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ORIGINAL ARTICLE

GnRH Antagonist Cetrorelix Administration Before hCG for Protection of Ovarian Hyperstimulation Syndrome

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Abstract

Objective Studying the effect of GnRH antagonist administration on the day of hCG to cases of IVF/ICSI with estradiol level above 5000 ng/dl for protection of ovarian hyperstimulation syndrome.

Design Prospective study.

Materials and Methods Sixty patients undergoing controlled hyperstimulation COH, for IVF/ICSI using long agonist and E2 level on the day of hCG, are above 5000 ng/dl, 52 patients received single dose of cetrorelix 0.25 mg on the day of hCG, and 8 patients received two doses of 0.25 mg/day cetrorelix started one day before the day of hCG.

Results There was no significant difference regarding patients BMI, number of stimulation days, recombinant FSH dose, and number of retrieved oocytes. Clinical pregnancy rate was 76.6% (46/60), in patients received single dose of antagonist PR were significantly higher 80.7% (42/52) versus 50% (4/8) in patients received two doses $p = 0.047$. Live birth rate was 50% (30/60), abortion rate was 20% (12/60), and preterm delivery was 20% (12/60). Mean E2 was 6853.2 ng/dl. Six patients developed moderate ovarian hyperstimulation OHSS (6/60) 10% and no cases of severe OHSS.

Conclusions GnRH antagonist administration on the day of hCG in cases undergoing IVF/ICSI with long agonist protocol is effective in protection of OHSS and does not affect the clinical pregnancy rate nor live birth rate.

Keywords Infertility · ICSI · OHSS · Antagonist

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Introduction

Ovarian hyperstimulation syndrome (OHSS) is the most serious iatrogenic complication of exogenous gonadotropin therapy used to mature multiple follicles for assisted reproductive treatments [1]. This syndrome was first described in 1943 when early forms of gonadotropins were used to stimulate or induce ovulation [2]. OHSS is characterized by bilateral, multiple follicular, and theca-lutein ovarian cysts and an acute shift in body fluid distribution—third-space fluid shift—resulting in ascites and pleural effusion [3].

The majority of severe OHSS cases follow ART, and the incidence varies owing to the variety of classification schemes; 33% of IVF cycles have been reported to be associated with mild forms of OHSS, whereas the more severe forms have been reported in 2–6% of IVF cycles [4] While mild OHSS is of no clinical relevance, moderate and sever OHSS which may progress up to massive ovarian enlargement, ascites, pleural effusion, oliguria, hemoconcentration and thromboembolic phenomena are a life-threatening complications [5].

OHSS may be early or late according to time of onset. Early OHSS presents 3–7 days after the ovulatory dose of hCG, whereas late OHSS presents 12–17 days after hCG administration. Early OHSS relates to excessive preovulatory response to stimulation, whereas late OHSS depends on occurrence of pregnancy and it is more likely to be severe [6].

Although the pathophysiology of this syndrome remains unknown, it is assumed that the vasoactive substances secreted by ovaries under hCG stimulation may play a key role in increasing the capillary permeability observed in OHSS [7]. To date, around 25 factors have been described as being involved in the regulation of cellular permeability. Angiogenic cytokines including vascular endothelial growth factor (VEGF), interleukin (IL)-6, IL-8, basic fibroblast growth factor (bFGF), tumor necrotic factor-α (TNF-α), IL-1β produced by multiple corpora lutea may be involved in OHSS. Of these [8], VEGF is one of the most important factors, while the effects of the others angiogenic factors on OHSS are vague [9].

Prediction of OHSS is the cornerstone of prevention. Prediction is based on identifying the criteria of the patient who would be high responder as well as the use of ultrasonography and estradiol assessment [10].

Lines of prevention of OHSS include both early and late preventive forms [11.] Primary prevention involves identifying risk factors for OHSS and choosing an appropriate ovarian stimulation regimen as a GnRH antagonist stimulation protocol [12] or using lower gonadotropin doses use in high-risk patients [13]. Secondary prevention involves recognizing patients who are over-responsive to gonadotropins and intervening to reduce the risk of OHSS while still trying to salvage the treatment cycle which includes coasting [14], vitrification of oocytes or embryos [15], GnRH antagonist administration in the luteal phase [16] and dopamine agonist use [17]. Other unique preventive measures include decrease in the dose of hCG, use of LH or GnRH agonist in triggering ovulation instead of hCG, administration of albumin and glucocorticoids use [18].

GnRH antagonists act via competitive binding to GnRH receptors, which result in prompt decrease in circulating concentrations of pituitary gonadotropins, particularly LH [19].

The current study was conducted to study the effect of GnRH antagonist administration on the day of hCG to cases of IVF/ICSI with estradiol level above 5000 ng/dl for protection against ovarian hyperstimulation syndrome.

Patients and Methods

Design Prospective study.

Setting Sixty women were recruited for the study among the patients prepared for ICSI in a private center in Alexandria, Egypt. The study was explained to them and written, and informed consent for participation was obtained.

Inclusion Criteria Included Age between 25 and 35, BMI not more than 35, male factor infertility doing ICSI using fresh semen sample, high responder patients and serum estradiol level more than 5000 pg/ml on the day of hCG administration.

Exclusion Criteria Included PCOS, endometriosis, previous ovarian surgery reducing ovarian reserve and AMH level less than 1.5 ng/ml.

After basal ultrasound examination to rule out exclusion criteria, all cases were stimulated using the long agonist protocol starting from mid-luteal phase of previous cycle using Decapeptyl 0.1 mg subcutaneously. Stimulation was started using hMG starting from second day of menses with suppression confirmed by estradiol level <50 pg/ml. All cases were monitored as usual by using ultrasound examination and hormonal evaluation including E2 and P4 serum values. Serum estradiol and serum progesterone levels were measured on the day of hCG administration. Participants were divided into two groups: Group A included 52 patients who received single dose of GnRH antagonist (0.25 mg cetrorelix) on the day of hCG administration, and Group B included 8 patients received two doses of 0.25 mg of cetrorelix started one day before the day of hCG.

Table 1 Comparison between pregnancy rate and baseline variables

	Mean	SD	Min	Max	*t* test	*p*
End thick						
Non-pregnant	11.071	0.896	10.00	12.00	4.830	0.032
Pregnant	11.970	1.442	8.00	16.00		
S. E2						
Non-pregnant	6853.286	982.547	5128.00	8100.00	0.983	0.326
Pregnant	7173.739	1080.199	5086.00	8830.00		
S. P4						
Non-pregnant	1.213	0.345	0.70	1.60	3.341	0.073
Pregnant	1.498	0.550	0.69	3.36		
Inf. ys						
Non-pregnant	4.429	3.413	1.00	10.00	0.573	0.452
Pregnant	5.391	4.359	1.00	17.00		
BMI						
Non-pregnant	27.464	6.396	19.49	37.89	0.194	0.661
Pregnant	26.717	5.283	18.37	41.18		
St. days						
Non-pregnant	11.429	1.342	9.00	13.00	6.935	0.011
Pregnant	12.478	1.295	10.00	15.00		
r.FSH						
Non-pregnant	143.667	26.768	112.50	187.00	0.031	0.862
Pregnant	146.324	49.728	1.00	225.00		
M2						
Non-pregnant	30.429	8.751	18.00	40.00	1.387	0.244
Pregnant	27.130	9.292	8.00	59.00		
Number oocytes						
Non-pregnant	37.429	8.993	20.00	48.00	5.657	0.021
Pregnant	30.739	9.277	13.00	60.00		
ET. day						
Non-pregnant	3.857	1.027	3.00	5.00	3.176	0.080
Pregnant	3.286	1.043	2.00	5.00		

Oocyte retrieval was performed 34–36 h after 10,000 IU of hCG were given. ICSI procedure was completed as usual, and embryo transfer was done on day 3 with cryopreservation of surplus embryos. Clinical pregnancy and live birth rates were observed for among the study group.

Statistical Analysis

The data were collected and entered into the personal computer. Statistical analysis was done using Statistical Package for Social Sciences (SPSS/version 20) software.

The statistical test used as follows:

Chi-square test were used for arithmetic mean, standard deviation, and for categorized parameters. While for two groups, *t* test was used for parametric data. The level of significant was 0.05.

Results

Baseline data of the include women were comparable regarding age, BMI and infertility duration. Ovarian reserve as evaluated using AMH and antral follicle count were also comparable (Table 1).

Stimulation days, recombinant FSH dose and number of retrieved oocytes were also comparable among the study group (Table 1).

Frequency of the cause of infertility is given in Table 2.

Clinical pregnancy rate was 76.6% (46/60) (Table 3).

In patients received single dose of antagonist, pregnancy rate was significantly higher 80.7% (42/52) versus 50% (4/8) in patients received two doses $p = 0.047$ (Table 4).

Live birth rate was 50% (30/60), abortion rate was 20% (12/60), and preterm delivery was 20% (12/60); mean E2 level was 6853.ng/dl. Six patients developed moderate

Table 2 Frequency of the cause of infertility

Cause	Frequency	Percent
Male	26	43.3
PCO	8	13.3
PCO/male	8	13.3
TESE	4	6.7
Tubal	10	16.7
Unexplained	4	6.7
Total	60	100.0

Table 3 Clinical pregnancy rate in the study group

Clinical PR	Frequency	Percent
Non-pregnant	14	23.3
Pregnant	46	76.7
Total	60	100.0

Table 4 Antagonist administration in relation to clinical PR

			Clinical PR		Total
			Non-pregnant	Pregnant	
Antagonist	Single dose	No.	10	42	52
	1.00	%	71.4%	91.3%	86.7%
	Two doses	No.	4	4	8
	2.00	%	28.6%	8.7%	13.3%
Total		No.	14	46	60
		%	100.0%	100.0%	100.0%
X^2			2.15		
p			0.047*		

ovarian hyperstimulation syndrome OHSS 10% (6/60) and no cases of severe OHSS.

Discussion

All ovarian stimulation protocols result in some degree of hyperstimulation, but in most cases, patients do not suffer adverse consequences [20]. Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic complication of ovulation induction and it is potentially life-threatening condition [21].

Although the pathophysiology of this syndrome remains unknown, it is assumed that the vasoactive substances secreted by ovaries under hCG stimulation may play a key role in increasing the capillary permeability observed in OHSS, especially VEGF [22]. After hCG administration, VEGF up-regulates during ovarian stimulation and has a strong permeability effect on endothelial cells. The amount of VEGF in the follicular fluid in patients with OHSS was noted to be frequently higher than in patients not affected by this complication. For this reason, VEGF is considered a possible candidate in relation to the increased permeability observed in OHSS with loss of fluid to the third space [23].

There are known factors whose the presence increases the likelihood of a high response to gonadotropins; thus, the risk of developing OHSS increases: younger age, a history of a good response to gonadotropins, thin women, polycystic ovary syndrome, blood group A and history of allergies. Risk factors during treatment cycles include presence of multiple follicles (>35 in COH, >6 in OI), high serum estradiol (>4000 pg/mL in COH, >1700 in OI), hCG luteal supplementation, elevated serum/follicular fluid VEGF levels and conception cycles (pregnancy) [24].

For this reason, primary preventive strategies begin by identifying patients at high risk of developing OHSS to individualize the ovarian stimulation protocol (gonadotropins dose, duration of FSH exposure, etc.), while secondary preventive measures applied once an exaggerated response to administration is detected, to avoid OHSS or to minimize its severity which include cycle cancelation, coasting, vitrification of oocytes or embryos, reduction in the dose of hCG, use of LH or GnRH agonist in triggering ovulation instead of hCG and dopamine agonist use [25].

On the other hand, in our study patients who were undergoing COH for IVF/ICSI using long agonist protocol with E2 level on the day of hCG administration are above 5000 ng/dl GnRH antagonist (cetrorelix) which was given for protection against OHSS, based on the fact that besides competitive binding to GnRH receptors, which results in prompt decrease in circulating concentrations of pituitary gonadotropins, particularly LH, GnRH antagonists were found to lower the VEGF concentrations in human granulosa lutein cell cultures, as well as the expression of VEGF and VEGF-R in the ovaries of hyperstimulated rates [26].

Also, the GnRH antagonist is reported to have a prominent luteolytic effect, which might prove to be an alternative way of reducing the excessive production of vasoactive cytokines from the corpora lutea responsible for OHSS development [27].

In conclusion, GnRH antagonist administration on the day of hCG in cases undergoing IVF/ICSI with long agonist protocol is effective in protection against OHSS and does not affect clinical pregnancy rate nor live birth rate.

Compliance with Ethical Standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in the study were in accordance with the ethical standards of the institutional and/or

national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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