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Original Research

Comparison of 3-Day and 7-Day Gonadotropin-Releasing Hormone Antagonist Treatment for the Prevention of Ovarian Hyperstimulation Syndrome in Women Undergoing Assisted Reproductive Technologies: A Prospective Randomized Control Pilot Trial

Vajiheh Hazari[1], Aida Najafian[2,*], Hamid Salehiniya[3,*]

[1]Department of Gynecology, School of Medicine, Birjand University of Medical Sciences, 9717853577 Birjand, Iran
[2]Department of Obstetrics and Gynecology, School of Medicine, Shariati Hospital, Tehran University of Medical Sciences, 1416753955 Tehran, Iran
[3]Department of Epidemiology and Biostatistics, School of Health, Social Determinants of Health Research Center, Birjand University of Medical Sciences, 9717853577 Birjand, Iran
*Correspondence: aidanajafian@yahoo.com (Aida Najafian); alesaleh70@yahoo.com (Hamid Salehiniya)
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Abstract

Background: Assisted reproductive technology (ART) protocols can lead to a serious and potentially life-threatening complication known as ovarian hyperstimulation syndrome (OHSS). The present study investigated and compared the effects of gonadotropin-releasing hormone (GnRH) antagonist (GnRH-ant) administration over 3-day and 7-day periods in women at high risk for OHSS. **Methods**: In this prospective randomized controlled pilot trial, an antagonist protocol was employed as part of ART in 41 patients aged 18 to 40 who were referred to the Infertility Center. After egg retrieval, subjects in group 1 received cabergoline in combination with 7 days of cetrorelix (one subcutaneous ampoule of cetrorelix once daily), while participants in group 2 received cabergoline along with 3 days of cetrorelix (one subcutaneous ampoule daily). Upon enrollment, participants were administered cabergoline tablets (Cabergolex 0.5 mg) at a dose of 0.5 mg orally at bedtime for 8 consecutive days. Ultrasound and clinical examinations were performed on the day of oocyte retrieval and on days 4, 8, and 14 thereafter to detect the occurrence of OHSS. Data were analyzed using SPSS version 22, with independent samples *t*-test and Chi-square test conducted at a significance level of <0.05. **Results**: The patients in the 3-day treatment group were aged between 30.30 ± 6.46 years, while those in the 7-day treatment group were between 29.09 ± 5.59 years, with no statistically significant difference between themean groups ($p = 0.528$). No hospitalizations were necessary in either the 3-day and 7-day treatment groups, and no cases of severe OHSS were observed. Moderate OHSS occurred in 6 patients (20%) in the 3-day treatment group and 5 patients (23.8%) in the 7-day treatment group, with no statistically significant difference between the groups ($p = 0.768$). **Conclusions**: A 3-day treatment appears to be as effective as a 7-day treatment in preventing OHSS. **Clinical Trial Registration**: This study is registered on the Iranian Registry of Clinical Trials (IRCT) at https://trialsearch.who.int/Trial2.aspx?TrialID=IRCT20201126049497N1 (registration number: IRCT20201126049497N1).

Keywords: GnRH antagonist; prevention; ovarian hyperstimulation syndrome (OHSS); assisted reproductive technology (ART)

1. Introduction

Women undergoing ovarian stimulation as part of assisted reproductive technology (ART) protocols are at risk of developing ovarian hyperstimulation syndrome (OHSS), a serious and potentially life-threatening complication [1, 2]. Controlled ovarian stimulation (COS) aims to boost oocyte production, but it may also have serious side effects [1]. Moderate and severe OHSS can occur in approximately 3% and 10% of all ART cycles, and in high-risk women, the incidence may reach up to 20% [3]. OHSS can lead to a range of symptoms, from mild abdominal discomfort and distention to more severe manifestations such as ascites, abdominal bloating, vomiting, nausea, diarrhea, and decreased urine output [4].

OHSS is characterized by increased capillary permeability, leading to fluid leakage from the intravascular space into the extravascular compartments, resulting in ovarian enlargement [1,2,5]. OHSS is caused when ovaries, are preprogrammed by follicle-stimulating hormone/luteinizing hormone (FSH/LH), are then exposed to human chorionic gonadotropin (hCG) [6]. The increased vascular permeability induced by vascular endothelial growth factor (VEGF) contributes to the pathogenesis of OHSS. VEGF is secreted by granulosa cells, and it is stimulated by hCG. Severe OHSS is linked to an increase in VEGF levels [1].

Preventing OHSS relies largely on the ability to predict its occurrence, and currently, no method can completely eliminate the risk [7]. However, the risk of OHSS is lower in elective frozen-thawed embryo transfer (FET) cycles compared to those involving fresh embryo transfer (ET) [8]. In addition, the risk of OHSS is not completely eliminated even with the use of cryopreservation [9]. How-

ever, OHSS prevention can be life-saving and is generally more advantageous than treatment. Early risk factors include a low body mass index (BMI), young age, polycystic ovary syndrome (PCOS), and previous OHSS [7]. The ovarian response to COS determines the secondary risk factors for OHSS. Its predictability is largely determined by ultrasound monitoring and serum estradiol (E2) during COS. The risk of OHSS increases when more than 14 growing follicles with a diameter of $\geq$11 mm are present on the day of stimulation, and when more than 14 oocytes are retrieved. An increased E2 level, particularly a serum concentration $>$2500 pg/mL, is considered a major predictive factor for OHSS, alongside other important factors [1].

The use of ovulation-inducing drugs, along with the rapid advancement of ART, has contributed to an increased prevalence of OHSS [10]. For the past two decades, *in vitro* fertilization-embryo transfer (IVF-ET) protocols have predominantly relied on the use of gonadotropin-releasing hormone (GnRH) antagonists (GnRH-ant) to prevent the surge of LH and inhibit the rise in E2 levels. A significantly lower incidence of OHSS and E2 concentrations has been observed with GnRH-ant compared to GnRH agonist (GnRH-a) [11].

Cabergoline, obtained from ergot alkaloids, has a powerful effect as a dopamine receptor agonist, specifically targeting D2 receptors [12]. Cabergoline inhibits the release of vascular endothelial growth factor receptor 2 (VEGFR2), thereby preventing increased vascular permeability. The study has assessed cabergoline as a preventive approach to decrease the risk of OHSS by employing varying doses and treatment protocols [13].

The results of the few studies conducted investigating the combined effect of these two drugs suggest that their concurrent use is more effective than monotherapy and reduces the risk of OHSS [14,15]. Considering that OHSS is a serious side effect of ART and with the increasing infertility rates, the use of infertility treatment methods is expected to rise in the future. Therefore, understanding effective prevention strategies is necessary to prevent the occurrence and consequences of this complication. As such, the present study aimed to examine and compare the effects of GnRH-ant administered for 3-day and 7-day periods, in combination with cabergoline, in women at high risk for OHSS.

2. Methods

2.1 Study Design

This study was a prospective randomized controlled pilot trial, registered on the Iranian Registry of Clinical Trials (IRCT) website (https://irct.behdasht.gov.ir/) under the code IRCT20201126049497N1. It was conducted at the Shariati Medical Training Complex in Tehran and Royesh Birjand Infertility Center. The clinical trial protocol adhered to the Consolidated Standards of Reporting Trials (CONSORT) checklist (Fig. 1).

2.2 Participants

Infertile women aged 18 to 40 years, undergoing ART and who were susceptible to OHSS, were selected as study subjects. They were referred to the Shariati Medical Educational Complex in Tehran and Royesh Infertility Center in Birjand, with visits from August 2022 to August 2023.

2.3 Inclusion Criteria

Infertile women aged 18 to 40, undergoing ART with a GnRH-ant protocol, and at risk of developing OHSS (defined as serum E2 levels greater than 3000 pg/mL, with more than 15 oocytes, or more than 20 follicles), were included in this study. Exclusion criteria included the presence of lung fibrosis, swelling or inflammation around the heart and lungs, high blood pressure, heart valve disease, liver disease, or an allergy to ergot derivatives or cabergoline.

2.4 Exclusion Criteria

Patients who did not adhere to the treatment protocol, became pregnant during the study period, or started other medications known to influence OHSS (such as metformin or calcium) were excluded from the study.

2.5 Study Implementation

Detailed information about the study, including the administration of medications, possible side effects, and procedural steps, were explained to the participants by the study coordinator. Participation was voluntary, and patients and patients were informed that they could withdraw from the study at any time without incurring any cost. All interventions were conducted in accordance with international ethical standards, ensuring the safety and well-being of the participants. All patients underwent FET during the study period.

2.6 Intervention

All patients included in this study underwent ovarian stimulation using the GnRH-ant protocol. Following confirmation of pituitary down-regulation on day 2 of the menstrual cycle (defined as endometrial thickness less than 5 mm), follicle-stimulating hormone (FSH; follitropin alfa, Cinnal-F CinnaGen, Tehran, Iran) was used. Age, antral follicle count, BMI, and anti-Müllerian hormone (AMH) levels were used to determine the starting dose of gonadotropins. Transvaginal ultrasound was used to monitor follicular growth. Along with gonadotropin, patients received 0.25 mg subcutaneous (SC) cetrorelix acetate (Cetronax Ronak Daro, Tehran, Iran) daily as an GnRH-ant when the follicle size reached 14 mm. When at least 3 follicles reached a minimum diameter of 18 mm and the total number of follicle count was 15 or more, indicating a risk of ovarian hyperstimulation, one ampoule of decapeptide (0.1 SC) along with one ampoule of hCG (5000 IU, intramuscular, Tehran, Iran) were administered as a trigger. Oocyte retrieval was done 36 hours later.

Then, subjects in group 1 received cabergoline for 8 days and SC cetrorelix (once a day) for 7 days after oocyte retrieval. Participants in group 2 received cabergoline for 8 days of plus subcutaneous cetrorelix (once a day) for 3 days after oocyte retrieval. Starting on the ovulation day, both groups received cabergoline tablets (Cabergolex 0.5 mg, Shahr Daro Company, Tehran, Iran) at a dose of 0.5 mg orally at bedtime for 8 consecutive days. A few days later, the incidence and severity of OHSS were investigated in the study subjects based on clinical and laboratory criteria, as well as vaginal ultrasound.

Clinical and ultrasound examinations were conducted on the day of oocyte retrieval and subsequently on days 4, 8, and 14 to monitor the occurrence of OHSS. Patients were advised to contact the research team if they experienced symptoms such as shortness of breath, decreased urine output, abdominal pain, postural dizziness, rapid weight gain, and abdominal distension.

2.7 Outcomes

The primary outcome measures were the occurrence of moderate to severe OHSS, the need for hospitalization, and the requirement for paracentesis.

2.8 Definitions

Based on the HERA (Hyper-response Risk Assessment) Delphi consensus for the management of hyper-responders in *in vitro* fertilization [16], outcomes were defined as follows:

Moderate OHSS: Characterized by abdominal distention, discomfort, nausea, vomiting, and diarrhea, accompanied by ovarian enlargement measuring 5 to 12 cm and the presence of ascites detected by ultrasonography [17,18].

Severe OHSS: Moderate OHSS features combined with clinical evidence of ascites, hydrothorax, and/or respiratory distress, as well as signs of hemoconcentration such as reduced blood volume, coagulation abnormalities, increased blood viscosity, and diminished renal perfusion and function [17,18].

Paracentesis (abdominal fluid drainage): Early and aggressive drainage of accumulated pelvic and abdominal fluid, causes shortness of breath, abdominal distension, and pain, performed under transvaginal ultrasound guidance [19].

2.9 Sample Size

In this pilot study, 41 patients were enrolled, with 20 patients in the 3-day treatment group and 21 patients in the 7-day treatment group.

2.10 Randomization

Eligible individuals were randomly assigned to two intervention groups—3-day group (n = 21) and 7-day group (n = 21)—using the balanced block randomization method with blocks of four. Patients were blinded to their group assignment. However, due to the nature of the interventions, the attending physicians were aware of the assigned treatments, and therefore, double-blinding was not applicable in this study.

2.11 Statistical Analysis

Data analysis was performed with SPSS version 22 (IBM Corp., Armonk, NY, USA). The normality of data distribution was considered using Kolmogorov-Smirnov test. The descriptive analysis presented the number, percentage, mean, and standard deviations (SD). Analytical comparisons were performed with independent samples *t*-test and the Chi-square test, with a significance level of less than 5%.

3. Results

A total of 41 patients participated in this study, with 20 patients in the 3-day treatment group and 21 patients in the 7-day treatment group. The mean age of patients in the 3-day treatment group was 30.30 $\pm$ 6.46 years, while in the 7-day treatment group was 29.09 $\pm$ 5.59 years. No significant difference was observed in terms of the mean age between the two groups (p = 0.528).

The mean BMI of patients in the 3-day treatment group was 28.56 $\pm$ 5.96 kg/m^2, while in the 7-day treatment group was 27.45 $\pm$ 5.67 kg/m^2. No significant difference in the mean BMI was observed between the two groups (p = 0.548). The mean number of stimulation days in the 3-day treatment group was 12.30 $\pm$ 2.83 days and in the 7-day treatment group was 10.57 $\pm$ 4.62 days. No significant difference was observed between the two groups (p = 0.159). The mean number of eggs obtained in the 3-day treatment group was 17.25 $\pm$ 7.37 eggs and in the 7-day treatment group, it was 18.14 $\pm$ 7.37 eggs, which difference was not statistically significant (p = 0.700). The mean number of embryos obtained in the 3-day treatment group was 10.25 $\pm$ 5.67 embryos, while in the 7-day treatment group 12.14 $\pm$ 6.94 embryos. No significant difference was observed between the two groups (p = 0.346). Additionally, no significant differences were observed between the two groups for other investigated variables, such as AMH, FSH, LH, and gonadotropin dose ($p > 0.05$). Further details are provided in Table 1.

None of the patients in either the 3-day and 7-day treatment groups required hospitalization, paracentesis, or developed severe OHSS. Moderate OHSS occurred in 6 patients (20%) in the 3-day treatment group and 5 patients (23.8%) in the 7-day treatment group, with no statistically significant difference observed (p = 0.768). However, the effect size was weak (φ = 0.046) (Table 2).

Overall, the results of the chi-square test revealed no statistically significant differences between the two study groups in terms of hospitalization, moderate OHSS, severe OHSS, or the need for paracentesis ($p > 0.05$). Therefore, it can be concluded that both a 3-day and a 7-day treatments are effective in preventing OHSS (Table 2).

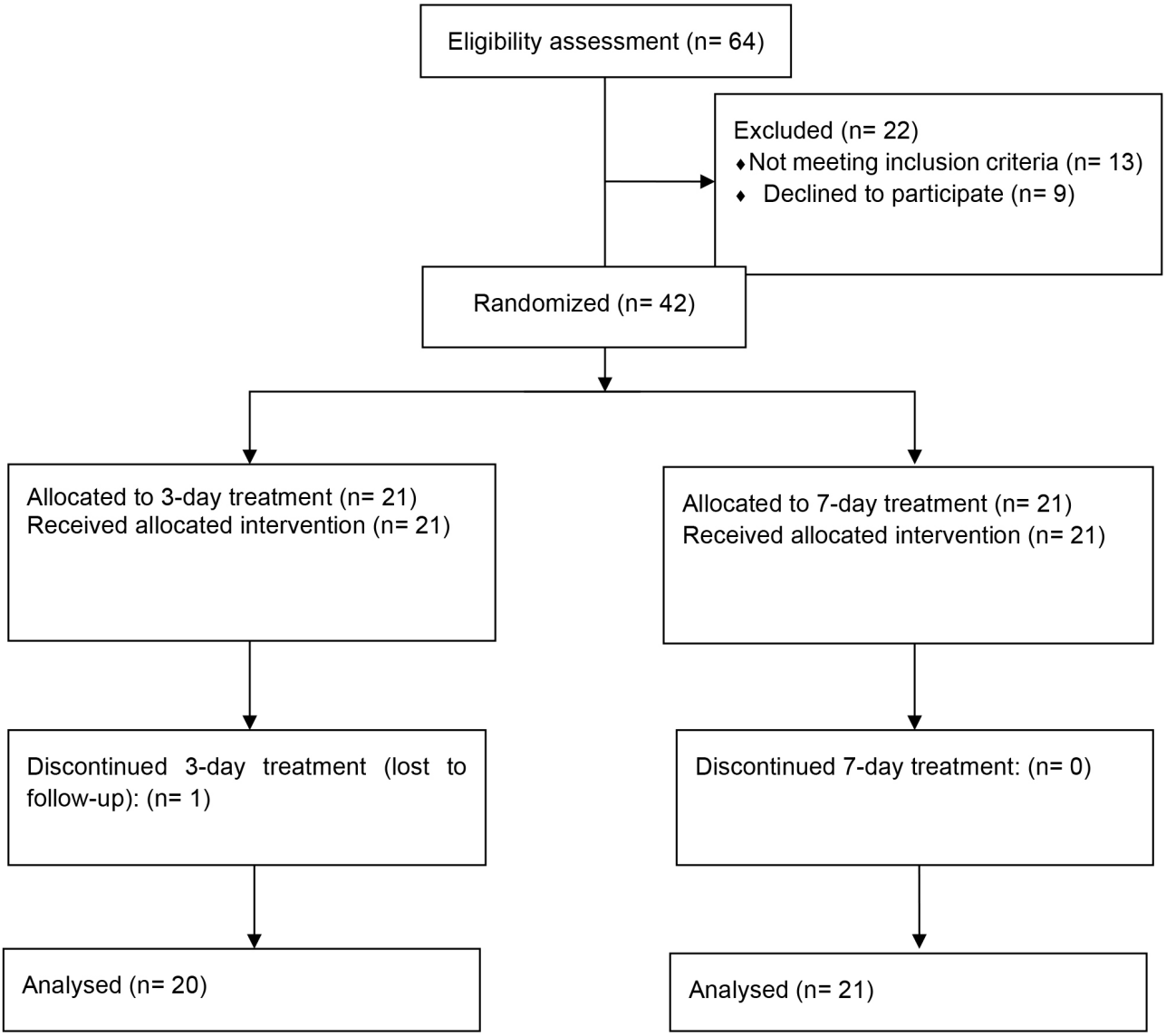

Fig. 1. CONSORT 2010 flow diagram of participant enrollment, allocation, follow-up, and analysis. CONSORT, Consolidated Standards of Reporting Trials.

4. Discussion

The results of this study, which compared the effects of 3-day and 7-day GnRH-ant treatment in preventing the occurrence of OHSS in women undergoing ART, showed no statistically significant difference between the participants of the two study groups in terms of the need for hospitalization, moderate OHSS, severe OHSS, or the need for paracentesis ($p > 0.05$). Our results indicate that the 3-day treatment is as effective as the 7-day treatment in preventing OHSS. However, it is important to note that the study's results have limited statistical power due to the small sample size. This result is consistent with the results of Lee D *et al*. (2017) [20], who studied 10 women with early OHSS after cryopreservation of all embryos. They concluded that the administration of GnRH-ant after embryo cryopreservation is both safe and effective for women with early OHSS.

However, they suggested that further investigation is needed to determine the optimal dose and duration of the GnRH-ant. In their study, the GnRH-ant (Cetrorelix 0.25 mg/day) was initiated during hospitalization and continued for 2 to 4 days.

Moreover, in the clinical trial of Wang *et al*. (2014) [21], the possibility and effect of administering Cetrotide during the early luteal phase were evaluated in patients at high risk of OHSS undergoing embryo freezing after ovulation. In the daily SC treatment group, patients received 0.25 mg of injectable Cetrotide between days 1 and 5 following oocyte retrieval, along with increased vascular volume and symptomatic treatment. They concluded that, compared to the control group that received the standard treatment, neither group showed significant differences in the incidence of severe OHSS, the hospitalization day, or the length of

Table 1. Comparison of baseline data between study groups.

Item	Study groups	Mean	SD	*p*-value
Age (years)	3 days	30.30	6.46	0.528
	7 days	29.09	5.59	
BMI (kg/m^2)	3 days	28.56	5.96	0.548
	7 days	27.45	5.67	
AMH (ng/mL)	3 days	7.92	3.44	0.533
	7 days	7.12	4.62	
FSH (mIU/mL)	3 days	4.842	1.53	0.866
	7 days	4.95	2.317	
LH (mIU/mL)	3 days	8.49	5.75	0.329
	7 days	6.81	5.08	
Stimulation days	3 days	12.30	2.83	0.159
	7 days	10.57	4.62	
Number of eggs	3 days	17.25	7.37	0.700
	7 days	18.14	7.37	
Number of embryos	3 days	10.25	5.67	0.346
	7 days	12.14	6.94	

BMI, body mass index; AMH, anti-Müllerian hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

Table 2. Comparison of clinical outcomes between study groups: hospitalization, moderate OHSS, severe OHSS, and paracentesis.

Item	Study groups	No	Percent (%)	*p*-value
Hospitalization	3 days No	20	100	-
	3 days Yes	0	0	
	7 days No	21	100	
	7 days Yes	0	0	
Moderate OHSS	3 days No	16	80	0.768*
	3 days Yes	4	20	
	7 days No	16	76.2	
	7 days Yes	5	23.8	
Severe OHSS	3 days No	20	100	-
	3 days Yes	0	0	
	7 days No	21	100	
	7 days Yes	0	0	
Paracentesis	3 days No	20	100	-
	3 days Yes	0	0	
	7 days No	21	100	
	7 days Yes	0	0	

OHSS, ovarian hyperstimulation syndrome. * Chi-squared test.

the luteal phase ($p > 0.05$). Furthermore they stated that in patients at high risk of OHSS undergoing embryo freezing, Cetrotide injection during the early luteal phase has no impact on serum steroid levels, and does not diminish the severity of occurrence of early OHSS.

One study has indicated that using a GnRH-ant rescue protocol in combination with cabergoline is more effective in preventing OHSS than cabergoline alone [15]. Moreover, the addition of cabergoline to a GnRH-a in patients at high-risk for OHSS during the luteal phase of fresh *in vitro* fertilization (IVF) cycles, and the subsequent administration of a GnRH-ant for 5 days during the luteal phase, significantly reduced the risk of mild and moderate OHSS and improved patient comfort compared to GnRH-a treatment alone [14]. A 3-day Cetrotide treatment initiated after oocyte retrieval, combined with cryopreservation of transferred embryos, has been considered a suitable treatment strategy for women undergoing GnHR-a induction protocol who are at high risk of OHSS [22].

Previous studies have shown that cabergoline reduces the incidence of mild and moderate OHSS by improving serum electrolyte levels, including sodium (Na^+) and potassium (K^+) concentrations. Electrolyte disturbances can increase the incidence of severe complications of OHSS, including arrhythmias and cardiac death. Therefore, in addition to examining patients' subjective symptoms (e.g., dizziness), measuring serum electrolyte levels have been recommended as an objective method to assess the severity of OHSS [14]. On the other hand, the addition of cabergoline prevented the increase in vascular hemoglobin concentration and probably minimized the risk of pulmonary embolism [23].

In addition, adding a GnRH-ant to the cabergoline-GnRH-a combination prevents ovarian enlargement and peritoneal fluid accumulation, reduces bloating and discomfort, regulates serum electrolyte concentrations, and prevents hemoconcentration [14].

In this study, it was shown that the simultaneous administration of GnRH-ant and cabergoline over a shorter duration (3 days) can effectively prevent moderate and severe OHSS, as well as patient discomfort. Similarly, Hebisha *et al*. [24] found that administration of GnRH-ant on the day of hCG was effective in protecting OHSS in patients undergoing *in vitro* fertilization/intracytoplasmic sperm injection (IVF/ICSI) with a long agonist protocol. Lainas *et al*. [25] also reported, based on ultrasound and laboratory parameters, that symptoms of severe OHSS began to decrease 7 days after the initiation of GnRH-ant therapy.

In general, OHSS remains difficult to diagnose and treat, and further research is recommended to elucidate its underlying pathophysiology and predictors. This is why most treatment approaches remain experimental [26]. One study has recommended serum E2 levels, suggesting that E2 levels can predict outcomes significantly better than serial maximal ovarian diameter (MOD) estimation [22]. Other contributing factors to the development of OHSS include hereditary components, such as the presence of interleukin (IL)-2 mRNA expression [27] as well as underlying conditions such as hypothyroidism [28,29].

This study has several limitations that warrant cautious interpretation of the results. Due to the implemen-

tation of the study during the coronavirus disease 2019 (COVID-19) pandemic, the willingness to perform elective procedures was reduced. Therefore, the main limitations of this study are the nature of the study (pilot study), small sample size, and the low statistical power due to weak effect size (Phi = 0.046). Additionally, the small sample size limited the ability to account for the potential influence of underlying conditions such as PCOS, insulin resistance, and BMI. On the other hand, future studies should be specifically designed to investigate the effects of additional factors including total dose of gonadotropins, peak E2 levels, number of blastocysts, implantation rate, and ongoing pregnancy rate. Lastly, this study did not distinguish between early and late OHSS.

5. Conclusions

The findings suggest that a 3-day treatment may be as effective as a 7-day treatment in preventing OHSS. However, further studies with larger sample sizes, high statistical power, and varied treatment durations are recommended to confirm these results.

Availability of Data and Materials

The datasets used and analyzed during the current study are available from the corresponding authors upon reasonable request.

Author Contributions

VH, AN, and HS designed the research study. VH and AN performed the research. HS analyzed the data. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was conducted in accordance with the Declaration of Helsinki. This study was approved by the ethics committee of Birjand University of Medical Sciences with code IR.BUMS.REC.1400.191. It was also registered with the code IRCTID: IRCT20201126049497N1 on the Iranian Registry of Clinical Trials website (https://irct.behdasht.gov.ir/). In addition, for all those eligible to enter the study, an informed consent form was completed in writing before entering the study.

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Conflict of Interest

The authors declare no conflict of interest.

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