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Can We Harvest More Mature Oocytes by Repeating Gonadotropin-Releasing Hormone Agonist Doses in Polycystic Ovarian Syndrome Patients at Risk of OHSS in Antagonist Cycles? A Randomised Clinical Trial

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Abstract

Background: There is an ongoing debate about the optimal dosage of gonadotropin-releasing hormone (GnRH) agonist for oocyte triggering in polycystic ovarian syndrome (PCOS) patients at risk for ovarian hyperstimulation syndrome (OHSS). In this study, we intend to ascertain whether the use of repeated doses of a GnRH agonist for oocyte triggering in these patients can enhance the outcomes of controlled ovarian stimulation (COS) for *in vitro* fertilization/ intracytoplasmic sperm injection (IVF/ICSI) cycles.

Materials and Methods: This randomised clinical trial enrolled 70 PCOS women candidates for IVF/ICSI with the standard antagonist protocol at Royan Institute (Tehran, Iran) from May 2020 to June 2022. Patients at risk of OHSS with oestradiol (E2) levels >3000 pg/ml on the day of trigger were randomly assigned to a control or experimental group. Group A (control group) patients received 0.2 mg triptorelin (Decapeptyl®) for final oocyte maturation. Group B (experimental group) patients received a second dose of 0.1 mg Decapeptyl®12 hours after their first dose, for a total dose of 0.3 mg. IVF/ICSI outcomes were compared between the groups.

Results: Ultimately, 35 women from the study group and 33 from the control group completed the treatment cycle. Both groups were comparable in terms of demographic characteristics, baseline hormonal profiles, and PCOS phenotypes. The dosage of gonadotropin, stimulation duration, number of retrieved oocytes, oocyte maturation rate, and oocyte recovery ratio did not significantly differ between the groups. No significant differences were found in terms of the number of blastocyst and cleavage embryos, nor the quality of obtained embryos between the groups. The mild to moderate OHSS rate was significantly lower in the study group (P=0.038).

Conclusion: A second dose of GnRH agonist 12 hours after the first dose did not improve the number and maturity of oocytes, or pregnancy outcomes in PCOS patients (registration number: NCT04600986).

Keywords: Assisted Reproductive Technology, Gonadotropin-Releasing Hormone Agonist, Polycystic Ovarian Syndrome

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Introduction

The use of gonadotropin-releasing hormone (GnRH) agonists, as a trigger for the final maturation of oocytes in the GnRH antagonist protocol, has revolutionised assisted reproductive technology (1, 2). Its shorter half-life leads to reduction or elimination of ovarian hyperstimulation syndrome (OHSS) in patients with polycystic ovarian syndrome (PCOS); therefore, the induction of final oocyte maturation with GnRH agonists compared to triggering with human chorionic gonadotropin (hCG) is more beneficial in IVF cycles for these patients (3-6).

However, there are concerns about the efficacy of GnRH agonists to achieve mature oocytes because of reports of empty follicle syndrome (EFS) and immature oocyte syndrome (7-9). Clinicians are hesitant to routinely administer GnRH agonists as triggers for final oocyte

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maturation; rather, it is used for PCOS cases and those with high ovarian response. The gonadotropin response following a trigger with GnRH agonists is shorter compared to the endogenous luteinizing hormone (LH) surge in a normal cycle (4-6). The expansion of cumulus cells and resumption of meiosis is 18 hours after the start of the LH surge (10), and the LH concentration must be above the threshold for 14–27 hours to maximise oocyte maturation (7). Because of the shorter duration and lower post-trigger LH levels, a solitary GnRH agonist dose might not adequately sustain elevated LH levels for 14-27 hours, which is the essential time for proper oocyte maturation. It has been postulated that recurrent administration of GnRH agonists prolongs LH secretion for as long as 14 hours (8). Chen et al. (7) concluded that repeated injections of GnRH agonist in an antagonist protocol led to a good oocyte yield, prevented OHSS, and improved cycle outcomes. However, a subsequent study by Vuong et al. (9) found no significant differences in terms of the number of mature oocytes and high-quality embryos between the different doses of triptorelin (0.2, 0.3, and 0.4 mg) used for final oocyte stimulation in oocyte donors. Deepika et al. (8) observed positive effects of repeating the agonist as a trigger for final oocyte maturation; however, in a recent study by Aflatoonian et al. (11), it was reported that a second dose of GnRH agonist administered 12 hours after the first dose had no positive effect on the number and the quality of obtained oocytes. The results of studies in this field are conflicting; therefore, the present randomised clinical trial is designed to evaluate the effect of repeating GnRH as trigger for final oocyte maturation on improving cycle outcomes in PCOS patients.

Materials and Methods

This was a randomised, open-label clinical trial approved by the Scientific Board and the Ethics Committee of Royan Institute, Tehran, Iran (IR.ACECR.ROYAN.REC.1398.110 and clinical trial number: NCT04600986). The study was conducted from May 2020 to June 2022. All infertile PCOS patients who referred to the Royan Infertility Clinic for their first in vitro fertilisation/intracytoplasmic sperm injection (IVF/ICSI) treatment cycle were screened. Patients who met the following criteria were included: i. PCOS diagnosis based on Rotterdam criteria, ii. 20-40 years of age, iii. Body mass index (BMI) >18 and <35 kg/m^2, iv. Indication for IVF/ICSI, v. Serum oestradiol (E2) ≥3000 pg/ml on the of day oocyte trigger, and vi. Provided written consent to take part in the research. Patients with severe male infertility (sperm extraction by surgery), indications for preimplantation genetic diagnosis, oocyte or embryo donation, surrogate uterus, moderate or severe endometriosis, history of uterine surgery, submucosal or intramural fibroids >5 cm, endometrial polyps, smoking or drug addiction were excluded from the study.

All patients received the GnRH antagonist protocol for controlled ovarian stimulation (COS). The details of the standard COS protocol at Royan Institute were explained in a previous study (12). Serum E2 and progesterone (P4) levels were measured on the day of the trigger, when three leading follicles >17 mm in diameter were observed. At this point, patients at risk for OHSS (E2 level ≥3000 pg/ml) were randomly allocated into two groups via a block randomisation list provided by the statistician. A sealed envelope was provided to the attending clinician for each eligible patient. The choice of triggering method was based on the grouping specified in the envelope. For patients in group A, final oocyte maturation was initiated using a single 0.2 mg dose of triptorelin (Decapeptyl®, Ferring, St-Prex, Switzerland) that was injected subcutaneously, 35 hours prior to oocyte retrieval. The women in Group B received an extra dose of Decapeptyl® (0.1 mg) 12 hours following the first dose. In both groups, serum LH and P4 levels were assessed 12 hours after the initial dose of Decapeptyl® and on the day of oocyte retrieval. A single-lumen oocyte retrieval needle guided by transvaginal ultrasound were used for oocyte retrieval 35 hours after the first dose, and while the patient was under intravenous sedation. An assessment for signs and symptoms of OHSS was performed according to the Golan and Weissman (13) classification system on the day of ovum pick up, and four and seven days later.

The standard IVF/ICSI or ICSI was performed based on the cause of infertility. The oocytes were cultured in SAGE 1-Step (Origio® culture media, Denmark) for three days (72-78 hours) after sperm insemination or injection. The embryos were scored according to the following quality criteria: excellent (≥6-8 cells and <10% fragmentation), good (≥6-8 cells and >10-20% fragmentation), or poor (<6-8 cells with >20% fragmentation and multinucleated blastomeres). Good quality embryos were selected for culturing up to the blastocyst stage or freezing. Blastocyst stage embryo quality was scored according to the Timofeeva et al. (14) classification as excellent (>3 AA), good (3-6 AB or 3-6 BA, 1-2 AA), average (3-6 BB, 3-6 AC, 3-6 CA, 1-2 AB, 1-2 BA), or poor (1-6 BC, 1-6 CB, 1-6 CC, 1-2 BB). All embryos were cryopreserved by the vitrification method, as previously reported (15).

All frozen embryo transfer (FET) cycles began with pre-treatment using oral contraceptive pills in an artificial cycle and a daily oral dose of 6 mg of E2. When transvaginal ultrasound (Affinity 70, Philips) examination showed an endometrial thickness of 7 mm or more, with a triple-layer appearance, it was considered mature. This was followed by endometrial preparation with either three or five days of injectable P4 for cleavage or blastocyst stage embryos, respectively. Embryo transfer was performed using a Sure-Pro Ultra catheter. Luteal-phase support continued for 14 days with vaginal P4 and E2. If pregnancy was achieved, this support was maintained until the 10th week of gestation.

Primary outcome was the oocyte maturity rate, which was calculated as the ratio of metaphase II (MII) oocytes to the total number of oocytes retrieved. Secondary outcomes were oocyte yield, fertilisation, blastocyst, and OHSS rates, in addition to post-trigger serum LH (IU/L) and P4 (ng/mL) levels, and pregnancy rate.

Statistical analysis

According to Deepika et al. (8), a sample size of 35 PCOS women per group was estimated to detect a difference of about 2.98 matured oocytes between the two groups, with 80% power at a 5% alpha level. Statistical analysis was performed using SPSS 22 (IBM Corp., Armonk, NY, USA). All data are shown as mean ± standard deviation (SD) or standard error (SE) and number (percent). Data were analysed using the two-tailed independent t test for quantitative data which distributed normally, and by Fisher's exact and chi-square tests for comparison of qualitative variables between groups, where appropriate. A $P<0.05$ was considered statistically significant.

Results

A total of 33 patients in the study group and 35 in the control group completed the treatment cycle (Fig.1). The mean ± SD for age and BMI showed no statistically significant differences between the two groups (31.34 ± 5.07 vs. 30.48 ± 5.04 years, P=0.487 and 26.72 ± 4.5 kg/m^2 vs. 27.16 ± 4.08 kg/m2, P=0.680). The type and duration of infertility were similar in both groups (P=0.686 and P=0.863, respectively). In addition, the cause of infertility and phenotypes of PCOS were not statistically significant between the groups (P=0.119 and P=0.356, respectively). The mean ± SD of the number of previous intrauterine insemination (IUI) and IVF/ICSI cycles were similar between both groups (P=0.959 and P=0.493, respectively, Table 1).

As per the data in Table 2, the analysis of hormonal profiles in both groups indicates that there were no statistically significant distinctions between the two groups concerning the levels of follicle stimulating hormone (FSH), LH, anti-Müllerian hormone (AMH), thyroid-stimulating hormone (TSH), and E2 on the day of oocyte trigger.

Table 1: Baseline characteristics of the study group patients

Variables	Group A (Decapeptyl® 0.2 mg) (n=35)	Group B (Decapeptyl® 0.3 mg) (n=33)	P value*
Age (Y)	31.34 ± 5.7	30.48 ± 5.04	0.487
BMI (kg/m^2)	26.72 ± 4.5	27.16 ± 4.08	0.680
FSH (IU/L)	5.85 ± 2.28	5.56 ±2.79	0.634
LH (IU/L)	7.09 ± 4.04	7.37 ± 4.29	0.786
TSH (IU/L)	2.03 ± 1.56	2.19 ± 1.94	0.715
AMH (ng/mL)	8.93 ± 4.43	10.49 ± 4.76	0.174
Free testosterone (nmol/L)	1.7 ± 1.4	1.3 ± 0.7	0.220
Infertility duration (Y)	5.95 ± 4.39	6.15 ± 4.83	0.863
Type of infertility			0.686
Primary	25 (71.4)	25 (75.8)	
Secondary	10 (28.6)	8 (24.2)	
Infertility causes			0.119
PCOS	25 (71.4)	16 (48.5)	
PCOS and male factor	14 (40)	17 (51.5)	
PCOS and tubal factor	4 (11.4)	25 (75.8)	
PCOS phenotype			0.356
A	13 (37.1)	12 (36.4)	
B	4 (11.4)	2 (6.1)	
C	14 (40)	10 (30.3)	
D	4 (11.4)	9 (27.3)	
Previous IUI cycles	2.00 ± 2.1	2.00 + 2.4	0.959
Previous IVF/ICSI cycles	0.37 ± 0.68	0.48 + 0.66	0.493
Levothyroxine consumption during IVF/ICSI cycle			0.569
Yes	14 (40)	11 (33.3)	
No	21 (60)	22 (66.7)	
Vitamin D consumption during IVF/ICSI cycle			0.920
Yes	11 (31.4)	10 (30.3)	
No	24 (68.6)	23 (69.7)	

Values are presented as the mean ± standard deviation (SD) or number (%). *; Independent t test and chi square test. P<0.05 indicates statistical significance, BMI; Body mass index, FSH; Follicle stimulating hormone, LH; Luteinizing hormone, TSH; Thyroid-stimulating hormone, AMH; Anti-Müllerian hormone, PCOS; Polycystic ovarian syndrome, IUI; Intrauterine insemination, and IVF/ICSI; *In vitro* fertilization/intracytoplasmic sperm injection.

Table 2: Ovarian stimulation cycle outcomes between the study groups

Variables	Group A (Decapeptyl®0.2 mg) (n=35)	Group B (Decapeptyl® 0.3 mg) (n=33)	P value*
Serum E2 level (pg/ml) on oocyte trigger day	4589.1 ± 1192.8	4592.9 ± 1115.2	0.975
Serum P4 level (ng/ml) on oocyte trigger day	0.89 ± 0.57	0.77 ± 0.32	0.307
Serum LH level (IU/L) 12 hours after oocyte trigger	56.33 ± 36.1	58.93 ± 36.3	0.768
Serum P4 level (ng/ml) 12 hours after oocyte trigger	10.9 ± 5.6	9.9 ± 3.7	0.410
Serum LH level (IU/L) on ovum pick-up day	9.7 ± 5.3	11.5 ± 5.5	0.190
Serum P4 (ng/ml) level on ovum pick-up day	13.5 ± 4.0	14.2 ± 3.5	0.452
Total number of gonadotropin ampoules used	29.54 ± 2.01	26.06 ± 1.4	0.164
No. of rFSH ampoules	26.06 ± 1.76	23.9 ± 1.21	0.222
No. of HMG ampoules	2.97 ± 0.66	2.06 ± 0.72	0.353
Stimulation duration (day)	11.26 ± 0.43	11.03 ± 0.29	0.668
Antagonist duration (day)	5.06 ± 0.20	4.58 ± 0.14	0.062

Values are presented as the mean ± standard deviation (SD). *; Independent t test. P<0.05 indicates statistical significance. HMG; Human menopausal gonadotropin, LH; Luteinizing hormone, rFSH; Recombinant follicle-stimulating hormone, E2; Oestradiol, and P4; Progesterone.

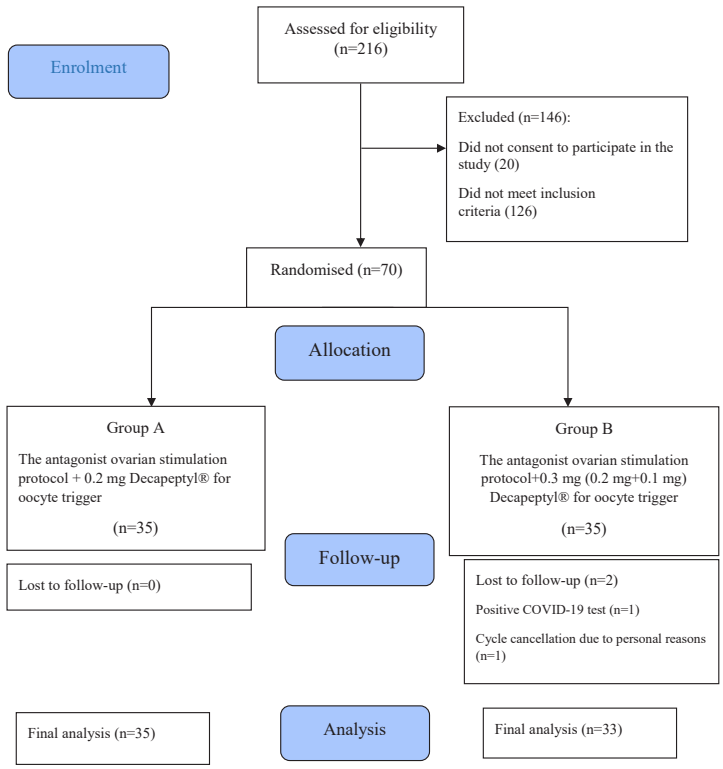

Fig.1: Study flowchart.

There was no significant difference between the two groups in the number of administered recombinant FSH (rFSH) and human menopausal gonadotropin (HMG) ampoules. The mean ± SD stimulation duration was 11.26 ± 0.43 days in group A and 11.03 ± 0.29 days in group B (P=0.668). The mean ± SD of the antagonist duration was 5.06 ± 0.20 days in group A and 4.58 ± 0.14 days in group B (P=0.062).

As shown in Table 3, the mean ± SD of the serum E2 and P4 levels on the day of the trigger and LH and P4 level 12 hours after the injection of the first dose of the trigger, as well as the levels of LH and P4 on the day of the puncture were not statistically significant between the two groups. Also, the mean ± SD of endometrial thickness in group A was 9.39 ± 1.95 cm and in group B, it was 8.99 ± 1.42 cm (P=0.345). There were no statistically significant differences between the two groups in terms of the mean ± SD of total number of retrieved oocytes, MII, MI, germinal vesicle (GV), and degenerated oocytes. Fertilisation rate was 0.64 ± 0.03 in group A and 0.66 ± 0.03 in group B (P=0.663). The frequency of women with mild to moderate OHSS was significantly lower in the intervention group (P=0.038). No cases of severe OHSS were reported in either group. Subsequently, no statistically remarkable difference was found between the two groups regarding the quantity and quality of the obtained embryos as well as the number of patients with frozen embryos at the blastocyst stage (Table 4).

Table 3: Oocyte retrieval outcomes between the study groups

Variables	Group A (Decapeptyl® 0.2 mg) (n=35)	Group B (Decapeptyl® 0.3 mg) (n=33)	P value*
Number of follicles >13 mm (on oocyte trigger day)	15.57 ± 5.02	18.48 ± 7.68	0.067
Endometrium thickness (cm)	9.39 ± 1.95	8.99 ± 1.42	0.342
Number of retrieved oocytes	20.31 ± 8.58	21.82 ± 6.93	0.431
Number of GV	1.6 ± 0.46	1.33 ± 0.57	0.715
Number of MI oocytes	0.74 ± 0.18	0.69 ± 0.17	0.855
Number of MII oocytes	17.62 ± 9.07	19.18 ± 7.55	0.431
Number of degenerated oocytes	0.34 ± 0.10	0.61 ± 0.21	0.250
MII morphology			0.422
Eumorphic	8 (22.9)	3 (9.1)	
Slightly dysmorphic	8 (22.9)	7 (21.2)	
Dysmorphic	15 (42.9)	17 (51.5)	
Highly dysmorphic	4 (11.4)	6 (18.2)	
Oocyte maturity rate	0.64 ± 0.20	0.68 ± 0.21	0.517
Oocyte recovery ratio	0.68 ± 0.27	0.83 ± 0.40	0.102
Fertilisation rate	0.64 ± 0.03	0.66 ± 0.03	0.663
OHSS (mild to moderate)	6 (18.2)	1 (2.9)	0.038

Values are presented as the mean ± standard deviation (SD) or n(%). *; Independent t test. P<0.05 indicates statistical significance. HMG; Human menopausal gonadotropin, LH; Luteinizing hormone, rFSH; Recombinant follicle-stimulating hormone, E2; Oestradiol, and P4; Progesterone.

Table 4: Comparison of the characteristics of the obtained embryos between the study groups

Variables	Group A (Decapeptyl® 0.2 mg) (n=35)	Group B (Decapeptyl® 0.3 mg) (n=33)	P value*
Total no. of obtained embryos	12.31 ± 5.81	13.85 ± 5.46	0.266
No. of embryos (blastocyst stage)	7.58 ± 4.09	8.91 ± 4.72	0.424
Total cases with frozen embryos in blastocyst stage	19 (54.3)	11 (33.3)	0.082
Total no. of AB grade frozen embryos	3.5 ± 0.10	3.3 ± 0.11	0.926
Total no. of B grade frozen embryos	3.2 ± 2.5	4.4 ± 3.5	0.214
Total no. of BC grade frozen embryos	1.0 ± 1.5	1.2 ± 1.9	0.728
Total no. of expanded blastocyst grade embryos	2.6 ± 0.09	4.5 ± 0.16	0.231

Values are presented as the mean ± standard deviation (SD)/error or number (%). *; Independent t test. P<0.05 indicates statistical significance.

Table 5: FET cycle outcomes between the study groups.

Variables	Group A (Decapeptyl® 0.2 mg) (n=35)	Group B (Decapeptyl® 0.3 mg) (n=33)	P value*
No. of transferred embryos	1.77 ± 0.88	1.67 ± 0.89	0.627
Endometrium preparation			0.665
E2 alone	12 (42.9)	11 (40.7)	
Mild stimulation	4 (14.3)	2 (7.4)	
Long agonist with E2	12 (42.9)	14 (51.9)	
Timing of embryo transfer			0.193
Cleavage stage	13 (44.08)	17 (63)	
Blastocyst stage	16 (55.02)	10 (37)	
Chemical pregnancy rate (per embryo transfer)	11/29 (37.9)	12/27 (44.4)	0.621
Clinical pregnancy rate (per embryo transfer)	9/29 (31)	7/27 (25.9)	0.770

Values are presented as the mean ± standard deviation (SD)/error or number (%). *; P<0.05 indicates statistical significance. E2; Oestradiol and FET; Frozen embryo transfer.

Discussion

The finding of the present study demonstrated that increasing the dose of GnRH agonist from 0.2 to 0.3 for the final oocyte trigger can reduce the risk of OHSS, but it has no effect on the oocyte recovery ratio, the number and quality of the retrieved oocytes, the quality of embryos, or clinical pregnancy rate.

Recently, GnRH agonist trigger has been accepted as the most appropriate method for oocyte trigger in patients with high ovarian response and at-risk for OHSS. Several previous studies reported an almost zero rate of OHSS along with good reproductive outcome compared to the hCG trigger (16). In Asia and Europe, the most acceptable method of triggering following stimulation in the antagonist protocol for PCOS patients is administration of a single dose of triptorelin (0.2 mg) (17). Although the GnRH agonist dose was selected for triggering empirically there was a risk of EFS always exists, therefore, several studies were conducted in this field to compare different doses and select an appropriate dose to achieve the best outcomes.

The results of our study were comparable with that reported by Vuong et al. (9), in which the cycle outcome was compared with different doses of triptorlin (0.2, 0.3, and 0.4). They concluded that the early and late luteal phase hormonal profiles (E2, P4, LH, and FSH) were similar, despite the use of different doses of triptorelin. We also found no differences in P4 and LH levels 12 hours after the first trigger and on the day of ovum pick up between the two different doses of triptorelin (0.2 mg versus 0.3 mg).

On the other hand, a prospective cohort study conducted by Chen et al. (7) assessed 44 patients who were high risk for OHSS in their IVF/ICSI-ET cycles. The patients received 0.2 mg triptorelin as a trigger at night and a second injection 12 hours later. The researchers observed positive effects on cycle outcome. They concluded that repeated injections of triptorelin, as a trigger in GnRH antagonist cycles, are associated with satisfactory oocyte yield, and this can reduce the incidence of OHSS to provide a sufficient clinical outcome. This can be a feasible and safe protocol for final oocyte trigger in patients at high-risk patients for OHSS. Deepika et al. (8) conducted a randomised clinical trial and demonstrated that the oocyte maturity rate in the group that received two doses of GnRH (0.3 mg in total) at a 12-hour interval was higher compared to the group that received single dose (0.2 mg). A repeated dose of GnRH agonist is presumed to lead to upregulation of LH receptors in luteinized granulosa cells, cumulus expansion (18), resumption of meiosis (19), and the recovery of more mature oocytes at the time of ovulation (1). Administration of a second dose of GnRH agonist after 12 hours appears to maintain the LH surge for a longer period of time, which is similar to the LH surge of a natural cycle and lead to an improved maturity rate of the retrieved oocytes. In contrast, Aflatoonian et al. (11), showed that a second dose of GnRH agonist 12 hours after the first dose had no effect on the maturity rate of retrieved oocytes. They reported no cases of EFS (empty follicular syndrome) in their study; however, they were uncertain about the role of LH level post-trigger on predicting cycle outcome. The results from various studies, including three RCTs, did not support any positive effect of repeating GnRH agonist on cycle outcome. In the present study, there were no cases of EFS observed at both trigger doses, and the rate of mild to moderate OHSS was significantly lower in the group that received the higher GnRH agonist dose (0.3 mg); therefore, it can be recommended that a higher dose of GnRH agonist could be used safely as trigger for final oocyte maturation in PCOS patients at higher risk of OHSS.

The strength of this study was the design, as a randomised clinical trial study in PCOS patients at risk of OHSS, and our following the outcome until clinical pregnancy. It is important to note that this study has some limitations, and its results should be interpreted with caution. For example, the study was conducted on a relatively small sample size, which may limit the generalisability of the findings. We only assessed two specific doses of the GnRH agonist, and other doses may have different effects on cycle outcome. Further research is needed to confirm the findings of this study and to explore the potential benefits and drawbacks of using different doses of GnRH agonists to trigger final maturation of oocytes in women with PCOS.

Keeping in mind that OHSS cases were significantly lower in our study group compared to that of the control group, the results of our study provide reassurance to clinicians and patients that repeating half a dose of GnRH agonist is a safe option for women with PCOS who undergo IVF. However, more RCT studies with larger sample sizes and longer follow-up are needed to more precisely evaluate the effect of a repeat dose.

Conclusion

A repeat dose of GnRH agonist trigger 12 hours after the first dose did not improve COH outcomes and pregnancy rates following FET cycles in PCOS patients at risk of OHSS in antagonist cycles. However, it was associated with a lower rate of mild to moderate OHSS.

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Authors' Contributions

M.H., S.H.H.; Designed the research. M.H., S.H.H., M.Z., P.E.Y., A.A.; Assisted with patient selection, Data collection, Interpretation of data, and Manuscript writing/editing. S.H.H., A.A.; Wrote the manuscript. S.V.; Helped with data analysis. All authors read and approved the final manuscript.

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