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ARTICLE

Gonadotrophin-releasing hormone agonist trigger and freeze-all strategy does not prevent severe ovarian hyperstimulation syndrome: a report of three cases

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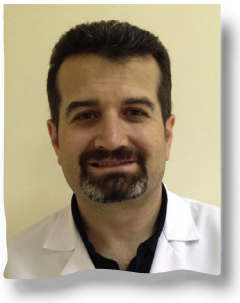

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Abstract Ovarian hyperstimulation syndrome (OHSS) is the most serious iatrogenic complication of IVF cycles. Although the development of effective treatment strategies for this syndrome is important, preventing OHSS is more crucial. Triggering ovulation with a gonadotrophin-releasing hormone (GnRH) agonist is one method used to avoid OHSS. In this paper, three patients who developed severe OHSS after undergoing GnRH agonist triggering and freezing of all embryos in a GnRH antagonist protocol are described. A review of the literature is also provided. This report highlights the ongoing risk of severe OHSS even after GnRH agonist triggering combined with freezing all embryos in GnRH antagonist cycles. Other prevention strategies might be considered for extreme hyper-responders.

KEYWORDS: freeze-all, GnRH agonist, OHSS, segmentation, trigger

Introduction

Ovarian hyperstimulation syndrome (OHSS) is the most serious iatrogenic complication of IVF cycles. Although the development of effective treatment strategies for this syndrome is important, prevention methods are more crucial. Several management options have been recommended to date, including low-dose, gonadotrophin-releasing hormone (GnRH) antagonists, reduced-dose human chorionic gonadotrophin (HCG) to trigger ovulation, avoidance of HCG, in-vitro

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maturation, cycle cancellation, coasting, insulin sensitizing agents, albumin, hydroxyethyl starch and dopamine agonists (Humaidan et al., 2010).

HCG is an excellent trigger for final oocyte maturation because of its homology with LH, extended half-life and simple manufacturing process. However, OHSS almost always requires either exogenous administration or the endogenous presence of this molecule (Kol and Humaiden, 2013). Therefore, alternate triggering options may be key in the prevention and management of OHSS. The introduction of GnRH antagonist protocols has enabled GnRH agonists to induce final oocyte maturation. The GnRH agonist displaces the GnRH antagonist in the pituitary gland, activating the GnRH receptor and resulting in a gonadotrophin surge similar to the natural midcycle surge (Kol and Humaiden, 2013).

Does GnRH agonist triggering completely prevent OHSS in all IVF cycles? The incidence of severe OHSS was reportedly 0.72% in GnRH agonist-triggered cycles in a high-risk patient group in which a single 1500 IU HCG injection was also used for luteal support at the time of oocyte retrieval. This incidence is lower than that of HCG-triggered cycles (2–3%) (Iliodromiti et al., 2013; Papanikolaou et al., 2006). On the other hand, Seyhan et al. (2013) reported a higher incidence of OHSS (26%) in high-risk patients undergoing a similar treatment protocol. Therefore, a segmented approach, including GnRH agonist triggering plus freezing of all embryos, was recommended for complete prevention of OHSS, especially for patients with an extreme ovarian response (Devroey et al., 2011; Seyhan et al., 2013).

Two cases of severe OHSS after GnRH agonist triggering combined with a freeze-all approach in a GnRH antagonist protocol were recently reported by Fatemi et al. (2014). They emphasized that the freeze-all strategy might not completely eliminate OHSS in all patients. Griesinger et al. (2011) also reported an early onset OHSS with this approach. It was, however, disputed as being a case of intraperitoneal haemorrhage rather than OHSS (Fatemi et al., 2014; Griesinger et al., 2011; Kol and Humaiden, 2013). We herein also describe three cases of severe early onset OHSS after a GnRH agonist trigger and freeze-all approach.

Materials and methods

Case 1

A 27-year-old woman had a 10-year history of infertility related to polycystic ovary syndrome. She had previously undergone two treatments involving gonadotrophin administration plus intrauterine insemination, and one failed IVF cycle. During both cycles, OHSS developed, and the woman's gynaecological examination revealed a normal uterus and polycystic ovaries on both sides. She had 22 and 18 antral follicles on her left and right ovary, respectively. Hysterosalpingography showed normal patency of both tubes. Her endocrine profile on the second day of menstruation was as follows: FSH 5.32 mIU/mL; LH 18.03 mIU/mL; oestradiol 48.2 pg/mL; and thyroid-stimulating hormone 1.19 mIU/L. Her body mass index (BMI) was 23.9.

A GnRH antagonist down-regulated cycle using cetrorelix (Cetrotide®; Merck Serono, Turkey) was carried out. Ovarian stimulation was started on menstrual cycle day 2 with 125 IU of recombinant FSH (rFSH) (Puregon®; MSD, Organon, Norway). Ultrasound scanning and hormonal blood analysis of oestradiol and LH was used for cycle monitoring. On cycle day 7 when the leading follicle diameter was 14 mm, GnRH antagonist was started. The oestradiol concentration was 4858 pg/mL on cycle day 8, and coasting was performed. The oestradiol concentration on the day of trigger (day 9) was 5985 pg/mL. The patient received a total dose of 775 IU of rFSH during stimulation. Final oocyte maturation was triggered by administration of 1 mg leuprolide acetate (Lucrin®, Abbott, Turkey). After 36 h, oocyte retrieval (OPU) was carried out. Ultrasonographic examination during OPU revealed that the number of follicles over 11 mm was 29. Twenty-seven oocytes were obtained; 15 of them were metaphase II, and 12 of them were fertilized after ICSI. In total, 10 embryos (day 2) were frozen. Hydroxyethyl starch (1000 mL) was also administered during OPU.

The patient was hospitalized owing to abdominal pain and distension 4 days after OPU. Ultrasonographic examination revealed enlarged ovaries (9 cm on both sides) and severe ascites. Her laboratory results indicated haemoconcentration: haemoglobin 15.3 g/dL; white blood cell count 24,000/μL; and haematocrit 50%. Hydroxyethyl starch (6%, 500 mL) was initially administered. Thereafter, albumin (25%) was administered in doses of 50 g infused over 4 h and repeated every 12 h as necessary. Ascites fluid (3000 mL) was drained by ultrasound-guided paracentesis. Low-molecular-weight heparin (Clexane; 4000 anti-Xa IU/0.4 mL), cabergoline (0.5 mg/day), and cetrorelix acetate (0.25 mg/day) were also administered during hospitalization. The patient was discharged on day 7 of hospitalization. Clinical pregnancy was achieved during the second frozen-thawed cycle.

Case 2

A 30-year-old woman had an 8-year history of infertility. She had menstrual irregularity with oligomenorrhoea, and her gynaecological examination revealed polycystic ovaries on both sides. She had 20 antral follicles on both ovaries. Her BMI was 31.2. Genetic analysis revealed 46,XX,45,XY,t(13;14)(q10;q10). Preimplantation genetic diagnosis was planned. The cycle was carried out with a GnRH-antagonist down-regulated cycle using cetrorelix (Cetrotide; Merck Serono). Ovarian stimulation was started on menstrual cycle day 2 with a daily dose of 225 IU of rFSH (Puregon; Organon, Norway). The gonadotrophin dose was relatively higher than in the first case because of the woman's high BMI. When the oestradiol concentration was 1661 pg/mL and the leading follicle diameter was 12.5 mm, the GnRH antagonist was started. The oestradiol concentration on the day of trigger (day 9) was 6041 pg/mL, and at least three follicles were larger than 17 mm in mean diameter. In addition, an endometrial polyp was detected on ultrasonographic examination. Final oocyte maturation was triggered by administration of 1 mg leuprolide acetate (Lucrin, Abbott, Turkey). Thirty-six h after the GnRH agonist injection, OPU was carried out. The ultrasonographic examination during OPU revealed that 52 follicles were over 11 mm. In all, 45 oocytes were retrieved, and ICSI was carried out with 20 of them. Because of the low quality of embryos, only four were frozen.