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Role of Aromatase Inhibitor to Enhance Ovulation in Poor Responder during Induction with Short Antagonist Protocol in Cases of Intracytoplasmic Sperm Injection

Reham El Khateeb*

Minia university campus Minia Govern rate, Egypt.

***Correspondence:**
Reham El Khateeb, Minia University Campus, Minia Govern rate, Egypt, Tel: +201000222994; E-mail: rehamelkhateeb78@yahoo.com.

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ABSTRACT

Objective: *Study the effect of aromataze inhibitor with short antagonist protocol to enhance ovulation response in patients expected to be poor responder undergoing ICSI.*

Methodology: *A prospective clinical trial included all patients expected to have poor ovulation response during ovarian stimulation for ICSI. Conducted in Maternity Hospital IVF unite and two tertiary referral infertility private clinics associated with the reproductive sciences division. 50 patients were enrolled in the study divided randomly into two groups. Study group patients were offered letrozole, 2.5 mg/day from day 1-5 of the menstrual cycle with HMG300 IU/day starting on first day of the cycle with follow up by Trans vaginal ultrasound (TVUS) when at least three follicles reach 14mm diameter, GnRh antagonist given 0.25 mg SC injection daily till the day of hCG injection. HCG (10,000 IU) was given when at least three leading follicles were 18mm followed by ovum pick up. Control group offered the same management without letrozole.*

Main Outcome Measures: *Primary outcome measure: Number of follicles reaches more than 18mm and number of metaphase II oocytes. Secondary outcome measure: clinical pregnancy rate.*

Results: *Improved response to HMG stimulation with letrozole co-treatment was evidenced by significant number of follicles measuring more than 18mm (5.3 ± 3.5.in the study group versus 3.9 ± 1.9 in control group (p value 0.003). The number of metaphase II oocytes was significantly higher in the study group (4.6 ± 2.4 Versus3.3 ± 0.6). During letrozole co treatment clinical pregnancy was achieved in (20%) of cases.*

Conclusion: *We demonstrated a good benefit of aromatase inhibitors for improving ovarian response to HMG in short antagonist protocol in patients expected to be poor responders.*

Keywords

Poor responders, Aromatize inhibitors, Antagonist protocol, ICSI.

Trial registration number **NCT02741154**.

Introduction

Although there is no standard definition for poor ovarian response, the European Society for Human Reproduction and Embryology has proved that at least two of the three features must be present in poor ovarian response: advanced maternal age or any other risk factor for poor ovarian response; previous poor ovarian response; or an abnormal ovarian reserve test (Bologna Criteria) [1].

Poor ovarian response to ovarian hyperstimulation is one of the biggest challenges and frustrating for both patients and clinician. Although many stimulation protocols have been used to improve outcomes in poor ovarian responders (PORs), there is a controversy which protocol is the most effective [2].

Despite the prediction of low response to ovarian stimulation remains problem different tests have shown variable success, including day 3 FSH, clomiphene citrate (CC) challenge test, and inhibin concentrations, antral follicular count and serum AMH also can predict low response to ovarian stimulation [3].

Several strategies have been proposed to improve outcome in low responders. The use of GnRHant is a commonly used protocol for pituitary downregulation for improving ovarian stimulation response in poor responders. Mechanism of action it leads to immediate, rapid gonadotropin suppression by competitively blocking GnRH receptors in the anterior pituitary gland, so prevent endogenous premature release of LH and FSH. Several RCTs did not show any significant difference in clinical pregnancy rate or number of oocytes retrieved with the use of GnRHant [4-20].

Aromatase is enzyme that inhibits the conversion of the androgens, androstenedione and testosterone, to estrone (E1) and E2. The development of more specific and potent aromatase inhibitors, including letrozole is orally active and is well tolerated with no significant side effects [21].

Methodology

The study is a prospective clinical trial. Approved by Department of Obstetrics and Gynecology faculty of medicine (Number: MUH20168) conducted in Maternity hospital IVF unite Minia University and two tertiary referral infertility private clinics associated with the reproductive sciences division. The study was conducted during the period from August 2016 to August 2017, all study details were explained to patients and informed consent was obtained before inclusion in the study. Enrolled patients with eligible criteria were randomized into two groups using simple randomization by sealed opaque envelops contain serial computer generated numbers. Control group offered induction with HMG 300 IU (Merional ®, IBSA, Turkey) daily start at first day of menses with follow up by trans vaginal ultrasound (TVUS) when at least three follicles reach 14mm diameter GnRh antagonist given 0.25 mg ganirelix SC (Orgalutran; NV Organon, Oss, the Netherlands) with continuous follow up. Ovarian follicular development was monitored by transvaginal ultrasonography and serum levels of E2 a HCG 10,000 IU (Profasi, Serono, Oakville, Ontario, Canada) was given to trigger ovulation when three leading follicles reached a diameter 18mcm. The hCG administration was followed by ovum pick up under transvaginal ultrasound guide. Fertilization of the aspirated oocytes was carried out in vitro, by ICSI. Embryos were examined for the number and regularity of blastomeres and the degree of embryonic fragmentation, and graded according to Cummins's criteria. All highest-quality embryos (including grade 1 and grade 2) were transferred on the day 5. Pregnancy was diagnosed by quantitative assay of serum B HCG 2 weeks after embryo transfer and clinical pregnancy was confirmed by identification of a positive fetal heart beat at 6-7 weeks' gestation by transvaginal ultrasonography. Study group received the same management plus letrozole (Femara; Novartis, East Hanover, NJ) was given at a dose of 2.5 mg from day 1 to 5 of the menstrual cycle with same protocol and follow up. Both groups were compared as regard primary and secondary outcomes.

Inclusion criteria

Patients indicated for ICSI due to (Ovarian factor, tubal factor and unexplained infertility.) and expected to be poor responder, had to meet at least two of the following criteria (age over 37 years; a history of ovarian surgery; antral follicle count of less than 6 on menstrual cycle day 2-3; and basal serum FSH concentration between 10 and 19 IU/l, serum AMH (0.5 -1 IU).

Exclusion criteria

High responder, endometriosis, male factor, uterine factors, ovarian mass or cyst, documented ovarian failure.

Statistical analysis

Primary outcome of the study was number of follicles reach more than 18mm, number of metaphase II oocytes if more, Secondary outcome was pregnancy rate. Data were presented as the mean + standard deviation (SD) in text and tables. Data were analyses by Student's t-test, Mann–Whitney U test and chi-squared test where appropriate. The one-way analysis of variance method was used for the comparison of hormone concentrations at different time-points. The Mann–Whitney U test was used for the variables of non-normal distribution. The significance was accepted for $P < 0.05$. All data were analyses using the Statistical Package for the Social Sciences for Windows (SPSS, Version 16.0).

Results

58 patients, characterized as poor responders according to the Bologna criteria. Eight patients were excluded due to treatment discontinuation because of poor stimulation response. Baseline characteristics of the patients in the two ovarian stimulation groups are presented in table 1. There were no differences in age, BMI, AFC, duration of infertility and serum level of AMH. The main indications for ICSI treatment were noted to be tubal factor, ovarian factor and unexplained. There were no differences in these infertility indications among the two stimulation groups.

Characteristic	Control group (n = 25)	Study group (n = 25)	P value
Age (y), mean ± SD	41.1 ± 4.1	42.8 ± 3.7	.156
BMI (kg/m^2), mean ± SD	21.3 ± 2.0	21.2 ± 2.2	.068
AFC (n), mean ± SD	4.5 ±2.5	4.7± 2.3	.746
Duration of infertility (y), mean ± SD	14.1 ± 3.0	14.1 ± 3.1	.480
Seum level of AMH	0.7 ± 0.5	0.7 ± 0.4	.229
Tubal factor	12 (48%)	14 (56%)	.606
Ovarian	5 (20%)	6 (20%)	.559
Unexplained	8 (32%)	5 (20%)	.515

Table 1: Baseline characteristics of the stimulation groups.

Table 2 describes the main outcomes in the two groups. The ovarian stimulation duration was significantly shorter in letrazole group than in the control group (6.97 ± 1.95 days and 9.4 ± 3.42 respectively). Significant differences were found in number of follicles measuring more than 18mm (5.3 ± 3.5.in the study group

versus3.9 ± 1.9 in control group (p value 0.003). The number of metaphase II oocytes (MII) was significantly higher in the study group (4.6 ± 2.4 Versus3.3 ± 0.6). Fertilization rate (2.1 ± 2.5 versus 1.0 ± 1.0) and pregnancy rate (20.0%versus 12%) both were in favor with study group.

Variables	Control group (n = 25)	Study group (n = 25)	P-Value
Stimulation duration (days)	9.4 ± 3.42	6.97 ± 1.95	.026
Number of follicles >18 mm on trigger day	3.9 ± 1.9	5.3 ± 3.5	0.003
Number of oocytes retrieved	3.7 ± 1.0	5.2± 1.8	0.001
Number of metaphase II (metaphase II) oocytes	3.3 ± 0.6	4.6 ± 2.4	0.008
Number of fertilized oocytes	1.0 ± 1.0	2.1 ± 2.5	0.019
Clinical pregnancy rate	12%	20.0%	0.412

Table 2: Main outcomes in the two stimulation group.

Discussion

Letrozole succeeded in inducing ovulation in an ovulatory woman with polycystic ovary syndrome (PCOS) [23-25] and enhancing ovulation in ovulatory women. Moreover, that when letrozole was used with FSH, a significant reduction occurred in FSH dose needed for controlled ovarian hyperstimulation [26,27]. Mitwally et al. demonstrated the benefit of letrozole in improving ovarian response to FSH stimulation in poor responders. The improved response is clearly shown by the significantly higher number of mature follicles and significantly lower doses of drugs used for induction [3].

In the current study we demonstrated the benefit of letrozole co treatment during ovarian hyperstimulation with short antagonist protocol in patients undergoing ICSI. This may be attributed to increase follicular sensitivity to endogenous FSH as a result of a temporary accumulation of intraovarian androgens, as the conversion of the androgen substrates to estrogen is blocked. Although there is no standard protocol for poor responder but several studies have proved better ovarian response with antagonist protocol. However the previous two studies started stimulation in the luteal phase [2,28].

In current study Letrozole co treatment was associated with a significantly higher number mature follicles and higher pregnancy rate. Letrozole decreases E2 in COH cycles that may be beneficial in avoiding the possible undesired effects of the supraphysiologic levels of E2 associated with ovarian hyperstimulation. Markedly elevated E levels have been reported to have harmful effects on the embryo and endometrium that endanger the chance of implantation and pregnancy [29,30].

This preliminary results of current study includes a small number of poor responder patients treated short antagonist protocol with lerozole however, our objective was to confirm the idea of adjuvant letrozole treatment can improve ovarian response in this selected group. We know that ICSI trail is so expensive. In low resources countries insurance did not cover the cost of treatment trial. Our aim is to improve patient response for stimulation, decrease HMG dose and avoid cycle cancellation that can markedly reduce stress and cost of ICSI trial. We encourage controlled prospective randomized trial in the future to confirm the benefit of letrozole co treatment in short antagonist protocol in poor responder.

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