FOSTERING FERTILITY despite ovarian hyperstimulation

BY JEFFREY M. GOLDBERG, MD
Ovarian hyperstimulation syndrome (OHSS) is the most serious complication of the medical treatment of infertile women. This potentially life-threatening iatrogenic condition has challenged physicians since the inception of ovulation induction more than 30 years ago. Despite a great deal of basic science and clinical research, its etiology eludes us. Thus, OHSS is difficult—though not necessarily impossible—to prevent and predict, and treatment remains supportive and symptom-directed.

OHSS ranges from mild ovarian enlargement to severe multisystem failure, with death occurring in approximately 1 in 400,000 to 500,000 superovulation cycles.1 Of the several staging systems that have been developed to help guide patient management, the one by Navot et al is most useful, as it introduces a fourth category of critical disease (Table 1).2 In general, mild to moderate OHSS is treated expectantly on an outpatient basis, while women with severe OHSS should be hospitalized. Critical patients are best managed in an intensive-care setting in consultation with other specialists. This article focuses primarily on OHSS requiring hospitalization.

**Pathogenesis**

There appear to be 3 underlying pathophysiological processes leading to OHSS: angiogenesis, increased vascular permeability, and vasodilation. OHSS originates in the ovaries. Its basic features are enlarged multicystic ovaries and increased vascular permeability, with intravascular fluid loss into the third space. Study of the hyperstimulated ovaries reveals multiple hemorrhagic follicular and corpus luteum cysts, stromal edema, and neovascularization. The ascites of OHSS is a transudate/exudate from the peritoneum and is not derived from the ovarian surface. OHSS only occurs following ovulation.

The true incidence of OHSS is difficult to ascertain, due in part to the use of different classification systems. The wide variation in patient selection and the degree of aggressiveness in superovulation regimens also has a bearing, as do differences in the diagnosis of milder forms of the syndrome. It is likely that some degree of OHSS occurs in nearly all patients treated with gonadotropins. Thus, mild disease perhaps should be considered an accepted consequence of ovulation induction,3 while severe disease has been reported in only about 0.1% to 2% of superovulation and assisted reproductive technology (ART) cycles.1,4

In rare instances, severe OHSS has been reported with spontaneous pregnancies.
and with the use of clomiphene citrate. It also has occurred during pituitary down-regulation with gonadotropin-releasing hormone (GnRH) agonists. For all practical purposes, however, human chorionic gonadotropin (hCG) as the ovulation trigger is a prerequisite for the development of OHSS.\(^1\) In fact, the risk of OHSS is greater, and the condition is more severe and protracted, if conception occurs due to stimulation of the ovaries by endogenous hCG.\(^1,5\) (Endogenous luteinizing-hormone [LH] surges rarely cause OHSS unless pregnancy occurs.) Early OHSS, described by Lyons et al, presents 3 to 7 days after exogenous hCG is given to trigger ovulation, while late OHSS develops 12 to 17 days after the administration of hCG and then only in pregnant cycles.\(^6\) With late OHSS, a rate of severe disease of 71.4% has been reported, while the rate of severe disease with early OHSS is 14.3%.\(^5\)

Pregnancy rates appear to be about 3 times higher in cycles involving severe OHSS than in OHSS-free cycles, probably due to the greater number of ovulated oocytes. However, the very high levels of 17ß-estradiol (E\(_2\)) associated with OHSS may have an adverse effect on oocyte quality and endometrial receptivity. This may account for the greater risk of spontaneous abortion (SAB) seen with the disorder (33.5% to more than 50%).\(^7\)

**Predicting OHSS**

All patients undergoing superovulation should be monitored via serum E\(_2\) levels and transvaginal ultrasonography (TVUS) of the ovaries. Risk factors for severe OHSS include young age (less than 35 years), lean habitus, high E\(_2\) levels, pregnancy, and a greater follicle number.\(^2\) In fact, the number of small (less than 9 mm) and intermediate-size (9 to 15 mm) follicles is positively correlated with worsening OHSS, as these follicles continue to grow and produce E\(_2\) following hCG administration.\(^8\)

Patients with polycystic ovary syndrome (PCOS) and/or a “necklace sign” on ovarian ultrasound also face increased risk.\(^2\) Hyperinsulinemic PCOS patients have higher E\(_2\) levels, more immature follicles, and an increased rate of OHSS with superovulation using follicle-stimulating hormone (FSH) than do normoinsulinemic PCOS patients. Women with PCOS also are more sensitive to gonadotropin stimulation due to a greater quantity of small antral follicles responsive to FSH.\(^9\) Because of this greater sensitivity, a “gentler” protocol with lower doses of these agents should be used. “Pure” FSH for superovulation was developed with these patients in mind, as they frequently have higher LH:FSH ratios. (The additional LH in the older formulations was felt to be detrimental.) Unfortunately, no difference between these regimens has been seen in clinical use.\(^10\)

Laparoscopic ovarian drilling may decrease the risk of OHSS in subsequent cycles in women with PCOS.\(^11\)

**TABLE 1 Staging OHSS**

<table>
<thead>
<tr>
<th>Grade 1</th>
<th></th>
<th>Grade 2</th>
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<tbody>
<tr>
<td>Abdominal distention and/or discomfort</td>
<td>Same as mild stage plus ascites on ultrasonography</td>
<td>Abdominal distention plus ascites on ultrasonography</td>
<td></td>
</tr>
<tr>
<td>Ovaries 5-12 cm</td>
<td>Ovaries &gt;12 cm*</td>
<td>Ovaries &gt;12 cm*</td>
<td></td>
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<tr>
<td>Massive ascites with or without hydrothorax</td>
<td>Hematocrit &gt;45†</td>
<td>Tense ascites with or without hydrothorax</td>
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<tr>
<td>WBC &gt;15,000</td>
<td>Oliguria</td>
<td>Hematocrit &gt;55</td>
<td></td>
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<tr>
<td>Oliguria</td>
<td>Creatinine 1-1.5 mg/dL</td>
<td>WBC ≥25,000</td>
<td></td>
</tr>
<tr>
<td>Creatinine clearance ≥50 mL/min</td>
<td>Liver dysfunction</td>
<td>Oliguria</td>
<td></td>
</tr>
<tr>
<td>Anasarca</td>
<td>Renal failure</td>
<td>Creatinine &gt;1.6 mg/dL</td>
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<tr>
<td></td>
<td>Thromboembolic ARDS</td>
<td>Creatinine clearance &lt;50 mL/min</td>
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*Ovarian size after follicle aspiration is not definitive, as the ovaries are not as large as after superovulation alone.
† Or ≥30% increase over baseline


continued on page 59
Because hypogonadotropic patients have a lower risk of OHSS than PCOS patients, some physicians have attempted to render PCOS patients hypogonadotropic using pituitary suppression with GnRH agonists prior to gonadotropin administration—with little success. In fact, the risk of OHSS is greater with protocols utilizing GnRH agonists for pituitary suppression in patients with or without PCOS.

Prevention

Since OHSS entails significant morbidity and the potential for mortality and lacks a specific treatment, clinicians should focus on prevention. Unfortunately, because we are unable to consistently identify patients at risk, preventive efforts will meet with only partial success.

As mentioned earlier, OHSS is dependent on hCG stimulation. Thus, it may be limited by reducing or eliminating exogenous hCG. One option is reducing the ovulatory dose of hCG from 10,000 IU to 5,000 IU, although we lack data supporting the efficacy of this approach. However, when exogenous progesterone (P₄) is given instead of hCG for luteal support, the risk of OHSS is decreased without compromising pregnancy or implantation rates.

Withholding hCG. Although withholding the ovulatory dose of hCG should avert OHSS, there is no consensus on the criteria for cycle cancellation. For example, if hCG were withheld based on the lowest E₂ level at which OHSS occurred, approximately 50% of pregnancy cycles would be cancelled.

Coasting. One way to avoid the frustration and financial loss that accompany the cancellation of cycles with high E₂ levels is to discontinue gonadotropins and “coast” the cycles until E₂ decreases to an acceptable range. The ovulatory dose of hCG then can be administered. Although this reduces the incidence of severe OHSS, longer coasting intervals also result in lower pregnancy rates.

Substituting GnRH agonists. As mentioned earlier, ovulation rarely occurs in gonadotropin-stimulated cycles in the absence of hCG as a surrogate LH surge. Although hCG and LH are structurally and functionally similar, hCG has a much longer plasma half-life. Thus, the stimulatory effect on the ovary persists much longer with hCG than with an endogenous LH surge, increasing the risk of developing OHSS.

GnRH and its agonists have been given at midcycle to induce an endogenous LH surge in patients at risk for OHSS. A single 0.5-mg subcutaneous dose of leuprolide acetate (Lupron; TAP Pharmaceuticals, Lake Forest, Ill) increases serum LH for 34 hours, whereas hCG levels remain elevated for 6 days following a single intramuscular injection of 5,000 IU. Although pregnancy rates with GnRH and hCG appear to be similar, data are insufficient to document a lower incidence of OHSS with GnRH.

Further, GnRH as the ovulation trigger can be used only in gonadotropin-stimulation protocols that do not include GnRH agonists.

Key points

- Ovarian hyperstimulation syndrome (OHSS) ranges from mild ovarian enlargement to severe multisystem failure, with death occurring in approximately 1 in 400,000 to 500,000 superovulation cycles.
- The basic features of OHSS are enlarged multicystic ovaries and increased vascular permeability, with intravascular fluid loss into the third space.
- Mild to moderate OHSS is treated expectantly on an outpatient basis, while women with severe OHSS should be hospitalized.
- Severe OHSS has been reported in 0.1% to 2% of superovulation and assisted reproductive technology (ART) cycles.
- Risk factors for severe OHSS include young age, lean habitus, high 17ß-estradiol (E₂) levels, pregnancy, and a greater follicle number.
if available. Although severe OHSS may still occur despite follicle aspiration, the serum E₂ levels are generally several-fold higher than permissible without aspiration.

Although follicle aspiration with IVF probably reduces the risk of early OHSS, late disease is still a threat if conception occurs. For this reason, cryopreservation of all embryos (for later transfer during a spontaneous ovulatory cycle) should eliminate that risk as well. The low rates of severe OHSS seen with oocyte donors testify to the effectiveness of this practice. In the near future, immature oocytes from unstimulated ovaries may be matured and fertilized in vitro with high efficiency, eliminating the need for exogenous gonadotropins and the risk of OHSS.

Albumin. Asch et al administered 50 g of albumin intravenously to 36 patients at risk for severe OHSS at oocyte retrieval for IVF, and none developed clinically significant OHSS. They hypothesized that albumin helps prevent OHSS by increasing oncotic pressure. Albumin also may act as a carrier protein to sequester a vasoactive substance secreted by the corpus luteum. However, the results of several subsequent studies were conflicting.

Further, although albumin appears to be safe, it is expensive and tends to cause flu-like symptoms such as low-grade fever, chills, myalgia, and urticaria. Since we are unable to reliably predict which patients will develop severe OHSS, the use of albumin for patients undergoing gonadotropin superovulation is not advised at this time.

Treatment of OHSS

Because OHSS may develop despite our best efforts to predict and prevent it, all patients should be thoroughly counseled about its risks and implications prior to treatment with gonadotropins. Once OHSS occurs, the most important determination to be made is which patients should be hospitalized.

Patients with mild OHSS should be placed on pelvic rest. That is, they should avoid any activity that could cause the enlarged cystic ovaries to rupture or undergo torsion. Fortunately, OHSS usually resolves spontaneously within 2 weeks of hCG administration, although it may take longer for the cysts to involute completely.

The management of moderate OHSS is outlined in Table 2. Patients should be placed on pelvic rest and advised to maintain adequate fluid intake and monitor their weight and abdominal girth daily. Any significant changes should be relayed to their physician immediately, as should decreased urine output, shortness of breath, nausea or vomiting, or worsening abdominal pain. A pregnancy test should be obtained if any of these effects occur, as the condition may deteriorate suddenly if conception occurs. In addition, patients should be monitored as needed with ultrasonography. Recommended laboratory studies include electrolytes, blood urea nitrogen (BUN), creatinine, and a complete blood count (CBC). Oral analgesics and antiemetics should be prescribed as needed.

As I mentioned at the beginning of this article, patients with severe OHSS should be hospitalized (Table 3). They should be restricted to bed rest with bathroom privileges and given a regular diet. Initial evaluation should include a CBC with platelets, coagulation profile, electrolytes, BUN, creatinine, liver function tests, early hCG, and continued on page 65
pelvic ultrasonography. Serum total protein, albumin, and osmolarity may be helpful, as well as urinary electrolytes and osmolarity. The hematocrit appears to correlate best with the severity of the syndrome, with higher values indicative of more severe disease.

If the patient is dyspneic and/or tachypneic, a chest x-ray should be obtained in addition to arterial blood gases or, at least, pulse oximetry. Daily monitoring of hospitalized patients includes weight, abdominal girth, CBC, electrolytes, creatinine, and BUN, with strict fluid intake and output. If the patient becomes oliguric, i.e., urine output of less than 30 mL per hour, a Foley catheter should be inserted. Central-venous-pressure (CVP) monitoring may be considered to better guide fluid replacement in the presence of renal or respiratory compromise or if the patient is hypotensive and/or tachycardic.

The underlying pathogenic mechanism of OHSS is increased vascular permeability with hypoproteinemia and a loss of fluid into the third space. In severe OHSS, this results in hypovolemia with decreased renal perfusion, which stimulates the proximal renal tubules to resorb sodium and water. Oliguria and increased urea absorption follow, causing azotemia and a rise in BUN. With less sodium reaching the distal tubules, the exchange for hydrogen and potassium decreases, resulting in hyperkalemia and metabolic acidosis.

Hypovolemia leads to hemoconcentration with increased plasma osmolarity. The increased intra-abdominal pressure from ascites compresses the vena cava and diminishes venous return and cardiac preload, further reducing arterial blood pressure, CVP, and renal perfusion. Cardiac output is maintained by compensatory tachycardia. Tense ascites can compromise respiratory function by increasing intrathoracic pressure and limiting diaphragmatic excursions.

Other abnormalities include a generalized stress reaction and neutrophilia due to hemoconcentration. Mild hepatocellular and cholestatic damage may result from increased vascular permeability and elevated E2 levels. Elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels have been reported in 25.8% of OHSS patients. However, the cholestatic jaundice with increased bilirubin, alkaline phosphatase, AST, and ALT generally resolve completely, requiring no intervention.

The goal of treatment for severe OHSS is restoring intravascular volume to reverse hemoconcentration and maintain urine output over 30 cc per hour. Normal saline is the crystalloid solution of choice for correcting hypovolemia, as more of it remains in the vascular space. It also contains no potassium. (Patients with hyperkalemia may require treatment with cation exchange resins.) Unfortunately, expanding the intravascular compartment with crystalloids may exacerbate the ascites, as only 20% of the infused volume remains in the intravascular space after 1 hour.

### Table 3

<table>
<thead>
<tr>
<th>Admission orders for severe OHSS</th>
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<tbody>
<tr>
<td>Daily weight and abdominal girth</td>
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<tr>
<td>Strict intake and output</td>
</tr>
<tr>
<td>Hemoglobin and hematocrit daily</td>
</tr>
<tr>
<td>CBC, PT/PTT, electrolytes, liver function tests, and hCG on admission and as indicated</td>
</tr>
<tr>
<td>Baseline ultrasonogram</td>
</tr>
<tr>
<td>Chest x-ray and arterial blood gases if short of breath</td>
</tr>
<tr>
<td>Bed rest with bathroom privileges</td>
</tr>
<tr>
<td>Heparin 5,000 USP units b.i.d. subcutaneously if hemoconcentrated</td>
</tr>
<tr>
<td>Regular diet</td>
</tr>
<tr>
<td>Normal saline IV at 120 cc/hr without added potassium</td>
</tr>
<tr>
<td>Continue progesterone for luteal support</td>
</tr>
<tr>
<td>Acetaminophen with narcotics as needed. Avoid NSAIDs</td>
</tr>
<tr>
<td>If hypovolemic, oliguric (&lt;30 cc/hr):</td>
</tr>
<tr>
<td>· Administer normal saline 1L/hr</td>
</tr>
<tr>
<td>· If no response, give albumin 50 to 100 g over 2 hr</td>
</tr>
<tr>
<td>· Administer furosemide only if still oliguric after hemoconcentration resolved</td>
</tr>
<tr>
<td>· Admit to ICU for central monitoring and dopamine if no response</td>
</tr>
<tr>
<td>Paracentesis for discomfort, shortness of breath, and/or persistent oliguria</td>
</tr>
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</table>

continued on page 68
When crystalloids alone are unable to reverse the oliguria, colloid solutions should be administered. Albumin is the preferred colloid, as it is the protein lost in OHSS and is associated with fewer risks than fresh frozen plasma or dextran. Fifty to 100 g of albumin may be administered every 2 to 12 hours as needed to restore urine output. A 50-g dose draws approximately 900 mL of extracellular fluid into the vascular compartment within 15 minutes. Unfortunately, albumin's oncotic effect is lost within 36 hours when it leaves the vascular space, which may worsen the OHSS.

Diuretics may be used if oliguria persists after restoring the intravascular volume, provided the patient is not hemoconcentrated or hypotensive. In general, however, diuretics should be avoided in OHSS, as they may further shrink an already contracted intravascular volume.

In some cases, oliguria may persist even after hemoconcentration has been corrected. This generally is the result of tense ascites, which reduces renal blood flow by compressing the renal vessels and decreasing cardiac output. In these cases, paracentesis often brings prompt symptomatic relief and diuresis. Paracentesis also is indicated for respiratory compromise, rising creatinine or falling creatinine clearance, and hemoconcentration unresponsive to fluid therapy. However, the removal of large volumes of fluid may lead to rapid reaccumulation with further intravascular volume depletion. Paracentesis should be performed using aseptic technique under ultrasound guidance to avoid intraperitoneal hemorrhage from puncture of the ovarian cysts. It may be accomplished abdominally or transvaginally.

While most experts would perform paracentesis for tense ascites for the indications mentioned earlier, there is no consensus as to whether patients should be subjected to paracentesis for less severe cases of ascites. Some physicians advise against routine paracentesis due to the risk of rapid fluid shifts, fistula formation, and infection, while others claim that it hastens the resolution of OHSS.

Renal-dose dopamine may be useful in pre-renal failure unresponsive to fluid therapy and surgery is indicated only in the presence of ovarian torsion, ectopic pregnancy, or cyst rupture.
paracentesis. It may enhance urine output and prevent acute tubular necrosis and frank renal failure requiring hemodialysis.\(^2\) Dopamine increases renal blood flow and glomerular filtration by dilating the renal vascular bed without affecting heart rate or blood pressure (BP). Patients administered dopamine should be managed in an ICU with CVP or Swan-Ganz monitoring.

Surgical treatment for OHSS is indicated only in the presence of ovarian torsion, ectopic pregnancy, or cyst rupture.\(^2,3\) (Intraperitoneal bleeding from ruptured ovarian cysts typically is accompanied by abdominal pain and a falling hematocrit in the absence of diuresis.\(^4\)) Surgery should be as conservative as possible and limited to the complication at hand, as ovarian changes in the syndrome are self-limited.

**Potential complications**

**Thromboembolism.** Thromboembolic disease complicates approximately 1 of every 128 cases of severe OHSS.\(^2\) Hemoconcentration, bed rest, and venous stasis from vena cava compression by the enlarged ovaries and ascites predispose to lower-extremity deep venous thrombosis (DVT). Interestingly, although 75% of thromboses described in the literature are venous, only 40% of those involve the lower extremities, while DVT of the head, neck, and upper extremities occur in 60% of cases. The remaining 25% of thromboses are arterial—mainly intracerebral.\(^2\) (In the general population, the incidence of upper-limb DVT is only about 4%, and arterial thrombosis is very rare in young women.) The mean time from hCG administration to the presentation of DVT was 38 days compared with 14 days for arterial thrombosis, suggesting a different pathogenic mechanism.

Although the etiology of upper-limb DVT and arterial thrombosis is uncertain, hypercoagulability is thought to play a role.\(^2\) However, most OHSS patients have normal coagulation profiles, even in the presence of hemoconcentration.\(^2\) Changes that occur in the coagulation profile of OHSS patients include increases in factor V, fibrinogen, profibrinolysin, D-dimers, fibrinolytic inhibitors, clot lysis times, and platelets. In addition, decreases have been observed in antithrombin III, \(\alpha\)\(^2\) plasmin inhibitor, prekallikrein, and activated partial thromboplastin time (aPTT). These changes cause an imbalance between coagulation and thrombolysis that may predispose patients to thromboembolic disorders.

While full anticoagulation with heparin is the treatment for thromboembolism in OHSS, it is controversial when, or if, prophylactic heparin should be used in the absence of abnormal coagulation. Prophylactic heparin is recommended for patients on bed rest who have compromised venous return and/or hemoconcentration.\(^12\) The duration of prophylaxis also is unclear, as thromboses have occurred following the complete resolution of OHSS—even when the patient has received heparin during hospitalization.

**Ovarian torsion.** Approximately 15% of OHSS patients experience ovarian torsion, 75% of whom are pregnant. The diagnosis of ovarian torsion may be difficult to make in OHSS, as the presentation of abdominal pain and tenderness, nausea, vomiting, and leukocytosis is common to both conditions. Prompt unwinding of the adnexa is essential to its preservation. Detorsion may be performed via laparotomy or laparoscopy, with care taken to avoid rupture of the ovarian cysts with the Veress needle and trocar insertion. (At the same time, however, it is recommended that the cysts be punctured or aspirated to facilitate unwinding the ovary.)

Laparoscopy in pregnancy poses a risk to the patient and her fetus due to decreased venous return from vena cava compression of the pneumoperitoneum and to hypercarbia from peritoneal absorption of the carbon dioxide used for insufflation. The risk is compounded by the fact that pregnant OHSS patients already are hypovolemic. To increase the margin of safety, an open technique for trocar insertion may be advisable to reduce the risk of injuring the enlarged ovaries and pregnant uterus. Gasless laparoscopy may eliminate the insults on venous return and acid-base balance.\(^2\)

**Pulmonary complications.** Twenty percent of
patients with severe OHSS experience pleural effusions. These effusions generally are right-sided and are commonly seen with tense ascites from seepage through diaphragmatic lymph vessels. The effusion usually improves with paracentesis.  

Adult respiratory distress syndrome (ARDS) is a rare complication. When it occurs, the patient experiences respiratory failure with refractory hypoxemia that fails to respond to 100% oxygen. The chest x-ray reveals diffuse bilateral alveolar infiltrates, and the pulmonary-arterial-wedge pressure is low. The patient should be intubated and ventilated with 100% oxygen with positive end-expiratory pressure (PEEP). If not treated promptly, 90% of these patients will go into cardiopulmonary arrest.  

When the patient experiences a life-threatening complication such as ARDS, renal failure, hypovolemic shock, and thromboembolic disease, therapeutic pregnancy termination may be considered when all other treatments have failed.  

Conclusion  

OHSS remains a feared complication of exogenous gonadotropin administration despite more than 3 decades of widespread clinical use of these agents. However, we are gaining a better understanding of the syndrome's pathogenesis, and new treatment options are being evaluated. It is hoped that the clinical availability of recombinant LH (to induce the ovulatory surge) and improvements in the in vitro maturation of immature oocytes will render exogenous gonadotropins obsolete. When that happens, OHSS will become an entity of historical interest only.  

REFERENCES  


The author reports no financial relationship with any companies whose products are mentioned in this article.