Ovarian hyperstimulation syndrome

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This case report describes a lady who presented with abdominal pain, hypotension and multiple ovarian follicles following egg collection and embryo transfer. She was provisionally diagnosed with Ovarian Hyperstimulation Syndrome (OHSS) and managed accordingly. This case study describes her clinical presentation, investigations, progress, management and outcome. No current laboratory diagnostic/prognostic markers are available for OHSS; the condition is currently diagnosed clinically. The subsequent discussion elaborates on the epidemiology, pathophysiology, clinical features, assessment, management and risk factors of OHSS, and aims to increase awareness of this important complication of infertility treatment to assist diagnosis, prevention and early institution of treatment.

Case Introduction

Mrs. SR is a 39 year-old G7P1M5E1 female who underwent egg collection and embryo transfer. Ten days following egg collection and six days following embryo transfer, she developed fever, abdominal pain, nausea and vomiting. She was initially managed in a private hospital with fluids and analgesia but remained febrile. Abdominal imaging demonstrated ascites and multiple enlarged ovarian follicles. Mrs. SR was transferred to a public hospital for further management under a provisional diagnosis of OHSS.

On initial assessment, she was noted to be tachycardic, hypotensive and febrile. Her oxygen saturation was 100% on supplemental oxygen. She was oliguric, cold and clammy. Her respiratory examination revealed bibasal crepitations and there was rebound tenderness of the abdomen. The remainder of the examination revealed no further abnormalities.

Background and medical history

Mrs. SR was investigated for infertility in 2006 with no cause identified. Her background history included four previous in vitro fertilisation (IVF) attempts, resulting in early trimester miscarriages and an ectopic pregnancy. Dilatation and curettage following twin pregnancy miscarriage in 2005 had revealed normal fetal tissue. In 2007, she successfully underwent IVF with an uneventful pregnancy and normal vaginal birth.

Mrs. SR's menarche was at age thirteen and her menses were since irregular. There was no history of polycystic ovarian syndrome (PCOS), sexually transmitted infections, vaginal discharge or pelvic inflammatory disease. She had a history of depression, obesity and asthma but was on no regular medications for these conditions. Her IVF medications included a GNRH-agonist, recombinant-FSH, hCG, and progesterone. She was allergic to penicillin and trimethoprim.

There was no significant family history reported by Mrs. SR. She consumed minimal alcohol and was a non-smoker.

Physical examination

On admission, Mrs. SR appeared unwell. She was dyspnoeic and unable to talk in full sentences. Her vital signs on admission are shown below in Table 1.

Mrs. SR was oliguric, cold and clammy, with no other signs of dehydration. She had abdominal rebound tenderness and voluntary guarding. There were no palpable abdominal masses or hernias.

Table 1. *Mrs. SR's vital signs on admission.*

Vitals on admission	
Heart rate	128
Blood pressure	90/60
Temperature	37.8 degrees Celsius
Oxygen saturation	100% on 5L/min oxygen
BMI	38.6

Her inspiratory effort was poor and there were bibasal crepitations. Cardiovascular examination was unremarkable.

Resuscitation/Initial Treatment

- Six litres normal saline
- IV ceftriaxone and metronidazole
- Supplemental oxygen (5L/min)

Diagnosis

A provisional diagnosis of OHSS was made. Differential diagnoses included ectopic pregnancy, bowel damage during egg-collection/implantation, unrelated bowel pathology (such as appendicitis/diverticulitis), ovarian torsion, ruptured ovarian cyst and drug fever.

Results of initial investigations are provided in Table 2.

Table 2. *Results of Mrs. SR's initial investigations.*

Investigations	
b-HCG	<5
Bedside echocardiography	No pericardial fluid
Blood culure	Gram positive cocci
Urine culture	Candida
CXR	Bibasal atelectasis No obvious signs of pulmonary embolus or pleural effusion

Outcome

Gynaecological and surgical teams reviewed Mrs. SR and agreed with the provisional diagnosis of OHSS. Due to her poor clinical status (respiratory symptoms and third space losses), Mrs. SR was intubated and managed supportively in ICU for nine days. Her symptoms gradually resolved and her blood results normalised during this time. She was transferred to the rehabilitation ward to facilitate her ongoing recovery and returned home five and a half weeks after her initial presentation.

This case demonstrates one of the more significant complications following egg harvest. A detailed discussion of OHSS, its pathophysiology, epidemiology, clinical symptoms and management follows.

Ovarian Hyperstimulation Syndrome

Incidence

The incidence of OHSS reported in different studies varies depending on the classification system used. A classification of severity and associated clinical features is given below in Table 3.

Globally, OHSS affects 100-200 women per 100,000 cycles annually (prevalence is 0.5-5% for severe forms). In Australia, 30% of the women undergoing IVF develop OHSS and 0.5-2% require hospitalisation. [1,2]

As demonstrated from Table 4, although the incidence of severe-OHSS from IVF is 0.1-2%, it is progressively increasing. [1,3]

Table 3. *OHSS severity and associated clinical features. [2]*

OHSS severity	Clinical features
Mild	Patients develop abdominal distension and pain. Ovarian size remains below 8 cm.
Moderate	Patients develop moderate abdominal pain associated with nausea and/or vomiting. Ultrasound shows ascites and ovarian size approaches 8-12 cm.
Severe	Patients develop clinically evident ascites with some progressing to develop hydrothorax. Patients also develop oliguria and ovarian size approaches greater than 12 cm. Pathological findings may include haemoconcentration and hypoproteinaemia.
Critical	Patients may have tense ascites and/or hydrothorax. Haematocrit is usually lower than 55% and white cell count decreases to less than 25,000/mL. Patients may develop thromboembolism, oliguria/anuria and/or acute respiratory distress.

Table 4. *Incidence of mild/moderate/severe forms of OHSS with gonadotrophin, clomiphine citrate and IVF. [1]*

Ovulation induction method	Incidence
Gonadotrophins	8.4-23% (mild forms)
	0.005-7% (moderate forms)
	0.008-10% (severe forms)
Clomiphine citrate	13.5% (mild forms)
	sporadic (moderate and severe forms)
IVF	3-6% (moderate form)
	0.1-2% (severe form)
	20-30% (mild form)

**Based on clinical presentation and laboratory findings, OHSS is defined as mild, moderate or severe. [1,3]*

Pharmacological ovarian stimulation in IVF

OHSS may arise from various forms of infertility treatments (gonadotrophins, clomiphine citrate or IVF). [4-7]

Clomiphine citrate is an oral tablet which induces ovulation. It is taken for three days, commencing on the second day following menstrual bleeding. Ovulation can be further aided by administration of metformin and subcutaneous abdominal injections of gonadotrophins (given for ≥10 days). These medications directly stimulate the ovaries to produce follicles. In some cases, progesterone and hCG are administered for a few days following ovulation until outcome is established. Following production of follicles, ovulation may be stimulated by monthly subcutaneous abdominal recombinant-hCG injections. [4,7]

Pathophysiology

OHSS is an iatrogenic complication of pharmacological ovarian stimulation. Its pathophysiology is not completely understood. It usually occurs a several days after follicular rupture following hCG administration, which promotes the release of vasoactive substances (histamine, serotonin, prolactin, interleukins, TNF-alpha, VEGF and so on) that affect the endothelial adherens junctions and result in trans-endothelial permeability. Consequently, there is third space loss (leading to shock, oliguria/anuria and/or electrolyte imbalances), haemoconcentration and an increased risk of clot formation. The overactive adhesion molecules and ovarian inflammatory response further promote OHSS by affecting folliculogenesis, ovulation, corpus luteum formation and luteolysis. These collectively result in the clinical features observed in OHSS. Strong links have been observed between hCG and the development of OHSS. In fact, more than one dose of hCG and progression to pregnancy following induction are risk factors for OHSS in patients receiving IVF treatment. [3,4,6-8]

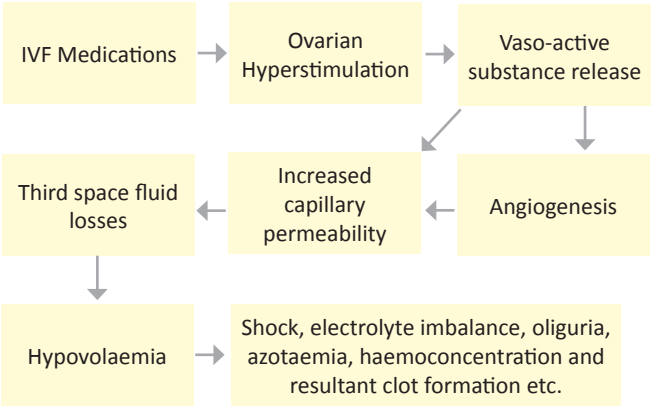

Figure 1. *Pathophysiology of OHSS. [3,4,6-8]*

Risk factors

Risk factors include oligomenorrohea, young age, low body mass index (BMI), PCOS, high dose exogenous, gonadotropins, high oestradiol (E2) levels, previous history of OHSS and more than twenty oocytes on oocyte retrieval. [3,4,7,8]

Clinical features

Patients generally develop symptoms four to five days after egg harvest. 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 described under the pathophysiology section. Complications of OHSS may manifest as thromboembolism, acute renal failure, respiratory compromise, hyperkalaemia and infection. These are further detailed in Table 3. [3-6]

Clinical assessment of patients with probable OHSS should include a complete history and examination. Work up should include basic haematological testing (including full blood count, urea/electrolytes/creatinine, liver function tests, beta-HCG and coagulation studies),

abdominal ultrasound, and chest x-ray. Further investigations should be performed based on individual circumstances. [3-6]

Treatment

Treatment for OHSS is primarily supportive. Current best practice guidelines advise management on an outpatient (for mild-OHSS) or inpatient (for severe-OHSS) basis. However, research is being conducted to better understand the pathophysiology and hence, diagnostic and prognostic markers and treatment options for OHSS. [2-6]

Outpatient basis

Currently, outpatients are symptomatically managed. It is recommended that they be regularly monitored and reviewed for weight changes, pain intensity, nausea, vomiting and bloating. If the condition worsens, patients are advised to report to their clinician. [2-6]

Inpatient basis

In contrast to outpatients, inpatients are more closely managed with strict fluid-balance assessment and electrolyte monitoring. Any electrolyte abnormalities should be promptly corrected. Treatment is symptomatic and includes anti-emetic medications, paracentesis (if required), analgesia and DVT prophylaxis. Diuretics may be used once the patient is haemodynamically stable and has a haematocrit >38%. Allied health staff (physiotherapist, dietician and psychologist) play a significant role decreasing morbidity. [2-5,7,8]

There is some controversy regarding fluid administration in OHSS. Currently, crystalloids and colloids are thought to be similarly effective in increasing intravascular volume. While paracentesis is used for symptomatic relief, and has been found to relieve respiratory symptoms in the acute setting, there is no data on its long term efficacy in symptom control. [4,5,7,8]

Conclusion

OHSS is a rare but potentially fatal complication of infertility treatment. Hence, it is extremely important to ensure continuing awareness of its causes, clinical manifestations, treatment, prevention and epidemiology. This will ensure early recognition and management of the condition and reduce morbidity and mortality.

Consent

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

Conflicts of Interest

None declared.

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References

[1] Delvigne A, Rozenberg S. Epidemiology and prevention of ovarian hyperstimulation syndrome (OHSS): A review. Hum Reprod Update. 2002;8(6):559-77.
[2] Jenkins J, Drakeley A, Mathur R. The management of ovarian hyperstimulation syndrome. National Guideline Clearinghouse [serial online] 1996 [updated 2010 April 26; cited 2010 May 2];[9 screens]. Available from:URL: http://www.guideline.gov/summary/summary.aspx?doc_id=11382&mode=full&ss=15
[3] Elchalal U.,Schekner JG. The pathophysiology of ovarian hyperstimulation syndrome: Views and ideas. Hum Reprod 1997;12(6):1129-37.
[4] American Academy of Family Physicians. Levels of Evidence in AFP. Am Fam Physician [serial online] 2010 [updated 2010; cited 2010 May 3];[2 screens]. Available from:URL: http://www.aafp.org/online/en/home/publications/journals/afp/afplevels.html
[5] The Royal Women's Hospital. Ovarian hyperstimulation syndrome: Management of severe OHSS in HDU. The Women's [serial online] 2009 [updated 2009; cited 2010 November 2]; [3 screens]. Available from:URL: http://www.thewomens.org.au/OvarianHyperstimulationSyndromeManagementofSevereOHSSinHDU
[6] Marcus S. Risks and complications of IVF treatment. IVF-Infertility.com [serial online] 2010 [updated 2010 February 14; cited 2010 November 2]; [2 screens]. Available from:URL: http://www.ivf-infertility.com/ivf/standard/complications/ovarian_stimulation/ohss.php
[7] Smith H, Gayer N, Lok D, *et al.* Ovulation induction: Patient information. Westmead Fertility Centre [serial online] 1998 January [updated 2009 December; cited 2010 April 20]; [5 screens].Available from:URL: http://www.westmeadivf.com.au/Docs/Ovulation_Induction.pdf
[8] Insler V, Lunenfeld B. Pathogenesis of ovarian hyperstimulation syndrome. Uptodate:for patients [serial online]. 2008 January [updated 2008; cited 2010 April 10]; [2 screens]. Available from:URL: http://www.utdol.com/patients/content/topic.do?topicKey=~bxxB9A5JrzRkJXZ
[9] Villasante A, Pacheco A, Pau E, *et al.* Soluble vascular endothelial-cadherin levels correlate with clinical and biological aspects of severe ovarian hyperstimulation syndrome. Hum Reprod 2008;23(3):662-7.