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A rare case of severe ovarian hyperstimulation syndrome with ascites and pleural effusion leading to ICU admission.

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Abstract

Severe ovarian hyperstimualtion syndrome is a rare but possible complication of ovulation induction. In this case report we present a case of 29 year old nulligravida, who required intensive care management due to massive ascites and mild pleural effusion and oliguria. With positive history of controlled ovarian stimulation for in vitro fertilisation, the patient was diagnosed with severe ovarian hyper stimulation syndrome. Other than symptomatic medical management, abdominal paracentesis was done for draining massive ascitic fluid collection resulting in gradual improvement. It may be well noted that there is production of not one but many mediators which are responsible for giving rise to OHSS that act in conjunction. These include prostaglandins cytokines interleukins, ovarian renin angiotensin system, vascular endothelial growth factor. Early diagnosis and timely multidisciplinary management is a key to save lives.

Keywords: Ascites, Intensive Care Unit, Ovarian Hyperstimulation Syndrome, Paracentesis, Pleural Effusion.

Introduction

Ovarian hyperstimulation syndrome (OHSS) is a potentially life threatening complication of ovulation induction therapy .First described in 1943 , with the first fatal case was reported in 1951 , not much data is available regarding the incidence of moderate and severe forms separately . In conventional IVF cycles mild OHSS is estimated to have an incidence of one third of cases whereas combined incidence of moderate to severe cases is 3.1 - 8 % [1]. Severe OHSS is characterised by any of

the features namely: clinical ascites with or without hydrothorax, oliguria (<30ml/hour or <300ml/day), an increase in ovarian size (>12 cm), hemoconcentration (hematocrit >0.45), hypercoagulability, and electrolyte imbalance (hyponatremia, hyperkalemia), hypoproteinemia (serum albumin < 35 g/dl), hypo-osmolality (<282 mOsm/kg). Rarely OHSS may lead to life-threatening complication like acute renal failure, acute respiratory distress syndrome, thromboembolism and haemorrhage from ovarian rupture.

Case Report

A 29 year old female, nulligravida admitted with complaints of abdominal distension , respiratory distress , multiple episodes of non-bilious vomiting and diarrhoea for past 4 days . Patient was being treated for acute gastroenteritis but she had worsening of her symptoms despite medical management. At the time of presentation she had a pulse rate of 124 beats per minute, BP- 120/70 mmHg, oxygen saturation of 96 % on room air with bilateral decreased air entry especially on right hemithorax more than left. Abdominal examination revealed massive abdominal distension with evidence of ascites with no palpable mass in abdomen. Per vaginal examination revealed a slightly bulky uterus of 6-8 weeks size, with bilateral forniceal fullness, no cervical motion tenderness and no other abnormality.

The patient had undergone IVF treatment with history of receiving gonadotropin injections - fixed GnRH antagonist (Cetrorelix) protocol with no prior OCP pretreatment, with injection hCG injection on day 12 of cycle along with dopamine agonist (cabergoline) given just prior to hCG injection , that is 6 days prior to onset of symptoms with history of ovum pickup 3 days prior to onset of symptoms . No procedure of embryo transfer was done as the qualities of embryos were unsatisfactory. She had previous history of two failed past IUI cycles. Patient had attained menarche at 14 years of age with normal regular menstrual cycles and USG pelvis done before IVF cycle revealed no abnormality such as hydrosalpinx or polycystic ovaries et cetera. Infertility workup done prior to IVF treatment revealed asthenospermia in husband's semen analysis .Patient's routine blood investigations, serum hormonal profile, serum microbiological assays (HbsAg, Anti HCV antibody, HIV I and II antibody) cervical cytology, hysterosalpingography, were all essentially normal before procedure of controlled ovarian stimulation with gonadrotropin antagonist protocol.

Laboratory investigations at the time of admission and discharge have been summarised in table 1. Abdominal and transvaginal sonography revealed an anteverted uterus of 5.5 x 3.7 x 5.5 cm size with endometrial thickness of 6 mm and enlarged bilateral ovaries with right ovary of 440 cc and left ovary of 370 cc size . Bilateral moderate pleural effusion (right more than left) , and gross ascites were also noted . No other abnormality was noted on other abdominal organs. Chest X-Ray showed right sided meniscus sign with diffuse right sided haziness in right hemithorax suggestive of pleural effusion on right side. A diagnosis of severe ovarian hyperstimulation syndrome was made based on elevated total leucocyte count , increased hematocrit (>45%) , elevated D-dimer levels , hypoproteinemia hyponatremia , hyperkalemia , enlarged ovaries and gross ascites with moderate pleural effusion in USG and chest X-Ray suggestive of pleural effusion .Patient was shifted to ICU on day 2 of admission as she had developed oliguria (<300ml /day urine output) and significant increase in abdominal girth (>3cm increase over 24 hours) . Single time abdominal paracentesis of 1.2 litre was done for massive ascites. Nephrology reference was taken for oliguria and renal function was supported by using

diuretics (injection furosemide 40 mg /day in two divided doses) for one day. ICU management also included antibiotics (injection ceftriaxone for 5 days) , albumin (colloid) infusion for two days , low molecular weight heparin therapy (0.4 mg subcutaneous once daily dose) for 72 hours of admission as thromboembolism prophylaxis. Pleural effusion was managed by chest physiotherapy and breathing exercises and no pleural fluid aspiration was done as patient showed no clinical signs of respiratory distress or failure. The general condition of the patient gradually improved over next few days following abdominal paracentesis and patient was discharged on day 10 of admission.

Table 1: It shows the laboratory investigation at the time of admission and at the time of discharge.

Lab parameters	Day of admission	Day of discharge
Haemoglobin	16.9 g/dl	9.9 g/dl
Total leucocytes count	21,500 cells /cu.mm	11300 cells /cu.mm
Platelets	5.45 lakh /cu.mm	3.25 lak /cu.mm
Haematocrit	47 %	35,6 %
Prothrombin time (control - 13.6 seconds)	16.3 seconds	13 seconds
INR	1,2	0,96
Fibrinogen	397 mg/dl	305 mg/dl
Activated partial thromboplastin time (control-30.9 seconds)	25 seconds	29.7 second
D-dimer	4.9 ugFEU/ml	1.0 ugFEU/ml
Serum creatinine	1.2 mg/dl	0.9 mg/dl
Serum albumin	2.4 g/dl	3.2 g/dl
Serum sodium	124 mEq/l	133 mEq/l
Serum potassium	5.6 mEq/l	3.8 mEq/l
C-reactive protein	3.39 mg/dl	<2 mg/dl
Serum Estradiol	10,251 pg/ml	

Discussion

Ovarian hyperstimulation syndrome (OHSS) is a serious but often self-limiting complication of ovulation induction, occurs with gonadotropin and rarely with clomiphene citrate [2]. It has been observed that OHSS developed in women of younger age group, of lower gravid, parity status, with pre-existing ovulation disorders and African race. In fact OHSS is two times more commonly seen in women with ovulation disorders with a 37% risk of it being severe .[3]

Amongst the causal factors, high level of Estradiol alone is less likely to cause OHSS unless hCG is also raised [4] . Estradiol levels are a reliable predictor of developing OHSS during ART, currently it is considered as a mere marker of granulosa cell activity. The hormone hCG is considered to be a fundamental in triggering OHSS. The pathogenic role of VEGF expression has also been hypothesised along with inflammatory mediators like interleukin - 6 all of which are associated with increased vascular permeability, hemoconcentration, elevated plasma estradiol concentration and inhibition of hepatic albumin production all of which leads to third space fluid loss, resulting in hypovolemia , hypoproteinemia ascites , pleural effusion and risk of thromboembolism [5]. Like

all hypovolemic condition even OHSS is associated with secondary reactive hyperaldosteronism via the renin-angiotensin cascade activation.

Management of OHSS is mainly supportive and multidisciplinary. In patients with raised hematocrit more than 45% or hypoalbuminemia or ascites, human albumin is the plasma expander of choice. Once plasma volume expansion is achieved, use of diuretics (furosemide) should be given to assist renal function . Overzealous or premature use of diuretics may aggravate hypovolemia and hemoconcentration leading to renal compromise and aggravate the risk of thromboembolism. Intravascular volume expanders like fresh frozen plasma and dextran have no advantage over albumin [6]. In patients with hydrothorax who are not symptomatic conservative management is sufficient. In severe OHSS prophylactic anticoagulation should be used.

Prevention strategies include coasting, use of albumin on the day if hCG injection, dopamine agonist, GnRH antagonist protocol for controlled ovulation stimulation (COS) in ART, replacement of hCG with single dose recombinant LH and in vitro maturation of oocytes. Coasting is a strategy in which administration of hCG is postponed in women with raised E2 levels till the estradiol levels are considered to be safe , during which period gonadotropin administration is either withheld or done with reduced dosage . In most published literature the cut-off for E2 level is between 2500-4000 pg/ml. Coasting clearly decreases level of E2 thereby preventing rise in VEGF which is a major culprit for pathogenesis of OHSS. However there is lack of trial to prove the efficacy of coasting strategy in preventing OHSS because OHSS is reported to have occurred in 9.4% of patients with coasting .[5] . Role of dopamine agonist that is cabergoline is worth mentioning in this context as well. Cabergoline inhibits binding if VEGF to its receptors thereby preventing the increased vascular permeability that leads to the incidence and severity of OHSS. The best time for its administration is reported to be few hours before hCG injection. Administration of dopamine agonist as a prophylactic measure appears to be effective without any adverse effect on subsequent pregnancy rates [7]. GnRH antagonist protocol as used in our patient's case has been associated with decrease in OHSS incidence however slight reduction in pregnancy rates has been noted.

Conclusion

Symptoms of OHSS can be masked and often be misdiagnosed as gastroenteritis. Severe OHSS should be suspected in women presenting with ascites and plural effusion with history of controlled ovarian stimulation (COS). It may be well noted that there is production of not one but many mediators which are responsible for giving rise to OHSS that act in conjunction. These include prostaglandins cytokines interleukins, ovarian rennin angiotensin system, vascular endothelial growth factor and nitric oxide [8]. Severe OHSS is a serious iatrogenic complication that can even lead to death if left untreated. Early diagnosis and timely multidisciplinary management is a key to save lives.

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Abbreviations

OHSS- Ovarian hyperstimulation syndrome

IVF - in vitro fertilisation

GnRH -gonadotropin releasing hormone

OCP - oral contraceptive pills

IUI - intra uterine insemination

USG - ultrasonography

hCG- human chorionic gonadotropin

HBsAg - hepatitis B surface antigen

Anti HCV - Anti hepatitis C virus

HIV - human immunodeficiency virus

INR - International Normalised Ratio

ICU- intensive care unit

ART - assisted reproductive technique

COS - controlled ovarian stimulation

E2 - estradiol

VEGF - vascular endothelial growth factor