

Ovarian Hyperstimulation Syndrome: A Rare Cause of Iatrogenic Pleural Effusion

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Abstract: Assisted reproductive technology (ART) has seen a boom in recent years, Ovarian hyperstimulation occurring as a rare and potentially fatal consequence of the ART is an uncommon cause of pleural effusion especially among chest physicians. Etio pathogenesis revolves around shift of intravascular to extravascular space under the influence of VEGF due to increased capillary permeability. The case reported here is that of a young nulliparous female with polycystic ovaries which is progressive and leads to a bilateral pleural effusion and acute respiratory distress needing oxygen and ICU management. The patient was managed with colloid management and fluid therapy. Also evidence of DIC and abnormal coagulation including DVT and Pulmonary embolism were evaluated and a final diagnosis was established to be OHSS. The pleural fluid reports were suggestive of a hemorrhagic exudative picture which regressed spontaneously after 7 days of ICU management. Possible preventive modalities include cancelling the cycle, coasting, individualizing the hCG trigger dose or using a GnRH trigger (for those using a GnRH antagonist protocol), the use of IV fluids at the time of oocyte retrieval, and cryopreserving/vitrifying all oocytes. Awareness among physicians including chest physicians is vital to ensure prompt diagnosis and appropriate care for such patients.

Keywords: Ovarian Hyperstimulation, Controlled Ovarian Stimulation, Pleural effusion, ARDS

1. Introduction

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 ovarian hyper stimulation syndrome (OHSS). Ovarian Hyper stimulation is a rare, iatrogenic complication of controlled ovarian stimulation (COS)¹.

Among the causes of the bilateral pleural effusion an uncommon cause includes the ovarian hyperstimulation syndrome². It usually presents with ascites and bilateral pleural effusion but in rare cases it may present with isolated pleural effusion and even unilateral massive pleural effusion^{3,4}. Although this syndrome is well recognized by obstetricians, as reflected in the gynaecologic literature, there is limited information among chest physicians. Due to the increased use of therapeutic strategies for infertility, the pulmonary complications of this syndrome should be suspected on clinical grounds and identified early to allow for more appropriate diagnosis and management.⁴

The exact etio pathogenesis is unknown but is likely due to shift of fluid into extravascular space. Raised intra-abdominal pressure as a possible etiology has also been linked to OHSS⁵

2. Case

Our patient a 26 yr. old/ nulliparous female without any addictions and comorbidities came with history of abortion followed by Dilatation and Curettage done in 2011. Patient has been on infertility medications since then (cyclical clomiphene and HCG injections). The patient had irregular

menstrual cycles with clinical and radiological features s/o Polycystic Ovarian Disease. The right sided ovary developed cystic changes without torsion and on follow up showed slowly progressive enlargement of the cystic changes and evidence of haemorrhage within the cyst. The left ovary also developed cystic changes on follow up. The patient had undergone laparoscopy and retrieval of ovum in 2013 following which 2 attempts at Intra Uterine Insemination (IUI) had been made but were not successful. The patient had been taking therapy including Estradiol, HCG and Clomiphene from a gynaecologist in private before presenting to our institute. The patient had received 3 HMG injection (Menotropins) and HCG 10,000 IU in the previous cycle for follicular stimulation. 2 weeks after the last dose of HMG, the patient presented to our institute with c/o abdominal distention and progressive breathlessness (MMRC/ NYHA grade 4) of 2 days duration. On admission, the patient had moderate hypoxia (Spo2 92% on room air) for which she was treated with supplemental oxygen. She was admitted in the ICU for above complaints. On examination the patient had abdominal distention and tenderness. X ray abdomen did not show any air fluid level or gas under diaphragm. The USG of pelvis and abdomen was s/o enlarged ovaries with multiple cysts of 5.6cm X 5.3 cm on right and 4.8 cm X 3.6cm on the left side with moderate ascites and bilateral moderate pleural effusion (R>L). Chest X ray done (Fig. 1) was s/o bilateral pleural effusion and normal underlying parenchyma. The patient was managed with IV antibiotics, IV fluids /colloids, prophylactic anticoagulation and maintenance oxygen therapy. Abdominal girth, urine output, Spo2 was monitored closely. There were no clinical findings to suggest DVT/ Pulmonary Embolism. The patient's pleural fluid was analysed after a diagnostic thoracentesis and was suggestive of haemorrhagic exudative pleural effusion. The pleural fluid reports showed reddish colour, protein: 3.8 gm

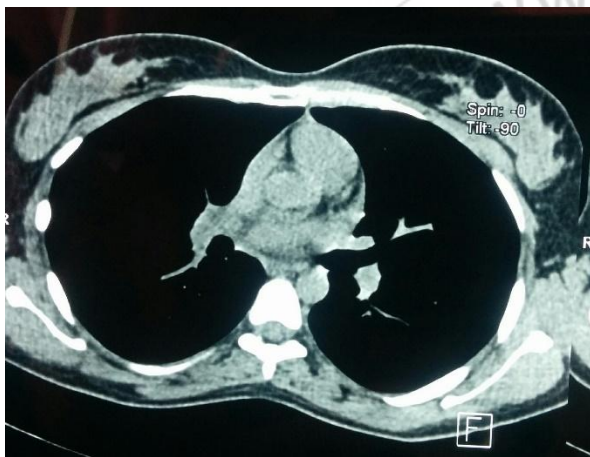
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% , glucose: 102.0 mg/dl, total counts of 200 cells/cmm (pauci cellular), polymorph: 30 % and lymphocytes: 70%. ADA: 7.20 IU/L (normal 0-30) and pleural fluid amylase: 94U/L (normal for serum 0-90).



Figure 1: Chest X Ray on admission



(a)



(b)

Figure 2 (a and b): CT Chest on Day 7 of admission

Liver function, renal function and serum electrolytes were within normal limits. Urine routine was s/o albuminuria which reduced later. The ESR was monitored and reduced on appropriate fluid management. Haemoglobin was 11.8 gm % and haematocrit: 35.4 % with normal counts maintained throughout admission.

Repeat USG chest and USG abdomen after 1 week of conservative management showed no pleural effusion or ascites. CT chest done to r/o rare possibility of pulmonary embolism or malignancy was also normal. TSH and coagulation profile done was within normal range. The patient had a height of 152 cm and weight loss of 5.7 kg (51.7 to 46 kg) from admission till discharge. The abdominal girth reduced from 80 cm to 71.5 cm during admission. The patient recovered completely over a period of 9 days in hospital.

Discussion: Ovulation induction therapy is one of the most important processes for assisted reproduction . A certain degree of ovarian hyper stimulation is desirable during these procedures, however an exaggerated response poses a risk of the potentially life threatening ovarian hyper stimulation syndrome (OHSS) and must be avoided. The incidence of moderate OHSS is estimated to be 3-6% and severe form may occur up to 0.1-3% of cycles. The incidence in high risk candidates may be up to 20 %.

The recognised high risk candidates for the ovarian hyper stimulation following the ovarian stimulation techniques are women with either hormonal or morphological signs of polycystic ovarian disease, high serum estradiol (E2 greater than 4,000 pg/mL) before human chorionic gonadotropin (hCG) \ administration, multiple follicular response (greater than 35), younger age, lean habitus 6, an Antral Follicle Count (AFC) >14 and basal Mullerian Hormone levels (AMH) prior to the COS have been shown to be more predictive. Metformin has also been used for the prevention of OHSS.¹

The management involves meticulous fluid and electrolyte balance using both crystalloids and colloids including albumin until hemoconcentration abates. Paracentesis is indicated for tight ascites, deteriorating kidney functions, and symptomatic relief. Diuretics may be prudently used once hemodilution is achieved. Dopamine may be used in reno protective doses to ensure adequate renal perfusion is maintained⁶. Dopamine agonists have been used without consensus and the use is not universally accepted as they may be less effective^{1,7}.

The etiopathogenesis of the syndrome mainly revolves around increase in capillary permeability. The major agent involved in the increased permeability is VEGF9, The expression of VEGF and VEGF receptor 2 (VEGFR-2) mRNA increases significantly in response to hCG, and peak levels coincide with maximum vascular permeability.^{1,9}

Increased capillary permeability and ovary enlargement are the principal characteristics of OHSS. Fluid escapes into the third space, resulting in hypovolemia. The severe OHSS is characterised by massive ovarian enlargement, pleural effusion, ascites, oliguria, hemoconcentration and thromboembolic phenomenon.¹⁰

Other agents at play include Estradiol, LH and hCG, interleukins and renin angiotensin system. Neither estradiol nor hCG may cause OHSS independantly but hCG may trigger OHSS in high doses⁶ as had occurred in our patient.

3. Conclusion

OHSS is a rare but potentially fatal iatrogenic condition. Preventing OHSS in high risk candidates during COS includes cancelling the cycle, coasting, individualizing the hCG trigger dose or using a GnRH trigger (for those using a GnRH antagonist protocol), the use of IV fluids at the time of oocyte retrieval, and cryopreserving/vitrifying all oocytes. Early recognition of symptoms of OHSS and prompt management should be initiated with focus on fluid balance. Identifying life threatening changes including deep venous thrombosis and massive pleural effusion with immediate management may be lifesaving.

4. Acknowledgment

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5. Glossary of Terms

VEGF: Vascular Endothelial Growth Factor.
GnRH: Gonadotropin Releasing Hormone.
OHSS : Ovarian Hyperstimulation Syndrome.
hCG : Human Chorionic Gonadotropin.
LH: Lutenising Hormone.
AMH : Antral Mullerian Hormone.
COS : Controlled Ovarian Stimulation
DIC : Disseminated Intravascular Coagulation.
DVT : Deep Venous Thrombosis

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