Ovarian hyperstimulation syndrome: A review for emergency clinicians

Douglas Timmons, MD, MPH, Tim Montrief, MD, Alex Koyfman, MD, Brit Long, MD

Department of Obstetrics, Gynecology and Reproductive Sciences, Jackson Memorial Health System/University of Miami Miller School of Medicine, United States

University of Miami, Jackson Memorial Hospital/Miller School of Medicine, Department of Emergency Medicine, 1611 N.W. 12th Avenue, Miami, FL 33136, United States

The University of Texas Southwestern Medical Center, Department of Emergency Medicine, 5323 Harry Hines Boulevard, Dallas, TX 75390, United States

Brooke Army Medical Center, Department of Emergency Medicine, 3841 Roger Brooke Dr, Fort Sam Houston, TX 78234, United States

Abstract

Introduction: A great deal of literature has recently evaluated the prevention and management of ovarian hyperstimulation syndrome (OHSS) in the outpatient setting, but there remains a dearth of research evaluating OHSS in the emergency department (ED) and its management.

Objective: This narrative review evaluates the underlying pathophysiology and clinical manifestations of OHSS and discusses approaches to patient care in the ED based on current literature.

Discussion: OHSS is an iatrogenic complication caused by an excessive response to controlled ovarian stimulation during assisted reproductive cycles (ART). OHSS complicates up to 30% of ART cycles, and many of these patients seek initial care in the ED. Risk factors for the development of OHSS include age < 35, history of polycystic ovarian syndrome or previous OHSS, and pregnancy. Emergency physicians will be faced with several complications including ascites, abdominal compartment syndrome, renal dysfunction, acute respiratory distress syndrome, thromboembolic disease, and hemodynamic instability. Critical patients should be evaluated in the resuscitation bay, and consultation with the primary obstetrics/gynecology team is needed, which improves patient outcomes. This review provides several guiding principles for management of OHSS and associated complications.

Conclusions: OHSS occurs in up to 30% of IVF cycles and carries a high morbidity. Effective care of the OHSS patient begins with early diagnosis while evaluating for other diseases and complications. Understanding these complications and an approach to the management of OHSS is essential to optimizing patient care.

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1. Introduction

Infertility affects 48.5–186 million people worldwide [1-3]. In the United States, approximately 12.1% of all women between the ages of 15–44 have difficulties conceiving naturally, and nearly 7.3 million women have at some point in their lives used fertility services [4]. While the overall rates of infertility have remained approximately the same over the last 20 years, the use of assisted reproductive technology (ART) has increased. Between 1996 and 2010, the number of ART cycles performed doubled, and the number of infants born as a result nearly tripled [5]. In 2016, there were 263,577 reported number of ART cycles performed, compared to 142,435 cycles in 2007 [6].

While ART is considered safe, women are at risk for developing ovarian hyperstimulation syndrome (OHSS), an important complication with significant morbidity and mortality [7-10]. OHSS is an iatrogenic complication caused by an excessive response to controlled ovarian stimulation [11-14]. As there is no consensus definition, the total number of OHSS cases is difficult to determine. However, within the literature, moderate to severe OHSS complicates 3–10% of all ART cycles, with an incidence of up to 20% in high risk women [15]. Many of these patients seek initial care in the emergency department (ED), accounting for 7.7 ED visits per 1000 cycles in 2014 [16]. There were 11,562 hospitalizations in the United States from 2002 to 2011 for OHSS, with approximately 4.4% of these patients experiencing a life threatening complication [17,18]. With the increasing use of ART, emergency department physicians need to be equipped with the knowledge to both diagnose and treat this complication.

2. Methods

This narrative review outlines the underlying pathophysiology and clinical manifestations of OHSS and discusses current approaches to patient care in the ED. A literature review of the PubMed and Google Scholar databases was performed with search date from 1980 to February 2019 for articles using the keywords ‘ovarian hyperstimulation’ OR ‘OHSS’ OR ‘ovarian hyperstimulation syndrome’ OR ‘assisted reproductive technologies’ AND ‘complications’, AND ‘emergency’ for production of this narrative review. Authors included case reports and series, retrospective and prospective studies, systematic reviews and meta-analyses, clinical guidelines, and other narrative reviews. Commentaries
and letters were excluded. The literature search was restricted to studies published in English. Initial literature search revealed over 550 articles. Authors reviewed all relevant articles and decided which studies to include for the review by consensus, with focus on emergency medicine-relevant articles, including guidelines. A total of 113 resources were selected for inclusion in this review. As this is a narrative review, authors did not pool individual study data.

3. Discussion

3.1. ART basics

ART cycles are classified based on the source of the egg (patient vs. donor) and the status of the embryo (fresh vs. frozen). There are 4 basic steps comprising an ART cycle: 1) Controlled ovarian hyperstimulation with exogenous gonadotropins, 2) Follicle aspiration (i.e., oocyte retrieval), 3) Fertilization/insemination of the retrieved oocyte with spermatozoa, and 4) Embryo transfer.

3.1.1. Controlled ovarian hyperstimulation

While natural cycle in-vitro fertilization (IVF) is possible (i.e., oocyte retrieval without medication induced controlled ovarian hyperstimulation), it is associated with lower pregnancy rates [19,20]. Almost all ART cycles undergo some form of controlled ovarian hyperstimulation prior to oocyte retrieval with the goal of maximizing high quality oocytes, while avoiding overstimulation and subsequent OHSS [21]. Ovarian stimulation typically occurs using either exogenous follicle-stimulating hormone (FSH) or exogenous human menopausal gonadotropin (hMG) [22]. Gonadotropin hormone-releasing hormone (GnRH) is another key regulator of the reproductive axis. During IVF, a GnRH antagonist or GnRH agonist is used to cause pituitary suppression to prevent premature ovulation [23]. The goal is to recruit the maximum number of mature follicles using ovarian stimulants (i.e., FSH or hMG), while preventing ovulation with either a GnRH antagonist or GnRH agonist until the desired follicle count or follicle size is achieved. Once desired count or size is achieved, a patient is then “triggered” to initiate the ovulatory cascade to lead to the final follicle maturation process [24]. The most common trigger medications used include recombinant human choriionic gonadotropin (hCG), GnRH antagonists, or GnRH agonists [25].

3.1.2. Ovarian hyperstimulation syndrome pathophysiology

The pathophysiology of OHSS relates to arteriolar vasodilation and increased capillary permeability resulting in intravascular volume shifting to the extravascular space (Fig. 1) [26-28]. Ovarian stimulation causes marked ovarian enlargement associated with an overproduction of pro-inflammatory and vasoactive cytokines leading to increased capillary permeability [29,30]. The use of hCG as an ovulatory trigger is associated with the development of OHSS, as hCG directly increases vascular endothelial growth factor (VEGF) production [31]. VEGF causes angiogenesis and increased vascular permeability. Similarly, the severity of OHSS has been directly linked to levels of VEGF [32,33]. Elevated levels of pro-inflammatory immune cytokines (i.e., interleukin-1β, IL-6, IL-8, and tumor necrosis factor α) are characteristic of OHSS and are associated with increased capillary permeability [34]. Clinical manifestations of OHSS can be connected to the increased vascular permeability and subsequent loss of protein-rich fluid to the extravascular space [35].

3.2. Risk factors

Numerous risk factors (Table 1) contribute to the development of OHSS [36]. Younger age and development of OHSS is thought to be due to a higher number of gonadotropin receptors available in a younger ovary, therefore, making them more susceptible to stimulation [37]. Polycystic ovarian syndrome (PCOS) also increases the risk of OHSS, specifically those with ultrasound evidence of >10 ovarian cysts measuring <10 mm in size [38]. Stimulation protocols using gonadotropin-releasing hormone (GnRH) antagonists for ovulation suppression have been shown to have a lower incidence of OHSS compared with protocols that use a GnRH agonist [39-42].

3.3. Clinical presentation

The signs and symptoms of OHSS are a result of marked vascular permeability and concomitant uterine and ovarian enlargement [37,44]. Initial symptoms develop gradually with abdominal distention and mild abdominal discomfort due to reproductive organ enlargement with cysts [14,44,45]. These cystic ovaries may enlarge as much as 12–25 cm in some cases and have the potential to rupture or hemorrhage, leading to peritonitis [11,14,37]. Similarly, these patients are at increased risk of ovarian torsion [37,46]. Increased capillary permeability leads to third spacing and subsequent intravascular volume depletion [47,48]. This pathophysiology underlies associated clinical features and severity as it correlates to increasing organ system involvement [49].

The first indication of OHSS is typically the development of ascites [37]. Accumulation of ascitic fluid in the peritoneal cavity leads to abdominal distention and pain, as well as increased intra-abdominal pressure (IAP) [50]. Increased IAP may result in end-organ dysfunction, affecting the renal, respiratory, gastrointestinal, cardiovascular, and hepatic systems [50]. As IAP rises above 12 mmHg, intra-abdominal hypertension (IAH) develops [51]. In severe cases, abdominal compartment syndrome (ACS) may occur, defined as a sustained IAP >20 mmHg with new organ dysfunction/failure [50-52]. Oliguria is one of the initial signs of IAH [50,51,53]. Intra-abdominal venous drainage is impaired, causing renal, intestinal, and hepatic edema [50]. This leads to hepatic injury, paralytic ileus, and intestinal edema characterized by severe emesis and diarrhea [37,49]. Further increases in IAP impairs splanchnic and hepatic perfusion resulting in local tissue hypoxia [50,51]. Approximately 30% of severe OHSS patients will have elevated levels of aspartate aminotransferase and alanine aminotransferase [54]. A concomitant elevation in γ-glutamline transpeptidase or alkaline phosphatase may also be seen [37]. Acute renal failure is typically characterized by hyponatremia due to a low serum osmolality and decreased urinary sodium excretion [37,47]. Hyponatremia may lead to cerebral edema, altered mental status, and neurologic complications [55]. Other metabolic abnormalities, including hyperkalemia and metabolic acidosis, may occur [43,56].

Leukocytosis, increased hematocrit, and thrombocytosis indicate hemococoncentration and inflammation [37]. Hemoconcentration predisposes to hypercoagulability and thrombotic events, complicating up to 10% of severe OHSS [37,50,57]. Pressure from enlarged ovaries or ascites on pelvic vessels and hypercoagulable states due to pregnancy or high estrogen levels are also risk factors [58,59]. Patients may have an underlying thrombophilia, including factor V Leiden mutation, protein C, protein S, and antithrombin III deficiencies and antiphospholipid syndrome [59,60]. Thrombosis typically occurs in the venous system, accounting for 81% of cases [47,50]. Venous locations of thrombotic events are, in order of decreasing frequency, the jugular, subclavian, lower-extremity, upper-extremity, cerebral, renal, and retinal veins [58,61-64]. Arterial embolism occurs primarily in the pulmonary, cerebral, central retinal, coronary, upper extremity, and lower extremity arteries [47,58,60].

Patients with OHSS are at a high risk for infection, as they are in a relative immunodeficient state with decreased levels of immunoglobulin A (IgA) and immunoglobulin G (IgG) [54,65]. >83% of hospitalized OHSS patients will have a febrile episode, with an infectious organism being identified in only one third of cases [65]. Urinary tract infections are present in 20.5% of this cohort, pneumonia in 3.8%, upper respiratory tract infection in 3.3%, intravenous line phlebitis in 2.0%, cellulitis surrounding the abdominal puncture site in 1.0%, postoperative wound infections in 1.0%, and gluteal abscess at the site of progesterone injection
in 0.5% [65]. Causative organisms include Klebsiella pneumonia, Pseudomonas aeruginosa, Proteus mirabilis, Escherichia coli, Proteus vulgaris, and Morganella morganii [65]. Increased endogenous production of pro-inflammatory cytokines likely plays a role as a non-infectious source of fever [37,44].

Critical patients may present with any combination of hypovolemic shock due to gastrointestinal losses or third spacing, septic shock due to an underlying infection, distributive shock from a severe inflammatory state, or obstructive shock secondary to pericardial effusion with cardiac tamponade or massive pulmonary embolism [37,47]. Pericardial effusions may be present in up to 17% of women with OHSS, although it is rarely associated with tamponade physiology [66,67].

3.4. Classification

Numerous attempts have been made to categorize and classify OHSS. Two forms have been described based on timing of presentation: an early form that typically occurs 3–7 days after ovulation triggering by hCG, and a late form occurring 12–17 days after hCG administration [68]. Early OHSS is caused by an excessive ovarian response to exogenous hCG, while late OHSS is due to excessive amounts of endogenous hCG from an implanting pregnancy [69,70]. The American Society for Reproductive Medicine has classified OHSS into 4 stages based on clinical and laboratory features (Table 2) [71]. Moderate to severe OHSS occurs in approximately 1–5% of ART cycles and in up to 20% of high risk patients [72,73]. The milder form of OHSS is seen in 20–30% of all in-vitro fertilization (IVF) cycles [74].
In patients with severe OHSS, 99% present with ascites, 54% with Fluctuance or drainage suggests the presence of a hematoma or abscess. warmth, or induration of injection sites suggests infection.

mild OHSS may have normal abdominal examination. Overlying ery- cracks upon auscultation [75]. In this same cohort, 92% presented with ARDS, and 2% with pulmonary embolism [75]. with dyspnea, and ultimately, 4% were diagnosed with pneumonia, 2% with ARDS, and 2% with pulmonary embolism [75]. Evaluation of the abdomen should focus on the presence of perito-neal irritation, masses, ascites, and infection, although patients with mild OHSS may have normal abdominal examination. Overlying ery-thema, warmth, or induration of injection sites suggests infection. Flucluance or drainage suggests the presence of a hematoma or abscess. In patients with severe OHSS, 99% present with ascites, 54% with gastrointestinal symptoms, 30% with oliguria, 13% with peripheral edema, and 6% with peritonitis [75]. Measurement of intra-abdominal pressure is useful when assessing for IAH or ACS. In patients with moderate or severe OHSS, pelvic examination should be deferred in order to decrease the risk of ovarian cyst rupture and associated intra-abdominal hemorrhage [37].

3.6. Considerations in laboratory and imaging

Laboratory and imaging studies should be pursued to confirm the diag-nosis of OHSS, evaluate for end organ dysfunction, and provide ac-curate prognostication of the patient’s clinical condition. It is beneficial to evaluate for electrolyte and metabolic abnormalities with a basic meta-bolic panel, venous blood gas, serum osmolality, and lactate level. Hepatic abnormalities should be investigated by obtaining liver enzymes, direct/indirect bilirubin, alkaline phosphatase, albumin, and coagulation studies, including fibrinogen. A pregnancy test and/or serum beta-hCG should be obtained to determine the outcome of the treatment cycle. A blood type and screen may be sent in cases of suspected intra-abdominal bleeding from hemorrhagic cyst rupture. A complete blood count typically reveals leukocytosis and thrombocytosis, which may suggest an underlying infection or hemoconcentration. Infectious workup may include urinalysis or peritoneal fluid analysis, as well as blood, urine, sputum, ascites, and peritoneal fluid cultures, as applicable. Similarly, C-reactive protein may provide insight into OHSS severity, although it carries a sensitivity of 69% and specificity of 71% for a diagnosis of OHSS when CRP ≥12 mg/L [76,77]. The clinician should have a low threshold for obtaining an electrocardiogram in these patients.

Imaging should be guided by the patient’s clinical presentation, his-tory, and underlying comorbidities. The diagnosis of OHSS should not be based solely on imaging. However, bedside ultrasound can evaluate ovarian size, presence of ascites, ovarian torsion, ectopic/heterotopic pregnancy, vascular thrombosis, interstitial pulmonary edema, pleural effusions, pericardial effusion, and any associated tamponade.
Ultrasound may be used to determine fluid status and fluid responsiveness to guide resuscitation [87]. Bedside examinations may be augmented by formal echocardiography, abdominal, or gynecologic ultrasound studies. Chest x-ray may detect pleural effusions or other pathologies [8,47]. In one study of patients with severe OHSS, 71% of patients had an elevated diaphragm on chest x-ray, 29% had evidence of a pleural effusion, and 20% had evidence of atelectasis [75]. Computed tomography pulmonary angiogram (CTPA) or ventilation/perfusion (V/Q) scan is often warranted in the evaluation for pulmonary embolism, while computed tomography (CT) of the abdomen and pelvis may help differentiate OHSS from other potential diagnoses [8,47]. Intravenous contrast is recommended to better evaluate the anatomic and vascular structures of interest. CT of the brain is warranted in the case if suspected cerebral edema. The possibility of pregnancy should be noted if advanced imaging is considered [8].

3.7. Management

Management of OHSS is dependent on severity and presence of comorbid conditions [37]. Early consultation with the obstetrics and gynecology team, as well as any needed subspecialties, is recommended. The treatment of OHSS is primarily supportive, and in most cases, OHSS follows a self-limited course that parallels the decline in serum h-βhCG [37,47]. Mild and moderate OHSS may be treated on an outpatient basis with symptomatic relief, monitoring, and close follow up in 2–3 days [47,49]. These patients should be counseled about the need to monitor fluid intake (approximately 2 L water daily) and output, body weight, abdominal girth, and the necessity of avoiding nephrotoxic medications, including non-steroidal anti-inflammatories [47,50]. Thromboprophylaxis with pregnancy-related low-molecular weight heparin (LMWH) doses (e.g. 40 mg enoxaparin or 5000 IU dalteparin daily) may be considered [47,60,62,88,89]. Clinically, progression of thromboembolism is seen in approximately 10% of cases, and appropriate anticoagulation must be implemented promptly in the emergency department [89,90]. Strict return precautions, including worsening symptoms, weight gain of 1 kg/day or more, and urine output <500 mL/day should be provided [50]. The patient should be aware that her condition may worsen if pregnancy occurs [50].

For severe cases of OHSS, management is aimed towards maintaining circulatory hemodynamics, mobilizing fluid from the third space back into the vessels, correcting hemoconcentration, and respiratory support. Restoration of adequate intravascular volume must always remain the first priority to ensure appropriate tissue perfusion and prevent the development of multiorgan failure. Correction of hypovolemia, hypotension, and decreased renal perfusion takes precedence, accepting that fluid administration may contribute to the accumulation of ascites [50]. Either normal saline or a balanced crystalloid solution is the initial resuscitation fluid of choice [37,50]. However, albumin can be used to expand plasma volume in the presence of severe hemoconcentration (hematocrit 45%), severe hyperalbinemia (serum albumin level ≤ 3.0 g/dL), or significant ascites with elevated IAP [37,50,91,92]. Other volume expansion agents including fresh frozen plasma, hydroxyethyl starch (HES), and dextran have been used with limited success in OHSS, but are not recommended as first-line agents [37,93-95]. Intravascular resuscitation should be titrated to maintain an adequate urine output (20–30 mL/h) and to reverse hemoconcentration [43]. The addition of vasopressor therapy may be needed to maintain adequate perfusion. While there is little empiric data to guide management, the underlying pathophysiology of OHSS favors norepinephrine and dopamine as potential options [96,97]. Dopaminergic agonists, including cabergoline, have been established as effective therapies for the prevention of OHSS via blockage of vascular endothelial growth factor expression [98,99]. Published data suggests that dopamine itself improves the clinical evolution of established OHSS, although no randomized controlled trials have been published to confirm its effectiveness [96,100].

Correction of severe electrolyte abnormalities plays an important role in OHSS management. Hyperkalemia in these patients should be managed in the usual fashion [101]. Salt or water restriction is not recommended, as this does not affect the patient’s weight, peripheral edema, intravascular volume status, or abdominal circumference [50]. Current evidence suggests that hypertonic saline solutions, either alone or in combination with colloid solutions, result in significant reduction in IAP while expanding intravascular volume and correcting hyponatremia present in OHSS [50,102,103]. Hypertonic saline (3%) may be considered as a 100–150 mL infusion over 5–10 min with a repeat bolus as needed in those with severe OHSS. The goal for serum sodium correction should be 1–3 mEq/L in the first hour [104].

Pulmonary support may involve thoracentesis, oxygen supplementation, non-invasive ventilation (NIV), or mechanical ventilation [37,47,105,106]. If ARDS develops, mechanical ventilation using 6 mL/kg of predicted body weight and plateau pressure < 30 cm H2O should be initiated [37,107]. The presence of ARDS presents a fluid management challenge, however, fluid therapy should be titrated to maintain systemic perfusion and adequate renal perfusion [37,107]. Diuretics may potentiate hemoconcentration and hypovolemia, predisposing the patient to venous thromboembolism, and should also be avoided if at all possible [37]. Glucocorticoids may provide some benefit in the treatment of ARDS in the setting of OHSS, with case reports reporting favorable outcomes with 30 mg/kg methylprednisolone [108].

While ascites is a hallmark feature of OHSS, paracentesis is not indicated in every OHSS patient. Indications for paracentesis include symptomatic complaints such as dyspnea, abdominal distention, and oliguria. Additional indications include evaluation for spontaneous bacterial peritonitis and the presence of IAH/ACS [50,91]. Serial IAP measurements and urine output should be obtained via a urinary catheter [91]. Based on current guidelines for the management of IAH and ACS, an IAP > 20 mmHg warrants peritoneal decompression through paracentesis [91,109]. While there is no required volume of peritoneal fluid to be removed, 1000 mL is an appropriate initial amount [50,110]. The average amount of peritoneal fluid drained during hospitalization is approximately 11 L. [111] However, there are reported cases of patients requiring up to 7.5 L on one occasion and 45 L in total during 1 hospitalization [112]. Large volume paracentesis may lead to rapid re-accumulation of ascites, removing proteins from the intravascular compartment, thereby worsening third spacing [37]. Ultrasound guidance should be utilized in order to avoid puncturing large ovarian cysts, with albumin infused as necessary to maintain intravascular volume [37,43].

Non-operative management of IAH/ACS should focus on the following: 1) evacuating intestinal contents via naso or oro-gastric tube placement, 2) evacuating any intra-abdominal space-occupying lesions (e.g. ascites), 3) improving abdominal wall compliance, 4) optimizing fluid resuscitation and 5) optimizing systemic and regional perfusion status [50,91]. Surgical management for OHSS is indicated in the presence of ovarian torsion, pregnancy termination, intra-abdominal hemorrhage, ectopic/heterotopic pregnancy, or ruptured cysts [37,113].

When infection is suspected, empiric antibiotic therapy should be initiated [37]. Empiric antibiotics should have broad coverage against
the most commonly encountered bacteria in this population, including *E. coli*, *K. pneumonia*, *P. aeruginosa*, *P. mirabilis*, and *P. vulgaris* [37,65]. We recommend an initial regimen of a third or fourth generation cephalosporin in combination with metronidazole. Alternative agents include imipenem-clavulanate, meropenem, doripenem, and piperacillin-tazobactam.

3.8. Disposition

Mild to moderate OHSS may be managed on an outpatient basis, while severe OHSS requires inpatient management [37,50]. Early consultation with the obstetrics and gynecology team as well as any subspecialties, is recommended. Patients presenting with severe abdominal pain or distention, intractable emesis, hemococoncentration, abnormal liver function studies, IAH/ACS, oliguria or anuria, hypotension, tachypnea, dyspnea, syncope, and/or electrolyte disturbances such as hyponatremia or hyperkalemia should be hospitalized [50].

4. Conclusion

Contemporary use of ART is increasing, and patients are increasingly presenting to the ED for complications. OHSS remains one of the most common complications, occurring in up to 30% of IVF cycles. Risk factors for the development of OHSS include age < 35, history of PCOS or previous OHSS, and pregnancy. OHSS may be categorized into mild, moderate, and severe presentations based on clinical, laboratory, and imaging parameters. OHSS may be complicated by concomitant infection, thromboembolism, acute respiratory distress syndrome, ACS, and severe shock. Effective care of the OHSS patient begins with early diagnosis while evaluating for other diseases and complications. Understanding these complications and an approach to the management of hemodynamically instability is essential to optimizing patient care.

Declaration of Competing Interest

None.

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