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FERTILITY PRESERVATION

Severe ovarian hyperstimulation syndrome associated with long-acting GnRH agonist in oncofertility patients

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Abstract

Purpose To report three cases of severe ovarian hyperstimulation syndrome (OHSS) among oncofertility patients receiving a long-acting GnRH agonist for ovarian suppression after controlled ovarian hyperstimulation (COH) with a GnRH antagonist protocol

Methods Chart abstraction was completed for three patients at a single academic medical center. Patients included were undergoing fertility preservation prior to gonadotoxic chemotherapy. All patients underwent COH with GnRH antagonist protocol and embryo cryopreservation immediately followed by ovarian suppression with long-acting GnRH agonist. Main outcome measure was development of OHSS.

Results Despite using GnRH agonist trigger and freezing all embryos, patients developed ascites, intermittent hyponatremia and hemoconcentration consistent with severe early-onset OHSS after receiving long-acting GnRH agonist immediately following oocyte retrieval for ovarian preservation.

Conclusions Risk of severe OHSS may be increased when a long-acting GnRH agonist is used for ovarian suppression immediately following oocyte retrieval. A delay in initiating long-acting GnRH agonist after oocyte retrieval in patients at high risk for developing OHSS should be considered.

Keywords Ovarian hyperstimulation syndrome (OHSS) · Oncofertility · Gonadotropin-releasing hormone (GnRH) antagonist · Long-acting GnRH agonist · GnRH agonist trigger · Lupron depot

Introduction

Ovarian hyperstimulation syndrome (OHSS) following controlled ovarian hyperstimulation (COH) is a potentially severe and even life threatening complication associated with Assisted Reproductive Technologies (ART) [1]. OHSS is categorized as mild, moderate, severe, and critical based on symptoms and laboratory values [1]. The onset of OHSS can be early (within 7 days of induced ovulation) or late (after 9 days). Patients commonly experience rapid weight gain and ascites with resultant bloating and discomfort as well as laboratory abnormalities including hemoconcentration and hyponatremia [1]. Severe OHSS is defined as clinical evidence of ascites, hydrothorax, severe dyspnea, oliguria/anuria, intractable nausea/vomiting, low blood/central venous pressure, pleural effusion, rapid weight gain, syncope, severe abdominal pain, venous thrombosis, severe hemoconcentration (hematocrit > 55%), elevated white blood cell count (> 25,000 mL), creatinine clearance < 50 mL/min, creatinine > 1.6 mg/dL, sodium < 135 meq/L, potassium > 5 meq/L, or elevated liver enzymes [2].

Widespread use of a GnRH antagonist protocol with GnRH agonist trigger (commonly known as "Lupron trigger"), in addition to avoiding initiation of pregnancy when ovaries are hyperstimulated through cryopreservation of all embryos ("freeze-only"), has minimized the risk of developing severe OHSS. Multiple trials utilizing GnRH agonist trigger reported no cases of OHSS using this method [3–5]. Only a few cases of severe OHSS have been reported while using GnRH agonist trigger and freeze-only, which have been attributed to rare mutations in the genes encoding GnRH, FSH, or LH receptors [6]. The therapeutic mechanism of this

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approach, in preventing severe OHSS, is theorized to be due to the elimination of endogenous and exogenous hCG. hCG induces massive luteinization of granulosa cells, which is believed to result in the production of vascular endothelial growth factor (VEGF) which can increase vascular permeability and potentially result in the development of OHSS. The long half-life of hCG leads to its higher bioactivity as compared to the endogenous LH surge induced by GnRH agonist trigger [7, 8].

Women undergoing ART for fertility preservation prior to gonadotoxic cancer treatments, such as chemotherapy, are often placed on a long-acting GnRH agonist shortly following oocyte retrieval for indications of menstrual suppression and/or ovarian protection. Multiple randomized control trials in early stage breast cancer patients have demonstrated decreased risks of premature ovarian insufficiency in women treated with long-acting GnRH agonists [9, 10]. The most commonly used GnRH agonists include leuprolide acetate for depot suspension (Lupron depot) given at a dose of 3.75 mg as a 1-month formulation or 11.25 mg for a 3-month formulation [9]. When a long-acting GnRH agonist is initially given, there is a short gonadotropin "flare" phase resulting in a rise in FSH, LH, and estradiol, which usually lasts for 7–14 days [11–13]. We hypothesize that the sustained gonadotropin elevation during the flare phase may mimic the effect of hCG and contribute to the severe OHSS cases reported here. Development of severe OHSS may be especially catastrophic for patients undergoing chemotherapy as this complication can result in delays in initiating cancer treatment as well as place the patient at risk for significant complications.

We report herein three cases of severe OHSS in cancer patients who underwent COH for fertility preservation with GnRH antagonist protocol and ovarian suppression with long-acting GnRH agonist immediately following oocyte retrievals.

Methods

Data collection

We conducted a retrospective chart review of three patients with newly diagnosed cancers who underwent ART for fertility preservation and developed severe OHSS from January 2018 to December 2019.

Ethics

All data was obtained from chart review and reported without any patient identifiers. IRB exemption from our institution was obtained for this study.

Results

Case 1

A 39-year-old gravida 0 female with a history of polycystic ovary syndrome (PCOS), class II obesity (BMI = 38 kg/m^2) and estrogen receptor positive/progesterone receptor positive invasive ductal carcinoma of the breast, presented for fertility preservation prior to initiating chemotherapy. Her baseline ovarian reserve assessments included an anti-Mullerian hormone level of 11.6 ng/mL and an antral follicle count of 23.

Her COH followed a random start GnRH antagonist protocol. The patient had been amenorrheic for several months prior to COH start, thus her menstrual cycle phase was unknown. A total of 3525 IU of gonadotropin was used. Letrozole 7.5 mg oral daily was used throughout her COH to decrease the level of estradiol. GnRH antagonist (cetrorelix) was added on stimulation day 8 to prevent ovulation. Ovulation was triggered on day 13 using a short-acting GnRH agonist (leuprolide, 4 mg). A total of 20 follicles greater than 14 mm were visualized on the day of the trigger. Her peak estradiol level was 581 pg/mL. She was started on cabergoline 0.5 mg PV for OHSS symptom prevention on the day of trigger. She did not report any symptoms at that time. Oocyte retrieval was completed 34 h after ovulation trigger. A total of 14 oocytes were retrieved. The low yield of oocytes was due to central obesity and posterior position of the ovaries. After the retrieval, the patient was continued on letrozole and cabergoline; however, the patient self-discontinued letrozole 2 days after retrieval. Postoperatively, she received doxycycline for infection prophylaxis and continued cabergoline for a total of 8 days per the standard practice at our institution.

On the evening of oocyte retrieval, the patient presented to the Emergency Department (ED) with abdominal pain. Ultrasound at that time showed a small amount of echogenic free fluid in the pelvis (exact size was not measured). Laboratory evaluation was notable for sodium of 133 mEq/L (normal range is 135–146 mEq/L) and hematocrit of 43% (baseline hematocrit was 44% at the start of stimulation). She was discharged home and recommended to increase intake of electrolyte rich fluids and to monitor for symptoms of OHSS. On the day after retrieval, she received a long-acting GnRH agonist (11.25 mg of depot leuprolide) in her oncologist's office for ovarian protection. The next day, she began chemotherapeutic treatment with 132 mg of doxorubicin and 1320 mg of cyclophosphamide. She also received 6 mg of pegfilgrastim.

Four days after her oocyte retrieval, she represented to the ED reporting weight gain, bloating, and abdominal pain. Laboratory evaluation was notable for elevated WBC count of 20,000 cells/uL (normal range, 4300–10,000 cells/uL), normal hematocrit of 41% and normal electrolytes. CT of the

abdomen and pelvis demonstrated bilaterally enlarged ovaries and moderate amount of free fluid in the pelvis. Symptoms were thought to be likely due to OHSS. Given concern for severe OHSS in the setting of active cancer diagnosis she was recommended to begin enoxaparin for thrombosis prophylaxis [1] and to continue cabergoline. She received a daily phone call to follow-up with her symptoms and daily weight. She was called back to the clinic on the 8th day post retrieval due to worsening abdominal pain and 2.5 kg of weight gain since the day of retrieval. Pelvic ultrasound in the clinic showed moderate to large amounts of peritoneal fluid measuring 11.29 × 5.65 cm in largest dimension, left ovary measured 10.2 × 9.8 cm, and right ovary measured 10.1 × 9.8 cm. Her sodium was 135 mEq/L and hematocrit was 45%. She was diagnosed with severe OHSS given ascites, rapid weight gain, and severe abdominal pain in addition to moderate hemoconcentration and leukocytosis [2]. The patient underwent therapeutic paracentesis and a total of 900 ml of blood-tinged yellow fluid was aspirated during the procedure. Given these findings, she was continued on cabergoline 0.5 mg PV and letrozole 7.5 mg was restarted for an additional 4 days. With these measures, her symptoms improved and no additional interventions were required.

Case 2

A 33-year-old G2P2002 female with newly diagnosed stage IIIB colorectal cancer status post-surgical resection presented for fertility preservation prior to adjuvant chemotherapy. Her baseline ovarian reserve test results included an anti-Mullerian hormone level of 8.1 ng/mL and an antral follicle count of 43.

She followed a random start GnRH antagonist protocol beginning in the follicular phase for COH and received a total of 2275 IU of gonadotropin. For stimulation days 1–7, she received 7.5 mg of letrozole, and for stimulation days 8 and 9 she received 10 mg of letrozole due to elevated estradiol level of 872 pg/mL. Our institutional practice is to give 5 to 7.5 mg letrozole daily with up-titration as needed for elevated estrogen levels during COH. GnRH antagonist (cetrorelix) was started on stimulation day 6. GnRH agonist (leuprolide, 4 mg) was given on stimulation day 9 to trigger ovulation. A total of 15 follicles greater than 14 mm were visualized on the day of trigger. Her peak estradiol level was 949.0 pg/mL. She was started on cabergoline 0.5 mg PV for OHSS symptom prevention on the day after trigger. She did not report any symptoms at that time. Oocyte retrieval occurred 34 h after ovulation trigger, and a total of 23 oocytes were retrieved. Postoperatively, she received doxycycline for infection prophylaxis and continued cabergoline for a total of 8 days per the standard practice at our institution. The day after retrieval, she received long-acting GnRH agonist (3.75 mg of depot leuprolide) at her oncologist's office for ovarian protection before starting adjuvant chemotherapy.

Two days after retrieval, she presented to the clinic reporting abdominal pain, bloating, and mild nausea. Transvaginal ultrasound showed a small amount of free fluid in the posterior cul-de-sac with three pockets seen measuring 3.7 × 1.2 cm, 1.5 × 1.5 cm, and 2.8 × 2.6 cm respectively. She was recommended to increase electrolyte intake and to monitor symptoms. Four days later, she presented to the clinic with worsening symptoms and 2.2 kg of weight gain. Laboratory results were notable for a WBC count of 10,530 cells/uL (normal range, 4300–10,000 cells/uL) and hematocrit of 45%. Pelvic ultrasound showed echogenic ascites with largest pocket measuring 6.8 × 4.3 cm in size, left ovary measured 6.8 × 6.1 cm, and right ovary measured 6.7 × 6.5 cm.

She followed up in the clinic the next day (7 days after retrieval) after she reported worsening bloating, severe abdominal pain, and concentrated urine. At that time, her weight had increased a total of 3.2 kg. Laboratory evaluation was notable for a persistently elevated WBC count of 10,210 cells/uL (normal range, 4300–10,000 cells/uL), Cr = 0.63 mg/dL, and CrCl > 60 ml/min. She was diagnosed with severe OHSS given rapid weight gain, severe abdominal pain, and moderate leukocytosis [2]. Her pain subsided with oxycodone and she was started on enoxaparin for thrombosis prophylaxis as well as amoxicillin-clavulanate for infection prevention due to her recent history of intra-abdominal surgery. The patient subsequently noted resolution of her symptoms with these supportive treatments.

Case 3

A 15-year-old G0 female with medulloblastoma status postsuboccipital craniotomy with posterior fossa brain tumor resection presented for fertility preservation prior to adjuvant chemotherapy and radiation. Her baseline ovarian reserve test results included an anti-Mullerian hormone level of 2.9 ng/mL and an antral follicle count of 38. The patient reported menarche at 13 years of age and irregular menses occurring every 2–4 months and lasting 5 to 7 days.

She followed a random start GnRH antagonist protocol for COH beginning in the luteal phase and received a total of 1500 IU of gonadotropin. Letrozole 7.5 mg oral daily was used throughout her COH to decrease the level of estradiol. GnRH antagonist (cetrorelix) was started on stimulation day 6. GnRH agonist (leuprolide, 4 mg) and 1500 IU of hCG were given on stimulation day 8 to trigger ovulation. Co-trigger was used out of concern for hypothalamic dysfunction in the setting of brain tumor and resection as well as immature hypothalamic development. However, a low dose of hCG was chosen in consideration of her risk of OHSS. A total of 24 follicles greater than 14 mm were visualized on the day of trigger. Her peak estradiol level was 379 pg/mL. She was started on cabergoline 0.5 mg PV for OHSS symptom prevention on the day of trigger and was asymptomatic at that time. Post

trigger hCG was 35 IU/mL. Oocyte retrieval occurred 34 h after ovulation trigger, and a total of 25 oocytes were retrieved. Postoperatively, she continued cabergoline for a total of 8 days per the standard practice at our institution. Two days after retrieval, she received long-acting GnRH agonist (3.75 mg of depot leuprolide) at her oncologist's office.

Six days after retrieval, she presented to the ED with loss of consciousness, decreased urinary output, and abdominal bloating. Laboratory results were notable for hCG level of 1 IU/mL, sodium level of 130 mEq/L, hematocrit of 37%, WBC count of 10,500 cells/uL (normal range, 4300–10,000 cells/uL). Pelvic ultrasound showed bilateral symmetric enlargement of the ovaries measuring 11.4 × 7.3 cm on the left and 9.5 × 8.8 cm on the right as well as large volume of echogenic ascites. She had gained 4.7 kg over the 6-day period post retrieval. Neurologic exam and electrocardiogram on presentation were within normal limits making acute neurologic or cardiac process less likely. She was diagnosed with severe OHSS given oliguria, rapid weight gain, clinical ascites, hyponatremia, and moderate leukocytosis [2]. She was admitted to the hospital where she received IV normal saline to correct hyponatremia and underwent therapeutic paracentesis to remove 1000 cc of straw-colored fluid. With these measures, her symptoms resolved, lab values normalized, and she was discharged to home after 24 h. She did not require additional interventions. She received her first dose of radiation on the day of discharge from the hospital and began chemotherapeutic treatment with vincristine three days after discharge (10 days after retrieval).

Discussion

Patients with oncologic diagnoses seeking fertility preservation prior to gonadotoxic treatments pose unique considerations for OHSS prevention and management. We present three cases of early-onset severe OHSS despite using a GnRH antagonist protocol with GnRH agonist trigger and freezing all embryos. Multiple randomized controlled trials have previously shown that a GnRH agonist trigger effectively eliminates OHSS after ART [3–5]. Cases of OHSS have been reported after GnRH agonist trigger although mutations in gonadotropin receptors were thought to be the cause [14–16]. Prior studies have also shown that risk of severe OHSS is very unlikely at hCG doses ranging from 1000 to 6500 IU [17–19]. Our third patient showed complete resolution of the low level of hCG elevation from the low-dose hCG co-trigger by the time of her presentation for OHSS, indicating hCG co-trigger was unlikely a contributing factor to her OHSS. Long-acting GnRH agonist has been shown to decrease the risk of premature ovarian insufficiency after chemotherapy in multiple studies in breast cancer patients, and is routinely recommended by the oncologists to start at least 1 week prior to the start of chemotherapy and throughout the duration of chemotherapy [20–26]. With the limited window between the completion of ovarian stimulation and the planned chemotherapy start, it was our routine practice to give long-acting GnRH agonist immediately or soon after the oocyte retrieval. All three of the presented cases received a long-acting GnRH agonist (depot leuprolide) immediately following oocyte retrieval. The oncologists choose either 1-month formulation (3.75 mg) or 3-month formulation (11.25 mg) which are equivalent in effects and side effect profiles, based on patient preference and the duration of chemotherapy.

We hypothesize that the sustained gonadotropin elevation during the flare phase of long-acting GnRH agonist may mimic the effect of hCG and contribute to the severe OHSS cases reported here. After the initial dose of long-acting GnRH agonist, LH increases up to 6 times its baseline level and will remain elevated for up to 14 days post administration [11, 27]. In contrast, the LH level after GnRH agonist trigger returns to baseline within approximately 24 h after administration [28]. The prolonged elevation of gonadotropins induced by the long-acting GnRH agonist during the first few days after oocyte retrieval may mimic the long half-life of hCG and thus induce continued luteinization of granulosa cells which leads to the production of VEGF, driving the development of OHSS.

Some circumstantial evidence supports our hypothesis. Long-acting GnRH agonists are commonly used outside the setting of ART to induce hypogonadism for the treatment of endometriosis, menstrual irregularities, precocious puberty, uterine fibroid, or sex hormone dependent cancers. Rare cases of OHSS have been reported in gynecological patients using these medications alone without any gonadotropin for ovarian stimulation [29, 30], indicating the initial flare effect from the long-acting GnRH agonists can induce ovarian hyperstimulation in susceptible patients. Sole administration of long-acting GnRH agonists used for pituitary downregulation and ovarian suppression without initiation of COH has also been reported to result in OHSS cases [30–36]. Similar to our presented cases, these reports have also postulated that the flare phase of depot GnRH agonists may result in ovarian hyperstimulation and the ultimate development of OHSS among select populations. If OHSS can occur with sole administration of long-acting GnRH agonists without ovarian stimulation as previously reported, it would not be surprising that OHSS can occur more often if it is used immediately after COH. Further investigation is needed to test our hypothesis. Even though the incidence of severe OHSS was markedly elevated in oncofertility patients who also received long-acting GnRH agonists soon after COH (3 in 22 total oncofertility cases in 2019 in our institution, as opposed to 0 in other patients), this complication is not universal. We caution the immediate use of long-acting GnRH agonist in oncofertility patients after COH who have baseline risk factors for OHSS such as

PCOS, high ovarian reserve and young age, and whose ovarian response during COH is above average. We recommend to wait for 1 to 2 weeks before administering long-acting GnRH agonist if the risk of OHSS is high, out of the consideration that the risk of OHSS is the highest within the first 7–10 days after ovulation trigger, and the flare phase of the long-acting GnRH agonist lasts for 7–14 days.

Prevention and early identification of OHSS is especially important in patients with cancer diagnosis who pursue fertility preservation before cancer treatments. While cancer treatment was not delayed in our presented cases, symptoms and complications from OHSS can interrupt initiation of cancer treatment which may affect survival or cancer recurrence rate. Cancer diagnosis and treatments can make OHSS more difficult to diagnose, as patients may have pre-existing disturbances in their blood cell counts, such as elevated white blood cell counts from hematological malignancies or use of granulocyte-macrophage colony-stimulating factor. Case 1 received pegfilgrastim 2 days after retrieval which is expected to reach peak serum concentration within 24–48 h after injection and maximal increase in absolute neutrophil count approximately 3–5 days after injection [37]. This may, in part, explain her marked leukocytosis at presentation to the ED. Recent surgical history or certain malignancies can lead to ascites, which may not be easily differentiated from pelvic fluid collection as a result of OHSS. Treatment of OHSS can also be more challenging, as patients commonly receive heavy fluid infusions in preparation for or during chemotherapy, and patients with hematological malignancies may need to receive blood product transfusion support, all of which make fluid management for OHSS more complicated. Lastly, severe OHSS is associated with increase in risks for both venous and arterial thrombosis and consideration of thromboprophylaxis has been previously recommended in these cases [1]. Patients with cancer diagnoses have elevated baseline thromboembolic risks and thus in the setting of severe OHSS, early initiation and potentially a lower threshold for administering prophylactic anti-coagulation in these patients should be considered, which was given in the first two cases. Patients with severe OHSS are usually instructed to delay the start of chemotherapy until the signs and symptoms of OHSS resolve to avoid superimposing the side effects from the chemotherapy agents. Whether or not chemotherapy may impact the resolution of OHSS by inducing apoptosis of the luteinized cells has not been studied.

Conclusion

We report three cases of severe early-onset OHSS in oncofertility patients despite the use of GnRH agonist trigger and freezing all embryos. Long-acting GnRH agonists given immediately following oocyte retrieval for ovarian suppression may increase risk for OHSS in susceptible patients by prolonging gonadotropin elevation. In a patient at high risk for developing OHSS, considerations should be given to delay the initiation of long-acting GnRH agonist for 1 to 2 weeks following oocyte retrieval to allow for resolution of luteinization before the flare phase.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval All data was obtained from chart review and reported without any patient identifiers. IRB exemption from our institution was obtained for this study.

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