A Case of Severe Ovarian Hyperstimulation Syndrome

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Abstract Ovulation induction has been an important mode of treatment of infertility. Ovarian stimulation may result in a supraphysiologic response leading to an iatrogenic complication known as the ovarian hyperstimulation syndrome (OHSS). This syndrome is potentially a lethal condition, the pathophysiologic hallmark of which is the accumulation of massive extravascular exudate combined with profound intravascular volume depletion and hemoconcentration. We report a case of severe OHSS with very large ovaries in a 35 year old case of embryo transfer. The patient presented to the emergency department with abdominal pain, massive ascites, respiratory distress and amenorrhea. The patient was managed symptomatically with no complications. Although ovarian hyperstimulation is a rare entity, it is important that the physician recognizes this condition. Prompt diagnosis and successful management is likely to avoid serious and rapid development of complications.

Keywords Ovarian stimulation · Ovarian hyperstimulation syndrome · Gonadotropin · Ovulation induction · Assisted reproduction · Anti cardiolipin antibodies

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Introduction

Ovarian hyperstimulation syndrome (OHSS) involves an increase in vascular permeability resulting in a fluid shift from intravascular to third space compartments such as the peritoneal and thoracic cavities. First described in 1943, the first fatal cases were documented in 1951 [1]. This syndrome occurs almost exclusively during assisted reproductive technology (ART) cycles, although OHSS might also occur during ovarian stimulation using gonadotropins and clomiphene citrate.

Case Report

The patient, a 35 years $P_0L_0A_3$ woman, was admitted in Emergency Department with respiratory distress and severe abdominal distension. Her pulse was 130/min, BP 130/80 mm Hg, oxygen saturation 90 %. The physical examination revealed reduced bilateral air entry into lungs and a severely distended abdomen with evidence of ascites but without any palpable mass in the abdomen.

The patient was on regular gonadotropins injection for infertility treatment, which continued even after she developed moderate fluid in the abdomen. This was followed by embryo transfer 15 days back. 4 days after embryo transfer, she developed uneasiness and got herself admitted to a local hospital, where she was treated for shock with a lot of intravenous fluid. This aggravated her condition and 6 days later, she was referred to our hospital.

Her menarche had occurred at the age of 12 years. Her cycles were irregular since then (4–5 days/2–3 months). She took multiple treatments for her irregular cycle (Bromocriptine and oral contraceptive pills). Her last menstrual period occurred 2 months back as she was down regulated

with GnRh hormones. Married 15 years back, her first conception through IVF 10 years back resulted in miscarriage at 6 weeks. Then, a twin conception by intracytoplasmic sperm injection resulted in spontaneous abortion at 20 weeks, 2 years back and an IUI conception resulted in spontaneous miscarriage 1 year back. Embryo transfer was done 15 days prior to admission to our hospital. She was a known case of hypothyroidism [L-thyroxine (75 µg)]. Family history was negative for both polycystic ovary syndrome and hydatiform mole. However both mother and sister had conceived after 5 years of marriage.

Laboratory tests revealed serum electrolytes, urea, creatinine, hemoglobin, MCV, MCH, MCHC, amylase, lipase, within reference ranges. Other laboratory results at admission were as under (reference values in parenthesis): total leucocyte count 32,500 cells/cumm (4,000–10,000), neutrophil 83 % (40–80), total red blood cell count 5.38 million/cumm (3.8–4.8), platelets 5.10 lakhs/cumm (1.5–4), hematocrit 47.9 % (45–50), prothrombin time 18.6 s (control 13), INR 1.40, activated partial thromboplastin time 42 s (control 28 s), total Bilirubin 1.7 mg/dL (up to 1), direct Bilirubin 1.2 mg/dL (up to 0.3), aspartate transaminase 48 U/L (0–35), alanine transaminase 54 U/L (0–35), Alkaline phosphate 160 U/L (30–279), Total protein 5.4 g/dL (6.5–8.1), albumin 2.6 g/dL (3.5–5), lactate dehydrogenase 245 U/L (266–500), D Dimer 5,336.36 ng/mL (<500), Antithyroid peroxidase 89.6 IU/mL (<34). Anti phospholipid antibodies and anticardiolipin antibodies IgG and IgM were positive. Protein C and protein S levels were low. The pleural fluid analysis revealed cell count 400/cumm, predominantly neutrophils, and no organism on gram stain. Ascitic fluid tested showed cell count 100/cumm, protein 3.5 g/dL, amylase 39 U/L.

Abdominal and transvaginal ultrasonography showed that the size of the uterus was 9.1 cm × 6.0 cm × 3.3 cm, endometrial thickness was 5.9 mm, right ovary 236 cubic cm, left ovary 290 cubic cm (Fig. 1) with multiple follicles, the largest measuring 40 × 30 mm. The uterine cavity had a large amount of ascites (Fig. 2). Echo showed normal LV systolic function along with presence of large pleural effusion (Fig. 3). A diagnosis of severe OHSS, was made based on elevated white blood cell count, hematocrit >45 %, elevated liver profile, elevated Ddimer, enlarged ovaries with multiple ovarian cysts in USG, Chest X-ray-pleural effusion, interstitial oedema, ascites.

The patient presented with shock, at admission. After management of shock, she was shifted to critical care unit. She was given symptomatic management with close monitoring. Daily clinical examination with abdominal girth measurements, weight, breath sounds, pleural tapping and paracentesis started and continued for 4–5 days. Average fluid removed was 1–2 L/day. She improved with

Fig. 1 USG features after 1 weeks of treatment (right ovary)

Fig. 2 Uterus with moderate ascites

Fig. 3 Chest X-ray on admission showing bilateral pleural effusion

Fig. 4 Chest X-ray after treatment

fluid restriction, antibiotics (piperacillin and tazobactam), heparin, albumin, cabergolin, progesterone. The serum HCG levels and TVS report from day 18 of embryo transfer were as shown in Table 1.

Laboratory parameters normalized and pleural effusion resolved (Fig. 4) and she was discharged after 24 days of hospital stay, in stable condition.

At follow-up after 1 week of discharge from hospital, her serum HCG level was 680 IU/mL. In spite of all pregnancy support, her HCG levels did not rise, neither was embryo seen in transvaginal sonography. She underwent suction evacuation for the missed miscarriage and products sent for karyotyping were normal. Six weeks after evacuation, the patient was asymptomatic and advised IVF with controlled ovarian stimulation protocol after 6 months.

Discussion

Ovarian hyperstimulation syndrome may rarely be associated with a spontaneous ovulatory cycle, usually in the case of multiple gestations, hypothyroidism or polycystic ovary syndrome [2]. Primary risk factors for the development of OHSS include young age, polycystic ovary syndrome (PCOS), prior OHSS, high basal anti mullerian hormone levels, while secondary risk factors are high or rapidly

rising estradiol (E2) levels, high number of follicles, high vascular endothelial growth factor (VEGF) and high Inhibin B levels [3]. As many as one in three (33 %) women develop mild OHSS. About one in 20 (5 %) women develops moderate or severe OHSS. A serum estradiol (E2) level of 12,315 pmol/L (3,354 pg/mL) on day 11 of ovarian stimulation gives a sensitivity and specificity of 85 % for the detection of women at risk for OHSS [4].

The syndrome is associated with the process of ovulation induced by luteinizing hormone or human chorionic gonadotropin. Following ovulation, one or more substances produced by the ovary are liberated in excess, increasing capillary permeability, resulting in the clinical features of the syndrome. It may well be that the syndrome is not triggered by a single mechanism but by the production and secretion of several substances acting in concert. These may include prostaglandins, cytokines, interleukins, the ovarian renin angiotensin system, vascular endothelial growth factor, and nitric oxide [5]. Enlargement of the ovaries causes abdominal pain, nausea and vomiting. When OHSS is classified as severe, the subsequent clinical picture is the result of increased vascular permeability and ascites, leading to dehydration with haemoconcentration [6]. The extravascular albumin-rich exudate accumulates in the peritoneal cavity, occasionally in the pleura, and rarely in the pericardiac space. Intravascular hypovolemia with

Table 1 Serum HCG levels and trans vaginal sonography findings

	Day 18	Day 20	Day 22	Day 24	Day 26	Day 28
Human chorionic gonadotropin	197.1	178.3	197.8	297.5	312.13	648.19
Transvaginal sonography	No sac No adnexal mass	No sac No adnexal mass	No sac No adnexal mass	Endometrium 12 mm No adnexal mass	Endometrium 14 mm No adnexal mass	Endometrium 15 mm No adnexal mass

concomitant development of edema, ascites, hydrothorax and/or hydropericardium can lead to life-threatening complications including thromboembolic events and even death [7].

Antiphospholipid antibodies (APLA) are a family of immunoglobulins that recognize a variety of plasma proteins in association with anionic phospholipids. These antibodies may lead to a number of clinical syndromes including venous and arterial thromboses, thrombocytopenia, and recurrent fetal loss [8]. Ovarian stimulation in infertile women with PCOS poses a particular challenge, as many of these women exhibit exaggerated response to clomiphene citrate, gonadotropins, ovarian drilling, insulin sensitizing agents or assisted reproductive technology (ART), resulting in an increased risk of ovarian hyperstimulation syndrome (OHSS) and multiple gestations [9]. The recent implementation of four new modalities, the GnRH antagonist protocol, GnRH agonist (GnRHa) triggering of ovulation, blastocyst transfer and embryo/oocyte vitrification, renders feasible the elimination of OHSS in connection with ovarian hyperstimulation for IVF treatment [10].

From the outset of treatment, our patient, who had severe respiratory distress, was protected from possible pulmonary emboli. We gave a low molecular weight heparin. Thoracocentesis is safe and efficient for the treatment of hydrothorax and lung collapse in cases of OHSS and may be repeated as often as necessary [11].

Conclusion

If the OHSS develops within an IVF protocol, it may be prudent to postpone the embryo transfer since the establishment of pregnancy can lengthen the recovery time or contribute to a more severe course as in our case. Physicians can reduce the risk of OHSS by monitoring gonadotropin therapy and by using this medication cautiously.

The patients with OHSS in early stage must be identified and treated urgently and with multidisciplinary management. If left untreated, OHSS can result in serious health complications and even death.

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