moderate to severe OHSS may still arise in GnRH antagonist protocols, particularly when human chorionic gonadotrophin (hCG) is utilised to induce final oocyte maturation in high-responder individuals (13).

The goal of this research is to assess the effectiveness of luteal phase cetrotide (Cetrorelix Acetate, Merck Serono, Inc.) starting on the day of oocyte retrieval and lasting for 3 days on the incidence of mild and moderate OHSS and vascular endothelial growth factor (VEGF) levels within females at elevated risk for the progression of OHSS who received a gonadotropin-releasing hormone antagonist induction protocol.

2. PATIENTS AND METHODS

This randomized case-control study was conducted from July 2021 to December 2022 in the IVF unit at Kasr Al Ainy Hospital, Faculty of Medicine, Cairo University. The local ethics committee approved the study protocol on June 10, 2021, under approval number MD_113_2021.

Sample Size

The sample size was determined by comparing the frequency of OHSS in high-risk females receiving an antagonist protocol with GnRH agonist trigger, both with and without the administration of the luteal phase GnRH antagonist cetrotide. Using the Fisher Exact test, the estimation was done by comparing two proportions from independent samples in a prospective investigation. The α-error level was set at 0.05, the power at eighty percent, and the intervention groups ratio at 1. Following an earlier study (14), the frequency of OHSS was 0% in the cetrotide group and 34.7% in the no cetrotide group. Consequently, to identify a difference of 25% in the frequency of OHSS, the minimum required sample size for each group is 50 participants. Additionally, to account for subjects who declined to participate or were lost to follow-up, the sample size was increased to 55 in each group. Sample size determination has been performed using PS Power and Sample Size Calculations software, version 3.0.11 for MS Windows (William D. Dupont and Walton D., Vanderbilt University, Nashville, Tennessee, United States of America).

The included participants were patients aged eighteen to forty with polycystic ovary syndrome, retrieved oocytes equal to or more than twenty, serum E2 levels of ≥5000 picograms per milliliter on the day of trigger, and an ovarian diameter of more than ten centimeters on the day of ovum retrieval. The exclusion criteria comprised patients over 40 with pulmonary, cardiac, or hepatic dysfunction and coagulation disorders.

All participants underwent complete history, body mass index (BMI), ultrasound assessments (Mindray DP5 (50/60HZ), and laboratory investigations to assess the uterine cavity and AFC calculations. Then, female patients were subjected to ovarian stimulation with gonadotropin recombinant FSH and hMG starting from the 2nd or 3rd day of the menstrual cycle. Monitoring was done through transvaginal ultrasounds every other day. An antagonist injection (Cetrotide) was started on the 6th day to prevent premature LH surge and continued until the trigger was prescribed using 0.2mg GnRHa (Decapeptyl®, 0.1mg, triptorelin acetate, Ferring) subcutaneously when at least two follicles reached a mean diameter of 18-20mm. Following thirty-six hours, transvaginal oocyte retrieval was carried out.

Randomization

All participants followed embryo freezing protocol and were randomly assigned into two equal groups: one receiving a cetrotide subcutaneous injection and the other receiving no cetrotide. The control group had traditional symptomatic management, whereas the study group had cetrotide subcutaneous injection daily for 3 days. Abdominal pain was assessed on days 0 (the day of oocyte retrieval), 3, and 5, and when found, it was graded utilizing a numerical pain visual analog scale. Patients were also evaluated for vomiting, a sense of abdominal distension, and nausea was scored utilizing verbal analog

scales. On day 5, after oocyte retrieval, patients underwent ultrasound scanning for ascites grading and maximum ovarian diameter (MOD).

The quantity of fluid accumulation in the peritoneal cavity, with the case in the anti-Trendelenburg position, was used to grade ascites, while blood samples were taken to determine the VEGF level (15–18). VEGF has been quantified using an ELISA approach utilizing human vascular endothelial growth factor ELISA kits. According to the Green Top guidelines, we graded all females who met the inclusion criteria based on the severity of their OHSS manifestations (19).

Statistical Analysis

Data were statistically summarized using mean ± standard deviation (± SD), interquartile range, median, or frequencies (number of cases) and percentages as appropriate. Due to the non-normal distribution of the information, the Mann-Whitney U test was utilized to compare numerical parameters among the examined groups. Chi-square (χ^2) tests, Monte Carlo tests, and Fisher's exact tests were conducted to compare categorical data. Two-sided p-values less than or equal to 0.05 are considered statistically significant. All statistical analyses were performed using IBM SPSS (Statistical Package for the Social Sciences; IBM Corp, Armonk, NY, United States) version 22 for Microsoft Windows.

3. RESULTS

One hundred ten (110) high-risk patients of developing ovarian hyperstimulation syndrome with the cancellation of fresh embryo transfer and cryopreservation of the whole embryos after oocyte retrieval were included in our study. Luteal administration of GnRH agonist was performed in 55 (cetrotide cohort), and clinical observation with traditional symptomatic treatment, including analgesics excluding nonsteroidal drugs, antispasmodics, and antiemetic therapy was performed in 55 (control cohort).

The results showed that patients of both groups showed non-significant differences concerning age, BMI, ovarian serum E2 on the day of trigger, and number of oocytes retrieved (P > 0.05), as represented in Table 1.

Table 1: **Clinical findings of the examined patients**

Examined variables		Cetrotide Cohort	Control Cohort	p-value
Age	min. – max.	27-37	28-38	
	mean ± S. D	31.9±2.4	31.7±2.6	0.564
	median (IQR)	31(4)	31(4)	
BMI	min. – max.	23-35	22-35	
	mean ± S. D	28.045±2.6	28.273±3.4	0.998
	median (IQR)	28(4)	28(6)	
Serum Estrogen	min. – max.	4500-12000	3800-11200	
	mean ± S. D	8270.36±1655.67	8740.73±1503.34	0.119
	median (IQR)	8400(2500)	9000(2050)	
Number of oocyte	min. – max.	22-50	22-40	
	mean ± S. D	31±9	29±5	0.184
	median (IQR)	29(8)	28(8)	

BMI: Body mass index, S.D: Standard deviation, Mann-Whitney U test *: Statistically significant at P ≤ 0.05

As shown in Table 2, Day 3 VAS pain scores were significantly lower in both groups than Day 0 scores and each other (P =0.000). Pain began to improve in the study group on days 3 and 5, and scores showed a progressively significant decline compared to Day 0 scores and the control group (P =0.000). Regarding ascites detection by ultrasound on Day 5, there patients had mild ascites in the study group and nine patients in the control group with statistically significant differences (P=0.002)

Table 2: **Pain score and Ascites of the studied patients during the follow-up days**

Studied variables			Cetrotide Cohort	Control Cohort	p-value
Pain score	Day 0	min. – max.	0-5	0-10	
		mean ± S. D	0.3±1	2.9±2.7	0.000*
		median (IQR)	0(0)	3(5)	
	Day 3	min. – max.	0-2	0-5	0.000*

		mean ± S. D	0.1±0.4	1.7±1.7	
		median (IQR)	0(0)	2(3)	
	Day 5	min. – max.	0-0	0-2	
		mean ± S. D	0±0	0.5±0.6	0.000*
		median (IQR)	0 (0)	0 (1)	
		No n= (%)	52 (94.5%)	46 (83.6%)	
Ascites	Day 5	Mild n= (%)	3 (5.5%)	9 (16.4%)	0.002*
		Moderate n= (%)	0 (0%)	0 (0%)	

S.D: Standard deviation, Mann-Whitney U test *: Statistically significant at P ≤ 0.05

A statistically significant difference was found regarding maximum ovarian diameter (MOD), which was measured by ultrasound on day 5 (P=0.000). Also, Serum vascular endothelial growth factor level was measured on day -5 with a statistically significant difference between the two groups (**P 0.000**), as presented in Table 3.

Table 3. **Maximum ovarian diameter and Vascular endothelial factor level on day 5**

Studied variables		**Cetrotide Cohort**	**Control Cohort**	**p-value**
maximum ovarian diameter	min. – max.	5-8.7	6-10	0.000*
	mean ± S. D	6.9±0.87	7.75±0.97	
	median (IQR)	7(2)	8(1)	
vascular endothelial factor level	min. – max.	270-520	280-592	0.000*
	mean ± S. D	374.75±62.6	455±77.8	
	median (IQR)	359(64)	446(115)	

S.D: Standard deviation, Mann-Whitney U test *: Statistically significant at P ≤ 0.05

Figure 1 represents the incidence of mild and moderate OHSS. Mild and moderate ovarian hyperstimulation syndrome incidence was significantly lower in the cetrotide cohort than in the control cohort (9.1% and 32.7%, respectively; (P = 0.005).

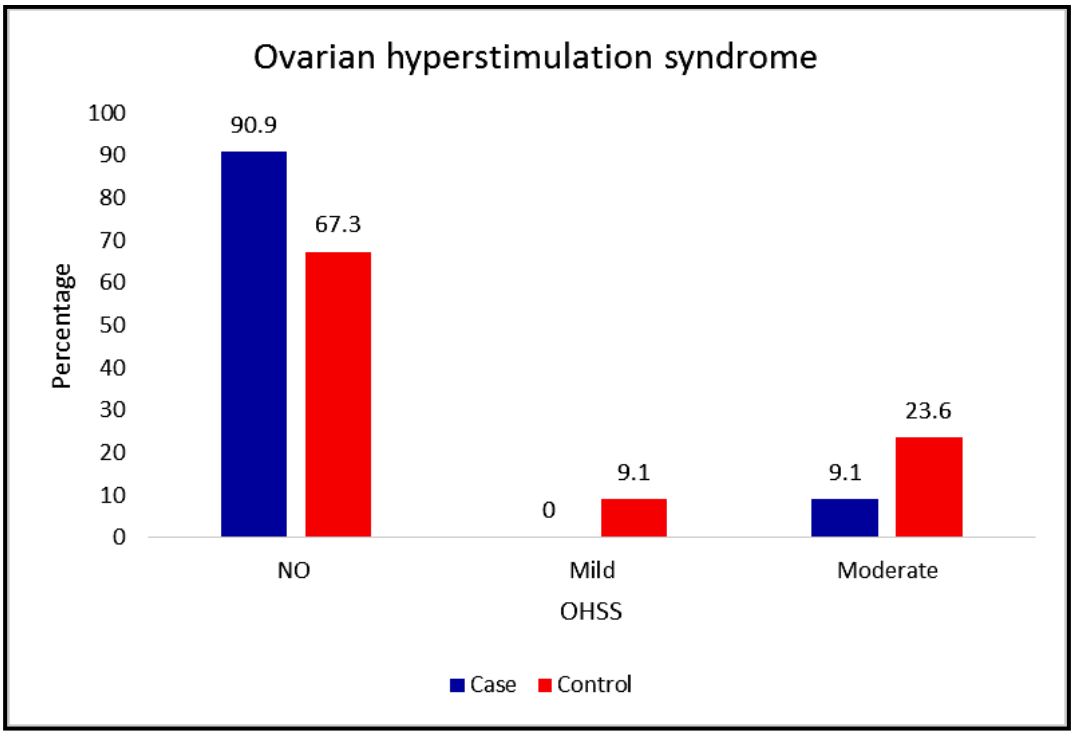

Fig 1. **The OHSS among the studied patients**

4. DISCUSSION

OHSS is a disease state that arises from ovarian stimulation, leading to fluid accumulation in body cavities, enlarged ovaries, and a subsequent decrease in circulating volume. This condition can impair organ perfusion and increase the risk of venous thrombosis (20,21). This study included 110 infertile women candidates for IVF at high risk for OHSS, randomized into the cetrotide cohort (n = 55) and the control (no-cetrotide) cohort (n = 55). The findings of this study concluded that the administration of cetrotide during the luteal phase successfully reduces the frequency of mild and moderate early ovarian hyperstimulation syndrome in females at high risk of developing ovarian hyperstimulation syndrome when all embryos are cryopreserved. Furthermore, this study revealed a significant reduction in serum vascular endothelial growth factor concentrations, ascites, and MOD after administration compared to the control cohort.

In agreement with our research, Chen et al. (22) **conducted a prospective cohort study** involving 105 cases of high-risk ovarian hyperstimulation syndrome in which all embryos were cryopreserved. The incidence of moderate and severe ovarian hyperstimulation syndrome in the control group was significantly lower than in the cetrorelix group (37.14% and 18.03%, respectively; P-value = 0.037). Within the control group, serum estradiol (P-value = 0.013), white blood cell count (P-value = 0.031), ascites volume (P-value = 0.036), EGR-1 (P-value = 0.025), and vascular endothelial growth factor concentrations (P-value = 0.015) were significantly higher on the sixth day of POR compared to the third day of POR. In contrast, the cetrorelix group did not demonstrate any increase between day 3 POR and day 6 POR, indicating that the symptoms of ovarian hyperstimulation syndrome were rapidly regressing. Cetrorelix intervention has been associated with both the severity and frequency of ovarian hyperstimulation syndrome (95% confidence interval 0.11–0.78, OR 0.29, P-value = 0.014).

Additionally, Salama et al. (23) conducted a study to assess the effectiveness and safety of a three-day cetrotide treatment initiated on the day of oocyte retrieval (Day-0) in 48 females who were at an elevated risk of developing OHSS following the GnRH agonist induction protocol. The authors concluded that the three-day cetrotide treatment following oocyte retrieval with embryo freezing may be a suitable treatment policy for females who were at an elevated risk for ovarian hyperstimulation syndrome and were given the GnRH-agonist induction protocol (23).

Lainas et al. (24) conducted a pilot observational cohort study involving 12 females diagnosed with severe early OHSS during IVF. The elective blastocyst cryopreservation was carried out alongside administering 0.25 milligrams of gonadotropin-releasing hormone antagonist for four days, from day five to day eight of the ovarian stimulation cycle. The primary results of their study showed that The greatest level of vascular endothelial growth factor (390.9 ±137.4 picograms per milliliter) appeared on five days of POR, which coincided with the diagnosis of severe OHSS (24). Compared with the POR on day five, there was a significant reduction in VEGF on day seven (302.8 ± 104.9 picograms per milliliter; P = 0.026), day nine (303.3 ± 148.3 picograms per milliliter; P = 0.007), and day eleven (252.6 ± 182.7 picograms per milliliter; P = 0.010). The decrease was correlated with an improvement in laboratory and ultrasound variables, suggesting that severe OHSS has regressed. Every female was treated at an outpatient level (24).

In another study conducted by Hosseini et al. (25), twenty-seven infertile females who were undergoing assisted reproductive techniques with early-onset OHSS were accepted. Ovarian stimulation with gonadotropins was initiated in all cases following the completion of desensitization with the long-term protocol. Control group cases received a daily dose of cabergoline for a week while all embryos were frozen. The examine group was given two consecutive dosages of GnRH antagonist (Cetrotide) (25). The Cetrotide group showed significantly lesser rates of moderate and severe ovarian hyperstimulation syndrome, hospitalization, or acute care for ascites tap. Neither group experienced any adverse effects. They concluded that GnRH antagonists seem to be an effective outpatient treatment with rapid onset activity and minimal side effects for the management of early OHSS (25).

As reported by Bonilla et al. (26) , who examined six infertile cases scheduled for embryo transfer that developed early-onset severe OHSS with hemoconcentration and ascites. A significant reduction in estradiol (E2) levels was observed a few days after therapy. The study group exhibited a faster rate of peritoneal fluid regression than the control group, as determined by ultrasound. Hematocrit levels remained comparable in both groups during follow-up. In two cases, a second bolus of the GnRH antagonist was administered due to clinical and biochemical findings during the four days of observation following the initial dose. None of the patients receiving GnRH antagonists required paracentesis (26).

Limitations

Our study's limitations include the statistical insignificance of the OHSS outcomes, which may be attributed to the restricted sample size. A substantial sample size represents another barrier that must be addressed in future studies. Similarly, the diverse age groupings represent a restriction to consider in future studies regarding age classification.

Conclusion

The research indicated that the occurrence of mild and moderate OHSS was markedly reduced in the cetrotide group compared to the control group. Pain scores on Days 0, 3, and 5, the presence of ascites on Day 5 (P=0.002), MOD (P=0.000), and VEGF levels were markedly elevated in the control group. The study determined that cetrorelix significantly lowers the

occurrence of early mild and moderate OHSS in high-risk women undergoing the antagonist regimen and diminishes serum VEGF levels. Our findings indicate that luteal administration of the GnRH antagonist (cetrotide) effectively diminishes both the incidence and severity of early OHSS symptoms in high-risk women. The potential mechanism of cetrotide may involve direct action on the ovary, resulting in a reduction of serum VEGF levels.

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