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OVARIAN HYPERSTIMULATION SYNDROME: A CHALLENGE

Obstetrics & Gynaecology

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ABSTRACT

Ovarian Hyperstimulation Syndrome (OHSS) is an iatrogenic life-threatening complication of ovarian stimulation that occurs during the luteal phase of the menstrual cycle or in early pregnancy commonly in women who undergo assisted reproductive technology. Early diagnosis and appropriate multidisciplinary management are essential for recovery and prevention of long-term complications. We present our case series of five patients who had undergone artificial reproductive techniques for infertility or voluntary oocyte donation. They presented with moderate to severe OHSS and were managed at our tertiary care center. Three cases had urine pregnancy test positive on admission. These patients were managed optimally by conservative methods. Three of them required suction evacuation in view of early gestation failure. Amongst the five cases, one was a rare case of spontaneous OHSS in case of severe hypothyroidism in a young adolescent girl.

KEYWORDS

ovarian hyperstimulation syndrome, spontaneous ovarian hyperstimulation syndrome, assisted reproductive technology, oocyte donation

INTRODUCTION

Ovarian hyperstimulation syndrome is the most serious complication of controlled ovarian hyperstimulation occurring in up to 5% of women undergoing In vitro fertilization or Intra uterine insemination (Neulen J, Yan Z, Raczek S, Weindel K, Keck C, Weich HA et al., n.d.). There are cases of OHSS reported in severe hypothyroidism and spontaneous pregnancy though rare. There has been an exponential growth in the use of donor oocytes for infertility treatment. Several factors responsible for this increasing demand of oocyte donation includes delayed child bearing, desire for parenthood among same sex couple and single individuals wishing for parenthood.

OHSS is characterized by cystic enlargement of ovaries and a fluid shift from intravascular compartment to extravascular space due to increased capillary permeability. The clinical manifestations include ovarian enlargement, ascites, oliguria, abdominal pain, electrolyte imbalance, respiratory distress syndrome and hypercoagulability. The objective of this paper is to discuss this life threatening complication of ovarian stimulation, its clinical presentation, diagnosis severity and management.

Case 1 –

A 29 years old nulligravida presented to emergency with complaints of abdominal distention, respiratory distress, multiple episodes of vomiting and diarrhea for 4 days. The patient had undergone IVF treatment with gonadotropin injections with hCG on day 12 of the cycle along with dopamine agonist cabergoline followed by ovum pickup. Embryo transfer was not done due to poor quality of embryos. Ultrasonography done after admission revealed enlarged bilateral ovaries with right ovary of 440 cc and left 370cc. Bilateral pleural effusion and gross ascites was noted. The diagnosis of severe OHSS was made based on elevated leucocyte count, raised hematocrit hypoproteinemia, hyponatremia, hyperkalemia, enlarged ovaries with ascites and pleural effusion. Patient was managed in intensive care unit. Single abdominal paracentesis was done 1.2 litre was drained. ICU management included antibiotics, low molecular weight heparin 0.4 mcg subcutaneous once a day and albumin infusion for 2 days. General condition of the patient gradually improved over few days and was discharged on day 10 of admission.

Case 2 -

15 years old girl presented in emergency with complaints of breathlessness, abdominal pain, distention and multiple episodes of vomiting and severe anemia. She was admitted in intensive care unit for evaluation. Ultrasonography was done which showed bilateral enlarged ovaries with moderate ascites. MRI was also done and diagnosis of moderate OHSS was made. Her blood investigations showed HB of 2 gm% and serum TSH of 150. The patient was managed conservatively, anemia was corrected by blood transfusion, endocrine reference was taken and started on thyroxine. Her symptoms improved and she was discharged after two weeks with advice to regularly follow up with endocrinologist. Repeat ultrasonography showed normal ovarian volume, no ascites and pleural effusion.

Case 3, 4 and5 -

These 3 cases presented to casualty with abdominal pain, breathlessness, abdominal distension, multiple episodes of vomiting and amenorrhea. They were admitted in ICU for medical management. All these patients were voluntary oocyte donors who had undergone ovarian hyperstimulation and developed OHSS. The ultrasound in all of them showed gross ascites, moderate pleural effusion, enlarged ovaries and single intrauterine pregnancy with no cardiac activity. Monitoring was done by checking for weight, abdominal girth daily. Strict input output charting was done. Hydration was maintained by intravenous fluids, antibiotics, analgesics for pain relief and antiemetics were given. Injection low molecular weight heparin 40mg once a day was started for thromboprophylaxis. Ascitic tapping was done in 2 cases to relieve breathlessness. They showed clinical improvement in 7-10 days.

Supportive treatment was given with micronized progesterone. Ultrasound was repeated after 14 days and all three cases showed early gestation failure with a significant reduction in ovarian size with no ascites and pleural effusion. Suction evacuation was done for missed abortion and patients were discharged.

Table 1: Risk Factors, Clinical And Ultrasound Features:

Sr No.	Obstetric Score	Risk factor	Clinical features	Abnormal Laboratory findings	Ultrasound on admission	Stage
1	Nulligravida	Ovarian hyperstimulation	distention , vomiting and diarrhea	Hematocrit 47% Creat 1.2 Sodium 124 Potassium 5.6	Bilateral ovaries bulky, Moderate ascites, and pleural effusion	5

2	Nulligravida	Severe hypothyroidism	Anemia, breathlessness, pain , distention	Hb 2gm% Sr TSH 150	Enlarged ovaries, ascites	3
3	Primigravida	Voluntary oocyte donation	Pain, breathlessness, distension, vomiting and amenorrhea	None	Ascites, pleural effusion, enlarged ovaries and single intrauterine pregnancy	4
4	Primigravida	Voluntary oocyte donation	Pain, breathlessness, distension, vomiting and amenorrhea	None	Ascites, pleural effusion, enlarged ovaries and single intrauterine pregnancy	4
5	G2p111	Voluntary oocyte donation	Pain, breathlessness, distension, vomiting and amenorrhea	None	Ascites, pleural effusion, enlarged ovaries and single intrauterine pregnancy	4

Fig. 1: The Chest X-ray showing pleural effusion

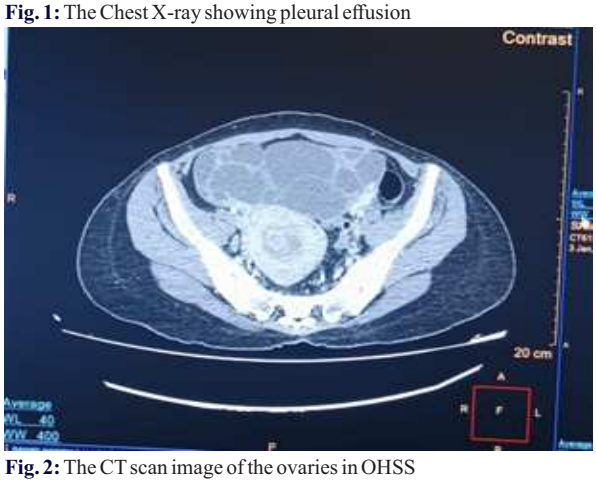

Fig. 2: The CT scan image of the ovaries in OHSS

DISCUSSION

OHSS is a rare but potentially fatal complication of excessive ovarian stimulation. It has a very serious impact on the patient's health and may cause severe morbidity even mortality. The incidence of OHSS varies from 1 to 14% in all IVF Cycles. Moderate cases of OHSS in all cycles are estimated to be between 3-6% while the severe life-threatening form that leads to hospitalization occurs in 0.1-3% (Navot D, Bergh PA & treatment. Fertil Steril 1992, n.d.). The syndrome is characterized by cystic enlargement of the ovaries and fluid shift from the intravascular to the third space due to increased capillary permeability and ovarian neoangiogenesis.

The pathophysiology of OHSS has not been completely elucidated but the underlying mechanism is related to increased vascular permeability in the region surrounding the ovaries and their vasculature (7). The trigger of OHSS is human chorionic gonadotrophin (hCG), which appears to act via vascular endothelial growth factor (VEGF), cytokines (IL-2, IL-6, IL-8), tumor necrosis factor-alpha and ovarian renin-angiotensin system, which are activated by gonadotropin which leads to increased vascular permeability and extravascular fluid accumulation in OHSS.

For cases of OHSS associated with assisted reproductive technology measures can be taken to prevent the occurrence. The key to primary prevention is recognizing risk factors and individualizing the stimulation protocol. Avoidance of hCG has been advocated in high-risk patients for OHSS. Other modality for prevention includes cycle cancellation, coasting, use of IV fluids at the time of oocyte retrieval, and cryopreserving/vitrifying (Fiedler K et al., n.d.) all oocytes. Recent evidence also demonstrates that the use of dopamine agonist such as cabergoline from the day of the HCG trigger can reduce the risk of OHSS (Gómez R, Soares SR, Busso C et al., n.d.). Furthermore, an individualized and highly monitored ovulation induction regime, with the use of gonadotropins at minimum dosage and duration is important to optimize the treatment regimen.

Despite the preventive measures being taken some patients develop OHSS. OHSS can be divided into two groups depending on the time of presentation. Early OHSS usually presents within 7 days of the HCG injection and is usually associated with an excessive ovarian response. Late OHSS typically presents 10 or more days after the HCG injection and is usually the result of endogenous HCG derived from early pregnancy. Late OHSS tends to be more prolonged and severe than the early form (Sridev S et al., n.d.). The symptoms of OHSS are not specific and there are no definitive diagnostic tests for the condition. Hence, care must be taken to exclude other serious conditions that may present similarly but require very different management. Full blood count, serum electrolytes and osmolality, pelvic ultrasound scan, and in selected cases, abdominal imaging are required. The combination of elevated hematocrit and reduced serum osmolality and sodium is indicative of OHSS (The et al., n.d.). Important differential diagnoses of OHSS include pelvic infection, pelvic abscess, appendicitis, ovarian torsion or cyst rupture, bowel perforation, and ectopic pregnancy (Hyperstimulation et al., n.d.).

The ovarian hyperstimulation syndrome has been classified in five grades as per the severity (Polished WZ & Fertil Steril 1969, n.d.) –
Grade 1 – Mild OHSS, Abdominal distension and discomfort
Grade 2 – Grade 1 disease plus nausea and/or diarrhea plus ovarian enlargement from 5-12 cm
Grade 3 – Moderate OHSS, features of mild OHSS plus ultrasonographic evidence of ascites
Grade 4 – Severe OHSS, 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 hemoconcentration, coagulation abnormalities and diminished renal perfusion and function

Rarely, OHSS may be associated with life-threatening complications, including renal failure, acute respiratory distress syndrome (ARDS), hemorrhage from ovarian rupture, and thromboembolism.

In our case series, case 2 reported with moderate OHSS while rest 4 were severe OHSS. In most of cases, OHSS results from ovarian hyperstimulation, however, this syndrome also occurs in the absence of these treatments. Risk factors of spontaneous OHSS include severe hypothyroidism, twin pregnancy, and polycystic ovarian disease. Though rare cases of spontaneous OHSS are reported. Case 2 was similar in a young girl with severe hypothyroidism. OHSS was reverted by correction of serum TSH. We had 3 cases in whom urine pregnancy test was positive when the came in the emergency. All of

them had undergone ovarian stimulation for infertility or oocyte donation. Even though supportive measures were given all of them had blighted ovum and suction evacuation was done. Reports have suggested an increased rate of preclinical pregnancy loss in women with early, but not late OHSS (Papanikolaou EG, Tournaye H, Verpoest W et al., n.d.). In cases 3 to 5, OHSS was associated with hydrothorax and ascites so they were graded as grade 4. They required ascites and pleural tapping to relieve the symptoms. In a similar case reported in Turkey of grade 4 OHSS (Gul T et al., n.d.), the patient had undergone ultrasound-guided ascitic fluid draining of 2 Litres fluid to relieve pain and dyspnea. In case 1 the patient was also given injection albumin.

Severe OHSS is a prothrombotic state due to haemoconcentration and vascular endothelial dysfunction. The incidence of thrombosis has been estimated to lie between 0.7% and 10% of cases of OHSS(Rova K, Passmark H et al., n.d.). Women with moderate to severe OHSS should be prescribed low molecular heparin and antiembolism stockings.

CONCLUSION

It is crucial to identify risk factors and adopt preventive strategies both before and at the time of ovarian stimulation. In women with a greater risk for OHSS; ovulation induction should be initiated with the least possible gonadotropin dose along with gonadotropin-releasing hormone (GnRH) antagonist. Implementing screening of donors for high-risk factors helps in early recognition and reduction in the incidence of OHSS, and related morbidity and mortality. Though spontaneous OHSS is rare, in patients with severe hypothyroidism presenting with ascites and pleural effusion with enlarged ovaries it should be suspected. Early diagnosis and timely multidisciplinary management are the keys to saving lives.

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