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ORIGINAL ARTICLE

The effectiveness of Hespan in reducing the incidence of severe hyperstimulation syndrome in polycystic ovarian disease patients☆

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Abstract *Objective:* Prophylactic IV administration of 6% hydroxyethyl starch solution (HES) has been shown to help in preventing moderate-severe ovarian hyperstimulation syndrome (OHSS) in patients at risk. This prospective study evaluates the effectiveness of HES extended use in preventing severe OHSS in patients with or without Polycystic Ovary Syndrome (PCOS) undergoing assisted reproductive technology. *Setting:* The study group included 45 patients with PCOS (Group 1) and the control group consisted of 98 non-PCOS patients (Group 2). *Materials and methods:* Patients in both groups received multiple HES doses to reduce risk of severe OHSS. The inclusion criteria included having serum estradiol (E2) $\geqslant$ 3000 pg/mL and/or $\geqslant$20 total follicles on day of HCG and to have an embryo transfer done. HES (500–1000 cc) was given daily starting on the day of oocyte retrieval for a mean number of 3.2 ± 0.8 days. *Results:* The percentage of patients who

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developed severe OHSS requiring pigtail catheter insertion or vaginal aspiration was significantly higher in Group 1 vs Group 2 (15.6% vs. 4.1%, $P = 0.017$). *Conclusion:* Prophylactic use of multiple doses of HES appears to be more effective in preventing severe OHSS in non-PCOS patients, but may have limited effect in PCOS patients.

1. Introduction

OHSS is a serious and sometimes life threatening complication of assisted reproductive technique (ART). Human chorionic gonadotropin (HCG) is thought to play a crucial role in the development of OHSS (1). Two distinct forms of severe OHSS have been described: early and late forms (2). Early OHSS is caused by the administration of exogenous HCG and it starts before the 10th day after oocyte retrieval. The late form is the result of endogenous HCG release in the event of pregnancy, and it starts after the 10th day following oocyte aspiration (2–4).

Because severe OHSS is potentially dangerous, its prevention should be the goal of all infertility specialists. Several strategies to prevent OHSS have been described in the literature. Such strategies included the use of low dose gonadotropins and frequent monitoring during controlled ovarian hyperstimulation (COS), cycle cancelation, coasting, freezing of all embryos and the use of gonadotropin releasing hormone (GnRH) agonist as an oocyte trigger in GnRH antagonist cycles (5,6).

In addition, several authorities proposed that prophylactic intravenous administration of fluids such as human albumin and HES may help in preventing severe OHSS. Some of the mechanisms by which these fluids may reduce the likelihood of OHSS include increasing the oncotic pressure, restoration of intravascular volume and inactivation of the vasoactive substances that play a role in OHSS (7,8).

This prospective study evaluates the effectiveness of HES extended use in preventing severe OHSS in patients with or without PCOS undergoing IVF-ET.

2. Materials and methods

The study included 143 patients who underwent IVF-ET at our center in the period between January 2006 and December 2008. All patients were determined to be at risk of OHSS. The inclusion criteria included having serum estradiol (E2) $\geqslant$ 3000 pg/mL and/or at least a total of 20 follicles on day of HCG and to have an embryo transfer done. Such criteria have been shown to increase the incidence of OHSS (9,10).

All patients received multiple doses of HES intravenously (500–1000 cc) to reduce the incidence of OHSS starting the day of oocyte retrieval for a mean number of 3.2 ± 0.8 days. The study was approved by the Institutional Review Board at Hurley Medical Center, Flint, Michigan. The study group included 45 patients with PCOS (Group 1) and the control group consisted of 98 non-PCOS patients (Group 2). The 45 patients in the study group (Group 1) were part of 122 PCOS patients who participated in a previously published prospective randomized study that compared the implantation rate and pregnancy outcomes in 2 groups based on the start day of GnRH antagonist during COS (11). PCOS was defined according to the Rotterdam criteria (12). The control group (Group 2) consisted of 98 non-PCOS patients who underwent IVF-ET treatment during the 3 year period of the PCOS study (11) and fulfilled the inclusion criteria of this study. All patients received oral contraceptive pills (OCP) [Desogen, Merck & Co., Inc., North Wales, PA 19454, USA] 21–35 days in the preceding cycle. All PCOS patients received Metformin hydrochloride (1000–1500 mg) (Glucophage, Bristol-Myers-Squibb, Princeton, NJ, 08543-4500, USA) starting one month before stimulation and continuing throughout treatment. PCOS patients were stimulated with rFSH (150–225 IU) starting on day 2 or day 3 of the cycle and nRH antagonist (Ganirelix) for pituitary suppression (starting on day 1 or day 5 of COS according to the protocol of the previously published PCOS study) (11). The initial dose of rFSH was determined based on BMI. If BMI was <28 kg/m^2, 150 IU of rFSH was administered daily, while if BMI was >28 kg/m^2, a dose of 225 IU was administered daily. The non-PCOS patients in the control group were stimulated with rFSH or mixed protocol and GnRH agonist or GnRH antagonist (Group 2). The two groups had different stimulation protocols because Group 1 had a fixed study protocol (11), while Group 2 had variable protocols.

In both groups patients with significantly high E2 levels (>1000 pg/mL) and small follicle sizes on treatment day 5 had their cycles canceled in order to avoid severe OHSS. If there were more than 3 mature follicles ($\geqslant 17$) with a large number of small follicles and E2 levels exceeded 3000 pg/mL on treatment day 7–8 or afterward, then coasting (no more rFSH or gonadotropins) was used for 1–3 days, until E2 level was less than 3000 pg/mL. After coasting, or if there was a potential for severe OHSS for other reasons, 500–1000 cc of HES (B. Braun Medical, Inc. Bethlehem, PA 18018, USA) was given intravenously on retrieval day and for up to two to three additional days, if needed. These measures are commonly used to reduce the incidence of severe OHSS when indicated. When three follicles were $\geqslant 17$ mm, 5000–10,000 IU HCG was administered thirty-six hours before oocyte retrieval. The dose of HCG was reduced to 5000 IU if risk of severe OHSS was high, as outlined above. Coasting policy was similar in both groups. Intracytoplasmic sperm injection (ICSI) was used to fertilize all mature eggs. We prefer to perform ICSI in all patients undergoing ART in our laboratory (11). The number of embryos that were transferred in both groups was according to ASRM guideline (13). Luteal phase support was the same in both groups. Starting on the second day after retrieval, Progesterone vaginal tablets T.I.D (Endometrin 100 mg Vaginal Insert, Ferring Pharmaceuticals, Inc., Parsippany, NJ, 07054, USA) or vaginal cream once a day (Crinone 8% Vaginal Gel, Watson Pharmaceuticals, Morristown, NJ 07962, USA), Progesterone in oil 100 mg I. M every other day (Progesterone in Oil 50 mg/mL Vial,