

Reducing the trigger dose of recombinant hCG in high-responder patients attending an assisted reproductive technology program: an observational study

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Abstract: Decreasing the dose of human chorionic gonadotropin (hCG) used to trigger final oocyte maturation in assisted reproductive technology programs is regarded as a useful intervention in the prevention of ovarian hyperstimulation syndrome, but the minimal effective dose has not been yet identified. In this study, the capacity of a reduced dose of recombinant hCG (r-hCG) to provide adequate oocyte maturation was tested for the first time. Thirty-five high-responder patients received a dose of 125 µg (half of the standard dose) of r-hCG for triggering final oocyte maturation. The number of oocytes retrieved per patient and the proportion of mature oocytes were evaluated. As a result, a mean number of 14 oocytes were retrieved, of which 85% were found to be mature (MII). There was only one patient developing a moderate form of ovarian hyperstimulation syndrome and not requiring hospitalization. It is suggested that r-hCG at 125 µg can be effective in triggering final oocyte maturation in high-responder patients. Additional properly powered and controlled studies are needed to support this contention.

Keywords: recombinant hCG, low dose, triggering oocyte maturation, OHSS

Introduction

Human chorionic gonadotropin (hCG) has been adopted in cycles of assisted reproductive technology (ART) to effect the final oocyte maturation. Exogenous hCG can be used as a surrogate luteinizing hormone because of the high degree of homology between the two hormones. The clinical use of hCG in controlled ovarian stimulation for ART cycles is favored by the longer circulating half-life (>24 hours) of this hormone in comparison to luteinizing hormone (60 minutes).¹ As major downside, hCG is a key determinant of ovarian hyperstimulation syndrome (OHSS), which is the major complication of controlled ovarian stimulation. The crucial role played by hCG in the initiation of OHSS is exemplified by the observations that when hCG is withheld, OHSS rarely occurs and that, on the other hand, multiple doses of hCG (as when hCG is used for luteal support) increase the incidence of OHSS.² More to the point, endogenous production of hCG, associated with the pregnant status, is known to increase both OHSS severity and duration.³ OHSS has been estimated to occur in 1%–14% of ART women, albeit severe forms of OHSS are seen in 0.1%–2% of patients.³ Since the mechanisms and etiological factors behind OHSS are known only in part, its prevention primarily relies on the identification of high-risk patients and the application of preventive measures. The risk factors for OHSS include young age, high antral follicle

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count, polycystic ovary syndrome or PCO-like ovary, and previous OHSS.⁴ The preventive measures include coasting, use of gonadotropin-releasing hormone (GnRH) antagonists, agonist trigger in GnRH antagonist cycles, dopamine agonist therapy, freezing of all the embryos, and decreasing the trigger dose of hCG. Focusing on this latter intervention, a crucial prerequisite to lower hCG exposure is the identification of the minimal effective dose, ie, the hCG dose effective in reducing the occurrence of OHSS and, at the same time, effective in ensuring a sufficient number of mature oocytes.

Under such a concept, the purpose of this pilot study was to test, since never done before, whether a reduced dose of r-hCG (125 µg) is sufficient to trigger final oocyte maturation in a group of patients developing a hyper response during a long pituitary downregulation protocol for ART.

Patients and methods

This prospective observational cohort study included 35 high-responder infertile patients attending our infertility unit for in vitro fertilization (IVF) treatment between November 2013 and September 2014. Informed consent was obtained from all patients participating in the study. The study followed principles in the Declaration of Helsinki. Approval was not sought from the IRB since decreasing the trigger dose of hCG is a validated clinical approach in the prevention of OHSS which is routinely used in our ART unit. The ovarian stimulation protocol consisted of a luteal-phase GnRH agonist downregulation with buserelin acetate (Suprefact; Sanofi-Aventis, Bridgewater, NJ, USA) administered as a nasal spray at a daily dose of 0.9 mg starting on day 21 of the preceding cycle. Ovarian stimulation with recombinant follicle stimulating hormone (FSH; Gonal-f; Merck Serono S.p.A, Rome, Italy) was started on day 3 of full menstrual flow if pituitary suppression was complete as assessed by the absence of ovarian cysts on ultrasound scan, the presence of small antral follicles (diameter 2–6 mm), and an endometrial thickness <5 mm. The initial recombinant FSH dose (150 IU/d) was adjusted based on the ovarian response. From the fifth day of stimulation, the follicle size and number were monitored daily. The recombinant hCG (r-hCG) was administered when at least three follicles of 18 mm were present. Patients having an estradiol level $\geq 3,000$ pg/mL but <5,000 pg/mL on the day of hCG administration were included in the study and received a dose of 125 µg of r-hCG (Ovitrelle; Merk Serono). This dosage is half of the current standard dose of r-hCG. Women with estradiol >5,000 pg/mL were coasted. Ovum pickup was scheduled 36 hours after r-hCG injection. All the IVF treatments were performed by intracytoplasmic sperm

injection (ICSI). All the collected oocytes were denuded and their nuclear maturation stage determined. Embryo transfer was performed 72–76 hours after ovum pickup. The luteal phase was supported with 600 mg of micronized progesterone vaginally administered from the day after oocyte retrieval. Pregnancy test was performed by dosing β hCG serum blood, 14 days after embryo transfer. Clinical pregnancy was defined as the presence of a gestational sac with fetal heart activity visible on ultrasound scan at 7 weeks of gestation. OHSS was classified according to the criteria proposed by Golan et al.⁵

Results

The mean age of the 35 high-responder women included in the study was 34.46 ± 4.27 years. They had a mean body mass index of 21.82 ± 2.93 kg/m² and a basal serum FSH of 6.83 ± 1.42 mIU/mL. The main indications for ART were tubal factor (34.28%), male factor (28.57%), ovulatory factor (2.85%), endometriosis (5.71%), combined factor (8.57%), and unexplained infertility (20.00%). The cycle outcome of the patients is listed in Table 1. The mean duration of stimulation was 11.18 ± 1.70 days. The total dose of FSH administered was $1,648 \pm 77$ IU. The mean number of follicles with diameter >14 mm was 13.56 ± 3.42 . The mean number of oocytes collected was 13.80 ± 4.40 , with the number of mature oocytes (MII) being 11.64 ± 4.40 . The percentage of MII/oocytes retrieved per patient was 84.9 ± 16.1 (95% CI –81.82%–88.18%). Fertilization and implantation rates were 88.0% and 14.74%, respectively. The mean number of transferred embryos was 2.71 ± 0.46 . There was a 34.26% (12/35) clinical pregnancy rate, with a 2.86% twin pregnancy rate. The delivery rate per clinical pregnancy was 83.33% (10/12).

With respect to OHSS incidence, only one case (2.86%) of moderate OHSS was recorded. The patient was 28 years old and had an estradiol level on the hCG day of 3,890 pg/mL, with 25 oocytes retrieved. The patient did not require hospitalization.

Discussion

The link between hCG exposure and occurrence of OHSS has long been recognized, and circulating levels of hCG, along with the number of follicles, have been identified as the most significant predictor of OHSS risk.⁶ Decreasing the dose of hCG administered to trigger final oocyte maturation may have the potential to reduce OHSS incidence.⁷ Unfortunately, the lowest effective dose for ART programs has not yet been established.⁸ Urinary hCG (u-hCG) is commonly given at 10,000 IU with the dose of 5,000 IU representing the standard low dose. The value of a reduced dose regimen of r-hCG

Table 1 Cycle outcome in women receiving a reduced dose of r-hCG (125 µg) to trigger final oocyte maturation

	125 µg r-hCG (n=35)
Total dose of FSH administered (IU)	1,648.00±77.04
Duration of stimulation (days)	11.18±1.70
Number of dominant follicles with diameter >11 mm	20.37±4.85
Number of follicles with diameter >14 mm	13.56±3.42
Number of oocytes retrieved	13.80±4.40
Number of mature oocytes (MII)	11.64±4.40
Percentage of MII/oocytes retrieved	84.9±16.1
Fertilization rate	88.0%
Implantation rate ^a	14.74% (14/95)
Number of transferred embryos	2.71±0.46
Good quality embryos	84.21% (80/95)
Biochemical pregnancy rate	5.71% (2/35)
Early spontaneous abortion rate	16.67% (2/12)
Clinical pregnancy rate	34.26% (12/35)
Twin pregnancy rate	2.86% (1/35)
Triplet pregnancy rate	0.00% (0/35)
Delivery rate per clinical pregnancy	83.33% (10/12)
Hormone serum levels	
On r-hCG day	
LH (mIU/mL)	1.26±0.75
Progesterone (ng/mL)	1.27±0.61
Estradiol (pg/mL)	3,619.97±455.70
hCG (mIU/mL)	0.45±0.07
On oocyte retrieval day	
LH (mIU/mL)	0.35±0.30
Progesterone (ng/mL)	25.28±13.62
Estradiol (pg/mL)	2,349.80±335.05
hCG (mIU/mL)	72.08±9.21
On embryo transfer day	
LH (mIU/mL)	0.34±0.17
Progesterone (ng/mL)	182.63±91.80
Estradiol (pg/mL)	1,606.21±176.20
hCG (mIU/mL)	24.36±6.75

Notes: Data are expressed as mean ± standard deviation. ^aImplantation rate was defined as the number of fetal heartbeats at ultrasound at 7 weeks after transfer divided by the number of embryos transferred.

Abbreviations: r-hCG, recombinant human chorionic gonadotropin; FSH, follicle stimulating hormone; LH, luteinizing hormone; hCG, human chorionic gonadotropin.

in triggering final follicular maturation has not yet been evaluated and formed the basis for this study. The obtained results suggest that a dose of r-hCG as low as 125 µg, corresponding to half of the standard dose, is feasible in triggering final oocyte maturation in high-responder patients. A mean number of 14 oocytes were retrieved after low-dose triggering. This number was comparable with the number of the follicles >14 mm (13.56±3.42) seen by ultrasound. Eighty-five percent of the collected eggs were found to be mature (MII). High progesterone levels were detected on oocyte retrieval day, indicating that the low r-hCG dose is effective in initiating early luteinization process.

As far as OHSS is considered, the reduced dose of r-hCG tested in this study did not fully prevent OHSS, since one patient developed a moderate form of the syndrome, not requiring hospitalization. Considering both safety and efficacy, 250 µg has been proposed as the dose of choice for triggering ovulation.⁹ This dosage corresponds to ~6,500 IU of u-hCG,¹⁰ and thus, the r-hCG dose tested in this study equals to 3,250 IU of u-hCG. In a pilot study involving 21 high-responder patients, Nargund et al¹¹ found that a u-hCG dose as low as 2,500 IU was fully effective in preventing OHSS without compromising success rates. Triggering with a single bolus of 2,000 IU of u-hCG was found to be feasible to prevent OHSS in a small group of six hyperresponders.¹² Abdalla et al¹³ reported that 2,000 IU was a less effective dose than 5,000 IU in ensuring adequate oocyte maturation, whereas doses of 5,000 IU and 10,000 IU were comparably effective. In randomized controlled trial in patients with polycystic ovary syndrome, Kolibianakis et al¹⁴ found comparable outcomes, in terms of fertilization rates and ongoing pregnancy, after triggering with u-hCG at 2,500 IU, 5,000 IU, or 10,000 IU. Nevertheless, triggering with 2,500 IU was associated with the lowest number of oocytes retrieved, the lowest fertilization rate, the lowest proportion of MII oocytes, and the highest proportion of patients with no embryos for transfer.¹⁴ The use of r-hCG offering high purity, high specific activity, and batch-to-batch consistency may help to precisely define the minimum effective trigger dose. Our results fit well with data from a retrospective review of IVF clinical data by Schmidt et al,¹⁵ showing a reduced dose of 3,300 IU of u-hCG as effective for final oocyte maturation with optimal fertilization rates and clinical pregnancy rates in high-response population. Kashyap et al⁷ assessed the impact of a sliding scale protocol for u-hCG trigger dose on OHSS incidence. The doses ranged between 3,300 and 10,000 IU depending on the estradiol level. Low-dose u-hCG appeared independently and significantly to reduce the risk of early and severe OHSS by factors of ~7 and ~4, respectively, without compromising the number of oocytes retrieved, the number of embryos available for transfer, or clinical pregnancy rates.⁷

Conclusion

It seems that a low r-hCG regimen does not compromise final oocyte maturation in high-responder women undergoing ICSI, although the lack of a control group and the small sample size limit the ability to make this conclusion as definitive. Further prospective randomized clinical trials on the same kind of population (ie, two groups of patients at the same risk of OHSS treated by full dose or alternatively

by half dose of r-HCG) are needed to corroborate these preliminary findings.

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Disclosure

The authors report no conflicts of interest in this work.

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