Severe ovarian hyperstimulation syndrome after gonadotropin-releasing hormone (GnRH) agonist trigger and "freeze-all" approach in GnRH antagonist protocol

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Objective: To report two cases with GnRH agonist triggering and a freeze-all approach in a GnRH antagonist protocol resulting in the development of severe ovarian hyperstimulation syndrome (OHSS), requiring hospitalization and peritoneal drainage.
Design: Two case reports.
Setting: A tertiary referral center and an obstetrics and gynecology department of a hospital.
Patient(s): Case 1 and case 2: severe OHSS with abdominal distension, ascites development, and hemoconcentration.
Intervention(s): Case 1 and case 2: diagnosed by clinical, hematologic, and ultrasound findings. Hospitalization, IV infusion, and peritoneal drainage.
Main Outcome Measure(s): Symptomatic treatment and prevention of further complication.
Result(s): Complete recovery.
Conclusion(s): Two cases of severe OHSS after GnRH agonist trigger in a GnRH antagonist protocol without the administration of any hCG for luteal-phase support. Clinicians have to be aware that even the sequential approach to ovarian stimulation with a freeze-all attitude does not completely eliminate OHSS in all patients. (Fertil Steril® 2014;101:1008–11. ©2014 by American Society for Reproductive Medicine.)
Key Words: GnRH antagonist, ovarian hyperstimulation syndrome, GnRH agonist triggering, freeze-all

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Ovarian hyperstimulation syndrome (OHSS) is the most serious, potentially lethal complication of controlled ovarian stimulation (COS) as part of assisted reproductive technologies (ART).

The majority of severe OHSS cases follow ART, and the incidence varies owing to the variety of classification schemes; 33% of IVF cycles have been reported to be associated with mild forms of OHSS, whereas the more severe forms have been reported in 2%–6% of IVF cycles (1).

Ovarian hyperstimulation syndrome is an exaggerated response to COS characterized by the shift of protein-rich fluid from the intravascular space to the third space (mainly

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the abdominal cavity) that occurs when the ovaries become enlarged owing to follicular stimulation (2). In stimulated cycles this shift in fluid is caused by increased vascular permeability in response to stimulation by either exogenous or endogenous hCG. Prostaglandins, inhibin, the renin–angiotensin–aldosterone system, and inflammatory mediators have all been implicated in the etiology of OHSS. However, vascular endothelial growth factor (VEGF) has been identified as the major mediator (3).

The clinical manifestations of OHSS reflect the extent of the shift of fluid into the third space and the resulting hemoconcentration due to intravascular volume depletion. Symptoms range from mild abdominal distention, due to enlarged ovaries alone or with an accompanying fluid shift into the abdomen, to renal failure and death as a result of hemoconcentration with thromboembolism and reduced perfusion of organs such as the kidneys, heart, and brain (4).

A number of strategies have been used to reduce the risk of OHSS, such as the use of a GnRH antagonist protocol with low gonadotropin doses and GnRH agonist (GnRHa) trigger instead of the gold standard hCG trigger, administered as a surrogate for the natural LH surge to induce final oocyte maturation (5). A bolus of GnRHa used in this context not only induces final oocyte maturation but also acts as a luteolytic agent and prevents the secretion of vasoactive substances, mainly VEGF, from the corpora lutea (6).

Although early studies reported a significant reduction in pregnancy rates as compared with an hCG trigger (7), this was later found to be caused by a severely compromised luteal phase, which could be restored by low-dose hCG supplementation and adequate luteal P support (7).

As a means to completely avoid the risk of OHSS development after ovarian hyperstimulation, a segmentation of the IVF treatment has recently been proposed (8). This strategy implies that the stimulation and trigger is separated from the ET. Thus, patients undergo ovarian stimulation with GnRH antagonist cotreatment and final follicular maturation with a bolus of GnRHa, followed by a total freeze of all embryos. Subsequently, embryos are transferred in preferably a natural cycle, whenever possible. According to the authors, this would completely eliminate OHSS due to the absence of either exogenous or endogenous hCG. Moreover, this strategy would provide a balance between efficacy and safety of IVF treatments, creating the "OHSS-free clinic" (8).

Having followed the above-mentioned strategy for high-risk OHSS patients, we hereby present two cases in which the segmentation approach resulted in the development of severe OHSS, requiring hospitalization and peritoneal drainage.

CASE REPORTS

Case 1: Abu Dhabi/United Arab Emirates

Clinical fertility history. A 29-year-old patient from the Sultanate of Oman treated in United Arab Emirates, with a regular menstrual cycle of 28–30 days, was seen at a tertiary referral center with a 9-year history of primary infertility. Hysterosalpingography was performed in 2009, showing normal patency of both tubes. The sperm count of the partner was normal. Both partners had a normal karyotype. The patient had a normal early follicular-phase endocrine profile of FSH 4.6 mIU/mL, P 0.4 ng/mL, E_2 75 pg/mL, and T_4 17.41 pmol/L. Her body mass index was 25.3 kg/m^2 (body weight, 69 kg). The basal ultrasound showed polycystic ovary-like ovaries, with more than a total of 25 antral follicles. Before treatment the patient was informed about the possibility of a freeze-all strategy, because a high number of retrieved oocytes was anticipated.

Ovarian stimulation protocol. The patient was stimulated in a fixed GnRH antagonist protocol. Stimulation with recombinant FSH (rFSH), 150 IU, started on day 2 of the menstrual cycle, and the GnRH antagonist was administered from day 5 of stimulation (ganirelix). The stimulation lasted for 9 days, during which the rFSH dose remained unchanged, and the patient received a total dose of rFSH of 1,350 IU. Final follicular maturation was induced with a bolus of GnRHa (triptorelin, 0.3 mg). The E_2 concentration on the day of trigger was 4,300 pg/mL, P 2.0 ng/mL, and LH 8.8 mIU/mL. The ultrasound examination showed six follicles of 16 mm in diameter, 20 follicles of 15 mm in diameter, and >20 follicles between 10 and 14 mm in diameter. A total of 30 oocytes were retrieved, resulting in the vitrification of 28 metaphase II oocytes. Because of the high number of follicles present at oocyte pickup, the dopamine agonist cabergoline (0.5 mg) was also administered after oocyte pickup on a daily basis.

Results, Case 1

Day 1 after oocyte retrieval the patient was seen at the emergency unit of the hospital with abdominal distension, pain, and OHSS symptoms. A blood count revealed severe hemoconcentration: hematocrit 50%, platelet count 329,000, white blood cell (WBC) 15,620 μL, and E_2 level 1,948 pg/mL. An ultrasound scan revealed moderately enlarged ovaries of 7 cm in diameter each and severe ascites.

The weight of the patient increased by 4 kg (73 kg). Her coagulation profile remained normal. She was treated with saline infusion, continuation of dopamine agonist (cabergoline 0.5 mg), and low molecular heparine (enoxaparin, 40 mg) and antithrombosis stockings. The urine output during the following days varied between 350 and 400 mL. Two days later the abdominal discomfort was more pronounced, and an ultrasound scan revealed an increase in ascites but no change in ovarian size. A vaginal ascites puncture was performed, resulting in the removal of 2,500 mL clear fluid. Before, during, and 2 hours after ascites puncture 2,400 mL of saline was administered, as well as 100 mL of albumin solution. To exclude natural conception, serum hCG was measured, with a negative result.

After drainage and IV infusion, the hematocrit decreased to 37.6%, WBC to 11,120, platelet count to 389,000, and hemoglobin (Hgb) was 12.5 g/dL. Three days later the patient was discharged and followed up in an outpatient clinic. Menses occurred as late as 14 days after the oocyte retrieval.

Case 2: India

Clinical fertility history. The patient was a 27-year-old para 2 oocyte donor, with a regular menstrual cycle of 30 days, without any medical or surgical history.