

Article

GnRH agonist versus recombinant HCG in an oocyte donation programme: a randomized, prospective, controlled, assessor-blind study



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Abstract

The use of gonadotrophin-releasing hormone (GnRH) agonists for triggering ovulation remains controversial. The primary objective of this study was to evaluate the incidence of ovarian hyperstimulation syndrome (OHSS) following GnRH agonist versus recombinant human chorionic gonadotrophin (HCG) as methods for triggering ovulation. A second aim was to compare the clinical outcome and embryo quality according to the two procedures. The cycle characteristics of 100 oocyte donors undergoing ovarian stimulation and IVF outcomes of their 100 oocyte recipients were analysed. Donors were prospectively randomized into two groups on the last day of ovarian stimulation: Group I received a single bolus of 0.2 mg of triptorelin and Group II received 250 µg of recombinant HCG. No differences were observed in the number of oocytes retrieved or in the proportion of metaphase II oocytes between the groups. The OHSS rate was higher in donors that received recombinant HCG ($P = 0.003$). Moreover, there was no significant difference between IVF parameters and outcome in the two groups. In conclusion, a GnRH agonist effectively triggers the final oocyte maturation in oocyte donors without negatively affecting implantation, pregnancy or miscarriage rates. Moreover, this regime effectively eliminates the risk of OHSS in this group of women.

Keywords: GnRH agonist, GnRH antagonist, IVF outcome, ovarian hyperstimulation syndrome, oocyte donation, recombinant HCG

Introduction

In a normal menstrual cycle, a cascade of events drive ovulation, and this cascade is initiated by a surge of luteinizing hormone (LH) from the pituitary, which induces resumption of oocyte meiosis and follicular rupture when received by the follicle. Since the endogenous LH surge is usually absent in patients undergoing long protocols, exogenous human chorionic gonadotrophin (HCG) is used to achieve final oocyte maturation and ovulation (Fauser *et al.*, 2002; Melo *et al.*, 2006). HCG is employed because it possesses the same α subunit and 85% of the amino acid residues of the β subunit of LH, and binds to the same LH/HCG

receptors (Golan *et al.*, 1989; Itskovitz *et al.*, 1991; Balasch *et al.*, 1994). Unfortunately, given its significantly longer half-life (>24 h versus 60 min for LH), HCG is associated with a high risk of ovarian hyperstimulation syndrome (OHSS) as a result of its sustained luteotrophic effect, characterized by the development of multiple corpora lutea and supraphysiological concentrations of oestradiol and progesterone (Empeaire and Ruffie, 1991; Itskovitz *et al.*, 1991; Kol *et al.*, 1996; Lewit *et al.*, 1996; Babayof *et al.*, 2006; Engmann *et al.*, 2006, 2008).

The introduction of gonadotrophin-releasing hormone (GnRH) antagonist protocols has offered an alternative to

HCG-induced ovulation triggering. The administration of a GnRH agonist, which induces an endogenous rise in both LH and FSH concentrations (initial flare effect), has been shown to effectively induce ovulation (Bentick *et al.*, 1990; Olivennes *et al.*, 1996; Buckett *et al.*, 1998; de Jong *et al.*, 2001; Griesinger *et al.*, 2006, 2007) and has been recommended as an important strategy for reducing the risk of severe OHSS in patients undergoing ovarian stimulation cycles (Empeaire and Ruffie, 1991; Itskovitz *et al.*, 1991; Lanzone *et al.*, 1994; Lewit *et al.*, 1996; Acevedo *et al.*, 2006; Babayof *et al.*, 2006; Engmann *et al.*, 2006, 2008). This phenomenon occurs because the GnRH antagonist achieves pituitary down-regulation by competitive inhibition with a relatively short action length, thereby maintaining the reaction ability of GnRH. The GnRH agonist is capable of displacing the antagonist from the receptor and inducing an initial activation (flare-up) prior to receptor down-regulation (Buckett *et al.*, 1998; Fauser *et al.*, 2002; Humaidan *et al.*, 2005).

However, the clinical efficacy of GnRH agonist triggering of ovulation requires confirmation. In a recent review and meta-analysis, only three relevant publications were identified after an extensive literature search (Griesinger *et al.*, 2006). Whereas some studies have reported comparable clinical outcomes after GnRH agonist and HCG triggering (Empeaire and Ruffie, 1991; Fauser *et al.*, 2002; Acevedo *et al.*, 2006; Engmann *et al.*, 2006; Eldar-Geva *et al.*, 2007), others have reported a lower pregnancy rate following the former (Humaidan *et al.*, 2005; Kolibianakis *et al.*, 2005; Orvieto *et al.*, 2006). The theories put forward in order to explain this poor IVF outcome are: (i) defective luteal phase due to insufficient stimulation of corpora lutea formation; (ii) damage in the developmental capacity of oocytes; and (iii) massive luteolysis leading to failure of the implantation process (Lanzone *et al.*, 1989; Beckers *et al.*, 2003; Empeaire *et al.*, 2004; Andersen *et al.*, 2006).

The oocyte donation programme is a powerful tool with which to discriminate the possible negative effects of GnRH agonist triggering on the implantation process (endometrial effect) from those attributable to the oocyte cohort (follicular effect). The primary objective of this study was to compare the incidence of OHSS in oocyte donors in whom final oocyte maturation had been triggered with GnRH α or recombinant HCG. The secondary objective was to evaluate implantation, pregnancy and miscarriage rates and embryo quality obtained after these two regimes for ovulation induction.

Materials and methods

Institutional approval

This project was approved by the institutional review board on the use of human subjects in research at the Instituto Valenciano de Infertilidad, and complies with the Spanish Law of Assisted Reproductive Technologies (14/2006). The ClinicalTrials.gov identifier is NCT00505817 (accessed 15 April 2009).

Study design

This randomized, controlled, assessor-blind study employed a prospective cohort and parallel groups, and was conducted in a private infertility clinic – Instituto Valenciano de Infertilidad – in Valencia, Spain, between March 2006 and March 2007. It consists of an explorative study to assess the effect of two strategies for triggering final oocyte maturation in oocyte donors submitted to ovarian stimulation on OHSS incidence, oocyte/embryo quality, expressed by IVF outcome and laboratory parameters.

Main inclusion and exclusion criteria

Oocyte donors

Oocyte donors eligible for this study were healthy women of 18–34 years of age, with regular menstrual cycles, with no family history of hereditary or chromosomal diseases, of normal karyotype, with body mass index (BMI) 18–29 kg/m², and who tested negative when screened for sexually transmitted diseases. The written informed consent of all subjects was necessary. Women with polycystic ovary syndrome were excluded from the study population (Garrido *et al.*, 2002).

Oocyte recipients

Recipients were women of 18–49 years of age, with BMI 18–29 kg/m², with male partners without severe male factor (<5 million fresh spermatozoa/ml, <5% normal forms and/or non-obstructive azoospermia). The recipient couple gave their written informed consent. Oocyte recipients ($n = 100$) were included in this oocyte donation programme because of menopause (33), low response (29), premature ovarian failure (28) and advanced female age (10). Cases with uterine pathologies (submucous or more than 2 cm intramural fibroids, polyps, adhesions, adenomyosis, or Müllerian defects) or a history of implantation failure and recurrent miscarriage were not included in the study population.

Randomization method

A total of 115 donors were recruited after fulfilling the inclusion criteria, and 100 of these were randomized. Ten donors were excluded due to poor ovarian response (less than four mature follicles), three due to >30% drop in oestradiol concentration and two due to poor administration of the medication (Figure 1).

The randomization visit took place on the day of recombinant HCG/triptorelin administration (three of more follicles with ≥ 18 mm). Donors were randomized into two groups by a study nurse, using computer-generated random numbers. Group I ($n = 50$) constituted the study group: final oocyte maturation was induced by a single bolus of 0.2 mg triptorelin s.c. (Decapeptyl; Ipsen Pharma, Barcelona). Group II ($n = 50$) constituted the control group: final oocyte maturation was induced by 250 μ g of recombinant HCG s.c. (Ovitrelle; Serono, Madrid).

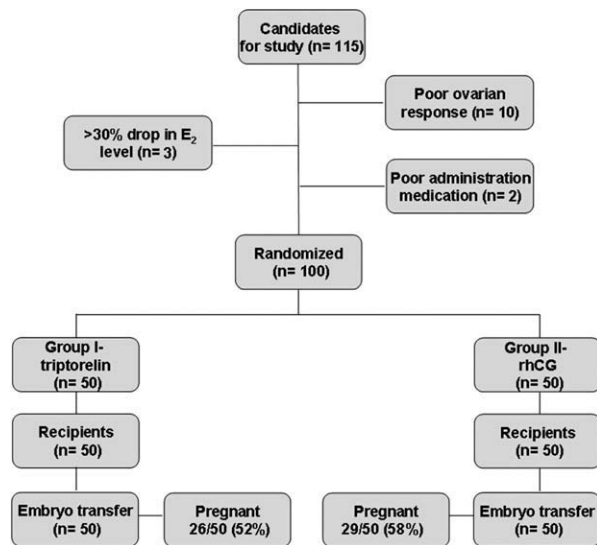


Figure 1. Flow chart of patients.

The study nurse coordinated the randomization process and distribution of medication throughout the ovarian stimulation cycles. All researchers, embryologists, laboratory personnel and sponsor staff, including the statistician responsible for the statistical analysis, were blinded to the allocation of treatment throughout the study.

Oocyte donors

The oral contraceptive pill (Neogynona; Schering, Madrid; 0.25 mg of levonorgestrel and 0.05 mg of ethinylestradiol) was taken by each patient for a total of 15 days. Transvaginal ultrasound was performed on day 2–3 of the subsequent menstruation period in order to confirm the quiescence of the ovaries, at which point ovarian stimulation was initiated.

In both groups, ovarian stimulation was performed with a fixed dose of 225 IU rFSH (Gonal; Serono) started on day 3 of menstruation and a daily 0.25 mg dose of GnRH antagonist (Cetrotide; Serono) was initiated when a leading follicle of 14 mm was observed. On day 5 of ovarian stimulation, the dose of gonadotrophin was adjusted according to oestradiol concentrations and follicular response. Serial transvaginal ultrasound examinations were performed to monitor follicular growth every 48 h.

When three or more follicles reached 18 mm in diameter, ovulation was triggered with a single bolus of 0.2 mg triptorelin s.c. in the case of the study group (Group I) and with 250 µg of recombinant HCG s.c. in the case of the control group (Group II). This was followed by transvaginal ultrasound-guided oocyte retrieval ~36 h later.

Serum oestradiol and progesterone concentrations were measured on the morning of HCG/GnRH agonist administration. Samples were tested with a microparticle enzyme immunoassay AxSYM System (Abbott Cientifico, Madrid). The serum oestradiol kit had a sensitivity of 28 pg/ml and intra-observer and inter-observer variation coefficients of 6.6% and 7.7%, respectively. The serum progesterone kit

had a sensitivity of 0.2 ng/ml, with intra-observer and inter-observer variation coefficients of 9.6% and 3.9%, respectively.

Groups were compared regarding ovarian stimulation parameters, number of oocytes retrieved, proportion of mature oocytes retrieved (number of MII oocytes/total oocytes retrieved, calculated for intracytoplasmic sperm injection patients only) and OHSS incidence. Subjects were weighed and haematological tests and ultrasound performed 2 days following oocyte retrieval and again 7 days later. Cases of OHSS were classified according to previously published criteria (Golan *et al.*, 1989).

Oocyte recipients

The protocol for hormonal replacement therapy (HRT) has been described previously (Melo *et al.*, 2006). Briefly, a baseline transvaginal scan was carried out prior to down-regulation to ensure that the uterus and ovaries were normal. Down-regulation was performed by employing an i.m. dose of 3.75 mg of triptorelin (Decapeptyl) beginning in the mid-luteal phase of the previous cycle. HRT was initiated on day 1–3 of the following cycle, and doses of oestradiol valerate (Progynova; Schering) were increased as follows: 2 mg/day for the first 8 days of treatment, 4 mg/day for the following 3 days, and at least 6 mg/day until the pregnancy test. On day 15, a scan was performed to evaluate endometrial growth. On the day after donation, 800 mg/day of micronized intravaginal progesterone (Progeffik; Effik Laboratories, Madrid) were added. Embryo transfer was performed under ultrasound guidance.

Embryos were classified according to cell number, symmetry and degree of fragmentation (Alikani *et al.*, 2000). The number of top-quality embryos was calculated by number of embryos cryopreserved plus number of embryos transferred. Serum β-human chorionic gonadotrophin (β-HCG) was measured in the recipients 16 days after oocyte retrieval from the donor. Clinical pregnancy was confirmed 2 weeks later if the existence of an embryo with

a heart beat was detected by transvaginal scan. Implantation rate was obtained by dividing the number of gestational sacs observed during the scan by the number of replaced embryos. Miscarriage rate was defined as the percentage of pregnancies that terminated before the end of week 20 of gestation after detection of the embryo's heart beat during the above-mentioned scan (Melo *et al.*, 2006).

Statistical analysis

Sample size calculation was performed considering the incidence of donor OHSS development in ovum donation cycles established to occur in 20% of the cases, to reduce its presence to 5%, with alpha error of 5% and beta error of 20%, by using the Normal corrected method, since prevalence of one group is lower than 20%.

Statistical analysis was performed by means of the chi-squared test and Student's *t*-test for categorical comparisons or Fisher's exact test, as appropriate. A *P* value of <0.05 was considered significant. Statistical analysis was performed using the Statistical Package for Social Sciences for Windows, version 11.0 (SPSS, Chicago) and MedCalc software (Belgium).

Results

Oocyte donor characteristics and ovarian stimulation parameters

As expected, no differences were found between age, BMI and antral follicle count on day 1 of ovarian stimulation in the two groups (Table 1). Regarding ovarian stimulation parameters, there were no differences in the duration of ovarian stimulation, rFSH dose or number of ampoules of the GnRH antagonist of the donors with respect to the

two regimes for triggering the final oocyte maturation (Table 1).

Moreover, concentrations of oestradiol and progesterone and number of follicles ≥ 14 mm on the day of recombinant HCG/triptorelin administration were similar in the two treatment groups. In addition, both groups had a similar number of oocytes retrieved and proportion of mature oocytes retrieved (Table 1). However, a higher OHSS rate was observed in donors who received recombinant HCG (0% versus 16%, $P = 0.003$) (Table 1). None of the oocyte donors whose final oocyte maturation was induced with triptorelin developed OHSS, while of the eight donors in the other group OHSS was observed to be mild in six, moderate in one and severe in one.

Oocyte recipient characteristics and IVF outcomes

With respect to recipient characteristics, no differences were found between age, BMI, waiting time with HRT until donation, endometrial thickness and mature oocytes received in the two groups (Table 2). Moreover, there were no differences between the groups in either fertilization ($P = 0.82$) or cleavage ($P = 0.86$) rates, or in the number of top-quality embryos ($P = 0.79$) or number of embryos transferred ($P = 0.92$) (Table 2).

Implantation (30.3% versus 27.2%) and clinical pregnancy (52.0% versus 58.0%) rates were similar in Group I and Group II, respectively. No differences were observed between the two groups regarding multiple-pregnancy rate (Table 2). Of the recipients receiving oocytes from donors in whom final oocyte maturation was induced by triptorelin, there were 22 singleton and four twin pregnancies. Recipients of oocytes from the other group had 26 singleton and three twin pregnancies. No triplets were observed.

Table 1. Demographic characteristics and ovarian stimulation parameters according to the regime used to trigger final oocyte maturation.

Parameter	Group I (GnRH α)	Group II (rHCG)
Number of subjects	50	50
Age (years)	24.9 \pm 3.7	23.9 \pm 3.9
BMI (kg/m ²)	23.5 \pm 2.9	23.1 \pm 3.1
Antral follicle count	15.3 \pm 5.2	17.1 \pm 4.7
Stimulation (days)	11.7 \pm 5.2	11.0 \pm 1.7
rFSH dose (IU)	2298 \pm 544	2260 \pm 431
GnRH antagonist (ampoules)	4.3 \pm 2.1	4.3 \pm 1.2
Oestradiol (rHCG/GnRH α day) (pg/ml)	1677 \pm 227	1419 \pm 122
Progesterone (rHCG/GnRH α day) (ng/ml)	0.79 \pm 0.36	0.81 \pm 0.57
Follicles ≥ 14 mm (rHCG/GnRH α day)	19.3 \pm 5.4	17.2 \pm 6.2
Oocytes retrieved	17.1 \pm 2.7	18.7 \pm 3.1
Proportion of MII oocytes	12.9/17.1	14.7/18.7
OHSS rate (%)	0/50 (0)	8/50 ^a (16)

Values are means \pm SD or *n* (%). BMI, body mass index; GnRH, gonadotrophin-releasing hormone; GnRH α , GnRH agonist; MII, metaphase II; OHSS, ovarian hyperstimulation syndrome; rFSH, recombinant FSH; rHCG, recombinant human chorionic gonadotrophin.

^aOHSS rate was significantly higher in Group II ($P = 0.003$).

Table 2. Recipient characteristics and IVF outcome according to the regime used to trigger final oocyte maturation.

Parameters	Group I (GnRHa)	Group II (recombinant HCG)
Number of recipients	50	50
Age (years)	39.1 ± 2.4	40.3 ± 2.1
BMI (kg/m ²)	25.1 ± 2.4	26.3 ± 2.1
Endometrial thickness (mm)	9.1 ± 0.4	8.3 ± 1.1
Number of oocytes received	17.1 ± 2.7	18.7 ± 3.1
Fertilization rate	9.7/12.9 (75.2)	10.7/14.7 (72.8)
Cleavage rate	8.7/9.7 (89.7)	9.7/10.7 (90.7)
Top-quality embryos	3.4 ± 0.4	3.5 ± 0.4
Number of embryos transferred	1.98 ± 0.27	1.98 ± 0.16
Implantation rate	34/112 (30.4)	29/107 (27.1)
Clinical pregnancy rate	26/50 (52.0)	29/50 (58.0)
Multiple-pregnancy rate	4/26 (15.4)	3/29 (10.3)
Miscarriage rate	4/26 (15.4)	3/29 (10.3)

Values are means ± SD or *n* (%). BMI, body mass index; GnRHa, gonadotrophin-releasing hormone agonist. There were no statistically significant differences between the two groups.

One anembryonic pregnancy and three spontaneous miscarriages occurred among recipients of oocytes from Group I, and there were three spontaneous miscarriages among the patients who received oocytes from Group II. There was no significant difference between the miscarriage rates of the two groups (15.3% versus 10.3%) (**Table 2**).

Discussion

As far as is known, the present study is the first prospective, controlled, randomized, assessor-blind trial performed to evaluate the effect on oocyte and embryo quality of a GnRH agonist used for triggering final oocyte maturation. Although previous studies have suggested that induction of final oocyte maturation with GnRH agonists produces poor IVF outcome ([Lanzone et al., 1989](#); [Beckers et al., 2003](#); [Emperaire et al., 2004](#); [Humaidan et al., 2005](#); [Kolibanakis et al., 2005](#); [Andersen et al., 2006](#); [Orvieto et al., 2006](#)), recent studies have provided data that challenge such conclusions ([Fauser et al., 2002](#); [Acevedo et al., 2006](#); [Engmann et al., 2006, 2008](#); [Eldar-Geva et al., 2007](#); [Griesinger et al., 2007](#)).

Damage of the corpus luteum, leading to an insufficient luteal phase, and a negative impact on oocyte/embryo and endometrium quality have been proposed as reasons for poor IVF outcome among women who receive a GnRH agonist to trigger final oocyte maturation ([Beckers et al., 2003](#); [Emperaire et al., 2004](#); [Humaidan et al., 2005](#); [Kolibanakis et al., 2005](#); [Griesinger et al., 2006](#)). GnRH receptors have been described in the human endometrium and corpus luteum ([Tavaniotou et al., 2002](#)), and may exert a direct negative effect on these structures. Recently, several authors have suggested that luteal-phase GnRH agonist or HCG administration can be used to improve the IVF outcome in these patients ([Humaidan et al., 2006](#); [Lambalk and Homburg, 2006](#); [Tesarik et al., 2006](#)). Moreover, [Fauser et al. \(2002\)](#) showed that corpus luteum formation after the endogenous FSH and LH surge induced by GnRH ago-

nists is physiological, leading to luteal-phase steroid concentrations close to those of normo-ovulatory cycles, and greater endometrial receptivity than that observed after administration of exogenous HCG. Similar findings were reported by [Lanzone et al. \(1994\)](#).

In standard IVF patients, it is difficult to separate the potential deleterious effects of GnRH agonist administration during the mid-cycle on the oocyte from those that are exerted on the endometrium, since both are simultaneously exposed to this medication. One strategy by which the endometrial factor can be discriminated from the quality of the oocyte/embryo cohort is to compare IVF outcome in frozen-thawed cycles with embryos obtained after a GnRH agonist versus HCG regime for triggering final oocyte maturation. Recently, [Griesinger et al. \(2007\)](#) studied the IVF outcome of 53 frozen-thawed cycles in patients receiving HCG and 32 frozen-thawed cycles in patients receiving GnRH agonist. They observed that the likelihood of live birth in frozen-embryo replacement cycles after GnRH-agonist triggering did not appear to be impaired. Moreover, [Eldar-Geva et al. \(2007\)](#) verified a similar outcome after transfer of cryopreserved embryos following both regimes, suggesting that there was no negative impact on oocyte/embryo quality when final oocyte maturation was achieved by GnRH agonist administration.

Another strategy is the oocyte donation programme, which offers a powerful tool with which to discriminate between the two factors. Choosing a donor patient helps to reduce the variability in oocyte quality that infertility may introduce. Oocyte donors are young and fertile, and tend to respond to ovarian stimulation with a large number of high-quality oocytes. Moreover, the recipient endometrium is spared from any potentially harmful side-effects of ovarian stimulation, including that of a GnRH agonist. [Acevedo et al. \(2006\)](#) observed no detrimental effect on oocyte/embryo quality in donors that received a GnRH agonist for triggering the final oocyte maturation.

The efficacy of this regime has been demonstrated in women undergoing ovarian stimulation (Olivennes *et al.*, 1996; Itskovitz *et al.*, 1991; Fauser *et al.*, 2002; Beckers *et al.*, 2003). In the present study, the number of oocytes retrieved and the proportion of mature oocytes obtained proved to be similar, suggesting that the GnRH agonist did not affect the process of oocyte maturation. Humaidan *et al.* (2005) retrieved significantly more MII oocytes after a GnRH agonist was used to trigger ovulation. The explanation for this result was that optimal oocyte maturation may have been achieved by a simultaneous and coordinated effect of a mid-cycle FSH and LH surge.

Replacing recombinant HCG with a single bolus of GnRH agonist for final oocyte maturation prevents OHSS and permits the continuation of the treatment cycle. Several authors have studied the applicability of this regime regarding this issue (Emperaire and Ruffie, 1991; Itskovitz *et al.*, 1991; Kol *et al.*, 1996; Lewit *et al.*, 1996; Babayof *et al.*, 2006; Engmann *et al.*, 2006, 2008). A shorter half-life of the endogenous LH surge and the subsequent pituitary suppression that leads to early luteolysis and a reduced luteal-phase steroidal concentration may explain the lower incidence of OHSS among patients submitted to GnRH agonist triggering (Lanzone *et al.*, 1989; Beckers *et al.*, 2003; Emperaire *et al.*, 2004; Andersen *et al.*, 2006). In the present study, none of the oocyte donors undergoing induction of final oocyte maturation developed OHSS while eight of the donors in the other group did. This finding is supported by previous reports in the literature.

A direct negative impact of GnRH agonist mid-cycle administration on the developmental capacity of the oocyte/embryo cohort has been reported (Humaidan *et al.*, 2005; Kolibianakis *et al.*, 2005; Andersen *et al.*, 2006; Griesinger *et al.*, 2006). This study's findings suggested no such detrimental effect by this regime on early embryo development, since similar fertilization and cleavage rates and numbers of top-quality embryos and embryos transferred were observed in both groups. Similarly, using the oocyte donation model, Acevedo *et al.* (2006) did not observe any differences in oocyte morphology or embryo quality.

Poor IVF outcome has been observed by several authors, but a recent meta-analysis by Griesinger *et al.* (2006) included only three trials that achieved methodological quality (Fauser *et al.*, 2002; Humaidan *et al.*, 2005; Kolibianakis *et al.*, 2005). They concluded that the use of a GnRH agonist to trigger final oocyte maturation in IVF compared well with HCG-triggered cycles with respect to the number of mature oocytes achieved and subsequent embryonic cleavage. However, the likelihood of an ongoing clinical pregnancy after GnRH agonist triggering was significantly lower than that following standard HCG treatment. In the present study, there was a trend towards a higher clinical pregnancy rate in recipients who received oocytes from donors with HCG-triggered cycles (58% versus 52%), although the difference was not statistically significant. Moreover, the miscarriage rate appeared to be similar, if somewhat lower in HCG-triggered cycles.

Oocyte donors are young and tend to have a high ovarian response, therefore presenting two risk factors for OHSS. Despite significant progress, there are no effective strategies for prevention of OHSS. Based on these findings and those of previous studies, it is believed that, once donors undergoing a GnRH antagonist protocol with a high ovarian response have been identified, the most effective strategy may be to trigger final oocyte maturation with a GnRH agonist. However, the possible damage effect of this treatment on endometrial quality must be studied, and the risk of a poor IVF outcome versus the possible beneficial effect on the OHSS rate must be taken into account.

In summary, the results of this study suggest that GnRH agonist instead of recombinant HCG effectively triggers final oocyte maturation in oocyte donors without a negative effect on implantation, pregnancy and miscarriage rates, and may be effective in the prevention of OHSS in this group of women.

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