

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.

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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 pa-

tient had a normal early follicular-phase endocrine profile of FSH 4.6 mIU/mL, P 0.4 ng/mL, E₂ 75 pg/mL, and T₄ 17.41 pmol/L. Her body mass index was 25.3 kg/m² (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 E₂ 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 μ L, and E₂ 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.

Ovarian stimulation protocol. The patient was stimulated in a fixed GnRH antagonist protocol. Stimulation started with rFSH, 187.5 IU, on day 2 of the menstrual cycle. A GnRH antagonist was administered from day 5 of stimulation (cetorelix acetate). The stimulation lasted for a total of 9 days, during which time the rFSH dose remained unchanged. The patient received a total of 1,687.5 IU of rFSH. Final follicular maturation was induced with a bolus of GnRHa (Decapeptyl, 0.2 mg). The E₂ concentration on the day of trigger was 3,578 pg/mL, and the ultrasound examination showed 10 follicles of 18–19 mm in each ovary. A total of 30 oocytes were retrieved, of which 22 metaphase II were donated.

Results, Case 2

Six days after oocyte retrieval the patient was admitted with pain and abdominal distension. Her laboratory results showed a Hgb of 12.8, hematocrit 47%, WBC 18,100, total platelet count 460,000, DLC 72/22/1/4/1, and normal coagulation profile. Her weight was 52.2 kg. Ultrasound examination revealed moderately enlarged ovaries; the right ovary was 7 cm in diameter and the left ovary 8 cm in diameter. Moderate amounts of ascites were seen. She was treated with saline infusion and daily treatment with dopamine agonist (cabergoline, 0.5 mg).

The following day, day 7 after the oocyte retrieval, the total urine output was only 400 mL, and 1 L of normal saline infusion was administered. On day 8 the body weight increased to 54.6 kg, and the urine output fell to 375 mL. A vaginal ascites puncture was performed, resulting in the removal of 3,700 mL of clear fluid. One hundred milliliters of albumin solution and 1 L of saline solution per 24 hours were infused. The Hgb decreased to 11.4, hematocrit 42%, WBC 11,700, the platelet count decreased to 434,000.

During the next 2 days the urine output increased, and the patient's overall condition improved. After 4 days of hospitalization the patient was discharged. Moreover, similar to the previous case, the GnRHa trigger apparently did not cause a clinical luteal-phase defect because the patient menstruated as late as 12 days after oocyte retrieval.

Discussion

Ovarian hyperstimulation syndrome is an iatrogenic complication of ovarian stimulation. Although the incidence of OHSS seems to be relatively low, 2% of all stimulated patients require hospitalization (1). Importantly, the consequences of OHSS may be lethal (5). Thus, because the number of IVF treatment cycles is constantly rising, reports regarding maternal mortality rates due to OHSS in The Netherlands and the United Kingdom suggest an incidence of three deaths per 100,000 IVF cycles performed (4).

Human chorionic gonadotropin has been the gold standard for final oocyte maturation as a surrogate for the mid-cycle LH surge for several decades. Because of structural and biological similarities, hCG and LH bind to and activate the same receptor. An important difference, however, exists between the half-life of LH and hCG: the half-life of LH is

60 minutes (9), whereas that of hCG is 24 hours (10). Because of its prolonged circulatory half-life, hCG exerts sustained luteotropic activity and may induce the occurrence of ovarian hyperstimulation syndrome.

During a GnRH antagonist cotreatment, the GnRH antagonist occupies the GnRH receptor without causing down-regulation, and once a bolus of GnRHa is introduced the GnRHa will displace the GnRH antagonist from the receptor, activating the receptor, which induces a release of gonadotropins (flareup). Although the GnRHa-induced surge effectively stimulates ovulation and oocyte maturation, differences exist regarding the duration and profile of the GnRHa-induced surge of gonadotropins when compared with that of the natural cycle (11). Thus, the GnRHa-induced surge lasts for approximately 24 hours, whereas in the natural cycle the endogenous LH surge lasts approximately 48 hours, leading to a significant reduction in the total amount of gonadotropins released during the GnRHa-induced surge.

The shorter duration of the endogenous LH surge induced by GnRHa triggering as compared with the continuous LH/hCG receptor stimulation for an estimate of 7–9 days with a bolus of 10,000 IU hCG, in combination with a negative impact of the supraphysiologic steroid level on LH secretion by the pituitary after COS, with a complete change in LH secretion pattern after agonist trigger, are the most plausible explanations behind the reduced risk of OHSS when GnRHa is used to trigger final oocyte maturation.

The GnRH agonist trigger is gaining momentum in the clinical use. In the IVF world survey from 123 clinics worldwide reporting on a total of 108,300 ART cases the incidence of GnRH agonist trigger varies from 5.2% to 36.1% of cases (12). In the same survey an “empty follicle” syndrome or no-oocyte retrieval was encountered by 11% of practitioners who used GnRH trigger. This is higher than the incidence of 3.5% empty follicle syndrome that has been reported previously by Castillo et al. (13). It is of importance that hypogonadotropic hypogonadic patients fail to have adequate LH surge after agonist trigger and as such are not included in the studies and such surveys (14).

To date there has been only one report of allegedly severe early-onset OHSS after GnRHa trigger in the English literature (15). However, this report was recently disputed as being a case of intraperitoneal hemorrhage rather than OHSS (16). Thus, a 30-year-old polycystic ovary patient was hospitalized and treated for OHSS with LMWH, dopamine agonists, and blood transfusion because of falling blood count. Blood-stained ascites (3.9 L) was drained from the peritoneal cavity 3 to 4 days after GnRHa trigger. This raised suspicion of a sub-acute intraperitoneal hemorrhage as a complication of the transvaginal oocyte retrieval. Importantly, the patient had no hemoconcentration, one of the clinical hallmarks of OHSS.

There has been one retrospective report of a high incidence of early-onset OHSS (22%) after GnRHa trigger, but in a population of high-responder patients who received a low-dose hCG rescue protocol despite the retrieval of between 50 and 65 metaphase II oocytes in some patients (17). In contrast, in a prospective pilot study (n = 12) in high-responder patients there was one case of late moderate OHSS that did not require hospitalization (18). The largest

randomized, controlled trial published to date in an OHSS high-risk population consisting of patients with a follicle count between 15 and 25 follicles (7) did not show any OHSS development, despite the use of the aforementioned low-dose hCG rescue protocol followed by a fresh embryo transfer. Importantly, the reproductive outcome was excellent and similar to that of hCG trigger. In the two cases reported here, no hCG was administered for luteal-phase support, and therefore these cases cannot be compared with previously published studies using luteal-phase hCG administration.

Sporadic and familial cases of spontaneous OHSS have generated an interest in genetic mechanisms for OHSS development independent of exogenous gonadotropins. Genetic studies of OHSS have focused on the FSH receptor (FSHR) gene and its mutations, as well as targeting VEGF receptors as a method to modulate OHSS. Activating mutations in the FSHR contributes to OHSS, whereas inactivating causes sterility. During the last decade, several cases of spontaneous and familial OHSS cases have been reported, suggesting a possible genetic cause for OHSS. The discovery of activating FSHR mutations that turn the receptor sensitive to stimulation by hCG (19) provided the first molecular explanation for OHSS development. In iatrogenic-caused OHSS, follicular recruitment and enlargement occur during ovarian stimulation with exogenous FSH, whereas in the spontaneous form follicular recruitment occurs later through the stimulation of the FSHR by the pregnancy-derived hCG or TSH. In both forms massive luteinization of enlarged ovaries follows, inducing the release of vasoactive mediators, leading to OHSS development.

In spontaneous OHSS cases the mechanism differs because pregnancy with rising hCG levels stimulates the abnormal FSHR receptor, causing excessive follicular growth and the associated clinical symptoms.

Activating mutations in the FSHR gene have been shown to confer a higher response to FSH, and therefore FSHR genotype may predispose women to OHSS. Although FSHR genotype cannot predict the risk of iatrogenic OHSS at present, it may be used to predict the severity of the condition.

Interestingly, in both patients apparently, no clinical luteal-phase defect occurred, because menses started between 12 and 14 days after oocyte retrieval instead of after 4 to 5 days, as is usually seen after GnRH α trigger and freeze-all. One might speculate that in these patients the presence of an activating GnRH receptor mutation caused a more-lengthy FSH and LH rise after the GnRH α trigger, which could explain not only the OHSS condition but also the normal duration of the luteal phase. However, activating LH receptor and/or FSHR mutations could also be involved. Importantly, the presence of any circulating hCG was excluded.

In conclusion, we report two cases of severe OHSS after GnRH agonist trigger in a GnRH antagonist protocol without the administration of any hCG for luteal-phase support. One might speculate whether GnRH receptor, FSHR, or LH receptor gene mutations have led to an OHSS predisposition. Future research is needed to establish a clinically useful connection between the receptor mutations and the occurrence and intensity of OHSS. 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.

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