Journal of Midwifery & Reproductive Health

JMRH.mums.ac.ir

Effect of Low-dose Human Chorionic Gonadotropin on the Prevention of Ovarian Hyperstimulation Syndrome and in Vitro Fertilization Outcome

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ARTICLE INFO

Article type:
Original article

Article History:
Received: 12-May-2016
Accepted: 15-Ap-2017

Key words:
Human chorionic gonadotropin
Infertility
Ovarian hyperstimulation syndrome

ABSTRACT

Background & aim: Ovarian hyperstimulation syndrome (OHSS) is a rare but most potentially life-threatening disorder in women under in vitro fertilization (IVF). This study aimed to determine the effect of low-dose human chorionic gonadotropin (hCG) on the prevention of OHSS and IVF outcome.

Methods: This single-blind non-randomized clinical trial was performed from October 2008 to November 2012 in Motahari Hospital, Urmia, Iran. Overall, 202 infertile women undergoing IVF treatment were divided into two groups based on OHSS risk factors. Then, 87 women with serum estradiol level of 5000-8000 pg/ml received 5000 units of intramuscular hCG, and 115 women with serum estradiol level of > 8000 pg/ml, who were at high risk for OHSS, received 1600 units of hCG. Data were analyzed using independent t-test and Chi-square test in SPSS, version 16.

Results: There were no significant differences in age, infertility duration, infertility factor, quality of embryo, pregnancy rate and number of abortions and OHSS rate between the groups (P>0.05). The group that received 1600 units of hCG was in a better condition regarding the mean number of ova (11.45±5.41 versus 9.24±4.24; P=0.01), mean number of good quality ova (11.10± 5.47 versus 8.68± 4.03; P=0.001), and mean number of embryos (7.38± 4.24 versus 5.53± 2.85; P=0.001). There was no significant difference in the rate of OHSS incidence and cancellation of embryo transfer between the two groups (1600 and 5000 units).

Conclusion: Overall, the current study indicated that prescribing 1600 units of hCG in women who are at risk of hypersensitivity reaction may induce similar or perhaps better results regarding the quantity and quality of ova and embryos, however, OHSS risk is not completely eliminated by using a lower dose of hCG. It is therefore suggested to perform randomized clinical trials with greater sample size to verify these results.

▶ *Please cite this paper as*:
Hajishafiha M, Gare-Agaji R, Azarakhsh Z, Pakniyat A, Mir-gaforwand M, Kiarang N. Effect of Low-dose Human Chorionic Gonadotropin on the Prevention of Ovarian Hyperstimulation Syndrome and in Vitro Fertilization Outcome. Journal of Midwifery and Reproductive Health. 2018; 6(4): 1409-1413. DOI: 10.22038/jmrh.2018.16525.1177

Introduction

Ovarian hyperstimulation syndrome (OHSS) is a life-threatening complication of controlled ovarian stimulation (1). Some rare cases of this syndrome were reported in spontaneous

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pregnancy, which were related to polycystic ovary syndrome, hypothyroidism, hydatidiform mole, gonadotropin-producing pituitary adenoma, and multiple gestation (2). OHSS occurs 3-7 days after hCG administration in sensitive women and within 12-17 days after hCG administration in the normal papulation (3).

Various prevalence rates have been reported for OHSS in several studies. In the largest cohort study, the mildest type of this disease, which is not clinically important, constituted 20-30% of cases (3), while the moderate to severe types comprised 1-10% of the cases (4), and the life-threatening type consisted of 1-2% of the cases (3, 5). Young and thin women with a history of OHSS, as well as women with polycystic ovary disease (PCOD), hyperprolactinemia, and hypothyroidism are at high risk for OHSS (3, 6).

Although the pathophysiology of OHSS has not been completely described, it seems to be related to ovarian enlargement, increased vascular permeability, and intravascular dehydration that are mediated by vasoactive mediators released by hyperstimulated ovaries under the influence of hCG (7). It has been demonstrated that OHSS is always caused by exogenous or endogenous hCG due to pregnancy (3, 8). Stopping IVF cycles and hCG injection prevent OHSS. However, this is not favorable since physicians are under pressure to achieve a successful outcome from IVF cycles (3). hCG is routinely used for the induction of oocyte maturation (9). hCG dosage and its continuous administration during the luteal phase are the most important risk factors for OHSS (6), and high serum concentrations of hCG may increase the risk of OHSS (9). Thus, it seems that the reduction of hCG dosage is a useful prophylaxis method for OHSS in order to decline the production and effects of vascular endothelial growth factor (VEGF) (10). Nonetheless, the minimum effective hCG dosage has not yet been determined (9).

Few international studies have been conducted on the reduction of hCG dosage. In this study, we aimed to investigate the effect of reduction of hCG dosage from 5000 units to 1600 units on OHSS incidence rate and IVF outcomes in patients with high risk for OHSS.

Materials and Methods

In a single-blind non-randomized clinical study, 202 infertile women who were candidates for assisted reproductive procedure and aged 18 to 40 years old were enrolled in the study to determine the effect of low-dose hCG on the prevention of OHSS and IVF outcome. The study was carried out from October 2008 through November 2012 in Motahari Hospital, Urmia, Iran.

All the participants underwent controlled ovarian hyperstimulation with gonadotropin/ GnRH agonist long protocol. The women were treated with 0.5 mg subcutaneous buserelin (gonadotropin Releasing Hormone agonist [GnRH], Superfact, Aventis, Germany) daily for 21 days. In case of absence of ovarian cysts in ultrasonography, human menopausal gonadotropin vial (HMG, Mengon; Ferring GmbH, Germany) or follicle-stimulating hormone (FSH) vial (Gonal-f; Merck Serona, Switzerland) was prescribed for patients, and Superfact was continued with a half-therapeutic dose regimen. After growing follicles to a diameter of 18-20 mm, intramuscular injection of hCG (IVF-C; Pregnil, Iran) was used to induce ovule maturation.

The criteria for high risk OHSS included young age, antral follicle counts of more than 30 in both ovaries, follicle size of larger than 14 mm, poly cystic ovaries on ultrasound and/or polycystic ovarian syndrome (PCOS), serum estradiol of more than 5000 pg/ml, and/or multiple follicular recruitments in both ovaries during ultrasound monitoring in controlled ovarian hyperstimulation on the day of hCG administration. The patients with serum estradiol of less than 5000 pg/ml were excluded. Embryo transference was not performed for those with discomfort in the lower abdomen, bulky ovum, nausea, abdominal distension, or other OHSS symptoms. In these cases, embryos were totally frozen and they were excluded from the study.

The patients were divided into two groups. The women with serum estradiol of 5000 to 8000 pg/ml received 5000 units of hCG and those with serum estradiol of higher than 8000 pg/ml (high risk for OHSS) received 1600 units (one third of vial 5000 units) of hCG.

After 34-36 hours of hCG injection, the ova were punctured under vaginal ultrasonography

guide. The ova were fertilized by the intracytoplasmic sperm injection (ICSI) technique and embryos were transferred into the uterine cavity through cervix 48-72 hours later.

Progesterone (100 mg/daily) was prescribed as the luteal phase support following embryo transference. Beta hCG (βhCG) was measured two weeks later, and if it was positive, vaginal ultrasonography was conducted to confirm pregnancy after two weeks, also the control ultrasound test was repeated to observe embryo's heartbeat at the 8th week of pregnancy. The patients were followed up until the 14th week of pregnancy. Quantity and quality of oocytes, and quantity and quality of the embryos, rate of pregnancy, frequency of abortion, and incidence rate of OHSS were investigated and compared between the groups.

The study followed the tenets of the Declaration of Helsinki; informed consent was obtained from all the participants, and the study was approved by the Ethics Committee of Urmia University of Medical Sciences.

To analyze the data, descriptive statistics including frequency, percentage, mean, and standard deviation and inferential statistics consisting of independent t-test and Chi-square test were employed in SPSS, version 16. P-value less than 0.05 was considered significant.

Results

A total of 202 women were enrolled, 87 of whom had serum estradiol of 5000-8000 pg/ml and received hCG at a dose of 5000 units and 115 with a serum estradiol of higher than 8000 pg/ml received 1600 units of hCG. The maximum serum estradiol level was 13750 pg/ml.

The mean age of the patients in the 1600 and 5000-unit groups were 28.35±3.98 years and 29.44±5.28 years, respectively (P=0.09). Ova and embryos of the patients were investigated . The total ova and embryos of the 5000-unit group were 804 and 480, respectively, and those in the 1600-unit group were 1321 and 854, respectively (Table 1).

Considering the ratio of total embryos to total ova, fertilization rates were 64.64% in the 1600-unit group and 59.70% in the 5000-unit group. There was a significant difference between the two groups regarding fertilization rate (P=0.001).

Embryos were not transferred in 17 out of 115 participants in the 1600-unit group due to OHSS symptoms (13 cases), non-formation of ovum (2 cases), and non-formation of embryo (2 cases). The rate of pregnancy in the 1600-unit group was 56.12%, of whom two cases had ectopic pregnancy and eight cases had abortion (15.09%).

The embryo was not transferred for 7 out of 87 participants in the 5000-unit group due to OHSS symptoms (4 cases), non-formation of ovum (2 cases), and non-formation of embryo (1 case). The rate of pregnancy in this group was 45%; 1 (2.77%) case was EP and 10 cases had abortion (28.57%). There was no significant difference between the two groups in terms of pregnancy rate (P=0.092) and frequency of abortion (P=0.171).

OHSS symptoms were observed in 13 (11.30%) women in the 1600-unit group and in 4 (4.59%) women in the 5000-unit group. Therefore, transfer of embryo was cancelled in these women and their embryos were frozen. No significant difference was observed between the two groups regarding OHSS rate and rate of IVF cycle cancellation (P=0.089). Only one case from the 1600-unit group had severe OHSS symptoms, and other cases only experienced mild symptoms.

Table 1. Frequency distribution of IVF cycles characteristics according to the hCG dosage

	hCG dosage		P- value t-test
	1600 units (n=115) Mean [SD]	5000 units (n=87) Mean [SD]	
Transferred embryo[2]	3.88[2.13]	4.06[1.89]	0.53
Total ovum [2]	11.45[5.41]	9.24[4.24]	0.01
High quality ovum *[1]	11.10[5.47]	8.68[4.03]	0.001
Low quality ovum[1]**	0.38[1.64]	0.49[1.18]	0.59
Total embryo [1]	7.38[4.24]	5.53[2.85]	0.001
Embryo - high quality [1]	3.18[3.07]	2.20[3.21]	0.123
Embryo –moderate quality[1]	3.10[2.81]	2.07[1.74]	0.003

Embryo - low quality[1]	1.21[0.57]	0.8[0.34]	0.144

** Metaphase 1, vacuolated or GV
* Metaphase 2
[2]Independent t-test
[1]Chi-square test

Discussion

There was a significant difference between the two groups regarding the mean number of ova per a cycle, and the 1600-unit group was in a better condition than the 5000-unit group. Shapiro et al. showed that hCG dosage does not significantly affect pregnancy rate or embryo implantation (9). Schmidt et al. (2004) indicated that reduced dose of hCG from 5000 units to 3300 units might result in similarity in ovum maturation (11). Abdalla et al. addressed a concern as to the number of matured ova in a group that had received 2000 units, while there was no difference between groups of 5000 and 10000 units, also they concluded that hCG dose should be at least 5000 units to acquire appropriate results in IVF (12).

Based on our results, frequency of high-quality ova in the 1600 unit-group was remarkably greater than that in the 5000-unit group. The rate of matured (appropriate) ova was similar to that in the study by Schmidt et al. (2004).

There was a significant difference between the two groups regarding mean embryo formation per cycle. The 1600-unit group was in a better condition than the 5000-unit group, which may be due to the great number of ova or higher quality of ova in the 1600-unit group. However, no significant difference was noted between the two groups regarding the frequency of high quality and low quality embryos, and only the frequency of embryos with moderate quality was greater in the 1600-unit group than that in the 5000-unit group.

In the current study, the rate of pregnancy to embryo transfer (pregnancy/ ET) was similar in the two groups, which is in line with the findings of previous studies. Nargund et al. reported pregnancy rate about 61.9% with receiving 2500 units of hCG (13). Abdalla et al. demonstrated a significant difference between three groups (i.e., 2000, 5000, and 10000 units) (12). Also, in a study by Schmidt et al. (2004), despite reduced hCG dose (3300 units) a similar pregnancy rate was observed in comparison with the 5000-unit group (11).

The fertilization rate in the 1600-unit group was better than the 5000-unit group, this finding is in contrast to the study of Schmidt et al. (11).

In this study, there was no significant difference regarding the rate of OHSS and cancellation of embryo transfer between the two groups. There was one case of sever OHSS that belonged to the 1600-unit group. Schmidt et al. showed that despite reducing hCG dosage to 3300 units, OHSS risk did not reduce in the high-risk group (11). In study a by Nargund et al., progress toward OHSS was prevented while hCG dose reduced from 5000 units to 2500 units in high-risk females without any change in the rate of successful IVF (13).

hCG has high half-time in the serum, thus, it leads to several side effects. Along the corpus luteum improvement, luteotrophic side effects and OHSS risk will be increased. Hence, hCG dosage reduction may be useful to reduce OHSS risk in high-risk women (11).

Future studies are recommended to study the minimum gonadotrophin dose for reducing the risk of OHSS and other side effects (14-16).

Conclusion

Overall, the current study indicated that 1600 units of hCG in women who are at risk of hypersensitivity reaction may induce similar or perhaps better results regarding the quantity and quality of ova and embryos, pregnancy rate, and abortion. OHSS risk was not completely eliminated by using a lower dose of hCG in women with hypersensitivity reaction. It is suggested to perform randomized clinical trials with greater sample sizes to verify these results.

Acknowledgements

The mentioned findings in this study were derived from a thesis by Dr. Zahra Azarakhsh under the title of “An investigation into the effects of low-dose HCG on the prevention of OHSS incidence and results of pregnancy in high-risk females under IVF” in clerkship course

(residency) in 2012 (date: 08/05/2012). The study was funded by the Western Azerbaijan University of Medical Sciences/ fertility healthcare studies center. We wish to thank Kowsar infertility center, the respected colleagues, and fertility healthcare research centers.

Conflicts of interest

The authors declare no conflicts of interest.

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