Early ovarian hyperstimulation syndrome is completely prevented by gonadotropin releasing-hormone agonist triggering in high-risk oocyte donor cycles: a prospective, luteal-phase follow-up study

In this prospective, follow-up study of 102 high-risk oocyte donors in their luteal phase, we found a complete absence of ovarian hyperstimulation syndrome (no signs of hemoconcentration or ascites) after the donors were triggered with a gonadotropin releasing-hormone (GnRH) agonist. Due to its powerful preventive effect, the GnRH antagonist protocol combined with a GnRH agonist trigger should preferentially be used in egg donors; in conjunction with an effective luteal support or embryo cryopreservation, the protocol could also be applied to high-risk in vitro fertilization patients. (Fertil Steril® 2010;93:2418–20. ©2010 by American Society for Reproductive Medicine.)

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

From the early 1990s until recently, several studies have confirmed that after triggering women with gonadotropin releasing-hormone (GnRH) agonist the incidence of moderate/severe early-onset ovarian hyperstimulation (OHSS) is significantly reduced, making this strategy potentially valuable for use in high-risk in vitro fertilization (IVF) patients or oocyte donors. Two randomized controlled trials with high-risk IVF patients (1, 2) confirmed the absence of moderate/severe OHSS and implantation rates seemed not to be affected by the use of vigorous luteal support. In the context of oocyte donation, the reduction in OHSS incidence was demonstrated both by retrospective series (3–5) as well as randomized clinical trials (6, 7). Our group has published the largest experience (4, 7) to date with GnRH-agonist triggered oocyte donor cycles. This strategy contributed in large part to the overall safety of our egg donation program, which is predominantly based on the use of the GnRH antagonist stimulation protocol (8).

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Received May 19, 2009; revised July 4, 2009; accepted August 11, 2009; published online October 2, 2009.
D.B. has nothing to disclose. J.J.G. has nothing to disclose. M.T. has nothing to disclose. K.S. has nothing to disclose. C.E. has nothing to disclose. O.C. has nothing to disclose.
Presented at the Annual ESHRE Meeting, Amsterdam, June 28–July 1, 2009.
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On the other hand, a small number of reports have described OHSS cases despite the fact that final oocyte maturation was induced by the GnRH agonist (9, 10). These cases occurred almost exclusively during conception cycles, which means that late-onset cases could be completely avoided only by combining GnRH-agonist triggering with an effective embryo cryopreservation program. In a proof-of-concept study of 20 high-risk IVF patients, Griesinger et al. (11) described an approach that focused on cumulative pregnancy rates and OHSS incidence. This study also presented data on luteal-phase follow-up evaluations of GnRH-agonist triggered IVF patients and found no signs of moderate/severe OHSS.

The exact degree of OHSS prevention and incidence of milder symptoms yet to be evaluated on a larger sample of high-risk patients. Therefore, to gather more information on the safety and side effects of GnRH-agonist triggering, we conducted a prospective study that evaluated clinical symptoms, and biochemical and ultrasound signs of OHSS in high-response oocyte donor cycles.

MATERIALS AND METHODS

The observational study period was between April and September 2008. Institutional review board approval was obtained and included donors consented to follow-up evaluations. Gonadotropin stimulation started from day 2 of the menstrual cycle with recombinant follicle-stimulating hormone (FSH) or purified human menopausal gonadotropin (hMG). The GnRH antagonist (Cetrotide, 0.25 mg/day) was introduced according to a multiple-dose, flexible protocol. In all high-risk cases, triggering was exclusively performed with 0.2 mg of subcutaneous triptorelin, and hCG was carefully avoided for inducing final oocyte maturation. Preventive cointerventions (i.e., coasting, or intravenous albumin administration) were not applied after GnRH-agonist triggering.

For the purpose of our study, donors who were at increased OHSS risk were scheduled 3 to 6 days after their oocyte retrieval for a single follow-up examination. Every patient was included only once in the study. Increased OHSS risk was defined as

0015-0282/10/$36.00
doi:10.1016/j.fertnstert.2009.08.036

≥20 follicles ≥10 mm on the last ultrasound scan and/or a final E_2 level of ≥4000 pg/mL, and/or ≥20 retrieved cumulus–oocyte complexes (COCs). At consultation, a physical examination and a vaginal and abdominal ultrasound scan were performed by a physician together with a blood analysis (blood count including leukocytes and hematocrit, liver, and renal function). We classified OHSS according to the criteria described by Navot et al. (12) and Aboulghar and Mansour (13) where ultrasound signs of moderate OHSS were defined as ovarian enlargement (5–12 cm) and evidence of ascites. It was considered to be "severe" when moderate OHSS was accompanied by severe hemoconcentration (Hct >45%), hyperleucocytosis, and kidney or liver dysfunction. We defined ascites as free liquid in the abdominal cavity detected by abdominal ultrasound, or by the presence of notable periovarian and periuterine liquid detected by vaginal ultrasound. The quantity of free liquid in the Douglas pouch was measured as described by Álvarez et al. (14). According to their observations, an average 3.5 ± 2.8 cm^2 fluid pocket was a routine finding in donors without OHSS risk, and only >9 cm^2 fluid pockets were considered as a significant amount of free pelvic fluid.

RESULTS

A total of 102 donors were prospectively enrolled in the study according to the inclusion criteria. Data regarding ovarian stimulation and luteal-phase follow-up evaluations are summarized in Table 1. No cases of moderate/severe OHSS were observed in the study group. Seven patients (6.8%) reported pain and moderate abdominal distension at the follow-up examination (without any concomitant biochemical or ultrasound sign of OHSS), but these symptoms completely disappeared a few days later at the onset of menses. No cases of ascites were detected with abdominal ultrasound. The mean area of fluid pocket in the Douglas pouch was 3.1 ± 3.8 cm^2. In eight patients, a fluid pocket >9 cm^2 was detected but without any clinical symptoms or hemoconcentration. The mean ovarian diameter was 49.7 ± 10.7 mm and 46.9 ± 9 mm for the right and the left ovary, respectively.

Luteal phase hematocrit values (37.7 ± 2.8) were statistically significantly lower than the basal values (39.7 ± 2.5) recorded in the same patient before ovarian stimulation ($P<.0001$). A transient, mild elevation (range: 28–104 IU/mL for ALAT and 39–60 IU/mL for ASAT) of hepatic enzymes was found in six patients (5.8%). Luteal leukocyte count and creatinine values were in normal ranges. The length of the unsupported luteal phase was 5.6 days.

DISCUSSION

Our observational study demonstrated that GnRH-agonist triggering completely prevented the development of early-onset OHSS (absence of hemoconcentration or accumulation of ascites) in high-risk oocyte donors.

In addition to clinical assessment, we also evaluated the objective ultrasound and biochemical signs of OHSS. Hemoconcentration is a particularly sensitive marker of the degree of OHSS severity (15). It is remarkable that mean luteal hematocrit values were significantly different (2 points lower) from basal values recorded in the same patient before ovarian stimulation, thus excluding any OHSS-related hemoconcentration. On the other hand, in our series in a small proportion of donors we detected a transient mild elevation of hepatic enzymes without accompanying hemoconcentration, ascites, or any other clinical sign of OHSS. It could be hypothesized that these alterations were related more to the ovarian stimulation itself (possibly mediated by elevated estradiol levels) than to OHSS (16).

In our series, the ultrasound OHSS markers found after a high ovarian response (Douglas fluid pocket or ovarian size) were almost identical to those found in patients without any OHSS risk (average ovarian diameter <5 cm and Douglas fluid pocket <3.5 cm^2). Although in a few patients (7.8%) the size of Douglas pouch fluid pocket was above the level (9 cm^2) that determined significant pelvic fluid, these patients did not present clinical symptoms or hemoconcentration. In our opinion, these cases cannot be classified

TABLE 1

Donor cycles and luteal phase follow-up evaluation.

	Mean ± standard deviation	Range
Mean donor age (y)	25.9 ± 4.4	18–35
Starting FSH dose (IU)	203.0 ± 35.0	112.5–300
Days of stimulation	10.1 ± 1.3	7–15
Total FSH (IU) used	1983.0 ± 476.0	1012.5–3375
Final estradiol level (pg/mL)	3337.0 ± 1825.0	143–8474
Number of follicles ≥10 mm	25.1 ± 6.2	13–42
Retrieved oocytes (COC)	19.8 ± 7.2	5–40
Basal hematocrit	39.7 ± 2.5[a]	34.1–45.7
Luteal phase hematocrit	37.7 ± 2.8[a]	26.5–46.4
Luteal leukocytes	7880.0 ± 1980.0	4240–13580
Serum ALAT (IU/mL)	20.0 ± 7.0	7–104
Serum ASAT (IU/mL)	16.0 ± 8.0	9–60
Serum creatinine	0.8 ± 0.1	0.6–1.1
Diameter, right ovary (mm)	49.7 ± 10.9	29.5–79
Diameter, left ovary (mm)	48.9 ± 9.0	28–71
Douglas pouch fluid pocket (cm^2)	3.1 ± 3.8	0–19.6

[a] Independent *t*-test ($P=.0001$).

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as moderate OHSS and are probably related to some degree of intraperitoneal bleeding that occurred after oocyte retrieval.

Recently, several pilot studies investigated the luteal-phase administration of different drugs (cabergoline, letrozole, or GnRH agonist/antagonists) as possible methods of OHSS prevention (14, 17, 18). Similarly to our study, they examined high-risk oocyte donors but with a smaller number of patients. Cabergoline, which is one the most investigated new drugs, reduced the occurrence of early OHSS but was not sufficient to completely eliminate it. Álvarez et al. (14) observed the occurrence of moderate/severe OHSS in 31.4% of his experimental group (compared with 62.5% in the high-risk control group). Moreover, Douglas fluid pocket measurements in the cabergoline-treated group of Álvarez et al. (14) were significantly higher than in our series. Therefore, our findings suggest that compared with other pharmaceutic interventions GnRH-agonist triggering is currently the most effective way of OHSS prevention.

This argument strongly supports the preferential use of a GnRH antagonist protocol coupled with GnRH-agonist triggering in the stimulation of oocyte donors. In addition to increased donor safety, the clinical management of oocyte donor cycles is also profoundly influenced. Cycle monitoring becomes much easier (reducing or even eliminating the need for hormonal assays), and interventions for OHSS prevention (coasting or cycle cancellation) are no longer necessary (5). It must be pointed out, however, that in a few patients (6% to 7%) some milder symptoms are still present and this is probably related to oocyte retrieval and/or a high ovarian response. Therefore, to minimize donor discomfort and to also avoid possible alterations in egg quality related to a high response, excessive stimulation of oocyte donors is still not recommended. It could be argued that one of the main limitations of our observational study is the absence of a control group triggered with human chorionic gonadotropin (hCG). Nonetheless, as pointed out by Kol and Solt (19), currently with the available body of evidence supporting the powerful preventive effect of GnRH-agonist triggering, any prospective study that exposes the control group to a hCG-mediated high OHSS risk could be considered unethical.

Our findings suggest that GnRH agonist triggering is highly efficient in preventing clinically significant early OHSS in oocyte donation cycles. Due to this fact, this stimulation protocol should become the treatment of first choice for egg donors; in conjunction with an effective luteal support or embryo cryopreservation, it could also be applied to high-risk IVF patients.

Acknowledgments: The authors thank Susana Bigas, Bibiana Celma, Olga Bautista, and Maia Ferrer for their help in the management of study patients, and Dr. Paul Maguire for the linguistic revision of the manuscript.

REFERENCES

1. Babayof R, Margalioth EJ, Huleihel M, Amash A, Zylber-Haran E, Gal M, et al. Serum inhibin A, VEGF and TNFα levels after triggering oocyte maturation with GnRH agonist compared with HCG in women with polycystic ovaries undergoing IVF treatment: a prospective randomized trial. Hum Reprod 2006;21:1260–5.
2. Engmann L, DiLuigi A, Schmidt D, Nulsen J, Maier D, Benadiva C. The use of gonadotropin-releasing hormone (GnRH) agonist to induce oocyte maturation after cotreatment with GnRH antagonist in high-risk patients undergoing in vitro fertilization prevents the risk of ovarian hyperstimulation syndrome: a prospective randomized controlled study. Fertil Steril 2008;89:84–91.
3. Shapiro BS, Daneshmand ST, Garner FC, Aguirre M, Ross R. Comparison of human chorionic gonadotropin and gonadotropin-releasing hormone agonist for final oocyte maturation in oocyte donor cycles. Fertil Steril 2007;88:237–9.
4. Bodri D, Guillen JJ, Galindo A, Mataro D, Pujol A, Coll O. 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. Fertil Steril 2009;91:365–71.
5. Hernandez ER, Gomez-Palomares JL, Ricciarelli E. No room for cancellation, coasting, or ovarian hyperstimulation syndrome in oocyte donation cycles. Fertil Steril 2009;91(Suppl):1358–61.
6. Acevedo B, Gomez-Palomares JL, Ricciarelli E, Hernandez ER. Triggering ovulation with gonadotropin-releasing hormone agonists does not compromise embryo implantation rates. Fertil Steril 2006;86:1682–7.
7. Galindo A, Bodri D, Guillen JJ, Colodron M, Vernaeve V, Coll O. Triggering with HCG or GnRH agonist in GnRH antagonist treated oocyte donation cycles: a randomised clinical trial. Gynecol Endocrinol 2009;25:60–6.
8. Bodri D, Guillen JJ, Polo A, Trullenque M, Esteve C, Coll O. Complications related to ovarian stimulation and oocyte retrieval in 4052 oocyte donor cycles. Reprod Biomed Online 2008;17:237–43.
9. van der Meer S, Gerris J, Joostens M, Tas B. Triggering of ovulation using a gonadotrophin-releasing hormone agonist does not prevent ovarian hyperstimulation syndrome. Hum Reprod 1993;8:1628–31.
10. Chun E. Severe OHSS can be prevented in GnRH antagonist protocol using GnRH agonist to trigger ovulation [abstract P-149]. Fertil Steril 2005;84(Suppl 1):S301.
11. Griesinger G, von Otte S, Schroer A, Ludwig AK, Diedrich K, Al-Hasani S, et al. Elective cryopreservation of all pronuclear oocytes after GnRH agonist triggering of final oocyte maturation in patients at risk of developing OHSS: a prospective, observational proof-of-concept study. Hum Reprod 2007;22:1348–52.
12. Navot D, Bergh PA, Laufer N. Ovarian hyperstimulation syndrome in novel reproductive technologies: prevention and treatment. Fertil Steril 1992;58:249–61.
13. Aboulghar MA, Mansour RT. Ovarian hyperstimulation syndrome: classifications and critical analysis of preventive measures. Hum Reprod Update 2003;9:275–89.
14. Álvarez C, Marti-Bonmati L, Novella-Maestre E, Sanz R, Gomez R, Fernandez-Sanchez M, et al. Dopamine agonist cabergoline reduces hemoconcentration and ascites in hyperstimulated women undergoing assisted reproduction. J Clin Endocrinol Metab 2007;92:2931–7.
15. Fabregues F, Balasch J, Manau D, Jimenez W, Arroyo V, Creus M, et al. Haematocrit, leukocyte and platelet counts and the severity of the ovarian hyperstimulation syndrome. Hum Reprod 1998;13:2406–10.
16. Fabregues F, Balasch J, Gines P, Manau D, Jimenez W, Arroyo V, et al. Ascites and liver test abnormalities during severe ovarian hyperstimulation syndrome. Am J Gastroenterol 1999;94:994–9.
17. Garcia-Velasco JA, Quea G, Piro M, Mayoral M, Ruiz M, Toribio M, et al. Letrozole administration during the luteal phase after ovarian stimulation impacts corpus luteum function: a randomized, placebo-controlled trial. Fertil Steril 2009;92:222–5.
18. Giles J, Requena A, Garcia-Velasco JA, Pacheco A, Pellicer J, Pellicer A. GnRH analogue for the prevention of ovarian hyperstimulation syndrome: a pilot study. Fertil Steril 2009;91(Suppl):1366–9.
19. Kol S, Solt I. GnRH agonist for triggering final oocyte maturation in patients at risk of ovarian hyperstimulation syndrome: still a controversy? J Assist Reprod Genet 2008;25:63–6.