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Isolated severe hydrothorax with respiratory distress as a main manifestation of ovarian hyperstimulation syndrome preceded by respiratory tract infection caused by *Haemophilus influenzae*

Ciężki, izolowany wysięk w jamie opłucnej z zaburzeniami oddychania poprzedzony infekcją dróg oddechowych *Haemophilus influenzae* jako główny objaw zespołu hiperstymulacji jajników

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Abstract

Introduction: *An isolated unilateral pleural effusion as the only presentation of ovarian hyperstimulation syndrome (OHSS) is very rare. This case is an unusual presentation of OHSS after a confirmed respiratory tract infection, with no other coexisting risk factors identified for this syndrome. We also imply that the presence of Haemophilus influenzae in bronchial fluid can increase local reaction to vasoactive cytokines.*

Case Report: *A 32-year-old woman presented at the Department of Reproductive Medicine and Gynaecology of the Pomeranian Medical University after 10 years of infertility with diagnosed hyperprolactinemia followed by bromocriptine treatment. The patient had three IUIs but no pregnancy was achieved. Therefore, ICSI was proposed. After an ovarian hyperstimulation, oocyte aspiration gave 8 oocytes. Although ICSI was performed in all of the oocytes there were 3 fertilizations. The ET of 3 embryos was carried out following 3 days of culture. Three weeks before the gonadotropin administration and a week before GnRH administration the patient had a respiratory tract infection with the most typical syndromes. The infection was treated successfully with over-the-counter medications and antibiotic .Three days after ET the patient was admitted to the ICU with signs of severe dyspnoea. The chest X-ray showed a large pleural effusion over the right lung. Upon admission, thoracocentesis was preformed and 1600 ml of clear fluid was aspirated. The bronchial aspirate showed evidence of Haemophilus influenzae and leukocytes. After three days of standard treatment the chest X-ray revealed no pathology. The patient was discharged asymptomatic on the 4th day of treatment. Serum beta-hCG level was negative on day 12 after ET.*

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Conclusions: *This case suggest that respiratory tract infection prior to stimulation may constitute a new independent risk factor for OHSS. However, the true relation between the respiratory tract infection and susceptibility to OHSS still awaits explanation. Recent or existing respiratory tract infection may be a relative contraindication for starting COH.*

Key words: **ovarian hyperstimulation syndrome** / **controlled ovarian hyperstimulation** / / **intracytoplasmatic sperm injection** / **pleural effusion** / / **respiratory tract infection** / **thoracocentesis** /

Streszczenie

Wstęp: *Izolowany jednostronny wysięk opłucnowy jako jedyna manifestacja zespołu hiperstymulacji jajników (OHSS) występuje niezwykle rzadko. Prezentowany przypadek jest kazuistycznym opisem wystąpienia zespołu OHSS po potwierdzonej infekcji układu oddechowego i wykluczeniu innych czynników ryzyka dla tego zespołu. Sugerujemy także, że obecność Haemophilus influenzae w płynie oskrzelowym może wzmacniać lokalną reakcję na wazoaktywne cytokiny.*

Opis przypadku: *32-letnia pacjentka zgłosiła się do Kliniki Rozrodczości i Ginekologii PAM po 10 latach starań o dziecko, leczeniu hiperprolaktynemii bromokryptyną i 3 nieskutecznych wewnątrzmacicznych inseminacjach nasieniem męża. Pacjentkę zakwalifikowano do programu zapłodnienia pozaustrojowego z bezpośrednim podaniem plemnika do komórki jajowej (ICSI/ET). Na tydzień przed podaniem agonistycznego analogu GnRH, na trzy tygodnie przed rozpoczęciem podawania gonadotropin pacjentka przeszła typową infekcję dróg oddechowych, która została skutecznie wyleczona antybiotykami. W wyniku kontrolowanej hiperstymulacji jajników otrzymano 8 oocytów. A w rezultacie ICSI 3 zapłodnienia. Na trzeci dzień hodowli do jamy macicy przeniesiono trzy zarodki. Trzy dni po transferze zarodków pacjentka zgłosiła na Izbę Przyjęć z objawami ciężkiej duszności. Prześwietlenie RTG klatki piersiowej wykazało rozległy naciek opłucnowy nad prawym płucem. W zaaspirowanym w trakcie torakocentezy płynie oskrzelowym stwierdzono obecność Haemophilus influenzae i leukocytów. Po trzech dniach standardowego leczenia obraz RTG klatki piersiowej nie wykazywał zmian patologicznych. Pacjentkę bez objawów duszności wypisano do domu czwartego dnia leczenia. Poziom beta-hCG w surowicy krwi na 12 dzień po transferze zarodków nie wykazał obecności ciąży.*

Wnioski: *Infekcja dróg oddechowych poprzedzająca stymulację może stanowić nowy niezależny czynnik ryzyka dla OHSS. Związek pomiędzy infekcją dróg oddechowych a podatnością na OHSS wymaga dalszych badań. Świeżo przebyta infekcja dróg oddechowych może stanowić względne przeciwwskazanie do rozpoczęcia kontrolowanej hiperstymulacji jajników.*

Słowa kluczowe: **zespół hiperstymulacji jajnika** / **kontrolowana hiperstymulacja jajników** / / **docytoplazmatyczne podanie plemnika** / **wysięk opłucnowy** / / **infekcja dróg oddechowych** / **torakocenteza** /

Introduction

Ovarian hyperstimulation syndrome (OHSS) is the main iatrogenic complication of ovarian stimulation with gonadotropins carrying significant morbidity and mortality rates [1, 2]. Increased capillary permeability plays a major role in the development of OHSS, possibly in conjunction with ovarian production of several substances acting in synergy [2]. Recent evidence argues for a critical role of several mediators, including the angiotensin cascade components and cytokines such as IL1, IL6, IL8, tumour necrosis factor alpha (TNF-α), endothelin 1 and vascular endothelial growth factor (VEGF) [3, 4]. Among them, VEGF seems to play the crucial role. It is known to stimulate endothelial-cell proliferation and angiogenesis. The levels of VEGF are not only correlated with OHSS but also seem to correlate directly with the degree of disease [3, 4, 5].

Case description

A 32-year-old woman presented at the Department of Reproductive Medicine and Gynaecology of the Pomeranian Medical University after 10 years of infertility.

She had irregular menstrual cycles with diagnosed hyperprolactinemia followed by bromocriptine treatment. Physical examination was normal with BMI of 24. On the third day of the cycle the FSH was 7,4mIU/ml, LH - 11,8mIU/ml and estradiol <20,0pg/ml. There was no evidence of polycystic ovaries on ultrasound. Hysterosalpingography demonstrated normal uterine cavity and obstructed left fallopian tube at its uterine end. Her husband's spermiogram revealed teratozoospermia (8% of normal sperm according to strict criteria). On her demand, she had three IUIs with ovarian stimulation with clomiphene citrate. No pregnancy was achieved. Therefore, due to the male factor, fallopian tube factor and unsuccessful IUIs, ICSI was proposed.

Following a cycle of oral contraceptives (Cilest; Janssen-Cilag, Belgium), she began her first treatment cycle with a long protocol of controlled ovarian hyperstimulation (COH). After desensibilization with a 3,75mg depot GnRH agonist (Diphereline SR; Beaufour Ipsen, France), she was given hMG (Menogon; Ferring, Germany), and recombinant FSH (Gonal F; Serono, Switzerland). A total dose of 1350IU of recombinant FSH and 675IU of hMG were administrated. The highest observed level of serum estradiol was 2936pg/ml

(the day of hCG administration), with total of 16 ovarian follicles with more than 12mm, and 6 follicles with more than 18mm in diameter. At the end of stimulation, 10 000 IU of hCG (Pregnyl; Organon, The Netherlands) was given 36h before the oocyte retrieval.

During the stimulation and luteal phase, prednison 5mg bid (Encorton; Polfa Pabianice, Poland) and acetylsalicylic acid 50mg daily (Acard; Polfa Warszawa, Poland) were administrated.

Transvaginal ultrasound guided needle oocyte aspiration gave 8 oocytes. All follicles larger than 10mm were aspirated. Although ICSI was performed in all of the oocytes: there were only 3 fertilizations. The ET of 2 grade A and 1 grade B embryos was carried out following 3 days of culture. The luteal phase was supported intravaginally with progesterone (Luteina; Adamed, Poland).

Three weeks before the gonadotropin administration and a week before GnRH administration the patient had a respiratory tract infection with the most typical syndromes and signs like cough, discharge from the nose, sore throat, hoarseness and fever (38,0-38,5°C). The infection was treated successfully with over-the-counter medications and antibiotic - amoxicillin 0,875g with clavulanic acid 0,125g bid (Augmentin; SmithKline Beecham, Poland).

Three days after ET the patient was admitted to the ICU with unfolding clinical signs of severe dyspnoea, mild abdominal pain, weakness, tachycardia and palpitation, dry cough and general discomfort. She was found to be pale and demonstrated decreased air entry sounds over the right hemithorax. Blood pressure was 140/95mmHg; pulse 112bpm, temperature 37,5°C. She was tachypnoeic with a respiratory rate of 21/min. The abdomen was soft with mild tenderness. Abdominal ultrasound showed enlarged ovaries with a maximum of 6cm, but no ascites was observed.

The chest X-ray showed a large pleural effusion over the right lung. The patient was not hemoconcentrated, her haemoglobin was 10,7g/l and haematocrit 30,0%. The other laboratory findings included increased white blood cell count of 12,9 G/l, decreased total protein concentration – 57g/l, O_2 saturation – 75%, and pCO_2 – 28,3mmHg. Urinalysis showed no abnormality.

Upon admission, thoracocentesis was preformed and 1600 ml of clear fluid was aspirated. The procedure significantly improved the patient's condition. Biochemical and bacteriological cultures revealed transudate with no evidence of malignancy. Total fluid protein was 4,1g/dl. However, the bronchial aspirate showed evidence of bacteria – *Haemophilus influenzae* (++) and leukocytes (qualitative method of assessment).

During the following three days she was treated with standard fluids, crystalloids, colloids and albumins (20% albumin solution; Biomed, Poland).

She also received treatment with 0,02g/0,2ml of LMWH s.c. (Clexane; Aventis, France) and cefazolin 2 x 1,0 i.v. (Kefzol; Eli Lilly, USA).

Her weight was stable and renal function was normal. The chest X-ray revealed no pathology. She was discharged asymptomatic on the 4th day of treatment. Serum β-hCG level was negative on day 12 after ET.

Discussion

This case is an unusual presentation of OHSS after respiratory tract infection. An isolated unilateral pleural effusion as the only presentation of OHSS is rare, however it may be the only extra-ovarian manifestation of the syndrome [5, 6, 7]. In the vast majority of OHSS cases, clinical symptoms of dyspnoea are found 9-14 days following hCG administration [8].

In this case symptoms occurred after 8 days of COH therefore this is the earliest appearance of pleural effusion after ovarian hyperstimulation [5, 6].

The manifestation of unilateral hydrothorax without ascites has no clear explanation [9]. In this case the pleural effusion was connected with enlarged ovaries without other clinical or biochemical manifestations of OHSS. According to our laboratory tests estradiol level <4000 pg/ml is not considered as a risk factor for OHSS.

The patient's history of respiratory tract infection shortly before the controlled ovarian hyperstimulation can give clues to help explain the unusual manifestation of OHSS. Bacterial *(Haemophilus influenzae* ++) infection of bronchial fluid can increase local reaction via release of vasoactive cytokines [10]. Lipooligosaccharide (LOS) originating from *Haemophilus influenzae* is a major stimulator of proinflammatory cytokines. LOS stimulates the release of IL-6, IL-8 and TNF-α in cultured human bronchial epithelial cell, and TNF-α, IL-1β, and IL-6 from human monocytes [10, 11].

One of these cytokines – IL-6 has vasoactive properties [12]. IL-6 is a potential mediator in the development of OHSS. Potentially increased local pulmonary concentration of IL-6 stimulated by pulmonary infection with *Haemophilus influenzae* could be the reason for increased responsiveness of endothelium towards stimulation of VEGF or IL-6 originating from others sources (e.g.ovary – *granular-luteal cells*). The local stimulation by proinflammatory cytokines can lead to the increased vascular permeability and leakage of the fluid to the third space and massive hydrothorax that was observed in this case [10].

In the previously described cases, one patient had a history of chronic sinusitis with postnasal drip and one had a history of recurrent chest infections, but otherwise the remaining patients were in good health [1, 5, 6].

Our patient presented no typical and distinct risk factors for OHSS like young age (she was not <30 years of age), low body weight, rapidly increasing estradiol levels (the estradiol level did nor exceed >4000pg/ml), high number of stimulated follicles, number of retrieved oocytes (8 only) nor history of PCOS. Therefore, respiratory tract infection occurred three weeks before COH, might have made our patient more susceptible to OHSS regardless of the remaining risk factors.

Conclusions

1. The respiratory tract infection prior to stimulation may constitute a new independent risk factor for pulmonary manifestation of OHSS. However, the true relation between the respiratory tract infection and susceptibility to OHSS still awaits explanation.
2. Recent or existing respiratory tract infection may be a relative contraindication for starting COH.

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