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Gonadotropin-Releasing Hormone (GnRH) Agonist Trigger in a GnRH Antagonist Protocol and Severe Ovarian Hyperstimulation Syndrome

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Authors' contributions

All of the authors contributed substantially to the paper. Author MR reviewed the cases, performed the literature search, and wrote the paper. Authors MV, MS and SG performed the literature search, as well as revised and edited the paper. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Aims: Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic and potentially life-threatening complication of ovarian stimulation. The best strategy to prevent it is to use a gonadotropin-releasing hormone (GnRH) agonist (GnRHa) to trigger final oocyte maturation in a GnRH antagonist protocol, followed by cryopreservation of all oocytes/embryos (freeze-all strategy). The objective of this study is to describe two cases of a rare occurrence of severe OHSS following GnRHa trigger in a GnRH antagonist protocol and freeze-all strategy.
Presentation of Case: Two patients (a 33-year-old patient, and a 31-year old patient) were submitted to in vitro fertilization (IVF). The ovarian stimulation started on day 2 of her menstrual cycle in a step-down GnRH antagonist protocol. The final oocyte maturation was induced with a bolus of 0.2 mg triptorelin in both cases. Due tothe risk of OHSS, all the embryos were

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cryopreserved and no embryo transfer was performed. In the case 1, two days after oocyte retrieval, the patient was seen at the emergency and was diagnosed with severe OHSS with bilateral pleural effusion. In the case 2, three days after oocyte retrieval, the patient was seen at the emergency unit and was diagnosed with severe OHSS. Both patients were managed in an intensive care unit.

Conclusions: Unless the substitution of human chorionic gonadotropin (hCG) by GnRHa triggering in antagonist cycles is done in combination with no embryo transfer (which is the best form of OHSS prevention), and unless it virtually completely eliminates the onset of OHSS, this complication may still occur in certain groups of patients.

Keywords: GnRH agonist trigger; ovarian hyperstimulation syndrome; OHSS; freeze-all.

1. INTRODUCTION

Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic, severe, and potentially life-threatening complication of ovarian stimulation, and it occurs in approximately 1%–14% of assisted reproductive technique (ART) cycles [1,2]. Human chorionic gonadotropin (hCG) is the most probable triggering factor of the syndrome [3]. After the administration of hCG, the expression of vascular endothelial growth factor (VEGF), as well as VEGF receptor 2 (VEGFR-2) messenger ribonucleic acid (mRNA), increases significantly, rising to a maximum that coincides with peaked vascular permeability (VP). These findings suggest that the syndrome can be prevented by inducing ovulation with a gonadotropin-releasing hormone agonist (GnRHa) instead of hCG, preventing VEGF overexpression [4].

The prevention of OHSS is the most important aspect of its management [5]. Many strategies have been proposed to avoid its development [1], but the best strategy is to use a GnRHa to trigger oocyte maturation in a GnRH antagonist protocol, followed by the cryopreservation of all oocytes/embryos (freeze-all strategy) [6]. Then, in a posterior cycle, the frozen–thawed embryo transfer can be performed in a receptive, non-stimulated endometrium in a natural cycle, or with endometrial priming [6]. Using this strategy, the incidence of OHSS in GnRH antagonist cycles is ~0% [7]. Apart from OHSS prevention, the freeze-all strategy may lead to improvements in *in vitro* fertilization (IVF) outcomes, with better results obtained when the elective frozen–thawed embryo transfer is performed, as compared to the fresh embryo transfer [8]. However, even in the freeze-all strategy, OHSS may occur [9].

The objective of this case report is to describe two cases of a rare occurrence of severe OHSS after GnRHa trigger in a GnRH antagonist protocol and freeze-all strategy.

2. PRESENTATION OF CASE

2.1 Case 1

A 33-year-old patient was referred to our center in January 2010 for an infertility workup. The patient has provided signed informed consent. The couple had a 2-year history of unknown infertility with no previous pregnancy or miscarriage. Her body mass index was 23.2 kg/m^2 (body weight, 67.8 kg). The sperm analysis of her partner was normal. Hysterosalpingography showed normal patency of both tubes. She had a regular menstrual cycle of 27 days and normal basal hormonal levels, as measured on day 2 of her menstrual cycle: follicle-stimulating hormone (FSH), 4.9 mIU/mL; luteinizing hormone (LH), 5.0 mIU/mL; E_2, 44 pg/mL; thyroid-stimulating hormone (TSH), 1.5; and free T_4, 1.36. The basal ultrasound showed around 14 antral follicles. It was the first IVF cycle of the couple.

Ovulation induction started on day 2 of her menstrual cycle in a step-down GnRH antagonist protocol, with 225 IU of recombinant FSH (rFSH; Gonal-F; Merck, Darmstadt, Germany). The GnRH antagonist (Cetrotide; Merck) was introduced from day 5 of stimulation. Final oocyte maturation was induced when three follicles reached 18 mm in diameter, after 11 days of stimulation, with a bolus of 0.2 mg of GnRHa (triptorelin; Gonapeptyl daily; Ferring; Kiel; Germany). The patient received a total of 1650 IU of rFSH. The hormonal profile on the day of trigger was: E_2, 2,721 pg/mL; progesterone (P), 0.7 ng/dL; and LH, 2.1 mUI/mL. The ultrasound examination showed eight follicles ≥18 mm in diameter, and ten follicles between 14–18 mm in diameter. Oocyte retrieval was performed 35 hours after the trigger by vaginal ultrasound-

guided aspiration. A total of 15 oocytes were retrieved; 13 were metaphase II, and all were inseminated (day 0) by intracytoplasmic sperm injection (ICSI), as a routine procedure in our center. On the following day (day 1), 11 oocytes were normally fertilized. On day 2, six embryos had good morphology (two to four cells, grade I/II) and were vitrified.

Two days after oocyte retrieval, the patient was seen at the emergency unit with mild abdominal distension, dyspnea, nonproductive cough, and clinical signs of dehydration. On physical examination, breath sounds were absent in ~2/3 of her bilateral lung fields. A blood count revealed severe hemoconcentration: hematocrit, 50.5%; white blood cell (WBC) count, 17,500/mm^3; and platelet count, 297,000. An ultrasound scan revealed around 700 mL of ascites and enlarged ovaries (right, 7 cm in diameter; left, 8 cm in diameter). A chest X-ray confirmed large bilateral pleural effusion. The treatment started with saline infusion, and thoracentesis was performed, with drainage of 2,200 mL of clear fluid. Deep venous thrombosis prophylaxis was started with low molecular weight heparin (enoxaparin, 40 mg/day). The symptoms and blood tests progressively improved, and after 5 days of hospitalization, the patient was discharged and followed up in an outpatient clinic.

2.2 Case 2

A 31-year-old patient was referred to our center in October 2012. The patient has provided signed informed consent. The patient had irregular menses (up to 3 months of amenorrhea), no other associated infertility factors, and no previous pregnancy or miscarriage. Her body mass index was 21.3 kg/m^2 (body weight, 59 kg). The sperm analysis of her partner was normal. Basal hormonal levels were measured on day 3 of her menstrual cycle: FSH, 5.1 mIU/mL; LH, 8.9 mIU/mL; E_2, 37 pg/mL; TSH, 1.7; and free T_4, 1.11. The basal ultrasound showed around 20 antral follicles.It was the first IVF cycle of the couple.

Ovulation induction started on day 2 of her menstrual cycle in a fixed GnRH antagonist protocol, with 150 IU of recombinant FSH (rFSH; Gonal-F; Merck, Darmstadt, Germany). The GnRH antagonist (Cetrotide; Merck) was introduced from day 5 of stimulation. The final oocyte maturation was induced when at least three follicles reached 18 mm in diameter, after 10 days of stimulation, with a bolus of 0.2 mg of GnRHa (triptorelin; Gonapeptyl daily; Ferring; Kiel; Germany). The patient received a total of 1,350 IU of rFSH. The hormonal profile on the day of trigger was as follows: E_2, 4,351 pg/mL; P, 1.2 ng/dL; and LH, 6.7 mUI/mL. The ultrasound examination showed six follicles ≥18 mm in diameter, and 17 follicles between 14–18 mm in diameter. Oocyte retrieval was performed 35 hours after the trigger by vaginal ultrasound-guided aspiration. A total of 20 oocytes were retrieved; 15 were metaphase II and were inseminated (day 0) by ICSI. On the following day (day 1), ten oocytes were normally fertilized. On day 3, seven embryos had good morphology (six to nine cells; grade I/II) and were vitrified. Because of the high number of follicles present on ultrasound on trigger day, the dopamine agonist, cabergoline (0.5 mg), was introduced per the patient's risk of OHSS.

Three days after oocyte retrieval, the patient was seen at the emergency unit with abdominal distension, dyspnea, vomiting, and the clinical signs of dehydration. A blood count revealed severe hemoconcentration: hematocrit of 46.9%; WBC count, 16,700/mm^3; platelet count, 325,000; and a normal coagulation profile. An ultrasound scan revealed a large amount of ascites and enlarged ovaries. She was treated with saline infusion and low molecular weight heparin (enoxaparin, 40 mg/day), and the dopamine agonist was continued. Vaginal paracentesis was performed, with drainage of 3,000 mL of clear fluid. Two days later, the abdominal distension evolved and another paracentesis was performed, with drainage of 1,500 mL of clear fluid. Two days later, after clinical and laboratorial improvement, the patient was discharged.

3. DISCUSSION

OHSS is an iatrogenic, potentially lethal condition, and it is still the major complication faced during controlled ovarian stimulation in IVF, associated with the presence of fluid in the third space, resulting in hypovolemia and its associated symptons [10]. There are some risk factors associated with the development of OHSS and that were present in our patients like: young age, low body mass index, high serum estradiol levels and a high AFC [10]. Thus, many strategies to prevent its occurrence have been developed, and the most effective is to substitute the use of hCG by GnRHa for final oocyte maturation, as well as to introduce the freeze-all

strategy [6]. Alternative strategy is the use of a dopamine agonist (as cabergoline) to prevent an increase in VP and reduce the severity of OHSS [2,10]. We used this strategy in one of the cases but it was not effective in reducing the severity of OHSS.

The concept of an OHSS-free clinic was developed by Devroey et al. [6], and was based on the combination of GnRHa trigger in a GnRH antagonist cycle and the cryopreservation of all embryos. The bolus of GnRHa would induce luteolysis due the short half-life of endogenous LH, as compared to the hCG trigger [11]. By not using hCG, all the VP modifications caused by its use would be avoided, preventing VEGF overexpression and the onset of OHSS [12].

But even when using this powerful alternative for prevention, OHSS may still occur, as was recently published [9] and subsequently described in this paper. The two cases described in this paper, in addition to the cases described by Fatemi el al. [9], suggest a puzzling and potentially worrisome possibility that OHSS may occasionally occur when GnRH agonists are administered alone to trigger final oocyte maturation [13]. Some hypotheses were put forth to explain these rare cases, such as the idea that this might occur due to the possible activation of mutations in the FSH and LH receptors, or it might be that the activation of a GnRH receptor mutation causes a more lengthy FSH and LH rise after the GnRHa trigger. There is also speculation that there is even an alternative mechanism that is not yet known [9].

4. CONCLUSION

In conclusion, unless the substitution of hCG by GnRHa triggering in antagonist cycles is done in combination with no embryo transfer (which is the best form of OHSS prevention), and unless it virtually completely eliminates the onset of OHSS, this complication may still occur in certain groups of patients. It is necessary to provide a close follow up of patients who are at risk of developing OHSS, even when the freeze-all embryos strategy is used.

CONSENT

All authors declare that 'written informed consent was obtained from the patient (or other approved parties) for publication of this case report.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCE

1. Nastri CO, Ferriani RA, Rocha IA, Martins WP. Ovarian hyperstimulation syndrome: pathophysiology and prevention. J Assist Reprod Genet. 2010;27:121-128.
2. Youssef MA, Van Wely M, Hassan MA, Al-Inany HG, Mochtar M, Khattab S, van der Veen F. Can dopamine agonists reduce the incidence and severity of OHSS in IVF/ICSI treatment cycles? A systematic review and meta-analysis. Hum Reprod Update. 2010;16:459-466.
3. Humaidan P, Quartarolo J, Papanikolaou EG. Preventing ovarian hyperstimulation syndrome: Guidance for the clinician. Fertil Steril. 2010;94:389-400.
4. Gómez R, Soares SR, Busso C, Garcia-Velasco JA, Simón C, Pellicer A. Physiology and pathology of ovarian hyperstimulation syndrome. Semin Reprod Med. 2010;28:448-457.
5. Aboulghar M. Symposium: Update on prediction and management of OHSS. Prevention of OHSS. Reprod Biomed Online. 2009;19:33-42.
6. Devroey P, Polyzos NP, Blockeel C. An OHSS-free Clinic by segmentation of IVF treatment. Hum Reprod. 2011;26:2593-2597.
7. Griesinger G, Schultz L, Bauer T, Broessner A, Frambach T, Kissler S. Ovarian hyperstimulation syndrome prevention by gonadotropin-releasing hormone agonist triggering of final oocyte maturation in a gonadotropin-releasing hormone antagonist protocol in combination with a 'freeze-all' strategy: A prospective multicentric study. Fertil Steril. 2011;95:2029-2033.
8. Roque M, Lattes K, Serra S, Solà I, Geber S, Carreras R, et al. Fresh embryo transfer versus frozen embryo transfer in *in vitro* fertilization cycles: A systematic review and meta-analysis. Fertil Steril. 2013;99:156-162.

9. Fatemi HM, Popovic-Todorovic B, Humaidan P, Kol S, Banker M, Devroey P, et al. Severe ovarian hyperstimulation syndrome after gonadotropin-releasing hormone (GnRH) agonist trigger and "freeze-all" approach in GnRH antagonist protocol. Fertil Steril. 2014;101:1008-1011.
10. deMouzon J, Goossens V, Bhattacharya S, Castilla JA, Ferraretti AP, Korsak V, et al. Assisted reproductive technology in Europe, 2007: results generated from European registers by ESHRE. Hum Reprod. 2012;27:954-966.
11. Kol S, Humaidan P. GnRH agonist triggering: Recent developments. Reprod Biomed Online. 2013;26:226-230.
12. Soares SR, Gómez R, Simón C, García-Velasco JA, Pellicer A. Targeting the vascular endothelial growth factor system to prevent ovarian hyperstimulation syndrome. Hum Reprod Update. 2008;14:321-333.
13. Filicori M. Preventing ovarian hyperstimulation with gonadotropin-releasing hormone agonist trigger: Is anything perfect? Fertil Steril. 2014;936-937.

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