



Research Article

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Evaluation of the efficacy of the addition of Diosmin to cabergoline for the prevention of ovarian hyperstimulation syndrome in high-risk women undergoing assisted reproductive technology

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Abstract

Background: The most serious iatrogenic complication of ovarian stimulation using fertility medications- is considered Ovarian Hyper-stimulation Syndrome (OHSS). The pathogenesis of OHS is attributed to increased vascular permeability causing too much fluid to move from intravascular space into the interstitial space. This can cause potentially serious problems such as dehydration, hypotension and reduced cardiac output. **Objective:** To investigate the value of using combined diosmin and cabergoline versus using cabergoline alone in avoiding OHSS in high-risk women exposed to assisted reproductive technique. **Methods:** A prospective cohort study- was carried upon 100 women suspected to be at high-risk for developing OHSS. They were randomly divided into two groups; group I (50 women) received diosmin in addition to cabergoline and group II (50 women) received cabergoline only. After oocyte retrieval, regular assessment clinically and by ultrasonography for all patients- were carried out to detect any evidence of OHSS. **Results:** The incidence of OHSS was reduced in group I (receiving diosmin combined with cabergoline) than group II (receiving cabergoline alone) 7.3% versus 16.2% respectively, with a statistically significant value($p=0.05$). Only, one case of group II developed severe OHSS. No difference in clinical pregnancy rate was recorded between both studied groups. Freeze-all practice was applied to 22 cases of our studied cases. **Conclusion:** The current study showed that combined use of diosmin and cabergoline- in high-risk women undergoing ART- was competent in avoiding OHSS than using cabergoline alone. Moreover, this combination does not affect pregnancy rate, miscarriage nor multiple pregnancy.

Keywords: Diosmin, Cabergoline, Ovarian hyperstimulation syndrome (OHSS).

INTRODUCTION

Ovarian hyperstimulation syndrome (OHSS) is a known serious iatrogenic complication of ovulation induction in controlled ovarian stimulation cycles [1].

The incidence of OHSS is mild in 33% of the cases, moderate in 3–6% of the cases with severe cases reaching only 0.1–2% [2,3]. The pathophysiology of OHSS remains unknown, however it is believed to be mediated by the administration of human chorionic gonadotrophin (hCG) in controlled ovarian stimulation (COS) cycles [4]. Human chorionic gonadotrophin (hCG) or luteinizing hormone (LH) following controlled ovarian stimulation by follicle-stimulating hormone (FSH) is responsible for most cases of OHSS.

It is the hCG action on the stimulated ovaries that leads to the production of numerous proinflammatory mediators with vascular endothelial growth factor (VEGF) as the chief player [5]. Numerous other mediators have been linked to the disease process such as angiotensin II, interleukin-6, insulin-like growth factor 1 (IGF-1) [6], epidermal growth factor (EGF), transforming growth factors (TGF) a and b, basic fibroblast growth factor (BFGF) and platelet-derived growth factor (PDGF [7–9]). Vascular endothelial growth factor-A (VEGF-A) acts on VEGF receptor-2 (VEGFR-2) causing angiogenesis and vascular hyperpermeability.

Thus, the increase of VEGF-A in OHSS is responsible for the increased vascular permeability [10,11]. The role of VEGF in increased vascular permeability has been demonstrated in stimulated female rats. [12].

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The increased capillary permeability leads to fluid shift to the third space [1] which in turn results in ascites or, pleural and pericardial effusions in more severe cases. Women categorized as severe cases are usually presented by hypovolaemia, with a loss of almost 20% of their calculated blood volume [13].

Cabergoline administration was shown to reduce the incidence of OHSS in women with polycystic ovarian syndrome and hyperprolactinemia [14]. Several animal and human studies confirmed the safety of cabergoline use during infertility treatment: fertilization, implantation and pregnancy [15]. Four systematic reviews have revealed that cabergoline reduces the incidence of moderate and/or severe OHSS without affecting implantation, pregnancy, and miscarriage rates [16].

Micronized purified flavonoid fraction (MPFF) is a semisynthetic drug which is composed of 90% micronized diosmin and 10% hesperidin [17]. MPFF is used to treat varicose veins and venous ulcers, hemorrhoids and lymphatic insufficiency [18]. MPFF exerts a venotonic action in these conditions leading to decrease in venous reflux and relieve of the edema through providing effective venous drainage [19]. Diosmin is a hesperidin-derivative bioflavonoid. Flavonoids have been demonstrated to exert anti-platelet, anti-ischemic, anti-allergic, and anti-inflammatory activities [20]. Diosmin can also reduce the release of inflammatory mediators, such as prostaglandin E2 (PGE2) and thromboxane A2 (TxA2) [21]. As MPFF decreases vascular permeability more than any of its single constituents, this suggests that the flavonoids present in its formulation have a synergistic action [22]. In a study on 20 patients with chronic venous disease, VEGF plasma levels were significantly decreased (98–57 pg/ml) in the patients after treatment with MFFP (Diosmin 500 mg twice daily for 60 days) [23].

Aim of the study

This study aimed at investigating the efficacy of combined use of diosmin and cabergoline versus using cabergoline alone- in avoiding OHSS in women undergoing ART, expected to be at high-risk

PATIENTS & METHODS

Study design and study women

This was a prospective interventional comparative clinical trial carried out at Gynaecology & Obstetric Department of Benha University Hospital and a private fertility centre, from April 2019 through December 2019. Ethical committee of Benha Faculty of Medicine approved the study protocol.

Patients who joined the study- were infertile females going- through intracytoplasmic sperm injection (ICSI) treatment who were categorized as high risk for OHSS.

High risk women for OHSS were defined as: previous occurrence of OHSS or > 24 antral follicles of the ovaries on base-line ultrasound examination (polycystic ovary) or during ovarian stimulation- increased number of small follicles (8- 12 mm) or high AMH (> 3.0 ng/mL) or rapidly rising serum E2 or high serum E2 at HCG trigger (>300 pg/ ml) or presence of >20 follicles on the day of retrieval, by ultrasound examination or >20 oocytes retrieved.

All participating women were given information leaflet about the study. A written informed consent was obtained from each participant.

All participating women underwent complete clinical, hormonal and ultrasound evaluations.

A hundred females joined after fulfilling the requirements. They were divided randomly into two groups; group I (50 women) received diosmin; 2 tablets (500mg) t.d.s for 2 weeks, in addition to cabergoline; 1 tablet (0.5 mg)/ day for 8 days, both were given orally starting at the

day of HCG injection. Group II (50 women) received cabergoline only; 1 tablet (0.5 mg)/day for 8 days, orally starting at the day of HCG injection.

Randomization and allocation to the groups was performed online by Research Randomizer.

COS procedures

The superovulation regimen used was long regimen using gonadotropin-releasing hormone agonist (GnRHa). All women had 1.3 mg of long-acting GnRHa (triptorelin acetate; Decapeptyl, Ferring, Germany) injected subcutaneous once daily in the abdomen on day 20

to suppress the pituitary. Intramuscular injection of Recombinant human follicle stimulating hormone (rhFSH Gonapur, Minapharm, Egypt) was given on day 3 of the next menstrual cycle, at an initial dose of 150- 300 U/day and subsequently modified daily according to follicle growth.

hCG was given on finding more than two dominant follicles having diameters of at least 18mm. Ultrasound follicular puncture was carried out 36 hours later- to retrieve the oocyte.

Follicular development was monitored by ultrasound

An intramuscular injection of 10 000 U of hCG (Choriomon, IBSA, Italy) was administered when the average diameter of two dominant follicles or more exceeded 18 mm . , and Oocyte retrieval was then performed 34 to 36 hours later by ultrasound-guided aspiration of the mature follicles.

Grading and diagnosis of OHSS

Ovarian hyperstimulation syndrome was confirmed and graded according to Golan classification. Golan classification combines various clinical and sonographic parameters to classify OHSS into different grades ranging from mild to severe. We mainly focused on moderate and severe grades. Women who complained from nausea, vomiting or ultrasound evidence of enlarged ovaries (5–12 cm) and/ or the detection of ascites defined the occurrence of moderate OHSS (24). However, ascites that can be detected clinically or hydrothorax detected by ultrasound or chest X-ray would grade the women as severe OHSS. Severe OHSS, was also confirmed in women complaining of oliguria or changes in blood tests as increased haematocrit level (>45%) or decreased S. albumin (<35 g/l) or increased blood viscosity. Cases with suspected severe OHSS or oliguria were hospitalized. Baseline clinical and ultrasound examinations were obtained from all cases on the day of embryo transfer, and then weekly until confirmation of pregnancy or occurrence of menstrual bleeding to detect the occurrence of OHSS. All patients had contacts to the fertility unit and/or emergency gynaecology unit if they experienced adverse effects and they were given written information of warning signs as vomiting, decreased urine volume, dizziness on standing, abdominal pain, enlargement of the abdomen and rapid weight gain. Cases were reviewed by qualified gynaecologist and appropriately managed. Women who were diagnosed with OHSS had more frequent appointments as an outpatient basis via phone contact or visits - until menstruation occurred or until fetal heart activity was detected in pregnant patients.

Statistical analyses

Statistical Analysis were done using statistical package (SPSS version 19, Armonk, NY, USA). The characteristics of study women included age, body mass index (BMI), duration of infertility, antral follicle count, length of stimulation, and retrieved oocytes number. . The observed incidence of moderate or severe OHSS, including more details on the average size of the ovary on the day of oocyte retrieval, full blood count values as white blood cell (WBC) count, and haematocrit at days 0 and 3 after oocyte retrieval were compared between the study groups.

Data were entered as numerical or categorical as appropriate and were described as mean and standard deviation. Categorical variables were described using frequency and percentage of the total. For non-normally distributed data, comparisons between two studied independent groups were carried out. Results were considered statistically significant when p value was less than 0.05.

The primary outcome of the study was the development of moderate and severe OHSS in participating women. Additional outcomes were clinical pregnancy rate and implantation rate.

RESULTS

One hundred women were recruited in this study. The clinical characteristics of the diosmin and combined groups are summarized in Table 1. There were no significant differences in basic characteristics

such as age, BMI, antral follicle count, number of retrieved oocytes, or length of stimulation between the two groups. Cycle characteristics are summarized in Table 1.

There was a statistically significant reduction (P=0.005) in the incidence of OHSS in group I (Diosmin+cabergoline) (7.3%) compared to group II (Cabergoline group) (16.2%) as shown in Graph 1. In our sample, only one case of severe OHSS was developed, this was in the group II (Cabergoline group). There was no difference in clinical pregnancy rate between both groups. Twenty-two cases of the whole sample underwent a freeze-all policy. There was only one case with severe OHSS in the cabergoline only group.

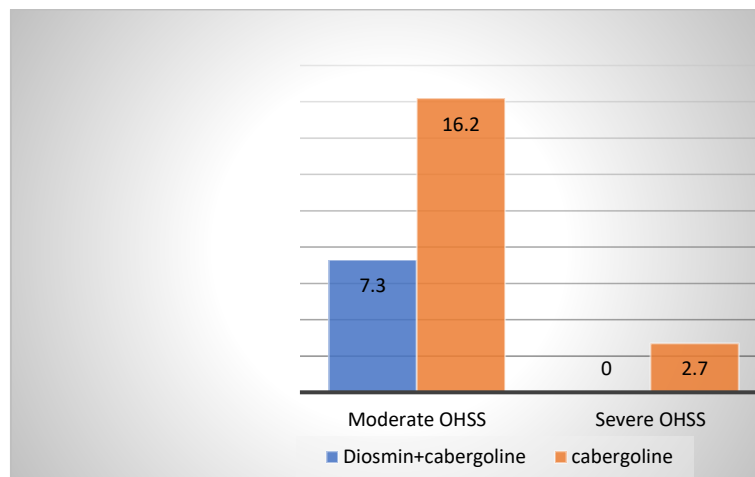
The secondary outcomes concerning fertilization, implantation, clinical pregnancy, and multiple pregnancy rates between groups showed no statistically significant differences (Table 2).

Table 1: Demographic characteristics and infertility status of women in both studies groups

| | Diosmin + Cabergoline group (n=41) | Cabergoline group (n=37) | P value |
|-----------------------------------|------------------------------------|--------------------------|---------|
| Mean age (years) | 28.1±4.8 | 29.1±5.7 | 0.17 |
| Number of FSH ampules (75 IU/Amp) | 27.83± 3.96 | 28.49±4.07 | 0.19 |
| years of infertility | 6.0±3.4 | 5.8±2.9 | 0.53 |
| Antral follicle count | 23.9±3.0 | 23.6±3.3 | 0.41 |
| BMI (kg/m ²) | 25.0±4.1 | 25.3±3.9 | 0.68 |
| Days of ovulation stimulation | 9.6±2.1 | 9.4±1.6 | 0.47 |
| Retrieved oocytes | 21.96±4.92 | 21.84±4.8 | 0.93 |

Table 2: Intracytoplasmic ICSI outcomes between both studied groups

| | Diosmin + cabergoline group (n=41) | Cabergoline group (n=37) | Z test | P value |
|--------------------------------|--------------------------------------|-------------------------------------|--------|---------|
| Fertilization rate (%) | 29/41 (70.7%) | 26/37 (70.2%) | 0.155 | 0.76 |
| Implantation rate (%) | 34/123 (27.64%) | 30/111 (27.03%) | 0.105 | 0.91 |
| Clinical pregnancy rate n (%) | 24/41 (58.5%) | 21/37 (56.7%) | 0.158 | 0.87 |
| Multiple pregnancy rate n (%) | 8/41 (9.75%) 2 triplet 6 twins | 7/37 (18.9) 2 triplet 5 twins | 0.066 | 0.94 |
| First trimester miscarriages n | 5/41 (12.19%) | 6/37 (16.21%) | -0.509 | 0.61 |



Graph 1: The percentage of cases who developed OHSS per group

DISCUSSION

This study evaluated the efficiency of cabergoline and diosmin in combination for preventing OHSS in high-risk women undergoing ART treatment in comparison to cabergoline alone. This is the first study to compare cabergoline combined with diosmin versus cabergoline alone in preventing moderate to severe OHSS in high-risk group (this is according to the best of our knowledge at the time of submission of the study).

Diosmin acts by inhibiting phosphorylation of VEGFR2, thus avoiding the increase in vascular permeability [25]. Promising results were obtained -when given to women with risk of developing OHSS after COS- if given in a daily dose of 0.5 mg starting on the day of hCG administration [26, 27]. Cabergoline on the other hand, increases adverse events mainly in the form of gastrointestinal symptoms [27].

A Cochrane systematic review in 2016 concluded that Dopamine appears to reduce the incidence of moderate and severe OHSS in high-risk group; without affecting the outcome of pregnancy if a fresh embryo transfer is performed [28]. The Cochrane review also showed no evidence of a difference between a dopamine agonist plus another active treatment versus another active treatment on the incidence of moderate or severe OHSS and live birth rate. However, the other active treatments included albumin, hydroxyethyl starch (HES) or prednisolone. Diosmin was not included in that Cochrane review [28].

Li et al., examined the efficacy of diosmin in preventing OHSS compared to placebo. Their study on 147 patients showed lower incidence of OHSS in diosmin group [29]. Saad et al., performed a study on 200 high risk women comparing cabergoline to diosmin in preventing moderate and severe OHSS. Diosmin was more effective in preventing severe OHSS rates than cabergoline [16].

The use of diosmin was successful in tackling the pathogenesis and complications of OHSS. There is evidence that diosmin is effective in decreasing the rate of moderate and severe cases of OHSS with a good safety profile concerning the implantation, pregnancy, and miscarriage rates [29]. There is a reasonable safety profile of using Diosmin in pregnancy. No embryo toxicity, nor any other significant effects on reproductive function were reported on the use of diosmin in pregnancy and the transplacental migration and passage into breast milk are minimal [30].

In this study, the addition of Diosmin to cabergoline significantly decreased the incidence of OHSS (7% compared to 14%) in high-risk women without affecting pregnancy rate, miscarriage or multiple pregnancy. Cabergoline is believed to be used to restrict the occurrence of OHSS. Diosmin decreases the level of VEGF and capillary permeability, so the combination may control both the pathogenesis and pathophysiology of OHSS. Diosmin is a cheap, well tolerated and readily available drug that has a good safety profile in pregnancy.

CONCLUSION

This study concluded that the combination of diosmin and cabergoline significantly reduced incidence of OHSS in high-risk women undergoing ART without affecting pregnancy rate, miscarriage or multiple pregnancy.

Limitations of the study

There are some limitations to our study, one of which is the comparatively small number of studied cases. Also, this was a single blind not double-blind study. Finally, all cases were induced using long protocol agonist only, so the effect of different induction protocols cannot be examined in this study.

Conflict of Interest

The authors declare no conflict of interest.

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