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RESEARCH ARTICLE

OVARIAN HYPER STIMULATION SYNDROME, CASE SERIES: A RISING IATROGENIC MENACE

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ABSTRACT

Ovarian hyperstimulation syndrome (OHSS) is a well recognized iatrogenic complication of assisted conception techniques, which uses pharmacological ovarian stimulation during assisted reproductive technology (ART). However, in most cases OHSS is self-limiting and requires supportive management and monitoring while awaiting resolution. In a minority of women undergoing treatment it can result in life-threatening complications such as thrombo-embolic phenomena and multiple organ dysfunctions. The key principles of OHSS management therefore are early recognition and the prompt assessment and treatment. The recent increase in the usage of ART will inevitably result in a rise in the number of cases of OHSS seen in the emergency department (ED), this will give the emergency physician an important role in expediting and optimizing treatment for these patients. Five cases in their early thirties with a history of nausea, vomiting, breathlessness and bloating after ovarian stimulation were enrolled. Cases were confirmed to be suffering from severe OHSS and received supportive management.

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INTRODUCTION

Ovarian hyperstimulation syndrome (OHSS) is a well recognized iatrogenic complication of assisted conception techniques, which uses pharmacological ovarian stimulation to increase the number of oocytes and therefore embryos available during assisted reproductive technology (ART) (Klemetti *et al*., 2005). Although the majority of presentations are mild, in a minority of women undergoing treatment, the ovarian response exceeds that aimed for and results in systemic capillary leakage, causing life-threatening complications such as thromboembolic phenomena and multiple organ dysfunctions (Stewart *et al*., 1997). However, in most cases OHSS is self-limiting and requires supportive management and monitoring while awaiting resolution. OHSS occurs in mild forms in 33% of in vitro fertilisation (IVF) cycles and in moderate or severe forms in 3% to 8% of IVF cycles (Delvinge and Rozenberg, 2002). Although it can occur in all age groups, it is less common in women over the age of 39 years (Bancsi *et al*., 2002). Women with more severe OHSS may require inpatient treatment to manage the symptoms and reduce the risk of further complications. The key principles of OHSS management therefore are early recognition and the prompt assessment and treatment of women with moderate or severe OHSS. The recent increase in the usage of IVF will inevitably result in a rise in the number of cases of OHSS seen in the emergency department (ED). Ultimately, this will give the emergency physician an important role in expediting and optimizing treatment for these patients.

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Methods: Review of medical records.

Case histories:

Case 1: OHSS presenting as acute respiratory distress syndrome

A 34 year woman (gravida 0), with history of PCOS and hypothyroidism, married for six years with primary infertility had underwent ovulation induction with clomifene citrate for several cycles. However her ovarian follicles failed to grow beyond a size of 8-9 mm each time. Now she had received clomifene citrate for five days and on day sixth her ovarian transvaginal sonographic (TVS) scan showed multiple follicles, measuring 3-4mm. She then underwent programmed ovarian stimulation and was treated first with a GnRH agonist (leuprolide) administered subcutaneously (s/c) to inhibit gonadotropin secretion, followed by a combination of GnRH-analog (GnRH-a) and follicle stimulating hormone (FSH)

administered subcutaneously to stimulate the development of ovarian follicles. The following ovarian follicular study showed multiple follicles with largest one being 18mm. She had then received a trigger of human chorionic gonadotrophins (HCG) of 5000 U s/c on day 14th. She was also continued on thyroid supplements, low dose aspirin and bromocryptine. Her E2 level was 3456 pg/ml on the day she received HCG. On the day 36nd she started with breathlessness with nausea/vomiting and presented to our ED. Clinical exam was revealing tachypenia, laboured breathing, absent breath sounds at lung bases with fine crepitations. Beta-human chorionic gonadotropin (beta-hCG) levels were raised and TVS at 5 weeks was revealing a gestational sac. Patient's evaluation was revealing type 1 respiratory failure with sao2 of 80%. X ray chest done with lower body lead screen was showing bilateral hilar fluffy infiltrates. The ultrasonography was showing mild ascites, bilateral mild pleural effusion and bulky ovaries with multiple cysts. Complete blood count, liver function tests, kidney function test were normal. Patient was started on supplemental oxygen, prophylactic heparin, with daily infusion of 40 g of human albumin. After six days of admission, patient started with severe pruritus and her bile salts were found to be raised. She was started on ursodeoxycholic acid. After ten days of admission her pruritus settled and she became symptomatically better. She was planned for uterine ultrasonographic scan before discharge, which however unfortunately showed an intrauterine fetal death with no cardiac activity and a small retroplacental hematoma. Patient was then subjected to dilatation and evacuation.

Case 2: OHSS presenting as massive ascites

A 36-year old woman (gravida 2), with a previous history of successful intracytoplamic sperm injection (ICIS) with embryo transfer for oligospermia of her husband, had underwent programmed ovarian stimulation and was treated first with a GnRH agonist (leuprolide) administered subcutaneously to inhibit gonadotropin secretion, followed by a combination of GnRH-analog (GnRH-a) and FSH administered subcutaneously to stimulate the development of ovarian follicles. FSH levels were reduced from 225 IU to 150 IU on day 9 because of oocyte hyperstimulation. The E2 level was 4,234 pg/mL two days before oocyte retrieval. Ten days after oocyte retrieval, IVF and embryo transfer the patient presented to our ED with severe nausea, vomiting, and abdominal bloating, and she was unable to eat or drink. Her abdomen was distended with shifting dullness and beta-hCG levels were raised. Patient's evaluation showed mild hyponatremia (129meq/l), with gross ascites and bulky ovaries on ultrasonographic scan. Ascitic fluid analysis was lymphocytic with wide gradient (SAAG : >1.1). Other investigations like complete blood count, liver function tests, and kidney function tests were normal. The patient was given ondansetron and IV hydration, prophylactic heparin, and daily human albumin. After ten days of admission patient became better and her abdominal scan showed that her ascites was gone and gestational sac was visible on TVS.

Case 3: OHSS presenting as left subclavain thrombosis

A 36-year old woman (gravida 1), with a history of genital tuberculosis with bilateral tubal block had successfully completed antitubercular regimen. She had now underwent IVF and embryo transfer. The patient was treated with leuprolide, FSH, and GnRH-analogue. The FSH dose was reduced from 225 to 150 IU on day 8 because of oocyte hyperstimulation. The E2 level was 4367 pg/mL 2 days before oocyte retrieval. The patient presented to our ED with nausea, vomiting and swelling of her left arm. Examination revealed a woman with swelling of her whole of left arm. Consequently, beta-human chorionic gonadotropin (beta-hCG) levels and abdominal ultrasound scan were requested. The beta-hCG returned was raised and the scan revealed bilateral ovarian enlargement with multiple cysts, mild ascites, uniting the symptoms and thus confirming the diagnosis of severe OHSS. The presence of thrombogenic risk factors and the clinical presentation gave the patient a modified Wells score of 4.5. Doppler study was suggestive of left subclavain vein thrombosis. Consequently, the patient was placed on therapeutic heparin, IV hydration, ondansetron and routine blood investigations, a d-dimer, and a clotting profile were requested. The d-dimer returned as raised, routine blood tests were normal. Subsequently, the patient was transferred to gynecology.

Case 4 and case 5: OHSS presenting as ascites and pleural effusion

We had seen two female patients of 36 and 38 years who had underwent ART for primary infertility. Both of them had underwent programmed ovarian stimulation and were treated first with a GnRH agonist (leuprolide) administered subcutaneously to inhibit gonadotropin secretion, followed by a combination of GnRH-analog (GnRH-a) and FSH administered subcutaneously to stimulate the development of ovarian follicles. On attaining ovarian follicular size of 18 mm they had received chorionic gonadotoponins, 1000 u s/c. Now they presented to our ED with severe nausea, vomiting, abdominal bloating with breathlessness. On evaluation they were found to have raised beta-hCG, with ultasonographic evidence of bilateral ovarian enlargement, moderate ascites and mild bilateral pleural effusion. Baseline investigations like complete blood count, liver function tests, kidney function test, arterial blood gas analysis, and serum electrolytes were normal. Both patients received supportive treatment for two weeks and after which they became symptomatically better. On discharge both were found to have gestational sacs on TVS and were put on gynaecological follow up.

DISCUSSION

This case series aims to highlight the importance of OHSS as an uncommon cause of myriad presentations, whose prevalence is likely to increase in the forthcoming years as a number of ART procedures are performed. Ovarian hyperstimulation syndrome is an iatrogenic complication of fertility management. The syndrome is usually associated with exogenous gonadotrophin stimulation although it is rarely seen with other agents like clomiphene citrate and gonadotrophin releasing hormones (GnRH). However, in most cases OHSS is self-limiting and requires supportive management only, in a minority of women it is associated with significant physical and psychosocial morbidity and has been associated with

maternal death. Assisted reproductive technology uses GnRH agonists/antagonists and gonadotrophins to stimulate the ovary. Following stimulation, human chorionic gonadotrophin (HCG) is used to initiate ovulation and maintain luteal phase. In a minority of women, the ovarian response exceeds and results in ovarian enlargement accompanied by over production of proinflammatory mediators. Chief among these is vascular endothelial growth factor (VEGF), but a variety of cytokines are likely to be involved in the pathogenesis and clinical features of OHSS (Braat *et al*., 2010).These agents alone or together produce a state of increased capillary permeability (Navot, 2001). Increased vascular permeability leads to loss of fluid into the third space, manifesting as ascites or, less commonly, pleural and pericardial effusions. Women with severe OHSS develop hypovolaemia, with approximately 20% loss of their blood volume in the acute phase of OHSS (Evbuomwan *et al*., 2000). This is associated with reduced serum osmolality and sodium which resets the osmotic thresholds of vasopressin and thirst to lower osmolality and sodium levels as they are able to concentrate and dilute their urine around the new, lower, level of osmolality. The prevalence of moderate to severe OHSS ranges from 1-10% in major IVF treatments (Brinsden *et al*., 1995) and in approximately 2% of all IVF cycles (Forman *et al*., 1990). There are various risk factors associated with the development of OHSS like young age (<35 years), asthenic body habitus, atopy or allergies, etc (Avecillas *et al*., 2004). The moderate OHSS is seen in 8% of induced cycles with clomiphene citrate (Avecillas *et al*., 2004). The risk of OHSS increases in women with a rapid rise in serum estradiol levels or in those with estradiol levels of more than 2500 pg/ml (Practice Committee of the American Society for Reproductive Medicine, 2004). Risk also increases with the number of developing follicles and the number of oocytes (>14) retrieved (Enskog *et al*., 1999) as well as the use of higher and repeated doses of HCG. Pregnancy not only increases, but also prolongs the duration and severity of symptoms of OHSS. A higher incidence of OHSS is seen in patients with polycystic ovarian syndrome (PCOS) (Delvigne and Rozenberg, 2002). The symptoms of OHSS are non specific and there are no specific diagnostic tests for the condition. The typical patient presents with abdominal distension and discomfort following the trigger injection and the timing of presentation following trigger injection divides patients into two groups: early and late OHSS. Early onset OHSS occurs within three to seven days after the administration of HCG and is caused by excessive preovulatory ovarian response to stimulation. Late onset OHSS typically presents 10 or more days after the hCG injection and is usually the result of endogenous hCG derived from an early pregnancy. Late onset OHSS is often more prolonged and severe than the early form (Mathur *et al*., 2000).

The symptoms of OHSS often begin with a sensation of bloating, abdominal discomfort, nausea, vomiting and diarrhea. As the disease advances the accumulation of fluid in the third space leads to ascites, pleural and pericardial effusion,oliguria, hemoconcentration (Hct >45%), raised white blood cell and platelet counts, hypovolemia and electrolyte imbalance (hyponatremia and hyperkalemia) (Schenker and Weinstein, 1978; Shanbhag and Bhattacharya, 2002; Balasch *et al*., 1996). Derranged liver function tests are seen in 30% of patients with OHSS (Fabregues et al., 1999). The plasma levels of renin, aldosterone, noradrenaline, antidiuretic hormone (ADH) and atrial natriuretic peptide (ANP) are increased (Balasch *et al*., 1996; Abramov *et al*., 1999), and ascitic fluid study reveals high protein and low cell counts (Abramov *et al*., 1999). Ovarian hyperstimulation Syndrome was classified by Rabau *et al*. into mild, moderate and severe as below (Rabau *et al*., 1967) and Navot *et al*. added a new stage, critical or life threatening OHSS (Navot *et al*., 1992). At times, OHSS may present with life-threatening complications, including renal failure, acute respiratory distress syndrome (ARDS), pulmonary edema, atelectasis, haemorrhage from ovarian rupture, and thrombo embolism (Braat *et al*., 2008; Whelan JG 3rd, Vlahos, 2000; Zosmer *et al*., 1987; Abramov *et al*., 1999; Al Omari *et al*., 2011). High incidence of infections is seen in OHSS (Abramov *et al*., 1998) and other rare complications include adnexal torsion and ovarian cyst rupture.

There is no specific treatment for OHSS and the treatment is mainly supportive. In the majority of patients OHSS is self-limiting and usually resolves over a period of 7–10 days (Nouri *et al*., 2014). Hence the objective of monitoring is to find the women of an increasing severity of OHSS and to start with further measures. Following are the worsening signs of OHSS of which the clinicians and patient should be aware of (Practice Committee of the American Society for Reproductive Medicine, 2008; Fábregues *et al*., 1998):

- Increasing abdominal distension and pain
- Shortness of breath
- Tachycardia or hypotension
- Reduced urine output (<1000 ml/24 hours)
- Positive fluid balance (>1000 ml/24 hours)
- Weight gain and increased abdominal girth
- Increasing haematocrit (greater than 0.45).

The patients with severe OHSS should undergo investigations like hematocrit, total blood count, electrolytes, liver function tests, renal function tests ultrasonography to measure the size of ovaries and presence of ascites (Avecillas *et al*., 2004; Practice Committee of the American Society for Reproductive

Classification of ovarian hyperstimulation, Syndrome (Rabau *et al*., 1967):

Mild ovarian hyperstimulation syndrome	Moderate ovarian hyperstimulation syndrome	Severe ovarian hyperstimulation syndrome	Life-threatening ovarian hyperstimulation syndrome
1.Urinary estrogen >150 > g/24h 2.Urinary pregnanediol >10 mg/24h 3.Enlargement of ovaries with or without palpable cyst formation	1.Abdominal distension, nausea 2.Urinary estrogen >150 > g/24h 3.Urinary pregnanediol >10 mg/24h 4.Enlargement of ovaries with or without palpable cyst formation 5.Vomiting and diarrhea	1.Variably enlarged ovary 2.Massive ascites with or without hydrothorax 3.Hematocrit N45% 4.WBC count N15,000 5.Oliguria 6.Creatinine level1.0-1.5 mg/dL 7.Creatinine clearance<60mL/min 8.Liver dysfunction 9.Anasarca	1.Variably enlarged ovary 2.White blood cell count >25,000 3.Hematocrit>55% 4.Creatinine level >1.6 mg/dL 5.Reduction in creatinine clearance <50mL/min 6.Oliguria 7.Renal failure 8.Tense ascites with or without hydrothorax 9.Thromboembolic phenomena 10.Acute respiratory distress syndrome

Medicine, 2004; Shanbhag and Bhattacharya, 2002; Borenstein *et al*., 1989). Oxygen saturation, chest radiograph and arterial blood gases should be done for all patients with dyspnoea. If respiratory status worsens or respiratory failure develops patients may need non invasive or invasive mechanical ventilation (Shanbhag and Bhattacharya, 2002; Borenstein *et al*., 1989). Crystalloids are initial fluids of choice and intravascular volumne should be maintained to prevent hemoconcentration and allow adequate urine output (Avecillas *et al*., 2004; Whelan JG 3rd, Vlahos, 2000). Human albumin is the plasma expander of choice in patients with hematocrit more than 45% or hypoalbuminemia less than 30 gm/L or ascites. Intravascular volume expanders like fresh frozen plasma and dextran have no advantage over albumin (Borenstein *et al*., 1989; Budev *et al*., 2005). Intravascular volume expansion with dextran has been associated with development of ARDS in patients with OHSS (Whelan JG 3rd, Vlahos, 2000; Budev *et al*., 2005). If ARDS develops patient should be ventilated with low tidal volume (6 ml/kg body weight) and plateau pressure less than 30 cm of water .In severe cases of OHSS prophylactic anticoagulation should be used and in presence of thromboembolism therapeutic anticoagulation is indicated (Avecillas *et al*., 2004; Practice Committee of the American Society for Reproductive Medicine, 2004).

Conclusion

This case series highlights an important message for the emergency physician and raises awareness of this increasingly common iatrogenic condition. A high index of suspicion, prompt recognition and early treatment is key to reduction of morbidity and mortality from OHSS.

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