

Aromatase Inhibitors Versus Cabergoline for the Prevention of Ovarian Hyperstimulation Syndrome: a Prospective, Randomized, Double-Blind Study

Original
Article

Walid M. Ataalla^a, Tarek Abd Elhamid^b

^aDepartments of Obstetrics & Gynaecology, ^bHistopathology, Faculty of Medicine, Tanta University, Egypt, Department, Tanta University, Egypt

ABSTRACT

Objective: To evaluate the effect of the aromatase inhibitor letrozole in the prevention of ovarian hyperstimulation syndrome (OHSS) in patients at risk during controlled ovarian hyperstimul (COH).

Design: This is a prospective, randomized, double-blind study on women at risk of the development of OHSS during COH using gonadotropin-releasing hormone (GnRH) antagonist protocol

Patients and Methods: This research was conducted at the Center of Assisted Reproduction, Om El-kora Hospital, Tanta, Egypt. Sixty patients, who were considered at risk of the development of OHSS during COH were enrolled in this study. Ovarian stimulation was performed using GnRH, whereas cabergoline (0.25 mg) given twice daily or letrozole (2.5 mg) twice daily from the day of oocyte retrieval for one week.

Results: In the cabergoline group, two cases (6.6%) developed mild OHSS and one case (3.3%) developed moderate OHSS versus 8 (26.6%) mild OHSS and 6 (20%) moderate OHSS in the letrozole group. On the other hand, there was no statistically significant difference in the number of cases that developed severe OHSS in both groups where only one case (3.3%) developed severe OHSS in the cabergoline group vs. two (6.6%) cases in the letrozole group.

Conclusion: Although letrozole administration during the luteal phase of ART cycles can reduce the high E2 level in hyper-responding patients, but it cannot prevent the development of early OHSS. On the contrary, Cabergoline can effectively prevent the development of early OHSS.

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Key Words: Aromatase Inhibitors, Cabergoline, OHSS

Corresponding Author: Walid Attalla., February 2017, Vol. 7, No. 1., **Tel.:** 01223488672 **E-mail:** wma646@hotmail.com

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INTRODUCTION

Prevention of OHSS can be either primary or secondary prevention. Primary prevention means tailoring IVF treatment protocols according to the patient's primary risk factors, while the secondary prevention means the methods used to prevent the progression to OHSS in patients already showed excessive response to ovarian stimulation¹. Individualizing IVF protocol includes modification of the starting dose of FSH, use of antagonist protocol instead of long agonist protocol, lowering the dose of hCG needed to trigger ovulation¹⁸ or using GnRHa for triggering ovulation in GnRH antagonist treated cycles¹⁹. Secondary preventive measures include coasting¹⁸, withholding hCG and cycle cancellation²⁰, cryopreservation of all embryos²¹, intravenous administration of albumin²² or hydroxyethyl starch (HES)²³ during or immediately after oocyte retrieval, use of cabergoline²⁴ or the vasopressin V1a receptor antagonist, relcovaptan²⁵.

Cabergoline, a dopamine antagonist prevents the VEGF effect on vascular system, i.e. reducing VEGF receptor 2 expression/ phosphorylation by a D2 receptor-mediated mechanism^{24, 26}. Cochrane Review by Tang *et al.* showed that cabergoline is effective in significantly reducing the incidence of moderate but not severe OHSS without significant effect on clinical pregnancy or miscarriage rates²⁷. More recently, a systemic review by Leitao *et al.* showed that cabergoline is effective in preventing the occurrence of both moderate and severe OHSS again without affecting clinical pregnancy rate²⁸.

Though the role of elevated E2 in OHSS has not been confirmed, estradiol concentrations on the day of hCG administration seem to play a role in OHSS development²⁹ and lowering E2 level helps to prevent OHSS³⁰. One way to decrease estradiol is aromatase

inhibitors and so this could be used to prevent OHSS when used in the early luteal phase by acting on the sustained corpora lutea.

Two randomized studies assessed the effect of letrozole administration in the luteal phase of IVF cycles in oocyte donors and both of them confirmed that letrozole reduces the luteal E2 levels in stimulated cycles^{31,32}.

PATIENTS AND METHODS

This prospective, randomized study was carried out in the Center of Assisted Reproduction, Om El kora Hospital, Tanta, Egypt. From January 2014 to December 2014, a total of 60 patients, who were considered at risk of the development of OHSS during COH were recruited. Informed consents obtained from all patients.

This study approved by the Clinical Research Ethics Committee.

Inclusion criteria

PCO patients and patients with ultrasonic picture of PCO, who became at risk of developing OHSS during controlled ovarian hyperstimulation using antagonist protocol. OHSS defined by serum E2 level > 3000 pg/ml and/or the development of ≥ 20 follicles larger than 12 mm in diameter on the day of HCG.

We included only patients who agreed to cryopreserve all embryos to avoid late OHSS and to avoid the possibility of lower pregnancy rates secondary to letrozole mediated lowering of oestradiol levels.

Exclusion criteria

Patients, with E2 levels of 3000- 3500 pg/ml, who refused to cryopreserve all embryos. Since our patients were given GnRH against for final oocyte maturation that could lower the risk of OHSS itself, patients with E levels >3500 Pg/ml were excluded.

All patients with E2 levels between 3000- 3500 pg/ml, who agreed to cryopreserve all embryos, were given HCG 5000 IU for triggering ovulation thereafter randomized by lottery into two equal groups. Group I (30 patients) received cabergoline 0.25 mg twice daily. Group II (30 patients) received letrozole 2.5 mg twice daily from the day of oocyte retrieval and for one week. Randomization was done with both the physicians and the patients blinded.

After oocyte retrieval patients were instructed to report any of the following symptoms; lower abdominal discomfort, nausea, vomiting, diarrhea, bloating,

abdominal distention, passing very small amounts of urine, swollen and tender leg or respiratory difficulty. Otherwise, ultrasound was performed for all patients one week after oocyte retrieval to measure ovarian size and for detection of ascitis.

IVF protocol:

All patients received antagonist stimulation protocol. All patients in each group received 150 IU of recombinant FSH, Gonal-F (Serono, Switzerland) daily for 4 days starting from the second day of menstruation. The dose of gonadotropins was adjusted according to the ovarian response on transvaginal ultrasound and serum oestradiol concentration starting from day 5 of stimulation. The GnRH antagonist cetrorelix 0.25 mg (Cetrotide, Serono Laboratories, Aubonne, Switzerland) was started in all patients on a fixed day which is day 5 of stimulation and continued until day of HCG administration. I.M. injection of 5000 IU of HCG (Choriomon, IBSA, Switzerland) or subcutaneous injection of 0.2 mg triptorelin (Decapeptyl; Ferring, GmbH, Kiel, Germany) were administered when at least three follicles reached ≥ 17 mm in diameter. Ultrasound guided transvaginal oocyte retrieval was performed 3436- hours later. All embryos were frozen in order to decrease the risk of late OHSS.

Hormone assay

In the cycle preceding the stimulation cycle, AMH (ng/ml) was measured on any day of the cycle. Serum E2 (pg/ml), LH (iu/l) and progesterone (ng/ml) were measured on the second day of menstruation of the stimulation cycle before starting gonadotropins. E2 was then measured during the stimulation cycle to assist monitoring of the ovarian response. Serum E2 level was compared in the two groups before stimulation, at day of hCG and 6 days after initiation of cabergoline or letrozole.

The development of mild, moderate or severe OHSS was compared in both groups.

RESULTS

This study included 60 patients. Patients were randomly distributed with 30 patients in each arm. Demographic data of the study patients are listed in Table 2. There were no significant differences in the patient characteristics in the two groups.

The ovarian responsiveness and treatment outcomes are compared in Table 3. No significant differences obtained between the two groups in E2 measurements before starting ovarian stimulation, on day 6 of stimulation or on the day of HCG. But a statistically significant

different revealed on day 7 after oocyte retrieval where E2 level was significantly lower in the letrozole group compared to the cabergoline group.

Regarding OHSS, two cases (6.6%) developed mild OHSS and one case (3.3%) developed moderate OHSS in the cabergoline group. This was significantly lower than

the number of cases that developed mild and moderate OHSS in the letrozole group which were 8 (26.6%) and 6 (20%) cases, respectively. On the contrary, no statistically significant difference obtained in cases that developed severe OHSS in both groups where only one case (3.3%) developed severe OHSS in the cabergoline group compared to two (6.6%) cases in the letrozole group.

Table 1: Patients' characteristics.

	cabergoline group (n = 30)	letrozole group (n = 30)	P value
Age (Y)	23.43 ± 3.115	24.53 ± 2.897	0.162
BMI (kg/m²)	21.93 ± 6.726	23.70 ± 2.667	0.186
Basal FSH (IU/L)	4.12 ± 0.941	3.87 ± 1.008	0.325
Basal LH (IU/L)	5.46 ± 1.339	5.49 ± 1.166	0.927
AMH (ng/ml)	5.05 ± 1.245	5.37 ± 1.266	0.338
Duration of infertility (Y)	3.09 ± 1.435	3.67 ± 1.155	0.09
Type of infertility			
Primary	23 ()	24 (%)	0.759
Secondary	7 (%)	6 (%)	0.759
Main causes of infertility			
Tubal disease	11 (%)	10 (%)	0.791
Male factor	13 (%)	12 (%)	0.798
Unexplained	6 (%)	8 (%)	0.549

*significant $P < 0.05$

Table 2: Criteria of stimulation cycles.

	Cabergoline group (n =30)	Mean ± SD	Letrozole group (n = 30)	Mean ± SD	P value
Days of stimulation	(9.0 -11.0)	10 ± 0.830	(8.0 -11.0)	9.63 ± 0.928	0.112
Number of 75 IU FSH ampoules	(16 – 25.0)	18.97 ± 2.833	(15.0 – 23.0)	18.7 ± 2.667	0.711
E2 (pg/ml)					
E2, prestimulation	(13.6 -44.6)	28.207 ± 8.780	(12.9 – 42.4)	28.110 ± 8.688	0.966
E2, at day 6 of stimulation	(1440.6 – 1811.2)	1699.7 ± 100.08	(1569.6 –1992.7)	1732.8 ±111.43	0.230
E2, at day of HCG	(3035.5 – 3480.7)	3221.9 ± 137.93	(3096.8 – 3469.1)	3277.0 ± 107.65	0.086
E2, 7 day after oocyte retrieval	(1466.2 - 1650.8)	1558.024 ± 59.24	(750.4 – 1050.9)	905.043 ±104.86	0.000*
No. of follicles on day of HCG	(24 – 28)	25.93 ± 1.28	(25 – 30)	26.57 ± 1.35	0.068
No. of oocytes per retrieval	(18 – 25)	20.6 ± 2.027	(20 – 25)	21.3 ± 2.351	0.222
OHSS					
Mild	2 (6.6 %)		8 (26.6 %)		0.038*
Moderate	1 (3.3 %)		6 (20 %)		0.045*
Severe	1 (3.3 %)		2 (6.6 %)		0.561

*significant $P < 0.05$

DISCUSSION

HCG for final oocyte maturation is well documented as the triggering factor for cascade of events, which results in the development of OHSS. These events were almost always accompanied by elevated serum E2 levels. Estradiol concentrations on the day of hCG administration seem to play a role in OHSS development²⁹. Rapid rise of E2 together with other factors as large number of developing follicles on the day of hCG administration (>14 follicles with a diameter of 11mm), and a large number of oocytes retrieved have been proposed as risk factors for developing OHSS¹⁷.

Coasting is a strategy to prevent OHSS by withholding gonadotrophins when a certain E2 level and/or a critical number of follicles are reached. When the E2 drops to a "safe" level, hCG is administered for final oocyte maturation. It is generally employed for a period less than 3 days¹⁸. It has been shown that levels of VEGF which is one of the vasoactive amines that play a role in the development of OHSS are reduced along with falling E2 levels during Coasting³³.

In this study, we used the aromatase inhibitor letrozole which blocks the aromatization of androstenedione to estrogen to reduce estradiol concentrations and may help in preventing early OHSS. Letrozole was used from the day of oocyte retrieval and not during the follicular phase to avoid any deleterious effect on folliculogenesis or oocyte maturation through lowering of estradiol or accumulation of androgens.

Two randomized studies assessed the effect of letrozol administration in the luteal phase of IVF cycles in oocyte donors. Both confirmed that letrozole reduces the luteal E2 levels in stimulated cycles^{31,32} a prospective randomized controlled pilot study. Six oocyte donors were randomized after COH and successful egg retrieval to receive either 2.5 mg of letrozole or a placebo. Donors were tested for serum estradiol, progesterone and LH on the day of hCG administration and day 4, 7 and 10 after oocyte retrieval. In the second study, twenty oocyte donors were randomized after COH and successful egg retrieval to receive either 2.5 mg of letrozole or a placebo (folic acid tablets) for 5 days from the day of ovum pick-up. Donors were tested for serum estradiol, progesterone and LH the day of hCG administration and day 4, 7 and 10. Both studies showed significantly reduced serum E2 levels at 4, 7 and 10 days after oocyte retrieval compared to controls. The first study showed no difference in LH levels among treatment and control groups while the second study showed that letrozole appeared to significantly increased LH levels on days 7 and 10 after retrieval.

Similar to our study, Fatemi et al, used letrozole in the early luteal phase for prevention of OHSS in a 21-year-old patient which was at high risk for the development of OHSS during COH. On Day 9 of stimulation, E2 level was 5000 pg/ml and 50 follicles were visualized. Noteworthy, HCG 5000 IU was used for final oocyte maturation because of limited experience of the physician on duty. The patient was given letrozol 2.5 mg twice daily and cabergoline 0.5 daily directly post oocyte retrieval up to the day of embryo transfer. 52 oocytes were retrieved of which 38 were Metaphase II. 23 oocytes were fertilized with ICSI, and on day three 13 embryos were biopsied for PGD. On day 5 after oocyte retrieval, one genetically normal embryo was transferred and at 7 weeks of gestation, a viable singleton pregnancy could be visualized on ultrasound. The patients did not develop any early nor late OHSS³⁴.

Wang *et al.* conducted a study on 281 patients who were potential candidates for developing OHSS after COH in ART cycles using long GnRH agonist protocol. All participating patients met at least one of the following criteria: (1) Number of retrieved oocytes ≥ 20 ; (2) mean number of follicles with a diameter greater than 14 mm was ≥ 20 ; (3) serum E2 concentrations reached $\geq 8\ 000$ pg/ml; (4) on the day of oocyte retrieval, the ovarian diameter was > 10 cm; and presentation of obviously symptoms of OHSS on the day of aspiration. Patients were given 6000–8000 IU of hCG for final oocyte maturation. The couples were counseled about the high risk of OHSS and all agreed to cancel fresh embryo transfer. Patients were divided into a treatment group (n = 161) and control group (n = 120). The patients in the treatment group were informed of treatment options: first group: received letrozole tab 2.5 mg twice daily for 5 consecutive days, second group: received mifepristone tab 25 mg twice daily for 3 consecutive days. Third group: received subcutaneous cetrotide 0.25 mg daily for 5 consecutive days. Fourth group: received the three drugs together at the same time. The control group: received no special medication. All patients started the medication on the day after oocyte retrieval. There was significantly lower E2 level on days 2, 5 and 8 after oocyte retrieval in the letrozole and three-drug combination therapy group than in the other three groups. There was no significant difference in serum LH concentration on the same days and progesterone concentration on day 8 after oocyte retrieval among the five groups³⁵.

A possible harmful effect of letrozole on oocyte maturation and embryo quality was revealed in previous studies. In context, *Ehsan, et al.* conducted a comparative study on one hundred and twenty patients who were potential candidates for developing OHSS after COH in assisted reproduction technology (ART) cycles using long GnRH agonist protocol. They compared the use of letrozole versus coasting in prevention of OHSS. Women

at risk for OHSS "i.e., with serum E2 >1634 pg/ml on day 8 of stimulation" were randomized to receive letrozole (2.5 mg/day if E2 level was ≥ 3000 pg/ml or every other day if E2 was <3000 pg/ml starting from day 8 of stimulation till the day before hCG) or to undergo coasting. Though number of metaphase II oocyte retrieved was similar in both groups, number of grade I egg and of grade I embryo was lower in letrozole group compared to coasting group³⁶. Similarly, administration of AI in late follicular phase resulted in significantly lower number of metaphase II oocyte in stimulated rhesus monkey³⁷.

On the other hand, It was observed that >50% drop of E2 from initial level does not compromise the oocyte quality and implantation but prevent OHSS³³. Moreover, oestradiol depletion in the vicinity of the oocyte did not impair its development, fertilization, development into morula, blastocyst and hatching blastocysts³⁷⁻³⁸. Additionally, the extremely high levels of E2 have a deleterious effect on gamete quality and/or uterine receptivity^{39,40}.

To avoid late OHSS and also to avoid any harmful effect of letrozole on the endometrium secondary to lowering of estradiol that could be reflected on implantation and pregnancy rate, we included only patients who agreed to cryopreserve all embryos.

In ART cycles, rapid changes in the hormonal levels occur during the luteal phase. Just before oocyte aspiration, supraphysiologic E2 concentrations are reached, which is followed by a dramatic fall in E2 after oocyte aspiration. There is a further fall in steroidal levels by day 9 of oocyte trigger as the trophic effect of HCG on the corpus luteum gets weaned off⁴¹. The impact of % E2 fall in the early and midluteal phase on pregnancy outcome during COH is controversial.

Stewart *et al*⁴² were the first to identify a significant difference in serum E2 concentrations between conception and nonconception cycles in fertile women undergoing donor insemination.

Using the long down-regulation protocol, Sharara *et al*⁴³ measured the ratio of E2 on day of HCG to midluteal E2 and found that sharp decline in E2 resulted in a significantly lower implantation and pregnancy rates. This raised the speculation that the E2 fall would compromise the peri-implantation endometrial development.

Alike, Levi *et al.* used the same protocol and found that the sharper the drop in E2 levels, the lower was the possibility of successful IVF outcome⁴⁴. It was speculated that insufficient exposure of the endometrium to E2 might lower or inhibit maintenance of the effects of some factors like leukemia inhibiting factor, interleukin-1, TNF- α , and interferone.

Also, the research by Ganesh *et al*⁴⁵ revealed that E2 on day 7 after ET was significantly higher in the conception group as compared to the non pregnant group.

On the other hand, Friedler *et al*⁴⁶ studied the luteal phase E2 levels and found no difference in the mean midluteal E2 levels and % of E2 decline in the conception versus non conception cycles.

Moreover, one meta-analysis compared the effect of adding E2 to progesterone versus progesterone alone for luteal phase support in GnRH agonist as well as antagonist cycles. It was concluded that addition of E2 to progesterone does not increase the pregnancy rate⁴⁷.

So, despite the decline of E2 after oocyte retrieval, there is certain E2 level above which pregnancy rate could be maintained. Thus, we need to know whether letrozole use during the luteal phase causes additional decline in E2 that may compromise endometrial development and pregnancy rate.

Our results showed that the incidence of mild and moderate OHSS was significantly lower with cabergoline compared to letrozole. But, no significant difference was detected in the incidence of severe OHSS between the two groups.

In a case report, Fatemi *et al* tested the co-administration of letrozole and cabergoline in the early luteal phase for prevention of OHSS in a high risk patient undergoing ovarian stimulation for IVF. Neither early nor late OHSS was developed. On day 5 after oocyte retrieval, one genetically normal embryo was transferred. By the 7th week of gestation, a viable singleton pregnancy was visualized by ultrasound³⁴.

In another trial, Wang *et al.* compared the use of letrozole, mifepristone, cetrotide and the three-drug combinations versus no use in the prevention of severe OHSS. No significant decrease in the incidence of severe OHSS in each of the four groups was obtained³⁵.

Interestingly, Ehsan *et al* compared the use of letrozole versus coasting in the prevention of OHSS, whereas no severe OHSS developed and only 5% of cases developed mild to moderate OHSS in the letrozole group. On the other hand, in coasting group 3.3% of patients developed severe OHSS and 8.3% of cases developed mild to moderate OHSS. But the difference between the two groups in the incidence of mild and moderate OHSS did not reach statistical significance. Also, no significant difference in pregnancy rate was obtained between the two groups³⁶.

CONCLUSIONS

Letrozole administration during the luteal phase of ART cycles can reduce the high E2 level in hyper-responding patients, but it cannot prevent the development of early OHSS in these patients. On the contrary, cabergoline can effectively prevent the development of early OHSS.

CONFLICT OF INTERESTS

There are no conflict of interest.

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