

# Case Report

## Pleural effusion following ovarian hyperstimulation\*, \*\*

Derrame pleural secundário à hiperestimulação ovariana

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### Abstract

Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic complication that occurs in the luteal phase of an induced hormonal cycle. In most cases, the symptoms are self-limited and spontaneous regression occurs. However, severe cases are typically accompanied by acute respiratory distress. The objective of the present study was to describe the clinical presentation, treatment, and outcome of pleural effusion associated with OHSS in three patients undergoing in vitro fertilization. The patients ranged in age from 27 to 33 years. The onset of symptomatic pleural effusion (bilateral in all cases) occurred, on average, 43 days (range, 27-60 days) after initiation of hormone therapy for ovulation induction. All three patients required hospitalization for massive fluid resuscitation, and two required noninvasive mechanical ventilation. Although all three patients initially underwent thoracentesis, early recurrence of symptoms and pleural effusion prompted the use of drainage with a pigtail catheter. Despite the high output from the pleural drain (mean, 1,000 mL/day in the first week) and prolonged drainage (for 9-22 days), the outcomes were excellent: all three patients were discharged from hospital. Although pleural effusion secondary to OHSS is probably underdiagnosed, the associated morbidity should not be underestimated, especially because it affects potentially pregnant patients. In this study, early diagnosis and appropriate supportive measures yielded favorable results, limiting the surgical approach to adequate pleural drainage.

**Keywords:** Fertilization in vitro; Ovarian hyperstimulation syndrome; Pleural effusion.

### Resumo

A síndrome de hiperestimulação ovariana (SHEO) é uma complicação iatrogênica que ocorre na fase lútea de um ciclo hormonal induzido. Na maioria dos casos, os sintomas são autolimitados e regredem espontaneamente. Entretanto, casos graves comumente cursam com desconforto respiratório agudo. O objetivo deste estudo foi descrever a apresentação clínica, o tratamento e os desfechos de derrame pleural associado a SHEO em três pacientes submetidas a fertilização in vitro. A idade das pacientes variou de 27 a 33 anos, e o aparecimento do derrame pleural sintomático (bilateral em todos os casos) ocorreu, em média, 43 dias (variação: 27-60 dias) após o início da terapia hormonal para a indução da ovulação. Todas as pacientes necessitaram de internação hospitalar para reposição volêmica maciça, e duas delas necessitaram de ventilação mecânica não invasiva. Embora todas as pacientes tenham sido inicialmente submetidas à toracocentese, a recidiva precoce dos sintomas e do derrame pleural fez com que se optasse pela drenagem pleural com cateter do tipo *pigtail*. Apesar do alto débito de drenagem (média de 1.000 mL/dia na primeira semana) e do tempo de drenagem prolongado (9-22 dias), os desfechos foram excelentes (alta hospitalar). Embora o derrame pleural secundário a SHEO seja provavelmente subdiagnosticado, a morbidade associada não deve ser subestimada, principalmente devido a seus efeitos em pacientes potencialmente gestantes. Neste série de casos, o diagnóstico precoce e as medidas de suporte clínico adequadas permitiram uma evolução favorável, limitando a abordagem cirúrgica a uma drenagem pleural adequada.

**Descritores:** Fertilização in vitro; Síndrome de hiperestimulação ovariana; Derrame pleural.

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## Introduction

Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic complication that occurs in the luteal phase of an induced hormonal cycle.<sup>(1)</sup> The pathogenesis of OHSS involves the effect of vasoactive substances (cytokines, interleukins, endothelins, the renin-angiotensin system, tumor necrosis factor, and endothelial growth factor) that are secreted upon ovarian stimulation and cause increased vascular permeability, with depletion of intravascular volume and massive extravasation of protein-rich fluid into the peritoneal space, the pleural space, and, less commonly, the pericardial space.<sup>(2-6)</sup>

In most cases, the clinical manifestations of OHSS are self-limited and OHSS resolves spontaneously within a few days, provided that appropriate supportive measures are taken.<sup>(6,7)</sup> However, OHSS has been associated with substantial morbidity, principally acute respiratory distress, and fatal complications have been reported in patients with severe or critical OHSS.<sup>(8)</sup> Information regarding OHSS is not widely disseminated, being primarily restricted to studies published in journals specializing in gynecology and obstetrics or human reproduction. The purpose of the present report was to describe the clinical presentation, treatment, and course of pleural effusion secondary to OHSS in three patients who were treated by the same thoracic surgery team at two private, tertiary care hospitals in the city of São Paulo, Brazil. The institutional review boards approved the study, and the three patients gave written informed consent.

## Case reports

Three patients, ranging in age from 27 to 33 years, were hospitalized because of progressive dyspnea and massive bilateral pleural effusion. All patients were receiving ovulation induction therapy for in vitro fertilization. Two of the patients had already undergone embryo transfer. The three patients presented with ovarian hypertrophy and various follicular cysts, with or without ascites. Pleural effusion was initially treated with bilateral thoracentesis (in two of the patients) or paracentesis (in one) for symptom relief. However, because of early recurrence of pleural effusion, drainage was subsequently performed with a pigtail catheter. As can be seen in Table 1, the daily output was very high. Nevertheless, no specific

measure other than aggressive fluid resuscitation was attempted in order to manage such a high drainage rate. The patients received intravenous injection of crystalloids (2,000-4,000 mL/day) and 20% human albumin solution (200-300 mL/day) for an average of 7 days. Two of the patients required noninvasive mechanical ventilation. The three patients responded favorably to the treatment given, and the length of hospital stay ranged from 9 to 17 days (in two cases, the chest tubes were removed at outpatient clinics, after the patients had been discharged). Further clinical and laboratory information is shown in Table 1.

## Discussion

The classification of OHSS can be based on clinical and laboratory parameters, as well as on ultrasound findings. According to its severity, OHSS can be classified as follows<sup>(3,5,7)</sup>:

- mild (abdominal distension and discomfort)
- moderate (ascites revealed only by ultrasound)
- severe (ascites revealed by physical examination, or the presence of pleural or pericardial effusion associated with hemoconcentration (hematocrit > 45% and leukocyte count > 15,000 cells/ $\mu$ L)
- critical (the symptoms described above are accompanied by hypotension, acute renal failure, and thromboembolic disorders due to elevated hemoconcentration: hematocrit > 55% and leukocyte count > 25,000 cells/ $\mu$ L)

Severe or critical OHSS has been reported to occur in less than 2% of patients.<sup>(5)</sup> The three cases described in the present report can be regarded as severe or critical, respiratory symptoms having manifested, on average, 43 days (range, 27-60 days) after the initiation of ovulation induction therapy. The symptoms of OHSS generally manifest within 4 or 5 days after egg harvesting, and OHSS tends to resolve spontaneously within a few days if pregnancy does not occur. However, if pregnancy occurs, OHSS tends to be more severe and last longer. Of the two patients who had previously undergone embryo transfer, only one remained pregnant, and there were no further complications during that pregnancy.

Accurate and effective medical history taking will inevitably reveal respiratory impairment secondary to the fertility treatment. However, the assessment of pleural effusion should be primarily based on the physical examination findings. The

**Table 1** – Clinical and laboratory data (at admission and over hospital stay) of the three patients with pleural effusion secondary to ovarian hyperstimulation syndrome.

Variable	Case 1	Case 2	Case 3
Age, years	27	30	33
Comorbidities	Polycystic ovary syndrome	None	None
Ovulation induction	Choriogonadotropin alpha	Choriogonadotropin alpha	Cabergoline + folic acid
Onset of symptoms	Day 4 after embryo transfer	Day 7 after embryo transfer	Day 3 after egg harvesting
Hematocrit at admission, %	40.5	53.7	47.0
Plasma leukocyte count, cells/ $\mu$ L	23,240	20,490	26,380
Thoracentesis at admission	Right: 1,000 mL; Left: 700 mL	Right: 1,600 mL; Left: 650 mL	Right: 1,200 mL; Left: 900 mL
Pleural fluid analysis	Transudate	Exudate	Transudate
Ascites (ultrasound finding)	No	Yes	Yes
Ovary size, cm <sup>3</sup>	Right: 261; Left: 348	Right: 547; Left: 428	Right: 983; Left: 339
Noninvasive mechanical ventilation	No	Yes	Yes
Other measures	None	Prophylactic enoxaparin (40 mg/day)	Antibiotic therapy for urinary infection
Length of hospital stay, days	9	17	14
Total drainage rate, mL in n of days	Right: 10,700 in 13 days Left: 6,640 in 9 days	Right: 22,360 in 22 days Left: no chest tube	Right: 11,580 in 12 days Left: 8,100 in 10 days
Obstetric course	Spontaneous abortion in gestational week 6	Successful, term twin pregnancy	Declined to proceed with fertility treatment

diagnosis should be confirmed preferably by ultrasound, given that radiation exposure should be avoided in potentially pregnant patients. The most common respiratory symptom is dyspnea, which is easily explained by the presence of fluid in the pleural cavity, affecting lung expansion and causing basal atelectasis. In addition, ascites, progressive ovarian enlargement, and paralytic ileus contribute to a worsening of respiratory distress.<sup>(9)</sup>

The abdominal discomfort commonly reported by patients is not necessarily due to ascites, but to the volume of each hyperstimulated ovary, which can be over 500 cm<sup>3</sup>, as occurred in one of the three cases described herein. Ascites formation is not related to rupture or extravasation of the enlarged ovaries but rather to the mechanisms of increased capillary permeability.<sup>(7)</sup>

Pleural effusion accompanied by ascites can be explained by the migration of fluid from the abdominal cavity to the thoracic cavity through pores in the diaphragm, influenced by negative intrapleural pressure.<sup>(3,6)</sup> However, the pathophysiology of isolated pleural effusion

(without ascitic fluid, as occurred in one of the cases reported here) is not entirely clear.<sup>(6)</sup>

The analysis of the pleural fluid revealed the presence of exudate in one of the cases and transudate in the other two cases, which is in accordance with other studies in the literature,<sup>(10)</sup> suggesting that there are multiple mechanisms involved in pleural effusion and underscoring the lack of precise information regarding its pathophysiology.

When pleural effusion recurs, pleural drainage reduces dyspnea significantly and improves respiratory function. Lung re-expansion and supplemental oxygen therapy are aimed not only at controlling the symptoms but also at correcting hypoxemia in potentially pregnant patients, minimizing the risk of more serious complications affecting the embryo.<sup>(2)</sup>

The severity of OHSS is intimately related to the degree of ovarian follicular response.<sup>(3)</sup> As individual response to ovulation induction is unpredictable, a preventive approach is practically impossible. However, special attention should be given to potential risk factors, some of which

were observed in the three cases reported here: being younger than 35 years of age; having been diagnosed with polycystic ovary syndrome; visually identifying more than ten ovarian follicles; and having plasma levels of estradiol higher than 2,000 pg/mL.<sup>(11)</sup>

It is likely that the accumulation of pleural effusion secondary to OHSS is underdiagnosed. However, a diagnosis of pleural effusion secondary to OHSS should be considered if the anamnesis includes currently undergoing or having recently undergone in vitro fertilization. The morbidity associated with OHSS should not be underestimated, especially because patients might be pregnant. Severe or critical OHSS is an indication for hospitalization, continuous hemodynamic monitoring being necessary until intravascular volume is re-established, which is accomplished by intravenous injection of crystalloid and colloid solutions. When the diagnosis is established early and appropriate supportive measures are taken, the prognosis of OHSS is favorable.

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