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ORIGINAL ARTICLE

The Outcomes of Gonadotropins Releasing hormone Antagonist (GnRH) Cycles with and without letrozole Co-treatment in Patients Undergoing ICSI

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ABSTRACT

Background: Letrozole is an aromatase inhibitor, which has been proposed as a great tool in ovulation induction and infertility management. This study aimed to evaluate whether the use of letrozole in combination with gonadotropins and GnRH antagonist is superior to gonadotropins and GnRH antagonist alone in women undergoing ICSI treatment.

Methods: This prospective randomized controlled trial was conducted during the period from October 2017 to March 2020 in a private fertility center. 112 participants were randomly allocated into two groups either intervention (Letrozole plus antagonist protocol) or control (antagonist protocol) groups. Participants were subjected to ovarian stimulation (OS) using a GnRH antagonist protocol. Only for the intervention group, letrozole was added from the second day of the cycle to the sixth day. On the day of hCG trigger, endometrial thickness, estradiol and progesterone level were assessed. The results were correlated to the outcomes of the Intracytoplasmic sperm injection (ICSI) cycle.

Results: Both the intervention and control groups wer balanced in respect to the demographic and clinical characteristics. The stimulation outcomes were comparable between the two studied groups. The clinical pregnancy rate and the ongoing pregnancy rate were comparable between both groups. There was no significant relation between the day of embryo transfer and either occurrence of clinical pregnancy or ongoing pregnancy among both groups' participants. **Conclusions:** Letrozole co-treatment in the first five days of gonadotropins stimulation in anatagonist cycles did not show any significant change in the pregnancy outcomes of ICSI cycles.

Key words: Letrozole ; Gonadotropin-releasing hormone antagonist; ovarian stimulation; Intra-cytoplasmic sperm injection

INTRODUCTION

Despite the acceptance and spread of the assisted reproductive technologies (ART), their efficacy is still suboptimal **[1]**. To improve the outcome of ART cycles, many therapies have been suggested in the last few years. Most of these therapies are currently given even though the quality of scientific evidence supporting their impact in improving the pregnancy outcomes after IVF cycles is still doubtful. One of the commonly used adjuvant therapies in ART cycles is letrozole **[2]**.

Letrozole is a third-generation aromatase inhibitor, has an important role in ovulation induction with endometrial sparing effect. It works by inhibiting the conversion of the androgens to estrogen and creating a low estrogen environment **[3]**. Letrozole is a desirable therapy due to its oral intake and low cost. The short half-life (~45 hours) permits rapid disappearing of the drug and optimal endometrial recovery before the implantation and early embryogenesis **[4]**.

In the light of the current clinical evidence, it has been proven that letrozole is safe therapy for use in the assisted reproductive technologies (ART) despite a warning letter from the original manufacturer **[5,6]**.

Many studies have suggested that letrozole co-treatment with the gonadotropins has been associated with favorable outcomes, including lower doses of gonadotropins, decrease the cost of the IVF cycle and increase the number and maturity rate of retrieved oocytes **[7-9]**. These favorable outcomes were particularly noticed in poor responder women **[10-13]**.

Furthermore, the co-administration with letrozole has been associated with avoiding the high level of estrogen seen with the stimulation of ovulation especially in particular disorders as endometriosis, breast cancer or those with an inherent clotting abnormality. Avoiding the supra physiological level of estrogen has been associated with improvement in the implantation rate and reduce risk of ovarian hyperstimulation syndrome (OHSS) **[14-18].** The addition of letrozole to gonadotropins in IVF cycles has been associated with improvement in the endometrial receptivity by increasing integrin expression in the endometrium and by lowering estrogen concentrations to more physiologic levels **[19-21]**. This study aimed to evaluate whether the use of letrozole in combination with gonadotropins and GnRH antagonist is superior to gonadotropins and GnRH antagonist alone in women undergoing ICSI treatment.

METHODS

This prospective randomized controlled trial was conducted during the period from October 2017 to March 2020 in a private fertility center. The minimum sample for this study was estimated to be 100 cases, in order to obtain a representative sample of our patient population considering the minimal invasive nature of our work. An expected dropout rate of 12% (due to cancelled fresh embryo transfer owing to risk of OHSS and/or other reasons was considered). Therefore, 112 participants were randomly allocated into two groups either intervention (Letrozole plus antagonist protocol) or control (antagonist protocol) groups, 56 participants in each group. Thereby, a study of independent cases and controls was planned with 1 control per case. All the study details were explained to patients and signed an informed written consent before inclusion in the study. The Institutional Review Board of the Faculty of Medicine-Zagazig University accepted the research (ZUIRB: 3791). The study was done according to the Code of Ethics of the World Medical Association (Declaration Helsinki) for Studies involving humans.

Women undergoing ICSI, who fulfilled the following inclusion criteria, were considered eligible for enrollment: women age 18-37 years and regular menstrual cycle (25-35). The exclusion criteria were: women who had unilateral oophorectomy, uterine abnormality or pathology, participants who refused to participate in the study and ICSI cycles with fresh or frozen TESE samples.

A comprehensive history was taken from each participant. Complete physical and gynecological examination was done to all participants. Transvaginal sonography was done to assess antral follicle count (AFC) and exclude uterine or adnexal pathology. Furthermore, Laboratory investigations were done before the ICSI cycle often involve testing of antimullerian hormone (AMH), TSH, free T4, prolactin, complete blood count, PT, PTT, INR. Liver function test, kidney function test, fasting blood glucose and viral markers.

Randomization

The recruited participants were randomly assigned to either group. Overall, 112 identical sealed envelopes were prepared; 56 contain intervention group and the other 56 envelops contain control group. These envelopes were saved with the research nurse. Every recruited participant was allowed to choose one envelop to determine to which group she was assigned.

Ovarian stimulation

Any hormonal abnormality or medical diseases were managed and adjusted prior to ovarian stimulation. Then only for intervention group, letrozole, one tablet daily (2.5 mg tablets; Novartis Pharma Services, Switzerland) was added from the second day of the cycle to the sixth day. Gonadotropins were given for all participants from the third day of the cycle. Gonadotropins therapy was tailored according to age, BMI, antral follicle count, antimullerian hormone level and any previous response. The dose of gonadotropins was modified according to folliculometry and serum estradiol concentration during follow up. GnRH antagonist (Cetrotide, 0.25 mg; Merk-Serono, Madrid, Spain) was added on the sixth day of gonadotropins stimulation (fixed) for most of the studied participants. However, in poor responder patients, antagonist was added flexibly when the dominant follicle ≥ 14 mm.

When at least 3 follicles reach ≥ 17 mm in mean diameter, 10000 IU of choriomon (IBSA, Institut Biochimique SA) was given to trigger ovulation. For

women at high risk of OHSS (defined as having ≥ 18 follicles, measuring ≥ 11mm on the day of final oocyte maturation **[22,23]**, triggering of ovulation was achieved by subcutaneous administration of 0.3 mg of triptorelin (decapeptyl, Ferring). These patients (6 in control group & 3 in the intervention group) underwent freeze all regimens. Then frozen embryo transfer was done in subsequent cycles.

On the day of hCG, endometrial thickness was measured by TVS as the maximum distance between the two interfaces of endometrium–myometrium junction in the longitudinal plane of the uterus **[24]**.

Additionally, 5 ml venous blood was withdrawn from participant on the hCG trigger day for the determination of serum estradiol (in pg/ml) and progesterone (ng/ml) by Electrochemiluminiscent (Roche diagnostic, Germany). For estradiol, the analytical sensitivity was 5pg/ml with total precision of 2.3%. For progesterone, the analytical sensitivity was 0.03ng/ml with total precision of 2.4%.

Oocytes were retrieved 34-36 hours after hCG trigger by vaginal ultrasound probe and oocyte aspiration needle. Then the oocytes were denuded of cumulus cells at least 2 hours after collection, graded morphologically and only oocytes at metaphase II were used for injection (ICSI). All semen samples were collected on the morning of ovum pick up after an abstinence period of 2-3 days; Semen analysis was performed according to WHO 2010 and strict Kruger's criteria and then prepared according to the semen sample criteria

Fertilized embryos were assessed and graded for their developmental characteristics in vitro at 48 hours (D2) and 72 hours (D3) after oocyte retrieval. Embryo grading was performed using the Istanbul consensus workshop on embryo assessment **[25]**. When at least ≥ 4 good quality embryos (≥ 6 cells on D3) were seen at D3, extended culture was allowed for D5 embryo transfer. 1-3 good quality embryos (either D3 or D5) according to the center protocol was transferred into the uterine cavity by embryo transfer catheter (Labotect, GmbH, Go¨ ttingen, Germany) under abdominal ultrasound guidance.

From the night of oocyte retrieval, all participants were asked to receive their luteal support. Luteal support was carried out using daily intramuscular progesterone 100 mg (Prontogest, IBSA, Italy) injection. Two weeks after the embryo transfer, serum quantative B-hCG level was measured using Elecsys 2010 (Roche, Germany). The analytical sensitivity was 0.5% IU/L with total precision of 2.1%.

Once positive pregnancy test, all participants were shifted for vaginal micronized progesterone insert, Endometrin (Ferring Pharmaceuticals) three times per day. Four weeks after embryo transfer, transvaginal sonography was performed to count intrauterine sacs and detection of pulsation.

Outcome variables

Primary outcome; Ongoing pregnancy rate, defined as evidence of intrauterine embryo/s with positive cardiac pulsation at 12 weeks.

Secondary outcomes; Clinical pregnancy: defined by ultrasonographic documentation of at least one fetus with cardiac pulsation. Ectopic pregnancy was also included **[26]**. Biochemical pregnancy loss: defined as a pregnancy diagnosed only by the detection of HCG in serum or urine and that did not develop into a clinical pregnancy **[26]**. Miscarriage rate: defined as fetal loss after confirmation of a gestational sac(s) on ultrasound **[26]**.

STATISTICAL ANALYSIS

The data were reviewed, entered and analysed using SPSS version 23 for processing of data. expressing it as number and percentage for qualitative data and mean + standard deviation (SD) for quantitative ones and we compare data using the 't' test to compare the mean of two independent classes. The results of the "t" value was reviewed using student "t" table at degree of freedom (df=n1 +n2 – 2) to detect the level of significance (p-value).

RESULTS

185 participants were eligible for recruitment in this study. From them, 73 were withdrawn from participation as 52 did not meet our inclusion criteria, 13 refuse to participate and 8 were drop out during follow up. 112 women were randomly allocated to either intervention (Letrozole plus antagonist protocol, number=56) or control (antagonist protocol, number=56) groups.

In the intervention group, 52 participants underwent fresh embryo transfer. Cancelled embryo transfer was done in 4 participants, 3 cases due to risk of ovarian hyper-stimulation syndrome (OHSS) and one due to failure of fertilization.

In the control group, 49 participants underwent fresh embryo transfer. Cancelled ET was done in 6 cases because of the risk of OHSS and all embryos were cryopreserved then frozen embryo transfer was done later and in one patient due to her choice to delay embryo transfer. These cases, with cancelled embryo transfer in both groups, were included in the analysis, according to the intention to treat principle.

There was no significant difference between studied groups regarding mean female age, BMI, type of infertility, infertility diagnosis, AMH level or previous trial failure as shown in (Table-1).

Stimulation outcomes between both groups are illustrated in (Table-2). The two groups were balanced regarding duration of stimulation, dose of gonadotropins, endometrial thickness, and estradiol and progesterone level on the HCG trigger day, number of oocytes retrieved, maturation rate, fertilization rate and mean number of embryos transferred.

Clinical pregnancy rate (either per started cycle or per embryo transfer) was comparable between both groups (P= 0.575& 0.24 respectively).

There were two cases of biochemical pregnancy loss in the intervention group and two cases of miscarriages (after the appearance of fetal cardiac pulsation) in the control group. There was one case of late onset OHSS in the control group.

The ongoing pregnancy rate per started cycle was (50% and 53.5%) in the control and the intervention group respectively, with no statistically significant difference (P= 0.425). Similarly, the ongoing pregnancy rate per embryo transfer was (57.1%) in the control group and (57.69%) in the intervention group, with no statistically significant difference (Table-3).

There was no significant relation between day of embryos transfer and either occurrence of clinical pregnancy or ongoing pregnancy among both groups' participants as shown in (Table-4)

Table (1): Demographic & clinical characteristics of study participants in the two groups

Parameter	Groups		Test	
	Group I (Control) N=56 (%)	Group II (Intervention) N=56 (%)	t	P
Age (year)	29.04±5.06	30.26±4.8	-1.3∞	0.196
BMI (kg/m²)	27.77±5.14	29.46±6.36	-1.422∞	0.158
Type of infertility **Primary** **Secondary**	 22 (39.3) 34 (60.7)	 28 (50.0) 28 (50.0)	 1.301	 0.254
Infertility diagnosis **Unexplained** **Tubal factor** **Male& female factor** **Male factor** **Endometriosis**	 18 (32.1) 8 (14.2) 11 (19.6) 18 (32.1) 1 (1.8)	 18 (32.1) 2 (3.57) 14 (25) 19 (33.9) 3 (5.4)	 MC	 0.489
AMH (ng/ml)	2.68 (0.49-6.3)	2.0 (0.81-6.0)	-1.826¥	0.068
Previous miscarriage	0(0-3)	0(0-3)	-1.332¥	0.183
Previous trial failure	0 (0.0-2.0)	0 (0.0-3.0)	-1.569¥	0.117

∞t: Student t test ¥ Mann Whitney U test MC: Monte Carlo test BMI: body mass index. Parameters described as mean ± SD, Median (range), number and percentage

Table (2) : Comparison of the stimulation outcomes in the two groups

Outcome parameters	Groups		Test	
	Group I (Control)	Group II (Intervention)	t/Z	P
Duration of stimulation (days)	11.71±2.33 (8.0-18.0)	11.04±1.99 (7.0-15.0)	1.38	0.170
Dose of gonadotropins (ampoules)	36.32±13.58 (16.0-88.0)	41.41±15.39 (16.0-84.0)	-1.852	0.067
Number of oocytes	15.0(5.0-26.0)	12.0(1.0-26.0)	-1.887	0.059
Maturation index	74.44±17.42	76.03 ± 21.62	-0.604	0.546
Fertilization index	73.93 ± 21.93	72.35 ± 23.97	0.511	0.609
Endometrial thickness (mm)	12.14±1.82	11.48±2.23	-1.711	0.090
E2 level on the hCG trigger day (pg/ml)	2800 (857-8400)	2315.5 (495-7898)	-1.625	0.104
P level on the hCG trigger day (ng/ml)	0.7 (0.10-2.2)	0.85 (0.34-2.07)	-1.851	0.064
Number of embryos transfer	2.125 ± 0.67	2.2 ± 0.44	0.656	0.514

t:Student t test Z:Mann Whitney U test Parameters described as mean ± SD , Median (range)

Table (3): Comparison of the cycle outcomes in the two groups

Cycle outcome parameters	Groups		Test	
	Group I (Control) Number (56) ET (49)	Group II (Intervention) Number (56) ET (52)	Test	P
Clinical pregnancy/ started cycle	30(53.5%)	31(55.3%)	Fisher	0.575
Clinical pregnancy rate/ET	30(61%)	31(59.6%)	Fisher	0.24
Miscarriage	2 (4%) (miscarriage)	2 (3.8%) (biochemical pregnancy loss)	Fisher	>0.999
Ectopic pregnancy	0(0.0)	1 (1.9%)	Fisher	>0.999
Ongoing pregnancy/started cycle	28(50%)	30(53.5%)	Fisher	0.425
Ongoing pregnancy rate/ET	28 (57.1%)	30 (57.69%)	Fisher	>0.999
Incidence of OHSS	1 (2%)	0(0.0)	Fisher	0.484

χ^2:Chi-Square test FET: Fischer exact test MC: Monte Carlo test ET: embryo transfer
Parameters described as number and percentage. Biochemical pregnancy loss: defined as a pregnancy diagnosed only by the detection of hCG in serum or urine and that did not develop into a clinical pregnancy

Table (4): Relation between day of embryo transfer and cycle outcomes among the studied groups

Outcome	Group I (control)		Test of significance	Group II (intervention)		Test of significance
	D3 N=15	D5 N=34		D3 N=18	D5 N=34	
Clinical pregnancy rate	10(66.7%)	20(58.8%)		11(61.1%)	20(58.8%)	p=>0.999
Ongoing pregnancy rate	9 (60%)	19(55%)		10(55.5%)	20(58.8%)	p=>0.999
Miscarriage	1 (6.6%)	1(2.9%)	p=>0.999	0 (0)	2(5.8%)	P=>0.999
Ectopic pregnancy	0 (0)	0 (0)		1(5.5%)	0(0.0)	p=0.333
Incidence of OHSS	1 (6.6%)	0(0)	p=0.306	0 (0)	0 (0)	

χ^2: Chi-Square test FET: Fischer exact test t Independent sample t test
N: number D3 day 3 D5: day 5 Parameters described as number and percentage

DISCUSSION

In 2005, Garcia-Velasco and his group have examined the effect of letrozole addition in the pregnancy outcomes following IVF cycles in their study on 147 patients (poor responder). They reported that adding letrozole (2.5 mg) for the first 5 days of gonadotropins stimulation had led to increase in the follicular fluid levels of androstenedione and testosterone and improved the outcomes of IVF cycles **[27])**. Since that time, many investigators have suggested favorable outcomes with the application of letrozole in the reproductive technologies with no significant side effects **[6,28,29]**.

In the current randomized controlled study, the impact of letrozole (2.5 mg) addition in the first five days of gonadotropins stimulation in antagonist cycles for patients undergoing ICSI trials was evaluated. The patients involved in the present study were randomly allocated into two groups: 56 participants in the intervention group (letrozole plus antagonist protocol) and other 56 participants in the control group (antagonist protocol).

Patient's characteristics as mean female age, BMI, type of infertility, infertility diagnosis, AMH level, and previous trial failure were comparable between the intervention and control groups.

In the current trial, both control and intervention groups were balanced regarding the duration of stimulation, dose of gonadotropins, endometrial thickness, estradiol and progesterone level on the day of HCG trigger, number of oocytes retrieved, maturation rate, fertilization rate, and mean number of embryos transferred. In accordance to our findings, many investigators failed to find significant change in the number of retrieved or fertilized oocytes after the addition of letrozole to ovarian stimulation **[7,14,27,30,31,32].**

In contrary to our finding, previous trials had reported that co-treatment of letrozole was associated with decrease in the duration of stimulation **[31]**, decline in gonadotropin doses **[9,32]**, increase endometrial thickness on the day of HCG trigger **[7,14]**, and also increase the number of oocytes retrieved **[9,27,31-33]**.

The primary outcome of this trial was ongoing pregnancy rate. Our finding revealed that co-treatment with letrozole could not show any statistically significant difference in the ongoing pregnancy rate in both studied groups. The ongoing pregnancy rate per started cycle was (50% and 53.5%) in the control group and the intervention group respectively, (P= 0.425). Similarly, the ongoing pregnancy rate per embryo transfer was (57.1%) in the control group and (57.69%) in the intervention group, (P >0.999).

Haas J suggested similar results and his group **[31]** in their retrospective cohort study of 174 normal responder patients. The study group was treated with letrozole (5mg) and gonadotropins from the first day of ovarian stimulation until ovulation trigger day. They concluded no significant difference in ongoing pregnancy rate between both studied groups.

However, our finding did not match with the results of other investigators who reported improvement in pregnancy rate after letrozole addition to gonadotropins **[27,32,34]**.

Mukherjee and co-workers had reported no cases of OHSS in the letrozole group compared to 7 in the control group in their randomized controlled trial on 94 infertile couples **[14]**. In consistent with their finding, the risk of OHSS was lower after letrozole addition as there was only one case of late onset OHSS in the control group. Also, freeze all embryos regimen was done in 6 cases in the control group and 3 cases in the intervention due to the risk of OHSS.

The lower risk of OHSS after letrozole addition may be explained by the result of an animal study (rat model of OHSS) which demonstrated that treatment with letrozole reduced vascular endothelial growth factor (VEGF) and increased pigment epithelium derived factor (PEDF). VEGF has been identified as one of the main causative factors in OHSS while PEDF has been shown to reduce anti-angiogenic activity of VEGF. The combined effect should lead to a reduction in OHSS incidence **[35].**

Notably, in our prospective, randomized, controlled study, we assessed letrozole effect in antagonist cycles in women undergoing ICSI trials without characterize the included patient to either high, average and poor responder. However, most of the previous trial investigated letrozole effect on ART cycles had targeted special group of population (poor responders) **[27, 31-33].**

Meanwhile, we assessed the effect of letrozole (2.5mg) addition to the first 5 days of gonadotropins stimulation. In contradiction to other trials where the dose of letrozole was 5 mg for the first 5 days of stimulation **[9]** or for the entire ovarian stimulation period **[31, 33].**

CONCLUSIONS

Finally, we concluded that letrozole co-treatment in the first five days of gonadotropins stimulation in anatagonist cycles did not show any significant change in the pregnancy outcomes of ICSI cycles. .

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