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OVARIAN HYPERSTIMULATION SYNDROME WITH LUNG COMPLICATION: CASE REPORT.

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ABSTRACT

Ovarian hyperstimulation syndrome is an iatrogenic complication of ovarian stimulation cycle commonly used for *in vitro* fertilisation. Fluid shift due to capillary leakage causes a wide spectrum of presentation. The lung complication of ovarian hyperstimulation syndrome are reported in about 10 per cent of severe cases and isolated pleural effusion without ascites is rare. Herein we report two cases of severe ovarian hyperstimulation syndrome with pleural effusion. Both of them were normal responder of ovarian stimulation and presented with dyspnoea, nausea and vomiting. Clinical findings revealed reduced air entry of lung field and pleural effusion without significant ascites. Symptomatic management and thoracocentesis prevented further deterioration and helped in satisfactory recovery.

KEYWORDS: Complications, *In vitro* fertilisation (IVF), Ovarian hyperstimulation syndrome (OHSS), Pleural effusion.

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ABSTRACT

Ovarian hyperstimulation syndrome is an iatrogenic complication of ovarian stimulation cycle commonly used for *in vitro* fertilisation. Fluid shift due to capillary leakage causes a wide spectrum of presentation. The lung complication of ovarian hyperstimulation syndrome are reported in about 10 per cent of severe cases and isolated pleural effusion without ascites is rare. Herein we report two cases of severe ovarian hyperstimulation syndrome with pleural effusion. Both of them were normal responder of ovarian stimulation and presented with dyspnoea, nausea and vomiting. Clinical findings revealed reduced air entry of lung field and pleural effusion without significant ascites. Symptomatic management and thoracocentesis prevented further deterioration and helped in satisfactory recovery.

KEYWORDS: Complications, *In vitro* fertilisation (IVF), Ovarian hyperstimulation syndrome (OHSS), Pleural effusion.

INTRODUCTION

Assisted reproductive technology is a new therapy in which ovarian hyperstimulation syndrome (OHSS) is a known complication. OHSS is characterized by ovarian enlargement from multiple ovarian cysts and shifting out fluid from the intravascular into the interstitial space.[1, 2] This may cause hypovolaemia, haemoconcentration, ascites, and electrolyte imbalance. In severe cases, it may leads to renal failure, pleural effusion, acute respiratory failure, thromboembolic events and even death.[3]

Common presentation of OHSS is nausea, vomiting, abdominal distension and discomfort.[2, 4] About one- third of conventional *in vitro* fertilisation (IVF) results in mild OHSS while the incidence varies from 3.1% to 8% for the combined moderate or severe OHSS.[5] Pleural effusion in OHSS is uncommon and it occurs in about 10 % of severe OHSS cases which usually accompanied by well-marked ascites.[3]

In our center, an average of 400 IVF cycles are done each year, and less than 20 cases of severe OHSS were reported. Herein

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we describe two rarely seen severe OHSS cases. These cases were different because they presented with the pulmonary symptom as the main and initial presentation with the absence of marked ascites.

CASE 1

A 42-year-old nulliparous woman, married for 4 years, had undergone an IVF cycle following two unsuccessful intrauterine inseminations (IUI) cycles. She had a history of invasive ductal carcinoma of the left breast and had completed the treatment. She had her first IVF cycle in December 2019 with no complications. In this cycle, she was stimulated with recombinant gonadotropin dose of 225 IU for 10 days and the final maturation with human chorionic gonadotropin (HCG) 10 000 IU resulted in 10 oocytes retrieved on day 14 of the cycle. Only two matured oocytes were available for intracytoplasmic sperm injection (ICSI) and she had fresh embryo transfer which was unsuccessful. Seven months later, she had her second IVF cycle and eleven oocytes were retrieved. A total of six matured oocyte underwent ICSI but only two fertilized. Fresh embryo transfer was done. Progesterone supplements were given for luteal phase support.

Three days after the embryo transfer, she started to experience non-productive cough and worsening dyspnoea. On assessment, she was noted to be breathless with reduced air entry in the left base on auscultation. Chest radiograph confirmed the findings of a small left pleural effusion with blunting of costophrenic angle (Figure 1).

She was admitted and pleural tapping drained about one-liter transudate fluid which was negative for acid fast bacilli on microscopy and culture. Ultrasound revealed an empty uterus with the largest follicles on the right and left ovaries measured 4.3 cm x 3.7 cm and 2.8 cm x 2.6 cm, respectively. There was no ascites. Otherwise, her renal and liver functions were normal with the hematocrit level of 0.38%. She was discharged well after five days of admission, but the outcome of the embryo transfer was unsuccessful.

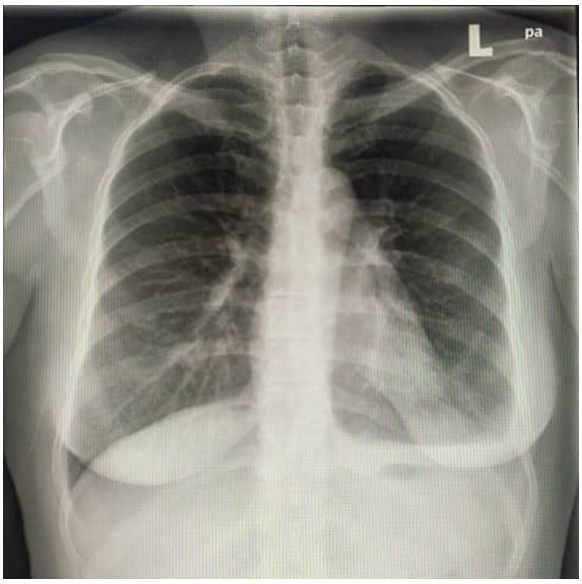

Figure 1: Case 1—Chest radiograph showed left sided pleural effusion. Click to enlarge)

CASE 2

A 36-year-old woman, with underlying hypertension, dyslipidemia, and polycystic ovarian syndrome (PCOS), had an IVF after failed two cycles of IUI. The ovarian hyperstimulation was initiated with 225 IU of gonadotropin for 10 days and HCG injection was given for final maturation. Three oocytes out of 8 grown follicles were retrieved on day 13 of the cycle. ICSI was carried out and only one embryo successfully achieved blastocyst stage and transferred. Progesterone and HCG were prescribed for the luteal phase support.

After 10 days of the embryo transfer, she presented with shortness of breath on exertion, which was gradually worsening and associated with pleuritic chest pain. During the assessment, she was tachypnea, afebrile with stable vital signs. Auscultation of the

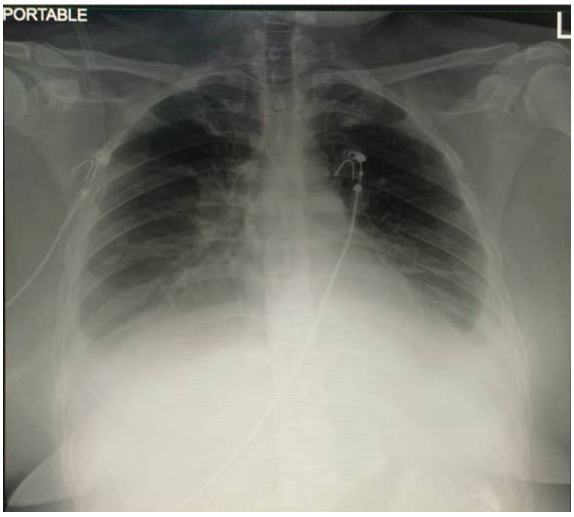

Figure 2: Case 2—Chest radiograph showed pleural effusion. (Click to enlarge)

lungs revealed reduced air entry bilaterally from mid-zone downward which was more on the right side. Pelvic ultrasound demonstrated enlarged bilateral ovaries (right: 6.43cm x 9.97cm x 9.7cm and left: 6.19cm x 5.4cm x 5.92cm) with absence of ascites. Her renal and liver functions were normal with a hematocrit of 0.49% and albumin of 25g/L. Electrocardiography was normal. The chest radiograph confirmed an extensive right pleural effusion (Figure 2).

She was admitted to the ward and thoracocentesis was performed which drained 1700 mls serous fluid. The peritoneal fluid cytology was reported as transudate effusion with negative acid fast bacilli on microscopy and culture. Her dyspnea improved over 5 days and she was discharged well after 7 days of hospital stay. One week later, she had fully recovered with a positive pregnancy signs from the ultrasound. However, the pregnancy ended with missed miscarriage at 10 weeks of gestation requiring suction and curettage.

DISCUSSION

OHSS is a negative iatrogenic effect of assisted reproductive treatment, especially related to IVF. The incidence of OHSS varies widely between 1–33% of IVF.[5] Among Asian or Pacific ethnicity, about 5.7% women are hospitalized with OHSS.[6] Severe forms of OHSS complicates about 3–8% of IVF cycles.[3] Pleural effusions can be seen in severe OHSS with incidence of less than 10%, but they are usually accompanied by marked ascites.[7, 8]

OHSS can be classified into mild, moderate, severe and critical OHSS. Mild form of OHSS is associated with mild abdominal pain, bloating, and ovarian enlargement. The moderate form includes nausea and / or vomiting, ascites in addition to previously mentioned symptoms. Existence of clinically apparent ascites, with or without pleural effusion, oliguria, changes in haemoconcentration, coagulation abnormalities and reduced renal function, is categorized as severe OHSS, while worsening of the mentioned features with tense ascites or large hydrothorax, thromboembolism, leucocytosis, and acute respiratory distress syndrome is classified as critical.[8] It can also be subdivided into early and late onset of OHSS. An excessive ovarian response to gonadotropin stimulation is associated with early onset of OHSS, while late onset OHSS is associated with endogenous HCG activity, produced by the implanting embryo.

The pathogenesis is only partially understood and it involves HCG-mediated vascular endothelial growth factor (VEGF) response. It is a signaling protein produced by the growing-stimulated follicles, which leads to increase vascular permeability and arteriolar vasodilation.[9]

Three theories are proposed for the formation of pleural effusion in OHSS. The most popular is associated with the release of vasoactive substances especially vascular endothelial growth factor (VEGF), following the exposure of hyperstimulated ovaries to HCG or luteinizing hormone (LH), rendering

capillaries highly permeability resulted in huge amount of protein-rich fluid shifts from intravascular, leading to ascites and pleural effusion.[3, 7, 8] The second theory is the involvement of lymphatic drainage via the thoracic duct into the right pleura, thus the right lung is more affected than the left side as seen in both cases.[3, 7, 8] The third theory is that transudation of ascitic fluid from the intra-abdominal cavity through multiple macroscopic defects in the tendinous portion of the diaphragm, presumably under the influence of negative intra-thoracic pressure, and usually on the right side. These diaphragmatic anatomical defects have been observed via open thoracotomy, laparoscopy, and post-mortem which are described as multiple macroscopic defects of thin membranes that covering the tendinous portion of the diaphragm.[3] However, the responsible mechanisms for the isolated pleural effusion in the absence of significant ascites as in these cases are not well understood and the second theory is the closest to explaining this phenomenon.

Recognized risk factors for severe OHSS are young age, low body mass index, presence of polycystic ovarian syndrome (PCOS), including the hyper responder in whom 20 or more oocytes retrieved during the IVF cycle.[10] But, as in the present cases, OHSS should not be ignored in normal responders of ovarian stimulation.

Hydrothorax as complication IVF treatment usually occurred as part of the late-onset type of the OHSS; more than seven days after HCG exposure as seen in both of our cases. Symptom generally resolves within one to two weeks but with a successful pregnancy, it can become more severe and can persists longer.[8] Respiratory decompensation is life-threatening that may be due to a decrease in lung volume from ascites, pulmonary embolism, and hydrothorax. Haemoconcentration (hematocrit value of ≥ 45%) and leukocytosis (white cell count of ≥15,000 cell/ml) were typically reported in 93% and 44% of the cases, respectively. These biochemical features have been considered as suggestive of OHSS and useful in differentiating hydrothorax associated with OHSS from other chest conditions such as pulmonary embolism.[7] Thus, serum parameters should be monitored and chest radiograph should be done to support the diagnosis.

Finally, multidisciplinary team management is preferred. This kind of cases should be nursed in an intensive care unit, with albumin infusion, and thromboembolic prophylaxis.[2, 8] Thoracocentesis is a safe procedure and should be performed to prevent further lung complications, as we did to both patients, and there are no reported complications arising from this procedure in the management of OHSS.[7]

CONCLUSION

The isolated pleural effusion as the complication of OHSS is probably not commonly highlighted because of its spontaneous resolution with a good outcome. Clinicians should have a high index of suspicion of pleural effusion when dealing with breathlessness in women following ovarian hyperstimulation. A detailed clinical evaluation and timely multidisciplinary team management with therapeutic thoracocentesis intervention is helpful in achieving a satisfactory recovery.

CONFLICTS OF INTEREST STATEMENT

The authors have no conflicts of interest to declare and consent has been obtained from patient and hospital authority to publish this article.

REFERENCE

1: Rajesh H, Lee W, Fook-Chong S, Yu S. Ovarian hyperstimulation syndrome: An analysis of patient characteristics in the Asian population. Singapore Medical Journal. 2011;52:168-74. [Accessed on 2022 March 12].

2: Mishra V, Roy P, Choudhary S, Aggarwal R, Hokabaj S, Saini SR. Ovarian hyperstimulation syndrome and pulmonary edema – a rare complication. International Journal of Reproduction, Contraception, Obstetrics and Gynecology. 2017;6(3):1154. doi: 10.18203/2320-1770.ijrcog20170607. [Accessed on 2022 March 12].

3: Mullin CM, Fino ME, Reh A, Grifo JA, Licciardi F. Symptomatic Isolated Pleural Effusion as an Atypical Presentation of Ovarian Hyperstimulation Syndrome. Case Reports in Obstetrics and Gynecology. 2011;2011:1-4. doi: 10.1155/2011/967849. [Accessed on 2022 March 12].

4: Iorio GG, Rovetto MY, Conforti A, Carbone L, Vallone R, Cariati F, et al. Severe Ovarian Hyperstimulation Syndrome in a Woman With Breast Cancer Under Letrozole Triggered With GnRH Agonist: A Case Report and Review of the Literature. Frontiers in Reproductive Health. 2021;3(37). doi: 10.3389/frph.2021.704153. [Accessed on 2022 March 12].

5: Khairy M, El-Toukhy T, Emovon E, Khalaf Y. Hydrothorax as the sole manifestation of ovarian hyperstimulation syndrome: unusual case and literature review. Reprod Biomed Online. 2007;14(6):715-7. Epub 2007/06/21. doi: 10.1016/s1472-6483(10)60673-6. PubMed PMID: 17579985. [Accessed on 2022 March 12].

6: Rotshenker-Olshinka K, Badeghiesh A, Volodarsky-Perel A, Steiner N, Suarthana E, Dahan MH. Trends in ovarian hyperstimulation syndrome hospitalization rates in the USA: an ongoing concern. Reproductive BioMedicine Online. 2020;41(3):357-60. doi: 10.1016/j.rbmo.2020.06.004. [Accessed on 2022 March 12].

7: Murray A, Rombauts L. Unilateral pleural effusion as the main presentation of "early onset"; severe ovarian hyperstimulation syndrome. Fertility and Sterility. 2004;81(4):1127-9. doi: 10.1016/j.fertnstert.2003.12.010.

8. Royal College of Obstetrician and Gynaecoligist. Management of Ovarian Hyperstimulation Syndrome, Green-top Guideline No. 5 (2106, February). [Accessed on 2022 March 12].

9. Cohen E, Lanzer JL, Mittal P. A Comparison of the Clinical Presentation of Ovarian Hyperstimulation Syndrome in a Partial Molar Pregnancy Case Versus a Fertility Treatment Case. Cureus. 2019;11(5):e4718. Epub 2019/07/30. doi: 10.7759/cureus.4718. PubMed PMID: 31355078. [Accessed on 2022 March 12].

10. Gat I, Shlush E, Quach K, Librach CL. The continuum of high ovarian response: a rational approach to the management of high responder patient subgroups. Systems Biology in Reproductive Medicine. 2015;61(6):336-44. doi: 10.3109/19396368.2015.1089607. [Accessed on 2022 March 12].