Unilateral hydrothorax as a sole and recurrent manifestation of ovarian hyperstimulation syndrome following in-vitro fertilization

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Acute unilateral hydrothorax may appear as the sole extra-ovarian expression of severe ovarian hyperstimulation syndrome (OHSS). This case report describes two such cases, in one of which the patient developed this rare complication in two consecutive ovarian stimulation cycles. Awareness is needed for the timely and appropriate diagnosis of this rare complication that occurs 9–14 days following human chorionic gonadotrophin (HCG) administration and may recur in consecutive stimulation cycles. Thoracocentesis and fluid balance maintenance are efficient modes of therapy resulting in good outcome.

Key words: acute unilateral hydrothorax/complications of ovarian stimulation/OHSS

Introduction

Ovarian hyperstimulation syndrome (OHSS) is a well known complication following ovarian stimulation which occurs in approximately 1–5% of the stimulated cycles for in-vitro fertilization (IVF) (Golan et al., 1989). The diagnosis and the classification of its severity incorporates clinical, laboratory and ultrasonographic parameters. Isolated hydrothorax developing acutely as the sole extra-ovarian manifestation of OHSS is a rare event – only four case reports were identified in a computerized literature search (Medline). The first report in 1975 (Jewelewitz and Van de Wiele, 1975) involved a case stimulated for in-vivo conception. Some 20 years later three other reports occurred in conjunction with ovarian stimulation for IVF (Kingsland et al., 1989; Daniel et al., 1995; Bassil et al., 1996). We report two such cases, in one of which the patient developed this rare complication in two consecutive ovarian stimulation cycles.

Case reports

Case one

A 29 year old healthy woman presented at our clinic after 3 years of secondary infertility. She had a previous spontaneous pregnancy and a normal delivery 4 years previously. Her history was consistent with regular menstrual cycles. Physical examination was normal. Hysterosalpingogram and hysteroscopy demonstrated a normal uterine cavity and bilateral patent Fallopian tubes.

Analysis of her husband’s spermatozoa revealed oligoasthenoteratozoospermia (sperm concentration 0.6×10⁶/ml, progressive motility 4%, normal morphology -6% by strict criteria). His medical history revealed torsion of the left testis in childhood and left orchiectomy.

Over the next 3 years the patient underwent eight trials of ovulation induction using clomiphene citrate and intrauterine sperm insemination (IUI) but no pregnancy was achieved. Therefore, because of male factor, an IVF–embryo transfer attempt with intracytoplasmic sperm injection (ICSI) was offered.

In July 1996 the patient began a long protocol of controlled ovarian stimulation using gonadotrophin-releasing hormone (GnRH) agonist (Decapeptyl® 3.75 mg; Ferring, Malmo, Sweden), for pituitary desensitization, followed by human follicle stimulating hormone (hFSH; Metrodin®; Teva Inc., Petach-Tiqva, Israel) for ovarian stimulation. Following a total dose of 22 ampoules (2 ampoules/day, for 11 days), and serum oestradiol concentrations reaching 2536 pg/ml and identification of ≥3 follicles of 17 mm diameter, human chorionic gonadotrophin (HCG) 10 000 IU was given 34 h before oocyte retrieval.

Transvaginal ultrasound guided oocyte aspiration was performed and a total of 27 oocytes were retrieved. ICSI was performed in 21 of them, 16 were fertilized, 13 embryos cleaved, and three embryos were transferred into the uterine cavity 2 days after the oocyte pick-up. The luteal phase support consisted of 1 week of progesterone in oil i.m. 50 mg/day which was stopped after 6 days because of severe local effects at the site of injection. Supplementation was changed to i.m. HCG 2500 IU, two doses at a 3 day interval. The remaining 10 embryos were of low quality (less than grade 2) and therefore were not considered for embryo cryopreservation.

Twelve days after oocyte retrieval the patient was hospitalized with severe dyspnoea, mild abdominal pain and weakness. The physical examination demonstrated decreased respiratory sounds over the right hemithorax. Blood pressure was 90/60, pulse 68, temperature 36.6°C, respiratory rate 30/min. The abdomen was soft with minimal tenderness. Abdominal ultrasound demonstrated enlarged ovaries but no ascites. Chest X-ray showed a massive pleural effusion through the right lung. The blood pH was 7.36, pCO₂ 39.4 mm Hg, pO₂ 74.1 mm Hg, O₂sat 97.1%. Haemoglobin concentration was 11.8 g/dl.
white blood cell count 13 900/mm$^3$, haematocrit 35%, platelet count 331 000/mm$^3$, prothrombin time and adjusted prothrombin time (APTT) within normal limits. Urinary sodium was 135 mMol/l, K 4.2 mMol/l, urea 2.1 mMol/l, protein concentration 50 g/l, albumin 30 g/l, creatinine 69 μMol/l.

At 8 h after her admission thoracentesis was performed and 1700 ml of clear fluid was aspirated. Biochemical cytological and bacteriological cultures revealed transudate with no evidence of malignancy or bacteria. Immediate improvement was reported by the patient. During the following three days she was also treated with i.v. crystalloids, colloids (haemacell), albumin and antibiotics. The laboratory tests were almost unchanged, her weight was stable, and she had satisfactory urinary output. The patient was discharged on the 4th day after admission, in good condition. A second chest X-ray, 2 weeks later, revealed no pathology. Unfortunately no pregnancy was achieved.

Three months later, in October 1996, the patient began a new long protocol of ovarian stimulation with GnRH agonist (Decapeptyl® 3.75 mg), followed by HFSH (total dose of 21 ampoules (2 ampoules/day for 10 days and 1 ampoule on day 11) and at the peak oestradiol concentration of >3000 pg/ml only 1 ampoule of HCG 5000 IU was administered 35 h before oocyte retrieval. Twenty-two oocytes were obtained, ICSI was performed on 20 mature oocytes, 11 fertilized, nine embryos cleaved and three embryos were transferred 2 days later. Five other embryos were cryopreserved. The luteal phase was supported by micronized progesterone (Uterogestan®; Besins-Isovesco, Paris, 200 mg × 3/day) intravaginally.

Five days after oocyte retrieval the patient presented again with mild dyspnnea and mild abdominal pain. The physical examination showed decreased respiratory sounds over the entire right hemithorax and mild tenderness and swelling of the abdomen. Respiratory rate was 16/min. The chest X-ray demonstrated a large right pleural effusion. Abdominal ultrasound revealed two 10 cm ovaries and minimal abdominal fluid collection. Haemoglobin was 10.9 g/dl, haematocrit 32.5%, white blood cell count 9800/mm$^3$, urinary protein 62 mMol/l, creatinine 76 mMol/l, urea, sodium, potassium were within normal limits. During her 3 days hospitalization she was treated with i.v. crystalloids and colloids. Her condition improved quickly and no thoracentesis was necessary this time. The laboratory tests remained almost unchanged. On the day of discharge, a second chest X-ray was performed and little effusion was noticed. One week later (13 days after embryo transfer) the pregnancy test was positive (blood β-HCG level of 284 IU/l). The patient remained under observation on a weekly basis and the blood β-HCG level rose up to >200 000 IU/l. Six weeks after embryo transfer a transvaginal sonography showed a twin intrauterine pregnancy with positive fetal heart rate. The patient was at that time free of any complaints.

**Case two**

A 33 year old healthy woman presented at our infertility clinic after 2 years of primary infertility. Her history consisted of regular menstrual cycles. Physical examination was normal, post-coital test was normal. The hysterosalpingogram and diagnostic laparoscopy failed to demonstrate any pathology.

Analysis of her husband’s semen revealed teratozoospermia (sperm concentration 38 × 10$^6$/ml, progressive motility 39%, normal morphology 2–4% by strict criteria). Hemizona assay was 100%. Genitalia were normal.

Over the next 2 years the patient underwent six clomiphene citrate cycles and three human menopausal gonadotrophin (HMG) cycles, combined with intrauterine insemination, but no pregnancy was achieved.

Because of male factor infertility, the patient was offered IVF–ICSI. She underwent a treatment cycle in January 1996, using a long protocol with GnRH agonist down-regulation followed by HMG/HCG (27 ampoules and 10 000 IU). Peak oestradiol concentration was 2082 pg/ml and 24 oocytes were retrieved. Seven embryos obtained following ICSI were transferred (three fresh and the other four following cryopreservation, during a natural cycle 3 months later), but no pregnancy was achieved. No side effect of the treatment was noticed.

The last treatment began in July 1996. A long protocol of ovarian stimulation was started with GnRH agonist (Decapeptyl® 3.75 mg), followed by HMG (a total dose of 20 ampoules, 2 ampoules/day, for 10 days), and HCG 5000 IU was administered 34 h before oocyte retrieval. The oestradiol concentration was >3000 pg/ml. Nineteen oocytes were obtained, ICSI was performed on 14 mature oocytes, seven were fertilized, seven embryos cleaved and three embryos were transferred. Luteal phase was supported by daily i.m. progesterone in oil, 50 mg/day. Five days after oocyte retrieval the patient presented with severe dyspnnea and mild abdominal pain. The physical examination demonstrated decreased respiratory sounds over the entire right hemithorax. Chest X-ray demonstrated massive right hydrothorax. Abdominal ultrasound showed enlarged ovaries and no ascites. Respiratory rate was 32/min, blood pressure 140/90 mm Hg, pulse 110/ min, temperature 37°C. Arterial blood pH 7.408, $P_{CO2}$ 30.8 mm Hg, $P_{O2}$ 79 mm Hg, $O_2$sat 95%, haemoglobin 15.4 g/dl, white blood cell count 20 000/mm Hg, haematocrit 46%, platelet count 263 000/mm$^3$, urinary Na 138 mMol/l, K 4.5 mMol/l, urea 6.5 mMol/l, protein 35 g/l, albumin 27 g/l. Because of the severity of the dyspnnea the patient was transferred to the intensive care unit (ICU).

Thoracocentesis was performed twice and 1500 ml and 3000 ml of clear fluid was aspirated consecutively. The fluid was a transudate and no signs of malignancy or infection were found. This treatment improved the patient’s condition dramatically and during the following days she was treated with crystalloids, colloids and albumin. The haemoglobin concentration dropped to 8.3 g% and the haematocrit to 25%. The other blood tests were essentially unchanged. The patient’s weight remained stable and the urine output satisfactory. Six days after admission she was discharged in good condition. A second chest X-ray revealed only minimal pleural effusion. Unfortunately the pregnancy test performed 14 days after embryo transfer was negative.

**Discussion**

The exact pathophysiology of acute hydrothorax as the sole presenting symptom of OHSS awaits clarification. Increased
Acute unilateral hydrothorax and OHSS

capillary permeability plays a major role in the development of OHSS, possibly in conjunction with ovarian production of several vasoactive substances working in synergy (Goldsman et al., 1995). Activation of both ovarian and renal renin-angiotensin systems (Delbaere et al., 1997) contribute factors such as cytokines (Friedlender et al., 1993; Revel et al., 1996) including vascular endothelial growth factor (McClure et al., 1994) which are involved in the development of massive extravasation of fluid and protein in conjunction with intravascular volume depletion, in a complex pathophysiological process reviewed recently by Elchalal and Schenker (1997). However, usually these changes occur over all serosal surfaces, with fluid accumulation mainly in the abdominal cavity. Thoracic involvement is usually secondary to ascites and the incidence of hydrothorax in OHSS is below 10%, mainly restricted to severe cases (Golan et al., 1989). How and why such changes may be localized only to one of the pleural surfaces, presenting as unilateral acute hydrothorax, is still enigmatic. In our patients as well as in the cases published by others, the pleural effusion was a transudate and infection or cancer was ruled out as a local pathological factor by cytological and bacteriological evaluation. The acute hydrothorax might appear on the right side [in both our two patients, the case by Kingsland et al. (1989), the case by Daniel et al. (1995)], predominantly on the right side [as in the first case by Jewelewitz and Van de Wiele (1975)] or the left side [as in the case by Bassil et al. (1996)]. The notable timing of appearance of the clinical symptoms of dyspnoea in all case reports was 9–14 days following HCG administration, concurring with the late appearing form of OHSS. Recurrence of the same symptomatology in the same patient might indicate an underlying pathology, such as local anatomical changes (i.e. in the diaphragm), although the patient’s work-up failed to show any specific factor responsible for this phenomenon. As the number of ovarian stimulation cycles for IVF increases constantly worldwide, it is important to draw awareness to a rare, sometimes recurrent manifestation of OHSS. Acute hydrothorax might significantly compromise the health of the individual developing it, but following thoracocentesis in combination with maintenance of both fluid balance and intravascular colloid pressure, the prognosis is very good.

References

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