

ATYPICAL OVARIAN HYPERSTIMULATION SYNDROME WITH ISOLATED PLEURAL EFFUSION BUT WITHOUT ASCITES OR HEMOCONCENTRATION

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Ovarian hyperstimulation syndrome (OHSS) is a potentially severe complication following ovarian stimulation. It has a clinical spectrum ranging from a mild form, which accounts for most cases, to moderate and severe forms that occur rarely but deserve special attention since they are life threatening [1]. Clinical manifestations of OHSS can be classified into (1) mild, with abdominal distension; (2) moderate, with ascites; (3) severe, with apparent ascites and/or effusion (pleural, rarely pericardial); and (4) hypovolemic shock, acute renal and respiratory failure, and thrombotic disorders [2]. This syndrome is an iatrogenic disorder, which is not yet fully understood, and carries a significant risk of morbidity and mortality. Despite close monitoring during ovarian stimulation, and following rigid guidelines and criteria for canceling the cycles, OHSS still occurs. Owing to the increased use of therapeutic strategies for infertility, the pulmonary complication of this syndrome should be suspected on clinical grounds and identified early to allow for more appropriate diagnosis and management [3]. We report a patient whose only manifestation of OHSS was unilateral pleural effusion with no ascites.

A 35-year-old woman came to our hospital for *in vitro* fertilization and embryo transfer treatment because of bilateral tubal occlusion. She received oral pills and a standard down-regulation regimen during the previous cycle before ovarian stimulation. Ovulation induction, using recombinant follicle stimulating hormone (r-FSH; 225 IU/day for 8 days, up to a dose of 1650 IU) and human menopausal hormone (HMG; 150 IU/day for 3 days, up to a dose of 450 IU), was then started on

day 3 after the cycle began. Human chorionic gonadotropin (hCG) 10,000 IU was administered when at least two follicles were ≥ 16 mm. The level of estradiol (E2) on the day of hCG administration was 2,052 pg/mL. There were eight oocytes harvested in this cycle, and three embryos were transferred back to her uterus after oocyte retrieval. Luteal phase support was given with oral progesterone without hCG. The postoperative course was uneventful until the day she came to the emergency room (ER).

Approximately 2 weeks following embryo transfer, she presented in our ER with severe dyspnea. On admission, the chest X-ray revealed a large isolated pleural effusion in the right lung (Figure 1). There was no ascites or extraordinary enlarged ovaries in her abdominal cavity. AQ There was no sign of hemoconcentration. Her white blood cell (WBC) count, hemoglobin level, and hematocrit (Hct) were 15,900/ μ L, 13.6 g/dL, and 38.6%,



Figure 1. Severe pleural effusion in the right lung field.

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Accepted: December 18, 2006



Figure 2. Moderate pleural effusion in the right lung field.



Figure 3. Complete resolution of the pleural effusion.

respectively. The electrolytes, and renal and hepatic parameters were all within normal limits. Her urine output was also normal. Conservative treatment with albumin infusion (albumin, 50 mg/day for 6 days, up to a dose of 300 mg) followed by diuretics was given during the six-day admission period, and the pleural effusion disappeared gradually and completely (Figures 2 and 3). The patient had an uneventful pregnancy and delivery.

OHSS is defined as an iatrogenic complication of ovarian stimulation. It can be extremely severe, with morbidity reaching 5% of *in vitro* fertilizations [4]. A recent Canadian study, where 771 patients were treated with gonadotropins, reported that severe OHSS occurred in 22 patients (3%), pleural effusion occurred in 5 (1%), and only one required thoracentesis (0.1%) [5]. OHSS is characterized by ovarian enlargement and increased vascular permeability, leading to marked transudation of a protein rich fluid from the vascular compartment into the peritoneal, pleural or, to a lesser extent, pericardial cavities. The intensity of the syndrome is related to the degree of ovarian follicular response to the ovulation-inducing agents. The syndrome can fall into four clinical categories of increasing severity: (1) mild, with abdominal distension and discomfort; (2) moderate, with ascites on ultrasound examination; (3) severe, with a clinically apparent ascites, with or without another effusion (pleural, rarely pericardial), and a hemoconcentration (Hct, 45%; WBC, 15,000/ μ L); and (4) critical, with, in addition to the above signs, hypovolemic shock, acute renal and respiratory failure, a marked hemoconcentration (Hct, 55%; WBC, 25,000/ μ L), and thrombotic disorders [2].

It has been shown that the development of OHSS is associated with the release of vasoactive substances into the peritoneal cavity and systemic circulation, either directly from the ovary or via an intermediate substance released from the ovary, causing increased capillary permeability and a shift of fluid from the intravascular volume into the third space [6]. The pathogenesis of OHSS is generally believed to represent the overproduction or altered expression of vasoactive substances of ovarian origin that are critical for follicle release or neovascularization of the developing corpus luteum [1]. Recent evidence argues for a critical role of several mediators, including various cytokines such as interleukin IL-1, IL-6, IL-8, and tumor necrosis factor. More recently, vascular endothelial growth factor has been identified as playing a significant role in the pathogenesis of OHSS in humans [2,6].

The unpredictable individual responses to ovulation inducers make the prevention of OHSS very difficult. Appropriate information should be given to the patient regarding the potential risks of the procedure [4]. The following risk factors have been identified: age younger than 35 years, the presence of a polycystic ovarian disease prior to stimulation, number of follicles > 10, estradiol serum concentration > 2,000 pg/mL, and an ongoing active pregnancy [1,7].

The case we report herein was atypical because of the isolated nature of the pleural effusion in the absence of ascites and hemoconcentration. Isolated hydrothorax may result from the combination of positive intra-abdominal pressure, negative intrathoracic pressure

and diaphragmatic defects that promote the transfer of intra-abdominal fluid into the pleural fluid, resulting in hydrothorax in the absence of abdominal fluid [8,9]. In our case and other reported cases, this preferential location might be explained by a capillary leak and exudation into the plural space due to decreased right lymphatic drainage compared to the left side [10,11]. Another possible explanation could be that defects in the tendinous portion of the diaphragm, which are more common in women and on the right side, allows the ascitic fluid to accumulate in the thorax, under the suctioning effect of negative intrathoracic pressure [12-14].

In conclusion, OHSS presenting with isolated pleural effusion usually has a benign course and spontaneously favorable outcome. Unilateral pleural effusion is usually in the right lung, which could be explained by a decreased right lymphatic drainage as compared to the left side and caused, possibly, by a diaphragmatic defect. Physicians need to be aware of this syndrome and the possibility of unilateral hydrothorax as the sole symptom of OHSS, in order to ensure a better, minimally invasive management of these potentially pregnant patients. Albumin infusion might be a safe and efficient option for the treatment of unilateral hydrothorax without thoracentesis.

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Author Query

AQ: Please check whether “abdominal cavity” rather than “abdomen” is appropriate here?