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Meticulous Management of a Case of Severe Ovarian Hyperstimulation Syndrome Using Dopamine Agonist and GnRH Antagonist: a Case Report

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Abstract

Ovarian hyperstimulation syndrome (OHSS) is characterised by increased capillary permeability and thus fluid shift from intravascular to extravascular compartment. Presence of abdominal distension causing discomfort to the patient, diameter of ovary more than 12 cm and ascites are the criteria to diagnose a case of severe OHSS. A, 28-year-old patient, P4L5 presented to our hospital, after ovulation induction and pick-up for oocyte donation, with abdominal distension and pain. She has history of severe OHSS, 4 months back as well. She was managed symptomatically, with close watch on her vitals, input-output, hematological and ultrasonological parameters. She was administered dopamine agonist in a dose of 1 mg/day and GnRH antagonist, injection cetrorelix 0.25 mg subcutaneously for 7 days. Paracentesis was also done twice for the patient under ultrasound guidance. Patient improved significantly over the course and was discharged in a stable condition.

Keywords: Dopamine agonists, Cabergoline, GnRH, Cetrorelix

Introduction

OHSS is a serious complication of artificial reproductive technology and its incidence is increasing. The syndrome is characterized by massive ovarian enlargement, ascites, pleural or pericardial effusion, oliguria, electrolyte imbalance, hemoconcentration, hypotension, thromboembolism, acute respiratory distress syndrome and death in severe conditions. OHSS can be of four types depending on the presence of symptoms into mild, moderate, severe and critical. Severe OHSS is defined by the presence of clinical ascites, oliguria (< 300ml/day), haematocrit > 0.45, hyponatremia (sodium < 135 mmol/l), hyperkalemia (potassium > 5 mmol/l), hypoproteinemia (serum albumin <35g/l) and diameter of ovarian size more than 12 cm (1). Early diagnosis and scrupulous management are the key to successful recovery. Antithrombotic measures, dopamine agonist and GnRH antagonists are considered to be useful in the treatment of established early OHSS as reported in various studies (2, 3).

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Case

A, 28-year-old, P4L5, patient presented to the emergency department of obstetrics and gynaecology of our hospital with complaints of abdominal distension and pain for 3 days. She also complaint of 8-10 episodes of vomiting and unable to tolerate orally. On enquiring, patient told that she was undergoing ovulation induction for oocyte donation. Patient was stimulated with GnRH agonist i.e. recombinant FSH 400 IU from day 2 of cycle for 5 days, injection HMG from 6^{th} to 10^{th} day in dose of 375 IU and 300 IU on 11-12^{th} day and GnRH antagonist, cetrorelix acetate 0.25 mg from day 5 to day 12. Injection Hcg, 10,000 IU was given and around 30 oocyte pick-ups were done 3 days back. As she developed, pain abdomen and distension, she was referred to our hospital for further management accompanied by an agent.

Her menstrual cycles were regular with average flow. She was para 4, live 5 with all vaginal deliveries with age of last child 5 years which was twin delivery and that was a spontaneous conception. There was no significant past

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suggestive of any chronic illness. There was significant history of ovarian hyperstimulation syndrome four months back which even required paracentesis.

On examination, general condition of the patient was average, her vitals were pulse rate 104 per minute, blood pressure 100/60 mmHg, respiratory rate 37/minute, saturation 98% on room air and temperature 37.5 degree Celsius. On cardiovascular examination, S1S2 were normal with no added sounds and on chest examination, air entry was decreased on right basal lung. On abdominal examination, abdomen was distended, with shifting dullness and tenderness in lower abdomen. Her abdominal girth was 35 inches. Her body weight was 53 kg.

All her investigations were done, including hemogram, haematocrit, coagulation profile, ABG, liver, kidney function tests and serum estradiol levels as depicted in Table 1. Chest Xray was done and was suggestive of right sided pleural effusion, figure 1. Ultrasound pelvis was done and showed anteverted normal size uterus with endometrial thickness of 10.1mm. Bilateral adnexa showed complex cystic lesions. Right side measured 4.5x3.5x 4.2cm (33 cc) and left side measured 5.4x5.3x 5.3cm (75.8cc) with peripheral as well as septal vascularity, ovaries were not seen separately. Moderate ascites was seen with no internal echoes.

Patient was catheterised and strict input and output monitoring was done. Vital monitoring, daily weight measurement, abdominal girth charting, and daily blood investigations (Table 1) were continued. Patient was given cabergoline 0.5mg on first day and was increased to 1 mg and was continued. Thromboprophylaxis with low molecular weight heparin was started with injection enoxaparin 40 mg subcutaneously. Intravenous fluids were administered and oral intake was encouraged as per thirst of the patient, once her vomiting settled with antiemetics. Pain relief was done with opioids.

On day 4 of presentation, patient's condition deteriorated, patient developed multiple episodes of vomiting, output decreased to less than 20-25 ml/hour, abdomen became tense, abdominal girth increased, body weight increased, hematocrit increased and serum sodium decreased. Ultrasound pelvis was done and size of right adnexal region was 7.0x9.9x7.9 cm (285 cc) and left adnexal region was 11.5x8.7x9.1 (470 cc) with ascites, figure 2. Decision to do ultrasound guided paracentesis was done and under all aseptic precautions, 800 cc of ascitic fluid was drained. 200 ml of 20 % albumin was transfused and injection cetrorelix 0.25 mg subcutaneously was administered. Ultrasound guided paracentesis was repeated on day 6 of presentation and 1.5 litres of ascitic fluid was drained. Size of ovaries gradually decreased to 103cc of right side and 92 cc of left side on day 11 of presentation i.e. after 13 days of oocyte pick-up and patient started menstruating.

Patient improved symptomatically and clinically over the time. She received total seven doses of cetrorelix acetate. Patient was discharged explaining her not to undergo ovulation induction in future.

Table 1: Biochemical and clinical parameters over the course of admission stay

Parameters	DAY 1 (admission)	DAY 3	DAY 4	DAY 6	DAY 7	DAY 11 (discharge)
Hemoglobin (gm%)	13.7	14.8	16	14.1	12.4	12.3
TLC	17400	20500	22500	14600	8540	5550
PLATELET COUNT	2.15	3.59	3.41	3.33	3.42	3.73
HEMATOCRIT	40.5	41.1	49.7	42.7	37.1	37
INR	1.00	1.00	0.95	0.93	0.93	0.97
BU/S CREAT	17/0.8	15/0.7	31/0.9	19/0.7	15/0.6	10/0.5
Na/ K	137/4.0	138/5.9	131/4.6	134/4.2	134/4.2	141/4.5
TBIL/ALT/AST/ALP	0.6/43/34/83	1.5/66/41/185	1.3/62/67/103	0.7/80/63/92	0.3/173/131/104	0.3/65/94/110
SERUM ESTRADIOL	> 3000 pg/ml					
Weight	53	54	55	55	54	50
Abdominal girth	37.5	37.5	38.5	38.5	35	32

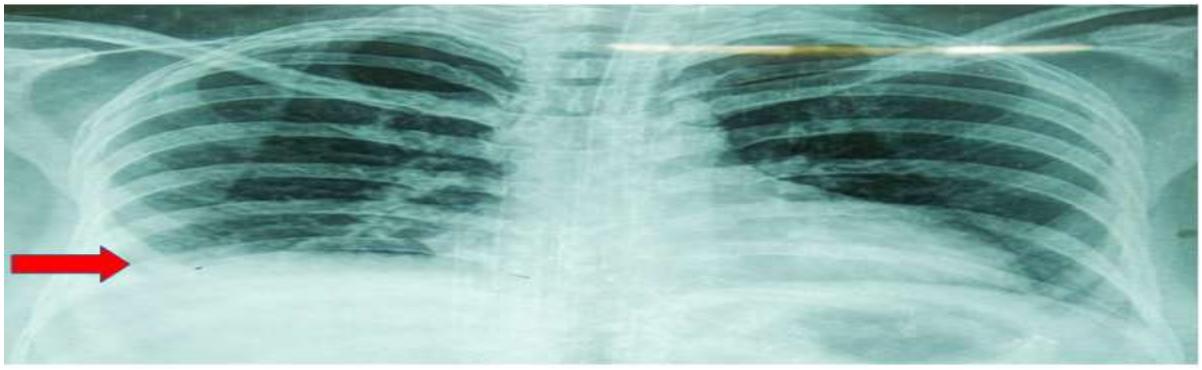

Figure 1: Chest X-RAY showing right sided pleural effusion, marked by red arrow

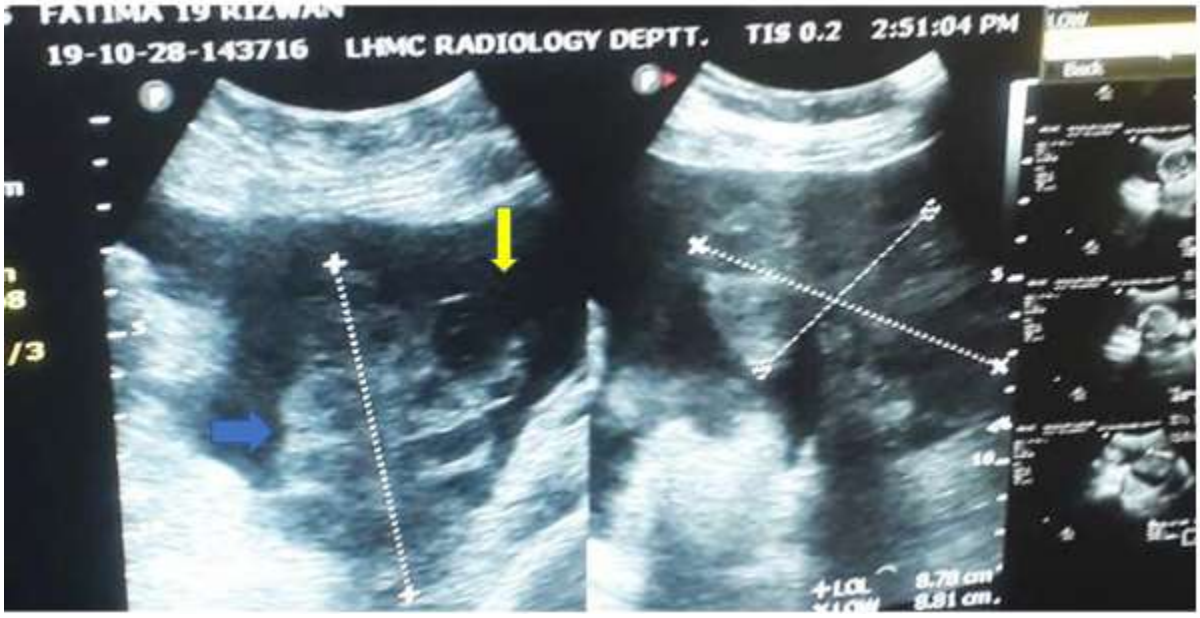

Figure 2: Uktrasound- Pelvis showing enlarged ovaries, marked by blue arrow and ascites marked by yellow arrow

Discussion

Ovarian hyperstimulation syndrome (OHSS) is a life-threatening complication of assisted reproductive technology. The symptoms of OHSS may vary from mild abdominal discomfort to multiorgan failure and in minority even death. The most common pathophysiology behind the symptomatology is increase in capillary permeability (4). This leads to shift of intravascular fluid to peritoneal cavity and rarely into pleural and pericardial effusion. The severity of intravascular volume depletion is correlated with increase in haematocrit and this can further lead to hypotension, thromboembolism, anuria and end organ failure. Disruption of endothelial cell tight junction have been responsible for increase in capillary permeability and is primarily due to increase in vascular endothelial growth factor (5). Other possible mediators of OHSS are inhibin, prostaglandins and inflammatory syndromes.

OHSS can be classified into mild (8-23%), moderate (1-7%), severe (0.5-5%) and critical depending on clinical and laboratory parameters. [6] It can be further divided into early and late, depending on the duration between injection Hcg for ovulation and presentation of symptoms. If the duration, was less than 7 days, it was defined as early OHSS. Our case was an early OHSS, of severe intensity leading to hospitalization. Risk factors leading to increase in the possibility of OHSS are young age, polycystic ovarian syndrome, high number of antral follicular counts or levels of anti- mullerian hormones, multiple follicles more than 20, high serum estradiol levels, conception in the same cycle, previous history of OHSS and high doses of exogenous gonadotropins (6). Among these, multiple risk factors existed in our case.

Timely diagnosis, intensive monitoring, supportive therapy and trained clinicians are the prerequisites for successful management of OHSS, especially cases of severe or critical variety.

Oral intake of fluids, guided by thirst, is the best approach to correct depleted intravascular volume. In addition, intravenous fluid can be given guided by the haematocrit, serum sodium levels and input-output monitoring. Thromboprophylaxis with low molecular weight heparin is required in all cases of severe or critical OHSS. Paracentesis is done under ultrasound guidance in cases of severe abdominal pain or in case patient developed respiratory distress. Intravenous colloid therapy is given after removal of ascitic fluid.

Dopamine agonist, cabergoline decreases VEGF mediated capillary permeability by inhibiting phosphorylation of VEGF-2R. In the first randomized clinical trial, cabergoline was used in the dose of 0.5 mg/day, starting from the day of ovulation trigger and was considered to be effective (7). Later, Baris Ata et al, reported that the dose of 0.5 mg/ day was no effective enough to prevent the development of OHSS or resolve it and thus they used 1mg/day (8).

GnRH antagonists when administered in patients with OHSS, work by causing sudden pituitary dysfunction leading to ovarian regression and thus symptom relief. Also, protein expression of VEGF and VEGF-R were reduced in cultured human-granulosa-lutein cells, that also helps in regression of OHSS symptoms. Lainas et al were the first to report use of GnRH antagonist for 7 days in 3 patients, that successfully recovered from severe OHSS (9). In a case series of 10 patients with severe OHSS done by Duyong Lee et al, GnRH antagonist was started on the day of hospitalization and continued for 2-4 days, depending on the clinical improvement of the patient (10). We started our patient on injection cetrorelix, on day 4 of hospitalization and decided to continue for 7 days and observed improvement in terms of her clinical, biochemical and radiological parameters.

Conclusion

High suspicion, early diagnosis, supportive therapy and intensive monitoring are the key to successful management of patients presenting with severe OHSS. More randomised controlled trials are needed to establish the dose and regimen of dopamine agonists and GnRH antagonist, that are considered to be highly effective in the management as well as prevention of severe OHSS. In patients with risk factors, especially history of OHSS, ovulation induction should be discouraged by the treating gynaecologists or planned carefully to avoid such life-threatening complication.

Clinical significance

This case report highlights the importance of history in patients planning for ovulation induction, as history of OHSS can be life threatening. Literature search suggests requirement of randomised controlled trials regarding optimal usage off available drugs, to ensure successful management of patients with severe OHSS.

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