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OVARIAN HYPERSTIMULATION SYNDROME AS A GROWING DIAGNOSTIC PROBLEM IN EMERGENCY DEPARTMENT SETTINGS: A CASE REPORT

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☐ **Abstract—Background: Ovarian hyperstimulation syndrome (OHSS) is a common complication of an in-vitro fertilization (IVF) procedure, which is usually clinically insignificant. However, without monitoring, it can progress into a life-threatening condition. With the increasing popularity of IVF technology, patients with OHSS may begin visiting emergency departments (EDs) more frequently. Case Report: We report the case of a patient admitted to the ED presenting with severe abdominal pain, cough, and nausea. An ultrasound examination was inconclusive. Computer tomography revealed enlarged ovaries and fluid in the pleural cavities, around the liver and spleen, between the bowel loops, and in the pelvis. This prompted physicians to review the patient's fertility issues. Consequently, the diagnosis of OHSS was made. Why Should an Emergency Physician Be Aware of This?: When the physician knows that the patient is undergoing IVF, the diagnosis of OHSS can be straightforward; without this information, it can be difficult. Having in mind the growing demand for infertility treatment, we present this case to increase awareness of possible clinical findings and complications of OHSS as a rare consequence of IVF. OHSS diagnosed via ultrasound can reduce the emotional, financial, and health burden of infertile couples and help them to fulfill their procreation plans without unnecessary delay.**

☐ **Keywords—ovarian hyperstimulation syndrome; IVF**

INTRODUCTION

Ovarian hyperstimulation syndrome (OHSS) is a rare but occasionally life-threatening complication of infertility treatment. The incidence of OHSS at various stages of in vitro fertilization (IVF) treatment or planned treatment are presented in Table 1 (1). Although it is associated mostly with IVF, OHSS can also be spontaneous in nature or be caused by pregnancy, trophoblastic neoplasms, pituitary adenomas, hypothyroidism, β-human chorionic gonadotrophin (hCG)-secreting tumors, or follicle-stimulating hormone-secreting neuroendocrine tumors (2).

OHSS symptoms include abdominal pain, decreased urine output, bloating, nausea, vomiting, diarrhea, dyspnea, and weight gain (1,2). The most severe and clinically important consequence is a fluid shift into the "third space," which leads to lower-extremity edema and ascites as well as pleural and pericardial effusion (3,4). Thromboembolic events also have been reported (5,6).

OHSS has been classified into different grades based on severity (mild, moderate, severe, critical) and timing (early and late) (2). It is important for emergency physicians to recognize and diagnose OHSS early as it allows for timely investigation before subsequent predictable

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Table 1. Incidence of Ovarian Hyperstimulation Syndrome*

	Prior to IVF Usage	Using Clomiphene Citrate	IVF Procedure
Mild	8–23%	13.5%	20–33%
Moderate	0.005–7%	Described sporadically	3–6%
Severe	0.008–10%	Described sporadically	0.1–2%

IVF = in-vitro fertilization.
* Adapted from Delvigne and Rozenberg. (1).

complications can develop. Here we present the case of a 29-year-old patient suffering from OHSS who was admitted to the emergency department (ED).

CASE REPORT

A 29-year-old female patient who was admitted to the ED presented symptoms of severe abdominal pain and distension, cough, nausea, and tachycardia (136 beats/min). No dyspnea was observed. Respiratory frequency was normal. The patient was pale and anxious. On palpation, muscle guarding and tenderness in the area of the ovaries was observed. The patient denied experiencing trauma and oncological disease. In laboratory tests, an increased level of white blood cells (19,300/μL), red blood cells (5.6 mln/μL), hemoglobin (17.4 g/dL), hematocrit (48.3%), C-reactive protein (4 mg/L), potassium (5.8 mmol/L), urea (50.1 mg/dL), glucose (127 mg/dL), and creatinine (1.25 mg/dL) were observed, as well as decreased levels of sodium (133 mmol/L) and estimated glomerular filtration rate (50 mL/min/m^2). An ultrasound examination was inconclusive, but showed large amounts of free fluid in the abdominal cavity and the pelvis. A computed tomography examination showed a large amount of free fluid surrounding the liver and spleen (Figure 1), between the bowel loops, and in the pelvis (Figure 2). There was also a considerable amount of fluid within the pleural cavities (Figure 3). Both ovaries were grossly enlarged, measuring 12 cm in diameter each (Figure 4). Multiple (>20) thin-walled, fluid-filled follicles within each ovary were observed—up to 3.5 cm in size (Figure 5). A vivid contrast enhancement of the wall of each follicle indicated the ovulatory phase of the menstrual cycle. In this physiological condition, however, only up to three corpora lutea with an enhanced rim may be evident, whereas the presence of multiple follicles was likely due to OHSS. These radiological findings prompted clinicians to ask the patient specifically about her fertility issues. She admitted that she had been undergoing hormonal stimulation ahead of an IVF procedure. After this information was revealed, the diagnosis of OHSS was made.

Figure 2. Axial computed tomography scan shows a large amount of free fluid between the bowel loops and within the recesses of the peritoneum.

DISCUSSION

The pathophysiology of OHSS has not been fully elucidated. It is known that administering follicle-stimulating hormone and luteinizing hormone followed

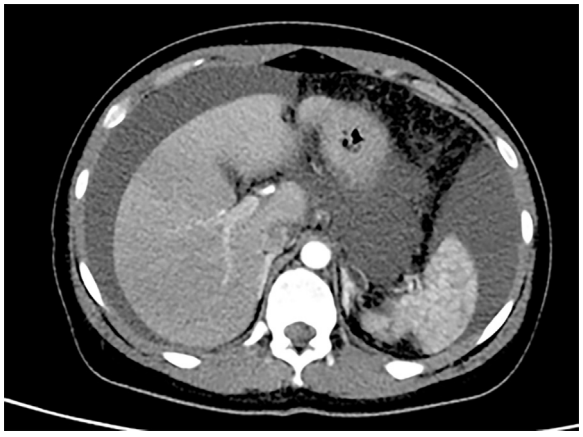

Figure 1. Axial computed tomography scan shows a large amount of free fluid surrounding the liver and the spleen.

Figure 3. Axial computed tomography scan shows bilateral pleural effusion. Fluid surrounding the liver is also noted.

Figure 4. Sagittal image shows two highly enlarged ovaries (12 cm in diameter each) filling almost all of the pelvis. Multiple follicles with enhancing walls can be seen.

by hCG leads to ovarian hyperstimulation. Although ovarian enlargement after stimulation with gonadotrophins is clear, the reason for the increased vascular permeability, which accompanies OHSS, remains to be elucidated. The hypothesis is that increased vascular permeability is due to a high level of estrogen, initially considered causative, has now been rejected. Vascular endothelial growth factor is the most probable reason for hyperpermeability, as its secretion is highly correlated to hCG levels (7). OHSS is generally mild and harmless.

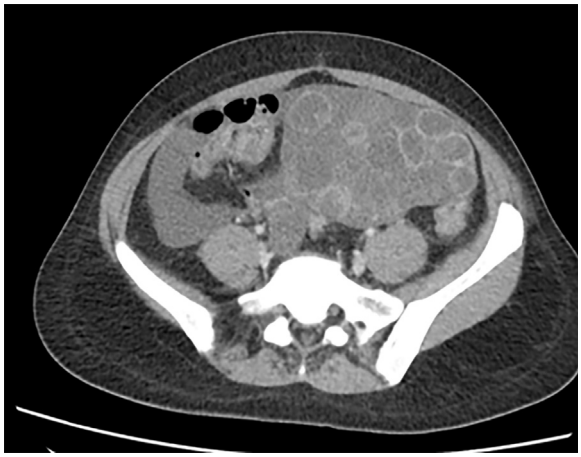

Figure 5. Axial computed tomography scan reveals an enlarged left ovary with multiple follicles. The enhancing walls of the follicles are visible.

Table 2. Classification of Severity of OHSS

Category	Features
Mild OHSS	• Abdominal bloating • Mild abdominal pain • Ovarian size usually < 8 cm*
Moderate OHSS	• Moderate abdominal pain • Nausea ± vomiting • Ultrasound evidence of ascites • Ovarian size usually 8–12 cm*
Severe OHSS	• Clinical ascites (±hydrothorax) • Oliguria (<300 mL/day or < 30 mL/h) • Hematocrit > 0.45 • Hyponatremia (sodium < 135 mmol/L) • Hypo-osmolality (osmolality < 282 mOsm/kg) • Hyperkaliemia (potassium > 5 mmol/L) • Hypoproteinemia (serum albumin < 35 g/L) • Ovarian size usually > 12 cm*
Critical OHSS	• Tense ascites/large hydrothorax • Hematocrit > 0.55 • White cell count > 25,000/mL • Oliguria/anuria • Thromboembolism • Acute respiratory distress syndrome

OHSS = ovarian hyperstimulation syndrome.
* Ovarian size may not correlate with severity of OHSS in cases of assisted reproduction due to the effect of follicular aspiration. Women demonstrating any feature of severe or critical OHSS should be classified in that category.

Its severity can vary from asymptomatic cases to ovary enlargement with cysts, nausea, shortness of breath, or pleurisy (1,8). Usually the first sign of imminent severe OHSS is bloating caused by ovarian enlargement, plus the presence of ascitic fluid in the peritoneal cavity. The movement of fluid to the interstitial or "third space" compartments is associated with the most dangerous and life-threatening complications. This "third spacing" can manifest clinically as lower-extremity edema, followed by accumulation of fluid in pleural cavities, which leads to depression of the diaphragm. The accompanying and progressive interstitial edema can impair respiratory system functioning. Intestinal edema also is associated with and may be causative of diarrhea and nausea (9). Liver damage caused by edema can be confirmed by laboratory tests. In severe cases, pericardial effusion appears. The loss of intravascular volume consequent to "third spacing" may contribute to renal injury, which results in electrolyte disorders such as hyponatremia and hyperkalemia. The "third space" shifting leads to hypovolemia and hemoconcentration. Hemoconcentration provokes hypercoagulability, which is the cause of the thrombotic events (10). Vascular embolic phenomena can appear in both arteries and veins; however, it is more common in veins (81%). The most common

Table 3. Proper Interview (Important Patient History Questions and Important Physical Examination Findings to Be Sought) from a Patient with Suspected OHSS*

History	Symptoms
• Time of onset of symptoms relative to trigger • Medication used for trigger (hCG or GnRH agonist) • Number of follicles on final monitoring scan • Number of eggs collected • Were embryos replaced and how many? • Polycystic ovary syndrome diagnosis?	• Abdominal bloating • Abdominal discomfort/pain, need for analgesia • Nausea and vomiting • Breathlessness, inability to lie flat or talk in full sentences • Reduced urine output • Leg swelling • Vulval swelling • Associated comorbidities such as thrombosis

OHSS = ovarian hyperstimulation syndrome; hCG = human chorionic gonadotropin; GnRH = gonadotropin-releasing hormone.
* Adapted from the Royal College of Obstetricians and Gynaecologists. Green-top Guideline No. 5. (2).

locations of thrombotic events are, in order of frequency: jugular vein, subclavian vein, lower-extremity veins, upper-extremity veins, and cerebral veins. Cases of embolized renal and retinal veins have also been reported. Arterial embolisms can occur in cerebral arteries, pulmonary arteries, coronary arteries, and lower-extremity arteries (5,9,11). Further deterioration of hypovolemia causes oliguria and anuria. In the critical stage, acute respiratory distress syndrome and sepsis may appear (2).

A radiological examination, usually based on ultrasound, typically reveals enlarged ovaries with multiple follicles, as well as free fluid in the abdominal and other body cavities (3).

Classification of OHSS, along with its clinical presentation, is presented in Table 2. Epidemiology data are incomplete due to different clinical manifestations, but a progressive increase in the incidence of severe OHSS has been reported. Unfortunately, no statistics about critical OHSS have been reported.

Several factors can contribute to the increasing incidence of OHSS. Women who suffered from it usually became pregnant significantly earlier than those who did not. They were also of lower gravidity, and were more likely to be of African descent and to have other ovulation disorders. Polycystic ovary syndrome is a predisposing factor. A correlation between the baseline number of follicles, the number of oocytes retrieved, and OHSS has also been reported. The increased frequency of OHSS among women with allergies needs further investigation. The correlation between OHSS and body weight seems to be insignificant (1,12).

Mild and moderate OHSS can be treated in outpatient settings. These patients should be informed about the need to measure fluid intake and output, to avoid using nonsteroidal antiinflammatory drugs due to possible consequent renal injury, and to adapt thromboprophylaxis with low-molecular-weight heparin. Paracentesis of ascitic fluid may be necessary; however, it can be performed in outpatient settings. Some reports indicate that using gonadotropin-releasing hormone agonists is an effective treatment of OHSS (13); however, similar to the

Table 4. Tests That Can Be Helpful When Diagnosing OHSS*

Examination	Investigations	Other Tests That May Be Indicated
General: assess for dehydration, edema (pedal, vulval, and sacral); record heart rate, respiratory rate, blood pressure, body weight. Abdominal: assess for ascites, palpable mass, peritonism; measure girth Respiratory: assess for pleural effusion, pneumonia, pulmonary edema	Complete blood count (CBC) Hematocrit (hemoconcentration) C-reactive protein (severity) Blood urea nitrogen (BUN), creatinine and electrolytes (hyponatremia and hyperkalemia) Serum osmolality (hypo-osmolality) Hepatic function tests (elevated enzymes and reduced albumin) Coagulation profile (elevated fibrinogen and reduced antithrombin) hCG (to determine outcome of treatment cycle) if appropriate Ultrasound scan: ovarian size, pelvic and abdominal free fluid. Consider ovarian Doppler if torsion suspected	Arterial blood gases D-dimer Electrocardiogram (ECG)/ echocardiogram Chest X-ray study Computed tomography pulmonary angiogram (CTPA) or ventilation/ perfusion (V/Q) scan

OHSS = ovarian hyperstimulation syndrome; hCG = human chorionic gonadotropin.
* Adapted from the Royal College of Obstetricians and Gynaecologists. Green-top Guideline No. 5. (2).

effectiveness of using dopamine agonists, the rationale for their application needs further research. If outpatient treatment is insufficient, the patient should be admitted to the emergency/intensive care unit. The most important therapeutic goals are pain relief, restoring proper fluid balance, managing ascites and effusions, and minimizing the risk of thrombosis (2,14).

WHY SHOULD AN EMERGENCY PHYSICIAN BE AWARE OF THIS?

The diagnosis of OHSS can be straightforward if relevant information from the patient's clinical history is given. Unfortunately, many patients are unaware of the clinical symptoms, which may occur as a consequence of ovarian stimulation that accompanies IVF attempts. As a result, they may fail to inform emergency physicians of their infertility treatments. The true value of the presented case is in pointing out that, in an era when IVF is gaining in popularity worldwide, OHSS may become a more frequent diagnostic entity in the ED. With higher awareness of OHSS among ED medical staff (both clinicians and radiologists), collection of the relevant clinical data (Table 3) and proper examinations at admission (Table 4) (2), the correct diagnosis could be established and the considerable radiation dose from the computed tomography scan can be avoided for most patients. Additionally, infertility treatment is a great emotional, financial, and health burden for infertile couples. Proper diagnosis of adverse events resulting from IVF made solely with ultrasound can help affected couples fulfill their procreation plans without unnecessary medical procedures and delay.

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