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Severe late-onset ovarian hyperstimulation syndrome presenting with liver dysfunction after in vitro fertilization: A case report

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ABSTRACT

Ovarian hyperstimulation syndrome (OHSS) is a feared complication of controlled ovarian stimulation (COS) and can be associated with significant morbidity and mortality. Risk factors for OHSS include a history of OHSS, young age, low body mass index (BMI), polycystic ovary syndrome, elevated serum levels of anti-Müllerian hormone (AMH), large number of recruited follicles, elevated serum levels of estradiol, and higher gonadotropin doses during COS. However, OHSS may develop in patients with minimal risk factors. We present the case of a patient with minimal risk factors who developed severe late-onset OHSS in early pregnancy with liver dysfunction requiring hospitalization. After hospital discharge, her pregnancy resulted in a term live birth. We recommend that clinicians include OHSS in the differential diagnosis of elevated levels of liver enzymes in early pregnancy.

1. Introduction

Ovarian hyperstimulation syndrome (OHSS) is a complication of controlled ovarian stimulation (COS) and can be associated with significant morbidity and mortality. [1] The pathophysiology of OHSS is not fully understood, but it involves increased capillary permeability and extravasation of fluid from intravascular spaces to the third space. [2] This is thought to be mediated by multiple vasoactive substances, including vascular endothelial growth factor (VEGF), which acts on VEGFR-2 receptors – found on vasculature as well as luteinized granulosa cells – to induce capillary permeability. While OHSS is primarily mediated by VEGF, other pro-inflammatory markers have been implicated, such as interleukin-6 (IL-6), insulin-like growth factor-1 (IGF-1), and transforming growth factor-β (TGF- β). [1]

OHSS is classified as mild, moderate, severe, or critical, based on the clinical presentation. Mild OHSS can present with abdominal distension, nausea, vomiting, or diarrhea. Moderate, severe, and critical OHSS can result in symptomatic ascites, hydrothorax, oliguria or anuria, renal failure, liver dysfunction with transaminitis, thromboembolism, adult respiratory distress syndrome, and sepsis.[1]–[3] OHSS can also be defined as "early" or "late," based on the onset of symptoms after administration of human chorionic gonadotropin (hCG). Early OHSS presents 3–7 days after exogenous hCG administration, with hCG potentiating VEGF to induce OHSS. Late OHSS presents about 12–17 days after the initial hCG administration, and commonly represents the rising endogenous hCG from early pregnancy. [4]

Reproductive endocrinologists are vigilant and risk-stratify patients to determine which patients are at high risk of OHSS. Common risk factors for OHSS include: polycystic ovary syndrome (PCOS), serum estradiol (E2) levels above 3500 pg/mL, development of ≥25 follicles during COS, retrieval of ≥24 oocytes, anti-Müllerian hormone (AMH) > 3.4 ng/mL, history of OHSS in previous COS cycle, use of ovulatory doses of hCG, and higher doses of gonadotropins, although a specific dosage threshold has not been identified. [1,5] Young age and lower body mass index (BMI) have been associated with OHSS, although the predictive value of these characteristics is unclear. The likelihood and severity of OHSS also increase in the setting of early pregnancy, as rising hCG levels from the placenta exacerbate ovarian stimulation and VEGF production. Late-onset OHSS appears more likely with multiple gestations. [6]

Under the CARE guidelines, we present a case of severe late-onset OHSS in a patient with minimal risk factors, to highlight the importance of considering OHSS in the differential diagnosis of liver dysfunction in early pregnancy. The patient provided consent for this

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Table 1
Summary of estradiol (E2) and endometrial thickness (ET) during COS.

Stimulation day	E2 (pg/ml)	ET (mm)
5	700	8.1
7	1895	10.2
9	2772	9.5

report.

2. Case Presentation

A 34-year-old nulliparous woman presented to an academic reproductive endocrinology and infertility clinic for evaluation of infertility. Her history was significant for hypothyroidism, obesity (BMI 32 kg/m^2) and male factor infertility secondary to hypogonadotropic hypogonadism. Her AMH was 5.2 ng/mL. She underwent COS with GnRH antagonist protocol with ganirelix acetate (Ganirelix ®), follitropin alfa (Gondal-F ®), and menotropin (Menopur ®). Her total gonadotropin dose was 2875 IU throughout stimulation. Transvaginal ultrasound (TVUS) on cycle day 9 showed 10 antral follicles on both ovaries, with the largest follicles measuring 20 mm on the left ovary and 21 mm on the right ovary. Serum E2 and endometrial thickness were documented throughout stimulation, as shown in Table 1. Subcutaneous hCG was administered on stimulation cycle day 9 and the patient underwent transvaginal ultrasound-guided oocyte retrieval 36 h later. Fourteen oocytes were retrieved. The patient underwent fresh elective single blastocyst transfer (Gardner grade 4AA). Eight blastocysts were cryopreserved.

Ten days after embryo transfer, the patient presented to the office with abdominal fullness and nausea, with ascites seen on ultrasound. Initial laboratory workup revealed β-hCG 181 mIU/mL, transaminitis with aspartate transaminase (AST) 92 U/L, alanine aminotransferase (ALT) 131 U/L, as well as moderate-severe hyponatremia. [7] Other causes of acute transaminitis, including hepatitis, were excluded. Based on her clinical presentation and laboratory findings, she was admitted for inpatient management of late-onset OHSS. Management included strict volume management with intravenous fluids and albumin. The patient's liver function tests peaked at the following levels: AST 112 U/L 14 days after embryo transfer (hospital day 5), and ALT 246 U/L 16 days after embryo transfer (hospital day 7). Serial liver function tests and sodium levels during admission are presented in Figs. 1 and 2. The patient improved and was discharged on hospital day 11 after resolution of transaminitis and hyponatremia. The remainder of her pregnancy was uneventful, and resulted in a term live birth. The timeline of events is set out in Fig. 3.

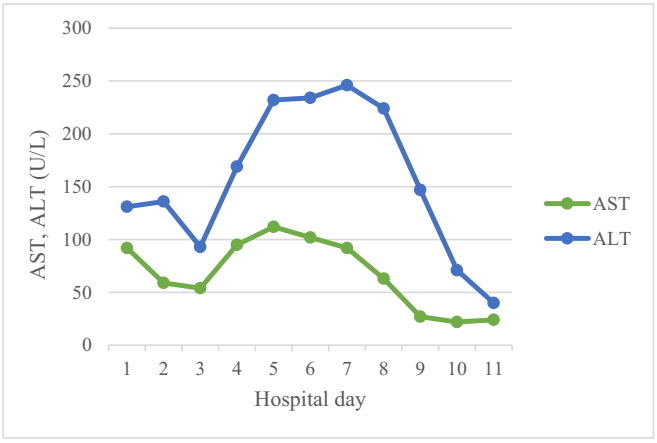

Fig. 1. AST and ALT derangements during hospital days 1–11. AST: aspartate aminotransferase; ALT: alanine aminotransferase.This description should go with Figure 1 (above)

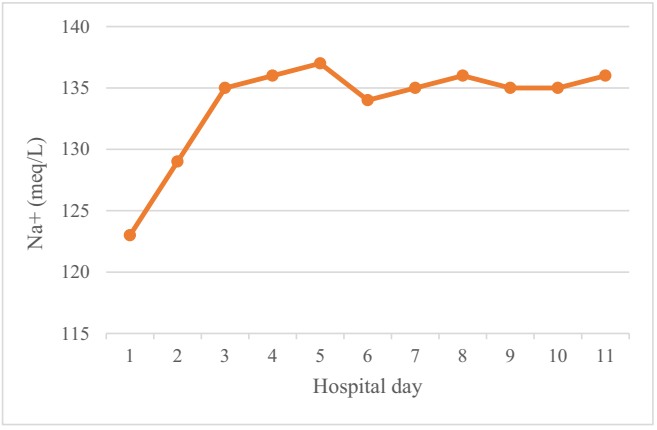

Fig. 2. Serum sodium (Na^+) levels from hospital day 1–11.

Fig. 3. Timeline of events.

Table 2
Differential diagnosis of elevated transaminases in pregnancy.

Diagnosis	Pregnancy trimester	Presentation	Evaluation	Notes
Ovarian hyperstimulation syndrome*	1st	Abdominal distention or bloating, nausea, vomiting, diarrhea, chest pain, orthopnea, oliguria/anuria, lower extremity swelling	Imaging: TVUS, CXR, LE dopplers Labs: CBC, CMP, UA, PT/INR, PTT	Suspect in patient with history of OI (rare), COS, or IVF
Hyperemesis gravidarum*	1st	Nausea, vomiting, weight loss, hyperthyroid symptoms	Labs: UA, CMP, amylase, lipase, TSH, free T4, T3	Possible complication: Wernicke's encephalopathy
Molar pregnancy*	1st	Vaginal bleeding, grape-like cysts on exam, nausea, vomiting, enlarged uterus (size greater than dates), hyperthyroid symptoms	Labs: quant b-hCG, CBC, CMP, TSH, free T4, T3, PT/INR, PTT Imaging: TVUS, CXR	Possible complication: gestational trophoblastic neoplasia
Gallbladder, biliary tract, or liver disease	Any	RUQ abdominal pain, fever, nausea, vomiting, jaundice, dark urine, clay-colored stools	Labs: CBC, CMP, amylase, lipase Imaging: RUQ U/S, CT,§ hepatobiliary scintigraphy, MRCP/ERCP	Possible complications: pancreatitis, peritonitis, sepsis
Drug-induced hepatitis	Any	Abdominal pain, jaundice, fatigue	Labs: CMP, PT/INR, PTT, blood alcohol test, drug screen, acetaminophen level Imaging: RUQ U/S	May consider liver biopsy for diagnosis
Infectious hepatitis (viral)†	Any	Fever, fatigue, loss of appetite, abdominal pain, jaundice, dark urine, clay-colored stools	Hepatitis panel (most commonly hepatitis A, B, C)	Transmission routes: hepatitis A (oral-fecal); B and C (bodily fluids)
Autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis	Any	Fatigue, abdominal pain, jaundice, enlarged liver, loss of appetite, spider angiomas	Labs: CMP, AMA, ANA, SMA IgG, hepatitis panel Imaging: RUQ U/S, cholangiogram, MRCP/ERCP	May consider liver biopsy for diagnosis. If untreated, may lead to cirrhosis and liver failure
Thrombotic event (Budd-Chiari syndrome, portal vein thrombosis)	Any	RUQ abdominal pain, jaundice, enlarged liver, ascites, abdominal distention	Labs: CMP, PT/INR, PTT Imaging: RUQ U/S, CT angiography,§ MRA	Possible complications: liver cirrhosis, hepatic encephalopathy
Intrahepatic cholestasis of pregnancy*	2nd, 3rd	Pruritus, absence of rash	Labs: Bile acids, hepatitis screening	Possible complication: intrauterine fetal demise
Pre-eclampsia*	2nd, 3rd	Chest pain, shortness of breath, headache, visual disturbances, third spacing	Labs: P/C ratio, 24 h UPT, CBC, CMP, LDH Imaging: CXR	May evolve to eclampsia
HELLP syndrome*	2nd, 3rd	General malaise, RUQ pain, nausea, vomiting	Labs: CBC, CMP, LDH Imaging: RUQ U/S, CXR	Possible complications: hepatic rupture
Acute fatty liver of pregnancy*	2nd, 3rd	Nausea, vomiting, abdominal pain, jaundice	Labs: CBC, CMP, LDH, PT/INR, PTT Imaging: RUQ U/S	Possible complications: hepatic encephalopathy, pancreatitis

* Occurs only in pregnancy or assisted reproduction.

† Consider parasitic and fungal infections.

§ Consider CT as second-line imaging modality if diagnosis uncertain after ultrasound, and after counseling patient regarding risks of radiation exposure in pregnancy.

3. Discussion

OHSS is an uncommon but serious iatrogenic complication of COS, with moderate to severe forms of OHSS occurring in about 1–5% of COS cycles. [1] Although the pathophysiology is undefined, the fluid shifts seen in OHSS are thought to be secondary to inflammatory mediators, primarily VEGF. Research also suggests dysregulation of the renin-angiotensin system, leading to elevated levels of antidiuretic hormone (ADH) and hyponatremia, which was seen in our case. [8] Patients with OHSS develop clinical signs of ascites and hypovolemia, leading to decreased end-organ perfusion, and they can present with liver dysfunction.

The mechanism of liver dysfunction in OHSS remains unclear but may be secondary to increased vascular permeability in hepatocellular cells leading to hepatic edema, or microvascular thromboses leading to end-organ ischemia. [6] Hepatic damage from increased E2 has also been proposed, [9,10] although one report did not find a correlation between E2 levels and liver function test derangements. [11] Liver biopsies of OHSS patients have shown focal distribution of fatty change in the periphery of hepatic lobules (acinar zone 1), and structural changes suggestive of an estrogen effect. [12,13] Another study, however, reported relatively normal histology despite lab values indicating liver dysfunction. [10] The timeframe and duration for which laboratory evidence of liver dysfunction may be expected are also unclear. Serum aminotransferase levels, measured by AST and ALT, are commonly used lab measurements of liver function. However, ALT is a more specific marker for liver tissue injury. In our case, while AST and ALT were both elevated, the patient had higher elevations in ALT. Based on a review of the literature, liver enzyme derangements do tend to resolve with resolution of OHSS. [11–14]

Transaminitis in OHSS was first reported in a 1988 case report, in which the patient received hCG luteal phase support after COS. [3] More recent reports have demonstrated severe OHSS with transaminitis, among other derangements, after COS in high-risk patients. [14,15] There is evidence that certain measures can reduce the risk of OHSS, including the use of GnRH antagonists COS cycles, GnRH agonist trigger, dopamine agonist administration at the time of hCG administration, freeze-all cycle, or metformin for PCOS patients. [1] However, these measures do not prevent OHSS, so clinicians should include OHSS in the differential diagnoses of elevated LFTs in early pregnancy.

During pregnancy, serum aminotransferases remain within normal limits. In the evaluation of a pregnant patient with transaminitis, the differential diagnosis is dependent on the gestational age. In the first trimester, the differential diagnosis includes OHSS, hyperemesis gravidarum, molar pregnancy, gallbladder/biliary tract disease, liver disease, viral or autoimmune hepatitis, drug-induced hepatitis, or thrombotic etiology. OHSS evaluation requires a detailed history and physical exam, laboratory evaluation (including complete blood count, complete metabolic panel, and possible coagulation studies), and transvaginal ultrasound to assess the severity of disease. Hyperemesis gravidarum (HG) is characterized by severe nausea/vomiting, weight loss, and/or electrolyte abnormalities in pregnancy. While not diagnostic, HG can present in the first trimester with transaminitis. Similar to OHSS, there is a higher ALT/AST ratio, and elevated transaminases often resolve with hydration and improvement of nausea/vomiting. Patients with HG do not exhibit signs of third spacing such as pulmonary edema or abdominal ascites, which can help distinguish it from OHSS in early pregnancy. A patient with molar pregnancy can present with vaginal bleeding in early pregnancy, nausea/vomiting, transaminitis, as well as hyperthyroid symptoms. On exam, uterine size may be significantly greater than gestational age, and grape-like cysts may be seen protruding from the vagina. Gallbladder disease, drug-induced, alcohol-induced, or viral hepatitis can present in any trimester. Workup may include metabolic profile, right upper quadrant abdominal ultrasound, and testing for viral hepatitis. Autoimmune hepatitis should also be considered. Venous thromboembolic events, which pregnant women are at increased risk of due to the hypercoagulable state of pregnancy, may also involve the liver, as seen in Budd-Chiari syndrome.

In the second or third trimesters, elevated liver enzymes may be seen in cholestasis of pregnancy; patients classically endorse pruritus in the absence of a rash. Evaluation should include bile acids and testing for viral hepatitis. Beyond 20 weeks of gestation, pregnancy-induced hypertensive disorders such as pre-eclampsia with severe features or HELLP syndrome must be ruled out in new-onset transaminitis. The differential diagnoses for elevated liver enzymes in pregnancy are listed in Table 2.

In conclusion, this case report highlights the importance of considering OHSS in the differential diagnosis of liver dysfunction in early pregnancy, particularly in the context of assisted reproduction. Further studies examining the long-term outcomes of patients who develop OHSS are warranted.

Table 2 abbreviations (in alphabetical order): AMA: Anti-mitochondrial antibody; ANA: Anti-nuclear antibody; b-hCG: beta human chorionic gonadotropin; CBC: complete blood count; CMP: complete metabolic profile; COS: controlled ovarian stimulation; CT: computed tomography scan; CXR: chest x-ray; ERCP: endoscopic retrograde cholangiopancreatography; LDH: lactate dehydrogenase; LE dopplers: lower extremity dopplers; IgG: immunoglobulin G antibodies; IVF: in vitro fertilization; MRCP: magnetic resonance cholangiopancreatography; MRA: magnetic resonance angiography; OI: ovulation induction; P/C ratio: protein to creatinine ratio; PT/INR: prothrombin time and international normalized ratio; PTT: partial thromboplastin time; RUQ: right upper quadrant; SMA: Smooth muscle antibody; TSH: thyroid stimulating hormone; TVUS: transvaginal ultrasound; UA: urinalysis; UPT: urine protein test.

Contributors

Jennifer J. Chae-Kim, the primary author, was involved in drafting the initial manuscript, editing the manuscript, and approved the final submission.

Robert Roman was involved in drafting the initial manuscript, revising the manuscript, and approved the final submission.

Kristina Hawkins was the attending physician involved in patient care, revised the manuscript and approved the final submission.

Larisa Gavrilova-Jordan was the attending physician involved in patient care, revised the manuscript and approved the final submission.

Conflict of interest

The authors declare that they have no conflict of interest regarding the publication of this case report.

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Patient consent

Obtained.

Provenance and peer review

This case report was peer reviewed.

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