

Emergency acute kidney injury that occurred during mid-pregnancy due to severe ovarian hyperstimulation syndrome: A case report

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Abstract

Ovarian hyperstimulation syndrome (OHSS) is a life-threatening complication of controlled ovarian hyperstimulation (COH) in fertility treatments. Severe OHSS may result in acute kidney injury (AKI) and poor pregnancy outcomes. Although rare, it is potentially fatal, posing a significant challenge for obstetricians, nephrologists, and critical care physicians. Here, we present a 32-year-old female at 22 weeks and 6 days gestation post-COH, hospitalised with nausea, vomiting, fatigue, and AKI. Her clinical course was complicated by haemodynamic instability, characterized by hypotension and oliguria, along with elevated serum creatinine levels, contributing to adverse pregnancy outcomes. She subsequently developed dyspnoea due to chylothorax, enlarged haemorrhagic ovaries, and massive ascites. She was treated with intravenous fluids, albumin, and anticoagulants, resulting in improvement of renal function (serum creatinine: 0.78 mg/dL, reference range 0.52-1.04 mg/dL at discharge). With the increasing use of assisted reproductive technologies, OHSS remains a significant clinical concern. Early diagnosis and multidisciplinary management are essential to mitigate risks.

Keywords: ovarian hyperstimulation syndrome (OHSS); pregnancy; acute kidney injury (AKI); assisted reproductive therapy (ART).

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Introduction

Assisted reproductive technology (ART) has been widely used for decades to help people conceive. Although generally considered safe, it still carries a risk of ovarian hyperstimulation syndrome (OHSS), with a reported incidence of 1–10% during in vitro fertilisation cycles.¹ In controlled ovarian hyperstimulation (COH), ovarian

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stimulation is achieved by administering exogenous follicle-stimulating hormone (FSH) or human menopausal gonadotropin to recruit multiple mature follicles. Human chorionic gonadotropin (hCG) is used for final oocyte maturation but may pose a potential risk for OHSS in high responders.

OHSS is characterised by an exaggerated ovarian response to ovulation induction, resulting in ovarian enlargement and fluid shift to the extravascular space. Severe OHSS is a potentially life-threatening condition associated with ascites, hydrothorax, ovaries >12 cm in diameter, and, in extreme cases, complications such as acute renal failure, acute respiratory distress syndrome (ARDS), ovarian torsion, and abdominal compartment syndrome (ACS).²

OHSS can present in early and late forms, typically occurring 3–7 days and 12–17 days after ovulation triggering, respectively. The exact pathogenesis of OHSS has not been fully elucidated; however, it appears that hCG stimulates the ovaries to release vasoactive substances, such as vascular endothelial growth factor (VEGF).³ It plays a crucial role as a major regulator of capillary permeability that is positively correlated with OHSS risk and severity.

The case of an acute kidney injury (AKI) due to severe OHSS is presented, which occurred in mid-pregnancy. The important aspects of its pathophysiology and management are highlighted.

Case Report

A 32-year-old previously healthy woman was admitted to Wenzhou People's hospital in China on August 6, 2023, with a 2-week history of nausea, vomiting, fatigue, and skin itching. She was 22 weeks and 6 days pregnant, achieved through controlled hyperstimulation (COH), with a 2-year history of infertility due to a diagnosis of polycystic ovarian syndrome (PCOS), with no prior pregnancies. She was administered 5 mg/day of letrozole tablets for 5 days, followed by 75 U/day of human menopausal gonadotropin (Lebaode®) intramuscular injection for 5 days, with ultrasound monitoring of follicular development. To induce ovulation, she received a hypodermic injection of 250 µg of recombinant hCG (OVITRELLE®, Merck Serono SPA) and 0.1 mg of a gonadotropin-releasing hormone (GnRH) agonist (Triptorelin®, Ferring GmbH, Germany), followed by

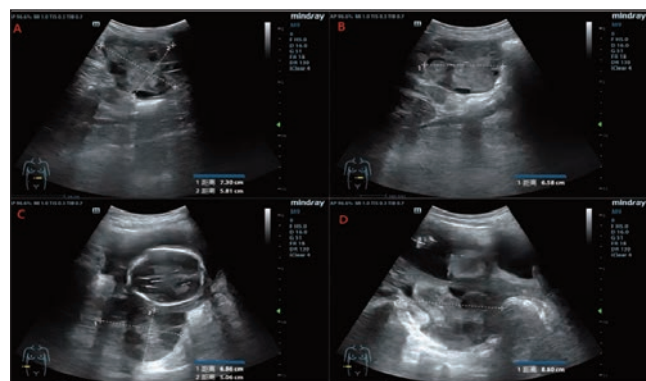


Figure-1: Ultrasonography of the patient's ovaries. Significant enlargement of the ovaries: left, 73.0 mm x 58.1 mm x 65.8 mm (A and B); right, 68.6 mm x 50.6 mm x 86.0 mm (C and D).

a repeat 250- μ g OVITRELLE[®] injection 3 days later.

On admission, vital signs were as follows: temperature, 36.7°C; heart rate, 116 bpm; oxygen saturation, 98%; breathing rate, 19 breaths/min; blood pressure, 88/48 mmHg; height, 160 cm; weight, 42 kg; and body mass index (BMI), 16.41 kg/m². Physical examination revealed no bilateral pulmonary rales, no cardiac murmurs, no costovertebral angle tenderness, and no peripheral oedema in the lower extremities. Ultrasonography showed an increased umbilical artery ratio, with S/D values of 6.86 (placenta proximal) to 7.61 (foetus proximal), a foetal heart rate of 150 bpm, and an amniotic fluid index of 183 mm. The ovaries were significantly enlarged (Figure-1).

The patient's condition rapidly deteriorated, with the development of oliguria, markedly elevated serum creatinine (9.52 mg/dL, reference range 0.52-1.04 mg/dL) and urea nitrogen (110.92 mg/dL, reference range 7.0-17.93 mg/dL), electrolyte imbalances (hypokalaemia, hyponatraemia, hypochloraemia, and hypocalcaemia). The laboratory findings are summarised in Table 1. The D-dimer level increased to 14.5 mg/L (reference range <0.5 mg/L), white blood cell count was 11.7×10^9 /L (reference range $(3.5-9.5) \times 10^9$ /L), haemoglobin level was 71 g/L (reference range 115-150 g/L), and platelet count was 241×10^9 /L (reference range $(125-350) \times 10^9$ /L). Lactate dehydrogenase (LDH) and aspartate aminotransferase (ALT) levels were slightly elevated at 396 U/L (reference range 120-246 U/L) and 58 U/L (reference range 7-40 U/L), respectively. Ultrasonography revealed loss of diastolic blood flow in the foetal umbilical artery and decreased foetal heart rate (115 bpm).

The patient was initially admitted for acute renal failure with electrolyte imbalance and was subsequently transferred to the intensive care unit due to haemodynamic instability. Supportive treatments, including intravenous infusion of red blood cells (5.5 U), fresh frozen plasma

Table-1: Patient's laboratory indicators.

	Day 1	Day 3	Day 5	Day 7	Day 15	Reference
Renal function						
Serum creatinine	9.52	6.90	4.56	2.79	0.78	0.52-1.04mg/dL
Urea nitrogen	110.92	85.15	92.15	85.54	13.16	7.0-17.93mg/dL
Uric acid	11.77	11.05	11.70	8.49	3.87	2.51-6.20mg/dL
Liver function						
ALT	39	17	8	8	5	7-40 U/L
AST	58	19	12	13	15	13-35 U/L
Total bilirubin	1.73	2.68	1.42	0.96	0.30	0.18-1.29mg/dL
Direct bilirubin		2.02	0.91	0.92	0.26	<0.23 mg/dL
Albumin	3.31	2.30	2.24	2.46	2.59	4.0-5.5 g/dL
Cardiac function						
LDH	396	376	252	179	147	120-246 U/L
Tn-I	0.024	0.311	0.261	0.068		<0.12ng/mL
		Day 2	Day 4	Day 6		
CK	44	71	40			30-135 U/L
Routine blood tests						
WBC	11.8	16.6	14.4	18.3	13.3	$(3.5-9.5) \times 10^9$ /L
HB	71	76	85	94	89	(115-150) g/L
Hct	22.4	25.8	26	28.4	28.3	(35-45)%
PLT	241	125	84	98	424	$(125-350) \times 10^9$ /L
Inflammatory indicators						
PCT	1.19	1.06		0.51		<0.06 ng/mL
CRP	4.3	35.7	85.9	8.5	30.6	<8.0 mg/L
Electrolytes						
K ⁺	3.2	3.7	3.2	3.0	3.7	3.5-5.3 mmol/L
Na ⁺	124	131	135		137	137-147 mmol/L
Cl ⁻	74	87	94		107	99-110 mmol/L
Ca ²⁺	1.7	1.91	1.87	1.94	1.83	2.11-2.52 mmol/L
P		2.86		1.56	0.82	0.85-1.51 mmol/L
Coagulation function						
PT	9.7	10.2	9.9	9.9		9.4-12.5 s
APTT	32.6	33.5	34.6	36.4		25.1-36.5 s
FDP	29.83	13.07	12.68	12.73		<5 mg/L
DD	14.5	5.34	6.81	6.78	4.17	<0.5 mg/L
Hormone						
fT3			3.4	2.3	1.4	3.1-6.8 pmol/L
fT4			21.9	9.2	5.5	12.0-22.0 pmol/L
TSH		<0.01	<0.01	0.12		0.27-4.2 mIU/L
PTH				128.9		15-65 pg/mL
hCG			13591	1065		<5.3 mIU/mL
Mammothrophic hormone				299.8		3.34-26.72 ng/mL
AFP		246.9	87.7	48		<7.0 ng/mL
CA125		124.5		152		<47.0 U/mL
LH				<0.1		mIU/mL
FSH				<0.1		mIU/mL
Oestradiol				>1101		pmol/L

Hydrothorax examination: triglyceride 234.63 mg/dL, total cholesterol 40.60 mg/dL, LDH 179 U/L, ADA 5 U/L, glucose 99.47 mg/dL, total protein 2.0 g/dL, karyocyte 723×10^6 /L, lymphocytes 43%, neutrophils 10%, macrophages 32%, hydrothorax cultured negative, exfoliated cells, TB-PCR negative, no malignancy evidence in imaging of positron emission tomography (PET).

Urine analysis: pH 6.0, specific gravity 1.010, urine protein +/-, urinary red blood cells 44/uL, urine sodium 60 mmol/L, urine chlorine 50 mmol/L, urine potassium 28.8 mmol/L, 24 h urine protein 763 mg (urinary volume 2911 mL), urine IgG 1.11 mg/dL (<0.96), urine transferrin 0.34 mg/dL (<0.24), microalbuminuria/urine creatinine 134.7 mg/gCr (3.0-40.0), urine $\alpha 1$ microglobulin 8.87 mg/L (<1.20), urine $\beta 2$ microglobulin 4.04 mg/L (<0.02), urine NAG/urine creatinine 30.85 U/mmolCr (0.01-1.30).

Others: ANAs, lupus anticoagulant, anticardiolipin antibody all negative; immunofixation electrophoresis, HBV, HCV, HIV, TP antigens negative; IgA 2.49 g/L (1.0-4.2), IgE 134.0 IU/mL (<100), IgG 10.5 g/L (8.6-17.4), IgM 1.26 g/L (0.5-2.8), C3 0.85 g/L (0.7-1.4), C4 0.13 g/L (0.1-0.4), C1q 230 mg/L (159-233); Coombs test negative; schistocytes not found in blood smear.

(1,020 mL), and albumin (20 g, 100 mL), were administered along with prophylactic doses of anticoagulants (Enoxaparin®, 2000 IU/day, hypodermic injection) and antibiotics (Cefoxitin®, 1.0 g/day, venoclysis); however, the patient's mental status and blood pressure continued to deteriorate. Noradrenaline (10 mg) was used to maintain her blood pressure. The patient subsequently delivered a stillborn infant and developed respiratory distress. Imaging revealed pleural effusion, fluid accumulation in the abdominal and pelvic cavities, and enlarged ovaries with intraovarian haemorrhage. Electrocardiography demonstrated nodal tachycardia with increased troponin-I (0.311 ng/mL, reference range <0.12 ng/mL) indicated an insufficient intravascular volume. Blood gas analysis revealed PaCO₂ 33.7 mmHg (reference range 32-45 mmHg); PaO₂ 71.0 mmHg (reference range 83-108 mmHg); pH 7.44 (reference range 7.35-7.45); lactic acid 2.53 mmol/L (reference range 0.2-1.8 mmol/L); bicarbonate radical 22.6 mmol/L (reference range 22-27 mmol/L); and base excess (-)1.2 mmol/L (reference range -3-3 mmol/L). Cardiac and lower extremity venous ultrasound results were normal. Thoracentesis yielded milky pleural fluid, and the patient was diagnosed with chylothorax.

After draining 2.7 L of fluid, dyspnoea improved. On day 3, the urine volume increased to 3 L; urine protein level was 763 mg; and urine alpha and beta microglobulin levels were 8.87 mg/dL (reference range <1.2 mg/dL) and 4.04 mg/dL (reference range <0.02 mg/dL), respectively, with significantly elevated urinary sodium, indicating acute tubular necrosis. The serum creatinine level decreased to 0.78 mg/dL on day 15. Renal function remained stable at discharge 3 months later. The intraovarian haemorrhage had also resolved.

Discussion

The pathogenesis of AKI due to severe OHSS can vary.⁴ Persistent nausea and vomiting may lead to pre-renal AKI, further depleting the intravascular volume. Severe ascites coupled with ovarian enlargement can cause intra-abdominal hypertension, compromising visceral blood flow in several organs, including the kidneys. Reduced kidney perfusion decreases glomerular filtration rate, leading to oliguria. Changes in perfusion can also have an effect on the liver function, including protein synthesis, wherein anticoagulation factors are depleted. Additionally, haemoconcentration due to a massive capillary leak can lead to thrombosis. Cases of AKI due to kidney artery thrombosis has been reported.⁵ In this patient, the presence of hypotension and tachycardia on admission suggested intravascular volume depletion as the primary contributor to AKI. The absence of postrenal obstructive causes, along with markedly elevated urinary sodium and

urinary β 2-microglobulin levels, supported a diagnosis of acute tubular necrosis. Renal puncture was not performed because the urine volume recovered rapidly, confirming renal tubular injury.

Pleural effusion commonly occurs in association with ascites in OHSS.⁶ Diaphragmatic defects have been identified in both surgical cases and post-mortem studies. In a systematic review of 30 cases of OHSS with pleural effusion,⁷ an exudate was reported in 66.7% and a transudate in 33.3%, while chylothorax was rarely reported. In the present case, chylothorax was diagnosed based on a pleural fluid triglyceride concentration >1.24 mmol/L. This could be attributed to a notable elevation in lymphatic pressure in the thoracic duct due to intra-abdominal hypertension, leading to extravasation of chyle into the pleural space, as observed in decompensated hepatic cirrhosis.⁸

The risk of thrombosis secondary to haemoconcentration and immobilisation should be carefully considered, and prophylactic anticoagulation should be initiated in patients with severe OHSS at the time of diagnosis. Severe OHSS is a hypovolaemic-hyponatraemic state, and intravenous fluid and human serum albumin are crucial for intravascular and end-organ perfusion. The binding properties of intravenous albumin may neutralise vascular permeability factors mediating OHSS. Some studies⁹ suggest that 6% hydroxyethyl starch may be more effective than albumin in the management of severe OHSS, demonstrating higher urine output, fewer requirements for abdominal paracentesis or thoracocentesis, and shorter hospital stays; however, evidence supporting the use of volume expanders alone in OHSS remains limited.

Paracentesis plays a key role in the management of severe OHSS. Abdominal, transvaginal, or thoracic paracentesis is often needed to alleviate dyspnoea or oliguria.¹⁰ Herein, the patient did not undergo abdominal paracentesis but instead underwent thoracic paracentesis. After draining 2.7 L of fluid, dyspnoea improved. To some extent, the diaphragmatic defect serves as an outlet, delaying the consequences of intra-abdominal hypertension and reducing the risk of pleural effusion.

Conclusion

This case presents a life-threatening, the mid-gestation onset of severe late OHSS following PCOS treatment, characterized by volume depletion-induced acute tubular necrosis, massive ascites, haemorrhagic ovaries, chylothorax, and foetal demise. Targeted resuscitation resolved renal impairment, underscoring the critical need for early multidisciplinary management, vigilant monitoring for signs of capillary leak and intra-abdominal

pressure, and routine thromboprophylaxis to mitigate the distinct maternal-foetal risks of mid-pregnancy OHSS.

Abbreviations: ALT: alanine aminotransferase; AST: aspartate aminotransferase; LDH: lactate dehydrogenase; Tn-I: troponin-I; CK: creatine kinase; WBC: white blood cell; HB: haemoglobin; PLT: platelets; Hct: haematocrit; PCT: procalcitonin; CRP: C reactive protein; K⁺: potassium; Na⁺: sodium; Cl⁻: chlorine; Ca²⁺: calcium; P: phosphorus; PT: prothrombin time; APTT: activated partial thromboplastin time; FDP: fibrin degradation product; DD: D-Dimer; fT3: free thyroid hormone 3; fT4: free thyroid hormone 4; TSH: thyroid-stimulating hormone; PTH: parathyroid hormone; hCG: human chorionic gonadotropin; AFP: alpha-fetoprotein; CA125: carbohydrate antigen 125; LH: luteinizing hormone; FSH: follicle-stimulating hormone; ADA: adenosine deaminase; TB: tuberculosis; IgG: immunoglobulin G; IgA: immunoglobulin A; IgE: immunoglobulin E; IgM: immunoglobulin M; C3: complement; C4: complement 4; NAG: N-acetyl-β-D-glucosidase; ANAs: antinuclear antibodies; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; TP: Treponema pallidum

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Author Contribution:

LNZ: Writing, editing and data collection.

LJH, SSD & MDW: Approved treatment and follow-up.

WH: Concep and Final approval.