CEOG Clinical and Experimental Obstetrics & Gynecology

Severe ovarian hyperstimulation syndrome in a naturally conceived singleton pregnancy after ovulation induction: a case report

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Summary

Objective: To present a case of severe ovarian hyperstimulation syndrome (OHSS) in a naturally conceived singleton pregnancy after ovulation induction. *Case:* A 31-year-old woman with polycystic ovarian syndrome (PCOS) underwent ovulation induction therapy. Six days later, she was admitted to the present hospital with the symptoms of OHSS. Ultrasonography confirmed the single live intrauterine pregnancy, as well as enlarged multicystic ovaries and marked ascites that required abdominal paracentesis. The woman was treated with intravenous infusion, exogenous colloid supplementation, essentiale liver treatment, rocephin anti-infective therapy for skin lymphangitis of left lower limb, and drainage of the ascites. She recovered by day 45 of admission. *Conclusion:* Severe OHSS may develop in women with PCOS who undergo ovulation induction therapy. Serious complications may develop rapidly and therefore OHSS must be treated urgently and with multidisciplinary management.

Key words: Ovarian hyperstimulation syndrome; Pregnancy; Ovulation induction.

Introduction

Ovarian hyperstimulation syndrome (OHSS) is a potentially life-threatening complication of ovarian hyperstimulation, mostly resulting from exogenous gonadotropin therapy. OHSS is characterized by a cystic enlargement of the ovaries and acute fluid migration from the intravascular space to the third space, due to capillary hyperpermeability [1], which leads to electrolyte imbalance, coagulopathy, edema, and ascites, as well as hemoconcentration, thrombosis, pleural and pericardial effusions, acute renal failure, respiratory distress syndrome in severe cases, and even death [2, 3].

OHSS is relatively common and its incidence is increasing with an increase in controlled ovarian hyperstimulation cycles. OHSS can be classified into mild, moderate, and severe forms [4], which occurs respectively in 20-33%, 3-8%, and 0.1-2.0% of women undergoing in vitro fertilization (IVF) [5-6]. Although the mechanisms involved in the occurrence of OHSS remain unclear, it is currently believed that its occurrence is associated with a wide range of factors including young age, low body weight, polycystic ovarian syndrome (PCOS), higher doses of gonadotropins, previous episodes of hyperstimulation, vascular endothelial growth factor (VEGF), renin-angiotensin system, inflammatory cytokines, α2 macroglobulin, etc. [7-13].

It has been reported that symptoms of OHSS do not vanish immediately after pregnancy, but may instead persist or even worsen due to the stimulation of human chorionic gonadotropin (hCG) and estradiol (E2) during pregnancy [14, 15]. In this report, the authors presented a 31-year-old woman who was diagnosed with severe OHSS in a naturally conceived singleton pregnancy after ovulation induction, and described the course of diagnosis and treatment.

Case Report

The present case concerns a 31-year-old woman with infertility due to PCOS. She had oligomenorrhea with menstrual cycle intervals of 30-180 days. After signing the informed consent, she started receiving ovulation induction therapy in the fertility center in the present hospital on May 5th, 2013. Specifically, she was subjected to daily stimulation with human menopausal gonadotrophin (hMG) (ten injections of hMG 75 IU in total). As a result, three mature follicles and ten small follicles developed as shown by ultrasonographic examination. The patient received a subcutaneous injection of short-acting decapeptyl (0.1 mg of triptorelin) when her serum E2 concentration reached 5,600 pg/ml. The patient began attempting to conceive when ultrasonographic exams confirmed that the follicles had disappeared at 48 hours following decapeptyl injection. She then received intramuscular injection of progesterone (40 mg, qd*7 days) and oral duphaston tablets (ten mg, bid). She started to complain of sickness, nausea, and vomiting with a distended abdomen on May 9th and developed oliguria on the next day (seven days after ovulation). Her serum level of hCG, progesterone, pro-

Revised manuscript accepted for publication November 24, 2015

Clin. Exp. Obstet. Gynecol. - ISSN: 0390-6663
XLIV, n. 2, 2017
doi: 10.12891/ceog3473.2017

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Table 1. — *Serum level of hCG, and progesterone (P) and E2 during the 45-day hospitalization.*

	Date	Gestational weeks	Serum HCG (IU/L)	Serum P (ng/ml)	Serum E2 (pg/ml)
1	May 10th	3	22.37	40	761.04
2	May 13th	$3^{3/7}$	59.42	40	2732.97
3	May 16th	$3^{6/7}$	251.86	60	4300
4	May 17th	4	424.61	60	4300
5	May 21st	$4^{4/7}$	1672	60	4300
6	May 22nd	$4^{5/7}$	2638	80	9765.123
7	May 24th	5	4618	79.28	9757.493
8	May 27th	$5^{3/7}$	8003	82.96	10068.66
9	May 29th	$5^{5/7}$	13170	83.93	8553.678
10	Jun 3rd	$6^{3/7}$	32423	85.57	8741.144
11	Jun 11th	$7^{4/7}$	59908	89.69	4647.411
12	Jun 17th	$8^{3/7}$	82043	120	3219.074
13	Jun 24th	$9^{3/7}$	96965	144.21	5782.016

Table 2. — *Summary of ascites during the 45-day hospitalization.*

	Date	Gestational weeks	Amount of ascites (ml)
1	May 14th	$3^{4/7}$	1500
2	May 16th	$3^{6/7}$	3700
3	May 18th	$4^{1/7}$	4300
4	May 20th	$4^{3/7}$	2000
5	May 21th	$4^{4/7}$	5400
6	May 23th	$4^{6/7}$	4400
7	May 28th	$5^{4/7}$	4000
8	May 30th	$5^{6/7}$	5500
9	Jun 5th	$6^{5/7}$	6300
10	Jun 9th	$7^{2/7}$	6000
11	Jun 14th	8	6100
	Total		49200

lactin, and E2 was 22.37 mIU/ml, 40.00 ng/ml, 22.51 mIU/ml, and 761.04 pg/ml, respectively. She then received intravenous infusion of dextran 40 and 10% glucose. On May 11th, she was admitted to the emergency unit in the present hospital with symptoms including bloating, nausea, vomiting, oliguria, and dark yellow urine. Vaginal bleeding, waist soreness, and stool abnormalities were absent. On examination she was pale and ill-looking, but was conscious and afebrile, weight: 59 kg, temperature: 37°C, pulse: 72/minute, blood pressure: 120/70 mmHg, and respiratory rate: 19/minute. Abdomen was distended with abdominal girth of 97 cm. She had normal abdominal breathing and bowel sounds and shifting dullness (+) without any abdominal tenderness. Based on the described clinical presentation, she was provisionally diagnosed as OHSS and pregnancy (an early intrauterine or ectopic pregnancy) and was then hospitalized in the hospital.

The patient was subjected to thorough exams immediately after admission. Routine blood tests revealed elevated red blood cell volume (0.534), hemoglobin (180.3 g/L), neutrophils (87.4%), white blood cells ($21.63*10^9$/L), normal platelets ($295*10^9$/L), and red blood cells ($5.61*10^{12}$/L). The level of fibrinogen was 5.23, and prothrombin time and partial thromboplastin time was 13.3 and 28.7, respectively. Liver and kidney function were both in normal range. Ultrasonographic examination identified no suspicious areas in the chest. She had a plump uterus with 13-mm endometrium. No gestational sac was present. The size of the left and right ovary was 79×68×67 and 88×65×84 mm, respectively. The fluid in the rectouterine pouch was 68×25 mm. The peritoneal effusion was indicated by anechoic areas in the lower abdomen (105×47 mm), the front of the right kidney (67×46 mm), in the left upper quadrant liver (97×26 mm), and before the liver (18 mm) in ultrasonographic exams.

The patient received intravenous infusion of dextran 40, saline, albumin, and fraxiparine. After one day of treatment, the urine volume significantly increased (approximately 2,800 ml in 24 hours). Symptoms of nausea and vomiting were alleviated, but the abdominal distension remained apparent, and the weight and abdominal girth obviously increased. On May 14th, abdominal distention was aggravated. The patients complained of poor appetite, difficulty breathing, and reduced amount of urine. Ultrasonographic exams revealed the presence of ascites 118 mm with bilateral pleural effusion (31 mm on the left and right 27 mm on the right). Her coagulation function was normal. Routine blood tests showed elevated red blood cell volume (0.494), neutrophils (89.4%), white blood cells ($14.00*10^9$/L), and normal hemoglobin (160 g/L). The serum levels of E2, progesterone, and hCG were 10030.0 pg/ml, 40.00 ng/ml, and 59.42 mIU/ml, respectively (Table 1). Abdominal paracentesis of 1,500 ml of ascites was performed due to intolerable abdominal distention and breathing difficulties. On May 16th, the patient developed abnormal liver function with elevated serum alanine aminotransferase (130 u/L) and aspartate transaminase (178 u/L) and then received liver treatment with essentiale forte. On May 18th, another abdominal paracentesis of 5,000 ml of ascites was performed due to persistent, intolerable abdominal distention. The patient was subjected to daily paracentesis until abdominal distention was alleviated on May 23th. On May 27th, liver function was restored and the treatment with essentiale was discontinued. The patient developed left leg swelling and slightly elevated skin temperature. But ultrasonographic exams identified no abnormities in bilateral iliac veins, inferior vena cava, bilateral lower extremity arteries, or lower extremity deep veins. A diagnosis of skin lymphangitis of left lower limb was made after the consultation from specialists in the peripheral vascular division of the present hospital. The patient received anti-infective therapy with rocephin and magnesium sulfate for topical application, and the swollen left leg subsided on June 5th. On June 10th, ultrasonographic exams demonstrated that left and right ovary was 81×74×66 mm and 74×59×67mm, respectively. The ultrasonography also identified an intrauterine gestational sac (36×19 mm), an yolk sac (five mm), and an embryo (14.5 mm) with heart beat, confirming the single live intrauterine pregnancy.

The patient developed recurrent abdominal distension with ascites, abdominal girth up to 103 cm and body weight up to 68 kg during hospitalization, and therefore was subjected to paracentesis for a total of 11 times resulting in the removal of approximately 4.92 L of ascites (Table 2). The patient received human serum albumin (ten g/unit*113 units) during hospitalization. After the symptoms especially abdominal distension were significantly improved, she was discharged on June 25th (a total of 45 hospital days). The baby was delivered, and both the mother and baby were completely healthy.

Discussion

The classifications of OHSS divided the clinical symptoms into three groups: mild, moderate, and severe according to its severity. Severe OHSS is the rarest and life-threatening form, characterized by symptoms such as nausea, an ovarian diameter > 12 cm, ascites, pleural effusion, haemoconcentration, and hepatic dysfunction. The present case falls within these limits, and was therefore diagnosed as severe OHSS. In the present case, severe OHSS in association with a naturally conceived singleton pregnancy after ovulation induction was observed in a 31-year-old woman with PCOS. Cases of severe spontaneous OHSS associated with pregnancy and PCOS have been previously reported [15, 16], thus sharing a common background of excess ovarian follicle growth as in the present case. Generally, it is much more difficulty to predict the occurrence of OHSS in a naturally conceived pregnancy after ovulation, compared with IVF probably due to an underestimation of the number of follicles and eggs in natural conception. In contrast, the number of follicles is easily determined during IVF.

OHSS is typically associated with gonadotropins during ovulation induction and rarely occurs after spontaneous pregnancy. Although the pathogenesis of OHSS is currently poorly understood, exogenous and/or endogenous hCG has been suggested as an etiologic factor. VEGF has been known to play an important role in the pathogenesis of OHSS [10, 17]. Therefore, it has been suggested that OHSS could be prevented by inducing ovulation with LH or GnRH analogs, which prevent the overexpression of VEGF [18]. However, in the present case, the occurrence of severe OHSS was observed in the patient subjected to ovulation induction with GnRH-a, suggesting a risk of OHSS associated with GnRHa-induced ovulation.

In the present case, early onset of OHSS with severe abdominal distention and oliguria developed at day 7 after ovulation probably due to low food and water intake associated with the patient's eating habit. Outpatient intravenous dextran infusion failed to alleviate the symptoms. Furthermore, the serum hCG level reaches 22 mIU/ml at day 7 after ovulation, whereas hCG typically begins to rise at day 9 after IVF and embryo transfer in a multiple pregnancy. In addition, since reduced serum E2 and/or progesterone level often indicates the alleviation of OHSS, the E2 and progesterone concentration in the present case remained high for over 40 days, with a peak level of 10,068.66 and 120.01 ng/ml for E2 and progesterone (Table 1), respectively, suggesting the disease persisted longer.

Several complications developed in the severe OHSS in the present case including abnormal liver function with elevated serum alanine aminotransferase, ascites, pleural fluid, and skin lymphangitis of left lower limb. Although the mechanism underling the elevated aminotransferases remains speculative, it has been suggested to be associated with hepatic cell destruction caused by ascites [19, 20], together with increased vessel permeability and hepatic edema in severe OHSS [21]. In the case reported here, pleural effusion occurred during the initial days of treatment. There are various comments on the cause of the pleural fluid. It is believed that high estrogen levels in the severe forms of OHSS usually cause pleural effusion [22], as in the present case (Table 1). Alternative explanation has been proposed that pleural effusion might originate from the fluid shift from abdominal ascites [22]. At day 20 after admission, the present patient developed left leg swelling with slightly high skin temperature that was diagnosed as skin lymphangitis of left lower limb and treated accordingly by specialists in the peripheral vascular division of the present hospital, suggesting that OHSS must be treated promptly with multidisciplinary management.

Management of OHSS should be tailored according to its severity. Generally, hospital admission should be recommended in women with severe OHSS, who will be subjected to at least daily assessment until resolution of the condition. Multidisciplinary management may be considered for women with severe OHSS who have developed persistent complications and need intensive care, including intravenous infusion of albumin and dextran 40 in order to increase the colloid osmotic pressure, anticoagulation treatment with heparin, increasing renal blood flow with dopamine, abdominal paracentesis to relieve distention, and aspiration of follicular fluid. In the present case, the patient underwent several abdominal paracentesis under ultrasound guidance during the 45-day hospitalization due to intolerable abdominal distension, resulting in the removal of large amount of ascites (4.92 L in total, Table 2). In addition, the patient received a large amount of albumin infusion (11 g/unit*113 units) to improve the microcirculatory haemodynamics, which is very rare among OHSS patients. Such a treatment would not be available in a hospital without sufficient stock of albumin.

In summary, OHSS is a relatively common and potentially life-threatening complication associated with ovulation induction. Infertility treatment in women with PCOS is a risk factor for OHSS. It is generally recommended to use GnRH-a as a substitute for hCG in ovulation induction, although there is still a risk of OHSS. For PCOS patients, a low-dose and step-up protocol should be carried out routinely to avoid the occurrence of OHSS. The patients with severe OHSS who have developed persistent complications must be treated urgently with multidisciplinary management. If left untreated, OHSS can result in serious health complications and even death. However, women should be reassured that there is no evidence of a risk of congenital abnormalities associated with OHSS, and pregnancy may continue normally despite the disease.

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