Acute respiratory failure following ovarian hyperstimulation syndrome

Antonello Nicolini,1 Alessandro Perazzo,1 Piergiorgio Gatto,1 Mario Santo,2 Monica Bonfiglio3

1SSD Pneumologia Ospedale di Sestri Levante (GE); 2SC Medicina d’Urgenza Ospedale di Lavagna (GE); 3SSD Rianimazione Ospedale di Lavagna (GE), Italy

ABSTRACT

Ovarian hyperstimulation syndrome is a serious and potentially life-threatening physiological complication that may be encountered in patients who undergo controlled ovarian hyperstimulation cycles. The syndrome is typically associated with regimes of exogenous gonadotropins, but it can be seen, albeit rarely, when clomiphene is administered during the induction phase. Although this syndrome is widely described in scientific literature and is well known by obstetricians, the knowledge of this pathological and potentially life-threatening condition is generally less than satisfactory among physicians. The dramatic increase in therapeutic strategies to treat infertility has pushed this condition into the realm of acute care therapy. The potential complications of this syndrome, including pulmonary involvement, should be considered and identified so as to allow a more appropriate diagnosis and management. We describe a case of a woman with an extremely severe (Stage 6) ovarian hyperstimulation syndrome who presented ascites, bilateral pleural effusion and severe respiratory failure treated with non-invasive ventilation. The patient was admitted to the intensive care unit because of severe respiratory failure, ascites, and bilateral pleural effusion due to ovarian hyperstimulation syndrome. Treatment included non-invasive ventilation and three thoracentesis procedures, plus the administration of albumin, colloid solutions and high-dose furosemid. Severe form of ovarian hyperstimulation syndrome is observed in 0.5-5% of the women treated, and intensive care may be required for management of thromboembolic complications, renal failure and severe respiratory failure. Pulmonary intensive care may involve thoracentesis, oxygen supplementation and, in more severe cases, assisted ventilation. To our knowledge, there have been only two studies in English language medical literature that describe severe respiratory failure treated with non-invasive ventilation.

Introduction

Ovarian hyperstimulation syndrome (OHSS) is a serious and potentially life-threatening physiological complication observed in women who undergo ovarian hyperstimulation therapy. It is characterized by a wide range of clinical and laboratory manifestations caused by the simple induction of ovulation or after fertility treatment or induction of multiple follicular development.1 OHSS is the result of an abnormal response to ovarian stimulation and is characterized by an excessive increase in the size of the ovaries, and of changes in the permeability of the capillaries that determine the passage of liquid out of the vascular system.2 This determines the formation of ascites and, therefore, pleural effusion with consequent hypovolemia, oliguria, hemocoencentration, electrolyte changes and, more rarely, disseminated intravascular coagulation. The less serious forms are observed in between 25% and 30% of cases of induction of multiple ovulation while the more serious forms have an incidence of 0.5-5%.2 Deaths have also been reported due to cerebral thromboembolism, acute renal failure, acute respiratory distress syndrome (ARDS) and cardiorespiratory arrest.1,4 The disease has been classified in various stages on the basis of the seriousness of the condition according to Golan criteria and modifications by Navot1,4 (Table 1).

Case Report

A 41-year old woman was admitted to the emergency unit because of a rapid weight increase, abdominal distension, general malaise, increasing dyspnea and dry cough. The same patient had a little time earlier followed a protocol of controlled ovarian stimu-
loration based on follicle stimulating hormone (FSH), gonadotropin releasing hormone (GRH) and human chorionic gonadotropin (HCG) ten days before in vitro fertilization. On admittance to the emergency unit (12 days after administration of the ovarian stimulation protocol), the patient presented the following clinical profile: respiratory rate 30/min, heart rate 112/min, blood pressure 95/65 mmHg, and body temperature 37°C. Chest examination showed a clear reduction in breath sounds on the bottom right side and wet sounds were heard on the bottom left.

Abdominal ultrasound showed the ovaries had increased in size with a modest ascites effusion. Echocardiogram showed no pericardial effusion. Chest X-ray showed massive pleural effusion involving almost all the right lung (Figure 1). Laboratory tests showed: HCG 724.4 mIU/mL, estradiol pg 4133/mL, red blood cells 2870

Tests showed: HCG 724.4 mIU/mL, estradiol pg

Severe OHSS Grade 4: moderate OHSS+clinically evident ascites and/or hydrothorax or impaired respiratory function

Severe OHSS Grade 4: moderate OHSS+clinically evident ascites and/or hydrothorax or impaired respiratory function

Severe OHSS Grade 4: moderate OHSS+clinically evident ascites and/or hydrothorax or impaired respiratory function

Severe OHSS Grade 4: moderate OHSS+clinically evident ascites and/or hydrothorax or impaired respiratory function

Severe OHSS Grade 4: moderate OHSS+clinically evident ascites and/or hydrothorax or impaired respiratory function

Table 1. Ovarian hyperstimulation classification and clinical profile.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mild OHSS: painful abdominal extension</td>
</tr>
<tr>
<td>2</td>
<td>Moderate OHSS: slight OHSS+ascites on echography</td>
</tr>
<tr>
<td>3</td>
<td>Severe OHSS: all the above+clinically evident ascites and/or hydrothorax or impaired respiratory function</td>
</tr>
<tr>
<td>4</td>
<td>Chronic OHSS: ascites hydrotonic, Hct&gt;55%, WBC 25x10^3/L, oliguria, creatinine ≥1.6, creatinine clearance &lt;50 mL/min, renal failure, thromboembolism, ARDS</td>
</tr>
</tbody>
</table>

OSS, ovarian hyperstimulation; Hct, hematocrit; WBC, white blood cells; ARDS, acute respiratory distress syndrome.

Table 2. Respiratory and hemogasanalysis parameters.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>0 h</th>
<th>1 h</th>
<th>12 h</th>
<th>24 h</th>
<th>48 h</th>
<th>36 h suspension</th>
</tr>
</thead>
<tbody>
<tr>
<td>RF</td>
<td>36</td>
<td>30</td>
<td>27</td>
<td>25</td>
<td>22</td>
<td>19</td>
</tr>
<tr>
<td>CPAP</td>
<td>21</td>
<td>50</td>
<td>45</td>
<td>40</td>
<td>30</td>
<td>25</td>
</tr>
<tr>
<td>FIO2%</td>
<td></td>
<td>6</td>
<td>16</td>
<td>8</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>PaO2</td>
<td>29.2</td>
<td>102</td>
<td>108</td>
<td>108</td>
<td>100</td>
<td>103</td>
</tr>
<tr>
<td>PaCO2</td>
<td>37.3</td>
<td>36.9</td>
<td>35.7</td>
<td>33.0</td>
<td>34.1</td>
<td>35.2</td>
</tr>
<tr>
<td>Ph</td>
<td>7.47</td>
<td>7.46</td>
<td>7.49</td>
<td>7.47</td>
<td>7.45</td>
<td>7.43</td>
</tr>
<tr>
<td>HCO3</td>
<td>21.7</td>
<td>22.6</td>
<td>26.2</td>
<td>25.5</td>
<td>24.8</td>
<td>24.2</td>
</tr>
<tr>
<td>PaO2/FIO2</td>
<td>139</td>
<td>205</td>
<td>240</td>
<td>272</td>
<td>333</td>
<td>412</td>
</tr>
<tr>
<td>Lactic acid (mmol/L)</td>
<td>1.0</td>
<td>1.1</td>
<td>0.9</td>
<td>0.7</td>
<td>0.7</td>
<td>0.6</td>
</tr>
</tbody>
</table>

RF, respiratory frequency; CPAP, continuous positive airway pressure; FIO2%, oxygen inspiration fraction; PaO2, arterial oxygen pressure; PaCO2, arterial carbon anhydrase pressure; HCO3, hydrogen carbonate; P/F, PaO2/FIO2, ratio.

Arterial blood gas (ABG) analysis showed PaO2 29.2 PaCO2 37.3 pH 7.478, PaO2/FIO2 139, lactic acid 1.0 mmol/L. The patient was, therefore, transferred to the intensive care unit and underwent thoracocentesis with extraction of 1500 cc of pleural liquid and treated with continuous positive airway pressure (CPAP) non-invasive ventilation with expiratory pressure and FIO2 50%. One hour after treatment with CPAP, ABG analysis showed PaO2 102 PaCO2 36.9 pH 7.46 and the PaO2/FIO2 ratio had risen to 205. It was decided not to intubate the patient.5 Respiratory and hemogasanalysis parameters are shown in Table 2. The patient was then treated with albumin, colloid and crystalloid solutions, dopamin mg/24 h, low weight molecular heparin (enoxaparin 4000 U/die), broad-spectrum antibiotics (ampicillin/sulbactam 12 g/die) and high-dose furosemide (250 mg/die). Four days later, a clear improvement was observed in the clinical profile and the patient underwent a second thoracentesis (1000 mL) and chest computerized axial tomography (Figure 2). Patient condition continued to improve and two days
later she was transferred to the pneumology department of the hospital in Sestri Levante. Here she had a third thoracentesis (800 mL) carried out under echography guidance (Figure 3). Seven days later, echography and chest X-ray carried out the day before the patient was discharged showed that the pleural effusion was almost completely reabsorbed (Figure 4). Given her general good condition, the patient was discharged.

The patient has given her informed consent to the treatment and to the publication of her case report.

Discussion and Conclusions

There have been some sporadic reports in the literature of the clinical manifestations of OHSS, such as respiratory complications (in particular pleural effusion), and ascites effusion, considered the main disease symptom, also confirmed by the few pulmonology reports.6-10 However, cases in which pleural effusion was the only disease symptom have also been described.7,11,12 OHSS is characterized by the flow of extravascular liquid resulting in depletion of intravascular liquid and the development of effusions, in particular ascites and pleural effusions. It is thought that pleural effusion is mainly due to the high estrogen level, to an increase in vascular endothelial growth factor (VEGF), of cytokines such as IL-2, IL-6 and IL-8, and finally of tumor necrosis factor-α (TNF-α), usually found in severe forms OHSS.10 Cases of unilateral pleural effusion (often right side) with minimum or absence of ascites effusion have al-

![Figure 1. Chest X-ray carried out in the intensive care unit showing almost complete opacit in the right lung with contralateral mediastinal shift due to massive pleural effusion.](image1)

![Figure 2. Chest computerized tomography: bilateral pleural effusion with clear right prevalence.](image2)

![Figure 3. Chest echotomography: evidence of moderate pleural effusion.](image3)

![Figure 4. Chest X-ray before discharge showing the almost complete resolution of the right-hand pleural effusion.](image4)
Various hypotheses have been developed regarding the pathophysiology of massive pleural effusion in the absence of ascites effusion: the flow of ascites liquid in the pleural cavity through the diaphragmatic lymphatic system, as in cirrhosis and Meigs’ syndrome, the presence of anatomical defects in the diaphragmatic membrane, more frequent in the right hemidiaphragm and prevalent in females. Rupture of these small malformations caused by the increased pressure resulting from the ascites and the negative physiological pressure in the chest could quite convincingly explain the presence of massive right pleural effusion in the absence or small presence of ascites effusion, such as that seen in our patient.13,14

With the progressive evolution of the disease life-threatening complications can develop. These include hypovolemia, hemorrhagic syndromes, hepatorenal syndromes, thromboembolism and ARDS.13 Different risk factors have been described related to the seriousness of the syndrome: age under 35 years, low body mass index, polycystic ovary syndrome,2 atopic syndrome, pregnancy.14 The syndrome has been classified in six levels of severity according to the Golan and Navot clinical criteria (Table 1).

In particular, in 1992 Navot3 added new criteria to define severe OHSS and identify life-threatening factors (Table 3). According to this classification, our case presents intermediate characteristics between grade 5 and grade 6. Furthermore, the presence of massive homolateral pleural effusion and the level of severity of the gas exchange deficit (paO2/FIO2 139), together with a respiratory profile that, according to the 1994 classification,15 could be described as acute lung injury/ARDS,16 could lead to our patient being classified as having among the more critical forms. The presence of massive pulmonary edema is rarely reported in the syndrome and is sometimes fatal,17 while pulmonary thromboembolism is more frequent (12%).18 Deep venous thrombosis is even more frequent, particularly in the upper body, as is arterial thrombosis, for which a hypercoagulability mechanism is probably involved.2,18 This could be the reason for the increased D-dimer levels. The tests carried out did not suggest a diagnosis of pulmonary embolism and the respiratory profile did not seem to us to explain the presence of the massive pulmonary pleural effusion, probably associated with low load interstitial-alarveolar acute pulmonary edema, as shown by the prompt response to CPAP therapy.

The use of non-invasive assisted ventilation has been described in the literature. There are few cases in the English language literature of which one was a patient treated with emergency laparatomy because of the massive ascites effusion and abdominal hemorrhage.19,20

In conclusion, a form of severe OHSS should be suspected in any female patient who presents ascites and/or pleural effusion with a case history of controlled ovarian stimulation. Although rare, this syndrome requires a multidisciplinary approach because of the risk of possible multi-organ complications and of signs and symptoms that could be life threatening.

References