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RESEARCH ARTICLE

# Late Onset Ovarian Hyperstimulation Syndrome: A Case Report

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## ABSTRACT

Ovarian hyperstimulation syndrome (OHSS) is a rare complication of controlled ovarian stimulation (COS) in patients undergoing in-vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI). Prior to the embryo transfer the risk of OHSS should be assessed for proper management upon incidence of this condition or using prevention guidelines beforehand. This case report presents a case of severe late-onset OHSS in a low-risk 29 years old nulliparous patient. The patient presented with severe abdominal ascites and liver dysfunction. The conservative treatment contained fluid and electrolyte intake control along with paracentesis of ascites.

KEYWORDS:
Late Onset, Ovarian Hyperstimulation Syndrome, Case Report.

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## INTRODUCTION

Ovarian hyperstimulation syndrome (OHSS) is a critical and life-threatening complication of controlled ovarian hyperstimulation (COS). Precise pathophysiology of OHSS is not yet fully understood, however, increased capillary permeability along with extravasation of fluids from intravascular spaces to extravascular spaces are among the classic physiologic alterations of OHSS. The vasoactive substances and proinflammatory cytokines such as vascular endothelial growth factor (VEGF), IL-6, IL-1β, insulin-like growth factor (IGF-1), and angiotensin II are also involved in the development of this condition (1, 2).

Based on the onset and severity of this condition, OHSS is categorized into early or late and mild, moderate, or severe. If OHSS presents 3 to 7 days after administration of human chorionic gonadotropin (hCG), it is identified as early, while responses later than 10 days are categorized as late (3). Mild OHSS can cause abdominal distention, vomiting, nausea, diarrhoea, and ovarian enlargement, while moderate OHSS may cause the same symptoms plus ascites. The severe form of OHSS can also cause dyspnoea, tachypnoea, hydrothorax, hypotension, renal and hepatic dysfunction, gross ascites, oliguria, and coagulation abnormalities. The main risk factors for OHSS include previous occurrence of OHSS, polycystic ovary syndrome, abnormal response to hCG, elevated serum oestradiol (E2), higher number of developed follicles during COS (more than 25), number of retrieved oocytes (more than 24), young age, and lower body mass index (BMI) (4-6). For prevention of occurrence or reoccurrence of OHSS, risk assessment should be performed by physician beforehand.

This case report aims at highlighting the importance of liver dysfunction as a rare complication of OHSS in patients and illustrates how this condition was properly managed.

### Case Presentation

A 29 years old nulliparous female patient underwent COS and Intracytoplasmic Sperm Injection (ICSI) according to the guidelines of the European society of human reproduction and embryology (ESHRE) (7). Based on the risk assessment, this patient was at low risk for OHSS with BMI of 24. 11 oocytes have been retrieved and after 3 days, 2 embryos were transferred. The patient received 150 Iu recombinant FSH (total dose = 1350 Iu) in an antagonist protocol and triggering with 10,000 Iu HCG (human chorionic gonadotropin) was done. Intramuscular Progesterone was administered (50mg progesterone in oil and 400mg vaginal progesterone) for luteal phase support. However, after 10 days, the patient returned to the hospital with nausea, mild dyspnoea, abdominal discomfort, and abdominal distention.

The ultrasound showed abdominal ascites and enlarged ovaries and ovarian hyperstimulation syndrome signs. Free fluid was seen in abdominal and pelvic regions. However, liver and gallbladder were normal and no signs of gallstones or other pathologies were seen. The examination revealed abdominal distention. The initial laboratory workup revealed a slight elevation in creatinine level (1.2 mg/dL), and transaminitis with aspartate transaminase (AST: 39 U/L) and alanine aminotransferase (ALT: 47 U/L). Serial laboratory tests revealed constant AST and ALT elevation. And it peaked at 22 days after embryo transfer (hospital day 12). The AST and ALT levels were 210 U/L and 213 U/L, respectively.

Due to abdominal discomfort, decrease of urine output, and mild dyspnoea, the patient underwent transvaginal paracentesis four times due to severe fluid accumulation every two days for eight days. 3500 mL, 2800 mL, 3000 mL, and 3000 mL fluid was accumulated during the first, second, third, and fourth session of paracentesis, respectively. The patient's fluid intake and output were controlled and for maintaining minimum urine output intravenous albumin and normal saline serum were administered. The patient also received enoxaparin initially after administration and antiemetics such as lansoprazole, dimethicone, and milk of magnesium for preventing constipation. Acetaminophen () was also administered for pain management. 2 mg of cephalosporin was administered as prophylaxis after transvaginal paracentesis.

After the fourth session of paracentesis, the patient was under observation. Although the abdominal ascites was still present, however, no sign of exacerbation was seen and the severity of her condition was effectively managed. Also, ultrasound revealed two gestational sacs and two foetal heart rates. The patient was discharged after the management of abdominal ascites, urine output, and improvement of general physical status. However, the patient underwent serial follow-ups for three months regarding the liver function. Serial laboratory tests were performed to measure ALT and AST level. After three months of follow-up, the liver function improved and AST and ALT levels decreased to 20 U/L and 18 U/L, respectively. The pregnancy continued without any further complication. The remainder of the pregnancy continued without any further complications, which resulted in a term delivery of two infants at the end of the 38th week with caesarean section. The infants had normal birth weight and normal APGAR (Activity, Pulse, Grimace, Appearance, and Respiration).

## DISCUSSION

OHSS is a serious complication of COS. Risk evaluation prior to COS in patients undergoing IVF or ICSI is crucial for prevention or management of this condition. The precise pathophysiology of OHSS is not yet fully understood, however, the fluid shifts are found to be primarily caused by inflammatory mediators such as VEGF. Elevation in serum levels of antidiuretic hormone (ADH) can subsequently cause hyponatremia. Liver dysfunction, ascites, and hypovolemia are also frequently found in OHSS patients (2, 8, 9). The ovarian hyperstimulation syndrome can become severe to the extent that can affect liver function test. According to the initial risk assessment of this patient she was considered a low-risk patient. The cause of OHSS may be due to twin pregnancy, and as it was expected the patients status improved within one month, as of early OHSS patients.

Previous studies have not completely elucidated the underlying cause of liver dysfunction in OHSS patients. However, as the vascular permeability and arteriolar vasodilation increases, the liver becomes more prone to hepatic oedema and microvascular thrombosis. This condition causes an end-organ ischemia which leads to liver damage (10, 11). Another explanation suggests that the hepatic damage is caused by increased level of serum oestradiol (E2). One study reported that serum E2 levels higher than 12 pmol/L on day eleven of COS can detect the risk of OHSS with the sensitivity and specificity of 85% (12).

Initial laboratory workup of AST and ALT levels can reveal the liver dysfunction in OHSS patients. Although ALT and AST levels both increase during OHSS, however, as ALT is a more precise marker for hepatic injury, ALT increase more than AST more frequently in OHSS patients. The differential diagnosis of liver dysfunction and transaminitis during gestation is time dependent. The differential diagnosis in the first trimester, as in our case, included OHSS, hyperemesis gravidarum (HG), molar pregnancy, gallbladder disease, viral or autoimmune hepatitis, alcohol or drug-induced hepatitis, and thrombotic event (5). Based on the physical exams, laboratory measurement and transvaginal ultrasound results, other causes have been ruled out. HG was ruled out based on the abdominal ascites. Absence of vaginal bleeding, abnormal uterine size, and cysts ruled out molar pregnancy. Infectious liver damage due to hepatitis A, B, or C was ruled out based on the negative test results and alcohol or drug induced liver damage was ruled out based on patient's history. Normal PT, PTT, and INR ruled out thrombotic event. Finally, ultrasound of the liver showed no sign of gallbladder disease. Our patient was in her first trimester, hence, HELLP syndrome,

pre-eclampsia, cholestasis of pregnancy, and acute fatty liver of pregnancy were not included in the differential diagnosis. While our patient's most serious complication was the high-rate of fluid build-up and severe abdominal ascites the medical management of her condition consisted of volume management, restoration and maintenance of fluid balance drainage of ascites, and prevention of hydrothorax. Primary risk assessment of IVF and ICSI candidates is the most important factor in prevention and management of OHSS (13). Lower exposures to gonadotrophins, albumin and hydroxyethyl administration, using GnRH antagonist protocols, in-vitro maturation, dopamine agonist administration, and non-steroidal anti-inflammatory administration should also be considered to lessen the risk of OHSS (4, 14, 15).

## CONCLUSION

In conclusion, this case report highlighted a rare complication of late onset severe OHSS and the management of this condition.

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