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Impact of letrozole on prevention of early-onset ovarian hyperstimulation syndrome in GnRH antagonist protocol: A Randomized Controlled Trial

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Abstract

Background: Letrozole is an aromatase inhibitor that decreases the risk of Ovarian Hyperstimulation Syndrome (OHSS) in assisted reproductive technology. We aimed to evaluate the clinical outcomes of high-risk patients undergoing different Intracytoplasmic Sperm Injection (ICSI) protocols, one with letrozole and one without.

Patients and Methods: This RCT was done at the assisted reproduction unit, Ain Shams University Maternity Hospital, from February 2022 to May 2023**.** A total of 170 infertile women with polycystic ovarian syndrome were enrolled and divided into two equal groups; the study group consisted of 85 women who received controlled ovarian stimulation with a conventional antagonist protocol and letrozole, and the control group consisted of 85 women who received controlled ovarian stimulation with a conventional GnRH antagonist protocol and a placebo.

Results: Letrozole could not decrease the incidence of total early-onset ovarian hyperstimulation syndrome compared with placebo treatment. Conversely, letrozole significantly reduced the severity and grades of early-onset OHSS in the study group. Letrozole significantly lowered the number of retrieved oocytes, which, according to our study results, was the only independent risk factor for OHSS. Letrozole also decreased estrogen on the day of the trigger injection. Also, letrozole did not affect biochemical/clinical pregnancy rates, total gonadotropin dose needed for induction of ovulation, endometrial thickness on the day of trigger, or embryos transferred per cycle.

Conclusion: In high-risk, PCO infertile women undergoing ICSI, letrozole had no role in the prevention of the development of early-onset ovarian hyperstimulation syndrome. But it decreases its severity if occurred.

Key words: Letrozole, hyperstimulation syndrome, ICSI

Introduction

Ovarian hyperstimulation syndrome (OHSS) is a significant side effect of assisted reproductive technology (ART) caused by controlled ovarian stimulation (COS). The occurrence rate of OHSS has been reported to reach 20% in high-risk women, and mild to severe OHSS can occur in 3.1 to 8.0 percent of in vitro fertilization (IVF) cycles[1].

The key to preventing Ovarian Hyperstimulation Syndrome (OHS) is accurately predicting its occurrence. While no therapy can eliminate OHS, it's better to avoid it altogether. Several risk factors are associated with OHS, including young age, low BMI, polycystic ovarian syndrome, and a history of prior OHS. Keeping these factors in mind can help prevent OHS[2].

Depending on the symptoms' onset time, OHSS can be classified as "early" or "late". Ovulation induction agent injection is followed by the start of early-onset OHSS within a few days. It displays the ovarian reaction to exogenous hormone stimulation. Because endogenous hCG is secreted as a result of pregnancy, late-onset OHSS manifests after this period, often between days 8 and 17 following treatment[3].

Additionally, ovarian hyperstimulation syndrome is predicted by the number of antral follicles. Antral follicle counts below 24 were associated with a higher risk of moderate-to- severe ovarian hyperstimulation syndrome, as revealed by Jayaprakasan et al. (2012)[4].

The ovary's response to carefully managed ovarian stimulation determines the secondary risk factors. Ultrasound monitoring and serum E2 testing are crucial to surveillance of ovarian hyperstimulation syndrome. A large number of growing follicles (>14 with a diameter of 11 mm) on the day of triggering and a high number of retrieved oocytes are risk factors for ovarian hyperstimulation syndrome[5].

When letrozole is co-administered with GnRH-Ant protocols from days 3 to 7 of the menstrual cycle, as opposed to traditional GnRH-Ant protocols, the incidence of OHSS is lower in PCOS patients with relatively high Anti-Müllerian Hormone (AMH) levels[6].

Letrozole prevented moderate and severe early-onset OHSS better than aspirin did in women at high risk, according to Qingyun Mai's study IN 2017[7].

Once cytochrome p450 enzymes are inhibited, aromatase inhibitors reduce estrogen production. The follicle-stimulating hormone release from the pituitary is gradually increased, encouraging folliculogenesis. As a result, the negative feedback mechanisms continue to function and lower the frequency of ovarian hyperstimulation syndrome during ovulation induction[8].

Letrazole's capacity to reduce E2 levels may cause this effect. It is generally known that LE, a powerful aromatase inhibitor, prevents the conversion of androgens to estrogens in the ovaries and in a variety of peripheral organs, hence reducing the number of circulating estrogens[9].

Aim of the Work

This study aims to evaluate the clinical outcome of patients at very high risk of

developing signs of early-onset ovarian hyperstimulation syndrome undergoing two different Intracytoplasmic sperm injection (ICSI) protocols (with or without letrozole).

Patients and Methods

The present prospective, double-blind, randomized controlled clinical trial was carried out on a total of 170 infertile women after giving their consent at the assisted reproduction unit, Obstetrics and Gynecology Department, Faculty of Medicine, Ain Shams University Maternity Hospitals from November 2022 to May 2023. The study gained ethical committee approval from the Faculty of Medicine

Ain Shams University FMASU MS 764/2022. The protocol was registered in the Pan-African clinical registry.

Patients' informed consent was obtained before enrolling in the study after explaining the nature, scope, and possible consequences of the clinical study.

Inclusion Criteria

Young adults with BMIs of 18 to 35 kg/m2 were enrolled in the study. A polycystic ovarian syndrome diagnosis was made following the Rotterdam consensus when two of the following three symptoms were present: Biochemical and clinical hyperandrogenism. Oligo or anovulation, and irregular menstruation. The size and shape of the ovaries, as seen on ultrasound, include the presence of 12 or more follicles, each measuring 2 to 9 mm in diameter, and larger ovaries (>10 cm3; determined using the formula length x breadth x thickness x 0.523).

Exclusion criteria

Women who have any endocrine or systemic problems, including obesity, abnormal uterine cavity (by hysterosalpingography or sonohysterography), letrozole hypersensitivity, any irregularity in the abdomen or ovaries that could prevent transvaginal sonography (TVS) examination from being appropriately done, Patients who were unable to cooperate with the researchers' requests for the duration of the study and those who refused to provide written informed permission was eliminated from the study.

Randomization

Using the sequentially numbered, opaque sealed envelopes (SNOSE) technique, we ensured that the randomization sequence was effectively allocated and concealed. The randomization groups were written on paper and kept in a sealed, opaque envelope with a serial number. As soon as the patient gives consent to participate, the researcher opens the sealed envelope and assigns the patient to the treatment group. The randomization process was computer-generated.

The study's primary outcome was the occurrence of early onset OHSS and its grades.

The Secondary outcomes were different outcomes of ICSI or biochemical or clinical pregnancy rates.

Sample Size Justification

The EPI Info 7 software was used to calculate the sample size, with a power of 80% and an alpha error of 0.05. Based on the study by Mai et al., 2017, a sample size of 75 women per group was necessary to detect the difference between the two groups. We increased 10 patients in each group to avoid any possible drop-outs.

Study interventions and procedures

All patients were divided into two equal groups: Group I (study group): Consisted of 85 women who received controlled ovarian stimulation with a conventional antagonist protocol and letrozole, and Group II (control group): Consisted of 85 women who received controlled ovarian stimulation with a conventional GnRH antagonist protocol and a placebo (in the form of folic acid tablets). Present and past history and infertility workup (including hormonal profile, TVUS, and semen analysis) were done. Reports of U/S done before starting the trial and possible disorders like uterine anomalies, hydrosalpinx, endometriotic cysts or any other abnormalities, ovarian size, basal antral follicular count (AFC).

Fixed antagonist protocol was used (on the sixth day of ovarian stimulation GnRH antagonist in Cetrotide 0.25 mg was introduced till the end of

stimulation). Stimulation was started on day 2 or 3 of the cycle using 75-150 IU of highly purified FSH (Gonapure). In group I, letrozole was added with a dosage of 5 mg per day starting from day 3 to day 7 of the cycle. Meanwhile, a placebo was added with the exact dosage in group II.

Folliculometry (by using ultrasound Mindary 20DP): The behavior of induced follicles was recorded by transvaginal U/S. 1st U/S was done on day six on FSH stimulation. Then, every other day, until at least 3 of the follicles reach a volume of 16-20 ml the trigger was given. The last E2 was recorded on the day before triggering. Triggering by using HCG in the form of Choriomon 5000-1000 IU intramuscular injection. U/S guided Vaginal oocyte retrieval was done 34-36 hours after triggering by using Mindary DP880 plus electronic endocavitary transducer: 65EC10EA (5.0/6.5/7.5MHz).

Intracytoplasmic injection was done

Embryo transfer: Fresh embryo transfer in the same cycle except if a number of oocytes retrieved > 20 oocytes freeze all policy was done *(Tarlatzi et al., 2017)*. Pregnancy test: Quantitative serum B-HCG was done 12 days after ET. Then repeated after 48 hours. 1st antenatal care visit for positive B-HCG: One month after ET (6 weeks GA), U/S was done to detect the number of Gestational sacs and fetal cardiac pulsation.

Assessment of patients for OHSS

Mild OHSS: Grade 1 - Abdominal distention and discomfort and Grade 2 - Grade 1 disease plus nausea, vomiting and/or diarrhea plus ovarian enlargement from 5 to 12 cm.

Moderate OHSS: Grade 3 - Features of mild OHSS plus ultrasonographic evidence of ascites

Severe OHSS: Grade 4 - Features of moderate OHSS plus clinical evidence of ascites and/or hydrothorax and breathing difficulties and Grade 5 - All of the above plus a change in the blood volume, increased blood viscosity due to hemoconcentration, coagulation abnormalities, and diminished renal perfusion and function (Kumar et al., 2011).

The patient returned seven days after oocyte retrieval to evaluate indices of OHSS. U/S was done to assess the size of the ovaries and the presence or absence of free fluid in the pelvis and abdomen. Patients were informed to report if any symptoms appeared before the planned visit. Treatment was offered to the patients if any cases were diagnosed as OHSS.

Statistical analysis

Statistical analysis was done using IBM© SPSS© Statistics version 24 (IBM© et al.) and MedCalc© version 20.218 (MedCalc et al., Belgium; https://www.medcalc.org; 2023). Continuous numerical data are presented as mean and standard deviation, and intergroup differences are compared using the unpaired t-test. Categorical data are presented as counts and percentages, and differences are compared using the Pearson chi-squared or Fisher's exact test. Ordinal data are compared with linear by linear association. Multivariable binary logistic regression analysis is used to examine the independent effect of letrozole on the occurrence of OHSS. P-values <.05 are considered statistically significant.

Results

There were no statistically significant differences between 2 groups regarding Age, BMI, or degree of severity of previous OHSS (Table 1). Table 2 shows no statistically significant differences between the 2 groups regarding basal hormonal or AFC on 2nd day of the cycle.

As shown in Table 3, only estrogen level on trigger day decreases statistically significantly in group I than in group II (P<0.001). In contrast, other parameters

Table 1. Baseline characteristics of patients in both study groups.

VARIABLE	LETROZOLE (N=85)	PLACEBO (N=85)	P-VALUE
Age (years)	31 ± 7	29 ± 4	.050
BMI (kg/m^2)	27.6 ± 2.8	27.3 ± 3.0	.422
History of OHSS	18 (21.2%)	26 (30.6%)	.161§
Severity of previous OHSS			.405
Mild (Grade 1-2)	18/18 (100%)	25/26 (96.2%)	
Moderate (Grade 3)	0/18 (0.0%)	1/26 (3.8%)	

Data are mean ± SD, count (percentage) or proportion (percentage)

Table 2. Hormonal and US variables at day 2 in both study groups.

VARIABLE	LETROZOLE (N=85)	PLACEBO (N=85)	P-VALUE
FSH on D2 (mIU/ml)	6.4 ± 2.0	7.3 ±8.9	.355
LH on D2 (mIU/ml)	7.33 ± 3.09	7.28 ± 6.09	.943
E2 on D2 (pg/ml)	42.76 ± 19.65	45.25 ± 37.85	.591
Prolactin on D2 (ng/ml)	14.71 ± 8.03	16.52 ± 10.04	.198
AMH on D2 (ng/ml)	5.31 ± 2.21	5.65 ± 2.90	.393
AFC on D2	21 ± 5	22 ± 4	.301

Data are mean ± SD

Table 3. Results of ICSI in both study groups.

VARIABLE	LETROZOLE (N=85	PLACEBO (N=85)	P-VALUE
Stimulation days	13 ± 3	12 ± 3	.847
Total gonadotropin dose (ampoules)	37 ± 14	37 ± 16	.907
Estrogen on hCG injection day (pg/ml)	2181.9 ± 1476.0	3576.4 ± 2265.0	**<.001**
Number of retrieved oocytes	12 ± 8	16 ± 12	**.007**
Endometrial thickness on D6 (mm)	6 ± 1	6 ± 1	.671
Endometrial thickness on Day of trigger (mm)	10 ± 2	11 ± 1	.517
Number of fertilized oocytes	8 ± 6	11 ± 8	.017
Fertilization rate (%)	69.9 ± 14.0	65.2 ± 17.6	.063

Data are mean ± SD.

show no statistically significant difference between the two groups.

Early-onset OHSS occurred in 35 patients in group I and 48 patients in group II. Table 4 shows a high statistically significant difference between the two groups regarding the grade of early-onset OHSS (P<0.001).

Table 4. Primary outcome measures in both study groups.

VARIABLE	LETROZOLE (N=85)	PLACEBO (N=85)	P-VALUE
Early-onset OHSS	35 (41.2%)	48 (56.5%)	**.046**
Grade of early-onset OHSS			**.004**
Grade 1	32/35 (91.4%)	31/48 (64.6%)	
Grade 2	3/35 (8.6%)	10/48 (20.8%)	
Grade 3	0/35 (0.0%)	4/48 (8.3%)	
Grade 4	0/35 (0.0%)	3/48 (6.3%)	
Grade of early-onset OHSS			**.027**
Mild (Grade 1-2)	35/35 (100%)	41/48 (97.9%)	
Moderate (Grade 3)	0/35 (0%)	4/48 (2.1%)	
Severe (Grade 4-5)	0/35 (0%)	3/48 (3.6%)	

Data are count or proportion (percentage)

Table 5 shows no statistically significant difference between the two groups regarding the outcomes of ICSI, biochemical, or clinical pregnancy rates.

The results of multivariable binary logistic regression analysis for the effect of letrozole on the occurrence of OHSS are shown in Table 6 and Figure 1. After adjustment for the effect of other predictors, there was no statistically significant relation between using letrozole and the occurrence of OHSS (odds ratio = 0.841, 95% CI = 0.369 to 1.918, p-value =.681). On the other hand, the number of retrieved oocytes was the only independent risk factor for

Table 5. Secondary outcome measures in both study groups.

VARIABLE	LETROZOLE (N=85)	PLACEBO (N=85)	P-VALUE
Fresh embryo transfer	63/85 (74.1%)	48/85 (56.5%)	**.016**
Number of transferred embryos			.109
1 Embryo	5/63 (7.9%)	2/48 (4.2%)	
2 Embryos	32/63 (50.8%)	19/48 (39.6%)	
3 Embryos	26/63 (41.3%)	27/48 (56.3%)	
Biochemical pregnancy (PP)	36/63 (57.1%)	22/48 (45.8%)	.237
Clinical pregnancy (PP)	20/63 (31.7%)	15/48 (31.3%)	.956
Biochemical pregnancy (ITT)	36/85 (42.4%)	22/85 (25.9%)	**.024**
Clinical pregnancy (ITT)	20/85 (23.5%)	15/85 (17.6%)	.343

Data are proportion (percentage); (PP) Per-protocol; (ITT) Intention to treat.

Table 6. Risk analysis for main outcome measures.

ANALYSIS	OUTCOME	RR	95% CI FOR RR	Z STATISTIC	P- VALUE	NNT (BENEFIT)	95% CI FOR NNT
Intention-to-treat (ITT)	OHSS	0.73	0.53 to 0.999	1.96	.050	6.54	3.3 (Benefit) to 225.9 (Benefit)
	Failed biochemical pregnancy	0.61	0.39 to 0.95	2.209	**.027**	6.1	3.3 (Benefit) to 41.1 (Benefit)
	Failed clinical pregnancy	0.75	0.41 to 1.36	0.943	.346	17.0	16.0 (Harm) to ∞ to 5.6 (Benefit)
Per-protocol (PP)	OHSS	0.73	0.53 to 0.999	1.96	.050	6.54	3.3 (Benefit) to 225.9 (Benefit)
	Failed biochemical pregnancy	0.80	0.55 to 1.17	1.154	.249	8.8	13.6 (Harm) to ∞ to 3.3 (Benefit)
	Failed clinical pregnancy	0.98	0.57 to 1.71	0.056	.956	201.6	5.9 (Harm) to ∞ to 5.6 (Benefit)

RR = relative risk, 95% CI = 95% confidence interval, NNT = number needed to treat (benefit)

OHSS (odds ratio = 1.315, 95% CI = 1.206 to 1.434, p-value <.001). The model had a good predictive with an area under the receiver-operating characteristic (ROC) curve 0.880 (95% CI =.832 to 0.929, p-value <.001) and a correct classification rate of 78.2% for a predicted probability >.5 (Figure 3). The best cut-off is a predicted probability >0.470 (sensitivity = 77%, specificity = 83%). The model's overall fit was good (Hosmer and Lemeshow chi-squared = 3.610, df = 8, p-value =.891). (Table 7 and Figure 2)

Table 7. Multivariable binary logistic regression analysis for the effect of letrozole on occurrence of OHSS.

							95% CI FOR EXP(B)	
VARIABLE	B	SE	WALD	DF	P- VALUE	EXP(B)	LOWER	UPPER
AMH on D2 (ng/ml)	0.157	0.115	1.871	1	.171	1.170	0.934	1.466
Age (years)	0.048	0.051	0.907	1	.341	1.050	0.950	1.159
History of OHSS (=1)†	-0.570	0.493	1.339	1	.247	0.566	0.215	1.485
PCO morphology on US (=1)‡	-0.072	0.651	0.012	1	.911	0.930	0.260	3.331
AFC on D2	0.057	0.046	1.553	1	.213	1.059	0.968	1.158
E2 on D2 (pg/ml)	0.000	0.006	0.006	1	.940	1.000	0.987	1.012
Number of retrieved oocytes	0.274	0.044	38.461	1	<0.001	1.315	1.206	1.434
Letrozole administration (=1)§	-0.173	0.421	0.169	1	.681	0.841	0.369	1.918
Constant	-6.377	2.354	7.337	1	.007	0.002		

95% CI = 95% confidence interval, df = degree of freedom, B = regression coefficient, Exp(B)= odds ratio, SE = standard error, Wald = Wald statistic
†. Reference category: No history of OHSS (=0)
‡. Reference category: No PCO morphology on US (=0)
§. Reference category: Placebo administration (=0)

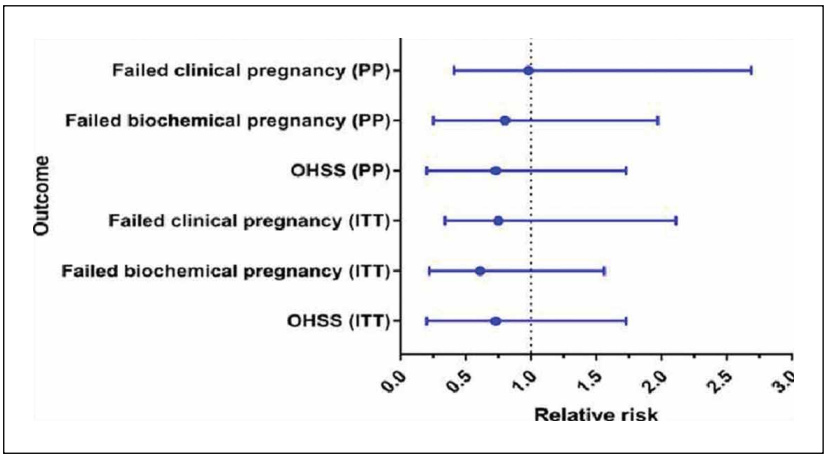

Figure 1. Relative Risk against Clinical pregnancy, biochemical pregnancy and OHSS.

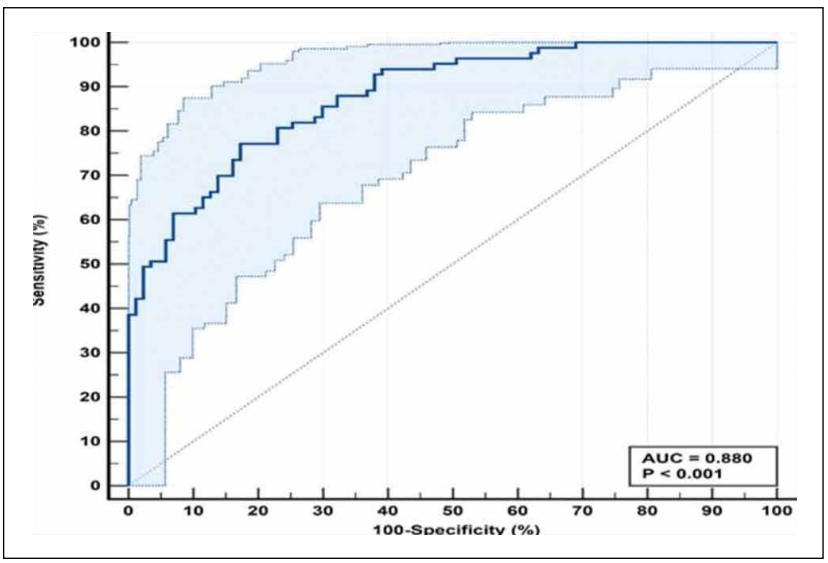

Figure 2. Area under the Curve showing sensitivity and specificity of Letrezole in predicting OHSS.

Discussion

Patients receiving ovarian stimulation may develop the rare but significant condition known as ovarian hyperstimulation syndrome (OHSS)[10].

In addition to nausea, vomiting, abdominal pain, and decreased urine production, it is characterized by ovarian enlargement. With ascites, hemoconcentration, and hypercoagulability, OHSS can, on occasion, progress into a life-threatening condition[11].

An integrated strategy for OHSS prevention links behavioral factors to the administration of pharmaceutical substances[12]. Letrozole has lately been touted as a promising alternative for preventing OHSS among medications used to treat the condition. The guidelines for "Prevention and Treatment of moderate and severe ovarian hyperstimulation syndrome" have

not yet officially acknowledged letrozole, despite the encouraging results reported by multiple research[13].

As a result, this study was done to evaluate the clinical outcomes of patients who had two different intracytoplasmic sperm injection (ICSI) procedures (with or without letrozole) and were at very high risk of developing early-onset ovarian hyperstimulation syndrome symptoms.

As far as we know, there are only a few studies in the literature that have evaluated the outcomes we are studying. Any studies that have contradicted our findings have done so for various reasons, such as using different methodologies, outcomes, and sample sizes than our study had at the time of enrollment.

Main Findings of our Study

As regards the first outcome of our study, letrozole could not decrease the incidence of total early-onset ovarian hyperstimulation syndrome compared with placebo treatment; on the other hand, letrozole statistically significantly decreased the severity and grades of early-onset OHSS in the study group.

Letrozole significantly lowered the number of retrieved oocytes, which was the only independent risk factor for OHSS, according to our study results. Letrozole also decreased estrogen levels on the day of the trigger injection.

Also, letrozole did not affect biochemical/clinical pregnancy rates, the total gonadotropin dose needed to induce ovulation, endometrial thickness on the day of trigger, or the number of embryos transferred per cycle.

Comparison of our results to similar studies

In 2023, *Di Guardo et al.* reported that the therapeutic aim of ART is the delivery of a healthy child following therapies like ovarian stimulation, during which it is critical to prevent any potential hazards for the mother. Over the years, methods and treatments intended to prevent and/or lessen the occurrence of OHSS have been researched since it is a rare but significant consequence of ovarian stimulation[10].

In 2008, *Fatemi et al.* agreed with us and revealed that After 5.0 mg of Letrozole was administered during the luteal phase, estrogen levels drastically dropped when compared to the placebo group[14].

In 2009, *Garcia-Velasco et al.* also agreed with us and stated that Letrozole's pharmacological action and its ability to considerably reduce estrogen levels during the luteal phase when administered in doses of 2.5 mg led to the suggestion that the drug might be used to prevent OHSS[15].

Contrary to our findings, several clinical studies conducted in the past few years have shown that letrozole is effective at lowering the occurrence of OHSS. However, Mai *et al. (2014)* and[7] did not come to the same conclusions, demonstrating that letrozole can merely lower estrogen levels without preventing the formation of the syndrome.

In this context, several authors questioned the existence of an effective Letrozole dose that can lower the incidence of OHSS and the timing of its administration. Similar to our findings, a relevant study in patients at high risk for OHSS demonstrated that oral doses of 2.5 mg, 5.0 mg, and 7.5 mg daily, given for five days straight after oocyte retrieval, can lower serum levels of VEGF and estrogen. Although the lesser doses of 2.5 mg and 5 mg showed just a modest tendency to limit the incidence of OHSS, the higher dosage of 7.5 mg determined a considerable reduction of OHSS incidence. as reported by Mai et al. *(2014)*[7].

Wang et al. (2013) described that the luteal phase is the best time to start taking letrozole, which can considerably lower blood estrogen levels on the second, fifth, and eighth days after egg

extraction. However, letrozole was ineffective in lowering the incidence of severe OHSS[16].

Choudhary et al. (2021) showed that letrozole

and ganirelix acetate are similarly beneficial for the overall prevention of OHSS; however, letrozole proved more effective in avoiding moderate OHSS. In addition, letrozole was less expensive and had higher patient satisfaction than GnRH antagonists[17].

It is worth mentioning, as of this writing, despite the existence of numerous studies regarding the use of letrozole for the prevention of OHSS, this drug is still not mentioned in the recommendation for "Prevention and Treatment of moderate and severe ovarian hyperstimulation syndrome" as reported by *Pfeifer et al (2016)*[18].

In addition, a recent systematic review and meta-analysis by *Zhao et al. (2020)* stated that Letrozole appeared to be ineffective for the prevention of mild, moderate, and severe OHSS, separately, but could reduce the incidence of overall OHSS as well as moderate and severe OHSS in high-risk women[19].

In a randomized control trial, *Tshzmachyan and Hambartsoumian, 2020* examined the impact of letrozole on OHSS rates in high-risk PCOS patients with increased Anti-Mullerian Hormone (AMH) receiving brief GnRH medication. They dissented from us by showing that co-treatment with Letrozole during gonadotropin stimulation was able to considerably lower the incidence of OHSS in comparison to the control group receiving standard brief GnRH therapy protocol and had lower blood estrogen levels[13].

According to a 2020 report by Zhao et al., letrozole should not be used as the first-line medication for the prevention of OHSS. Letrozole had no therapeutic effect on the prevention of mild, moderate, and severe OHSS separately[19].

According to previously published studies, the amount of VEGF and the severity of OHSS have a positive association. Sa*hin et al. (2016)* found that letrozole could successfully lower the level of VEGF in a rat model of OHSS[20].

In 2018, *Haas et al.* proposed that letrozole increases the secretion of FSH and LH by lowering serum estrogen levels. These hormones act directly on granulosa cells and may be the source of the enhanced VEGF secretion[21].

The co-administration of LE to the traditional antagonist protocol greatly lowers the cost of the IVF therapy without compromising the primary pregnancy outcome, according to further researchers[22-24].

Strengths and limitations of the study

Our main strength is that our study is a well-organized prospective, double-blind, randomized controlled clinical trial and that it was carried out on a total of 170 infertile women (adequate number). The limitation of the study is that it is a single-center study, which could contribute to a statistical bias

Recommendation for further studies

Multi-center studies with a large number of patients are needed to study the effect of adding letrozole in ICSI protocols to decrease the risk of OHSS.

Conclusion

In high-risk PCO infertile women undergoing ICSI, letrozole decreased the severity and grades of early-onset OHSS in the study group, lowered the number of retrieved oocytes, and decreased estrogen on the day of the trigger injection.

Author Contributions

All authors jointly contributed to the conception and design of the study.

AH AH: Design of the study, helped with the literature review, revision of results and data analysis, writing of the manuscript, and submission to the journal.

F GM. AS: The study's design, literature review, and manuscript were revised.

AG EK: Registering the trial, obtaining ethical committee approval, reviewing the literature, participating in the data collection, and recruiting patients.

IA G: design of the study, revision of the review of literature, and revision of the manuscript

AM A: Design of the study, helped in the review of literature, revision of results and data analysis, and contributed to writing the manuscript

Funding

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Study registration:

The study was registered in the Pan-African Clinical Trial.

Disclosure of Interest

The authors declare no conflict of interest.

Ethics Approval

Following local regulations, the protocol gained ethical and research approval from the Faculty of Medicine Ain Shams University FMASU MS 764/2022.

Informed Consent

Informed consent was taken from all patients, We Confirm that all methods were performed according to the relevant guidelines and regulations according to the Declaration of Helsinki.

Data Sharing

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

Acknowledgment

Not applicable.

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