Isolated Unilateral Pleural Effusion Without Ascites in Late Onset Ovarian Hyperstimulation Syndrome: A Case Report and Review of Literature

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ABSTRACT

Isolated pleural effusion is a rare presentation of severe OHSS. Two to four percent of women of reproductive age have subclinical hypothyroidism which is an uncommon association of late onset iatrogenic OHSS. This report describes an unusual patient with isolated unilateral pleural effusion and subclinical hypothyroidism as the only manifestation of late onset OHSS in a singleton pregnancy following in vitro fertilization (IVF). We have summarized current literature related to isolated pleural effusion in late OHSS and evaluated its pathophysiology and treatment options. Albumin infusion may be considered as a plasma expander whenever there is a planned third space drainage. Thyroid profile test in asymptomatic patients planning IVF will help to identify subclinical hypothyroidism. OHSS is a self-limiting condition and a timely diagnosis with aggressive management can be lifesaving.

Keywords: Late Onset Ovarian Hyperstimulation; Isolated Pleural Effusion; Hypothyroidism; Thoracocentesis; Albumin.

INTRODUCTION

Ovarian hyperstimulation syndrome (OHSS) is a serious and potentially life-threatening complication of ovarian stimulation. The overall incidence is approximately 33% of all in vitro fertilization (IVF) cycles with clinical manifestations varying from mild to severe (Irani et al., 2017). Severe OHSS ranges from 0.5–4% but may be underreported (Irani et al., 2017). It is characterized by massive ovarian enlargement following an exaggerated response to stimulation by follicle-stimulating hormone (FSH) in the presence of luteinizing hormone (LH) or human chorionic gonadotropin (hCG) with a shift of protein rich fluid to the extra vascular compartment, resulting in the development of ascites and/or pleural effusion, hypovolemia, electrolyte imbalance, renal and hepatic dysfunction. In the most marked cases, thromboembolic events may occur as a result of hemoconcentration and coagulation disturbances. The main pathophysiology is an increased vascular permeability secondary to the overproduction of vaso-active mediators like vascular endothelial growth factor (VEGF) and several pro-inflammatory cytokines from the enlarged ovaries. Higher human chorionic gonadotropin (hCG) and Thyroid stimulating hormone (TSH) levels are thought to play a crucial role in the development of the syndrome.

CASE REPORT

A 34-year-old woman with history of regular cycles, BMI 22.68 and an antral follicular count (AFC) of 29, presented on Day 13 of embryo transfer to the emergency room with breathlessness,

dry cough, nausea, vomiting and abdominal pain. Her β HCG was positive. She had undergone IVF for unexplained infertility, using Antagonist Protocol with low dose injections of FSH (125 IU/day SC; Puregon), starting from Day 3 of her cycle. Total dose of FSH was 1125 IU over 9 days. Estradiol level on Day 11 was 2712 pg/ml. Her folliculogram showed 15 follicles between 11–20 mm and hCG (10,000 IU) was administered. Eighteen eggs were retrieved. She was asymptomatic post-retrieval. A single Day 5 embryo was transferred and luteal phase supported with vaginal progesterone. At emergency, there was decreased air entry in the right middle and lower zones. Her abdomen was soft and bowel sounds present. There was a 4 kg weight gain since the day of oocyte retrieval.

Ultrasound of abdomen and chest showed bilateral enlarged ovaries ($10.8 \times 8.0 \times 7.2$ cm and $9.5 \times 6.2 \times 6.0$ cm) with minimal fluid in abdominal cavity and a moderate right pleural effusion (Fig. 1). Haematocrit was 43.1. There was no leucocytosis; β HCG was 412 and liver enzymes were raised.

The patient was offered admission and a right-sided thoracocentesis performed. The chest catheter yielded 2 L of pleural fluid in 24 hours followed by 1.16 L in the next 24 hours. S. albumin was trended and showed a decreasing trend. Albumin was replaced. This significantly improved the breathlessness. A total of 4.5 L of pleural fluid was aspirated in 5 days. The drain was removed on the 7th day when the output was <100 ml/day. Her thyroid profile revealed subclinical hypothyroidism with TSH 3.84, Ft4 13.1 for which levothyroxine was started. A scan 2 weeks later showed a viable intra-uterine pregnancy with no free fluid.

Fig. 1. Right pleural effusion

STATISTICAL ANALYSIS

Mean values and percentages were calculated as appropriate. Values were expressed as mean $\pm$ SEM (standard error of the mean).

DISCUSSION

Isolated pleural effusion without significant ascites in severe OHSS was initially reported in 1975 and since then there have been 30 reports (Irani et al., 2017). Out of these, 18 had “early” OHSS and data was unavailable in 2 reports. There are only 10 reports of late onset pleural effusion without ascites (Bassil et al., 1996; Friedler et al., 1998; Gregory and Patton, 1999; Rabinerson et al., 2000; Roden et al., 2000; Tansutthiwong et al., 2000; Khairy et al., 2007; Tang et al., 2007; Gupta et al., 2009; Mullin et al., 2011) (Table 1). The mean age of patients with isolated pleural effusion was 34.4 ± 1.94 years (range: 21–41). The mean Estradiol level on the day of hCG trigger was 2816.2 ± 718 pg/ml. Though there is no cut off value of E2 above which OHSS is precipitated, the risk seems to increase above 2000 pg/ml. The patient of Rabinerson et al. (2000) had an E2 level of 7340 pg/ml which explains the onset of OHSS. All patients received hCG trigger for final oocyte maturation (100%). The mean number of oocytes retrieved was 13.6 ± 2.0 . There were 2 patients who underwent ≥ 2 embryo transfer which resulted in a twin pregnancy.

Gregory et al. (1999) performed GIFT and data is not available for the remaining patients. Most of the reports are from the time when multiple embryo transfer was the norm. Single embryo transfer is a common practice only in recent years and our patient is the only documented singleton pregnancy with isolated hydrothorax in late OHSS. There were 2 patients (20%) who received hCG as a luteal phase support after oocyte retrieval which explains OHSS. We could not find any obvious cause in the remaining 5 patients (Bassil et al., 1996; Gregory and Patton, 1999; Rabinerson et al., 2000; Mullin et al., 2011; Irani et al., 2017). All the patients developed symptoms between 15–23 days after ovum retrieval (mean of 18 ± 0.8 days). There was hemoconcentration (mean hematocrit of $42.2 \pm 1.7\%$) with leucocytosis [mean white blood cell (WBC) count of 13828 ± 696 cells/ μ l]. Eighty percent of the patients required thoracentesis and the mean volume drained was 3371.4 ± 817.8 ml. The condition resolved in 7–12 days in all cases with a mean hospital stay of 5 ± 1 days. All patients had an ongoing active pregnancy (100%) but the pregnancies following GIFT ended in first trimester miscarriage.

“Early” OHSS occurs within 10 days of oocyte retrieval following exogenous hCG given for final trigger. HCG has a half-life of 24 hours and would be <10 μ /ml after 10 days in the absence of an ongoing pregnancy. Endogenous hCG starts rising shortly after implantation when the trophoblastic cells invade the spiral arteries and this induces the “late” OHSS. It activates the intra-ovarian renin-angiotensin system leading to angiogenesis and prostaglandin release (Cabar, 2016). The granulosa cells of the hyperstimulated ovaries secrete vasoactive substances such as vascular endothelial growth factor (VEGF), interleukins, tumor necrosis factor- α (TNF- α) and endothelin causing mesothelial hyper permeability with fluid leakage from the intra-vascular space, generating a massive third space collection. Though hCG levels peak at 10–12 weeks gestation, the initial exponential rise has a doubling time of 30.9 ± 3.7 hours which plateaus between 11 and 12 weeks (Ertzeid et al., 2000). Growth hormone, LH and FSH levels are suppressed by chorionic gonadotropins. This explains the onset of late OHSS in the initial weeks of conception more commonly and its self-limiting course.

Pleural effusion is reported in about 10% of severe OHSS, usually accompanied with marked ascites (Gregory and Patton, 1999). The pathophysiology of isolated pleural effusion in OHSS is still unknown. The ascitic fluid may enter the pleural space through diaphragmatic lymphatics and the thoracic duct present predominantly on the right side of the chest. Another route of transfer are the weak diaphragmatic defects, more commonly on the

Table 1. Summary of study reports of isolated pleural effusion in late OHSS.

Type of study	Age (yrs)	E2 on hCG trigger day (pg/ml)	No. of oocytes retrieved	No. of embryos transferred	Luteal support (hCG)	No. of days after OR	Hct (%)	Vol. drained (ml)	Hospital stay (days)
Mullin et al. (2011)	41	695	18	2	0	18	48.4	2750	3
Gregory and Patton (1999)	32	2663	17	GIFT	0	15	46	1150	4
Tang et al. (2007)	35	2052	8	3	0	21	38.6	Not applicable	6
Tansutthi wong et al. (2000)	38	3322	10	4	6000 IU	16	44	2700	4
Gupta et al. (2009)	21	1272	10	N/A	0	18	34	Not applicable	7
Roden et al. (2000)	33	N/A	N/A	N/A	0	16	48	N/A	N/A
Bassil et al. (1996)	39	260	11	N/A	0	16	44	2500	12
Freidler et al. (1998)	29	2536	27	N/A	5000 IU	16	35	1700	4
Rabinerson et al. (2000)	35	7340	13	N/A	0	21	N/A	6800	7
Khairy et al. (2007)	41	N/A	9	N/A	0	23	42	6000	2

hCG — Human chorionic gonadotropin; GIFT — gamete intra-fallopian transfer; OR — oocyte retrieval; E2 — estradiol; IU — international units; N/A — not available.

right side. The mildly increased intra-abdominal pressure causes the defects to rupture and the negative intra-thoracic pressure allows the fluid to enter the pleural space (Beji et al., 2008).

Though there are reports of spontaneous OHSS with hypothyroidism, we could not find any report of iatrogenic OHSS with overt/subclinical hypothyroidism. De Leener et al. (2006) classified spontaneous OHSS into four types based on clinical presentation and the underlying triggers. Type I is associated with a mutated follicle stimulating hormone receptor (FSHR). FSHR gene mutations have been described in patients with OHSS in the first trimester with normal hCG levels. These mutations cause a loss of ligand binding specificity and increase the ovarian response to circulating FSH or the response of the FSHR to hormones which share similar structure to FSH such as hCG or TSH (Yilmaz et al., 2018). It may cause recurrent spontaneous OHSS. Type II is secondary to high levels of hCG as in hydatidiform mole and multiple gestations and is the most common type. Type III is related to hypothyroidism. Type IV is due to ectopic FSH secreting tumors and FSH/LH secreting pituitary adenomas.

In women of reproductive age, the prevalence of subclinical hypothyroidism ranges from 2–4% and can lead to infertility and poor obstetric outcomes (Konstantinos et al., 2011). TSH is the most sensitive indicator of subtle thyroid dysfunction and even small variations in free T4 concentrations result in large alterations in TSH (Konstantinos et al., 2011). Thyroid abnormalities can appear before the presence of antithyroid antibodies which make TSH a better standardized measurement for detection of thyroid dysfunction in infertile patients (Vanquero et al., 2006). The exact mechanism by which OHSS might occur in patients with hypothyroidism is not clearly understood. A rapid increase in serum E2 concentration during controlled ovarian hyperstimulation (COH), results in an increase in thyroxine binding globulin (TBG) production; which in turn reduces the free thyroxine (fT4) concentrations. This induces TSH production from the pituitary gland (Gesthimani et al., 2011). TSH and hCG, as well as their respective receptors, share structural homologies (Gesthimani et al., 2011) thereby contributing to aggravation of late onset OHSS. It has also been suggested by Rotmensch and Scommegna that in hypothyroid patients, there is a preferential synthesis of estriol via the 16-hydroxylation pathway instead of the normal 2-hydroxylation pathway. Estriol being less potent than estradiol causes an increased gonadotropin release due to decreased feedback regulation. This may result in excessive ovarian stimulation (Ilanchezhian et al., 2015). The Endocrine Society suggests that TSH levels should be <2.5 µIU/ml in the first trimester of pregnancy (Konstantinos et al., 2011). But there are no guidelines on the optimum TSH levels during COH. Thyroid profile test is not a mandatory test during ART work up in asymptomatic normal cycling patients. The American College of Obstetricians and Gynecologists and The Endocrine Society do not recommend thyroid disease screening in the general population attempting conception. But hypothyroidism has been implicated as a causal factor in spontaneous OHSS (De Leener et al., 2006). So, it may increase the risk of developing OHSS in a patient undergoing ovarian stimulation.

Presence of late onset pleural effusion, even in the absence of ascites, is most likely to be secondary to an ongoing active pregnancy. Prompt initiation of thoracentesis can cause a dramatic improvement in clinical status and shorten the duration of hospital stay. Albumin infusion (preferably 20%) is safe and should be considered during a planned drainage of third space with or without hypoalbuminemia (Kwik et al., 2015).

Though biochemical parameters are useful in differentiating hydrothorax associated OHSS from other chest conditions but

leukocytosis may not always be present even in severe OHSS with late onset pleural effusion. Our case is unusual because, although the patient was stimulated with a low dose gonadotropin and underwent only a single embryo transfer, yet she developed massive right-sided pleural effusion. Associated subclinical hypothyroidism may have increased the severity of her OHSS. But we need more data to substantiate this.

CONCLUSION

OHSS can present without the usual risk factors and with a wide range of clinical manifestations ranging from massive ascites with abnormal biochemical parameters to no ascites with normal biochemical parameters. It usually has a self-limiting course with a favourable outcome. Aggressive treatment with prompt third space drainage and albumin replacement can rapidly improve the prognosis.

At present, we have inconclusive evidence regarding the effect of ovarian stimulation on thyroid function and vice-versa. The relevance of preconception subclinical hypothyroidism in infertile patients undergoing ART has not been extensively studied. Prospective analysis of a larger cohort is necessary to assess the association of late onset OHSS with subclinical hypothyroidism and to justify universal evaluation of thyroid function in women undergoing ovarian stimulation. However, in view of an uncommon presentation, such a study may not be feasible and our best knowledge is from case reports and reviews.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

COMPLIANCE WITH ETHICAL REQUIREMENTS

The authors declare that the article is original, neither the article nor any part of it is under consideration for publication anywhere else and has not been previously published anywhere. We have declared all vested interests. The article, if published, shall be the property of the journal, and we surrender all rights to the editor when requested. The authors also had taken permission from the patient before surrendering the manuscript.

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