

Isolated pleural effusion as sole presentation of Ovarian Hyperstimulation Syndrome

Jenna Lipson, Maureen Kelly

ABSTRACT

Introduction: Isolated pleural effusion in severe OHSS is a rare occurrence and is typically associated with high peak estradiol. This case highlights that pleural effusion in setting of severe OHSS can occur in the absence of most of the recognized risk factors for OHSS, including in patients with a low estradiol. It is also the first case report of isolated pleural effusion in OHSS where a Cabergoline rescue protocol was used. **Case Report:** A 32-year-old known to have Polycystic Ovarian Syndrome (PCOS) underwent Controlled Ovarian Stimulation with hCG trigger, followed by cryopreservation. Her Estradiol on day of hCG trigger was 1761 pg/ml. Due to her history of PCOS, she was started on Cabergoline for prevention of OHSS. On day 7 following hCG trigger, the patient noted new onset of gastroesophageal reflux which was progressive until presentation the emergency room on day 9 for chest pressure. Her abdominal exam was benign. Cardiac workup was negative. She was diagnosed with bilateral pleural effusions (R>L) by CT scan, thought to be secondary to OHSS. She underwent a right thoracentesis where a 450cc of pleural fluid was drained from the right hemithorax. Following the procedure, her symptoms resolved. **Conclusion:** This report suggests that low/normal E2 is not protective against development of severe

OHSS. Additionally, it suggests that the use of cabergoline in COS cycles may decrease the overall severity of OHSS in high risk patients.

Keywords: Cabergoline, Ovarian hyperstimulation syndrome, Pleural effusion, Severe OHSS

How to cite this article

Lipson J, Kelly M. Isolated pleural effusion as sole presentation of Ovarian Hyperstimulation Syndrome. J Case Rep Images Obstet Gynecol 2018;4:100040Z08JL2018.

Article ID: 100040Z08JL2018

doi: 10.5348/100040Z08JL2018CR

INTRODUCTION

Ovarian hyperstimulation syndrome (OHSS) is the most serious complication that can occur in controlled ovulation stimulation (COS) cycles with gonadotropins during assisted reproductive technology (ART). The syndrome is classified as either mild, moderate, or severe, and is characterized by ovarian enlargement with massive third spacing of fluid, causing a variety of clinical symptoms [1]. In addition to enlarged ovaries and abdominal distention, which characterize mild OHSS, severe OHSS is characterized by the presence of hemoconcentration, thrombosis, severe abdominal distension and pain, intractable nausea/vomiting, oliguria, pleural effusion and respiratory distress, and possible electrolyte abnormalities [1]. The incidence of OHSS is quoted to be as high as 33% of all cycles in some case reports [2]. According to the World Health Organization (WHO), the incidence of severe OHSS is estimated to be 0.2% to 1% of all stimulation cycles [3, 4].

The proposed mechanism of action in the development

Jenna Lipson¹, Maureen Kelly²

Affiliations: ¹Resident, Pennsylvania Hospital, University of Pennsylvania Health System Department of Obstetrics and Gynecology, Philadelphia, PA USA; ²Medical Director, Society Hill Reproductive Medicine, Philadelphia, PA, USA.

Corresponding Author: Jenna Lipson, MD, 800 Spruce Street, 2 Pine East Building, Philadelphia, Pennsylvania 19107, USA; Email: Jenna.lipson@uphs.upenn.edu

Received: 13 September 2018

Accepted: 03 December 2018

Published: 24 December 2018

of OHSS is initiated by human chorionic gonadotropin (hCG) administration for final follicular maturation and ovulation trigger, which acts as the catalyst for OHSS. In the susceptible patient, hCG leads to up-regulation and overexpression of vascular endothelial growth factor (VEGF) in the ovary. Vasoactive-angiogenic substances are then released which cause an increase in the vascular permeability, potentially massive third spacing of fluid, and ultimately severe OHSS [1, 3]. Pleural effusions are not unusual in severe hyperstimulation (<10%), but they are usually accompanied by marked ascites. The isolated finding of pleural effusions without ascites as a presentation of severe OHSS a rare finding and is not addressed in the available OHSS scoring tables [5].

Aside from administration of B-hCG ovulation trigger, risk factors for OHSS include: prior episode of OHSS, age <35, low BMI, presence of PCOS, high or rapidly increasing estradiol levels (>3500 pg/mL), number and size of stimulated follicles, number of oocytes retrieved (risk increases with increasing number of oocytes), an ongoing active pregnancy [1, 5–7]. When severe OHSS occurs, its treatment typically involves expectant management and treatments used to reduce symptoms of fluid overload. There are, however, many well studied treatment strategies and therapies for use during the ovarian stimulation process that help to decrease the incidence of OHSS. For example, there is strong evidence to support using a course of dopamine agonist, Cabergoline, starting at the time of hCG trigger to reduce the incidence of OHSS [7].

This case highlights that pleural effusions in setting of severe OHSS can occur in the absence of most of the recognized risk factors for OHSS [8]. It is also the first case report of isolated pleural effusion in OHSS where a Cabergoline rescue protocol was used.

CASE REPORT

A 32-year-old Go female with polycystic ovarian syndrome (PCOS) who presented for treatment of infertility. Aside from her PCOS diagnosis, her infertility work up was otherwise unremarkable. Her partner's semen analysis was significant for sperm morphology of 3% on Kruger assay. All other semen parameters were normal.

She initially had failed three cycles of Clomid/ Intraurine Insemination (IUI), thus the decision was made to proceed with In vitro fertilization (IVF) with Intracytoplasmic sperm injection (ICSI). She began ovarian stimulation with at home injections of Follistim (Ravensburg, Germany) 75 units and Menopur (Parsippany, NJ) 75 units for 13 days. On day 13, her estradiol (E2) level was 1761 pg/ml with 10 follicles > 16mm and total of 6 follicles between 14-15.9 mm. That day she received a hCG ovulation trigger of 10,000 units. An egg retrieval procedure was performed 36 hours later without complication and 19 eggs were collected. Plan

for cryopreservation of all good-quality embryos for a planned frozen embryo transfer. Based on her prior diagnosis of PCOS, the patient was started on Cabergoline 0.5mg per day for 8 days for prevention of Ovarian Hyperstimulation Syndrome (OHSS).

The patient was doing well until day 7 after hCG trigger, when she first noted symptoms of reflux. Review of symptoms was negative. She was eating and voiding without issue. She denied any chest pain or shortness of breath. The following day (day 8) she was seen in the office for worsening chest pressure and reflux symptoms. Office transvaginal ultrasound showed mildly enlarged ovaries consistent with recent controlled stimulation and moderate ascites in the pelvis, measuring approximately 100cc. The lungs were also evaluated with ultrasound and no fluid was seen in the pleural space. She was instructed to stop Cabergoline, as it was thought her symptoms may be due to the relatively common GI side effects of the drug. The next day (day 9 after trigger), the patient was feeling better, however noticed an increased respiratory rate with walking. She denied abdominal pain but did mention a sensation of "fullness"/ early satiety since her egg retrieval procedure. Given she otherwise had no signs of OHSS she was sent directly to the Emergency Department for further work up.

In the Emergency Department, her vital signs were normal, including an oxygen saturation of 95-98% on room air. Her physical examination was significant for absent breath sounds at the right lung base and decreased breath sounds at the left lung base. Her physical examination was otherwise unremarkable, specifically, her abdomen was soft, non-tender, and non-distended. Laboratory evaluation demonstrated negative B-hCG, Hemoglobin/Hematocrit 10.8 g/dl / 34%, WBC 12.8 x10E3/uL, electrolytes within normal limits and negative D-Dimer. Echocardiogram showed normal sinus rhythm.

Pelvic Ultrasound was performed which demonstrated "Enlarged bilateral ovaries containing multiple small follicles/cysts" (right ovary 3x8x4.1 cm and left ovary 5.7x7.5x6.5 cm) in association with "a moderate volume simple ascites in the cul de sac", measuring approximately 80cc. Chest X-ray (Figure 1) and CT scan of the chest were significant for large right and small left pleural effusions. There was no evidence of pulmonary embolism. She was admitted for a cardiac workup and thoracentesis.

On hospital day 2, the patient had an uncomplicated thoracentesis with interventional radiology with drainage of 450cc of serous fluid. A CXR performed after the procedure showed normal lung expansion and small persistent pleural effusion. The patient was seen by Cardiology who performed a TTE with an ejection fraction of 65-70%. Given her negative workup, the etiology of her effusion was felt to be an atypical presentation of Ovarian Hyperstimulation Syndrome. Following the procedure, the patient had improvement of her symptoms and she was discharged home on hospital day 2 in stable condition with close outpatient follow up in place.

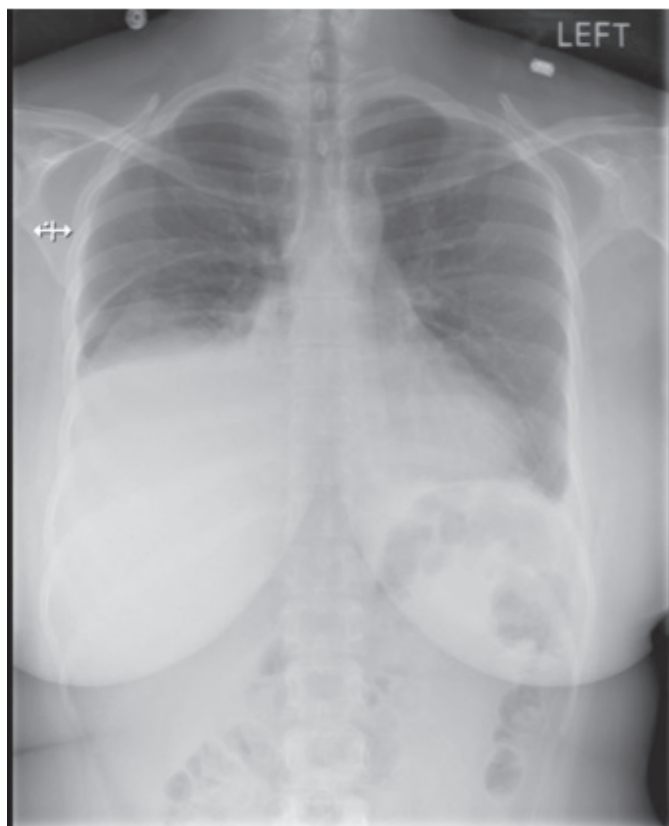


Figure 1: Chest X-ray demonstrating large right sided and small left sided pleural effusion.

DISCUSSION

To our knowledge, of all of the documented cases of pleural effusion as sole presentation of OHSS, this is the lowest peak E2 that has ever been described with this presentation. In a recent systematic review of 30 cases of pleural effusions as sole presentation of OHSS between the years of 1960-2016, the average peak E2 in these reported cases was 3110 ± 330 pg/mL, which is almost double of the peak E2 of our patient [9]. Although our patient had a diagnosis of PCOS putting her at higher risk of OHSS, her relatively low E2 level (1761) was the reasoning behind the decision to give a hCG trigger, rather than a lupron trigger.

According to the literature, the peak E2 level above which is considered “high risk” is somewhat arbitrary. Whelan et al, hypothesized that the significance that estradiol level, follicular size and quantity of oocytes retrieved have in the development of OHSS is likely due to the overall high physiologic level at which the ovary is functioning, rather than the independent contribution of these individual variables. The level of serum estradiol which one could be considered at high risk for OHSS has been reported as >3500 in multiple cases reports and review articles [5, 7]. As seen in our patient, severe OHSS can occur even in patients with as low as half of that, and a low E2 does not seem to protect against or deter risk. The question of whether or not all patients with PCOS should

receive a lupron trigger rather than hCG, regardless of E2 level, is one that requires further research.

Our case is also unique as, to our knowledge, this is the first case report of isolated pleural effusion in OHSS where a Cabergoline “rescue” protocol was used. In the 2012 Cochrane review of two placebo controlled trials, administration of dopamine agonist, Cabergoline, significantly decreased the risk of OHSS in women undergoing controlled ovarian stimulation and had received an hCG trigger. Dopamine agonists such as Cabergoline work by inhibiting VEGF receptor phosphorylation and thereby decrease vascular permeability. It is currently recommended in women at high risk for OHSS who have received hCG [1, 3, 10].

It is unclear if Cabergoline provided any benefit in this case, although certainly possible. Levin et al. demonstrated in *in vitro* studies that VEGF is not only correlated with OHSS but also has a dose-dependent relationship with the degree of disease [11]. There is growing evidence in the literature that dopamine agonists may actually decrease the severity of OHSS when used in COH cycles [7]. Using these conclusions, one could postulate that the reason for relatively mild 3rd spacing of fluid and thus the relatively small the pleural effusion was due to the down regulation of VEGF by Cabergoline. In the 2018 systematic review of 30 cases between 1960-2016, Ninety percent of the patients underwent thoracentesis with average of 4332 ± 769 mL drained, as compared to 450 mL drained in our case [9].

The strength of this case is how quickly the diagnosis was recognized and treated. Diagnosis of OHSS should be made with clinical history (ie There should be a history of ovarian stimulation followed by ovulation or administration of hCG) and a high index of suspicion [8]. As in this case, it is important to rule out other cardiac and pulmonary etiologies as well.

CONCLUSION

Pleural effusion as sole presentation of severe Ovarian Hyperstimulation Syndrome (OHSS) is a very rare occurrence. This case is unusual in that the patient had a peak E2 level of about 50% of what has previously been described (1761 vs 3500). Although the peak E2 level above which is considered “high risk” is arbitrary, it does not seem that a low/normal E2 is at all protective against development of OHSS. Additionally, even if Cabergoline is not successful in preventing the occurrence of OHSS, the use of a Cabergoline rescue protocol may decrease the clinical severity of OHSS and should be used routinely in patients who have risk factors or OHSS.

REFERENCES

1. Busso CE, Soares SR, Pellicer A. Pathogenesis, clinical manifestations, and diagnosis of ovarian

hyperstimulation syndrome. UpToDate 2018.

2. Mullin CM, Fino ME, Reh A, Grifo JA, Licciardi F. Symptomatic isolated pleural effusion as an atypical presentation of ovarian hyperstimulation syndrome. *Case Rep Obstet Gynecol* 2011;2011:967849.
3. George K, Aleyamma T, Kamath M, et al. Symptomatic unilateral pleural effusion: A rare presentation of ovarian hyperstimulation syndrome. *J Hum Reprod Sci* 2010 Jan;3(1):49–51.
4. Binder H, Dittrich R, Einhaus F, et al. Update on ovarian hyperstimulation syndrome: Part 1–Incidence and pathogenesis. *Int J Fertil Womens Med* 2007 Jan–Feb;52(1):11–26.
5. Whelan JG 3rd, Vlahos NF. The ovarian hyperstimulation syndrome. *Fertil Steril* 2000 May;73(5):883–96.
6. Roden S, Juvin K, Homasson JP, Israël-Biet D. An uncommon etiology of isolated pleural effusion. The ovarian hyperstimulation syndrome. *Chest* 2000 Jul;118(1):256–8.
7. Practice committee of the american society for reproductive medicine. Electronic address: ASRM@asrm.org; Practice committee of the american society for reproductive medicine. Prevention and treatment of moderate and severe ovarian hyperstimulation syndrome: A guideline. *Fertil Steril* 2016 Dec;106(7):1634–47.
8. 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 Jun;14(6):715–7.
9. Irani M, Robles A, Gunnala V, Chung P, Rosenwaks Z. Unilateral pleural effusion as the sole clinical presentation of severe ovarian hyperstimulation syndrome: A systematic review. *Gynecol Endocrinol* 2018 Feb;34(2):92–9.
10. Tang H, Hunter T, Hu Y, Zhai SD, Sheng X, Hart RJ. Cabergoline for preventing ovarian hyperstimulation syndrome. *Cochrane Database Syst Rev* 2012 Feb 15;(2):CD008605.
11. Levin ER, Rosen GF, Cassidenti DL, et al. Role of vascular endothelial cell growth factor in ovarian hyperstimulation syndrome. *J Clin Invest* 1998 Dec 1;102(11):1978–85.

Author Contributions

Jenna Lipson – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Maureen Kelly – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor of Submission

The corresponding author is the guarantor of submission.

Source of Support

None.

Consent Statement

Given this case report does not contain identifying information, informed consent was not obtained in accordance with the University of Pennsylvania IRB guidelines.

Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.

Copyright

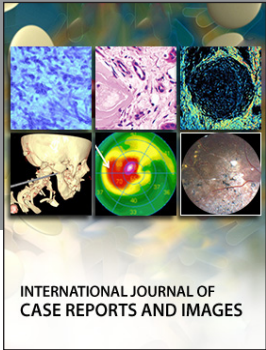
© 2018 Jenna Lipson et al. This article is distributed under the terms of Creative Commons Attribution License which permits unrestricted use, distribution and reproduction in any medium provided the original author(s) and original publisher are properly credited. Please see the copyright policy on the journal website for more information.

Access full text article on other devices



Access PDF of article on other devices





INTERNATIONAL JOURNAL OF
CASE REPORTS AND IMAGES



VIDEO JOURNAL OF
CLINICAL RESEARCH



VIDEO JOURNAL OF
BIOMEDICAL SCIENCE



INTERNATIONAL JOURNAL OF
HEPATOBIILIARY AND
PANCREATIC DISEASES



INTERNATIONAL JOURNAL OF
BLOOD TRANSFUSION AND
IMMUNOHEMATOLOGY



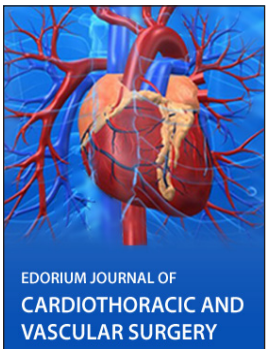
EDORIUM JOURNAL OF
OPHTHALMOLOGY



Submit your manuscripts at
www.edoriumjournals.com



EDORIUM JOURNAL OF
MEDICINE



EDORIUM JOURNAL OF
CARDIOTHORACIC AND
VASCULAR SURGERY



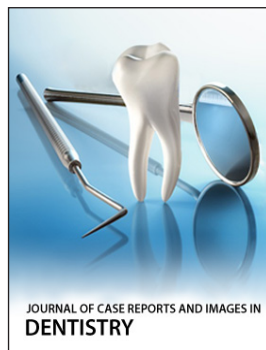
JOURNAL OF CASE REPORTS
AND IMAGES IN ORTHOPEDICS
AND RHEUMATOLOGY



EDORIUM JOURNAL OF
PSYCHOLOGY



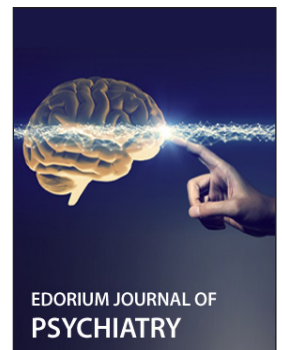
EDORIUM JOURNAL OF
CELL BIOLOGY



JOURNAL OF CASE REPORTS AND IMAGES IN
DENTISTRY



EDORIUM JOURNAL OF
CANCER



EDORIUM JOURNAL OF
PSYCHIATRY



JOURNAL OF CASE REPORTS AND
IMAGES IN INFECTIOUS DISEASES



EDORIUM JOURNAL OF
ANATOMY AND EMBRYOLOGY



EDORIUM JOURNAL OF
SURGERY



JOURNAL OF CASE REPORTS
AND IMAGES IN PATHOLOGY



EDORIUM JOURNAL OF
ANESTHESIA