

# Thrombosis of Subclavian and Internal Jugular Veins Following Severe Ovarian Hyperstimulation Syndrome: A Case Report

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## Abstract

**Background:** Ovarian hyperstimulation syndrome (OHSS) is a serious, albeit rare, complication of fertility treatment. In its severe form, it may be life-threatening.

Increased vascular permeability with hemoconcentration is the hallmark of the syndrome. Vascular thromboembolism is a significant potential complication.

**Case:** A previously healthy 26-year-old nulligravid woman developed severe OHSS following an in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) treatment cycle. She required hospitalization for treatment comprising IV fluid replacement, albumin infusion, paracentesis, and prophylactic heparin. She presented two days after discharge from hospital with left arm edema and neck pain. Subclavian and internal jugular vein thrombosis was diagnosed.

**Conclusion:** OHSS is a serious complication of treatment for ovulation induction and is a significant risk factor for vascular thrombosis. Patients remain at risk even if given prophylactic heparin. The clinical presentation of OHSS may be unusual and late, indicating the importance of vigilance on the part of all physicians caring for patients who have undergone fertility treatment.

## Résumé

**Contexte :** Le syndrome d'hyperstimulation ovarienne (SHO) est une complication grave, bien que rare, de la prise en charge de l'infertilité. Dans sa forme grave, il peut constituer un danger de mort.

Une perméabilité vasculaire accrue et une hémococoncentration constituent le signe distinctif du syndrome. La thromboembolie vasculaire constitue une complication potentielle importante.

**Cas :** Une nulligravide de 26 ans auparavant en santé en est venue à présenter un SHO grave à la suite d'un cycle de traitement « fécondation *in vitro*/injection intracytoplasmique d'un spermatozoïde (FIV/IICS) ». La patiente a dû être hospitalisée en vue de recevoir un traitement composé d'un remplacement liquidien IV, d'une perfusion d'albumine, d'une paracentèse et d'un traitement prophylactique à l'héparine. Deux jours après avoir

obtenu son congé de l'hôpital, elle présentait un œdème au bras gauche et des douleurs au cou. Une thrombose de la veine sous-clavière et de la veine jugulaire interne a été diagnostiquée.

**Conclusion :** Le SHO est une complication grave du traitement visant le déclenchement de l'ovulation et constitue un facteur de risque important en ce qui a trait à la thrombose vasculaire. Les patientes demeurent exposées au risque, même lorsqu'on leur administre un traitement prophylactique à l'héparine. Le tableau clinique du SHO peut être inhabituel et tardif, ce qui indique l'importance de la vigilance de la part de tous les médecins qui offrent leurs services à des patientes ayant subi un traitement contre l'infertilité.

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## INTRODUCTION

Ovarian hyperstimulation syndrome is the most serious complication of assisted reproductive technology. It results from an excessive ovarian response to stimulation during fertility treatment. The reported incidence of OHSS varies widely because a variety of classification schemes is used to estimate it. Mild forms of OHSS have been reported in as many as 33% of IVF cycles. However, the severe forms have been reported in 3.1% to 8.0% of IVF cycles.<sup>1</sup>

In its severe form, OHSS is characterized by massive ovarian enlargement, hypovolemia, hemoconcentration, and hypoalbuminemia. There is a significant fluid shift from the intravascular to the extravascular compartment. This “third spacing” can give rise to ascites formation, pleural effusion and peripheral edema.<sup>2–4</sup> Thromboembolic events, a rare complication of OHSS, are believed to be related to the associated hemoconcentration and the hyperestrogenic environment.

We report a case of severe OHSS following IVF-ET that was complicated by unusual and serious thrombosis of the subclavian and internal jugular veins. This thrombus developed despite prophylaxis with LWMH.

**Key Words:** Severe ovarian hyperstimulation syndrome (OHSS), thrombosis, subclavian vein, internal jugular vein, IVF-ET

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**THE CASE**

The patient, a healthy 26-year-old nulligravid woman, was referred to our Assisted Reproductive Technology Unit for IVF-ET. She and her husband had an eight-year history of primary infertility. She had regular menses, and a sonohysterogram demonstrated a normal uterus and patency of both fallopian tubes. Her past medical history and family history were unremarkable. She was on no medication and was a non-smoker.

Her husband, a healthy 43-year-old with four children from a previous relationship, had undergone a vasectomy nine years previously. He was azoospermic following an unsuccessful reversal of vasectomy.

The couple wished to undergo treatment with IVF/ICSI and testicular sperm extraction.

The patient used a combined oral contraceptive preparation for 21 days followed by buserelin (a GnRH agonist) 0.2 mg subcutaneously per day, beginning five days before discontinuing the oral contraceptive preparation continuing until the day of hCG injection.<sup>5</sup> Ovarian stimulation using 150 IU of rFSH was then introduced beginning on cycle day three and continued for eight days for a total dose of 1200 IU. The patient self-injected hCG on day 10 of stimulation, at which time the serum E<sub>2</sub> level was 16 736 pmol/L. Administration of rFSH had been withheld for two days because the serum E<sub>2</sub> level had risen above 10 000 pmol/L. On the day of hCG injection, the patient had 15 follicles  $\geq$  15 mm in mean diameter. To reduce the potential for OHSS, the patient was instructed to reduce the dose of hCG from 10 000 IU to 5000 IU.<sup>2</sup> Transvaginal oocyte retrieval was performed 35 hours after hCG administration. Following aspiration of fluid from approximately eight follicles in one ovary, no oocytes were found. Follicular fluid, urine, and serum were all negative for  $\beta$ -hCG. Further investigation revealed that the patient had mistakenly

injected herself with the hCG diluent rather than the reconstituted hCG. Once this error was identified, hCG 10 000 IU was injected subcutaneously, and a second oocyte retrieval was scheduled for 35 hours later. The serum E<sub>2</sub> level was not measured before the "second" dose of hCG was given. At this second retrieval, six oocytes were obtained, and all were injected with previously cryopreserved testicular sperm extraction sperm. One 8-cell and one 4-cell embryo, each of medium quality, were transferred to the uterus on the third day after retrieval. Micronized progesterone 200 mg was inserted intravaginally three times daily for luteal support.

Three days after embryo transfer, the patient presented with signs and symptoms of mild to moderate OHSS: she had abdominal bloating, mild nausea, pelvic discomfort, abdominal distension, and bilateral ovarian enlargement up to 9 cm. Her weight and vital signs were stable. Laboratory studies, including hemoglobin, hematocrit, white blood cell count, renal function, and electrolytes showed normal results.

Five days later, the patient presented with rapidly worsening symptoms, including abdominal distension and discomfort, nausea, dyspnea and increasing weight gain. Laboratory studies showed hemoconcentration (hematocrit 54%, hemoglobin 179 g/L), leukocytosis (WBC  $26 \times 10^9$ /L), and hypoalbuminemia (serum albumin 24g/L). The serum  $\beta$ -hCG level was 157 IU/L. A clinical diagnosis of severe OHSS associated with early pregnancy was made,<sup>3</sup> and the patient was hospitalized for fluid management and paracentesis through an intraperitoneal drainage catheter. She required intravenous fluid therapy with large volumes of crystalloid, and she received 25% albumin intravenously at six-hour intervals to maintain her intravascular volume. Maintaining intravenous access was difficult because of peripheral edema, so a peripherally inserted central catheter line was inserted through the left basilic vein. The patient received prophylactic heparin (initially fractionated heparin 5000 IU subcutaneously twice daily, then tinzaparin 4500 IU subcutaneously once daily). The progressive rise in serum  $\beta$ -hCG suggested that the pregnancy was viable. The patient's condition improved after seven days of active management, and she was discharged from hospital 11 days after admission. The peripherally inserted central catheter line was removed and prophylactic tinzaparin was discontinued at the time of discharge.

Forty-eight hours after discharge, the patient presented with acute swelling of the left arm and pain radiating up to the left side of the neck. No motor or sensory deficits were identified. Doppler ultrasound of the left arm and neck showed an extensive left subclavian vein thrombosis extending into the left internal jugular vein. Treatment with

**ABBREVIATIONS**

E <sub>2</sub>	estradiol
ET	embryo transfer
FSH	follicle stimulating hormone
GnRH	gonadotropin-releasing hormone
hCG	human chorionic gonadotropin
ICSI	intracytoplasmic sperm injection
IVF	in vitro fertilization
LH	luteinizing hormone
LMWH	low molecular weight heparin
OHSS	ovarian hyperstimulation syndrome
VEGF	vascular endothelial growth factor

**Table 1. Classification of OHSS**

Mild	Moderate	Severe
<ul style="list-style-type: none"> <li>• Ovaries <math>\leq</math> 5 cm</li> <li>• Abdominal distention/discomfort</li> <li>• Nausea, vomiting, diarrhea</li> </ul>	Mild Plus <ul style="list-style-type: none"> <li>• Ovaries 5–12 cm</li> <li>• Sonographic evidence of ascites</li> </ul>	Moderate Plus <ul style="list-style-type: none"> <li>• Ovaries <math>&gt;</math> 12 cm</li> <li>• Clinical ascites and /or hydrothorax</li> <li>• Respiratory compromise</li> <li>• Hypovolemia, hemoconcentration oliguria, coagulopathy or liver dysfunction</li> </ul>

Adapted from Aboulghar et al.,<sup>4</sup> Schenker et al.,<sup>20</sup> and Golan et al.<sup>34</sup>

tinzaparin 10 000 IU subcutaneously once daily was initiated and provided rapid relief of symptoms. A pelvic ultrasound done at six weeks' gestation showed a live intrauterine dichorionic twin pregnancy. After consultation with a hematologist, a thrombophilia screen (including antithrombin, protein C, protein S, activated protein C resistance, factor V Leiden mutation, prothrombin 20210 A variance, lupus anticoagulant, anti-nuclear antibodies, and antiphospholipid antibody) was carried out with negative results.

The pregnancy was subsequently uneventful until 24 weeks and 6 days of gestation, when the patient developed preterm labour. She delivered twin female infants weighing 647 g and 600 g. She continued with prophylactic tinzaparin treatment for three months post partum.

## DISCUSSION

Supraphysiologic stimulation of the ovaries is a key component of the current regimens of controlled ovarian hyperstimulation for assisted reproductive technology. Its aim is to optimize the numbers of oocytes and embryos available while keeping ovarian response within safe limits.<sup>4</sup> Although some degree of ovarian hyperstimulation occurs in all women who respond to ovulation induction, it should be distinguished from the clinical entity of ovarian hyperstimulation syndrome.<sup>4</sup> Unfortunately, OHSS can occur despite careful monitoring and application of preventive measures. OHSS is characterized by a continuum of severity ranging from a mild, self-limiting condition to a serious, potentially life-threatening, complication. Severe OHSS complicates about 0.5% to 5 % of all ovulation induction cycles<sup>6</sup> and can cause significant morbidity and, rarely, mortality.<sup>7,8</sup>

Traditionally, OHSS has been classified into mild, moderate, and severe, using clinical manifestations and laboratory and ultrasonographic findings. A recent modified classification of OHSS has been introduced<sup>4</sup> (summarized in Table 1). Recognizing patients with risk factors for OHSS (Table

2) is the first step in preventing this condition, but up to one third of cases of severe OHSS occur in patients considered to be at low risk.<sup>9</sup>

Patients with OHSS present with a combination of the clinical manifestations shown in Table 3.

## Pathogenesis of OHSS

The pathogenesis of OHSS remains enigmatic. Although the great majority of OHSS cases follow ovulation induction therapy, it may rarely occur following spontaneous pregnancy. The risk of OHSS is increased in multiple gestation or molar pregnancy,<sup>10</sup> likely related to higher circulating levels of  $\beta$ -HCG.

Human chorionic gonadotrophin, either exogenous or endogenous, seems to be the pivotal stimulus of the syndrome in a susceptible woman.<sup>11</sup> The hyperestrogenic state generated by ovulation induction therapy has been widely implicated in the genesis of OHSS. A possible genetic predisposition to the spontaneous form of OHSS has recently been explored. A potential mutation of the hCG-lutenizing hormone receptor gene has been identified as a predisposing factor.<sup>12</sup> Similarly, other recent case reports described mutations in the FSH receptor.<sup>13,14</sup> This spontaneous form of OHSS could potentially provide clues to a better understanding of the iatrogenic form of the syndrome, which accounts for the great majority of OHSS cases.

In addition, a possible role of immunological and non-immunological mediators has been suggested by numerous studies. These include VEGF, renin, angiotensin, estrogen, prostaglandins, histamine, prolactin, interleukins, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and endothelin-1. With the exception of VEGF, only scant data support an important role for any of these mediators. Recently, a growing body of evidence suggests that VEGF is the most likely modulatory factor in the pathogenesis of OHSS.<sup>15</sup> It has been shown that VEGF, mediated in part by nitric oxide, causes increased endothelial permeability. Inhibition of nitric oxide reverses this increased permeability.<sup>3</sup>

It is currently believed that the increased permeability of endothelial surfaces is the key factor in the genesis of OHSS-associated morbidity. Moreover, high levels of VEGF were found to be responsible for the systemic manifestations associated with this condition and may also be directly correlated with its severity.<sup>16</sup> Although roles of these factors in OHSS seem biologically plausible, the complex interactions and intercellular signalling between them have not yet been fully elucidated.

A key feature of OHSS in all its forms is increased capillary permeability leading to a global increase in vascular permeability in virtually all vascular beds of the body. As a result, the “vascular leak syndrome” develops. Most of the clinical features of the disease can be attributed to this phenomenon. Fluid sequestration in the peritoneal space and, sometimes, the pleural cavity results in ascites and pleural effusion. Moderate or severe fluid shift leads to significant intravascular hypovolemia and hemoconcentration. Without appropriate IV fluid therapy, this can lead to hypotension with a drop in central venous pressure. Likewise, impaired renal perfusion results in prerenal azotemia and oliguria, which, if untreated, can result in acute renal failure.

### Thromboembolic Phenomena

By far the most sensitive indicator of the severity of OHSS is hemoconcentration (as measured by hematocrit) with increased blood viscosity.<sup>17</sup> Severe hemoconcentration may also cause polycythemia and leukocytosis (leukocyte count of  $22 \times 10^9/L$ ). Hemoconcentration and fibrinolytic system activation are ominous signs of imminent thromboembolism.<sup>17</sup>

Vascular thrombosis is the most serious complication of OHSS and has been reported in many sites of the body, including internal jugular, subclavian, axillary, ulnar, popliteal, cortical, mesenteric, coronary, and cerebral vessels. A review of thromboembolic events associated with ovulation induction between 1964 and 1997 was reported by Stewart et al.<sup>18</sup> During this interval, 54 cases were reported, and 66% of them (35/54) were associated with OHSS. The majority of cases (75%) had thrombosis of venous sites, with 60% of these developing in the veins draining the upper extremity, head or neck area. A more recent review by Rao et al. identified an additional 42 cases of thromboembolic events, 90% of which were associated with OHSS.<sup>19</sup> Slightly more than half (55.5%) had thrombosis of venous sites, with 85% of these developing in the venous system draining head, neck area, and upper extremity.

The etiology of OHSS-associated thromboembolic events is not completely understood. According to Schenker and

**Table 2. Risk factors for OHSS**

Young age < 35 years
Low body mass index
Previous history of OHSS
Pregnancy
Polycystic ovary syndrome
GnRH agonist protocol
Rapidly increased serum estradiol levels
Multiple ovarian follicles
hCG luteal supplementation

Adapted from Delvigne et al.,<sup>1</sup> Gardner et al.,<sup>5</sup> and Enskog et al.<sup>33</sup>

**Table 3. Clinical manifestations of OHSS**

Lower abdominal pain/discomfort/distension
Ascites
Weight gain
Peripheral edema
Nausea, vomiting, or diarrhea
Breathing difficulty
Oliguria
Generalized edema (anasarca)
Pleural effusion
Hypovolemic shock

Adapted from references Delvigne A et al.<sup>3</sup> and Budev et al.<sup>47</sup>

Weinstein,<sup>20</sup> major changes in ovarian hormone production induced by FSH stimulation play a role. Several changes have been demonstrated in the hemostatic system during OHSS. Hemoconcentration and activation of the coagulation cascade, increased activity of the thrombin-antithrombin III and plasmin-antiplasmin complexes, elevated platelet levels, and increased fibrinogen levels have all been reported in patients with OHSS<sup>21</sup> and can induce a hypercoagulable state.<sup>22</sup> The net effect of these hemostatic alterations is disruption of the delicate balance between coagulation and thrombolysis. It is still unclear how some patients with OHSS may develop vascular thrombosis despite being treated with prophylactic heparin.<sup>23</sup>

Two aspects of OHSS-associated thrombosis are noteworthy. First, not all patients with severe OHSS will develop vascular thrombosis. Conversely, some patients who undergo IVF treatment, but do not develop OHSS, may still be at risk for thrombosis.<sup>24,25</sup> In these cases, additional risk

factors such as an inherited or acquired hypercoagulable state may need to exist for thrombosis to occur. Second, the risk for thrombosis may remain for days to weeks after the clinical resolution of OHSS. This delay in presentation may result from the reduced metabolism of estradiol secondary to prolonged hepatic dysfunction often associated with OHSS.<sup>26</sup>

### Management of OHSS

In the majority of cases, particularly in the absence of pregnancy, OHSS is self-limiting.<sup>4</sup> Bed rest and maintenance of oral hydration usually suffice in this situation. More severe cases require medical and supportive management. Meticulous monitoring of hemodynamic stability, hematocrit, white blood cell count, serum electrolytes, coagulation profile, and renal and liver function is necessary. Intravenous hydration with normal saline remains the mainstay of treatment, with the goal to achieve and maintain euolemia and a normal urine output. When crystalloids alone are insufficient to achieve this goal, plasma expanders such as human albumin are indicated. Their use may at times be counterproductive, since albumin is transported across the “leaky” vascular walls to the extravascular space, increasing the potential for the development of progressive ascites, pulmonary congestion, and peripheral edema. Patients who develop tense ascites benefit greatly from the placement of an indwelling peritoneal catheter,<sup>27</sup> which provides immediate relief of abdominal distension and discomfort, and allows continued intravenous rehydration. Monitoring of urine output provides a good assessment of fluid status and resolution of OHSS, the hallmark of which is the onset of a vigorous diuresis.

Measures should be taken to reduce the risk of thromboembolism in patients with severe OHSS. Anti-embolic stockings may reduce the risk as well as helping to control peripheral edema. More importantly, such patients should receive prophylactic subcutaneous heparin. The reported standard dose is 5000 units of unfractionated heparin given twice daily.<sup>3</sup> Low molecular weight heparin such as tinzaparin may also be used. Thrombosis prophylaxis is especially critical in patients with severe hemoconcentration, a previous history of vascular thrombosis, or an acquired or inherited thrombophilia (e.g., antithrombin III deficiency, factor V Leiden mutation, protein C or protein S deficiency, anti-cardiolipin antibodies, or anti-nuclear antibodies), because the coexistence of any of these factors with hemoconcentration or hyperestrogenism markedly increases the risk of vascular thrombosis.<sup>28</sup> Difficulty with peripheral intravenous access due to peripheral edema or intravascular volume depletion may necessitate placement of a central venous catheter. While this may be necessary to maintain intravascular

volume, it may also increase the risk for the development of thrombosis, as happened in our patient.

Because of the possible serious consequences of thromboembolism, it has been suggested that patients be screened for inherited and/or acquired thrombophilia prior to undergoing ovulation induction therapy. Two recent studies came to opposite conclusions about this issue.<sup>29,30</sup> In the first, the authors concluded that screening for thrombophilia in an IVF general population cannot be justified when the clinically relevant end point is the prevention of one thrombotic event in patients developing severe OHSS.<sup>29</sup> They also concluded that the estimated cost of preventing one thrombotic event as a consequence of screening for some types of thrombophilia is prohibitively high. In the second study, an association between thrombophilia and severe OHSS was identified.<sup>30</sup> This association may substantially affect treatment decisions both during ovulation induction and later in life. The authors suggested that screening for thrombophilia may be worthwhile in two subsets of patients: women with a family or personal history of thrombosis who undergo ovulation induction, and women who develop or have developed severe OHSS after ovulation induction treatment.

At present, there is insufficient evidence to support or prohibit the routine use of LMWH in patients with severe OHSS.

### Prevention of OHSS

The best means of avoiding the consequences of OHSS is to prevent it occurring.<sup>1,31</sup> Identification of women at high risk, by considering the woman's age, BMI, basal FSH level, the identification of polycystic ovaries or polycystic ovary syndrome, and previous response to ovarian stimulation (if any), is important in determining the most effective and safe gonadotropin dose. Vigilant monitoring of the ovarian response to stimulation using transvaginal ultrasound and serum E<sub>2</sub> measurements is vitally important. A positive correlation between the presence of multiple (> 4.2) secondary follicles of size 14–16 mm and the development of severe OHSS has been found.<sup>32</sup>

Many studies have shown that serum E<sub>2</sub> levels are closely and positively correlated with the syndrome.<sup>30</sup> Since OHSS has occurred in women with serum E<sub>2</sub> levels < 1000 pg/mL (< 3671 pmol/L), it is thought that the rate of increase in serum E<sub>2</sub> is a more valuable predictor of OHSS than the absolute level.<sup>33</sup> This should be considered in conjunction with the number of follicles seen on ultrasound.<sup>34</sup>

Numerous studies have shown the effectiveness of a range of preventive measures for OHSS. These include the following:

- **Withholding hCG administration (cycle cancellation)**

This is considered to be the most effective preventive step. Its effectiveness is based on the well-established fact that the development of OHSS is utterly dependent on exposure to either exogenous or endogenous hCG. The role of withholding hCG administration is twofold: it induces apoptotic changes in granulosa cells, and this in turn reduces estrogen secretion and prevents luteinization with the associated release of cytokines and other vasoactive mediators that trigger and maintain OHSS.<sup>11</sup> Some investigators suggest withholding hCG in non-IVF cycles when peak serum E<sub>2</sub> levels exceed 2000 pg/mL (7340 pmol/L), and in IVF cycles when peak serum E<sub>2</sub> exceed 15 000 pmol/L.<sup>35</sup>

- **Withholding gonadotropins (coasting)**

This is the most frequently used preventive method in assisted reproductive technology cycles. Withholding or reducing the dose of gonadotropins causes smaller follicles to undergo atresia. As a result, the granulosa cell pool is diminished, with less estrogen produced. One of the advantages of this strategy is reduced cycle cancellation. The effectiveness of this strategy in different patient groups, the timing and duration of coasting, the timing of hCG administration, and the potential impact on pregnancy rates are issues that remain controversial. A review of relevant studies has been recently published.<sup>36</sup> A Cochrane review assessing the effect of coasting in the prevention of OHSS following superovulation in assisted reproduction treatment showed no difference between women who undergo coasting and women who do not in the incidence of moderate and severe OHSS and in the clinical pregnancy rate.<sup>37</sup> The authors of this review thought there was insufficient evidence to determine whether coasting is an effective strategy for preventing OHSS. A recent review of 10 studies suggested that coasting be initiated when the serum E<sub>2</sub> concentration exceeds 3000 pg/mL (11 013 pmol/L), but not unless the lead follicles are 15 to 18mm in diameter, and that the duration of coasting be limited to four days or less, in order to prevent the associated decline in implantation and pregnancy rates that often occur after longer periods of coasting.<sup>38</sup> The decision to initiate coasting should be individualized, with appropriate counselling and careful evaluation of each patient's risks and benefits.

- **Using LH to trigger final oocyte maturation**

The use of exogenous recombinant LH (rLH) as an alternative to hCG for final oocyte maturation and ovulation (in non-IVF cycles) has been suggested as a means of reducing the risk of OHSS. Recombinant LH has a shorter half-life than hCG (1–5 hr for rLH vs. > 1 day for hCG), and

therefore causes a much shorter duration of stimulation of corpora lutea than hCG, thus reducing the incidence of OHSS.<sup>39</sup>

- **Follicular aspiration**

In IVF patients, this method may help to remove the source of inflammatory and non-inflammatory mediators, including VEGF, that have been implicated in the genesis of this syndrome.

- **Using gonadotropin-releasing hormone agonists/antagonists**

A GnRH agonist (leuprolide 0.5–1.0 mg) can be given for final oocyte maturation, because it induces a sustained release (lasting > 24 hrs) of endogenous LH and FSH, thereby avoiding the effect of using hCG. This option is ineffective if a GnRH agonist has been used for pituitary down-regulation and is therefore an option only in cycles in which a GnRH antagonist has been used to prevent an LH surge.<sup>40</sup>

- **Embryo cryopreservation**

Another alternative to cycle cancellation in patients at risk for OHSS is oocyte retrieval and cryopreservation of embryos. This avoids pregnancy and the consequent rising titres of hCG, both known to exacerbate the syndrome. It is considered reasonable management in patients at high risk for OHSS to avoid transfer of fresh embryos and instead to undertake cryopreservation of all embryos.<sup>41</sup>

- **In vitro maturation of immature oocytes**

This is considered more suitable for patients with identified risk factors for OHSS, particularly polycystic ovary syndrome. After either no follicular stimulation or minimal stimulation, retrieval and in vitro maturation of immature oocytes is carried out. This has resulted in acceptable pregnancy rates,<sup>42</sup> although they are not comparable to those following controlled ovarian hyperstimulation and IVF using mature oocytes.

- **Intravenous albumin administration at the time of oocyte retrieval**

As noted, the hallmark of OHSS is the marked extravasation of intravascular fluid to the extravascular space. Several authors have proposed that the prophylactic administration of albumin at the time of oocyte retrieval may reduce the incidence of OHSS by increasing and maintaining intravascular oncotic pressure, thus reducing “third spacing,” and by “scavenging” vasoactive factors and other putative intermediates that have been implicated in the pathogenesis of OHSS.<sup>43–45</sup> A Cochrane review concluded that intravenous albumin administration helps to reduce the incidence.<sup>46</sup> Since this meta-analysis was based on a limited number of patients in randomized trials, additional randomized trials with larger numbers are clearly needed to determine if this intervention can actually prevent OHSS.

As our understanding of the pathophysiology of OHSS improves, more effective and reliable preventive measures may become available.

## CONCLUSION

Ovarian hyperstimulation syndrome is a serious and potentially life-threatening complication of assisted reproductive technology. In this report, we present an unusual case of severe OHSS complicated by a large thrombosis of the subclavian and internal jugular veins. This event occurred despite prophylactic anticoagulation with LMWH.

Thrombosis is a rare but life-threatening complication of OHSS. The clinical presentation of thrombosis in patients undergoing ovulation induction therapy can be both unusual and late. Therefore, all physicians providing care to these patients should have a high index of suspicion for this potential complication. Timely diagnosis and immediate initiation of treatment are crucial.

All patients with severe OHSS should receive prophylactic anticoagulation with heparin (either unfractionated or LMWH). Screening of all patients for inherited or acquired thrombophilia before initiation of any ovulation induction treatment remains controversial.

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