Management of severe ovarian hyperstimulation syndrome with thawed plasma

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ABSTRACT

Severe ovarian hyperstimulation syndrome remains one of the life threatening complication of assisted reproductive technology. In refractory cases of late ovarian hyperstimulation syndrome (OHSS), clinicians are left with limited therapeutic options. We report a case of refractory OHSS which was managed successfully using thawed plasma. Thawed plasma transfusion could be potential therapeutic option for managing patients with severe ovarian hyperstimulation not responding to conventional treatment.

KEY WORDS: Ovarian hyperstimulation syndrome, thawed plasma, ART

INTRODUCTION

Ovarian hyperstimulation syndrome (OHSS) remains one of the most serious complications of assisted reproductive technology (ART) and is not always preventable. Main pathophysiology is increased permeability of capillaries to plasma proteins leading to fluid shift from intravascular to extravascular compartment, which clinically manifests as ascitis, pleural effusion, oliguria, hemoconcentration and electrolyte abnormalities.[1,2]

Though a lot of preventive measures are described in order to prevent OHSS, the therapeutic options for OHSS are mainly supportive (intensive fluid management, monitoring of biochemical, and radiological parameters), apart from few active interventions such paracentesis, intravenous albumin, and anti-thrombotic prophylaxis.[1-4] Few patients with critical late OHSS do not improve even after all these measures and the treating clinicians are left with very few difficult options namely – termination of pregnancy and, less commonly, bilateral partial oophorectomy.[5]

CASE REPORT

A 27-year-old female with primary infertility was seen in our unit in March 2011. She had regular periods and her body mass index was 25 kg/m^2. Her baseline investigations were normal and ultrasound report revealed polycystic ovaries. Her husband's semen-analysis report revealed azoospermia. His clinical and biochemical findings were suggestive of obstructive azoospermia. After counseling regarding the treatment options available, a diagnostic percutanous epididymal sperm aspiration was performed which revealed presence of motile sperms. The couple decided to go ahead with ART.

Cycle programming was done using combined oral contraceptive pills and controlled ovarian hyperstimulation was started after onset of menstruation using with recombinant follicle stimulating hormone (FSH) and multiple dose flexible antagonist (0.25 mg) regimen was followed. Injection human chorionic gonadotrophin (hCG) 5000 international units (IU) intramuscular was administered once more than three follicles reached a diameter of 17 mm. Serum estradiol (E2) on the day of hCG trigger was more than 3800 pg/mL and expected number of follicles was 14-15. She underwent ultrasound guided transvaginal oocyte retrieval and a total of 13 metaphase II oocytes were retrieved. She received 100 ml infusion of human albumin (20% solution) over 4 h, prophylactically after oocyte retrieval. Intracytoplasmic sperm injection was performed using surgically retrieved sperms and 10 fertilized oocytes were obtained the next day. On day 2, three grade 2 cleavage embryos were transferred.[6] Supernumerary embryos were cultured and eventually two blastocysts were cryopreserved.

Patient received luteal support in the form of daily vaginal micronized progesterone 400 mg twice daily and was given intramuscular injection of progesterone 100 mg weekly twice. The patient was advised to take high protein diet and to maintain the total fluid intake/output records which was evaluated once in 3 days for signs and symptoms of OHSS.

On post-retrieval, day 9, the patient presented with complaints of severe abdominal discomfort, vomiting, difficulty in breathing and decreased urine output. Her abdominal girth had increased from 72 cm to 84 cm. Her blood test revealed hemoconcentration (hematocrit was 54%), raised liver enzymes, and low sodium (122 mEq/L). An ultrasound of the abdomen revealed bilateral enlarged ovaries (right ovarian size was 11 × 10 × 9 cm and left ovarian size was 10 × 8 × 8 cm) with significant ascitis [Figure 1]. Chest X-ray (an abdominal shield was used) showed bilateral pleural effusion. The patient was diagnosed with severe OHSS and admitted to the intensive care unit. Intravenous fluid administration, analgesics, anti-emetics, and prophylactic anti-coagulation with low molecular weight heparin 2500 IU subcutaneously were initiated. After stabilization, patient underwent therapeutic pleural tap and ultrasound-guided abdominal paracentesis. A total of 2.5 L of ascitic fluid was drained. The patient's symptoms were relieved temporarily. The patient's clinical and biochemical parameters were monitored on a daily basis. The patient was advised to wear elastic stockings and high protein diet intake. Infusion of human albumin was also given once daily.

However, within 2 days the patient had recurrence of abdominal discomfort and difficulty in breathing due to collection of ascitic fluid. A repeat paracentesis was carried out and further 2.5 L of fluid was drained out. Barring low albumin levels (2.1 g/dL) rest of the biochemical parameters were stabilizing (hematocrit 34%). However, despite a high protein diet and daily infusion of albumin, the albumin levels kept deteriorating. Further she developed severe anaphylactic reaction after human albumin infusion on day 13 post-retrieval, which necessitated discontinuation of infusion. Despite all prophylactic measures prompt recognition and early aggressive treatment of OHSS, the patient's condition did not show any signs of improvement. She had rapid re-accumulation of ascitic fluid and due to worsening of symptoms, we had to resort to repeated paracentesis in order to relieve her of her discomfort. However, the serum albumin levels had fallen to alarming levels (1.7 g/dL) partly due to ascitic fluid tapping. The patient developed signs and symptoms hypoalbuminemia in the form of generalized puffiness of the body, face and limbs, and developed vulval edema. Her serum beta HCGs levels were 30 mIU/L (day 10, post-retrieval). With early pregnancy, worsening late OHSS, and severe hypoalbuminemia, rapid re-accumulating of ascites and drainage lead to loss of protein rich fluid, inadequate replacement of protein lead to further lowering of albumin, further contributing to rapid re accumulation of ascitis. Abdominal paracentesis was done 6 times and on day 20, after consulting the medical oncologist, who was familiar with treatment of rapidly accumulating ascitis, as a last resort we decided to transfuse the patient with thawed plasma.

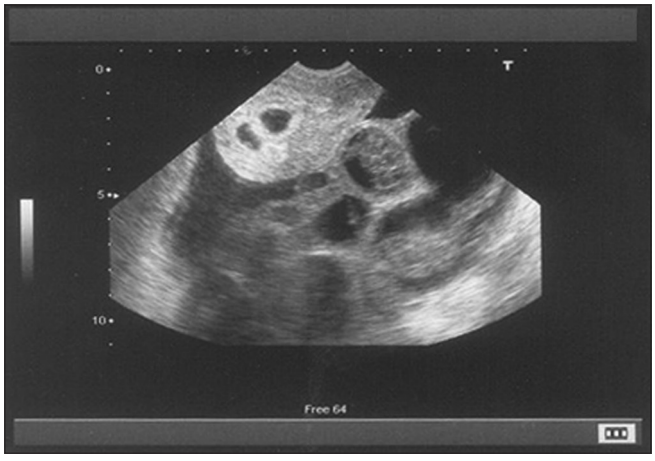

Figure 1: Ultrasound image showing twin gestation with enlarged ovaries and fluid in pouch of douglas

Patient was transfused four units of thawed plasma in 48 h. The transfusion volume was calculated (10-15 mL/kilo body weight). This resulted in a dramatic improvement in the patient's condition as reflected by significant increase in urine output and stabilization of abdominal girth (indicating no clinically significant re-accumulation of ascitic fluid). Most importantly her serum albumin level started rising (2.5 g/dL immediate post-transfusion). No further paracentesis was required and patient was discharged day 26 post-retrieval.

The patient's serum beta HCG levels on day 18 after oocyte retrieval was 522.4 mIU/L and after 14 days the transvaginal ultrasound revealed twin intrauterine gestation sacs with a yolk sac and a fetal pole in each sac but no cardiac activity [Figure 1]. Subsequently, a repeat ultrasound was done a week later and the patient was diagnosed with missed abortion and the pregnancy terminated. The patient was discharged and planned for frozen embryo transfer at a later date.

DISCUSSION

Although OHSS is one of the serious complications encountered by infertility specialist in day-to-day clinical practice, most cases fall under to mild/moderate category, which can be managed on an outpatient basis.

However, 0.2-2% cases fall under severe OHSS and

require hospitalization.[2,5] Various biochemical and clinical manifestation such as hemoconcentration, oliguria, hypotension, electrolyte imbalance, thrombo embolic event, renal failure, cardiac arrhythmia, and multi-organ failure are associated with severe OHSS and few cases of death following severe OHSS have been reported.[1,2,7]

Management of severe OHSS includes daily monitoring of fluid intake and output volume, abdominal girth, weight gain, leukocyte count, hematocrit, and electrolytes. Base line investigations should include liver and kidney function tests, prothrombin time/activated partial thrmoboplastin time, and chest X-ray (in case of pulmonary complaints) and ultrasonography for assessing size of ovaries and ascitic fluid volume.[1]

Fluid management to maintain intravascular volume and adequate urine output using crytalloids (5% dextrose in normal saline). Sometimes intravenous albumin (100 ml of 20% solution, over 4 h) is given to expand intravascular space and replenish the albumin.[1]

Thromboprophylaxis should be initiated by starting subcutaneous heparin (5000 units daily twice). Paracentesis can be resorted if there is severe discomfort/pain, compromised renal output or pulmonary compromise either abdominally or transvaginally.[8] Early OHSS has relatively shorter course and usually does not last beyond 14 days, but if the patient conceives and develops late OHSS, then the course can be more protracted.[1]

In our case, patient developed severe OHSS which further worsened and developed into critical OHSS. Routine conservative measures were instituted and patient was put under intensive care. Due to development of pleural effusion and ascitis, the patient complained of dyspnoea, hence pleural tapping followed by abdominal paracentesis was done to relieve the respiratory symptoms. In view of drop in serum albumin levels, intravenous albumin was given. However, after three doses, patient developed severe reaction to albumin, precluding its further usage. However, due to rapid collection of ascitic fluid and consequent development of dyspnea, frequent paracentesis was resorted to ameliorate the symptoms.

This lead to further fall in albumin levels and with oral high protein intake proving to be highly inadequate, alternative means of albumin replacement became imperative. Hydroxy ethyl starch was considered as an alternative volume expander, but due to albumin levels falling below 2 g/L, finally thawed plasma was considered. Inputs from medical oncologists were taken regarding usage of thawed plasma in such clinical conditions where rapid albumin replacement was required. It served the dual purpose of rapid albumin replacement and volume expander. We decided to use it after weighing its risks and benefits due to continued deterioration in the patient's condition and lack of viable alternatives to reverse the trend.

Dramatic improvement in the patient's clinical condition with increased urine output and no further increase in ascitic fluid were noted. The serum albumin level also increased by approximately 0.8 gms/dL following the thawed plasma transfusion within 48 h. No further paracentesis was required and the patient was discharged and followed up on outpatient basis. Unfortunately, it turned out to be a non-viable pregnancy which was terminated.

Thawed plasma differs from thawed fresh frozen plasma in having lower amount of certain coagulation factors such as factor V and VIII. Usage of thawed plasma for volume expansion and albumin replacement is not among the recommended indications.[9] Concerns regarding transmission of transfusion related infections remain. However, such worries are there even with intravenous albumin. Theoretically speaking, a more rapid replacement of albumin using thawed plasma may help resolve the pathology earlier precluding the need for termination of pregnancy. However, we need to further evaluate our findings before advocating such measures.

Although rare, the case highlights a dilemma faced by infertility specialists while treating critical OHSS. When the duration of OHSS gets unduly prolonged and few commonly used therapeutic measures do not bring any improvement in the patient's condition, drastic measure like termination of pregnancy remain the only practical option with the clinician. Laparotomy and bilateral partial oophrectomy has been suggested as another aggressive step short of termination of pregnancy.[5] Our case demonstrates an alternate therapeutic measure before such drastic measures are called for. Further studies are needed to establish the role of thawed plasma as a therapeutic alternative in severe OHSS.

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