Severe ovarian hyperstimulation syndrome requiring recurrent large-volume paracenteses until 21 weeks' gestation: a case report

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Objective: To report a case of severe ovarian hyperstimulation syndrome (OHSS) persisting into the late second trimester of a singleton pregnancy.
Design: Case report.
Setting: Academic tertiary care center.
Patient(s): A 29-year-old woman with severe OHSS after fresh embryo transfer after controlled ovarian hyperstimulation requiring intervention until 21 weeks' gestation in a singleton pregnancy.
Intervention(s): Thorough evaluation of an unusual case of severe OHSS and medical/procedural management of its sequelae in the setting of ongoing pregnancy.
Main Outcome Measures(s): The clinical development of severe OHSS during pregnancy and its effect on pregnancy outcomes.
Result(s): Severe OHSS persisted until 21 weeks' gestation with reaccumulating ascitic fluid, which impacted pregnancy outcomes.
Conclusion(s): Clinicians should be aware of the risk of severe OHSS and its possible effect on pregnancy outcomes beyond the first trimester. (Fertil Steril Rep® 2022;3:275–9. ©2022 by American Society for Reproductive Medicine.)
Key Words: Ovarian hyperstimulation syndrome, FET, frozen embryo transfer, IVF, in vitro fertilization

INTRODUCTION

The advancement of assisted reproductive technology (ART) has led to an increased number of ART cycles resulting in pregnancies and live births. Because ART is a commonly used fertility modality, it is essential to be aware of rare adverse events associated with this technology. Controlled ovarian hyperstimulation with gonadotropins and a human chorionic gonadotropin (hCG) trigger can, in rare cases, cause an exaggerated ovarian response, known as ovarian hyperstimulation syndrome (OHSS). Ovarian stimulation and subsequent multifollicular development with elevated estradiol levels lead to the characteristic increase in ovarian size. The stimulation of multiple corpus lutea elicits an inflammatory response leading to the release of inflammatory markers, vascular endothelial growth factor (VEGF), and the renin-angiotensin-aldosterone system activation (1, 2).

Increasing ovarian size in mild cases of OHSS can cause abdominal pain and distension, nausea, vomiting, and diarrhea. In severe cases of OHSS, the inflammatory response can lead to increased vascular permeability resulting in leakage of fluid out of the intravascular compartment (2). This can manifest clinically as hypotension, oliguria, ascites, anasarca, or pulmonary edema. These patients may require hospital admission and occasionally intensive care. Patient risk factors for OHSS include low body mass index, young age, polycystic ovary syndrome, high estrogen level before hCG trigger, or a history of OHSS (3). Patients with

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polycystic ovary syndrome, high estradiol levels, or increased follicle number or size benefit from altering their ovulation induction protocol to prevent OHSS. This can be achieved with the use of lower doses of gonadotropins or a gonadotropin-releasing hormone agonist trigger (4).

In cases of OHSS without an associated embryo transfer, symptoms usually resolve within 7–10 days. In cases of a coinciding pregnancy, OHSS typically lasts until 10 weeks of gestation but rarely extends past the first trimester (5, 6). Here, we report a case of severe OHSS requiring multiple hospitalizations and serial large-volume paracentesis until 21 weeks of pregnancy.

CASE REPORT

Our patient is a 29-year-old G3P0020, otherwise healthy woman with 2 prior spontaneous first trimester losses with negative recurrent pregnancy loss workup and a diagnosis of unexplained infertility. Her antimüllerian hormone level was 2.4 ng/mL. She underwent 1 cycle of in vitro fertilization (IVF) at an outside infertility clinic using an antagonist protocol with a dose increase to receive a maximum of 225 IU of recombinant follicle-stimulating hormone (FSH) and 150 IU of human menopausal gonadotropin during her stimulation. During IVF treatment, her body mass index ranged from 32–34 kg/m^2. Her peak estradiol level was just <3,000 pg/mL at the time of trigger, for which hCG was used. She had 17 oocytes retrieved, of which 13 were mature and 10 were successfully fertilized with conventional insemination. Four blastocyst embryos developed, and she underwent a single blastocyst fresh embryo transfer with cryopreservation of the 3 supernumerary embryos. Two days after the embryo transfer, she developed symptoms consistent with OHSS, including nausea, vomiting, anorexia, shortness of breath, and abdominal distension. Additionally, ascites and enlarged ovaries were noted on ultrasound investigation. Her laboratory test results revealed a hematocrit level of 40%. She was initially managed as an outpatient with serial ultrasound evaluations and culdocenteses as needed (a total of 11 procedures over 5 weeks) but continued with a recurrent accumulation of ascites, and the worsening of symptoms required hospitalization.

At 9 weeks of gestation, while admitted to a community hospital, a paracentesis was performed, yielding 4 L of ascites fluid, and the patient was started on intravenous fluids and albumin. Given malnutrition, she was also started on peripheral parenteral nutrition. She was discharged when she was able to tolerate oral intake. She had several readmissions with similar presentations requiring large-volume paracenteses, intravenous fluids, albumin supplementation, and peripheral parenteral nutrition. No further workup had been initiated at that time because the presumed diagnosis of OHSS had been maintained. Given the continued worsening of symptoms, the decision was made to transfer the patient to an academic tertiary care center for further management and workup at 13 weeks of gestation.

On presentation to the academic center, the patient was admitted to the antepartum service and underwent a thorough evaluation of her recurrent ascites. Admission laboratory testing result was unremarkable. Tumor markers were notable for elevated Ca-125 levels of 287 U/mL and α-fetoprotein levels of 18.9 ng/mL, consistent with ongoing pregnancy. Otherwise, lactate dehydrogenase, carcinoembryonic antigen, and CA 19-9 levels were within normal limits. A computed tomography scan of the chest, abdomen, and pelvis was obtained, given the recurrent ascites and the need to rule out other etiologies (Fig. 1). The low risk of radiation and contrast exposure during pregnancy was discussed with the patient who elected to proceed. The computed tomography scan revealed a moderate to large amount of intraabdominal and intrapelvic ascites, a moderate-to-large left pleural effusion, a small pericardial effusion, and bilateral multicystic enlarged ovaries. She underwent Interventional Radiology (IR)–guided paracentesis of 2.8 L, which revealed cytopathology negative for malignancy.

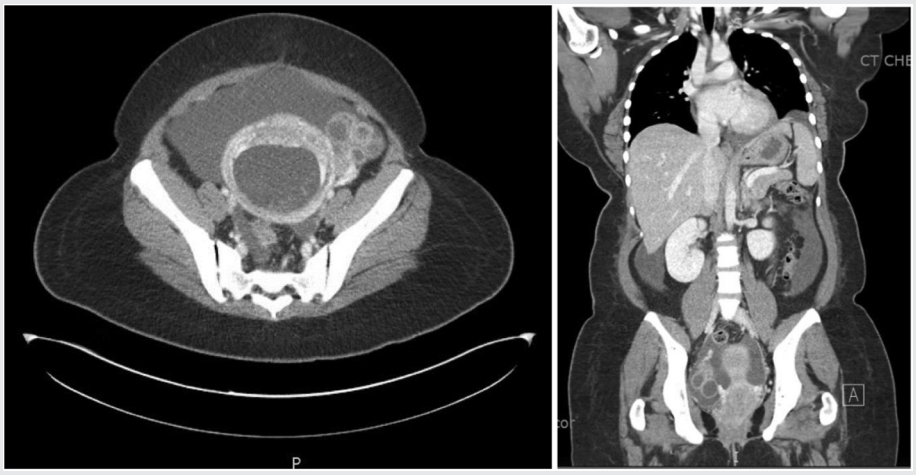
Gynecologic oncology department was consulted, and a transvaginal ultrasound was recommended to further explore the ovaries. The transvaginal ultrasound revealed enlarged ovaries (right ovary up to 5.2 cm and left ovary up to 6.1 cm), both with simple appearing cysts consistent with OHSS (Fig. 2). Further investigation included evaluation for gestational trophoblastic disease with quantitative β-hCG and cell-free deoxyribonucleic acid to evaluate for triploidy. The β-hCG level was 41,000 mIU/mL, and the cell-free deoxyribonucleic acid was within normal limits. Additionally, reproductive hormone levels were checked to rule out a gonadotropin secreting adenoma. Laboratory workup revealed that the levels of the FSH, luteinizing hormone, and estradiol were <0.1 IU/mL, 0.5 IU/L, and 1492 pg/mL, respectively. A whole exome genetic testing was considered to investigate for an FSH receptor gene mutation; however, this was not possible to be performed during admission.

The patient's intake/output was carefully measured, and urine output remained adequate. She did not require any maintenance intravenous fluids. Her nausea was controlled with a scheme of doxylamine, vitamin B6, diphenhydramine, and ondansetron as needed. A nutrition consultation was obtained given her hypoproteinemia. She was discharged on hospital day 4 after she reported improving symptoms.

She returned to the hospital 1 week after discharge with reports of worsening nausea, vomiting, and inability to tolerate oral intake. She underwent a repeat IR–guided paracentesis with drainage of 1.4 L. After further discussion with the IR department, she was scheduled as an outpatient for weekly ultrasound evaluations with paracentesis based on the symptoms and ultrasound findings. She received serial paracentesis until 21 weeks' gestation, with a total of 22 paracenteses during her pregnancy.

At 21 weeks of gestation, she developed abdominal cramping and vaginal spotting. She presented to a community hospital and was found to be 2 cm dilated. In this setting, she received a rescue cerclage because of cervical incompetence hypothesized to be secondary to increased intraabdominal pressure from reaccumulating ascites. Before the procedure, her cervix progressed to 4 cm dilatation with prolapsing membranes. At 21 weeks and 3 days, a McDonald cerclage was placed without complications. The cervix was noted to be closed at the end of the procedure. After cerclage placement, the patient continued to have recurrent nausea and emesis. At this time, she had an evaluation for

FIGURE 1



Computed tomography images of chest, abdomen, and pelvis with intravenous contrast showing right and left ovaries with multiple follicles as well as ascites (transverse section on left, coronal section on right).

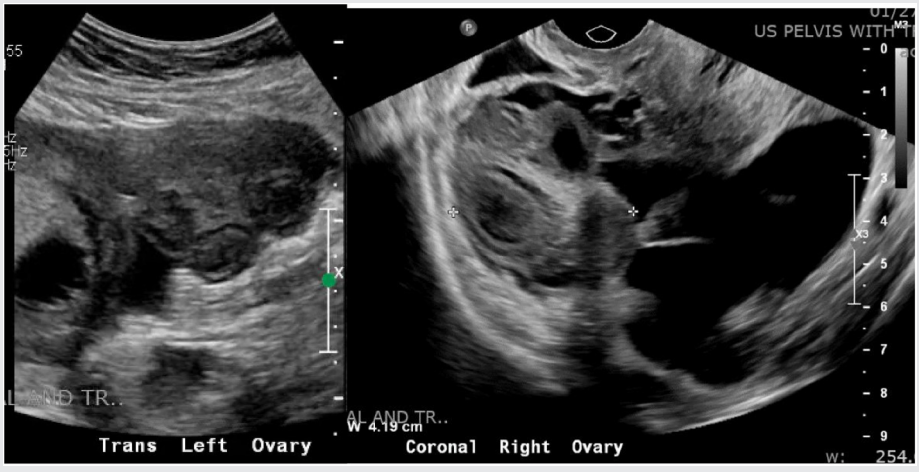
Henshaw. Severe OHSS until the late second trimester. Fertil Steril Rep 2022.

reaccumulating ascites, and 800 mL was removed by IR given the risk of continued Valsalva leading to preterm rupture of membranes. After the paracentesis, she was again found to have prolapsing membranes through the cervix.

At 22 weeks of gestation, the patient had preterm premature rupture of membranes. The patient's abdominal distension and vomiting improved. A repeat ultrasound was performed without reaccumulating ascites noted. She received a course of betamethasone starting at 22 weeks and 5 days of gestation. Repeat ultrasound evaluations did not reveal recurrent ascites, and the patient denied the return of OHSS-related symptoms. At 28 weeks and 5 days gestation, the patient went into preterm labor, and thus her cerclage was removed. She was started on a rescue course of betamethasone. She quickly progressed in labor and had an uncomplicated vaginal delivery. The birth weight of the neonate was 1,120 g, and the American Pediatric Gross Assessment Record scores were 6, 5, and 9 at 1, 5, and 10 minutes, respectively. The infant's neonatal intensive care unit course was complicated by pulmonary hypertension and chronic lung disease likely secondary to pulmonary hypoplasia. At 81 days of life, the neonate was transferred to a neonatal transitional care facility.

This case report does not contain identifiable information. Additionally, the images are anonymized, and the individual cannot be identified from them. Patient consent was not requested or required for this case report.

FIGURE 2



Transvaginal ultrasound showing enlarged ovaries with multiple follicles.

Henshaw. Severe OHSS until the late second trimester. Fertil Steril Rep 2022.

DISCUSSION

Although a serious complication of ART, OHSS is an uncommon adverse physiologic reaction complicating approximately 1% of IVF cycles (7). Severe cases of OHSS requiring hospitalization are even rarer and may manifest as adult respiratory distress syndrome, pulmonary thromboembolism, or ascites and abdominal compartment syndrome (8–10). Severity markers of OHSS have been proposed recently, including intraabdominal pressure, ascites index, and ovarian volume, although these remain to be validated in terms of clinical utility and prognostic value (10).

Late-onset OHSS, defined as symptoms starting 12–17 days from hCG administration, is typically more severe and more likely to require hospitalization (11). Patients with OHSS with a concurrent pregnancy have a higher risk of developing late-onset and severe OHSS as a result of the additional endogenous hCG that is released from the placenta (11). Even then, late-onset OHSS is usually short-lived, resolving during the first trimester (5, 6). Given the higher levels of hCG, late-onset OHSS is more likely in those with multiple pregnancies, which has been reported previously in the literature (12–14). Additionally, O'Brien et al. (15) reported a case of severe late-onset OHSS in the setting of trisomy 21 and markedly elevated β-hCG levels. From our literature review, this is a unique case of severe OHSS starting in the first trimester of a singleton pregnancy with normal hCG levels and persisting until 21 weeks' gestation.

The pathophysiology of OHSS begins when the luteinizing hormone surge associated with ovarian stimulation triggers VEGF messenger ribonucleic acid expression. The VEGF levels in peritoneal fluid samples from patients with OHSS exhibit elevated levels of VEGF, facilitating vascular permeability through VEGF receptor-2 activation and downstream activation of nitric oxide synthase (16, 17). We hypothesize that certain patients may harbor polymorphisms in VEGF receptors or other alterations in downstream VEGF signaling. This abnormality may cause these patients to become particularly susceptible to small fluctuations in VEGF, rendering them more likely than others to develop severe OHSS than most women who undergo ovulation induction and do not experience this dramatic effect. Future work investigating the pathogenesis and possible treatments of OHSS should determine whether VEGF receptor mutations may be associated with the risk of OHSS development and whether VEGF-receptor antagonists such as bevacizumab may be useful in severe, especially life-threatening cases of OHSS. Alternatively, mutations in the FSH receptor may underlie some cases of OHSS (18). Advances in availability, cost, and rapidity of whole-genome sequencing or targeted genetic sequencing will likely aid in elucidating the underlying causes of OHSS and a host of adverse and difficult-to-predict reactions to interventions routinely provided in medical practice. With such developments, cases similar to this could be anticipated or even avoided.

This rare presentation of OHSS demonstrates the importance of multidisciplinary care in medicine. In a case of severe persistent OHSS in pregnancy, care coordination can help improve outcomes for the patient and the developing fetus. In our case, the collaboration between reproductive endocrinology and infertility, gynecologic oncology, maternal-fetal medicine, and IR departments allowed for insight from multiple health care perspectives. This joint effort allowed for a thorough workup of our patient. Additionally, once the developing fetus reaches viability, it is important to involve neonatal pediatrics for an additional perspective and patient counseling on outcomes and expectations.

Severe OHSS is a rare complication of IVF. In OHSS with concurrent pregnancy, most cases resolve during the first trimester. Although rare, the patient, in this case, had severe OHSS manifestations until the late second trimester of a singleton pregnancy. This case report highlights the importance of further research to investigate the pathophysiology of OHSS to identify those at risk and improve prevention and treatment strategies. Additionally, it is crucial to recognize that severe OHSS can produce significant morbidity for the patient and the fetus.

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