Severe ovarian hyperstimulation syndrome in an oocyte donor despite preventive strategies

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We present a rare case of severe ovarian hyperstimulation syndrome (OHSS) in a 19-year-old woman undergoing a second donation cycle of controlled ovarian hyperstimulation. The patient developed severe OHSS despite the implementation of preventive strategies and required hospitalization for 14 days, including treatment in the intensive care unit. The underlying pathophysiology that triggers this extreme systemic response in certain patients, despite the implementation of preventive measures, remains unknown. Continued research efforts are necessary to improve our understanding and management of this condition.

Keywords: Case report; Freeze-all strategy; GnRH agonist trigger; Oocyte donor; Ovarian hyperstimulation syndrome

Introduction

Assisted reproduction procedures are generally regarded as safe. However, these approaches necessitate controlled ovarian hyperstimulation as well as surgical intervention under general anesthesia for oocyte retrieval.

One potentially life-threatening complication of assisted reproduction techniques is ovarian hyperstimulation syndrome (OHSS). Many factors contribute to this condition, the most important of which appears to be the release of high concentrations of vascular endothelial growth factor (VEGF) from the multiple corpora lutea that form following ovarian hyperstimulation [1]. This excessive release of VEGF leads to increased vascular permeability, which causes fluid to shift into third spaces, particularly the peritoneal and pleural cavities. Clinical manifestations include edema, ascites, abdominal pain, hemococoncentration, and respiratory distress. In severe cases, the syndrome can progress to renal failure and even result in death [2].

To mitigate this risk, various preventive strategies have been employed. Traditionally, administration of a human chorionic gonadotropin (hCG) bolus at the end of stimulation has been used to mimic the luteinizing hormone (LH) surge, thereby inducing final oocyte maturation before retrieval. However, hCG maintains the activity of the corpora lutea, which prolongs VEGF secretion and increases the risk of OHSS. As an alternative, the administration of a gonadotropin-releasing hormone (GnRH)-agonist bolus is now preferred because it triggers an endogenous LH surge with a shorter half-life than exogenous hCG. This approach leads to faster luteolysis and prevents the sustained secretion of VEGF [3].

Thanks to these precautions, the incidence of OHSS has decreased from approximately 2% of all cycles [4] to 26% of the small subset of women at high risk for OHSS [5] and, most recently, to the near disappearance of the syndrome [6]. Nonetheless, despite prevention efforts, isolated cases of OHSS continue to occur, as demonstrated by the present report.

Case report

We describe the case of a 19-year-old Caucasian woman who was undergoing a second cycle of controlled ovarian hyperstimulation for oocyte donation at our center and developed a rare case of OHSS.

The patient was a healthy woman with no previous medical history. All pre-stimulation assessments and routine analyses required for
donor eligibility yielded normal results. These included body mass index (20.04 kg/m²), complete blood count, liver and kidney function tests, hemostasis assessments, blood glucose measurement, serological tests for infectious diseases, and genetic screening. Additionally, we evaluated risk factors for OHSS: the patient’s anti-Müllerian hormone level was 2.3 ng/dL, her antral follicle count was approximately 12 per ovary, and no diagnosis of polycystic ovary syndrome was established.

In the first treatment cycle, the patient underwent ovarian stimulation using a short antagonist protocol. The basal LH level was 8.66 mIU/mL, and ultrasound imaging revealed 18 antral follicles. Stimulation commenced on day 3 of the menstrual cycle with a daily dose of 225 IU of urinary follicle-stimulating hormone (FSH; Fostipur; IBSA Iberia). Starting on day 5 of stimulation, a GnRH antagonist (ganirelix, Orgalutran; Organon) was introduced concurrently with the gonadotropin injection at 2:00 PM. The stimulation proceeded for a total of 8 days, with the FSH dose remaining constant throughout, resulting in a cumulative FSH administration of 1,575 IU. Ovarian maturation was ultimately induced with a bolus of GnRH agonist (triptorelin 0.2 mg, Decapeptyl, Voluson P8; GE HealthCare). At this point, the patient’s estradiol level was 4,768 pg/mL, her LH level was 3.18 mIU/mL, and her progesterone level was 1.86 ng/mL. Ultrasound examination showed 30 follicles, each measuring between 14 and 20 mm in diameter.

Thirty-six hours later, a total of 36 follicles were punctured. This yielded 27 oocyte-cumulus complexes, all containing metaphase II (MII) oocytes, which were subsequently vitrified. The measured LH level was 4.90 mIU/mL. The patient was discharged 60 minutes after the procedure in good health and experienced no complications in the subsequent days. Five days post-procedure, she experienced normal menstruation.

A second ovarian stimulation for oocyte donation was conducted 1 year after the initial procedure, utilizing a short GnRH antagonist protocol (ganirelix 0.25 mg). This regimen commenced on the third day of the menstrual cycle, with a daily self-administered dose of 225 IU of urinary FSH (Fostipur) at 2:00 PM. The basal LH level was 23.58 mIU/mL, and ultrasound revealed 24 antral follicles. On the 6th day of stimulation, the ultrasound scan identified a total of 36 follicles, each measuring between 11 and 15 mm in diameter. At this point, the urinary FSH dose was reduced to 150 IU, and the ganirelix (0.25 mg) was introduced as a GnRH antagonist to prevent premature ovulation.

The next evaluation took place 48 hours after the prior one, on the 8th day of ovarian stimulation. Ultrasound revealed a total of 26 follicles—six measuring 18 mm, 10 measuring 17 mm, and 10 measuring 16 mm—and the presence of free fluid in the pelvis. The estradiol level was 4,465 pg/mL, the LH concentration was 17.08 mIU/mL, and the progesterone level was 1.59 ng/mL. The patient reported discomfort, which included abdominal swelling, mild abdominal pain, and intermittent vomiting. Consequently, ovulation was induced using a GnRH agonist (triptorelin 0.2 mg). Oocyte retrieval was performed 36 hours later, yielding a total of 40 oocytes, 36 of which were at the MII stage.

Following the standard post-retrieval protocol, the patient was discharged 2 hours later in good clinical condition. Ultrasound revealed multiple corpora lutea, a minimal amount of free fluid in the pelvis, and no signs of active bleeding. Given the absence of severe symptoms of OHSS, no additional preventive measures, such as dopamine agonists, were administered that day.

Three days after oocyte retrieval, the patient returned to the fertility center with severe abdominal pain and swelling, limb edema, vomiting, and general discomfort. Although her vital signs were within normal ranges (blood pressure 110/70 mm Hg, temperature 35.8 °C, oxygen saturation 98%), clinical examination indicated a tender abdomen upon palpation and oliguria (0.4 mL/kg/hr). Ultrasound imaging revealed enlarged ovaries and free fluid accumulation in the pelvic cavity, distributed within both paracolic gutters and the peritoneal space.

Blood analysis ruled out pregnancy (beta-hCG <5 mIU/mL) and revealed signs of hemococoncentration (hematocrit 52.9%, hemoglobin 17.9 g/dL), leukocytosis (17,100/μL), and normal levels of hepatic function, ions, and coagulation parameters. Despite receiving intravenous fluids, analgesia, and antiemetic treatment, the patient showed no clinical improvement. Consequently, we decided to transfer her to the hospital for further management with a diagnosis of OHSS.

At the hospital, the patient underwent comprehensive treatment that included intravenous fluids, low-molecular-weight heparin, diuretics, antiemetics, and analgesia. Despite these interventions, her clinical condition deteriorated; this included the development of bilateral pleural effusion, with approximately 1 L in each hemithorax. The patient was admitted to the intensive care unit for 7 days to receive symptomatic treatment and close monitoring of her vital signs. After a total of 14 days of recovery, she was discharged from the hospital, having fully recovered.

Discussion

The first reported case of OHSS following the use of a GnRH agonist trigger was documented by Griesinger et al. [7] in 2011. However, a subsequent review by Kol and Humaidan [8] suggested that the incident was likely an intraperitoneal hemorrhage rather than true OHSS. To our knowledge, to date, only six cases of severe OHSS in a segmented cycle have been reported [5,9,10].
Our case involves a young oocyte donor who developed OHSS during only her second hyperstimulation cycle, despite both cycles using the same medication (urinary FSH Fostipur) at the same initial dosage (225 IU daily, administered subcutaneously) and over the same short duration (8 days). It remains unclear why the patient developed OHSS in the second cycle but not in the first.

One possible contributing factor to the development of OHSS is the number of oocytes retrieved. In the two cycles, we obtained 27 and 36 MII oocytes, respectively; both numbers exceeded the thresholds described by Humaidan et al. [11] and Mocanu et al. [12] as increasing the risk for OHSS. However, no evidence suggests that the risk of OHSS escalates with an increasing number of follicles beyond this threshold, so we do not consider this to be the cause of the syndrome arising in the second stimulation. Furthermore, over the past 2 years, we have performed more than 20 ovarian retrievals in women with 40 or more follicles measuring greater than 14 mm, yielding a range of 19 to 44 MII oocytes, without any cases of OHSS. None of these parameters has been shown to represent an independent risk factor for predicting the occurrence of OHSS with satisfactory accuracy. However, when combined with serum estradiol levels on the day of ovulation induction, the predictive accuracy is improved [1]. Unfortunately, due to the extreme rarity of OHSS in donors when ovulation is triggered by a GnRH agonist, we do not routinely measure estradiol levels unless we believe the information may inform a specific clinical decision.

The other difference between the two cycles in the present patient was the addition of 225 IU of urinary FSH in the morning of the same day as the GnRH agonist bolus. Ganirelix exerts a pituitary effect that lasts approximately 48 hours, whereas the effect of urinary FSH extends for 3 days or more. Therefore, a prolonged and exaggerated FSH effect may have been present without antagonist inhibition. However, using a GnRH agonist trigger can lead to a luteal phase deficiency, potentially preventing the rise of VEGF and the subsequent development of OHSS. The use of FSH to stimulate ovulation, either alone or with an hCG bolus, has long been proposed [13,14] and appears to yield comparable results to other triggering methods (hCG, GnRH agonist, or a combination of both) in terms of the number of oocytes retrieved, the fecundation rate, and the production of good-quality embryos. Nevertheless, the impact on the luteal phase or the incidence of OHSS has not been well documented. However, we did not encounter a single case of OHSS after adding FSH to the GnRH bolus, which we did frequently to promote additional follicular growth before final maturation.

It appears reasonable to hypothesize that these patients may exhibit heightened sensitivity to the effects of gonadotropins, as suggested in other series of similar cases. Studies of spontaneous OHSS have focused on the potential role of the FSH receptor [15,16]. This research identified a mutation in the receptor genes that rendered it highly sensitive to hCG, leading to spontaneous and recurrent OHSS episodes during pregnancy. Our case stands out as hCG was entirely uninvolved, as confirmed by blood tests; the donor was not pregnant and had not received exogenous hCG for treatment.

Fatemi and colleagues reported an abnormal sensitivity to gonadotropins in 2014, noting an unusually extended luteal phase in their patients. They observed that in a segmented cycle, menstruation typically occurs only 4 or 5 days after ovulation induction due to a clinical luteal phase defect caused by the GnRH agonist trigger [3]. However, in cases involving abnormal gonadotropin sensitivity, menstruation was delayed and typically occurred after 12 to 14 days, as demonstrated in our patient. This prolonged luteal phase suggests a potential LH- or hCG-like action that may maintain luteal function longer than expected, possibly contributing to ovarian hyperstimulation even without exogenous hCG administration [3].

Montanelli et al. [17] discovered that a mutation in the FSH receptor also resulted in increased sensitivity to thyroid-stimulating hormone (TSH). This cross-reactivity may stem from the shared alpha subunit of FSH, TSH, LH, and hCG, along with the fact that their respective receptors evolved from a common gene. In the present case, the patient’s TSH levels were not measured, as this is not a standard part of donor screening. Nevertheless, the patient showed no clinical signs of thyroid disease, had no history of thyroid issues, and reported no use of any related medications. Consequently, altered thyroid function is not suspected to be the cause of this patient’s ovarian hyperreactivity.

The final distinction between the patient’s two cycles was the higher basal LH level observed during the second stimulation (23.58 mIU/mL) compared to the first (8.66 mIU/mL). The measurements of LH levels in this clinical case were taken 1 year apart, meaning that variables such as stress, body mass index, and changes in dietary supplementation may have influenced the results. However, the most notable factor was that the patient had been on hormonal contraceptives before the first cycle but had not used them prior to the second stimulation a year later. Given the observed variability in LH levels between the patient’s cycles, we analyzed LH levels in a sample of our oocyte donor cycles (Figure 1). Specifically, we documented the minimum and maximum LH levels across cycles that yielded 30 or more MII oocytes. The median LH level was 7.11 mIU/mL, with a minimum of 0.08 mIU/mL and a maximum of 34.73 mIU/mL, demonstrating the considerable variability of LH levels among healthy women. We observed two patients with basal LH levels exceeding 20 mIU/mL who did not exhibit any symptoms or signs of OHSS. From our experience, and in the absence of data from other research groups, high basal LH levels alone do not seem to be a risk factor for OHSS. Nonetheless, this warrants further investigation in a...
larger patient series.

In conclusion, this case exemplifies the risk of severe OHSS in patients without hCG, either exogenous or endogenous. This complication was anticipated to disappear with the introduction of in vitro fertilization cycle segmentation; however, it still occurs today. While these cases are extremely rare at present, the underlying mechanisms and prevention methods require further clarification.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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