A Early Development of Severe Ovarian Hyperstimulation Syndrome following Ovulation Induction

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ABSTRACT

Ovarian Hyperstimulation is a rare but potentially fatal complication of ovarian stimulation during treatment of infertility. Worldwide the incidence of this syndrome is increasing due to liberal use of invitro fertilization for management of infertility. The syndrome is characterized by cystic ovarian enlargement and abnormal capillary permeability due to secretion of vasogenic substances by ovaries. The syndrome is classified into early and late variants with early variants usually mild to moderate in severity. We present a case of severe ovarian hyperstimulation syndrome (OHSS) developing early in a 25-year female while undergoing In-vitro fertilization (IVF). Six days after ovulation induction, the woman developed ascites, bilateral pleural effusion and acute renal failure with ultrasound abdomen revealing bilateral cystic enlargement of ovaries. JMS 2011;14(1):30-32

Key words: Ovarian hyperstimulation, ovulation induction, in-vitro fertilization, IVF

OHSS is an iatrogenic complication of the luteal phase and/or early pregnancy after ovulation induction (provoking ovulation in anovulatory women) or of ovarian stimulation (in the context of intrauterine insemination or in vitro fertilisation). It ranges in severity from mild self limiting illness to a potentially fatal one. The pathophysiological hallmarks of the syndrome are cystic enlargement of the ovaries and abnormal capillary permeability resulting in third space fluid loss. Treatment is largely supportive with emphasis on adequate fluid resuscitation. Though Early OHSS is usually mild we report a case of 25 year old Female who developed Severe OHSS within one week of ovulation induction while undergoing In-vitro fertilization (IVF) with Embryo Transfer on account of oligospermia in her husband.

Material and Methods

A 25 years old Female with insignificant medical history in the past underwent IVF with Embryo Transfer after her husband was found to have Oligospermia. Patient initially received Gonadotropin Releasing Hormone (GnRH) analogue for downregulation of Pituitary function followed by Recombinant Follicle Stimulation Syndrome (rFSH) for ovarian stimulation that was followed by Human Chorionic Gonadotropin (HCG) for ovulation induction. Six days after receiving HCG patient developed abdominal discomfort and distention. One day later patient developed breathlessness and had decreased urine output and was admitted in our hospital. On examination patient was conscious with apparent respiratory distress, had a pulse of 118 per minute and Blood Pressure of 80/50 mmHg. She had clinical signs of Bilateral Pleural effusion and Ascites. Rest of the clinical examination was unremarkable.

Investigations revealed leucocytosis of $18,800/\text{mm}^3$ with 90% neutrophils. Blood Urea was 104 mg/dl and Serum creatinine 2.2 mg/dl. Liver Function Tests revealed raised AST and ALT of 117 mg/dl and 155 mg/dl respectively with low albumin levels of 2.3 mg/dl. Urine examination was normal.

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ECG revealed Sinus Tachycardia. X-Ray chest was suggestive of Bilateral Pleural Effusion. Ultrasound Abdomen [Figures 1-3] was reported as massive ascites with bilateral enlargement of ovaries with multiple cystic areas of varying sizes. Volumes of Right and Left ovaries were 480 and 450 ml respectively. Ascitic Fluid analysis revealed a cell count of 200 / ccm with 92% Lymphocytes, Proteins of 5.3 gm/dl and Albumin 1.8 mg/dl.

Patient was diagnosed as Ovarian Hyperstimulation Syndrome, Severe Grade 4 as per Golan's Severity criteria (Table 1). She was managed with Intravenous Fluids (Normal Saline) with regular monitoring of vitals. Supplemental Oxygen was given and Therapeutic Thoracentesis was done in view of respiratory distress. Prophylactic Heparin (Unfractionated) was given to prevent any thrombotic complication. Patient showed improvement after two days of treatment. Her Blood Pressure

FIGURE 1: USG Abdomen showing Enlarged Left Ovary with Multiple cystic spaces

FIGURE 2: USG Abdomen showing Enlarged Right Ovary with Multiple cystic spaces.

FIGURE 3: USG Abdomen showing Ascites

Table 1: Golan's Severity Scoring in OHSS14

Grade of OHSS	Mild	Moderate	Severe
1.	Abdominal distention and discomfort		
2.		Criteria of grade 1 plus nausea, vomiting, and/or diarrhea. Ovaries enlarged 5-12 cm	
3.			Criteria of mild OHSS plus echographic signs of ascites
4.			Criteria of moderate OHSS plus clinical signs of ascites and/or hydrothorax and respiratory distress
5.			All of the above plus changes in blood volume and viscosity, hemoconcentration, Coagulation disorders, and decreased renal output and function
6.			Life threatening form

stabilized with fluid resuscitation. Respiratory distress settled. Abdominal Girth decreased from 109 cm to 92 cm and weight decreased from 67 Kg to 53 Kg in six days. Patient menstruated on 6th day thereby ruling out pregnancy. Patient was discharged on 7th day after becoming asymptomatic and normalization of Renal Function Tests.

Discussion

OHSS is usually a complication of Assisted Reproduction Technology (ART) but can be rarely spontaneous.¹ Familial cases of OHSS have been reported due to mutations in FSH receptor gene.² The syndrome is caused by abnormal and excessive response of ovaries to stimulation during ART and its incidence is related to the stimulation regime used with a high incidence when Gonadotrophins are used. Moderate OHSS is seen in 8% of stimulation cycles using clomiphene citrate.³ Worldwide the incidence of OHSS is increasing due to liberal use of IVF for management of infertility.⁴ A number of risk factors predispose the patients to development of OHSS (Box 1).⁵

The two hallmarks of OHSS are Cystic enlargement of Ovaries and Secretion of Vasoactive substances especially Vascular Endothelial Growth Factor (VEGF) leading to abnormal capillary permeability with loss of Intravascular fluid into third space.⁶ OHSS is classified into Early and Late variants. Early OHSS occurs within 3 to 7 days after ovulation induction, is usually mild to moderate in severity and is caused by exogenous HCG. Late variant occurs after 10 days of ovulation, is usually severe and related to placental HCG secretion. The clinical features of OHSS are related to four Pathophysiological

Box 1: Risk Factors for Development of OHSS

1. Higher dose or Repeated hCG Administration
2. Anovulatory Cycles (PCOD)
3. Estradiol – Rapid Rise or Level > 2500 pg/ml
4. Multiple Follicles (> 10 in each ovary of 4-10 mm)
5. Retrieval of > 14 Oocytes
6. Pregnancy
7. Low Body Mass index

mechanisms, 1) Ovarian enlargement, 2) Abnormal capillary permeability, 3) Hypercoagulability, and 4) Decreased IgA and IgG levels.

Ovarian enlargement causes abdominal discomfort, nausea, vomiting and bloating sensation. Abnormal capillary leakage causes third space fluid collection in the form of ascites, pleural or pericardial effusion. Severe loss of volume can lead to hypotension, shock and organ dysfunction due to tissue hypoperfusion. Hypercoagulability in OHSS leads to both venous and arterial thrombosis and Pulmonary Thromboembolism has been described.^{7,8} Venous Thrombosis is remarkable for its predilection for veins of neck and upper limbs. Arterial Thrombosis usually involves the Cerebral vessels. Low levels of Immunoglobulins IgA and IgG predispose patients of OHSS to infections of which Urinary Tract infections are the most common.⁹

Laboratory data is characterized by hemoconcentration (Hct >45%) and raised white blood cell and platelet counts.¹⁰ Hyponatremia and Hyperkalemia may be seen. Abnormal liver function tests are seen in 30% of patients with OHSS.¹¹ Hypoalbuminemia is universal. Raised serum creatinine points to severe OHSS. Low levels of IgA and IgG are seen in patients with severe OHSS and predisposes to infections.¹² The plasma levels of renin, aldosterone, noradrenaline, antidiuretic hormone [ADH] and atrial natriuretic peptide [ANP] are increased.^{10,12} Urinary sodium concentration is low in most patients. Ascitic fluid study reveals high protein and low cell counts.¹² Complications of OHSS are Pulmonary Oedema, ARDS, DIC or Hepatic Dysfunction. Surgical complications include Ovarian Torsion, rupture and Haemorrhage.

Treatment of OHSS is largely supportive. Medical management is mainly to maintain circulatory function and prevent organ dysfunction. The intravascular volume should be maintained to prevent hemoconcentration and allow sufficient urine output. Initial fluid of choice is crystalloids.³ Intravascular volume expansion with dextran has been associated with development of ARDS in patients with OHSS.¹³ In patients with hematocrit more than 45% or hypoalbuminemia less than 30gm/L or ascites, human albumin is the plasma expander of choice. In severe cases of OHSS prophylactic anticoagulation should be used. In presence of thromboembolism therapeutic anticoagulation is indicated.^{3,5}

Conclusion

OHSS can be a severe complication of infertility treatment

and fatalities have been reported. The affected patients are usually young females who otherwise have no significant illness and hence it is important for healthcare providers to be aware of its clinical features, complications and management to prevent its disastrous outcome. Management is largely supportive with emphasis on adequate fluid resuscitation and prevention of complications especially venous and arterial thrombosis.

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