Cabergoline in Prevention of Ovarian Hyperstimulation Syndrome and Its Effect on Outcome In Intracytoplasmic Sperm Injection Cycles

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Abstract: ***Background:*** The most serious and potentially life threatening iatrogenic complication of controlled ovarian hyperstimulation (COH) is a severe form of ovarian hyperstimulation syndrome (OHSS). It complicates less than 0.5-2% of *In Vitro* Fertilization (*IVF*) cycles which cause mortality in 1/45000 – 1/50000 per infertile women receiving gonadotrophins. The diagnosis and severity of OHSS were determined using standard criteria. OHSS has been treated empirically over the years, because it is Pathophysiology remained unknown. Vascular endothelial growth factor (VEGF) is a powerful mediator of vascular permeability; it is also strongly implicated in the initiation and development of angiogenesis in the developing embryo and in adult tissue undergoing profound angiogenesis, such as cycling endometrium and the luteinizing follicle. It also plays an important role in the growth and maintenance of ovarian follicles and corpus luteum by mediating angiogenesis. ***Objectives:*** To compare the effects of cabergoline in the prevention of ovarian hyperstimulation syndrome (OHSS) in high-risk women underwent ICSI. ***Study design:*** Prospective randomized trial. ***Patients and Methods:*** The study included an intervention and a control group. Cabergoline group: 30 patient's received 0.25mg cabergoline tablet per day starting on day of hCG injection and continued for 8 days. Control group: cabergoline tablet was not given after hCG injection in 30 patients. ***Results:*** There was no significant difference between baseline characteristics or ovarian stimulation parameters from the two groups. The incidence of OHSS in the cabergoline-treated group, was significantly (P=0.01) lower than that in the control group (12% vs. 36%). Higher rates of clinical and chemical pregnancy were observed after cabergoline administration in ICSI cycles. ***Conclusions:*** The present study showed that cabergoline reduces the incidence of OHSS in ICSI cycles. Women at high risk of OHSS, cabergoline can be administered as soon as the hCG injection to prevent early OHSS. Higher rates of clinical and chemical pregnancy were observed after cabergoline administration in ICSI cycles.

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1- Introduction

Ovarian hyperstimulation syndrome (OHSS) is a potentially life-threatening situation, and thus regarded to be the most serious complication of assisted reproduction treatment (ART). It is characterized by the presence within the ovaries of multiple luteinized cysts, which leads to ovarian enlargement and secondary complications such as increased capillary permeability and fluid shift to the third space.[1]

Findings at 2008 have identified vascular endothelial growth factor (VEGF) as the major molecule responsible for increased capillary permeability.[1] The production of VEGF in ovarian follicles increases during stimulation period, and results in a rapid increase in vascular permeability upon binding to type 2 VEGF receptors.[1] Although, cytokines and growth factors (interleukins IL-2, IL-6, IL-8, IL-10, and IL-18), histamine, prolactin, prostaglandins and renin-angiotensin have been proposed as participants in OHSS pathophysiology, the exact responsible factor is under debate.[2]

Standard treatments for OHSS are generally conservative, and potentially life-threatening complications of OHSS, which require costly long-term hospitalizations, render prophylactic measures a must.[3,4]

Some approaches, which are based on the pathophysiology of OHSS, are now applied for its prevention. Studies show a reduced incidence of OHSS when recombinant luteinizing hormone (rLH) or a gonadotropin releasing hormone (GnRH) analogue is used to trigger the final steps of oocyte maturation. Prophylactic administration of cabergoline, a dopamine agonist, is associated with a significant reduction in the incidence of symptoms and signs of moderate to severe OHSS. This drug inhibits vascular endothelial growth factor 2 (VEGFR-2) phosphorylation and signaling. Its use is not associated with an inferior ART outcome or obstetric/neonatal complications.[2,4-6]

Bused upon this consideration this study was conducted to compare the effects of cabergoline in the

prevention of the early onset ovarian hyperstimulation syndrome (OHSS) in high-risk women underwent ICSI.

2- Material and Methods

This prospective randomized study was performed in the Assisted Reproductive Technologies Unit, Benha University Hospital and in private IVF centers. The study protocol was approved by the Local Ethics Committee and written informed consents were obtained before the study started.

High risk patients were defined as young females, who had antral follicle counts of more than 15, poly cystic ovaries on ultrasound scan and/or polycystic ovarian syndrome (PCOS), serum estradiol of more than 2500 picogram per milliliter (pg/ml) and/or multiple follicular recruitments in both ovaries during ultrasound monitoring in controlled ovarian hyperstimulation (COH) (More than 20 follicles > 12 millimeter (mm) on the 10^{th} of the cycle)[2].

The inclusion criteria were an age of 25- 30 years, high risk of developing OHSS. Polycystic ovarian syndrome was diagnosed according to Rotterdam criteria.[8] According to the Rotterdam criteria, patients with two of the three characteristics including: 1) oligomenorrhea/ amenorrhea, 2) clinical (hirsutism) finding of hyperandrogenism, or 3) polycystic ovaries on transvaginal sonography, were included in the study. Metabolic features of PCOS patients were not of concern in this study; therefore, insulin resistance and androgen index were not measured. The oligomenorrhea/amenorrhea and polycystic appearance of ovaries were seen in more than two third of the PCOS patients.

All patients were on long protocol starting gonadotrophin releasing hormone analogue (Gn Rh) on midluteal phase of the proceeding menstrual cycle. After confirmation of down regulation (basal E2 level > 35 pg/ml.), ovulation induction was started using human menopausal gonadotrophin 3 ampoule per day, and the dose was adjusted according to response. When 3 or more leading follicles reaching 18-20 mms, 10000 IU of hCG was given, oocyte retrieval was done 34 hours later. Ultrasound guided intrauterine embryo transfer (ET) of 3 embryos was done after 48 hours.

The participants were divided in two groups. The first group (cabergoline group) comprised 30 women treated with 0.25 mg of cabergoline (Dostinex®, Pharmacia Italia S.P.A, Italy) every day for eight days commencing on the day of hCG administration. If OHSS occurred, the standard conservative and supportive management for OHSS was employed. The second group (control group) was comprised of 30women, who were similar to the former group with respect to age as well as the number and quality of the retrieved oocytes, number and quality of the transferred embryos, and the sperm quality. The latter group did not receive Cabergoline; however, their OHSS (if occurred) were managed conservatively according to our standard protocols after hospital admission. All OHSS patients were admitted to the hospital, and the diagnosis of OHSS as well as its severity was performed according to a standard definition.[9] The standard classification categorizes the disease based on its severity to mild, moderate, and severe OHSS. In mild OHSS, patients often report mild abdominal distention and soreness, nausea, vomiting, and ovarian enlargement between 5 to 12 cm. Moderate diseases were characterized by the presence of abdominal ascites on ultrasound examination. Severe diseases were diagnosed when there are clinical signs of tense ascites, hydrothorax, shortness of breath, hemoconcentration, hypercoagulability, or any complications of OHSS such as renal failure, thromboembolism, or acute respiratory distress syndrome (ARDS).[9]

The investigators filled out a standard questionnaire for each participant. Data were collected from the questionnaires through complete history taking, general examination.local examination, laboratory notes and ultrasound reports. Age, number of retrieved oocytes, number of follicles on day of hCG administration, assessment of mean ovarian diameter (MOD), estradiol level on the day of hCG administration were recorded. Chemical pregnancy was detected by the measurement of serum beta-hCG 14 days after the embryo transfer. The existence of clinical pregnancy was confirmed using transvaginal ultrasound scan, which was scheduled two weeks later to detect the gestational sac of pregnancy. Patients were followed until the detection of fetal heart pulsation. Early OHSS (mild, moderate and severe). Early OHSS was defined as the onset of the syndrome during the first 9 days after HCG administration. All of the patients were checked for any complaints or side effects of cabergoline, however, none of them reported any side effects.

Statistical analysis

Quantitative data are presented as mean ± SD. Quantitative and qualitative data were analyzed using Student's t test, and Chi-square or fisher's exact test, respectively. The data were analyzed using Statistical Package for Social Sciences (SPSS version 14, (SPSS Inc., Chicago, IL). A *p* value of less than 0.05 was considered statistically significant.

3- Results

The mean age was 27.47 years for cabergoline group and 27.87 years for control group, with no significant deference (*P* value= 0.626). Both groups are comparable for age. Also, there was no significant

difference between the two groups in terms of infertility duration, serum estradiol levels on the day of hCG administration, body mass index (BMI) and serum levels of FSH and LH (Table 1). Moreover, there was no significant difference between the number of follicles and mean ovarian diameter (Table 1). The incidence of OHSS in cabergoline group was 4 (13.3%) total cases, [3(10%) mild OHSS and 1(3.3%) moderate OHSS] and in control group was 13 (43.33%) total cases, [9(30%) mild OHSS and 4(13.3%) moderate OHSS]. Statistical evaluation showed significant deference between the incidence of OHSS in both groups (*P* value =0.035) (Table 2). The incidences of no, mild and moderate and OHSS in cabergoline-treated groups were 86.7%, 10% and 3.3%, and in the control group were 56.7%, 30 %, 13.3%, respectively (Table 2). There was significant deference between the studied groups according to chemical pregnancy, positive serum β HCG (*P* value =0.039) (Table 2). There was significant deference between the studied groups according to fetal heart pulsation (*P* value =0.028) (Table 2).

Table 1: Baseline characteristics of patients in cabergoline-treated and control groups

Baseline characteristics	Cabergoline (n=30)	Control (n=30)	*P* value
Age (year)	27.47±2.18	27.87±1.53	0.626
Duration of infertility(Year)	6.67±2.28	6.27±1.86	0.459
E_2 level(pg/ml)	3610.3± 842.65	3686.6± 834.76	0.726
Number of follicles	16.3±2.52	17.37±2.13	0.82
Mean ovarian diameter MOD(cm)	7.43±2.11	8.3±2.07	0.114
BMI (kg/m^2)	24.86±6.83	24.08±3.65	0.596
FSH (IU/L)	5.88±1.5	5.54±1.6	0.90
LH (IU/L)	7.28±2.1	5.21±1.9	0.78

Values are presented as mean± SD or frequency (percent).

Table 2: The outcomes of ovarian stimulation in cabergoline-treated and control groups

Outcome of ovarian stimulation	Cabergoline (n=30)	Control ((n=30)	*P* value
OHSS	4(13.33%)	13 (43.33%)	0.001
No	26(60.5%)	17(39.5%)	0.08
Mild	3 (25.0%)	9 (75.0%)	0.023
Moderate	1 (20.0%)	4 (80.0%)	0.047
Chemical pregnancy(Positive β HCG)	19(63.3%)	11 (36.7%)	0.039
Clinical pregnancy(Positive fetal heart pulsation)	17(89.5%)	5(45.5%)	0.028

Values are presented as mean ±SD or frequency (percent). HCG; human chorionic gonadotrophins; OHSS; ovarian hyperstimulation syndrome.

4- Discussion

OHSS is an iatrogenic complication of ovarian stimulation that occurs during either the luteal phase or early pregnancy. The most common form occurs a few days after the induction of the follicular rupture following the administration of hCG when follicular growth has been medically induced. The most serious and potentially life threatening iatrogenic complication of COH is a severe form of OHSS. OHSS has been treated empirically over the years, because it is pathophysiology remained unknown, the underlying feature of OHSS is increased capillary permeability leading to a fluid shift from the intravascular space to third space compartments. As this is an iatrogenic complication of a non-vital treatment with a potential fatal outcome, the syndrome remains a serious problem for specialists dealing with infertility. [14]

Cabergoline, a dopamine agonist inhibiting VEGFR-2 phosphorylation and signalling, effectively reduced the incidence of OHSS and cycle cancellation without any adverse effects on pregnancy. The findings of the present study are in agreement with those of previous studies.[3,5,6,10]. Considering the physical and psychological consequences along with medical costs like hospitalization, every intervention to decrease VEGF expression or antagonizing its effects would be valuable.

The ovary is the main source of cytokines and VEGF, which are mediators that cause increased

capillary permeability and ascites. It has been suggested that parameters of ovarian activity during stimulation such as serum levels of estradiol and number of oocytes retrieved correlate closely with VEGF gene expression.[1] Cabergoline decreases the phosphorylation of VEGFR2.[10] Animal studies have demonstrated that the expression of gene for tyrosine hydroxylase enzyme, which is the rate-limiting enzyme in dopamine synthesis, is significantly lower in rats with overstimulated ovaries.[11] High VEGF expression and activity in OHSS seem to be associated with reduced dopamine production. Cabergoline significantly reduced VEGFR2-dependent vascular permeability in rats with OHSS. Moreover, serum levels of progesterone and rates of luteal apoptosis remained unchanged, suggesting the absence of a luteolytic effect of cabergoline.[12]

Alvarez and colleagues,[3] conducted a randomized, placebo-controlled double-blind clinical trial in oocyte donors at risk of OHSS, and found that the incidence of moderate or severe OHSS was significantly reduced in the cabergoline-treated group, without an adverse effect on ovarian function. In a retrospective analysis,[6] Alvarez and colleagues showed that implantation and clinical pregnancy rates in women who received cabergoline for the prevention of OHSS was similar to those in women matched for age, embryo quality, and semen parameters.

Another study,[13] compared early OHSS, defined as the onset of the syndrome during the first nine days after HCG administration, and late OHSS, characterized by the onset of the syndrome after 10 days after HCG administration. Cabergoline decreased the risk of early OHSS significantly. There was significant difference between the two groups in terms of pregnancy.[13] Though not a randomized clinical trial, the findings of our study, namely decreasing the incidence of early OHSS, are in agreement with those of such a report.[13] Although the incidence of mild OHSS decreased. Moreover, the effects of the cabergoline found in the present study are in agreement with those of previous publications.[3-6,10]

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