Non-invasive ventilation for the treatment of acute respiratory failure following ovarian hyperstimulation syndrome: report of two cases and a brief review of the literature

Ventilația non-invazivă pentru tratamentul insuficienței respiratorii acute urmând sindromul de hiperstimulare ovariană: prezentare a două cazuri și scurtă revizie a literaturii

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Abstract

The ovarian hyperstimulation syndrome (OHSS) is a serious but rarely fatal complication of medical interventions that seek to induce fertility; it is typically encountered in women who undergo controlled ovarian hyperstimulation, but there are very rare patients who have genetic defects who present with OHSS. In recent years, its pathogenesis has been elucidated; this knowledge will decrease the frequency of this syndrome. Clinical signs may include any or all of the following: rapid weight gain, ascites, oliguria, hemoconcentration, leukocytosis, along with intravascular hypovolemia, hyponatremia, and hyperkalemia. If the patient is not diagnosed early, ascites, pleural and more rarely pericardial effusions, severe respiratory failure and ARDS, hypercoagulability with tromboembolism and multiple organ system failure can occur. Due to the increased use of therapeutic strategies for infertility (particularly those using human chorionic gonadotropin), the systemic, particularly the pulmonary, complications of this syndrome must be identified early to allow appropriate diagnosis and management. We describe two cases of women with extremely severe OHSS presenting bilateral pleural effusions, and severe respiratory failure ($paO_2/FiO_2 < 200$) treated with non-invasive ventilation (NIV). The severe form of OHSS varies between 0.5% and 5% , depending on the population studied: intensive care may be required for management of tromboembolic complications, renal failure and severe respiratory failure. The diagnosis of severe OHSS was made, largely based on bedside ultrasonography showing increased ovarian size, mild ascites and bilateral pleural effusions. Owing to severe respiratory failure the patients were admitted to Respiratory Intermediate Care. Pulmonary intensive care may involve thoracentesis, oxygen supplementation and in more severe cases assisted ventilation. There are only a few studies in English that describe severe respiratory failure treated with non-invasive ventilation, but all of them have had good outcomes.

Keywords: *ovarian hyperstimulation syndrome, severe respiratory failure, non-invasive ventilation*

Rezumat

Sindromul de hiperstimulare ovariană (SHO) este o complicație severă dar rareori fatală a intervențiilor medicale menite să inducă fertilizarea; se întâlnește cel mai frecvent la femei la care se practică hiperstimularea ovariană controlată, dar sunt foarte rare la paciente cu defecte genetice ce se prezintă ca SHO. În ultimii ani, patogeneza sindromului a fost elucidată; această cunoaștere va reduce frecvența sindromului. Semnele clinice pot include oricare din următoarele sau pe toate: creștere rapidă în greutate, ascită, oligurie, hemoconcentrare, leucocitoză, alături de hipovolemie intravasculară, hiponatremie și hiperpotasemie. Dacă diagnosticul nu se pune rapid, pot apărea ascită, revărsate pleurale și mai rar și pericardice, insuficiență respiratorie severă și sindrom de detresă, hipercoagulabilitate cu trombembolism și insuficiență multiplă de organe. Datorită creșterii utilizării strategiilor terapeutice pentru infertilitate (mai ales cele folosind gonadotropină umană corionică), complicațiile sistemice și mai ales pulmonare ale sindromului trebuie identificate precoce, pentru a permite un diagnostic și management potrivite. Prezentăm două cazuri de femei cu SHO extrem de sever, cu revărsate pleurale bilaterale și insuficiență respiratorie severă ($PaO_2/FiO_2 < 200$) tratate cu ventilație non-invazivă (VNI). Formele severe de SHO apar între 0,5 și 5%, în funcție de populația studiată. Poate fi necesară terapia intensivă pentru managementul trombembolismului, insuficienței renale și insuficienței respiratorii severe. Diagnosticul de SHO s-a făcut în principal pe echografia la pat, relevând creșterea în dimensiuni a ovarelor, ascita moderată și revărsatele pleurale bilaterale. Datorită insuficienței respiratorii severe, pacientele au fost admise în secția de Terapie Intensivă Respiratorie. Terapia intensivă poate implica toracocenteză, suplimentare a oxigenului și în cazuri mai severe, ventilație asistată. În literatura medicală de limbă engleză există doar puține studii care să descrie insuficiența respiratorie severă tratată cu ventilație non-invazivă, dar toate arată rezultate pozitive.

Cuvinte-cheie: *sindrom de hiperstimulare ovariana, insuficiență respiratorie severă, ventilație non-invazivă*

Introduction

The ovarian hyperstimulation syndrome (OHSS) is a serious and potentially lethal physiological complication that classically occurs in female patients who undergo cycles of ovarian hyperstimulation. It is rarely seen in absence of fertility therapies and is much more common when human chorionic gonadotropin is used[1]. The recent Canadian classification[1] is cumbersome, so we have used an older and more descriptive system. OHSS is characterized by a broad spectrum of clinical and laboratory manifestations caused by exogenous administration of substances used for simple induction of ovulation, medically assisted procreation, or the induction of multiple follicular growth[1,2].

OHSS is due to an abnormal response to ovarian stimulation and characterized by an excessive increase of the size of the ovaries (both 5-12 cm in their largest diameters)[1] and increased capillary permeability. This allows the passage of fluid from the vascular system to the extravascular space[1-5]. This results in the formation of ascites and pleural effusions, along with hypovolemia, oliguria, hemoconcentration, electrolyte abnormalities, and rarely disseminated intravascular coagulation[3-5].

The milder forms are noted in 25-30% of induction cycles for multiple ovulation, whereas more severe forms have a variable incidence from 0.5 to 5%[2,3]. Cases of deaths due to cerebral thromboembolism, acute renal failure, ARDS, and cardiopulmonary arrest have also been reported[2-6]. The syndrome is classified in various stages depending on the severity according to the criteria suggested by Golan, which were later modified by Navot[7,8] (Table 1).

Case reports

Case 1

A 42 year-old patient was admitted to the Emergency Department complaining of abdominal distension, dry cough and increasing dyspnea. The patient had recently been undergoing controlled ovarian stimulation protocol based on follicle-stimulating hormone (FSH), gonadotropin-releasing hormone (GRH) and human chorionic gonadotropin (hCG) that preceded the 11-day in-vitro fertilization. At the time of admission to the Emergency Department (14 days after administration of the ovarian stimulation protocol), clinical examination revealed: respiratory rate, 35 breaths per minute; heart rate, 120 beats per minute; blood pressure 95/55 mmHg with body temperature 37.4°C. Auscultation of the chest showed a paucity of the breath sounds in both basal lung zones and numerous rales in both median and basal lung zones. Abdominal ultrasound showed a significant symmetrical increase in ovarian size with mild ascites; echocardiography revealed a modest pericardial effusion. Chest X-ray showed a bilateral pleural effusion (Figure 1a). Among the serum levels measured the most significant were: hCG 704.6 mIU/ml, estradiol 4,419 pg/ml (normal levels in the non-pregnant female is <5 mIU/ml and 112-443 pg/ml at menstrual cycle peak respectively). Essential laboratory evaluations were performed: hemoglobin 10.7g/dl (12.0-15.8 g/dl), hematocrit 31.0% (35.4-44.4%), white blood cells, $14.4x10^9$/l, C-reactive protein 15.8 mg /l (<10mg/l), sodium 132 mEq/l (136-146 mEq/l) , potassium 3.29 mEq/l (3.5-5mEq/l), calcium 8.37 mg/dl (8.7-10.2 mg/dl), AST 50 U/l (12-38U/l), ALT 66 U/l (7-41 U/l), total protein 5.86 g/dl, (6.7-8.6 g/dl), albumin 3.02 g/dl (3.5-5.5 g/dl), LDH 321 U/l, (115-211), fibrinogen 608 mg/dl (233-496), antithrombin III 92% (75-125%) d-dimer 1.76 (nv < 0.50).

The arterial blood gases (ABG) in room air revealed PaO_2 36.0 mmHg, $PaCO_2$ 33.7 mmHg, pH 7.47, PaO_2/FiO_2 171, lactic acid 1.2 mmol/l, and in oxygen therapy administered via Venturi mask at an inspiratory flow (FiO_2) of 50% demonstrated: PaO_2 65.0 mmHg, $PaCO_2$ 34.5 mmHg, pH 7.46, PaO_2/FiO_2 130, lactic acid 1.2 mmol/l. The patient was treated with non-invasive ventilation (NIV) using the NIV dedicated ventilator (Philips Respironics V 60), setting to 9 cmH_2O expiratory pressure and FiO_2 40% and oro-nasal mask. After 1 hour of treatment with CPAP, ABG was repeated: PaO_2 88 mmHg, $PaCO_2$ 36.4 mmHg, pH 7.44; the PaO_2/FiO_2 ratio had risen to 220. The patient continued NIV with rapid improvement (9). She was also treated with albumin (200 ml per day), crystalloids (2000 ml per day), dopamine 400 mg/24 hours, low molecular weight heparin (enoxaparin 4000 U/day), broad-spectrum antibiotics (ceftriaxone 2 g/day) and high dose furosemide (250 mg/day).

The following day clinical signs significantly improved and the patient was much improved both in clinical and laboratory parameters. The ABG demonstrated: PaO_2 80 mmHg, $PaCO_2$ 41.1 mmHg, pH 7.38, PaO_2/FiO_2 320 with FiO_2 25%. The NIV was stopped. A second chest X ray performed two days later showed an almost complete resolution of pleural effusion and pulmonary edema (Figure 1b). Three days later, following the complete resolution of the complications of ovarian hyperstimulation, the patient was discharged in good condition.

Table 1 Clinical classification of OHSS

Mild OHSS	Grade 1	abdominal distention and discomfort
	Grade 2	Grade 1 + nausea, vomiting and/or diarrhea, increased ovarian volume
Moderate OHSS	Grade 3	mild OHSS + ascites ultrasound evidence
Severe OHSS	Grade 4	moderate OHSS + clinically evident ascites and/or hydrothorax or breathing difficulties
	Grade 5	OHSS all previous + hypovolemia with hemoconcentration (Hct> 45%, white cells count > 15.000?), decreased renal function (oliguria, creatinine 1.0-1.5, creatinine clearence ≥ 50 ml/min.),liver dysfunction, anasarca
Critical OHSS	Grade 6	massive ascites ± hydrothorax, Hct> 55%, white cells count> 25.000?, oliguria, creatinine ≥ 1.6, creatinine clearence <50 ml/min, renal failure, thromboembolic phenomena, ARDS

Hct = haematocrit; **ARDS** = acute respiratory distress syndrome

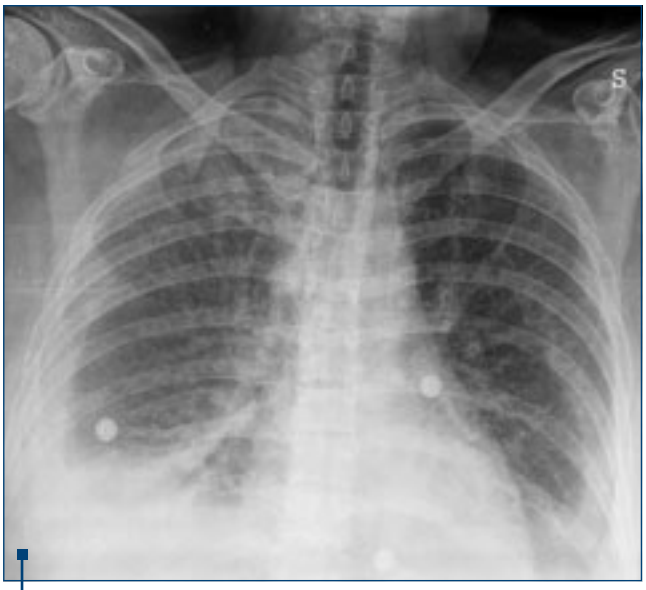

Figure 1a. *Chest X-ray at admission: bilateral pleural effusions and interstitial reticular*

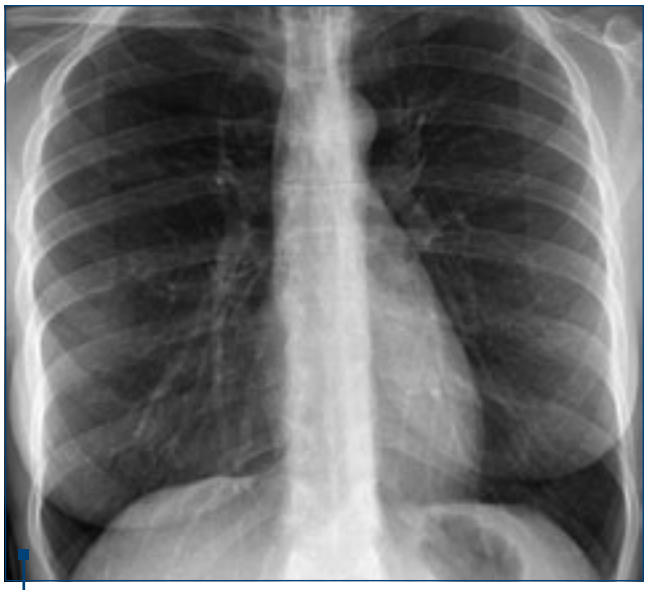

Figure 1b. *Chest X-ray before discharge: almost complete resolution of the radiological picture*

Case 2

This 38 year-old patient was admitted to the Emergency Department because of onset of rapid weight gain, abdominal distension, malaise with increasing dyspnea and dry cough.

The patient had recently been undergoing controlled ovarian stimulation protocol using FSH, GnRH and HCG that preceded the 11-day in-vitro fertilization. At the time of admission to the Emergency Department, she presented the following clinical picture: respiratory rate, 32 breaths per minute; heart rate 116 beats per minute; blood pressure 90/60 mmHg with body temperature 37°. Auscultation of the chest showed a decrease in the breath sounds in the right lung and crackles in the basal left lung zones. Abdominal ultrasound showed an increase in bilateral ovarian size with mild ascites; echocardiography, without pericardial effusion. Chest X-ray showed a massive pleural effusion involving most of the right lung. (Figure 2a). Among the laboratory studies, the most significative were: hCG 698.8 mIU/ml, estradiol pg 4288/ml hemoglobin 10.4g/dl, hematocrit 30.9%, white blood cells, 13.1x10^9/l, C-reactive protein 13.2 mg/dl, sodium 131 mEq/l, potassium 3.35 mEq/l, calcium 8.44 mg/dl, AST 49 U/l, ALT 70 U/l, GGT 50 U/l, total protein 5.90 g/dl, albumin 3010 mg/dl, ferritin 201.0 g/l, LDH 266 U/l, fibrinogen 588 mg/dl, antithrombin III 100% , d-dimer 1.87. Normal laboratory values are given in Patient 1's description. Thoracentesis was performed immediately with extraction of 1500 cc of pleural fluid. The initial ABG performed with the administration of oxygen via Venturi mask FiO2 50% demonstrated: PaO2 60.1 mmHg, $PaCO_2$ 36.9 mmHg, pH 7.48, PaO_2/FiO_2 120, lactic acid 1.2 mmol/l. She was admitted to the Respiratory Intermediate Care Unit (the patient refused insertion of a pleural drainage tube). She underwent NIV using dedicated NIV platform ventilator (Respironics V60) setting to 12 cmH_2O expiratory pressure and FiO_2 45% and oro-nasal mask. After 1 h of treatment with CPAP, ABG demonstrated PaO_2 94 mmHg, $PaCO_2$ 39.9 mmHg, pH 7.45 and the PaO_2/FiO_2 ratio had risen to 213. The patient continued the NIV (9). The improvement of respiratory parameters and ABGs are reported in Table 2. She was also treated with I.V. albumin (200 ml per day), I.V. crystalloids (2,000 ml per day), dopamine 400 mg/24 hours, low molecular weight heparin (enoxaparin 4,000 U/day), broad-spectrum antibiotics (piperacillin/tazobactam 18 grams/day) and high dose furosemide (250 mg/day). After 36 hours the patient showed improvement; NIV was withdrawn. Three days later she significantly improved and the patient was transferred to Pulmonary Ward, where underwent a second thoracentesis (900 ml of fluid were drained). Pleural fluid analysis yielded a transudate. Three days later she underwent a third thoracentesis of 600 ml. Five days later, following the complete resorption of pleural effusion demonstrated by chest X-ray performed on the day prior to discharge (Figure 2b), the patient was dismissed in good general condition.

The two patients gave informed consent for publication of these case reports along with accompanying images. No patient can be identified from the material in this paper

Discussion and conclusions

Ascites and ovaries often larger than 5 cm are cardinal signs of this syndrome. Among the clinical manifestations of OHSS, respiratory complications (particularly the pleural effusion, pulmonary edema and respiratory failure) have been sporadically reported in the literature[10-19]. However, several cases have been described in which pleural effusion was the only sign of the syndrome[11-16].

The cases of unilateral pleural effusion (often right) with minimal or no ascites are described in the literature, although they are uncommon[14,15]. Pulmonary edema complicating OHSS has been reported as a low-pressure edema, leading to acute respiratory distress syndrome requiring intensive care[20,21]. Regarding the pathophysiology of pleural

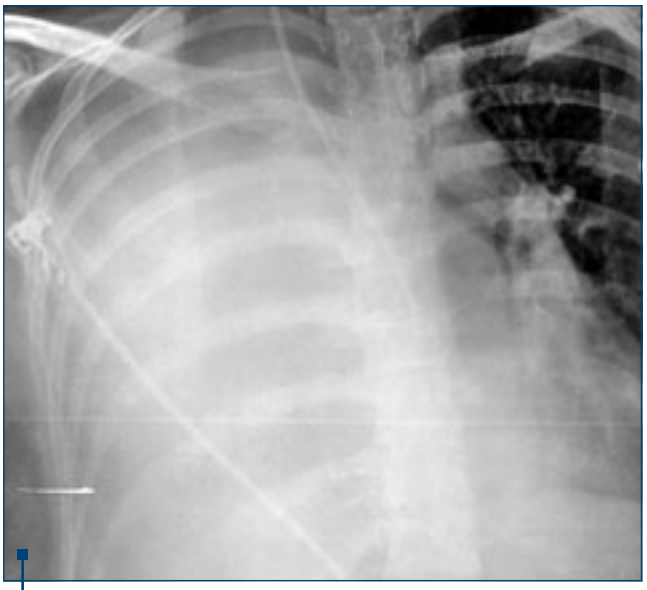

Figure 2a. *Chest X-ray at admission: opacity of the most of the right lung with contralateral mediastinal shift due to massive pleural effusion*

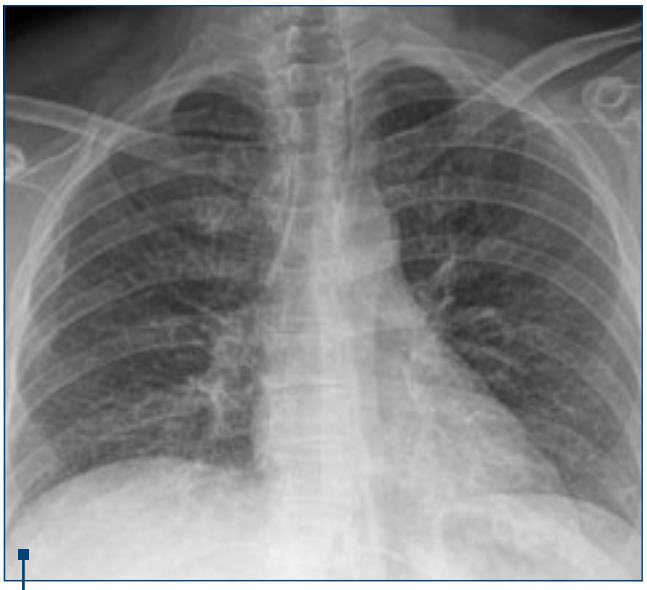

Figure 2b. *Chest X-ray before discharge showing the almost complete resolution of the right pleural effusion*

effusion in the absence of massive ascites, several hypotheses have been formulated: the passage of ascitic fluid into the pleural cavity through the diaphragmatic lymphatic system (as in hepatic cirrhosis and Meigs' syndrome); the presence of anatomical defects of the membranous part of the diaphragm, principally the right hemidiaphragm. The rupture of these small malformations caused by increased pressure due to ascites and/or the physiological negative pressure existing inside the thorax could convincingly explain the presence of massive right pleural effusions in the absence of ascites (case 2).[16,17].

Complications endanger the lives of patients. These include poor management of hypovolemia as well as difficult to manage entities: hemorrhagic syndromes, hepatorenal syndromes, thromboembolism and acute respiratory distress syndrome (ARDS)[18,20,21]. Several different risk factors related to the severity of the syndrome have been described: age (under 35 years), low BMI, polycystic ovarian syndrome[2], ectopic syndromes and pregnancy[3,20]. Urine pregnancy tests must be performed at least twice a week during ovarian stimulation.

Golan and Navot's classification (Table 1) place our patients between grade 5 and grade 6. Moreover, the presence of massive pleural effusion predominantly on the right and the level of severity of deficit of the gas exchange (a low PaO_2/FiO_2 ratio), within a framework that according to Berlin ARDS criteria[22] could be classified as mild ARDS, placing these two patients among the critical forms of respiratory disease. The presence of massive pulmonary edema is rarely reported in the syndrome and sometimes with fatal outcome[23]; more frequent is pulmonary thromboembolism (12%)[1-3]. Even more common are deep venous thrombosis, in particular the upper parts of the body, and arterial thrombosis (likely a result of hypercoagulability)[1,2,20]. In the literature, hemoconcentration is often seen[1,22,23]; it is our opinion that the dilution of the intravascular space is an intermediate stage that is a precursor to subsequent hemoconcentration which increases thromboembolic events (which were not seen in our patients). Ascites, hypotension, and sudden weight gain (the cardinal signs of the syndrome) must be monitored by the fertility team and by the patient at home. A scale and a measuring tape for

Table 2 Respiratory parameters and arterial blood gases

	0 h	1 h	12 h	24 h	48 h	36 h withdraw
RR	36	30	27	25	22	19
CPAP		12	12	8	8	5
FiO_2%	50	45	45	40	30	25
PaO_2	60	94	108	108	100	103
$PaCO_2$	36	39	35	35	34	36
pH	7.48	7.46	7.45	7.44	7.43	7.42
HCO_3	22.4	22.6	26.2	25.5	24.8	24.2
P/F	120	213	240	272	333	412
Lactic acid mmol/L	1.2	1.1	0.9	0.7	0.7	0.6

RR = respiratory rate; **CPAP** = continuous positive air way pressure; **FiO_2%** = oxygen inspiratory fraction; **PaO_2** = oxygen arterial pressure; **$PaCO_2$** = carbon monoxide arterial pressure; **P/F** = PaO_2/FiO_2 ratio

abdominal umbilical circumference is an excellent "early warning system" if used once or twice daily. OHSS is typically characterized by the passage of fluid into the extravascular space; it follows an intravascular fluid depletion. In the literature, hemoconcentration is often seen[1,22,23]; it is our opinion that the dilution of the intravascular space is an intermediate stage that is a precursor to subsequent hemoconcentration which increases thrombo-embolic events (which were not seen in our patients). Emergency Department physicians should ask the patient about ongoing fertility protocols as well as personal and family history. Due to the increased use of therapeutic strategies for infertility, the systemic complications of this syndrome must be identified early to allow appropriate diagnosis and management. A normal hCG does not exclude serious problems such ovarian torsion or displacement (often from mass lesions). Abdominal ultrasound is required to exclude potentially lethal entities uterine or ectopic pregnancy in a hemodynamically comprised patient. Unilateral ovarian or adrenal masses can have the same presentation. Each such patient requires the physician's full attention. Complications can occur with alarming velocity. Moreover, it has been shown that patients with OHSS have hyperdynamic circulation with increased cardiac output, plasma concentration of atrial natriuretic peptide (ANP) and a high pulmonary capillary wedge pressure[24,25]; these factors may explain the rationale for the use of NIV in that these factor reflect cardiac problem induced by OHSS[1,23-25]. Noninvasive ventilation in OHSS has been rarely described in the literature. There are only a few cases in the English medical literature, but always with good outcomes[14,19,25]. High levels of estrogens lead to increased vascular endothelial growth factor (VEGF); increased release of cytokines such as IL-2, IL-6 and IL-8; the renin-angiotensin system, aldosterone, and ANP; and higher levels of tumor necrosis factor-alpha (TNF-α)[1,3,5,11,18]: all of which increase cellular and vascular permeability. Many clinical entities do the same. The pathogenesis of OHSS is now known[3,5,26]. It begins with high levels of hCG stimulating large numbers of granula-lutein cells which induce increases in mRNA vascular endothelial growth factor (VEGR) and up regulates VEGR-2 receptors. The levels of hCG, VEGR and VEGR-2 receptors are highest when the vascular permeability is highest; the former causes the latter[3,26]. This starts a cascade effect, bringing the other categories of paracrine factors into play. The study of extremely rare mutations in the FSH receptor gene (e.g., substitution of adenosine instead of guanine at the first base of codon 567 in exon 10 of this gene) which causes receptor resistance (poor binding in the paracrine environments of the ovaries). These very rare mutations drive the normally low levels of local hCG high in the local pituitary and especially the ovaries paracrine environments and can induce "spontaneous" OHSS particularly during the luteal phase[3,26]. This is a molecular model for "iatrogenic" OHSS. The use of protocols without hCG (i.e., using FSH and GnRH) virtually eliminate OHSS[3,25,26].

In conclusion, a severe form of OHSS should be suspected in any female patient presenting with ascites and/or pleural effusion with history of controlled ovarian stimulation. This syndrome requires a multidisciplinary approach to avoid the risk of multi-organ complications and events that put at risk the life of the patient. Early diagnosis and aggressive treatment are the critical factors that prevent fatal outcomes. ■

Conflict of interest: The authors declare no conflicts of interest.

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