

East African Medical Journal Vol. 92 No. 1 January 2015

OVARIAN HYPERSTIMULATION SYNDROME (OHSS): CASE REPORT

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SUMMARY

There has been a rapid increase in the number of couples receiving treatment for infertility with Assisted Reproductive Technology (ART) in recent years. While there is robust evidence supporting the efficacy and safety of ART, it is important to be aware of the risks, the most serious of which is OHSS. A case of OHSS, a rare complication of COS, which is potentially fatal, is presented. Patient with secondary infertility (Para 0 + 1), who had had IVF - COS followed by oocyte retrieval and subsequent embryo transfer. She presented at Accident and Emergency Unit, Nairobi Hospital, with dyspnea, chest pain, abdominal pain and distension. A diagnosis of OHSS with pulmonary thromboembolism was made. She was admitted to Intensive care unit (ICU). She was managed with oxygen by mask, intravenous fluids, anticoagulant and albumen in Intensive Care Unit with fully recovery. The case study presents her clinical manifestations, investigation, progress, management, outcome and preventive measures.

INTRODUCTION

OHSS is a rare potentially fatal complication of infertility treatment. Therefore, it is critical to ensure continuous understanding of its cause, clinical presentation, treatment, prevention and epidemiology. This will ensure early recognition, management of the condition and hence reduce morbidity and mortality. Physicians should always be aware of the risk of OHSS in patients undergoing COS, as it can be fatal. It has been well established that the trigger of OHSS is Human Chorionic Gonadotropin (HCG), which appears to act via vascular endothelial growth factor (VEGF) (5). The objective of this paper is to describe this life threatening complication of ovarian stimulation, Ovarian Hyperstimulation syndrome (OHSS).

CASE REPORT

Thirty-six years old patient, Para 0+1 Gr2, who presented at five weeks gestation with dyspnea, chest pain, abdominal pain and swelling. She had conception by IVF where COS has been done, oocyte

retrieval and consequently three embryo transfer.

In accident and emergency the following investigation were performed:

Haemogram:

Hb	14.3 g/dl	WBC	84
Neutrophils	78.8	Lymphocytes	15.8
Platelets	163 x 10 ³		
D Dimer	- 4,950ug/l (Normal 0-500)		
Troponin I	- 0.06ng/m (Normal 0.1)		
Procalciton	- 0.11		
Serum BHCG	- 14,006 iu		

Pelvic abdominal – uterus normal size, endometrial thick, and ovaries– markedly enlarged. Mildly hypoechoic, with large follicles.

Right ovary - 17.4 cm³, Left ovary- 30.2 cm³–enlarged
Massive ascites. Liver and kidneys were normal. (Repeat pelvic ultrasound after one week indicated two intrauterine gestations).

2D Echo: Left pulmonary artery clot. Moderate pulmonary arterial hypertension. Good left ventricular systolic function.

Chest X-ray: Pleural effusion.

Doppler velocimetry: No deep venous thrombosis.

An impression of ovarian hyperstimulation syndrome with pulmonary thromboembolism was made.

The patient was admitted to intensive care unit. The treatment commenced was Oxygen by mask for 24 hours.

- IV Clexane 80 iu 12 hrly
- IV Albumin 100mls 12 hrly
- IV Paracetamol 1 gm. 8 hrly
- Per vaginal progesterin's

After one day in ICU, she was discharged to High Dependence Unit and in the wards for five days. She was discharged home on clexane and progesterins per vaginally.

DISCUSSION

A certain degree of ovarian hyperstimulation is desirable during COH, however exaggerated response poses risk of potentially life threatening condition (12,13). OHSS is a less common iatrogenic condition but potentially fatal complication of ovarian stimulation resulting from excessive ovarian stimulation. (1,13). It is the most serious complication of COS as part of assisted reproductive technologies (ART) (2). It still has a very serious impact on the patients' health and may cause severe morbidity even mortality (13). The incidence of OHSS varies from 1% to 14% in all In Vitro Fertilization (IVF) Cycles (1). Moderate cases of OHSS in all cycles is estimated to be between 3-6% while the severe life threatening form that leads to hospitalisation occur in 0.1-3% (3). The syndrome is characterised by cystic enlargement of the ovaries and fluid shift from the intravascular to the third space due to increase in a capillary permeability and ovarian neoangiogenesis (4).

It is mainly associated with the multifollicular response encountered in gonadotropin stimulation but can occur with use of clomiphene Citrate and gonadotropin releasing hormone (5). Spontaneous OHSS rarely occurs in natural conception; however, cases have been reported. (6).

Pathophysiology: The pathophysiology of OHSS is unknown but the process is related to increased vascular permeability in the region surrounding the ovaries and their vasculature (7). It has been well established that the trigger of OHSS is Human Chorionic Gonadotrophin (HCG), which appears to act via vascular endothelial growth factor (VEGF) (5). VEGF is a member of the transforming growth factor - B (TGF - B) superfamily, also known as vascular permeability factor, has emerged as one of the factors most likely involved in the pathophysiology of OHSS (8). VEGF increases vascular permeability

allowing degree of protein rich fluid. Other factors like angiotensin II, insulin-like growth factor, (IGF-I), epidermal growth factor (EGF), basic fibroblast growth factor (BFGF), platelet-derived growth factor (PDGF), interleukin - 1B (IL-1B) and IL - 6 may also play a part in the pathogenesis either directly or via VEGF (8).

Classification: To understand OHSS and its management, one must be aware of its classifications of severity grades of OHSS are as follows (10).

Mild OHSS

- Grade 1 - Abdominal distension and discomfort.
- Grade 2 - Grade 1 disease plus nausea and/or diarrhea plus ovarian enlargement from 5-12 cm.

Moderate OHSS

- Grade 3 - features of mild OHSS plus ultrasonographic evidence of Ascites.

Severe OHSS

- Grade 4 - features of moderate OHSS plus clinical evidence of Ascites and /or hydrothorax and breathing difficulties.
- Grade 5 - all of the above plus a change in the blood volume, increased blood viscosity due to haemoconcentration, coagulation abnormalities and diminished renal perfusion and function. The patient presented had severe OHSS at grade 5.

Clinical features: Patients generally develop symptoms four to five days after oocyte retrieval. Initial symptoms of mild disease may include nausea and abdominal distension or discomfort. Disease progression is generally marked by the persistence of symptoms and the development of vomiting, weight gain, ascites, pleural effusion, hypoalbuminaemia and other symptoms. Complication of OHSS may manifest as thromboembolism, acute renal failure, respiratory compromise, hyperkalaemia and infection (11, 12). The patient presented the patient had ascites, pleural effusion and pulmonary thromboembolism. Clinical assessment of patient with probable OHSS should include complete history and examination. Work-up should include basic hematological testing (including full blood count, urea/electrolytes/creatinine, liver function test, beta HCG and Coagulation studies) abdominal ultrasound and chest X-ray.

Risk Factors for OHSS: These are; young age, a history of elevated response to gonadotropins, Previous OHSS, Polycystic Ovarian Syndrome (PCOS), or Isolated PCOS characteristic, high basal antimullerian hormone (AMH) (cut off 3.36 ng/ml), high antral follicle (AFC) - (AFC more than 14, predicts hyperstimulation) and elevated Inhibin - B levels (15, 16,17). Basal AMH levels prior to COS have also been shown to be predictive for OHSS (19).

Moreover, AMH may be a better predictive marker of excessive ovarian response to COS than age, basal Follicle Stimulating Hormone (FSH), and estradiol (E2) on the day of HCG administration, and has been shown to be at least as good as AFC. Furthermore, AMH predicts ovarian response independently of age and PCOS (19,20).

Prevention: Prevention of OHSS is a multi-stage process. The key to the primary prevention of OHSS during COS is recognising risk factors and individualising the ovarian stimulation protocol. Avoidance of HCG has been advocated in high-risk patients for OHSS. It has been shown that the administration of a Gonadotrophin Releasing Hormone (GnRH) agonist to induce final oocyte maturation after ovarian stimulation, which is feasible in a GnRH antagonist protocol, results in a reduced risk of moderate-to-severe OHSS by rapid demise of the corpora lutea (CL) (18). Other modality for the prevention of OHSS, include canceling the cycle, coasting, individualising the hCG trigger dose, the use of IV fluids at the time of oocyte retrieval, and cryopreserving/vitrifying all oocytes (2). Recent evidence also demonstrates that the administration of a dopamine agonist, such as cabergoline or quinagolide, from the day of HCG trigger can reduce the incidence of OHSS by inhibiting the phosphorylation of VEGFR-2 in response to hCG (21,22).

Albumin has both osmotic and transport functions, properties that underscore its potential for the prevention of OHSS (24). A Cochrane review of five RCTs clearly showed a benefit associated with the administration of IV albumin at the time of oocyte retrieval in patients at high risk of OHSS, with no effect on pregnancy rate (25). Calcium gluconate solution administration, half hour before ovum pickup resulted in a considerable lower incidence of OHSS and prevented serious OHSS in high risk patients such as polycystic ovarian syndrome. The dosage of calcium gluconate (10%) is 10 mls, diluted in 200 mls of physiological saline (27). The use of exogenous progesterone in luteal support instead of HCG supplemental doses may decrease the risk of OHSS, irrespective of the administration of GnRH agonist or HCG in midcycle (28). The patient presented did not have any preventive prophylaxis. The key factors to prevent OHSS are experience in ovulation induction therapy, knowledge of its pathophysiology and identification of the risk factors. Furthermore, individualized and highly monitored ovulation induction regime, with the use of gonadotropins at minimum dose and duration, are paramount to optimizing the treatment regime.

Treatment: Treatment of OHSS is primarily supportive. Mild OHSS, which due to the very nature of COS

occurs in most patients, and moderate OHSS with no clinical evidence of ascites or enlarged ovaries are not associated with complications and as a result do not require specific treatment. Mild OHSS and moderate OHSS can be treated symptomatically and patients monitored on an outpatient basis. It is recommended that they regularly monitor and review for weight changes, pain intensity, nausea, vomiting and bloating (26). The severe OHSS are managed as inpatients and may require intensive care admission. They are closely managed with strict fluid-balance assessment and electrolyte monitoring. Treatment is symptomatic and includes anti-emetic medication, paracentesis (if required), analgesia and DVT prophylaxis. Diuretic may be used once the patient is haemodynamically stable and has a hematocrit > 38%.

Some workers have advocated fluid administration; crystalloids and colloids are thought to be similarly effective in increasing intravascular volume. Strict fluid intake and output is advocated. Rapid initial hydration may be accomplished with a bolus of intravenous fluids (500-1000 mls). Thereafter fluid should be administered judiciously. Albumin is the most preferred volume expander as it is effective and helps to maintain urine output. Albumin (25%) in doses of 50-100 mls is infused over four hours and repeated every four to twelve hourly interval, as necessary (5). Other fluid expanders such as HES, Mannitol and fresh frozen plasma may be used. Dextran has been associated with development of adult respiratory distress and is best avoided.

Paracentesis has been used to relieve respiratory symptoms in the acute setting. Ultrasound guided paracentesis is indicated for patients with ascites that causes pain, compromised pulmonary function (e.g. Tachypnea, hypoxia, hydrothorax) or oliguria or anuria that does not respond to appropriate fluid management (26). Pleural tap may be required if hydrothorax is causing dyspnea. The patient addressed in this presentation had treatment of low dose heparin and intravenous albumin.

CONCLUSION

An increased vascular permeability related to increased VEGF secretion is mainly responsible for the signs and symptoms associated with OHSS. OHSS is a rare but potentially fatal complication of infertility treatment. Therefore, it is critical to ensure continuous awareness of its cause, clinical presentation, prevention and epidemiology. It is important to look for the risk factors and adopt preventive strategies both prior to and during stimulation. This will ensure early recognition, management of the condition and hence reduce morbidity and mortality. While the safety and efficacy of ART is well established, physicians should always be aware of the risk of OHSS in patients undergoing COS, as it can be fatal.

CONSENT

Informed consent was obtained from the patient and hospital for the publication of this case report.

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