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CASE REPORT

Acute Kidney Injury Complicating Ovarian Hyperstimulation Syndrome: A Case Report
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Summary

Ovarian Hyperstimulation Syndrome (OHSS) is a known iatrogenic condition resulting predominantly from an exaggerated response to ovarian stimulation during fertility care. The pathology is characterized by increased capillary permeability, resulting in fluid leakage from the vascular compartment, with third-space fluid accumulation and haemoconcentration. We report a case of severe OHSS in a 33-year-old Para 0+2 woman following in-vitro fertilization and embryo transfer. She was presented with abdominal pain and distension, dyspnoea, jaundice, reduced urinary output as well as sonographic features of enlarged ovaries with ascites. She had a miscarriage 20 hours before the presentation and recovered fully with multidisciplinary treatment, including haemodialysis. Though OHSS is rare and unpredictable, with varying morbidity and mortality rates, it is pertinent that proper patient selection, early diagnosis, and timely intervention may prevent or lessen some complications associated with this condition.

Keywords: Acute Kidney Injury, Assisted Reproductive Technology, Controlled Ovarian Hyperstimulation, Gonadotropins, Ovarian Hyperstimulation Syndrome.

Introduction

Ovarian hyperstimulation syndrome (OHSS) is a complication of fertility treatment where pharmacological ovarian stimulation is utilized to increase the number of oocytes available during assisted reproductive technology (ART).[1] In a minority of women undergoing treatment, the ovarian response exceeds the targeted level, resulting in a clinical condition with specific pathophysiology.[1] Ovarian hyperstimulation syndrome is the most significant complication of controlled ovarian hyperstimulation and is associated with notable physical and psychosocial morbidity and occasional mortality.[2] Although most cases of OHSS are self-limiting, there is a need for supportive management and monitoring while envisaging spontaneous resolution. Women with more severe OHSS may require in-patient care with a thorough evaluation and focused treatment to minimize the risk of further complications. The
fundamental principles of OHSS management, therefore, include early recognition as well as prompt assessment and treatment of women with moderate or severe OHSS. Overall, prevention of OHSS is crucial and involves proper patient selection. Therefore, fertility experts should have a high index of suspicion in the management of women at risk of this life-threatening complication, and a decent communication channel should be established between the caregivers and the clients during ovarian stimulation.

Case Description

Mrs AB, a 33-year-old Para 0-2 realtor, was admitted to the Federal Medical Centre, Abeokuta, Ogun State following a referral from a privately-owned fertility care hospital, with complaints of progressive abdominal distension of seven weeks duration, yellowish discoloration of the eye, and reduced urinary output of a week duration. There was a background history of secondary infertility due to bilateral, non-patent fallopian tubes. Mrs AB had in-vitro fertilization and embryo transfer at a private fertility care hospital using the Short Protocol with Buserelin and Human Menopausal Gonadotropin (hMG). The dose was increased due to non-responsiveness as the Antral Follicular Count (AFC) on transvaginal ultrasound scan (TVUSS) was four. Ovulation was triggered with 10,000IU of human Chorionic Gonadotropin (hCG) following the increase in AFC, and oocyte retrieval was done 36 hours later. Mrs AB developed mild abdominal pain with bloatedness. Still, the fertility experts were not informed, and she had embryo transfer fifth day after oocyte retrieval, while the luteal phase was supported with Progestogens. Following embryo transfer, the abdominal pain increased in severity and was associated with a sudden onset of abdominal distension. She had abdominal paracentesis three days after embryo transfer, and this was repeated two days later on account of recurrent abdominal pain and unresolved ascites. She started early pregnancy care at the referral hospital following a positive serum pregnancy test. Mrs. AB was monitored with an ultrasound scan and was re-admitted at a gestational age of five weeks when another abdominal paracentesis was done. She was subsequently discharged after the temporary resolution of the symptoms. Unfortunately, Mrs AB had a complete miscarriage at a gestational age of eight weeks and subsequently, developed jaundice and oliguria; hence the referral to our centre.

At presentation, she was acutely ill-looking and in respiratory distress, moderately dehydrated, icteric, not pale, and afebrile (37°C) with generalized oedema, and her body weight was 90kg. There was tachypnoea (RR - 30cycles per minute) with widespread crepitations and reduced breath sound quality in the lower lung areas bilaterally. The oxygen saturation was 94% in room air, and other vital signs were essentially normal. The abdomen was distended with mild tenderness, abdominal girth was 114cm, organs could not be palpated, and ascites were demonstrable by fluid thrill.

Abdominopelvic and transvaginal ultrasound scans revealed an empty uterus with bilateral multilocular cystic ovarian masses (Right ovary-100mm X 80mm X 60mm, left ovary- 90mm X 70mm X 70mm) with gross ascites and hepatomegaly as shown in Figure 1 and 2.

Laboratory studies revealed Haemoglobin-10g/dl, Packed cell volume - 30%, White Blood Cell count -15,000/mm³, Platelet count 350,000/mm³. Serum Sodium - 126mmol/L, Potassium - 6.9mmol/L, Chloride - 99mmol/L, Bicarbonate - 17mmol/L, Urea - 171mg/dl, and Creatinine - 11.8mg/dl. The liver function tests showed elevated conjugated bilirubin, reduced total protein, and decreased albumin, and other
parameters like fasting blood sugar, clotting profile, thyroid function tests, and serological studies were normal. The patient belonged to blood group "O" Rhesus "D" - positive, and the haemoglobin genotype was AA. The Chest X-ray showed features of pleural effusion, as shown in Figure 3.

An assessment of acute kidney injury secondary to severe OHSS with pulmonary oedema and complete miscarriage was made. Mrs. AB was admitted, and the nephrologists, pulmonologists, hepatologists, and intensivists evaluated her clinical state and contributed to her clinical state.
management. She was catheterized for urinary output monitoring. She also received intravenous fluids, antibiotics, intravenous calcium gluconate, and 50% Dextrose/water 1:1 dilution, intravenous soluble insulin 10IU stat, subcutaneous Clexane 40mg 12hrly and intravenous albumin (25%) 200mls slowly. She had four sessions of haemodialysis and received two sessions of blood transfusion. The abdominal girth and body weight were serially monitored in addition to surveillance using ultrasound scan and laboratory blood investigations. The patient was discharged on the 16th day of admission. The pleural effusion and ascites resolved spontaneously following the above treatment regimen. Before the discharge, her clinical and laboratory evaluations were repeated, and all the parameters assessed were normal. Abdominal girth and weight at discharge were 79cm and 76kg, respectively. Mrs AB’s clinical improvement was sustained, and she was discharged for follow-up visits. The renal and liver function tests, as well as an ultrasound scan at the last follow-up visit, were normal. She was counselled on the need for controlled ovarian hyperstimulation in her next attempt at in-vitro fertilization, preferably six months after the present episode. She was also given the options of cryopreservation of embryo, ovum donation, and cancellation of the cycle when OHSS is suspected in subsequent fertility attempts.

![Figure 3: Chest X-ray showing evidence of pleural effusion](image)

**Discussion**

Ovarian Hyperstimulation Syndrome was first described in 1943, but the first fatal case was documented in 1951.[1] This syndrome can either be spontaneous or iatrogenic, but the latter is relatively common, occurring in up to 5% of women undergoing in-vitro fertilization (IVF) or intrauterine insemination (IUI) procedures. [1] Iatrogenic OHSS occurs mainly during ART
cycles using gonadotropins, although it might also occur during ovarian stimulation using clomiphene citrate.\textsuperscript{[2]} Exposure of ovaries to the human chorionic gonadotropin (hCG) or luteinizing hormone (LH), following controlled ovarian stimulation with follicle-stimulating hormone (FSH) or human menopausal gonadotropin (hMG) underlies most cases of OHSS.\textsuperscript{[2]} Trigger of hyperstimulated ovaries due to the administration of hCG leads to the production of pro-inflammatory mediators acting in concert with vascular endothelial growth factor (VEGF), which is commonly implicated.\textsuperscript{[8]} The index patient had hMG for ovarian stimulation and hCG as a trigger. Acute kidney injury resulting from OHSS could be attributed to intravascular volume depletion, kidney oedema from increased capillary leakage, raised intra-abdominal tension, and obstructive uropathy due to ovarian enlargement.\textsuperscript{[6]}

Ovarian Hyperstimulation Syndrome can be classified based on symptoms, ultrasound as well as laboratory findings into mild, moderate, severe, and critical. It can also be classified into early (occurring within 3-7 days) and late (happening within 2-17 days) based on the onset of symptoms after ovulation triggered with hCG.\textsuperscript{[9]} The risk factors that are likely to amplify the response to ovarian stimulation include young age, a history of elevated response to gonadotropins, previous OHSS, and polycystic ovary syndrome (PCOS).\textsuperscript{[6]} Other risk factors include absolute levels or rate of increase of serum oestradiol, follicular size and number, and number of oocytes collected.\textsuperscript{[9]} The index patient had a higher dose of gonadotropin due to initial non-response.

Despite close monitoring during ovarian stimulation and rigid guidelines and criteria for cancelling cycles, OHSS still occurs.\textsuperscript{[2,3]} The complications can be multisystemic, resulting from increased capillary permeability manifesting in the clinical picture of this syndrome.\textsuperscript{[1]} In the severe form of the disease, the resultant extravasation of albumin-rich exudates in the peritoneal, pleural, and pericardial space with intravascular hypovolaemia is accompanied by the development of oedema, ascites, hydrothorax, and pericardiac effusion which can be life-threatening.\textsuperscript{[3]} Other complications, including thromboembolic phenomenon, acute kidney injury, respiratory distress syndrome, and even death, could occur.\textsuperscript{[1]} The index patient had pleural effusion, ascites, and acute kidney injury.

The severity of the condition determines the management of OHSS. The treatment could be supportive and multidisciplinary, especially in severe cases like the index case.\textsuperscript{[1]} Most patients are admitted for observation because of the unpredictability of this condition, as mild presentations can rapidly progress to severe forms.\textsuperscript{[1]} The administration of intravenous fluids using crystalloids or colloids for volume replacement is recommended to maintain adequate urinary output and reverse the ongoing haemoconcentration. Crystalloids and colloids are similarly effective in increasing intravascular volume.\textsuperscript{[6]} Albumin is a viable option as a volume expander as it effectively helps to maintain urinary output, especially in cases of persistent haemoconcentration.\textsuperscript{[7]}

Anticoagulation therapy such as Low Molecular Weight Heparin (LMWH) and Thrombo-Embolic Deterrent (TED) are recommended to prevent and treat thromboembolic events.\textsuperscript{[1]} Depending on the severity of ascites, paracentesis may be needed if respiratory and renal compromises are present.\textsuperscript{[10]} Intermittent and continuous aspiration of ascitic fluid is beneficial in severe OHSS as this would significantly improve renal perfusion with increased creatinine clearance and optimal urine output.\textsuperscript{[8]} The mechanism by which removal of ascitic fluid increases urine outputs in the severe form of this condition includes a reduction in intra-abdominal pressure compressing the
in inferior vena cava, an increase in venous return, and enhanced renal perfusion with resultant optimization of kidney function. Other procedures may include transvaginal aspiration and thoracentesis in patients with significant respiratory compromise. Haemodialysis is beneficial for severe cases of renal injuries, as seen in the index case. Rarely, surgical intervention may be indicated in life-threatening cases of ovarian torsion and rupture.

The key to preventing OHSS during controlled ovarian stimulation is recognizing the risk factors and individualizing the ovarian hyperstimulation protocol by appropriately using individualized controlled ovarian hyperstimulation (iCOS). Some cardinal preventive strategies include the use of Long GnRH agonist protocol, GnRH antagonist protocol, low dose gonadotropins, adjuvant therapy like insulin sensitizer (metformin), dopamine agonist (Carbagoline), and close monitoring of patients with AFC, serum oestradiol levels and basal AMH. The index patient was monitored with AFC, but there was no evidence of serum oestradiol level or AMH from the referral note. Also, coating, ovulation triggered with short-acting GnRH agonist or reduction of the ovulatory dose of hCG, aspiration of immature oocytes with in-vitro maturation, luteal phase support with progestogens, and follicular aspiration after hCG administration are some of the documented preventive modalities. Furthermore, prevention of OHSS could involve Oocyte Retrieval and cryo-preservation of the oocytes or Oocyte retrieval plus in-vitro fertilization and cryopreservation of embryo, delayed embryo transfer until after resolution of symptoms, and in extreme cases, cancelling of the treatment cycle. The index patient was counselled on these preventive steps during her follow-up clinic session.

Conclusion

Artificial Reproductive Technology is becoming increasingly acceptable in Nigeria and other low-income countries. This surge in the utilization of (ART) has led to the rising incidence of OHSS. It is pertinent that proper patient selection, close monitoring, early detection, and conforming to rigid guidelines and criteria for cancelling cycles may avert or ameliorate the progression of the syndrome to prevent untoward complications.

Ethical consideration

Informed consent was obtained from the patient to use her data in this publication.

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Authors’ Contributions: All the authors conceived the study. JOS and TOO did a literature review. TNA, JOS, and TOO drafted the manuscript. TNA, JOS, and LBRT revised the draft for sound intellectual content. All the authors approved the final version of the manuscript.

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