A severe case of ovarian hyperstimulation syndrome with pulmonary thromboembolism
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Citation

Abstract
Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic, life-threatening complication of ovarian stimulation. Renal and hepatic dysfunction, thrombosis, pulmonary edema, cerebral infarcts and adult respiratory distress syndrome are the leading causes of morbidity and mortality seen in severe cases. Here we report a case of OHSS with pulmonary thromboembolic event. Although the pathogenesis of thromboembolic events occurring during OHSS is not clear, it is probable that rising levels of estradiol may trigger hypercoagulability. Thromboembolic events seen with oral contraceptives and hormone replacement therapy support this hypothesis.

INTRODUCTION
Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic life-threatening complication of ovarian stimulation which is being increasingly recognized due to the higher number of women undergoing assisted reproductive techniques. OHSS is almost exclusively associated with ovulation induction with gonadotropins, or occasionally clomiphene citrate, and it is frequently seen during in vitro fertilization (IVF) cycles. OHSS is classified as moderate or severe according to clinical and laboratory findings. In this classification, mild cases are omitted from the classification since a mild form can occur in most patients after ovarian stimulation, but the condition has no complications and does not require any specific treatment (Table 1) [1]. Renal and hepatic dysfunction, thrombosis, hydrothorax, cerebral infarct and adult respiratory distress syndrome (ARDS) are the leading causes of morbidity and mortality seen in severe cases.

Thromboembolic complications in IVF cycles usually occur after the administration of human chorionic gonadotropin (hCG), and are seen in the arterial (cerebral, extremity, femoral, popliteal, myocardial) or venous (neck and upper extremity) systems [2].

In patients undergoing therapeutic strategies for infertility, the pulmonary complications of OHSS should be suspected on clinical grounds and identified early to allow for appropriate diagnosis and management.

We report herein a case of severe OHSS with pulmonary complications.

CASE REPORT
A 36 years old multigravida with unexplained secondary infertility underwent a protocol of controlled ovarian stimulation using a luteal long protocol. A total dosage of 120 IU of Gonadotropin Releasing Hormone (Lucrin®, Abbott), 2000 IU of recombinant Follicle-Stimulating Hormone (Puregon®, Schering Plough), and 10,000 IU of hCG (Pregnyl®, Schering Plough) was given to the patient. In vitro fertilization was not performed due to developing OHSS.

The patient was referred to our clinic with marked dyspnea and abdominal distention at day 19 after the onset of treatment. She was apyretic on examination and had a respiratory rate of 26 breaths/min and pulse rate of 114 beats/min. Her blood pressure was 110/70 mmHg. She presented no clinical signs of cardiac failure or of deep vein thrombosis. She had clinical evidence of ascites and abdominal tenderness and distention. The chest radiograph showed bilateral massive pleural effusion. Laboratory findings included a moderate hypoxemia (P0₂, 71 mmHg; PC0₂, 30 mmHg on room air), a normal hematocrit level (31 %) and an increased white blood cell count (21,000 cells/L). Her hepatic biological parameters were normal, while an increase in renal functional tests (urea 80 mg/dL and creatinine 1.42 mg/dL) was found. The plasma estradiol
level was 2584 pg/mL, D-dimer level was 638 mcg/L and β-HCG concentration was 1.5 IU/mL. She also had a heterozygotic Factor V Leiden mutation. The abdominopelvic ultrasonograph showed diffuse ascites and bilateral enlarged follicular cysts. Pleural effusion was an exudate (48 g/L of proteins) with a predominance of hyperactivated mesothelial cells and no other cellular abnormality. Lower extremity venous Doppler ultrasonography and echocardiography of the patient were both within normal limits. She has diagnosed as suffering the worst stage (Severe OHSS, Grade C) of OHSS.

The patient was treated with 20% intravenous albumin infusion at a dosage of 50 ml/day for 7 days, and she also received low molecular weight heparin (4500 IU/day) as antithrombotic prophylaxis. Because her dyspnea did not improve during follow-up, drainage was performed, with a total of 2500 ml of serous fluid being obtained by three thoracenteses and 5500 ml of serous fluid by two paracenteses.

Although there was no finding consistent with pulmonary thromboembolism in thorax computerized angiography, her dyspnea did not improve. Pulmonary thromboembolism was then diagnosed by ventilation perfusion sintigraphy, and anticoagulation therapy with coumadine at a dosage of 5 mg/day started.

Over some days, her clinical situation improved, and she was discharged home on the thirteenth day of hospitalization.
We report here a severe case of OHSS with the complication of pulmonary embolism in the context of an induction of ovulation in an IVF cycle without the transfer of embryo.

OHSS is defined as an iatrogenic complication of ovarian stimulation. The incidence of OHSS in all its grades is estimated at 4%, with the incidence of severe OHSS being between 0.25% and 0.9% [3-4]. The intensity of the syndrome is related to the degree of the follicular response in the ovaries to the ovulation-inducing agents. The pathophysiology of this syndrome has not been completely explained, but several risk factors have been reported to increase its incidence, including polycystic ovary syndrome (PCO) [5], high serum estradiol (> 2500 pg/ml), hCG supplementation of the luteal phase, women < 35 years, and the occurrence of conception in the cycle of treatment [6]. In these cases, patients should be carefully monitored with repeated ultrasonographic examinations and plasma hormonal determinations.

OHSS is a threat to every woman undergoing ovulation induction and is potentially lethal in its severest form [7]. Severe OHSS is characterized by growth of multiple large follicles with massive extravascular protein-rich fluid shift. This may lead to hypovolemia, hemoconcentration, oliguria, and electrolyte disturbance [8]. The dynamic fluid changes may lead to ascites, renal failure, ARDS, and thromboembolic phenomena [9]. The enlarged ovaries, composed of follicular and luteal cysts, may cause intra-peritoneal bleeding or torsion, requiring immediate surgical intervention.

The ideal treatment of OHSS is prevention, but there has been only limited success in this goal. The unpredictable individual response to ovulation inducers makes the prevention of OHSS very difficult.

A venous thromboembolic event, which is one of the major complications of OHSS, has been reported as occurring in 0.08-0.11% of IVF cycles [10]. This risk is increased by ten times if the patient is also pregnant [11]. Although the pathogenesis of thromboembolic events occurring during OHSS is not clear, it is probable that rising levels of estradiol may trigger hypercoagulability. Thromboembolic events seen with oral contraceptives and hormone replacement therapy support this hypothesis. Although most studies have reported an increase in von Willebrand Factor (vWF), factor 8, factor 5, and fibrinogen levels and a decrease in antithrombin, and protein C and S levels, there is no diagnostic test for the detection of increased coagulation risk [12-13].

Furthermore, 41% of women experiencing venous thrombosis have known thrombophilias [10]; in our case, we detected a heterozygotic factor V Leiden mutation. Thrombophilias should be kept in mind always in patients suffering from venous thrombosis.

Properly conducted studies including large numbers of patients are required in order to determine the best methods of prevention and management.

References
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