

# Evaluation of intravenous hydroxyethyl starch, intravenous albumin 20%, and oral cabergoline for prevention of ovarian hyperstimulation syndrome in patients undergoing ovulation induction

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**Background:** The purpose of this study was to compare the three different strategies, intravenous (IV) hydroxyethyl starch (HES), IV human albumin (HA), and oral Cabergoline (Cb) in the prevention of ovarian hyperstimulation syndrome (OHSS). **Materials and Methods:** In this prospective randomized clinical trial, 91 women at high risk of developing OHSS were allocated into the three groups, group one received 2 vial (2 × 50 ml) IV HAs, in group two, 1000 ml of 6% HES was administered IV, both groups 30 min after oocyte retrieval within 4 h. Group three, 31 infertile patients received oral Cb 0.5 mg daily for 7 days after oocyte retrieval. Patients were visited 14 ± 1 days after *in-vitro* fertilization and if  $\beta$ -human chorionic gonadotropin level >10, transvaginal ultrasonography was performed 2 weeks later to confirm intrauterine pregnancy. Patients were followed up weekly for 3 months for signs of OHSS and were also informed about the signs of OHSS and asked to contact immediately if any symptoms of were detected. **Results:** None of the participants in group HES developed severe OHSS and only 3 patients (10%) developed mild to moderate OHSS. The incident of severe OHSS was significantly higher in albumin group compared to Cb and HES group ( $P = 0.033$  and  $P < 0.001$ , respectively). Also, the probability of developing severe OHSS was higher in Cb group than group HES ( $P = 0.031$ ). **Conclusion:** The findings from this study suggest that administration of 1000 ml of HES 6% has a higher prophylactic effect compared to administration of IV HA and oral Cb.

**Key words:** Cabergoline, human albumin, hydroxyethyl starch, ovarian hyperstimulation syndrome, ovarian induction

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## INTRODUCTION

Ovarian hyperstimulation syndrome (OHSS) is of the most serious complications of ovary stimulation<sup>[1]</sup> and is classified as mild, moderate, and severe. The incidence rate of mild form of this clinical condition after *in-vitro* fertilization (IVF) is 33% and for moderate and severe form, the incidence rate is 3-6% and 1-3%, respectively.<sup>[2]</sup> The corner stone of this syndrome is shifting of fluid from vessels into the intracellular space.<sup>[3,4]</sup> Although the underlying pathophysiology still unknown but vascular

endothelial growth factor (VEGF) through interaction with VEGF receptor-2, human chorionic gonadotropin (hCG), and interleukin 6 and interleukin 8 are suggested to be the mediators of vascular permeability.<sup>[5]</sup> Fluid therapy, thromboembolic prophylaxis, and ascites control are suggested as possible treatments. Yet, no definite treatment is available for this syndrome, and therefore therapy is supportive and conservative according to the severity of symptoms. Other suggested strategies are cycle cancelation, use of gonadotropin-releasing hormone (GnRH) agonist, coasting, and intravenous (IV) albumin.<sup>[6,7]</sup> First introduced by Asch *et al.*,<sup>[8]</sup> many randomized clinical trials demonstrated the potential

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protective role of IV albumin in the prevention of OHSS.<sup>[9-11]</sup> However, some studies suggest that human albumin (HA) does not decrease the incidence of OHSS<sup>[12]</sup> and that due to possible side effects, HA is not recommended<sup>[13,14]</sup> in OHSS prevention. Hydroxylethyl starch (HES), another colloid solution was also suggested as an alternative to HA in the prevention of OHSS. A recent study on 9 RCTs revealed that compared to albumin, HES demonstrated a significant decrease in the incidence of severe OHSS.<sup>[10]</sup> The effect of Cabergoline (Cb), a dopamine agonist which dephosphorylates VEGFR-2 and, therefore, inhibits the development of new vessels and vascular hyperpermeability was studied in a few studies. Alvarez *et al.* demonstrated that Cb reduces moderate OHSS in patients undergoing assisted reproduction.<sup>[15]</sup> Another randomized clinical trial comparing HA and Cb showed that low dose oral Cb decrease both incidence and severity of OHSS.<sup>[16]</sup> Up to now, no study was designed to evaluate the prophylactic effect of these three strategies at a time. The aim of this study is to compare the effect of IV HA, HES, and Cb in preventing OHSS in patients at severe risk of developing severe OHSS, who undergo IVF.

## MATERIALS AND METHODS

### Patients

This study was designed as a randomized clinical trial to compare the efficacy of the three different strategies Cb, HA, and HES in the prevention of OHSS following IVF. Ninety-one eligible patients referring to Al-Zahra hospital and Isfahan fertility center during July 2012-October 2013 for IVF were enrolled in the study by convenient sampling method. Inclusion criteria were being at high risk of developing OHSS, which was either one of the followings: Estradiol value >3000 pg/ml and/or more than 20 follicles on the day of HCG administration and/ or previous history of OHSS. Written consent was obtained from all the participants. Patients with any history of drug sensitivity or co-morbidity were excluded. The study was approved by Isfahan Ethical Committee of Isfahan University of Medical Sciences (project number: 392298).

### Follicle stimulation protocol

All the patients went through a same stimulation protocol. The patients were given oral contraceptive for one cycle. On day 21<sup>st</sup> of menstrual cycle, GnRH-agonist was started with a daily dose of 1 mg subcutaneously and was continued for 10 days or until bleeding occurs followed by 0.5 mg daily SC until at least two follicles  $\geq 17$  mm in diameter were detected in transvaginal ultrasound, human menopausal gonadotropin (HMG) 150 IU daily was started on the 3<sup>rd</sup> day of menstruation for 7-12 days until at least two follicles  $\geq 17$  mm in diameter were detected in transvaginal ultrasound. Transvaginal ultrasound was conducted every

2 days from 5<sup>th</sup> day after HMG administration up to detection of favorable follicles mentioned above. After maturation of follicles was confirmed on ultrasonography, GnRH-agonist, and HMG was stopped and hCG, 5000 IU was administered Intramuscularly. Meanwhile, serum estradiol level was measured 5 days after HMG administration and on the day of hCG injection. Vaginal suppository of progesterone 400  $\mu$ g daily is started after hCG administration. Patients considered high risk according to the criteria mentioned above were enrolled in the study. Thirty-six hours after administration of hCG, oocyte retrieval was performed through vaginal ultrasound-guided procedure. IVF was performed and fertilized embryos were then transferred into uterus.

### Treatment

Ninety-one eligible patients were randomly assigned into three groups using random number table. Group one, consisted of 30 patients, received 2 vial ( $2 \times 50$  ml) HAS (octabin 20%, Octapharma, Switzerland) IV 30 min after oocyte retrieval within 4 h. In group two ( $n = 30$ ), 1000 ml of 6% HES (Voluven, Fresenius Kabi, Germany) was administered IV 30 min after oocyte retrieval within 4 h. Group three, 31 infertile patients were treated with oral Cb (Dostinex, Pfizer, Italy), 0.5 mg daily for 7 days after oocyte retrieval.

Patients were visited  $14 \pm 1$  days after IVF and if  $\beta$ -hCG level >10, transvaginal ultrasonography was performed 2 weeks later to confirm intrauterine pregnancy.

Patients were followed up weekly for 3 months for signs of OHSS and were also informed about the signs of OHSS and asked to contact us immediately if any symptoms of were detected. OHSS was diagnosed according to criteria defined previously by Golan *et al.*<sup>[17]</sup> Mild OHSS was defined as abdominal distension and discomfort with or without nausea, vomiting and/or diarrhea, with enlarged ovaries, and moderate OHSS was defined as mild OHSS plus ascites proved by ultrasound, and severe OHSS was present if features of moderate OHSS were present along with ascites and/or hydrothorax and difficulty breathing or all the mentioned criteria with plus change in blood volume, hemoconcentration and increased blood viscosity, coagulation abnormality, and diminished renal perfusion and function.

### Statistical analysis

Data were analyzed using SPSS (Version 16, SPSS Inc., Chicago, IL, USA). Results were presented in means  $\pm$  standard deviation. Statistical analysis was performed using Chi-square test, and one-way ANOVA when appropriate. The defined level of statistical significance was  $P < 0.05$ .

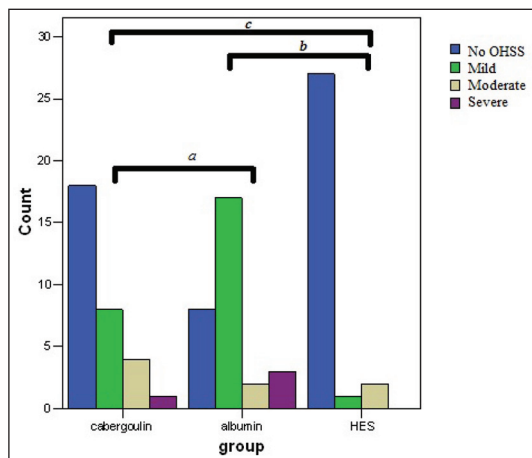
**RESULTS**

In this study, 91 patients were included and divided into three groups of albumin, HES, and Cb each consisted of 30, 30, and 31 subjects, respectively. None of the patients demonstrated adverse reaction due to the administration of HES, Cb or HA.

The mean age of patients was  $31.53 \pm 3.51$ . There was no significant difference between each group regarding gravidity, parity, death, ectopic pregnancy, abortion, and mean age ( $P = 0.18, P = 0.13, P = 0.92, P = 0.41, P = 0.25, P = 0.08$ , respectively). The baseline characteristics of the patients are demonstrated in Table 1.

Of all the participants in this study, 38 women developed OHSS (41.8%), a most frequently mild form with 28.6%. Eight patients developed moderate (8.8%) and four patients (4.4%) developed severe OHSS.

Table 2 demonstrates the incident OHSS in each group of participants. None of the participants in group HES developed severe OHSS and only 3 patients (10%) developed mild to moderate OHSS. Meanwhile, in Cb group, 4 (13%) patients developed moderate OHSS while two patients (7%) in albumin group developed moderate OHSS. However, a total of 19 patients (63%) developed mild to moderate OHSS in albumin group which was higher than that of Cb with total of 12 patients (39%) with mild to moderate OHSS. The incident of severe OHSS was significantly higher in albumin group compared to Cb and HES group ( $P = 0.033$  and  $P < 0.001$ , respectively). Also, the probability of developing severe OHSS was higher in Cb group than group HES ( $P = 0.031$ ). The differences between the groups were depicted in Figure 1. You should also compare the incident of OHSS in total in the two groups.



**Figure 1:** Frequency of mild, moderate, and severe ovarian hyperstimulation syndrome in three groups of study. HES: Hydroxyl ethyl starch. a: Difference between cabergoline and albumin groups,  $P = 0.033$ . b: Difference between albumin and hydroxyl ethyl starch groups,  $P < 0.001$ . c: Difference between cabergoline and hydroxyl ethyl starch groups,  $P = 0.031$

**DISCUSSION**

OHSS is an iatrogenic complication of ovarian stimulation in assisted reproductive technology (ART). It varies from a cystic enlargement of ovaries in a mild form to life-threatening clinical condition in more severe forms, needing hospitalization, and prompt therapy. Many preventive strategies and suggested such as volume expanding through IV albumin and HES, and GNRH agonists such have be as Cb. The findings from this study suggest that administration of 1000 ml of HES 6% has a higher prophylactic effect compared to administration of IV HA and oral Cb and that administration of one dose HES 6% on the day of ovum pick up is related to a lower risk of developing severe OHSS in infertile patients going through IVF.

To our knowledge, no study has evaluated the risk of developing severe OHSS in the three different groups of patients receiving IV HA, Cb, and HES. Many other studies have previously compared the effect of HA, HES, and Cb with a control group or together with each other. König *et al.* were

**Table 1: Baseline characteristics of patients at severe risk of developing OHSS undergoing IVF**

Variables	Mean $\pm$ SD or Frequency	P
Age	A: $30.67 \pm 3.55$	0.27
	C: $31.94 \pm 3.73$	
	H: $31.96 \pm 3.21$	
Gravidity $\leq 1\%$ ( $>1\%$ )	A: 96.7 (3.3)	0.27
	C: 87.1 (12.9)	
	H: 93.3 (6.7)	
Parity $\leq 1\%$ ( $>1\%$ )	A: 100	0.07
	C: 90.3 (9.7)	
	H: 100	
Death Never % ( $\geq 1\%$ )	A: 96.7 (3.3)	0.37
	C: 93.5 (6.5)	
	H: 100	
Ectopic pregnancy Never % ( $\geq 1\%$ )	A: 100	0.22
	C: 93.5 (6.5)	
	H: 90 (10)	
Abortion Never % ( $\geq 1\%$ )	A: 93.3 (6.7)	0.82
	C: 93.5 (6.5)	
	H: 96.7 (3.3)	

A = Albumin group; C = Cabergoline group; H = HES group; SD=Standard deviation; OHSS = Ovarian hyperstimulation syndrome; IVF = *In-vitro* fertilization; HES = Hydroxyl ethyl starch

**Table 2: Incident OHSS among three groups**

Group	OHSS n (%)				P
	Mild	Moderate	Severe	Without OHSS	
Albumin (n=30)	17 (56)*	2 (7)	3 (10)	8 (27)	<0.05
Cabergoline (n=31)	8 (26)	4 (13)	1 (3)	18 (58)	<0.05
HES (n=30)	1 (3)	2 (7)	-	27 (90)	<0.01
Total	26	8	4		

P: Each group versus other two groups. OHSS = Ovarian hyperstimulation syndrome; HES = Hydroxylethyl starch

the first to report a significant reduction in the development of moderate to severe OHSS after use of HES 6%. Of all 51 infertile patients who received a 6% HES solution, only one patient developed moderate OHSS and it significantly differed of that of placebo group with an incident rate of 14% for moderate to severe OHSS.<sup>[18]</sup> These finding was in accord with our study that none of the patients in HES group had severe OHSS. Only two patients developed moderate OHSS in HES group, leading the incident rate of 6% for moderate OHSS. In another study, 16 patients with severe OHSS were hospitalized and received either albumin (10 patients) or HES (6 patients) as a colloid solution. The results revealed that 6% HES solution may be even more effective than HA in the treatment of severe OHSS.<sup>[19]</sup> However, their sample size was small, and HES was used after OHSS was established, compared to our study in which HES was used as a prophylactic agent on the day of ovum pick up.

Compared to HES and Cb, the incident of severe OHSS was higher among patients who received HA. Also, the incident rate for a mild form of OHSS in patients receiving albumin was significantly higher than HES and Cb. Although some studies have shown the effect of albumin in reducing the incidence of severe OHSS,<sup>[8-11]</sup> many recent studies have demonstrated that HA is not a proper intervention in preventing OHSS<sup>[14,19]</sup> due to side effects and the possibility of worsening OHSS.<sup>[20]</sup>

Different strategies have been suggested for the administration of HES. In this study, we preferred to use the previously suggested dose of 1000 ml 6% HES solution. Gokmen *et al.* used a dose of 500 ml and reported to be as effective as the routine dose of 1000 ml.<sup>[13]</sup>

The effect of Cb as a prophylactic therapy for OHSS was studied in several surveys;<sup>[15,16]</sup> however, no study compared the effect of Cb and HES. Our results showed that the incident of moderate to severe OHSS was significantly higher in those patients who received Cb than those who were administered HES ( $P = 0.031$ ).

Our results reveal that by administrating 1000 of 6% HES on the day of oocyte retrieval, the incidence of OHSS will be minimized in patients at high risk of developing this clinical condition, compared to administration of Cb and HA.

Our study was the first one to compare the effect of these three strategies on a group of infertile women undergoing ART. Further studies with focusing on drug dosage and timing of administration are highly recommended.

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### Conflicts of interest

There are no conflicts of interest.

### AUTHOR'S CONTRIBUTION

AG and NM were designed the study, NM collected data with NH, final draft were prepared by all authors and submitted to this journal.

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