

Severe Ovarian Hyperstimulation Syndrome Complicated by Bilateral Ectopic Gestation

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Ovarian hyperstimulation syndrome is a frequent complication of ovulation induction in the polycystic ovarian syndrome patients. In some patients it may induce severe morbidity, with ovarian enlargement, ascites, hydrothorax, low blood pressure, and hemoconcentration, oliguria which may end in renal failure, liver dysfunction and thrombotic episodes. It is also well known that pregnancy aggravates the severity of hyperstimulation and makes management more complicated. We describe here a case of severe and prolonged hyperstimulation which was complicated by bilateral ectopic pregnancy and review the challenges and measures associated with its prevention and treatment.

Introduction and background

Several authors have confirmed the efficacy and safety of the low-dose gonadotropin ovulation induction in polycystic ovarian syndrome (PCOS) patients¹⁻⁵. It is now established that the low-dose-step-up induction of ovulation is the method of choice in clomiphene-resistant cases of PCOS⁶. As a complication, mild ovarian hyperstimulation syndrome (OHSS) occurs in 4.9% of cases, moderate in 1.5% and very rarely the severe form. It is fair to say now that where gonadotropin therapy is needed the *low-dose step-up protocol* has the highest ratio of effects compared to side effects.

This case study reports an unusual case of persisting OHSS in infertile women with PCOS, who was receiving treatment with recombinant FSH. Her clinical course was further complicated by

underlying bilateral ectopic gestations. This case was reported because of its rarity together with the clinical and therapeutic challenges it posed.

Case report

A 28-year-old, nulliparous Bahraini woman who was married for 18 months, was referred from a private clinic to Accident and Emergency Department with history of lower abdominal pain and nausea of 12 hour duration. Her history suggested that she received investigations and treatment for primary infertility and oligomenorrhea, associated with PCOS in that private clinic. In the previous two weeks prior to admission she received 21 injections of Puregon (recombinant follicle stimulating hormone). Treatment was started on the third day of cycle and the dosage adjusted according to the follicular size. Her last menstrual period was 8 weeks

earlier. On admission, there was no vaginal bleeding, chest pain or shortness of breath. Her vital signs were normal. The chest was clear. Abdominal examination revealed marked tenderness in the iliac fosse. Bilateral, lower abdominal masses equal to 18 week's pregnancy size were palpable. The pregnancy test was negative. Ultrasound scan of lower abdomen revealed bilaterally enlarged multiple ovarian cysts. The largest was 3 cm. in diameter. The uterus was empty with a

In view of these findings laparotomy and repair of a ruptured right ovarian cyst was performed

thickened endometrial interphase. Free peritoneal was seen in the Pouch of Douglas. A diagnosis of ovarian hyperstimulation syndrome was made. CBC, liver function tests, coagulation profile and chest X-ray were done. After admission to the Gynecological ward the patient continued to have lower abdominal pain and vomiting and was noticed to be oliguric. Her albumin was 27 g/l, the Hb 7.5 g/dl, haemtocrit 0.53 l/l, Creatinine 130 u mol/l. She was put on 4 liters of 0.5 NaCl drip, Fragmin (fractionated heparin) injection, anti-emetic and IV Rocephin (cephetriacon).

Twelve hours after admission she developed increasing difficulty of breathing and continued to be oliguric. A physician was consulted and advised the following investigations: Arterial blood gases (ABG), chest X-ray, ECG and cardiac enzymes. He advised continuation with hydration and to give Lasix (frusemide) 120 mg IV. Meanwhile, the patient developed dyspnea, tachypnea, hypotension and sweating. The ECG showed sinus rhythm, ABG indicated

normal saturation and evidence of metabolic acidosis. Urea and electrolytes were normal except for Magnesium level which was 0.64 m mol/dl, and replaced with Mg sulphate. It was decided then to move the patient to the ICU, however, in the following hours she slightly improved. On the third day of admission the patient became dyspneic again and complained of abdominal distension. She was reevaluated by a physician who repeated the chest X-ray, ABG, and albumin level. The results showed bilateral pleural effusion hypoalbuminemia, metabolic acidosis and generalized anasarca. The physician advised: pulse oximetry, oxygen, correction of acidosis with bicarbonate, tapping of the ascetic fluid and to insert chest drainage. Other tests such as blood sugar, acetone lactic acid and serum Calcium were requested. In the following day she had a 8.5 Fr. Pigtail catheter inserted under ultrasound guidance into the peritoneal cavity. A similar 8 Fr catheter was inserted in the right pleural space. Total drainage of 3.8 liters occurred and the patient had no dyspnea; she had markedly improved. Albumin replaced with infusion which continued for the next two days. On day 9, she was asymptomatic and advised discharge from hospital.

One day later she was readmitted to hospital with lower abdominal pain, shortness of breath, tachypnea, tachycardia, abdominal distension and severe vulval edema. A chest X-ray revealed recurrence of pleural effusion and the abdomen was also distended with ascetic fluid. Ascitis tapping was repeated draining 1.5 litre, albumin infusion and Lasix were given. Respiratory difficulty increased and admission to the ICU was sought, however there were no beds available. In the labour ward, a pleural tapping was repeated, echocardiography ECHO showed normal heart chambers, good left ventricular function and normal valves. There was no pericardial effusion. The abdominal and pleural taps revealed hemoperitonium and

hemothorax. Complete blood count together with coagulation profile, fibrinogen, LFT, D dimer test, fibrin degradation products (FFP) and six units of packed cells were cross-matched.

In view of these findings laparotomy and repair of a ruptured right ovarian cyst was performed. Aspiration of multiple cyst in both ovaries was done. No evidence of ectopic pregnancy was found. The patient was ventilated during surgery but spontaneous respiration was later reestablished. The early post operative period was uneventful.

On day 11 of her second admission the patient was still draining from the pleural and abdominal taps, and the serum albumin required replacement. On day 12 the patient complained of recurrence of abdominal pain. Ultrasound was conducted and done and showed no intrauterine gestational sac. No adnexal mass apart from few persistent ovarian cysts were observed, however, B-hCG was 2877 units. The patient gradually recovered. She was advised on the possibility of ectopic gestation and then discharged with a later appointment to repeat the B-hCG test.

Ten days after second discharge, she was readmitted with right quadrant pain of

Several precautions and treatment regimen have been suggested in order to minimize the risk of OHSS

one day duration. Her Hb dropped to 7.5 Gm% and was transfused with two units of blood. Although the ultrasound scan showed no intra or extra uterine gestational sac, apart from multicystic ovaries and free fluid in the peritoneum

it was decided to do an exploratory laparotomy as the B-hCG was rising and ectopic gestation cannot be excluded. In the following morning the operation was done and the findings were as follows: hemoperitonium of 1.8 liter, bilateral cystic ovaries, the left tube was the site of ruptured ectopic for which salpingectomy was performed, and the right tube was tortuous and distended with blood. Despite attempt at salvaging the patency of this tube it was not possible. The histopathology reports confirmed the presence of ectopic trophoblastic tissues in both tubes. The patient made good recovery and was discharged home on the six postoperative day.

Discussion

Infertile patients with PCOS are particularly sensitive to treatment with gonadotropins which are used for induction of ovulation⁵. Several precautions and treatment regimen have been suggested in order to minimize the risk of OHSS: (1) ultrasound measurement of the polycystic ovary prior to the ovarian stimulation (2) serial measurements of the follicles or their function during treatment by ultrasound and urinary assay of B-estradiol and the adjustment of the gonadotropins dosage accordingly. (3) To follow a low-dose protocol particularly when administering puri-

fied estrogen or the recombinant forms of gonadotropins. (4) Administration of gonadotropins only if the diameter of the follicle is ≥ 16 mm. (5) Withholding the hCG injection if the follicles were very large. All these measures were applied with the aim of minimizing the risk and severity of OHSS⁹.

If the patient does not become pregnant during the first cycle, she should begin her next cycle with a dose that is half an ampoule less than the maximal dose of the previous cycle

The step-up protocol⁶⁻⁷ consists of starting the stimulation cycle on the third day of cycle with 75 IU of a highly purified FSH preparation as SC daily injection. Stimulation is monitored by ultrasonography and estradiol determination. The stimulation is continued

until the largest follicle is 16-18mm in diameter. At this time injections of hCG 5000-10000 IU are given IM to induce ovulation. Human chorionic gonadotropin is withheld when, at the time the largest follicle is 18 mm, more than three follicles are greater than 16mm or more than six follicles greater than 13mm are present, or the estradiol level exceeds 300 p mol/l.

If after the end of 10 days of stimulation no sign of follicular growth observed, the FSH is increased by half an ampoule per day, this is repeated every 7 days as long as follicular growth is absent. If multi follicular growth occurs during the first cycle on one ampoule per day, the next cycle is started with half an ampoule per day. This repeated every seven days as long as the follicular growth is absent.

If the patient does not become pregnant during the first cycle, she should begin her next cycle with a dose that is half an ampoule less than the maximal dose of the previous cycle. This dose is maintained for seven days. Another precaution against OHSS in cases of PCOS is that no luteal support is given either by progesterone or by hCG. Further more it is recommended not to use GnRH analogs in combination with the low-dose step-up protocol. It is quite

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unusual if the above precautions were followed to encounter a case of severe or persisting OHSS unless a pregnancy ensues. In such cases, severe and persistent OHSS could mask any bleeding from the gestational endometrium unless the possibility of ectopic pregnancy was kept in mind. An early negative B-hCG should not exclude this possibility and serial ultrasound and B-hCG should be done in all cases of severe OHSS.

Once severe OHSS occurs, hospitalization is indicated for managing this condition. Management include the giving of IV fluid hydration, correction of the electrolytes imbalance and treating the cardiovascular and coagulation changes. Serial ultrasound and B-hCG are essential for monitoring the progress of the case. Occasionally paracentesis may be used as a minimally invasive form of diagnosis in cases of severe OHSS after ovulation.

To the best of the authors' knowledge there have been only four similar cases

reported in the last five years: one reported from China⁹, the second two were cases of OHSS with heterotopic pregnancies⁹⁻¹⁰ and the fourth, a case of OHSS complicated with primary peritoneal pregnancy¹¹.

In reviewing our reported case we cannot be sure about the type of induction protocol done other than that she received 21 injections of Puregon and that no injection of chorionic gonadotropin was given. We also note that on her first day of admission there was no evidence of pregnancy by the B-hCG or ultrasound, but this can be understood because she was in her sixteenth day of cycle. After the initial abdominal tapping and other management she improved and discharged home eight days later.

At the time of the second admission, the main problem was the recurrence of signs and symptoms of severe OHSS for which her management was directed. Late during that admission the pregnancy test became positive with a rising

titer, but the ultrasound showed an empty uterus with no evidence of extra uterine gestation. This was sufficient to raise the suspicion of ectopic, however, the possibility of an early intra uterine pregnancy that cannot be recognized on ultrasound at this very early stage was also considered. The hemoperitonium which occurred later was associated with a ruptured ovarian cyst and during the laparotomy the tubes were inspected and no evidence of ectopic pregnancy was found.

Prior to the second discharge the B-hCG titer was 4850 IU but the ultrasound failed to show any evidence of intra or extra uterine pregnancy. She was nevertheless warned about the possibility of ectopic and advised to return if she develops any symptoms.

We conclude that this case was complicated enough, and although one is always wiser in retrospect, the lesson is that the possibility of ectopic gestation should always be kept in mind in managing cases of OHSS.