Ovarian hyperstimulation syndrome

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Objective: **Ovarian hyperstimulation syndrome (OHSS) is a rare iatrogenic complication of ovarian stimulation usually occurring during the luteal phase or during the early part of pregnancy. OHSS is a potential complication of ovarian induction by almost every agent used for ovarian stimulation. Today, due to aggressive treatment protocols including the development of *in vitro* fertilization and cryopreservation with the goal of obtaining sufficient numbers of oocytes and embryos, an increased risk of developing OHSS is present. OHSS is now becoming increasingly more recognized due to the higher number of women undergoing assisted reproductive techniques.**

Design: **Review of the literature regarding ovarian hyperstimulation syndrome.**

Methods: **A review of the epidemiology, pathophysiology, risk factors, classification, clinical features, and treatment and prevention of OHSS.**

Conclusion: **OHSS can be thought of as the loss of control over the hyperstimulation of the ovaries. Although the prevalence of the severe form of OHSS is small, it is important to remember that OHSS is usually an iatrogenic complication of a nonvital treatment that has the potential for a fatal outcome. Therefore, critical care physicians play an integral part in the care of these patients and therefore should be familiar with and recognize the various clinical manifestations and potential outcomes of this entity. (Crit Care Med 2005; 33[Suppl.]:S301–S306)**

KEY WORDS: ovarian hyperstimulation syndrome; *in vitro* fertilization; assisted reproductive techniques; polycystic ovary syndrome; gonadotropin stimulation

Ovarian hyperstimulation syndrome (OHSS) is a rare iatrogenic complication of ovarian stimulation usually occurring during the luteal phase or during the early part of pregnancy (1). The syndrome was first described in 1943 as "syndrome d'hyperluteinisation massive des ovaries" when early forms of gonadotropins (gonadotropic preparations from pregnant mare serum or sheep pituitary gland preparation and urine from pregnant females) were used to stimulate or induce ovulation. The first fatal case of OHSS was described in 1951 with oliguric renal failure as the primary complication leading to death (2). Since the original descriptions of OHSS, it appears that OHSS is a potential complication of ovarian induction by almost every agent used for ovarian stimulation. Today, due to aggressive treatment protocols including the development of *in vitro* fertilization and cryopreservation with the goal of obtaining sufficient numbers of oocytes and embryos, an increased risk of developing OHSS is present. Essentially, OHSS can be thought of as the loss of control over the intended therapeutic hyperstimulation of the ovaries (3). OHSS is now becoming increasingly more recognized due to the higher number of women undergoing assisted reproductive techniques. Severe or life-threatening forms of OHSS can lead to multiple complications necessitating intensive care admission. The prevalence of the severe form of OHSS is small, with values reported ranging from 0.5% to 5% of stimulated ovarian cycles resulting in severe OHSS. But it is important to remember that OHSS is usually an iatrogenic complication of a nonvital treatment that has the potential for a fatal outcome with an estimated mortality rate of 1/450,000–50,000 patients (4–6). Therefore, critical care physicians play an integral part in the care of these patients and should be familiar with and recognize the various clinical manifestations and potential outcomes of this entity.

The most common form of OHSS occurs a few days after follicular rupture or follicular aspiration for IVF after follicular growth has been medically stimulated or induced with the administration of either gonadotropins, or rarely clomiphene citrate. Gonadotrophin-releasing hormore (GnRH) agonist or antagonists do not cause OHSS but are typically used in combination and may exacerbate the process. Rare cases have been described of a spontaneous form of OHSS, which may present in the absence of any treatment at the beginning of a spontaneous pregnancy due to mutations in the follicle stimulating hormone receptor (7, 8).

The cardinal features of OHSS include marked ovarian enlargement due to ovarian stimulation leading to overproduction of ovarian hormones and vasoactive substances including cytokines, angiotensin, and vascular endothelial growth factor, which contribute to an increase in capillary membrane permeability and acute third space fluid sequestration in the form of ascites, hydrothorax, and anasarca (9). The fluid shift from the intravascular space to the interstitial spaces contributes most to the mortality associated with OHSS (10). The clinical manifestations are a result of the increased capillary membrane permeability resulting in a loss of protein-rich fluid. A massive extracellular exudative fluid accumulation in addition to severe intravascular volume depletion and hemoconcentration eventually leads to multiple organ failure. The etiology of OHSS is complex and many aspects remain unclear, but it appears that hCG, whether exogenous or endogenous (e.g., pregnancy derived), is a central factor in triggering OHSS. In fact, severe OHSS can be almost totally pre-

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Table 1. Factors that may be involved in the development of ovarian hyperstimulation syndrome

Human chorionic gonadotropin
Vascular endothelial cell growth factor
Estradiol
Ovarian renin-angiotensin system
Interleukin-6
Prostaglandins
Insulin
Von Willebrand factor
Cytokines
Endothelial-cell adhesion molecules
Angiotensin
Histamines
Endothelin-1
Ovarian kinin-kallikrein system

Table 2. Risk factors associated with development of ovarian hyperstimulation syndrome (OHSS)

Young age (<35 yrs)
Low body mass index—asthenic habitus
Polycystic ovary syndrome
History of atopy or allergies
High serum estradiol
Previous episode of OHSS
Increased number of developing follicles
Higher or repeated doses of exogenous human chorionic gonadotropin
Gonadotropin-releasing hormone—agonist protocol
Pregnancy

Data from Ref. 4.

vented by withholding the ovulation-induced trigger of hCG. The risk of OHSS is decreased if progesterone is substituted for hCG for luteal support (11, 12). Therefore, hCG likely may induce the release of a mediator that has potent effects on the vascular system, which may be responsible for the clinical consequences of OHSS and may play a crucial role in the development of this syndrome. Several additional factors are highly involved in the progression of OHSS (Table 1), including vascular endothelial growth factor (VEGF), estradiol, ovarian renin-angiotensin, interleukin (IL)-6, prostaglandins, insulin, Von Willebrand factor, and other cytokines. VEGF is likely the main cytokine involved in the pathogenesis of OHSS. It is the main angiogenic substance that leads to increased capillary membrane permeability, which is responsible for large fluid shifts in OHSS (13). A serum rise in VEGF is noted to be a marker for subsequent development of OHSS, and interestingly enough, plasma VEGF levels correlate with the clinical severity of OHSS, and changes in the VEGF levels in the ascitic fluid have been correlated with the clinical course in OHSS (14–16). High levels of both renin and aldosterone in spontaneous OHSS seems to further support the role of ovarian renin-angiotensin in the pathogenesis of OHSS. Navot et al. (17) noted a correlation between plasma renin activity and the severity of OHSS. This elevation of renin appears to be of ovarian origin in OHSS. In fact, it was recently noted in a rabbit model that the use of angiotensin-converting enzyme inhibitors decreased the incidence of OHSS by 40% (11).

The reported incidence of OHSS is highly variable according to the various published reports due to inconsistency in severity classification methods and due to different methods of ovarian induction employed leading to OHSS, which are not comparable in terms of therapeutic goals or strategies. Before the use of *in vitro* fertilization, the incidence of mild OHSS using gonadotropins ranged from 8.4% to 23% and from 0.008% to 10% for more severe forms of OHSS (5). It has been estimated that ≥100–200 women are affected annually from severe OHSS out of 100,000 cycles of aggressive reproductive techniques. In the largest case series of severe OHSS, by Abramov et al. (18), the number of cases of severe OHSS after *in vitro* fertilization increased from an estimated 0.06% in 1987 to 0.24%. This increase in the incidence of severe OHSS was above that of total *in vitro* fertilization activity. Although the incidence of severe form of OHSS is low, its incidence is progressively increasing (18).

Multiple risk factors have been implicated in the development of OHSS (Table 2) including age <35 yrs, possibly due to higher number of gonadotropin receptors available in a younger ovary making them more likely to respond to stimulation. The presence of polycystic ovary syndrome appears to be a major predisposing factor to the development of OHSS in a number of studies (19, 20). Delvigne et al. (21) found that the basal hormone profile in OHSS patients usually revealed similar variables, as noted in polycystic ovary syndrome patients, including hyperandrogenism, anovulation, and elevated ratio of luteinizing hormone to follicle-stimulating hormone. Patients with a phenotypical ultrasonographic presentation of polycystic ovary syndrome demonstrated by the presence of ten or more ovarian cysts <10 mm in size also were noted to have a higher incidence of OHSS (4). In a prospective study by Navot et al. (22), the body mass index in OHSS patients was significantly lower than in a control population without OHSS, although there is still some debate regarding the importance of this variable. Patients with severe OHSS also have been noted to have an increased presence of atopy, since the pathophysiologic changes that occur in the ovaries during OHSS closely resemble an overactive inflammatory response with the involvement of various cytokines. Enskog et al. (23) hypothesized that differences in the immunologic sensitivity of patients may be a predictive sign of OHSS.

It is clear that the incidence of OHSS is related to the stimulation regimen used to stimulate ovulation. Clomiphene citrate is only rarely associated with the severe form of OHSS, although a more moderate form can be encountered in about 8% of stimulation cycles using this drug (24). A recent meta-analysis demonstrated no difference in the occurrence of OHSS with the use of urinary-derived gonadotropins or recombinant follicle-stimulating hormone (25). The use of gonadotropin-releasing hormone antagonists is reported to have a decreased incidence of OHSS, although this is still the subject of disagreement (26). An increased risk of OHSS also has been noted in women who experience a rapid rise in serum estradiol levels or in whom an estradiol concentration >2500 pg/mL is noted (9). In addition, the risk of OHSS also rises with the number of medium-sized developing ovarian follicles and the number of oocytes (>14) retrieved during assisted reproductive technology (23). The risk of severe OHSS is increased significantly with the use of hCG, with the use of higher and repeated doses of hCG to induce superovulation and with assisted reproductive technique cycles for luteal phase support (1). Pregnancy not only increases the likelihood of OHSS but prolongs the duration and severity of OHSS symptoms.

Multiple preventive measures have been considered to lower the risk of OHSS in cases where potential risk factors have been identified during the stimulation cycle, including delaying the administration of hCG until estradiol levels plateau or decrease, using a lower dose of hCG in high-risk patients, using exogenous progesterone during the luteal phase instead of hCG, and using 25% albumin during oocyte retrieval (9). For every 18 women at risk for severe OHSS, albumin infusion will prevent one case (27). Evidence exists for follicle aspiration to reduce corpus luteum progesterone production, but results are variable

Table 3. Classification of ovarian hyperstimulation syndrome (OHSS)

Mild OHSS	
Grade 1	Urinary estrogen >150 μg/24 hr
	Urinary pregnanediol >0 mg/24 hr
	No palpable enlargement of ovaries, no palpable cyst formation
Grade 2	Urinary estrogen >150 μg/24 hr
	Urinary pregnanediol >10 mg/24 hr
	Palpable enlargement of ovaries with or without palpable cyst formation
Currently mild OHSS defined as enlarged ovaries; grades 1 and 2 are no longer used.	
Moderate OHSS	
Grade 3	Abdominal distension, nausea
	Urinary estrogen >150 μg/24 hr
	Urinary pregnanediol >10 mg/24 hr
	Palpable enlargement of ovaries with or without palpable cyst formation
Grade 4	Vomiting and diarrhea in addition to grade 3 criteria
Severe OHSS	
Grade 5	Large ovarian cysts, ascites, or hydrothorax in addition to grade 4 criteria
Grade 6	Alterations in blood viscosity in addition to symptoms of grade 5
Life-threatening OHSS	
	Variably enlarged ovary
	White blood cell count >25,000
	Hematocrit >55%
	Creatinine level >1.6 mg/dL
	Reduction in creatinine clearance <60 mL/min
	Oliguria
	Renal failure
	Tense ascites with or without hydrothorax
	Thromboembolic phenomena
	Acute respiratory distress syndrome

Data from Refs. 1 and 29.

with this prevention method and cannot be relied on (28).

OHSS was first classified based on laboratory and clinical finding by Rabau et al. (29) in 1967 into three clinical categories (mild, moderate, severe), which were further modified by Schenker and Weinstein (30) in 1978 into six grades, based on the severity of symptoms, signs, and laboratory findings. The stages of OHSS that are clinically relevant include moderate, severe, and the recently proposed critical or life-threatening OHSS, with the latter two being more commonly encountered by the intensive care unit physician (Table 3). In addition, OHSS can also be classified based on onset of symptoms or laboratory abnormalities. Early-onset OHSS generally occurs 3–7 days after an induced preovulatory response to stimulation by hCG. Late-onset OHSS occurs after 7 days due to a pregnancy-related increase in hCG levels. Late-onset OHSS is clinically more severe and is related poorly to preovulatory events (31).

The clinical symptoms and signs of OHSS are a result of marked circulatory dysfunction secondary to increased vascular permeability and marked arterial dilation leading to fluid shifts from the intravascular to the extravascular space (3, 32). This fluid shift is considered the cardinal event of OHSS. The first indication of OHSS is the formation of a small amount of ascites found on ultrasonographic evaluation. But massive accumulation of extravascular exudates can lead to tense ascites, pleural or pericardial effusions, electrolyte derangements, oliguric renal failure, hemoconcentration, and hypovolemia with or without hypovolemic shock (1, 3, 5). Initial symptoms of early OHSS begin gradually with bloating and abdominal discomfort, which may progress to severe emesis, diarrhea, shortness of breath, reduced urine output, and subsequent accumulation of palpable ascites after day 7, suggesting potentially severe OHSS (33). The cystic ovaries may enlarge and reach large sizes >12 cm and have the potential to rupture or hemorrhage or lead to torsion and severe abdominal pain. Ultrasound examination of patients with OHSS usually reveals enlarged ovaries with numerous follicular cysts and ascites. Abdominal computed tomography can also be used to visualize ovarian enlargement and ascites in patients with OHSS. Physical exam in patients with severe OHSS may reveal weight gain and increased abdominal girth due to ascites and signs of hypovolemia.

Several electrolyte imbalances may occur, including an increase in hematocrit indicating hemoconcentration (hematocrit >45%), leukocytosis, and thrombocytosis, which reflect a general inflammatory state as well as hemoconcentration (34). Hemoconcentration >55% indicates a life-threatening situation. Ascites is often found in conjunction with oliguria with decreased urinary sodium excretion and hyponatremia due to a low serum osmolality. Severe hyponatremia can lead to cerebral edema, resulting in altered mental status and neurologic complications (35). Hyperkalemia and metabolic acidosis also can be noted as a result of decrease urinary sodium exertion. Renal hypoperfusion leads eventually to oliguria and severe renal failure. In most cases of OHSS, the creatinine levels are usually within normal limits, but in severe forms of OHSS an elevated serum creatinine is observed (36). Liver abnormalities in OHSS include elevated levels of aspartate aminotransferase and alanine aminotransferase in about 30% of patients with severe OHSS, which can sometimes be associated with an elevation in γ-glutamine transpeptidase or alkaline phosphatase (37). Most hepatic manifestations or abnormalities disappear with the recovery from OHSS. A relative immunodeficient state is present in patients with severe OHSS due to lower levels of immunoglobulins (Ig) including IgG and IgA, potentially placing these patients at a higher risk for nosocomial infections (38, 39). More than 83% of patients with severe OHSS will have at least one febrile episode for 24 hrs. In approximately one third of these cases, the fever can be attributed to infection (in most situations due to urinary tract infection), but in more than two thirds of cases no infectious agent can be identified. In febrile patients in whom infection was the etiology, the causative responsible organisms included *Proteus mirabilis*, *Klebsiella pneumonia*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Morganella morganii*, and *Proteus vulgaris*. Other sources of fever may include endogenous production of cytokines including IL-1, IL-6, IL-8, and tumor necrosis factor (3).

Thromboembolic events are a devastating complication of severe OHSS that can occur despite appropriate therapy and can ultimately lead to death. The incidence of thromboembolic events in severe OHSS is unknown, but Serour et al. (40) reported the highest incidence found in the literature of approximately 10% in patients with severe OHSS. The cause for OHSS-associated thromboembolic disease is not clearly understood but is thought to be related to

high estrogen concentrations, low circulation of plasma volume, and hemoconcentration (41). But it has been noted that uncommon locations are often involved including upper limbs and cerebral and cardiac vessels (3). Central retinal artery occlusion secondary to thrombosis has also been noted (42).

Multiple pulmonary manifestations of severe OHSS exist including the development of lobar pneumonia most commonly affecting the left lower lobe, pulmonary embolism, unilateral or bilateral hydrothorax, and pulmonary atelectasia. Acute respiratory distress syndrome (ARDS), although not common, has a high rate of morbidity if not recognized and managed appropriately in patients with severe OHSS. More than 90% of patients with ARDS and severe OHSS will develop pulmonary fibrosis or cardiac arrest if the syndrome goes unrecognized. With adequate treatment, more than 50% of patients will recover without sequelae (4).

The treatment of OHSS is aimed at supportive conservative measures until the condition resolves. In most cases, the syndrome follows a self-limiting course that parallels the decline in serum hCG. Patients with mild manifestation of OHSS can be managed in the outpatient setting with oral analgesics and careful monitoring for syndrome progression. Worsening OHSS or escalation in symptoms and signs can still be monitored in the outpatient setting but with a low threshold for hospitalization. Although the moderate form of OHSS usually subsides within 2–3 wks, patients may progressive to severe or life-threatening disease rapidly, especially of pregnancy occurs. Close observation of these patients is recommended, and serial estimations of β-hCG should be followed to confirm conception. In patients with moderate or severe OHSS, pelvic examination should be avoided to decrease the risk of ovarian cyst rupture and possible potential acute intra-abdominal hemorrhage (43). In severe OHSS, assessment of the hemodynamic and respiratory status is the initial step in the management of this high-risk condition. Patients need placement of intravenous access promptly with at least two large-bore peripheral catheters or central venous subclavian catheter placement due the lower risk of thrombosis and ability to measure central venous pressures to assist with fluid management (1). An indwelling urinary bladder catheter should be placed for close monitoring of urinary output as well as to measure abdominal pressures to assess for abdominal compartment syndrome. The need for continued catheterization in the intensive care unit should be evaluated daily to reduce the risk of a catheter-related infection.

All patients should have daily serological testing including measurement of white blood cell count hemoglobin concentration, measurement of hematocrit, and serum electrolytes and liver function tests. An abdominal ultrasound is required to ascertain the size of the ovaries and to determine the presence of ascites. In patients with shortness of breath, a chest radiograph, oxygen saturation by pulse oximetry, and arterial blood gas analysis may be necessary (the possibility of pregnancy should be noted if chest radiograph or computed tomography is considered). In addition, a high index of suspicion must be maintained for the presence of a pulmonary embolism, and a ventilation/perfusion study may be indicated. In patients with a worsening shortness of breath and decline in respiratory status, endotracheal intubation and mechanical ventilation may be needed. In addition, an electrocardiogram and eventually echocardiogram should be ordered to determine the presence of a pericardial effusion.

Medical therapy should be aimed at maintaining effective circulating volume and mobilizing fluid from the third space back into the vessels and preventing and countering hemoconcentration. Normal saline with or without dextrose is the crystalloid fluid of choice, but in severe cases albumin can be used as a plasma expander in cases of severe hemoconcentration (hematocrit $>45\%$), severe hypoalbuminemia (serum albumin level <3.0 g/dL), or tense ascites. Fluids containing potassium should be avoided due to decreased urinary sodium excretion and the potential for hyperkalemia (33). Diuretics can potentially lead to hemoconcentration and hypovolemia, increasing the risk of venous thromboembolism, and should also be used judiciously. Other volume expanders including dextran and fresh frozen plasma have been used in severe OHSS with limited success (44, 45). In terms of management of the pulmonary manifestations of OHSS, conservative therapy including observation and therapeutic thoracentesis for hydrothorax should be followed. If ARDS develops, mechanical ventilation should be instituted using lower tidal volumes, 6 mL/kg of predicted body weight, and plateau pressure ≤ 30 cm H_2O may decrease mortality and increase the number of days free from ventilatory support (46). Other causes for ARDS including infection should also be investigated. Fluid management in OHSS-associated ARDS may be problematic, but the goal of fluid therapy should be to maintain systemic perfusion and adequate renal perfusion (47). The use of glucocorticoids, although controversial in ARDS, may have some role in the treatment of ARDS in the setting of OHSS where prompt regression of ARDS occurs after steroid pulse treatment (48).

Anticoagulation should be initiated if a thrombotic or thromboembolic event is suspected. Routine administration of prophylactic anticoagulation should be part of standard care (3).

Abdominal paracentesis is the most common procedure performed in severe cases of OHSS. Paracentesis may be needed for symptomatic relief of tense ascites but may also indicated in the setting of oliguria, increasing creatinine or decreasing creatinine clearance, and hemoconcentration refractory to medical therapy (43). Evacuation of a large volume of ascitic fluid allows for decreased abdominal pressure and improvement in renal blood flow, venous return, and cardiac output. In an effort to avoid puncture of the enlarged ovarian cysts, ultrasound-guided needle paracentesis (transabdominal or transvaginal) may be indicated. The volume of fluid removed at any one occasion or how often ascitic fluid should be removed has not been established. In severe cases, biweekly or triweekly drainage may be required. An alternative to frequent paracentesis may be the placement of a pigtail catheter for continuous drainage for severe ascites. A recent prospective trial using the pigtail catheter in severe refractory cases of ascites demonstrated relatively good outcomes (49). Large volume ascites removal may lead to rapid accumulation of ascites and further depletes proteins lost from the intravascular compartment. In turn, this low intravascular protein concentration leads to further accumulation of fluid within the pleural and peritoneal space. Some investigators have suggested the use of autoreinfusion of aspirated ascitic fluid after filtering it and increasing both protein and albumin concentrations and reinfusing it intravenously every 6 hrs (50). Peritoneovenous shunting in conjunction with continuous autotrans-

fusion system of ascites has been used in isolated cases of severe OHSS to improve IgG levels in the sera (38). In theory, the administration of exogenous intravenous immunoglobulin may also have some benefit in terms of decreasing the rate of bacterial infectious in critical OHSS, although no formal randomized trials exist supporting this. In the case of suspected infection, empirical antibiotic therapy should be started and then subsequently tailored depending on further bacterial data. The choice of empirical antibiotics should be guided by several factors including the patient's indigenous flora, the severity of disease, risk factors for infection, and patterns of local intensive care unit antibiotic resistance. Empirical antibiotic use should take into account the most commonly encountered pathogens involved in many of these cases, including *E. coli*, *P. aeruginosa*, *K. pneumoniae*, *P. mirabilis*, and *P. vulgaris* (15).

Uncontrolled studies or animal studies have indicated that nonsteroidal antiinflammatory drugs (indomethacin), antihistamines, and angiotensin-converting enzyme inhibitors have some potential as effective therapies for OHSS, but no large randomized control trials exist to support the use of these therapies (1, 51, 52).

Surgical intervention for OHSS should be avoided unless hemorrhage of an ovarian cyst, cystic rupture, or torsion of the ovary is suspected. The surgical approach should be conservative, with minimal manipulation and hemostasis achieved in order to preserve the ovarian integrity, which may be achieved through a laparoscopic approach. Ovarian hemorrhage should be suspected in the setting of a decreased hematocrit without other evidence of decreasing hemoconcentration. Ovarian torsion is a rare complication of pregnant patients with OHSS, which may present with initially with lower abdominal pain and tender abdominal mass (53). Late diagnosis of this clinical entity can lead to a devitalized ovary that is beyond salvage. Termination of pregnancy through medical abortion using mifepristone may be necessary in a few rare cases, especially with severe complications of OHSS that are refractory to medically therapy in effort to decrease serum hCG levels.

Once the hemoconcentration declines and diuresis occurs, most complications resolve and the majority of patients with severe OHSS are able to leave the hospital after 7–8 days, but their stay may be shorter if no pregnancy is involved. Longer periods of time to recover may occur in severe forms of OHSS associated with pregnancy requiring 2–4 wks of hospitalization.

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