CASE REPORT

Unilateral Massive Pleural Effusion as the Only Principal Manifestation of Severe Ovarian Hyperstimulation Syndrome

ARB-AROON TANSUTTHIWONG,^{1,2} CHARTCHAI SRISOMBUT,¹ and ARAM ROJANASAKUL¹

INTRODUCTION

Ovarian hyperstimulation syndrome (OHSS) is an important complication of gonadotropins in assisted reproductive technologies. Its pathogenesis is still unknown. The main pathophysiology of this syndrome is an increase of vascular permeability leading to hemoconcentration and increased fluid in the third space. The manifestation of this syndrome may range from a common, mild form with minimal discomfort to life-threatening complications with ascites, hydrothorax, and multiorgan failures.

Pleural effusions in patients with OHSS are usually accompanied by tension ascites, presumably as the consequence of generalized extravasation of fluid or ascitic fluid seepage through diaphragmatic lymphatic vessels (1). Unilateral massive pleural effusion in the absence of ascites is a rare event, with only 13 cases reported from English literatures, and yet the exact mechanism is still enigmatic. Here, we report a case and review the pathophysiology proposed.

CASE REPORT

(A 38-year-old healthy woman presented at reproductive endocrinology unit in Ramathibodi Hospital after 6 years of primary infertility. Her menstrual his-

tory was regular and physical examination was unremarkable. The basal body temperature chart was biphasic but the hysterosalpingogram revealed unilateral tubal obstruction. Her husband was healthy with normal semen analysis. Ovulation induction and intrauterine inseminations were attempted twice without success. Assisted reproduction with in vitro fertilization and embryo transfer (IVF-ET) was advised.

A long protocol of pituitary suppression with gonadotropin-releasing hormone (GnRH) agonist (Suprefact E; Hoechst) was used, followed by ovarian stimulation with human menopausal gonadotropin (hMG) (Humegon; Organon, Rotterdam, Holland), 225 IU/day. After a total dose of 39 ampoules [2925 IU of human follicles-stimulating hormone (hFSH)] over a 13-day period, transvaginal sonography revealed 9 follicles with > 15 mm in diameter and serum estradiol level of 3322 pg/ml (12,194 pmole/liter), 10,000 IU of human chorionic gonadotropin (hCG) (Pregnyl; Organon, Rotterdam, Holland) was administered. Thirty-six hours thereafter, on the day of oocyte retrieval, transvaginal sonography revealed 14 mature follicles and 10 oocytes were retrieved. Two days later, four embryos of good quality were transferred into the uterine cavity. Luteal phase support consisted of hCG 1500 IU, injected intramuscularly every 3 days with daily natural micronized progesterone (Utrogestan; Piette Laboratories, Brussels, Belgium) administered orally 600 mg/day.

The patient presented 12 days after oocyte retrieval with a 3-day history of dyspnea and orthopnea without cough. The physical examination was normal except for dullness on percussion and decreased respiratory

¹ Division of Reproductive Endocrinology, Department of Obstetrics and Gynaecology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Rama VI Road, Bangkok 10400, Thailand.

² To whom correspondence should be addressed.

sound over her right hemithorax. Her blood pressure was 100/70 mmHg, pulse 100/min, temperature 37°C, and respiratory rate 24/min. The abdomen was soft on palpation, not tender, and without sign of ascites. Laboratory findings including serum electrolytes, blood urea nitrogen, creatinine, liver function tests, and urinalysis were all within normal range. Coagulogram was only slightly prolonged with international ratio of 1:24. Hematocrit was 44%. Chest X ray revealed massive right pleural effusion with normal left hemithorax (Fig. 1). Transvaginal sonography demonstrated a right ovary measuring 5.9×4.2 cm and a left ovary measuring 4.6×3.9 cm, both containing multiple small cysts. No ascites were observed (Fig. 2).

The patient was hospitalized and thoracentesis was performed, draining 1200 ml of clear, yellowish fluid. One hundred milliliter of 25% human albumin was infused. The patient experienced gradual improvement in respiration and her chest X ray showed slight decrease in effusion level. Her serum hCG level was 98.2 mIU/ml, 10 days after embryo transfer. On the third day of admission, she remained dyspnic, thus necessitating a second thoracentesis and 1500 ml of clear, yellowish fluid was drained. Another 1100 ml of 25% human albumin was infused. The patient reported immediate improvement in respiration and her chest X ray revealed marked decrease in effusion level. On the 14th day after embryo transfer, her serum hCG was 963.3 mIU/ml, and she was discharged feeling well on the next day. Antenatal care was uneventful. Nine months afterward, healthy twin infants, weighing 2560 and 2450 g, were uneventfully delivered by cesarean section. Postpartum examination was normal without effusion, ascites, or ovarian mass detected.

DISCUSSION

After the first report by Jewelewicz and Van de Wiele (2) in 1975, more cases of unilateral massive pleural effusion as the isolated manifestation of OHSS had been recognized, yet the exact mechanism of the disease is still unclear.

From a thorough search on Medline, there were 13 such cases reported from only eight articles in English literature (2–9). The age group of these patients varied, from 24 to 39 years (mean, 31.2 years). Most women had no prior history of any disease, and the cause of infertility also varied, from unexplained to polycystic ovary, male factor infertility, and chronic anovulation. The syndrome can occur after both controlled ovarian hyperstimulation for intrauterine insemination and in

vitro fertilization, and can occur regardless of whether GnRH agonists were prescribed (5,8) or not (2–4, 9). Human menopausal gonadotropins or FSH with hCG were used in every cases. Hemoconcentration was evident, although the hematocrit varied from 35 to 51.4% (mean, 44.3 %). Serum estradiol levels on the day of hCG administration were elevated in all cases but none exceeding 3500 pg/ml. Number of follicles ranged from 7 to 27 (mean = 14). The syndrome also occurred without luteal support by hCG (2–5, 8, 9). All cases occurred after ovulation, 6–14 days after hCG administration, and most occurred in the conception cycles. In 12 of the 14 cases, pleural effusion appeared on the right side, including this case. Chemical analysis of the fluid obtained from paracentesis revealed both transudate (4,5,7,8) and exudate (3,6,9). Pregnancy outcomes were normal in 4 cases (2,4,5) (two cases were twins (5), including this case), while in three cases spontaneous abortion occurred in the first trimester (3,9). After paracenteses and fluid management, the patients recovered in about 6 days.

The pathophysiology of OHSS has been implicated as the result of increased capillary permeability triggered by the ovaries under hCG stimulation, presumably mediated by factors belonging to the renin–angiotensin systems and cytokines such as interleukins, tumor necrosis factor– α , endothelin-1, and vascular endothelial growth factors (VEGF) (1,10). The increased capillary permeability leads to fluid accumulation in the third space, resulting in pleural effusion and ascites. The consequently decreased intravascular volume can lead to blood hypercoagulability and thromboembolic phenomenon. Pleural effusion is generally believed to be a product of fluid seepage from capillaries themselves or from intrabdominal fluid shift via lymphatic channels (1,6,11).

However, the finding of unilateral pleural effusion in the absence of ascites has always puzzled previous investigators. Daniel et al. (4) and Bassil et al. (5) suggested some pathological condition of the serosal surfaces of the pleura or the peritoneum. Man et al. (6) and Wood et al. (7) suggested that the serous exudative effusion supports the presence of increased capillary permeability in a single lung. Man et al. (6) also attributed the preferential right side of the disease to decreased lymphatic drainage compared to the left side as in congestive heart failure. But Friedler et al. (8), who discovered the recurrence of the transudative effusion with the same symptomatology in the same patient, suggested that this might indicate an underlying pathology such as local anatomical changes in the diaphragm. After reviewing previous reports, Gregory

et al. (9) thought the findings of both transudate and exudate might suggest multiple mechanisms of the disease and debated the role of circulating factors such as cytokines and VEGF, which should promote systemic rather than localized pathology.

Although chemical analysis of pleural fluid was not performed in this patient, the case was most likely due to OHSS by ruling out other causes of lung pathology and the symptoms that occurred related to ovarian stimulation and embryo transfer.

We agree with the concept that there might be some factor causing localized increased capillary permeability of the pleura. Or the syndrome might occur due to some degree of pulmonary thromboembolism from hypercoagulability, which can result in unilateral hydrothorax. However, the definite diagnosis should require pulmonary ventilation-perfusion scans, which had not been done due to the fear of potential harm to the fetus.

In summary, we report the manifestation and management of OHSS with isolated pleural effusion after ovarian stimulation and IVF-ET. The disease appears to be reported in increasing frequency due to the wide use of gonadotropins, yet the exact mechanism is still unknown and awaits more reports and further clarifications.

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