Triggering with human chorionic gonadotropin or a gonadotropin-releasing hormone agonist in gonadotropin-releasing hormone antagonist-treated oocyte donor cycles: findings of a large retrospective cohort study

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Objective: To compare pregnancy rates and the incidence of ovarian hyperstimulation syndrome (OHSS) in donor stimulation cycles where final maturation of oocytes was induced with recombinant hCG or GnRH agonist.
Design: Retrospective, cohort study.
Setting: Private infertility clinic.
Patient(s): A total of 1171 egg donors performing 2077 stimulation cycles.
Intervention(s): Controlled ovarian hyperstimulation of egg donors with GnRH antagonist protocol triggered with recombinant hCG (rhCG; 250 μg) or GnRH agonist (triptorelin 0.2 mg) based on the physician's decision.
Main Outcome Measure(s): Proportion of mature and fertilized oocytes per donor cycle; clinical, ongoing pregnancy and implantation rate in recipients; and incidence of moderate/severe OHSS in oocyte donors.
Result(s): The proportion of mature oocytes was comparable, whereas the difference in the fertilization rate reached statistical significance (65% vs. 69%). No significant differences were observed in the implantation rate or clinical and ongoing pregnancy rates per ET. The incidence of moderate/severe OHSS was 1.26% (13/1031; 95% confidence interval [CI], 0.74–2.15) and 0% (0/1046; 95% CI, 0.00–0.37) in the rhCG and GnRH agonist groups, respectively.
Conclusion(s): Recipient outcome was not significantly different when using oocytes from GnRH antagonist–treated donor cycles triggered with hCG or GnRH agonist. However, GnRH agonist triggering was associated with a lower incidence of moderate/severe OHSS in egg donors. (Fertil Steril® 2009;91:365–71. ©2009 by American Society for Reproductive Medicine.)

Key Words: Oocyte donation, GnRH antagonist, GnRH agonist triggering, OHSS

The substitution of hCG with a GnRH agonist as a triggering agent of final oocyte maturation has been described in a clinical setting from the early nineties (1–5); nevertheless, its widespread use was hampered by the fact that it could be applied only to ovulation induction or non-down-regulated gonadotropin-only IVF cycles. With the advent and increasing use of GnRH antagonist protocols, a renewed interest in GnRH agonist triggering has emerged. Uncontrolled, observational trials described a beneficial effect virtually eliminating ovarian hyperstimulation syndrome (OHSS) in high-risk patients (6, 7). On the other hand, randomized clinical trials (8, 9) performed in normal-responder IVF patients have shown disappointing results in terms of pregnancy rates, probably due to a pronounced luteal phase insufficiency. Controversy still exists as to the possibility of a modified luteal phase support regimen that could counterbalance the negative effect of GnRH agonist triggering (10–12).

The favorable outcome observed in frozen-thawed embryo replacement cycles supports the hypothesis (13, 14) that oocyte developmental potential and embryo quality remain unaffected after GnRH agonist triggering. This finding is further supported by analyzing the outcome in oocyte donation cycles. To date, only small-scale studies are available (15, 16). These found comparable pregnancy rates but could not evaluate the effect of GnRH agonist triggering on OHSS incidence due to their small sample size.

The development of a simple and safe treatment protocol is of paramount importance in the setting of oocyte donation, in which treatment risks for the donor should be minimized as much as possible. In recent years, the clinical practice of

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our oocyte donation program has gradually changed in favor of the use of the GnRH antagonist protocol for donor stimulation (17). This enabled us to introduce the GnRH agonist triggering especially in high-risk patients. The aim of our retrospective study was to compare the proportion of mature and fertilized oocytes per donor cycle; to compare the clinical, ongoing pregnancy and implantation rates in recipients; and to determine the incidence of moderate/severe OHSS on a large cohort of oocyte donation cycles.

MATERIALS AND METHODS

Donors

All consecutive oocyte donation cycles performed in a private fertility center in which donors were treated with a GnRH antagonist stimulation protocol and reached oocyte retrieval were analyzed retrospectively. The study period was between November 2003 and March 2007. In our center, during the study period the GnRH antagonist protocol was used in the majority of oocyte donor cycles (72%). Oocyte donation was performed according to the Spanish Act on Assisted Reproduction. Donation was anonymous and altruistic, and donors were required to be between 18 and 35 years of age. A conventional clinical and psychological workup was performed, including karyotype. Institutional Review Board approval was not required for the present study because of its retrospective nature and because of the fact that study data were constantly managed in a way that excluded the identification of subjects.

Ovarian Stimulation

Donors were stimulated with recombinant FSH (Gonal-F, Serono; or Puregon, Organon, Madrid, Spain) or purified hMG (Menopur, Madrid, Spain; Ferring, Madrid, Spain) from day 2 of their menstrual cycle with an average starting dose of 225 IU. The first control (ultrasound and serum E_2) was normally performed after 5 days of stimulation, and the daily gonadotropin dose was adjusted individually according to the ovarian response. The GnRH antagonist (Cetrotide; Serono, Madrid, Spain) was introduced according to a multiple-dose protocol (0.25 mg/day) when a leading follicle of 14 mm and/or an E_2 level of 400 pg/mL were present. Triggering was performed when at least three follicles $\geq$18 mm were present, either with 250 μg recombinant hCG (rhCG; Ovitrelle; Serono, Madrid, Spain) or with 0.2 mg of triptorelin SC (Decapeptyl, Ipsen Pharma, Barcelona, Spain). The triggering agent was chosen by the physician who performed the last control, taking into account the total number of follicles and/or the final serum E_2 level. Coasting was initiated when E_2 levels exceeded 6000 pg/mL. Altogether, 33 cycles (2.8%) were coasted; all but two of them were triggered with the GnRH agonist. The outcome of these cycles was not significantly different from the other noncoasted cycles (data not shown). The oocyte retrieval was scheduled 36 hours after triggering. The last dose of the GnRH antagonist was injected $\leq$24 hours before triggering. A secular trend was observed in the use of the GnRH agonist triggering with an increasing use during the study period. Nonetheless, because in our program no significant differences were observed in fertilization, pregnancy, and implantation rates during the examined period (data not shown), the above fact probably did not influence the final results.

Donor Follow-up and Management

After oocyte retrieval, all donors were informed about the possible symptoms of OHSS and about preventive measures. They were also counseled to avoid sexual intercourse until their next menstrual period. From the day of the oocyte retrieval, systematic follow-up was performed by telephone, and, if necessary, donors were managed on an outpatient basis until 2 weeks after the procedure. Every donor was encouraged to present for check-up if experiencing any symptoms. On consultation, a physical examination, vaginal and abdominal ultrasound scan, and blood analysis (blood count including leukocytes and hematocrit, liver and renal function, ionogram, and coagulation tests) were performed. The outpatient management was bed rest, fluid balance monitoring, and symptomatic therapy for relief of pain and discomfort. OHSS was classified according to criteria described by Navot et al. (18). Donors diagnosed with mild/moderate OHSS were followed up every 48 hours until the complete resolution of the syndrome had been achieved. Donors were hospitalized when there was a high risk of developing severe OHSS or if there was no clinical improvement during outpatient management. Inpatient treatment was conducted according to a previously published conservative medical approach (19).

Recipients

Before treatment, careful clinical assessment was carried out in the oocyte recipient candidates including a general physical and gynecological examination, blood tests (hematology, biochemistry, and serology), a cervical smear, and a pelvic ultrasound scan. The uterine cavity was assessed by either a hysterosalpingography or hysteroscopy. Oral estradiol valerate (Progynova, Schering Spain, Madrid, Spain) was used in a constant-dose regimen for the endometrial preparation. Patients on standby received up to 6 mg a day, and the duration of the treatment varied in accordance with the availability of the oocytes. From the day of the oocyte retrieval, 800 mg of micronized vaginal P (Utrogestan, Laboratorio Seid, Barcelona, Spain) was added.

Intracytoplasmic Sperm Injection (ICSI) Procedure and Embryo Assessment

The ICSI procedure was performed routinely to avoid immature oocytes being given to the recipients and to increase fertilization rate. Less than three mature (metaphase II [MII]) oocytes were not attributed to recipients.

Developing embryos were classified according to their morphological appearance using a modification of the combined embryo score described by Coroleu et al. (20), taking into account the number of blastomeres, their form, and the

percentage of cytoplasmic fragmentation, with an optimal quality embryo scoring maximum of 10. Embryos were transferred into the uterine cavity almost exclusively on day 2 or 3 after the ICSI procedure. The ET procedure was performed using abdominal ultrasound guidance.

In case of pregnancy, hormone therapy was continued during the 100 days after the embryo replacement. Each pregnancy with at least one intrauterine sac revealed by ultrasound approximately 5 weeks after transfer was considered to be a clinical pregnancy. The implantation rate was defined as the ratio of gestational sacs to the number of embryos transferred. Miscarriage was defined as a first-trimester pregnancy loss occurring after the first ultrasound scan (sixth to seventh week of pregnancy) but before the confirmation of an ongoing pregnancy. Only pregnancy losses documented earlier by the presence of gestational sac(s) were considered as first-trimester miscarriages, otherwise they were considered as biochemical pregnancies. Ongoing pregnancy was defined as a viable pregnancy confirmed on an ultrasound scan performed at 12 weeks.

Outcome Measures

Primary outcome measures were the proportion of mature (MII) and fertilized oocytes per donor cycle as well as clinical and ongoing pregnancy rates and implantation and miscarriage rates in recipients. The secondary outcome measure was the incidence of moderate/severe OHSS in oocyte donors.

Statistical Analysis

For the statistical analysis concerning the primary outcome measures, only the first cycle of every donor was included. For the calculation of OHSS incidence, all donor cycles were taken into account. Values are expressed as mean ± SD. Metric variables were analyzed by the independent *t*-test, and nominal variables by the χ^2-test. $P<.05$ was considered statistically significant. Although currently no data are available about the exact risk reduction in OHSS related to GnRH agonist triggering (21), it is reasonable to suppose that such an effect would be detectable only in large cohorts. One must take into account the low occurrence of moderate/severe OHSS if clinically not significant mild cases are excluded. The study of Papanikolaou et al. found a 1.2% rate of early-onset moderate/severe OHSS in GnRH-antagonist treated IVF patients triggered with hCG (22). Power calculations performed with data from the present study showed that it was sufficiently powered (at a statistical power of 78% and an alpha-error of 5%) to detect a four-fold difference in the occurrence of clinically significant OHSS.

RESULTS

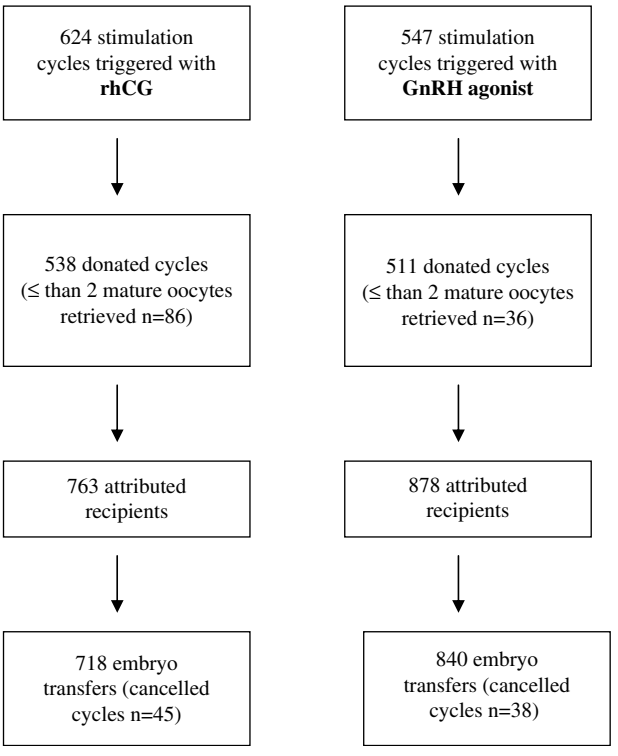
A total number of 2077 stimulation cycles that reached oocyte retrieval performed on 1171 donors were analyzed retrospectively. For the statistical analysis, only the first cycle of every donor was included (1171 cycles).

In 624 stimulation cycles, the triggering agent was rhCG, whereas in 547 cycles, a GnRH agonist was used to induce final oocyte maturation. A flow chart of patient events in the study is depicted in Figure 1. Stimulation data and other measures of donor outcome according to the triggering agent used are shown in Table 1. No differences were observed in stimulation days and total FSH dose between the two groups, whereas the mean donor age was significantly lower in the GnRH agonist group. Final E_2 levels, the follicular count at the last ultrasound, and the number of retrieved oocytes (cumulus-oocyte complexes and mature) were higher in the group triggered with a GnRH agonist. The rate of nonattributed donor cycles (less than three mature oocytes retrieved) was significantly higher in the hCG group. The proportion of mature (MII) oocytes was not significantly different. The difference in fertilization rates after ICSI reached statistical significance ($P=.003$), whereas fertilization failure occurred at a comparable rate in the two groups.

Mature oocytes were attributed to 763 and 878 recipients, respectively. Embryo replacement ensued in 718 and 840 cycles, respectively. Data on recipient outcome according to the triggering agent used in the donor cycle are shown in Table 2. No significant differences were observed in the number and the quality of transferred embryos or clinical and ongoing pregnancy rates between the two groups. Implantation and miscarriage rates were also comparable. There were no

FIGURE 1

Flow-chart of study events.



Bodri. GnRHa versus hCG trigger in donor cycles. Fertil Steril 2009.

TABLE 1

Description of donor cycles according to the triggering agent.

Triggering agent	rhCG	GnRH agonist	*P*
No. of cycles	624	547	—
Mean donor age	26.5 ± 4.1	25.5 ± 4.1	<.0001[a]
Days of stimulation	10 ± 1.68	9.9 ± 1.5	.61[a]
Total FSH used, IU	2256 ± 536	2175 ± 529	.1[a]
Final E_2 level, pg/mL	2241 ± 1099	3128 ± 1520	<.0001[a]
No. of follicles ≥18 mm	3.1 ± 1.8	4.1 ± 2.6	<.0001[a]
No. of follicles ≥16 mm	6.0 ± 2.5	8.5 ± 3.6	<.0001[a]
No. of follicles ≥14 mm	9.2 ± 3.8	13.5 ± 4.9	<.0001[a]
No. of follicles ≥10 mm	14.5 ± 6.1	21.5 ± 7.4	<.0001[a]
No oocytes retrieved, n (%)	3 (0.48%)	6 (1.09%)	.23[b]
No attributed recipient (≤2 MII oocytes) n, (%)	86 (13.7%)	36 (6.5%)	.0002[b]
Retrieved oocytes (COC)	9.8 ± 5.8	13.6 ± 7.3	<.0001[a]
Mature (MII) oocytes	6.9 ± 4.3	9.2 ± 4.8	<.0001[a]
Proportion of MII oocytes (%)	69.6 ± 24.1	68.9 ± 18	.56[a]
Fertilized (2PN) oocytes	5.1 ± 3.2	6.8 ± 3.8	<.0001[a]
Fertilization rate (%)	65 ± 24	69 ± 20.1	.003[a]
Fertilization failure, n (%)	9 (1.67%)	5 (0.97%)	.33[b]

Note: Values are mean ± SD.
[a] Independent *t*-test.
[b] χ^2-square test.

Bodri. GnRHa versus hCG trigger in donor cycles. Fertil Steril 2009.

differences observed in twinning and triplet rates between the two groups.

Moderate/severe OHSS was diagnosed in 13 donors. OHSS occurred only in cases in which rhCG was used as a triggering agent. Ultrasound and/or clinical evidence of ascites were found in all patients. Hemoconcentration (hematocrit ≥45) was found in six patients, whereas elevated liver enzymes were found in five cases. Six patients required hospitalization, and four of them were severe OHSS cases. The mean duration of hospital stay was 7.0 days (range, 4–9 days). Ascites puncture was performed by culdocentesis in one patient. All donors recovered completely within 2 weeks of oocyte retrieval, with outpatient management alone or after hospitalization. Consequently, the incidence of moderate/severe OHSS in the group triggered with rhCG was found to be 1.26% (13/1031; 95% CI, 0.74–2.15), whereas no cases (0/1046; 95% CI, 0.00–0.37) were observed in the group triggered with the GnRH agonist.

DISCUSSION

In our retrospective, cohort study, when comparing two large groups of GnRH antagonist-treated donor cycles triggered with two different pharmacological agents, we found no significant difference in the proportion of mature oocytes per donor cycle, whereas the difference in fertilization rates reached statistical significance. Furthermore, measures characterizing recipient outcome (clinical and ongoing pregnancy rates and implantation and miscarriage rates) were also not statistically different. We did, however, observe a significantly lower incidence of moderate/severe OHSS in donor cycles triggered with the GnRH agonist. The rate of donor cycles in which no recipient could be attributed due to the low number of retrieved mature oocytes (less than three) was significantly higher in the hCG group. This could be ascribed to the inherent bias in the follicular count between the two groups as hCG was systematically used in cycles with fewer follicles. Although in our study the differences in fertilization rates between the two groups reached statistical significance (65% vs. 69%; *P*=.003), this is probably a chance finding due to the large sample size and seems not to have any clinical significance because it does not really affect recipient outcome. The above findings suggest that oocyte and subsequent embryo quality is not altered by GnRH agonist triggering and that pregnancy rates are similar when replacing embryos to a recipient's endometrium unaffected by the pronounced corpus luteum insufficiency observed in IVF patients.

GnRH agonists administered in the midcycle are capable of eliciting the gonadotropin surge from the hypophysary, which is necessary to provoke final oocyte maturation (2, 23, 24). The GnRH agonist–induced surge, however, has a shorter duration and a different profile compared with the natural surge or especially compared with hCG administration (2). This difference has also been elegantly demonstrated

TABLE 2

Recipient outcome.

	rhCG	GnRH agonist	*P*
Number of allocated recipients, n	763	878	—
Cancelled cycles, n	45	38	.16[a]
Embryo replacements, n	718	840	—
Transferred embryos per recipient, mean ± SD	1.93 ± 0.4	1.93 ± 0.32	.87[b]
Mean embryo score, mean ± SD[c]	8.5 ± 1.2	8.6 ± 1.1	.3[b]
Clinical pregnancy rate,[d] n (%) (95% CI)	305/718 (42.4) (38.9–46.1)	326/840 (38.8) (35.5–42.1)	.33[a]
Implantation rate,[e] n (%) (95% CI)	404/1386 (29.1) (26.8–31.6)	421/1624 (25.9) (23.8–28.1)	0.13[a]
Miscarriage rate n (%) (95% CI)	55/305 (18) (14.1–22.7)	56/326 (17.1) (13.4–21.6)	.81[a]
Ongoing pregnancy rate,[d] n (%) (95% CI)	250/718 (34.8) (31.4–38.3)	270/840 (32.1) (29–35.3)	.43[a]
Twins,[e] n (%) (95% CI)	93/305 (30.4) (25.5–35.8)	93/326 (28.5) (23.9–33.6)	.69[a]
Triplets,[e] n (%) (95% CI)	3/305 (0.98) (0.34–2.85)	1/326 (0.31) (0.05–1.72)	.28[a]

[a] χ^2-square test.
[b] Independent *t*-test.
[c] To calculate the mean embryo score, only cleavage-stage embryos (day 2–3) were taken into account (out of 3010 embryos, 43 compacted embryos and four blastocysts could not be scored with the combined embryo score).
[d] Per ET.
[e] According to gestational sacs observed at the sixth – seventh gestational week's ultrasound scan.

Bodri. GnRHa versus hCG trigger in donor cycles. Fertil Steril 2009.

at the follicular level by studying follicular fluid obtained during oocyte retrieval (25). The study of luteal phase endocrine profiles also showed significantly lower steroid levels after GnRH agonist triggering as compared with triggering with hCG (26–28). This is due to a quick, irreversible luteolysis that could be mediated by pituitary down-regulation and/or by some other as yet unknown mechanism (15, 29). This fact is of particular interest in the prevention of OHSS as it is universally acknowledged that the syndrome is closely related to the presence of multiple overstimulated corpora lutea. The concept of GnRH agonist triggering has gained wide popularity after demonstrating complete prevention of clinically significant OHSS in high-risk patient groups (6, 7).

Nonetheless, subsequent randomized clinical trials that evaluated pregnancy outcome in IVF cycles dampened the initial enthusiasm (8, 9). Griesinger et al. (21) in their meta-analysis analyzing the three available randomized clinical trials at the time of writing concluded that GnRH agonist triggering yields a comparable number of oocytes capable of undergoing fertilization and subsequent embryonic cleavage as compared with hCG. The proportion of mature oocytes, fertilization rates, and mean embryo score were also comparable. This hypothesis was further supported in a follow-up study of the previously mentioned randomized clinical trials that evaluated live-birth rates after frozen-thawed embryo replacement cycles (14). Moreover, in a recent proof-of-concept study, a favorable outcome was observed after GnRH agonist triggering and elective cryopreservation in high-risk IVF patients (13). The above-mentioned meta-analysis could not draw any conclusions regarding OHSS incidence from the available data. On the other hand, the prospective study of Babayof et al. detected a significant reduction in OHSS incidence in a high-risk group that was characterized by a majority of patients with polycystic ovarian morphology and high oocyte yield (26).

Until methods are found that prove to be unequivocally efficient in improving outcome in IVF patients after GnRH agonist triggering, as stated in the above-mentioned meta-analysis (21), this approach could still be successfully applied in oocyte donation cycles insofar as it represents a safe treatment concept for the oocyte donor and provides a good outcome for the recipient. So far only small-scale studies have evaluated the outcome of GnRH agonist triggering in oocyte donation cycles (15, 16). The only randomized clinical trial published to date (15) found no significant difference in the number of obtained oocytes, fertilization rates, or recipients' clinical pregnancy and implantation rates. Shapiro et al. (16) found similar results in their retrospective study of comparable size. Although in line with our findings, these studies were insufficiently powered to detect any difference in

clinically significant OHSS. Acevedo et al. (15) with 30 donors in each treatment arm detected a significant difference in favor of the agonist group (4/30 vs. 0/30). Nevertheless, all of their OHSS cases were of a mild degree. Shapiro et al. (16) found only one case of OHSS in the hCG group requiring culdocentesis.

The current study has several limitations mainly due to its retrospective nature. At the beginning of the study period, no clinical experience was yet available as to the preventive effect of GnRH agonist triggering on OHSS; therefore the distinction between low- and high-risk groups was made on a somewhat arbitrary basis. The choice of the triggering agent could also be influenced by the individual physician who scheduled the oocyte pick-up procedure depending on his/her personal experience. Furthermore, as doctors were not blinded to the triggering agent used when attending donors who presented for check-up after oocyte pick-up, it could influence their readiness to diagnose OHSS. The calculated incidence of OHSS could also be influenced by co-interventions such as coasting, although this was used in only a very small proportion of cases. In our opinion, even if the data of current study were obtained from the everyday clinical practice and not from a thoroughly designed randomized clinical trial, the retrospective evaluation of so large a cohort is still justified.

In conclusion, the findings of our retrospective study from a cohort that is, to our knowledge, the largest published in the literature so far contribute to the growing body of evidence that supports the hypothesis that oocyte developmental potential and embryo quality are not affected by using the GnRH agonist for final oocyte maturation. Because of the observed significantly lower occurrence of moderate/severe OHSS in egg donors, this particular stimulation protocol could be preferentially used in high-responder donors, thus minimizing treatment risks. Prospective randomized studies of a larger size are still warranted to evaluate more precisely the effectiveness of GnRH agonist triggering in a more homogeneous population of donor cycles that includes normal responders.

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