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IN VITRO FERTILIZATION

The effect of cabergoline on folicular microenviroment profile in patients with high risk of OHSS

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Abstract

The aim of this study to evaluate the effect of cabergoline on follicular microenvironment by measuring follicular fluid (FF) insulin like growth hormone –I (IGF-I), antimullerian hormone (AMH), inhibin B and hepatocyte growth factor (HGF) levels in women with PCOS and high risk of ovarian hyperstimulation syndrome (OHSS). In this prospective cohort study, 41 women with PCOS undergoing controlled ovarian hyperstimulation for assisted reproduction and having the high risk factors for OHSS are included. The women in the study group ($n = 15$) received cabergoline for OHSS prevention while the women in the control did not received any medications for OHSS prevention. FF samples were collected during oocyte pick-up procedure for all women were determined using commercially available ELISA kits. Concentrations of FF IGF-I, AMH, inhibin B and HGF were assessed. In the study group FF AMH (2.96 ± 1.27 versus 1.91 ± 0.64 ng/mL), Inhibin B (1339.47 ± 198.56 versus 1200.09 ± 133.64 pg/mL), HGF (5623.21 ± 2411.09 versus 3787.42 ± 2269.89 pg/mL) and IGF-I (298.60 ± 37.80 versus 219.90 ± 71.40 pg/mL) concentrations were significantly decreased compared with control group. Cabergolin prevents OHSS in high risk patients by disrupting FF hormone microenvironment.

Keywords

AMH, cabergoline, follicular fluid, IGF-I, inhibin B, HGF, ovarian hyperstimulation syndrome

History

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Introduction

Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic serious and potentially fatal complication of ovarian stimulation, affecting 1–14% of all IVF/ICSI cycles [1]. In severe form, massive enlargement of ovaries that leads to sequestration of fluid in to third space resulting, hemoconcentration, ascites, pleural effusion, coagulopathy and reduced organ perfusion [2–4]. Hospitalization is needed for 1.9% of the cases [5]. In brief, OHSS can be classified into early and late form. In early form, which is caused by human chorionic gonodotropin (HCG) induced ovarian response and is detected 3-9 days after HCG administration. Late form is related to endogenous HCG and is diagnosed 10–17 days later [6]. In both types needs serum HCG levels to increase [7].

Dopamine agonists have been proposed as a prophylactic treatment for OHSS in women with high risk of OHSS; however, the possible mechanism of action has not been clearly known [8,9]. In experimental studies, inhibition of vascular endothelial growth factor based pathway was proposed as a possible action of mechanism of dopamine agonists [10,11]. However, the role hepatocyte growth factor (HGF), insulin like growth factor-I (IGF-I), inhibin B and antimullerian hormone (AMH) on cabergoline action in OHSS prevention has not been known.

HGF is an 87-kDa growth factor which has angiogenic and proliferative effects in primary epithelial cell cultures. Within the ovary, HGF controls numerous key functions which collectively regulate the growth and differentiation of ovarian follicles; these include cell growth, steroidogenesis, and apoptosis within theca cells and/or granulosa cells [12]. HGF also have angiogenic effects [13]. HGF in theca cells in bovine ovary first demonstrated by Parrott than subsequent studies demonstrated HGF in granulosa cells [14,15]. HGF level in follicular fluid (FF) may help to understand the cabergoline effect on OHSS prevention.

Insulin-like growth factors which are proinsulin-like small peptides plays a major role in autocrine and paracrine regulation follicular development. Especially, IGF-I is related to gonodotrophin dependent stimulation of steriodogenesis [16,17].

Anti-Mullerian hormone (AMH) and Inhibin-B are also related to follicular responsiveness to FSH [18,19]. AMH suppresses steroidogenesis in human granulosa cells [20]. It also reflects the follicle pool of the ovary [19,21,22]. Inhibin B is the member of the TGF-β superfamily and suppresses FSH secretion from the pituitary without affecting LH secretion [18,19]. All these cytokines have special role in ovarian folliculogesis and oocyte maturatiin. These cytokines may also have role on OHSS pathogenesis. To our best of knowledge, there is no study in the literature reporting the effect of cabergoline on FF microenvironment in women with high risk of OHSS.

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The objective of this study is to compare the FF IGF I, AMH, inhibin B and HGF levels between cabergoline administered and not administered group. In those terms, we aim to reveal cabergoline effect on follicular microenvironment.

Materials and method

In this prospective age and body mass index (BMI) matched cohort study, a total of 41 women with PCOS diagnosed and treated for primary infertility at the Department of Obstetrics and Gynecology, Etlik Zubeyde Hanim Womens' Health and Teaching Hospital were included. Polycystic ovary syndrome was diagnosed according to the criteria of the Rotterdam (European Society of Human Reproduction and Embryology/ American Society for Reproductive Medicine-sponsored PCOS consensus workshop group) [23]. The protocol was approved by the Institutional Ethical Research Committee.

The study duration was planned as 1 year. In the first 6 months of the study, all women having the inclusion criteria were allocated to study group. Following women with PCOS and high risk for OHSS study group ($n = 15$) allocation, in the second 6 months of the study, women who were age- and BMI-matched with the study group were selected for the control group. During the study period, following assessment of the number of patients having the inclusion criteria and admitted in the second 6 months of the study were higher than the number of patients who admitted in the first 6 months of the study, we decided to have the control group as 1:2 matched. However, at the end of the study duration we had only 26 patients for control group. Matching was performed on day of HCG.

Main inclusion criteria were development of more than 14 leading follicles larger than 10 mm and serum estradiol more than 3000 pg/ml at the end of ovulation induction with long luteal ovulation induction protocol. The patients in study (15 patients) was administered cabergoline (Dostinex tablet, Phizer, Istanbul, Turkey, started on day of HCG, 0.5 mg/day for 8 days) for prevention of OHSS, the patients ($n = 26$) in the control group had no manipulation for prevention of OHSS and age-, BMI-matched with the study group. OHSS was diagnosed and classified as described by Humaidan P et al. [24]. Mild OHSS was described as the presence of pelvic discomfort, abdominal distension, ultrasonic evidence of ascites in pouch of Douglas and enlarged ovaries. Moderate OHSS was described as the presence of pelvic discomfort, abdominal distension, ultrasonic evidence of ascites in pouch of Douglas and pelvis, enlarged ovaries and abnormal hematological profiles (Hematocrite >45%). In the presence of severe OHSS, the following objective (fluid in pouch of Douglas, fluid around uterus (pelvis), fluid around intestinal loops, hematocrite >45%, white blood cells >15,000/mm^3, low urine output <600 mL/24 h) and subjective criteria (pelvic discomfort, abdominal distension, breathing difficulty, ovarian enlargement and pregnancy occurrence should be present.

All patients included in study were administered long luteal protocol for ovulation induction. For pituitary down regulation leuprolid asetat 1.0 mg (Lucrin daily 5 mg, Abbot, Istanbul, Turkey) was started mid-luteal phase of the previous cycle. After pituitary down-regulation, the agonist dose was reduced to half, and recombinant FSH (Gonal-F; 150 IU/day, Serono, Geneva, Switzerland) was added until either the leading follicle reached a mean diameter of 18 mm or two or more follicles reached a diameter of 17 mm. Than recombinant HCG (Ovitrelle, Serono, Geneva, Switzerland 250 μg) was administered and transvaginal oocyte retrieval was performed after 36 h later. The luteal phase was supported daily with 8% progesterone gel (Crinone, Serono) starting on the day of oocyte retrieval, and continuing for another 6–8 weeks in cases in which a pregnancy was achieved. A single high quality day 3 embryo transfer was performed.

Morphology of oocyte and embryo quality assessments were performed based on previously reported scoring system [25,26]. Basically, abnormal features of oocyte were grouped as extracytoplasmic, including fragmented first polar body, abnormal first polar body, large perivitelline space, abnormal zona pellucida and abnormal oocyte shape; and cytoplasmic, including vacuoles, granularity, refractile body and brown oocytes. Morphologically evaluated oocytes were scored from best to worst as Score 7; MII oocyte with no abnormal feature, Score 6; MII oocytes with one abnormal feature, Score 5; MII oocytes with more than one abnormality, Score 4; MI oocyte with no abnormal feature, Score 3; MI oocytes with one abnormal feature, Score 2; MI oocytes with more than one abnormality and finally Score 1 for GV with any abnormality. Day 3 embryo was scored from best (point 5) to worst (point 1) based on the previously reported embryo evaluation criteria including, the number and equality of blastomeres, the percentage of fragmentation and the existence of multinucleus [25,26].

FF samples were collected in whole group, on day of oocyte pick-up. FF was obtained from the puncture of ovarian follicles (14–20 mm in diameter). The FF was obtained only from the follicles that had an mature (MII) egg. Following the removal of the oocytes, FF was processed by centrifuge at 500 × g for 15 min to separate out cellular contents and debris. Samples of FF visibly contaminated with blood were excluded from the study. The supernatant was transferred to sterile polypropylene tubes and was stored at −70 °C until assayed.

Four markers (Antimullerian hormone, Inhibin B, Hepatocyte growth factor, Insulin like growth factor-1) with commercially available ELISA kits were studied in FF samples. IGF-1 (catalog number ELH-IGF1-001, RayBiotech, Inc., Norcross, USA), HGF (catalog number ELH-HGF-001, RayBiotech, Inc, Norcross, USA), AMH (catalog number DSL-10-14400, Diagnostic Systems Laboratories, Webster, TX, USA) and inhibin B (catalog number DSL-10-84100i, Diagnostic Systems Laboratories) concentrations were measured by ELISA.

The intra- and inter-assay coefficients of variation were as follows: for AMH 3.3% and 4.8%; for IGF-1 < 10% and <12%; for inhibin B 3.5% and 6.2%; for HGF < 10% and <12%, respectively.

Statistical analysis

FF hormones concentrations were compared between the study and control groups using a Chi-Square test. The statistical software package SPSS (version 11.0; SPSS Inc., Chicago, IL) was used for the statistical analysis, and results were considered statistically significant at p values of <.05. Clinical pregnancy was defined as the presence of a gestational sac with accompanying fetal heart beats under ultrasound 4 weeks after embryo transfer.

Results

A total of 41 FF samples and the corresponding oocytes with mature nuclei at metaphase II were collected. The comparsion of some clinical and laboratory characteristics in cabergoline administered group (group I), and control group (group II) are given in Table 1.

Oocyte quality score in cabergoline administered group was 5.56 ± 0.44 compared to 4.27 ± 1.54 in control groups; $p < 0.05$. However, there was no statistically significant difference in embryo quality score in both groups.

In the study group FF AMH (2.96 ± 1.27 ng/ml versus 1.91 ± 0.64 ng/ml, $p = 0.005$), Inhibin B (1339.47 ± 198.56 pg/ml versus 1200.09 ± 133.64 pg/ml, $p = 0.021$), HGF (5623.21 ± 2411.09 pg/ml versus 3787.42 ± 2269.89 pg/ml,

Table 1. Comparison of some clinical and laboratory characteristics in cabergoline administered group (group I), and control group (group II).

Parameter	Group I ($n=15$)	Group II ($n=26$)	p Value
Female Age (yr.)	25.00 ± 3.60	28.61 ± 4.50	NS
Cycle number (no.)	1.53 ± 0.52	1.46 ± 0.50	NS
Infertility duration (yr.)	4.86 ± 1.40	4.23 ± 1.03	NS
Cause of infertility (%)			
PCOS + Mild male infertility	4 (26.7%)	6 (23.1%)	NS
Only PCOS	11 (73.3%)	20 (76.9%)	
Body mass index (kg/m^2)	22.67 ± 1.55	24.49 ± 3.20	NS
Basal antral follicle count (no.)	14.40 ± 1.30	14.46 ± 1.17	NS
Amount of total FSH used (IU/L)	1912.00 ± 233.33	1769.23 ± 310.83	NS
Length of ovarian stimulation (day)	10.20 ± 1.15	10.53 ± 1.10	NS
Mean E2 on HCG day (pg/mL)	3580.67 ± 376.78	3582.35 ± 292.12	NS
Mean number of oocytes retrieved (no.)	17.60 ± 8.69	17.53 ± 8.34	NS
Mean number of MII oocytes retrieved (no.)	11.80 ± 6.10	13.00 ± 4.08	NS
Mean oocyte quality score (no.)	5.56 ± 0.44	4.27 ± 1.54	0.025
Mean day 3 embryo quality score (no.)	4.05 ± 0.57	4.24 ± 0.62	NS
Fertilization ratio (%)	89.33%	90.10%	NS
Mean number cryopreserved embryo (no.)	4.60 ± 2.20	4.93 ± 1.82	NS

Values are given as mean ± SD or number of patients (percentage).
NS; non-significant. Mann–Whitney U test or Chi-square tests were used for comparison.

$p=0.021$) and IGF-1 (298.60 ± 37.80 pg/ml versus 219.90 ± 71.40 pg/ml, $p<0.001$) concentrations were significantly decreased compared with control group.

No cases of OHSS were observed in cabergoline administered group, while the OHSS rate was 57.7% (15 patients) in control group. In control group, 13 patients (50.0%) developed mild OHSS, two patients developed moderate OHSS. For all women with OHSS; OHSS was resolved with supportive therapy. There was no statistically significant difference in clinical pregnancy rates between study and control groups (46.7% in cabergoline administered group versus 42.7% in control group, $p>0.05$).

Discussion

The prevention of OHSS is important for clinician since it is the most serious complication related to assisted reproduction techniques. The improvements in the understanding of the pathophysiology of OHSS makes possible to introduce alternative treatment modalities. Cabergoline, dopamine agonist, is associated with significant reduction in the incidence of symptoms and sign in severe and moderate OHSS, and also significantly reduces the chance of developing OHSS [24].

Gomez et al. revealed that low dose cabergoline, dopamine receptor 2 agonist, reverses vascular endothelial receptor 2 (VEGF-2) dependent vascular permeability without affecting luteal angiogenesis [10]. Cabergoline minimizes VEGF-2 phosphorylation through binding to receptor than this leads to increases VEGFR- endocytosis in endothelial cells [10,27]. However in other growth factors, changes have not been investigated between the patients who received cabergoline or not. In our study, the aim was to investigate the follicular microenvironment differences between in cabergoline administered group and not administered group. AMH, Inhibin B, HGF, IGF1 levels are compared between two groups. Levels of AMH, Inhibin B, HGF, and IGF1 are significantly lower in cabergoline administered group. Inhibin B and AMH may predict the OHSS status because they are good indicators of ovarian response to FSH stimulation and can thus predict the number of responding follicles according to literature [28,29].

In this study, it is revealed that the cabergoline received group has lower AMH levels. Literature showed that folicular fluid AMH levels negatively correlated with age and total gonadotropin dose and positively correlated with the number of mature follicles on hCG day [19]. In our study also similar correlations between AMH and age and total gonadotropin dose were found. AMH levels are markedly elevated in PCOS patients, this finding may help to explain the cabergoline influence on reducing severity of OHSS [18,19,30]. Also it has been suggested that AMH may reduce both aromatase activity and the number of LH receptors in FSH-stimulated granulosa cells [31]. By this way AMH probably suppress the steroidogenesis in granulose cells [20]. This may explain the effects of the cabergoline on reducing severity of OHSS other than VEGF phosphorylation pathway.

According to the previous studies, as AMH there is a positive correlation between inhibin B levels and number of follicles, number of oocytes retrieved, and embryo scores [32,33]. In one study, higher serum Inhibin B concentration in the OHSS group during the gonadotropin stimulation and also at the day of oocyte retrieval were reported [34]. However, another study was failed o find significant relationship between elevated FF inhibin B and OHSS [18]. Inhibin B was found to be lower in cabergoline received patients in our study. Inhibin B is produced in and released from the ovarian granulosa and luteal cells, so inhibin B reflects the developing cohort of follicles in the cycle [28]. Thus, decreasing levels of inhibin B may help to explain action of cabergoline in our study.

In this study, HGF levels in FF was also investigated. It was revealed that several intraovarian growth factors work with the gonadotropins and facilitate the folliculogenesis through an array of autocrine and paracrine mechanisms which control follicle growth and steroidogenesis. FSH stimulates a profound increase in cyclic AMP production in granulosa cells. This may trigger cascade of events like steroidogenesis [12]. HGF acts through protein tyrosine kinase (PTK) domain and initiates a cascade of events that leads to follicular growth and ovulation [12,35]. In one experimental study, the authors found that HGF increase granulosa cell proliferation, the number of pre-antral and early antral follicles in ovary organ cultures and a significant increase in the diameters of follicles in individual follicle cultures [36]. The role of HGF in pathogenesis of OHSS has not been investigated. Based on above study [36] findings HGF may be involved in the pathogenesis of OHSS by increasing the number of granulose cell and also stimulating the expression of the FSH receptors.

In our study, we found that HGF levels were lower in cabergoline administered group that was statistically significant. Cabergoline may decrease the HGF induced granulose cell proliferation and follicle size increment and all these effects may decrease the incidence of OHSS.

Another marker that investigated was IGF1 which is potent anabolic agents, structurally related to insulin, and can influence growth processes in every system of the body and also in ovarian folliculogenesis. This stimulating effect is modulated by binding proteins (IGFBPs). IGF-I stimulates steroidogenesis in synergy with gonadotrophins and the activity of aromatase; in addition, it modulates the effects of FSH and LH [16,37–39]. The IGF-I induced granulose cell estradiol production in folliculogenesis has been reported previously [40]. In this study, we observed that cabergoline administered group has lower IGF-1 levels. This may suggest that cabergoline may decrease the FF IGF-1 levels, which may than decrease the estradiol levels. This event may consequently improve the severity of OHSS.

We believed that cabergoline for patients with high risk factors for OHSS disrupt FF micro environment by decreasing the levels of growth factors (AMH, HGF, IGF-I and inhibin B) for folliculogenesis. Cabergoline decreases the incidence of OHSS and also increases the oocyte quality scores by decreasing estradiol production stimulatory ovarian growth factors. The half-life elimination of cabergoline is 63–69 h, the time to peak is 2-3 hours [41]. The rapid action on FF growth factor levels may be attributed to the rapid action of cabergoline.

To our knowledge, the role of cabergoline in the pathogenesis of OHSS prevention via FF growth factors levels has not been described in such a group of women with PCOS. The main limitation of this study is the low number of patients in both groups.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing the article.

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