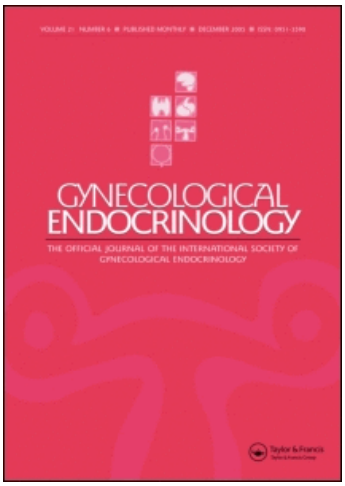

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Triggering with HCG or GnRH agonist in GnRH antagonist treated oocyte donation cycles: a randomised clinical trial

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Triggering with HCG or GnRH agonist in GnRH antagonist treated oocyte donation cycles: a randomised clinical trial

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Abstract

Aim. To compare donor and recipient outcome after inducing the final oocyte maturation with hCG or GnRH agonist in GnRH-antagonist treated oocyte donation (OD) cycles.

Methods. Two-hundred fifty-seven oocyte donors were enrolled to participate in a clinical trial in a private fertility centre. After stimulation with 225 IU rFSH and Cetrorelix 0.25 mg/day, 212 oocyte donors were randomised with sealed envelopes for triggering with recombinant hCG (Ovitrelle 250 μgr, $n = 106$) or a GnRH agonist (triptorelin 0.2 mg, $n = 106$).

Results. The number of retrieved COCs (12 ± 6.3 vs 11.4 ± 6.4), mature oocytes (8 ± 4.6 vs 7.5 ± 4.1), the proportion of mature oocytes ($67.2 \pm 20.4\%$ vs $67.1 \pm 20.9\%$) and fertilisation rates ($67.8 \pm 23.5\%$ vs $71.1 \pm 22.1\%$) were comparable. Clinical, ongoing pregnancy and live birth rates were not statistically different in the corresponding recipient groups. Nine cases of mild and one case of severe OHSS occurred in hCG group, whereas no cases were detected in GnRH agonist group.

Conclusions. The findings of our RCT suggest that donor and recipient outcome are comparable in OD cycles triggered with hCG or a GnRH agonist. Furthermore, the risk of OHSS seems to be reduced considerably, therefore the combination of a GnRH antagonist protocol with GnRH agonist triggering constitutes a safe treatment option for egg-donors.

Keywords: In-vitro *fertilisation, oocyte donation, GnRH antagonist, GnRH agonist, OHSS*

Introduction

Since the advent and the worldwide spread of oocyte donation (OD) [1], the indications of this particular treatment option grow continually with a concomitant increased demand for egg-donors. The regulation of egg donation and the availability of egg-donors require information of risks related to egg donation to prospective oocyte donors. The safety of these potential donors is one of the goals of all egg-donation programmes. One of the most feared risks of a controlled ovarian stimulation (COS) either in IVF patients or egg donors is the ovarian hyperstimulation syndrome (OHSS). The classical protocols for a COS have been using the GnRH agonists to avoid the spontaneous LH surges and the consequent cancellation of the cycle. In these cases, the final follicle maturation and ovulation triggering have been induced using hCG either purified from pregnant woman urine or the latest recombinant version available in the market. The latter doesn't seem to represent a substantial change, other than its purity in terms of the final objective, the ovulation [2].

The current availability of drugs like GnRH antagonists with their different action mechanism compared with GnRH agonist (mostly its quick suppression on the endogenous gonadotrophines and its reversibility), allows us to think of other possible options to trigger the final follicle maturation and ovulation, such as inducing a flare-up effect with GnRH agonist. From a theoretical point of view, the ovulation induced by the flare-up effect with the agonist would be a more physiological way (FSH and concomitant LH peak, also the duration of LH surge) compared with the hCG effect [3,4]. This fact could diminish some of the possible complications after triggering of the ovulation. One of these complications, already mentioned, is the OHSS in its different grades (mild, moderate or severe), especially in its early presentation, usually associated with the ovarian

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stimulation, other than the late presentation, usually related with pregnancy [5].

Current evidence seems to show that in the context of GnRH antagonist protocol for COS for IVF patients, the ovulation triggering with GnRH agonist have comparable results in terms of embryological laboratory results but a possible lack in the patient's luteal phase that ends in poorer pregnancy rates, compared with hCG [6–8]. In the context of an egg donation programme, where patients are not going to get pregnant, GnRH agonist triggering seems to provide a simple, safe and effective treatment protocol. To date only retrospective cohort studies [9] or small-scale randomised clinical trials [10] have been published on the effect of GnRH agonist triggering in OD cycles. Our study has been designed to provide more evidence on this subject.

Materials and methods

Patients

A prospective, randomised, open-label study was performed between September 2005 and March 2007 in a private fertility centre. Pregnancy follow-up was conducted until November 2007. The oocyte donors were between 18 and 35 years old and had a BMI less than 30 kg/m^2 and regular (26–35 days) menstrual cycles. Donors with a previous history of low response to ovarian stimulation, with polycystic ovaries or using oral contraceptive pills were excluded. OD was performed according to the Spanish Act on Reproduction in a voluntary, anonymous and altruistic manner. In the antagonist protocol, the ovarian stimulation began with 225 IU of recombinant FSH (Gonal-F, Serono, Madrid, Spain) from day 2 of the menstrual cycle, and the GnRH antagonist (Cetrotide, Serono, Madrid, Spain) (0.25 mg/day) was introduced at the presence of a 14 mm leading follicle and/or estradiol level $\geq$400 pg/mL according to a multiple-dose, flexible protocol. The first control (ultrasonography and serum estradiol) was performed after 5 days of stimulation and the daily dose of rFSH was adjusted individually according to the ovarian response. Triggering was performed when at least three follicles of $\geq$18 mm were present, either with 250 μgr recombinant human choriogonadotrophin (rhCG) (Ovitrelle, Serono, Madrid, Spain) or with 0.2 mg of triptorelin s.c. (Decapeptyl, Ipsen Pharma, Barcelona, Spain) according to the randomisation procedure. The oocyte retrieval was scheduled 36 h after triggering. The last dose of the daily GnRH antagonist was injected $\leq$24 h before triggering. Donors could be included only once in the study. The randomisation was performed at the time of the last ultrasound control by a study nurse with sealed, opaque envelopes. Donors with a final estradiol level $\geq$4.500 pg/mL and/or $\geq$20 follicles $\geq$14 mm at their last control were excluded from randomisation and triggered with the GnRH agonist because of a high OHSS risk. Donors who needed coasting were also excluded from randomisation. Donors were followed-up for 2 weeks after oocyte retrieval. OHSS was classified according to criteria described by Navot et al. [11].

A total of 274 recipients cycles were included in the study (in some cases donor oocytes were given to more than one recipient). All recipients were $\leq$50 years old and the main indications of egg donation were premature ovarian failure, reduced ovarian reserve or a history of previous failed IVF cycles. All recipients who had ovarian function were down regulated with the administration of a long-acting GnRH agonist (Decapeptyl, i.m. 3.75 mg, Ipsen Pharma, Barcelona, Spain) in the mid-luteal phase of their cycle. Thereafter oral estradiol valerate (Progynova, Schering, Spain) was used in an initial progressive dosage to 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 donor's oocyte retrieval, 800 mg of micronised vaginal progesterone daily (Utrogestan, Laboratorio Seid, Spain) was added.

ICSI procedure and embryo assessment

The ICSI procedure was performed routinely in order to avoid immature oocytes being given to the recipients and to increase fertilisation rate. Less than three mature (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. [12], taking into account the number of blastomeres, their shape and the percentage of cytoplasmic fragmentation, with an optimal quality embryo scoring maximum 10. Embryos were transferred into the uterine cavity almost exclusively on day 2 or 3 after the ICSI procedure. The embryo transfer procedure was performed using abdominal ultrasound guidance. In case of pregnancy, hormonal replacement therapy was continued during 100 days following the embryo replacement. Each pregnancy with at least one intrauterine sac revealed by ultrasonography 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 (6–7th week of pregnancy). Ongoing pregnancy was defined as a viable pregnancy confirmed on an ultrasound scan performed at 12 weeks. Live birth was defined as the delivery of a viable infant after the 24th pregnancy week. The study was approved by the

Ethical Committee of our institution and informed consent was obtained from all participants.

Outcome measures

Donor outcome measures were the duration of stimulation, total FSH dose, final E2 levels and follicular count at the last ultrasound control, the number of retrieved oocytes (COC and MII) and fertilisation rate. The incidence of mild and moderate/severe OHSS was also registered. Outcome measures in recipients were clinical, ongoing and live birth rates as well as implantation and miscarriage and twinning rates.

Statistical analysis and sample size calculations

Values are expressed as mean $\pm$ SD. Metric variables were analysed by the independent *t*-test or the Mann–Whitney U-test according to their distribution. Nominal variables were analysed by the Chi-square or the Fisher's exact test as appropriate. $P < 0.05$ was considered statistically significant. According to Daya S [13] when comparing different ovarian stimulation protocols the difference of two mature (MII) oocytes between the groups is usually considered clinically significant. Using data obtained in a previous clinical trial of our group [14] (8.4 ± 4.4 MII oocytes were obtained in the GnRH antagonist group) sample calculations showed that a total of 212 oocyte donors (106 per treatment arm) would be needed to detect the above-mentioned difference (at a power of 90% and significance level of 5% with a two-tailed test).

Results

Out of 257 oocyte donors that fulfilled eligibility criteria, 212 were prospectively randomised at the last follicular control to receive rhCG or a GnRH agonist for the induction of final oocyte maturation. Forty-five patients were excluded from randomisation because of a high OHSS risk according to criteria included in the study design ($n = 33$), coasting ($n = 5$), low ovarian response ($n = 6$) or any mistake during treatment ($n = 1$). A flow chart of patient events is depicted in Figure 1. All 33 patients who were excluded for high OHSS risk were subsequently triggered with a GnRH agonist. No cases of OHSS were observed in this group. Stimulation data and other measures of donor outcome according to the triggering agent used are shown in Table I. The donor groups were comparable regarding to their age and BMI. No differences were observed in stimulation days, total FSH dose, final estradiol levels, the follicular count at the last ultrasound and the number of retrieved oocytes (COCs and mature) between the groups. The proportion of mature (MII) oocytes and fertilisation rates after ICSI were comparable, whereas fertilisation failure occurred once in each group. The rate of non-attributed donor cycles (less than three mature oocytes retrieved) was similar. Nine donors had mild and one donor a severe OHSS in the rhCG group. This patient was diagnosed as having ascitis and elevated liver enzymes and was successfully managed on an outpatient basis. No OHSS cases occurred when the GnRH agonist was used as a triggering agent.

Mature oocytes were attributed to 142 and 132 recipients, respectively. In a total of 72 donor cycles (37%) oocytes were distributed to more than one recipient. Recipient groups were comparable regarding age and indications for OD. Embryo replacement ensued in 140 and 129 cycles, respectively. Data on recipient outcome according to the triggering agent used in the donor cycle are shown in Table II. No significant differences were observed in the number and the quality of transferred embryos or clinical pregnancy, ongoing pregnancy and live birth rates between the two groups. Implantation and miscarriage rates were also comparable. Although significantly more twins were observed in the GnRH agonist group at the first ultrasound scan ($P = 0.047$), this difference was not any more significant at delivery ($P = 0.18$).

Discussion

In the present clinical trial following randomisation to triggering with hCG or GnRH agonist no significant differences were observed in donor cycle outcome measures such as the number of retrieved oocytes (COCs and MII), proportion of mature oocytes, fertilisation rate and fertilisation failure. Moreover recipients' ongoing pregnancy and live birth rates as well as implantation and miscarriage rates were comparable between the two treatment arms. Although the difference in the twinning rate reached low statistical significance (0.047) in favour of the GnRH agonist group, it was probably a chance finding related to sample size. Beside comparable donor and recipient outcomes no OHSS cases were observed in the GnRH agonist group.

The final maturation of oocytes during ovarian stimulation is usually induced with hCG, which is potent surrogate to natural LH. Alternatives such as triggering with LH, native GnRH hormone or the GnRH agonist were proposed to overcome the side-effects of hCG [15]. Since the introduction of GnRH antagonist-based stimulation protocols in the clinical practice a renewed interest emerged in GnRH triggering. It was found that the surge evoked by the agonist has a shorter duration and a different profile, as compared with the natural surge or especially to hCG administration [4]. The study of luteal phase endocrine profiles also showed significantly lower steroid levels after GnRH agonist

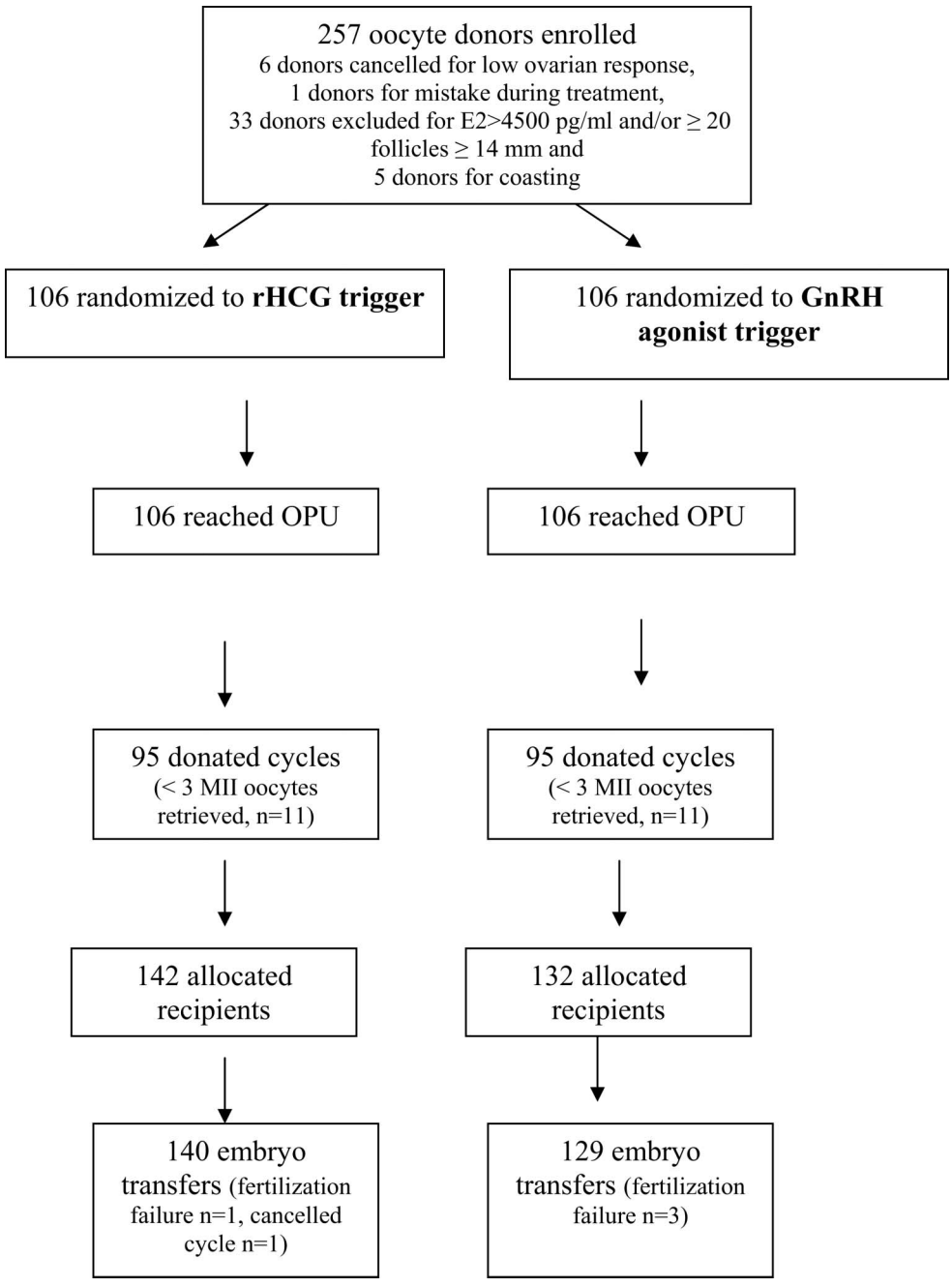

Figure 1. Flow-chart of patients treated in the study.

triggering as compared with hCG [3,16,17]. The absence of over-stimulated corpora lutea is the key to OHSS prevention [18].

Observational, uncontrolled reports on the use of the GnRH agonist to induce final oocyte maturation were published since the early nineties [4,19,20]. Later on a number of randomised clinical trials were performed in such different settings like IVF patients at high OHSS risk, normoresponder IVF patients or egg donors. Clinical trials performed in high risk patients with polycystic ovaries [16,21] showed that whereas in the control group the rate of moderate/severe OHSS cases reached 15–31%, in turn after GnRH agonist triggering no cases occurred. Complete OHSS prevention (at least that of clinically significant moderate/severe cases) was already demonstrated since the earliest studies on GnRH agonist triggering [22]. The body of evidence accumulated to date leaves no place to doubt regarding the benefits of GnRH agonist triggering, to the point that any further prospective trial comparing hCG with the GnRH agonist in high OHSS risk patients could be considered as unethical [23].

Randomised clinical trials conducted in normoresponder IVF patients [7,8] confirmed that after GnRH agonist triggering the number of obtained

Table I. Description of donors and donor cycle outcomes.

Triggering agent	rhCG	GnRH agonist	*P*
Number of randomised patients	106	106	–
Age	26.6 ± 3.6	25.8 ± 3.9	0.13[a]
BMI	22.8 ± 2.9	22.9 ± 2.9	0.62[a]
Days of stimulation	10 ± 1.5	9.9 ± 1.4	0.57[b]
Total rFSH (IU) used	2237 ± 435	2188 ± 357	0.37[a]
Oestradiol on triggering day (pg/mL)	2233 ± 870	2038 ± 852	0.1[a]
Number of follicles ≥18 mm	3.4 ± 1.7	3.7 ± 1.9	0.07[b]
Number of follicles ≥16 mm	6.7 ± 2.6	7 ± 2.7	0.28[b]
Number of follicles ≥14 mm	10.4 ± 3.6	10.6 ± 3.6	0.32[b]
Number of follicles ≥10 mm	16.4 ± 5.8	16.7 ± 6.1	0.53[b]
COC retrieved	12 ± 6.3	11.4 ± 6.4	0.12[b]
Mature oocytes retrieved	8 ± 4.6	7.5 ± 4.1	0.38[b]
Proportion of mature oocytes (%)	67.2 ± 20.4	67.1 ± 20.9	0.79[b]
No attributed recipient (<3 MII oocytes retrieved) *n* (%)	11 (10.3)	11 (10.3)	1[c]
Fertilisation rate (%)	67.8 ± 23.5	70.1 ± 22.1	0.14[b]
Fertilised oocytes (2PN)	5.9 ± 3.4	5.8 ± 3	0.83[b]
Fertilisation failure *n* (%)	1 (0.94)	1 (0.94)	1[d]

Values are mean ± SD.
[a]Independent *t*-test.
[b]Mann–Whitney U-test.
[c]Chi-square test.
[d]Fisher's exact-test.

Table II. Description of recipients and recipient outcome.

Triggering agent	rhCG	GnRH agonist	*P*
Number of allocated recipients	142	132	–
Age (mean ± SD)	40.6 ± 4.6	40.6 ± 4.8	0.96[c]
Indication of oocyte donation			0.26[e]
Menopause *n* (%)	30 (21%)	21 (16%)	
Previous failed IVF cycles *n* (%)	40 (28%)	30 (23%)	
Reduced ovarian reserve *n* (%)	71 (50%)	78 (59%)	
Others *n* (%)	1 (1%)	3 (2%)	
Embryo replacements	140	129	–
Transferred embryos per recipient, mean ± SD	1.92 ± 0.4	1.93 ± 0.4	0.86[d]
Mean embryo score, mean ± SD[a]	8.5 ± 1.1	8.7 ± 1.1	0.09[d]
Clinical pregnancy rate[b] (%)	54/142 (38)	53/132 (40.1)	0.81[e]
Implantation rate (%)	62/269 (23)	69/249 (27.7)	0.34[e]
Miscarriage rate (%)	12/54 (22.2)	12/53 (22.6)	0.96[e]
Ongoing pregnancy rate[b] (%)	42/142 (29.5)	41/132 (31)	0.84[e]
Twins at 6–7th pregnancy week (%)	6/54 (11.1)	16/53 (30.1)	0.047[e]
Triplets at 6–7th pregnancy week (%)	1/54 (1.8)	0/53 (0)	0.32[f]
Live-birth rate[b] (%)	42/142 (29.5)	40/132 (30.3)*	0.92[e]
Twins at birth (%)	6/42 (14.2)**	12/41 (29.2)***	0.18[e]

[a]To calculate the mean embryo score only cleavage-stage embryos (day 2–3) were taken into account (out of 518 embryos, 8 compacted embryos and one blastocyst could not be scored with the combined embryo score).
[b]per recipient cycle (including recipient failures without embryo transfer).
[c]Independent *t*-test.
[d]Mann–Whitney U-test.
[e]Chi-square test.
[f]Fisher's exact-test.
*One patient delivered a stillborn child at the 35th pregnancy week.
**Two cases of spontaneous embryo reduction occurred (one case of twin to singleton and another case of a triplet to a twin).
***Four cases of spontaneous embryo reduction occurred (twin to a singleton).

oocytes, the proportion of mature oocytes, fertilisation rates and embryo quality were comparable with the hCG group. Ongoing pregnancy rates were, however, disappointingly low in these studies despite enhanced luteal support. Further research is still ongoing on finding an effective luteal support after GnRH agonist triggering [24,25] or on such concepts as ''dual trigger'' [26]. A subsequent follow-up study of one of the above mentioned trials [27] showed that the developmental potential of frozen-thawed embryos is similar to that of the control group. This was proved to be the basis for an effective OHSS prevention strategy in IVF patients at high OHSS risk [28].

In the setting of OD a small scale retrospective study [9] showed favourable results with comparable donor and recipient outcome. Similar findings were confirmed by a recent retrospective report of our group [29], however on a much larger sample of egg donors. Given that the incidence of clinically significant moderate/severe OHSS in oocyte donors is relatively low (1.2%), only large size trials could detect any significant difference. A Spanish group [10] was the first to publish the results of a randomised clinical trial comparing the two different triggering agents in oocyte donor cycles treated with the GnRH antagonist protocol. Using a sample of 30 patients per treatment arm they found no significant difference in the number of retrieved and fertilised oocytes or pregnancy and implantation rates in recipients. Another RCT of comparable size [30] – published in an abstract form – reported similar findings among oocyte donors with high ovarian response. In both previous reports OHSS occurred only in the group triggered with hCG in approximately 17% of the donors. These cases were, however, of a mild degree and therefore of less clinical significance. Although in line with the findings of the present clinical trial the previous ones were still insufficiently powered, therefore a larger, adequately powered RCT remained warranted in the context of OD.

As a limitation of our study it could be mentioned that mature oocytes were distributed to more than one recipient in approximately one third of donor

cycles. Although this could be considered as a methodological error, the comparison between recipients groups did not show any significant difference. This egg-sharing policy is widely practiced in many large OD programmes, a fact which is also reflected in most studies on OD.

In summary, the findings of our randomised clinical trial confirm that the GnRH agonist is as effective as hCG in inducing final oocyte maturation in oocyte donor cycles. Although currently there is no benefit in applying GnRH agonist trigger to normoresponder IVF patients, in the context of OD, this strategy could still be universally applied. Future ovarian stimulation protocols and current coasting and cancellation criteria for egg donors might be substantially influenced by this fact. Further research could still be conducted on different GnRH agonists as triggering agents or on exploring the safety and the limits of OHSS prevention in egg donors.

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