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Taiwanese Journal of Obstetrics & Gynecology 50 (2011) 2–10
www.tjog-online.com

Review Article

Update on management of ovarian hyperstimulation syndrome

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Accepted 7 September 2010

Abstract

Ovarian hyperstimulation syndrome (OHSS) is a relatively common complication of ovarian stimulation and can be life threatening. The pathophysiology of OHSS is characterized by increased capillary permeability, leading to leakage of fluid from the vascular compartment, with third-space fluid accumulation and intravascular dehydration. The increased intra-abdominal pressure indicated that OHSS may be considered a compartment syndrome. Vascular endothelial growth factor, also known as vascular permeability factor, has emerged as one of the mediators intrinsic to the development of OHSS. Conventional management is focused on supportive care until the spontaneous resolution of the condition. The standard of care for treatment—monitoring of appropriate clinical parameters, fluid balance management, thrombosis prophylaxis, and ascites treatment—should prevent severe morbidity in most cases. This review will cover inpatient and outpatient management. The potential therapeutic approach targeting the vascular endothelial growth factor system will be discussed.
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Keywords: Abdominal compartment syndrome; Dopamine agonist; Intra-abdominal pressure; Ovarian hyperstimulation syndrome; Paracentesis

Introduction

Ovarian hyperstimulation syndrome (OHSS) is a relatively common complication of ovarian stimulation and can be life threatening [1]. In severe cases, a critical condition develops with massive ascites, marked ovarian enlargement, pleural effusion, electrolyte imbalance, and hypovolemia with hypotension and oliguria [2].

Unlike tumor angiogenesis, OHSS is self-limiting and will undergo gradual resolution with time. Conventional management is focused on supportive care until the spontaneous resolution of the condition. This review will explore the pathophysiology of OHSS and its management. The potential therapeutic approach targeting the vascular endothelial growth factor (VEGF) system will be discussed. Improved understanding of the pathogenesis of OHSS should facilitate more individualized *in vitro* fertilization (IVF) treatment protocols and minimize the occurrence of OHSS [3].

Pathophysiology

The pathophysiology of OHSS is characterized by increased capillary permeability, leading to leakage of fluid from the vascular compartment, with third-space fluid accumulation and intravascular dehydration [4]. The cause of OHSS is unknown, but it may be mediated by vasoactive cytokines secreted in excess by hyperstimulated ovaries [5], and it is believed that these ovarian factors are secreted by corpora lutea in response to human chorionic gonadotropin (hCG) stimulation [6–8].

Proinflammatory cytokines [interleukin-1β (IL-1β), IL-6, IL-8, and tumor necrosis factor-α] have been implicated as mediators of the acute-phase response [9], which is characterized by capillary leakage similar to that seen in OHSS. VEGF, also known as vascular permeability factor, has emerged as one of the factors most likely involved in the pathophysiology of OHSS [10]. VEGF is an angiogenic cytokine, which is a potent

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doi:10.1016/j.tjog.2011.01.014

stimular of the vascular endothelium and appears to play an integral role in follicular growth, corpus luteum function, and ovarian angiogenesis. In human, hCG administration increased VEGF expression in granulose-lutein cells [11]. High serum, peritoneal fluid, and follicular fluid VEGF, IL-6, and IL-8 concentrations have been correlated with the development of OHSS and its severity [7,12−15]. Hence, the inhibition of vascular permeability appears to be an attractive and novel therapeutic approach to preventing and treating OHSS (Fig. 1).

Hemodynamic changes of OHSS

The clinical manifestations originate from the combination of decreased intravascular space and the accumulation of protein-rich fluid into body cavities and interstitial space. This "third spacing" causes depletion of the intravascular space. Loss of intravascular volume leads to hemodynamic changes manifested as hypotension, severe tachycardia, and decreased renal perfusion as well as hemoconcentration. Hemoconcentration with increase in blood coagulability is responsible for arterial and venous thrombotic phenomena in patients with OHSS [16]. Loss of intravascular volume combined with decreased renal perfusion results in electrolyte abnormalities (hyperkalemia, hyponatremia), increase in hematocrit and white cell count, and decrease in creatinine clearance.

The most common symptom of OHSS (abdominal discomfort) is because of the development of ascites. Accumulation of protein-rich fluid in the peritoneal cavity leads to abdominal distention and increased intra-abdominal pressure (IAP).

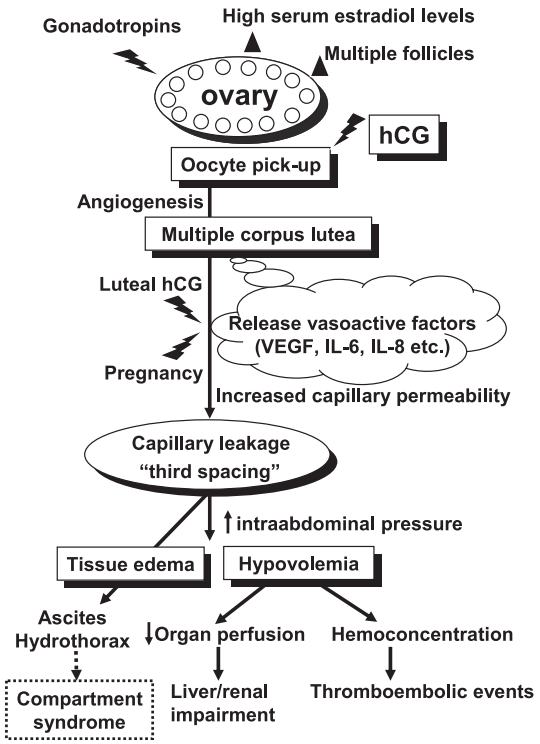

Fig. 1. Pathophysiology of ovarian hyperstimulation syndrome. hCG = human chorionic gonadotropin; IL-6 = interleukin-6; IL-8 = interleukin-8; VEGF = vascular endothelial growth factor.

Increased IAP has deleterious effects on end-organ function and may compromise respiratory, cardiovascular, renal, gastrointestinal, and hepatic system homeostasis [17,18]. An understanding of the pathophysiology of increased IAP is useful in the management of OHSS.

Changes in IAP have a great impact on renal function and urine production. One of the first visible signs of intra-abdominal hypertension (IAH) is oliguria, which occurs at an IAP of 15−20 mmHg [19]. Renal dysfunction secondary to increased IAP results from the decrease in cardiac output, direct compression of renal vessels and parenchyma with decreased renal blood flow, increased renal vascular resistance, and redistribution of renal blood flow from the cortex to the medulla. Experimental studies demonstrated that IAP >15−20 mmHg was associated with decreased glomerular filtration rate and oliguria, which progressed to anuria when IAP values exceeded 30 mmHg [20]. The same is true for all the intra-abdominal low-pressure vessels that supply the intestines. Initial venous compression results in parenchyma edema. Intestinal edema is responsible for the nausea and the diarrhea, which often occurs in patients with OHSS.

Increased IAP leads to decreased splanchnic and hepatic perfusion with tissular hypoxia. Animal studies showed a significant impairment of hepatic artery and portal vein blood flow at IAP of 10 mmHg and decreased mesenteric blood flow at IAP of 20 mmHg [17]. Liver edema is manifested with an increase in liver function tests [15]. The increase in IAP leads to elevation of the diaphragm with increased intrathoracic and pleural pressures, resulting in progressive reduction in lung and chest wall compliance. Pulmonary function may be compromised in cases of severe OHSS by several mechanisms that act synergistically: elevation of the diaphragm, accumulation of fluid in the pleura, and interstitial edema [21]. Although pleural effusion is generally thought to be a consequence of pronounced ascites, associated with a shift of liquid from the peritoneal cavity to the pleura, isolated pleural effusion without concomitant ascites has been reported as the only symptom of OHSS [22−24]. The pathogenesis of isolated hydrothorax in cases of OHSS remains unclear.

OHSS may be considered as an abdominal compartment syndrome

The increased IAP indicates that OHSS may be considered a compartment syndrome. IAH is defined by a sustained or repeated pathologic elevation of IAP ≥12 mmHg. Abdominal compartment syndrome (ACS) is defined as a sustained IAP >20 mmHg that is associated with new organ dysfunction/failure [25,26]. Primary ACS is a condition associated with injury or disease in the abdominopelvic region. Secondary ACS refers to conditions that do not originate from the abdominopelvic region, such as sepsis and capillary leak syndrome, major burns, and other conditions requiring massive fluid resuscitation, yet resulting in the signs and symptoms commonly associated with the ACS [25].

The most important factor responsible for the development of ACS might be excessive fluid administration, which can

shift to the third space because of increased capillary permeability. The hemodynamic changes associated with moderate to severe OHSS strongly resemble those of an ACS [27].

Increased IAP has been documented for 20 OHSS patients in the literature [28,29], with increased IAP reported in moderate and severe OHSS cases. Cil et al [28] documented an IAP of 54 cm H_2O by bladder catheter, equivalent to 40 mmHg, which satisfies criteria for ACS. Another study found mean IAP of 17.5 ± 1.24 cm H_2O, equal to 12.9 ± 0.91 mmHg, in 19 OHSS patients with varying symptoms including decline in respiratory function, tense ascites, oliguria, or a combination of these [29]. It should be noted that a rapid increase in IAP may affect symptoms and signs. Based on these observations, and the well-established link between IAH and organ dysfunction, it is logical to consider how IAP measurement may correlate with the disease severity in OHSS patients [27].

Classification of OHSS

Conventional OHSS staging has relied on clinical symptoms and laboratory findings to categorize severity of disease. The most popular classification system for staging OHSS is that of Golan et al [30]. This system incorporated the use of transvaginal sonography for both estimating of ovarian enlargement and detection of ascitic fluid. The detection of ascites establishes the diagnosis of moderate OHSS. Subsequent modifications defined a group of critical or complicated OHSS and added to the severe category of the syndrome [31,32].

It should be remembered that OHSS is a dynamic situation. The clinical symptoms and signs of OHSS exhibit a continuum of scope and severity that defies attempts at specific classification. A moderate OHSS patient may progress within hours or days to a severe case. Therefore, clinicians cannot be overcautious in patient monitoring of moderate or even mild OHSS. Management of patients with OHSS should be therefore based on the severity of the syndrome according to a simple, but comprehensive classification.

In 2003, the Practice Committee of the American Society for Reproductive Medicine proposed a simplified classification of the syndrome into mild, worsening, and serious [33,34]. It also defined criteria for outpatient or inpatient management. Progression of illness is recognized when symptoms persist, worsen, or include ascites that may be demonstrated by increasing abdominal girth or ultrasound evaluation. Serious illness was defined by the presence of abdominal pain plus one or more of the following signs: rapid weight gain, tense ascites, hemodynamic instability, respiratory distress, progressive oliguria, and laboratory abnormalities. Laboratory criteria for women with serious illness include: hemoconcentration (hematocrit >45%), leukocytosis (white blood cell count >15,000), sodium less than 135 mEq/L, potassium of more than 5.0 mEq/L, elevated liver enzymes, and serum creatinine of more than 1.2 mg/dL. According to the Practice Committee, most patients with serious illness require hospitalization.

A division of OHSS into "early" and "late", depending on the time of onset, may be useful in determining the prognosis [35,36]. OHSS presenting within 9 days after the ovulatory dose of hCG is likely to reflect excessive ovarian response and the precipitating effect of exogenous hCG administered for final follicular maturation. OHSS presenting after this period reflects endogenous hCG stimulation from an early pregnancy [35]. Late OHSS is more likely to be severe and to last longer than early OHSS.

Advanced stages of OHSS share a hemodynamic pathophysiology with ACS. Measurement of IAP may help to classify the stage of OHSS [27]. The potential importance of IAP in classification of the severity of OHSS requires further studies.

Management

The best treatment in OHSS is prevention. However, there are no precise methods to completely prevent severe OHSS [37,38]. Conventional management of OHSS is focused on supportive care until the spontaneous resolution of the condition. The standard of care for treatment [39]—monitoring of appropriate clinical parameters, fluid balance management, thrombosis prophylaxis, and ascites treatment—should prevent severe morbidity in most cases.

An understanding of the pathophysiology of increased IAP and OHSS is useful in the management of OHSS. Nonoperative management strategies are now recognized as playing a vital role in both the prevention and treatment of organ dysfunction and failure because of elevated IAP [40]. The nonoperative management of IAH/ACS can be summarized using five therapeutic goals: (1) evacuate intraluminal contents; (2) evacuate intra-abdominal space-occupying lesions (e.g. ascites); (3) improve abdominal wall compliance; (4) optimize fluid administration; and (5) optimize systemic and regional tissue perfusion [41]. These fundamental management concepts remain appropriate for OHSS patients with elevated IAP.

The present section will cover outpatient and inpatient management. The potential therapeutic approach targeting the VEGF system will be discussed.

Outpatient management

Patients with mild manifestation of OHSS do not require any specific treatment. Outpatient surveillance is, nevertheless, mandatory to detect cases that may progress to moderate or severe OHSS. Most patients with moderate OHSS still can be managed on an outpatient basis, but they require more careful evaluation including daily weight and abdominal girth measurement, physical and ultrasound examination to detect increasing ascites, and to measure ovarian size. Oral fluid intake should be maintained at no less than 1 L per day. Women should be encouraged to drink to thirst, rather than to excess. Strenuous exercise and sexual intercourse should be avoided. Strict bed rest is unwarranted and may increase risk of thromboembolism. Discomfort may be relieved with acetaminophen or opiate medications if severe. Nonsteroidal anti-inflammatory agents are not recommended because they may compromise renal function in patients with OHSS [42]. If symptoms are worsening, weight continues to increase at 1 kg/day or more, or urine

output is decreasing (<500 mL/day), the patient should be brought back to the office for physical examination, ultrasound, and laboratory evaluation include hematocrit, electrolytes, and serum creatinine. The patient should be aware that her condition may worsen if pregnancy ensues.

An alternative strategy for treatment of OHSS consists of early intervention with paracentesis in an outpatient setting. In 1994, Shrivastav et al [43] reported a comparison of inpatient versus outpatient management of severe OHSS and concluded that outpatient management was a safe and effective treatment alternative. The efficacy of outpatient treatment has been confirmed in subsequent studies [44–46] and has recently been shown to be cost effective [47]. In aggressively treating OHSS with paracentesis before the development of symptoms including weight gain, hemoconcentration, electrolyte imbalance, or renal abnormality, only 9.4% of patients ultimately required hospitalization for repetitive culdocenteses [44]. Smith et al [45] reported 25 of 29 (86%) patients with severe OHSS were managed as outpatients with transvaginal paracentesis with no complication. They have demonstrated that outpatient transvaginal paracentesis may be used safely in the management of patients with even severe OHSS. Therefore, there has been a trend toward the use of outpatient management with paracentesis for moderate to severe OHSS. Early intervention to avoid progression, rather than waiting passively, remains an attractive approach that deserves prospective evaluation.

Hospitalization management

Women with serious illness or severe OHSS require hospitalization for more careful monitoring and aggressive treatment. Careful and frequent reevaluation of the hospitalized patient with severe OHSS is essential. Clinical examination includes an assessment of hydration and cardiorespiratory system. Abdominal circumference and weight should be recorded at admission and daily until resolution. Fluid intake and output should be recorded and monitored on at least a daily basis. Urine output of less than 1,000 mL/day is a matter of concern.

Biochemical monitoring should include serum electrolytes, renal and liver function tests, a coagulation profile, and blood count. Sonographic examination provides assessment of ovarian size and the presence of ascites as well as pleural, or pericardial effusions. A chest X-ray and pulse oximetry are mandatory for any patient with respiratory symptoms and signs suggestive of hydrothorax, pulmonary infection, or pulmonary embolism. Assay of β-hCG will help to diagnose pregnancy as early as possible.

Pain and ascites can easily mask adnexal torsion, ovarian rupture, and acute intra-abdominal hemorrhage. Serial clinical and laboratory evaluations provide the means to monitor progression of illness and to recognize evidence of resolution.

Optimize fluid administration

The management of OHSS is essentially supportive, aiming at refilling the arteriolar bed, maintaining circulatory hemodynamics, and preventing hemoconcentration [39]. It is well known that hypovolemia potentiates the pathophysiologic effects of elevated IAP and predisposes patients to developing multiple system organ failure [17]. Maintenance of adequate intravascular volume must always remain the first priority to ensure appropriate tissue and organ perfusion and avoid the development of multisystem organ failure. Hospitalized patients require intravenous (IV) fluid management to address the acute need for volume expansion while also considering the marked increase in vascular permeability. Correction of hypovolemia, hypotension, and oliguria has highest priority, accepting that fluid administration may contribute to the accumulation of ascites.

Rapid initial hydration may be accomplished with bolus of IV fluid (1,000 mL normal saline) to maintain adequate urine output and reverse hemoconcentration [39]. If urine output response is adequate and hematocrit normalizes, switch to dextrose 5% normal saline and maintain at the rate of 125–150 mL/hr while monitoring very closely every 4 hours. If urine output is inadequate in response to fluid bolus and the hematocrit does not reflect a change toward euvolumia, IV crystalloid fluids may be stopped and albumin (25%) in doses of 50 g, infused more than 4 hours, and repeated at 4- to 12-hour intervals as necessary, is an effective plasma expander [34] (Fig. 2).

Diuretic therapy is usually contraindicated in patients with hemoconcentration as these patients are intravascularly volume depleted secondary to capillary leak. After the patient is

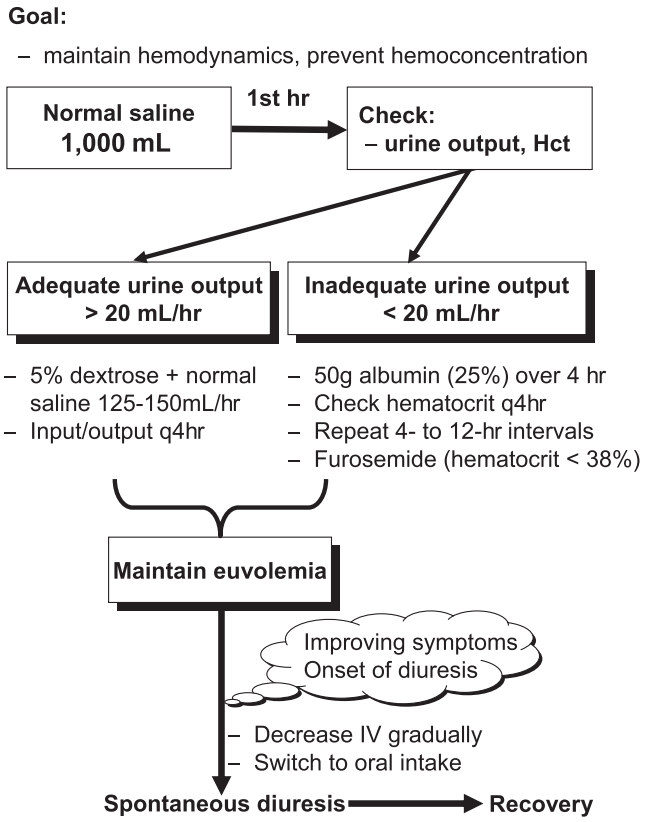

Fig. 2. Fluid management of ovarian hyperstimulation syndrome. Hct = hematocrit.

hemodynamically stable and their hemoconcentration state has resolved (hematocrit <38%), however, diuretics (e.g. furosemide, 20 mg IV) in combination with colloids may be considered to mobilize the third-space edema.

As soon as the intravascular volume and electrolyte changes have been corrected, and the patient has adequate urine output and onset of a brisk diuresis, she can be switched to oral intake. After the patient can tolerate oral intake and has adequate urine output she could be discharged at home.

The use of hypertonic crystalloids

Hypertonic saline has been in clinical use for many decades. The range of concentrations used clinically varies from 1.8% to 30% saline. Its osmotic and volume-expanding properties make it theoretically useful for a number of indications. In addition to the ability of hypertonic solutions to withdraw intracellular water to increase plasma volume, hypertonic saline may decrease microvascular fluid loss during states of elevated microvascular leak [48].

The mechanism of action of hypertonic saline is predominantly through the marked osmotic shift of fluid from the intracellular to the interstitial and intravascular space [49]. Endothelial cell volume increases as a result of water accumulation. An important effect of hypertonic saline-induced osmotic fluid shift is the normalization of endothelial cell volume.

Hypertonic saline has been shown to be anticoagulant *in vitro* when 5−10% of blood has been replaced with 7.5% hypertonic saline [50]. This equates to an approximate dose of 3.5−7 mL/kg of 7.5% hypertonic saline. No significant side effects were reported. The anticoagulant properties make it beneficial for OHSS patients who are at particular risk of thromboembolism.

In severe OHSS, patients always present electrolyte imbalance (hyponatremia, hyperkalemia) at the time of hospitalization. Hyponatremia may be dilutional as a result of antidiuretic hormone hypersecretion. Ayus et al [51], in a prospective study of 33 patients, successfully and safely treated symptomatic hyponatremia with a prolonged infusion (average of 17 hours) of 5% hypertonic saline. One to two milliliters per kilogram per hour of 3% hypertonic saline has been suggested to raise the serum sodium by 1−2 mmol/hr. A consensus statement in 2005 suggested that 3% hypertonic saline be used for symptomatic patients, either as a 100 mL of rapid infusion followed by 100 mL/hr, or at a rate of 1−2 mL/kg/hr [52]. Safety concerns with the use of hypertonic saline center mostly on the consequences of an acute hyperosmolar state. Further potential side effects include hyperchloremic acidosis and hyperosmolar renal failure [53]. There are far fewer studies using continuous infusions of hypertonic saline.

Current evidences suggest that hypertonic saline solutions, either alone or in combination with colloid solutions, can be used with good effect in certain circumstances [49,54]. The use of hypertonic saline has been demonstrated to result in significant reductions in IAP, decreased fluid requirements, and decreased risk of subsequent secondary ACS [54]. The use of hypertonic and/or colloid resuscitation fluids should therefore be strongly considered in any patient with elevated IAP [40]. However, it is unclear what the ideal concentration, formulation, or volume of hypertonic saline is. Future studies will hopefully elucidate the precise risk benefit ratio for the use of hypertonic saline solutions in OHSS patients, and define the most appropriate mode and means of administration as well as the optimal mode of monitoring for adverse effects.

Paracentesis

The presence of ascites is the hallmark of OHSS. In fact, symptoms resulting from ascites are often the most common reason for hospitalization. One goal of OHSS management is to prevent progression in disease severity. However, aspiration of ascitic fluid (paracentesis) is not indicated in every patient with OHSS. Current indications for paracentesis are based on symptomatic complaints of dyspnea, abdominal distension and pain, or oliguria. Navot et al [31] suggested that paracentesis is the single most important treatment modality in life-threatening OHSS not controlled by medical therapy.

Immediately after paracentesis, characteristic hemodynamic changes occur including decreased IAP, improved venous return, and improved renal and uterine perfusion [55]. Removal of ascites up to 7.5 L on one occasion and 45 L in total by serial vaginal paracentesis may be safe in patients with severe OHSS [56]. In patients with cirrhosis, the maximal hemodynamic effect was demonstrated after removal of >750 mL of ascites fluid [57]. Our experience showed that a marked relief of compression symptoms occurred after removing the first 1,000 mL of ascitic fluid [55]. However, incomplete tapping might result in rapid recollection of ascites, requiring retapping.

Serial IAP measurements may prove to be helpful in monitoring severe cases of OHSS. Based on existing literature for the management of IAH and ACS, an IAP >20 mmHg warrants decompression [25], which in OHSS patients is accomplished by paracentesis. If OHSS is considered to be a compartment syndrome, then early intervention with paracentesis even for moderate cases where ascites is found would seem the most logical plan of care [27].

Outpatient management with vaginal paracentesis at early stages of OHSS has been proposed as a safe and effective modality of treatment [43−45,47]. However, such management protocols often include multiple visits and drainage procedures with increased cost and inconvenience. Although severe OHSS can be managed on an outpatient basis, many physicians still recommend hospitalization of patients presenting with this condition [34,39]. Patients who fail to tolerate oral fluids, are dehydrated or require supportive care, such as pain control, should be hospitalized.

Repeat paracentesis may be indicated for fluid reaccumulation in patients with moderate or severe disease who again become symptomatic [55]. The placement of a catheter instead of multiple needle paracentesis would permit complete drainage through one, rather than several, interventions. Several reports have described the use of an indwelling transabdominal pigtail catheter placement for continuous drainage of ascites in patients with OHSS [58,59]. Percutaneous placement of a pigtail catheter has been demonstrated as

a safe and effective treatment modality for the management of ascites in severe OHSS [59]. It may represent an attractive alternative to multiple paracentesis.

Thromboprophylaxis

There are no firm data indicating either the value of diagnostic tests or heparin prophylaxis to prevent thromboembolic complications during controlled ovarian stimulation and in patients who develop OHSS [16]. However, as thromboembolism is a potentially life-threatening complication, thromboprophylaxis should be considered for patients who develop moderate to severe OHSS. Low-molecular weight heparin (LMWH) should ameliorate the risk of thrombotic complications, and thromboprophylaxis using pregnancy-related LMWH doses (e.g. 40 mg enoxaparin or 5,000 IU dalteparin daily) is now part of many recommended treatment protocols [60]. LMWH has been favored over unfractionated heparin because of ease of administration and lack of monitoring needed. In women who do not conceive, thromboprophylaxis may be discontinued with resolution of OHSS. For women who do conceive, continuation until the end of the first trimester, or even longer, depending on the presence of additional risk factors and course of the OHSS.

OHSS can be more unpredictable in severity and course in women who are pregnant. Clinically, progression of thromboembolism is seen in approximately 10% of cases suggests that adequate anticoagulation must be implemented promptly [60]. Pregnant women with OHSS and thromboembolic complications face a treatment dilemma. Successful management has been reported in a pregnant woman with OHSS and superior sagittal sinus thrombosis, and continuation of pregnancy has been considered safe [61]. The appropriate duration of therapy for thromboembolism in this situation is not yet established, although idiopathic venous thromboembolism is generally treated for 6 months. If, however, an early pregnancy has been diagnosed in the patient with critical complications of OHSS, the pregnancy may need to be terminated to prevent further deterioration of her condition.

Novel medical treatments

Dopamine and dopamine agonist

Dopamine has been used in oliguric patients with severe OHSS, resulting in significant improvement in renal function [62,63]. Dopamine produces its renal effect by increasing renal blood flow and glomerular filtration. This is accomplished by means of stimulation of the dopaminergic receptors present in the vascular kidney. Ferraretti et al [62] reported on the successful treatment of seven patients with severe OHSS using low doses of dopamine (4.32 mg/kg body weight/24 h) by peripheral infusion. Tsunoda et al [63] reported on 27 hospitalized patients, because of OHSS and refractory to the initial therapy with IV albumin, were treated by docarpamine (an oral dopamine prodrug). In 19 (86.4%) of 22 patients treated, clinical symptoms associated with ascites were gradually improved after administrating docarpamine. Oral docarpamine administration could be one of the options in the management of patients with OHSS using dopamine therapy. However, dopamine receptor 2 (DR-2) agonist, cabergoline, seems to be more effective and tolerated than dopamine.

It was recently found that dopamine or DR-2 agonists inhibit vascular endothelial growth factor receptor 2-dependent vascular permeability and angiogenesis through DR-2 of endothelial cells [64]. In a rat OHSS model [65], administration of a dopamine agonist, cabergoline, inactivates vascular endothelial growth factor receptor 2 and prevents the increase in vascular permeability. Alvarez et al [66] conducted a pilot study on patients at risk of developing OHSS who were given cabergoline (0.5 mg/day) orally from the day of hCG for 9 days. They observed that ascites, hemoconcentration, vascular hyperpermeability, and OHSS were significantly reduced. They further demonstrated that implantation and pregnancy outcome were not affected by cabergoline treatment [67]. Another prospective randomized study [68] also showed that cabergoline reduces the early onset of OHSS with no changes in pregnancy, implantation, or miscarriages rates. Recently, a systematic review and meta-analysis of four randomized trials comparing the prophylactic effect of the dopamine agonist, cabergoline, versus no treatment in IVF cycles showed that prophylactic treatment with cabergoline reduces the incidence, but not the severity of OHSS, without compromising pregnancy outcomes [69].

Cabergoline, however, has been associated with valvular heart disease when administered chronically in patients with Parkinson's disease [70]. Quinagolide is a nonergot-derived DR-2 receptor agonist. The use of quinagolide does not seem to be associated with an increased prevalence of heart complications [71]. Dopamine agonists are also differentiated by their pharmacokinetic profile, as indicated by a much shorter half-life of quinagolide ($\sim$17 hours) compared with cabergoline ($\sim$63–69 hours), thus minimizing exposure during organogenesis when used in an IVF setting. These two features make quinagolide an interesting dopamine agonist for use in prevention of OHSS. A randomized, double-blind, multicentre study [72] suggests that quinagolide at a dose of 200 μg/day reduces the frequency of moderate/severe early OHSS without compromising pregnancy or treatment outcome. The findings from this study may be especially relevant for oocyte donation programs and for patients with postponed embryo transfer.

One may concern that starting cabergoline after disease manifestation would not provide sufficient time to stop rapidly deteriorating clinical conditions in OHSS patients. The use of gonadotropin-releasing hormone (GnRH) antagonists has been associated with a significantly lower risk of OHSS compared with GnRH agonist [73]. The mechanism of action of the lower risk of OHSS has not been definitely determined, but GnRH antagonist is reported to have a prominent luteolytic effect [74]. Lainas et al [75] reported on successful management of severe early OHSS by reinitiating GnRH antagonist 3 days after oocyte retrieval in combination with embryo cryopreservation. Rollene et al [76] described an outpatient

treatment protocol for OHSS that resulted in rapid normalization of symptoms with minimal side effect. Four consecutive patients of early onset OHSS were prescribed 0.5 mg of cabergoline by mouth daily for 7 days and 250 g of ganirex subcutaneous to be repeated once in 24 hours and all embryos were frozen. No side effects were reported and no patients required hospitalization. They concluded that dopamine agonists and GnRH antagonists, when given together at the time of diagnosis of OHSS, appear to work rapidly and effectively to diminish the clinical symptoms of the disease [76]. The potential benefit of finding an outpatient treatment of OHSS with rapid onset and minimal side effects warrants further investigation into this protocol.

Doxycycline

Doxycycline, a tetracycline derivative, has been shown to inhibit angiogenesis in human model [77]. Fainaru et al [78] have demonstrated that oral doxycycline prevents VEGF-induced vascular permeability, IL-2-induced pulmonary edema, delayed-type hypersensitivity reactions, and tumor vessel hyperpermeability in mice. They recently reported that doxycycline directly inhibits vascular hyperpermeability in a mouse model of OHSS in a dose-dependent manner [79]. Doxycycline decreased the gonadotropin-induced general edema formation, the development of ascites, and the direct permeability of peritoneal blood vessels. Importantly, doxycycline did not affect angiogenesis in the corpus luteum, but rather the vascular hyperpermeability effect caused by the gonadotropin-induced proangiogenic milieu [79]. Doxycycline's potential in preventing/treating human OHSS warrants further studies.

Conclusions

OHSS represents one of the most important complications of ovarian stimulation. The syndrome should be respected for its potential to cause critical morbidity or even death. Experience with ovulation induction therapy and knowledge OHSS pathophysiology and clinical features are key to preventing and managing OHSS.

Conventional management is focused on supportive care until the spontaneous resolution of the condition. If OHSS is considered to be a compartment syndrome, then early intervention with paracentesis would seem the most logical plan of care. Recently, there has been a trend toward the use of outpatient management with early paracentesis for moderate to severe OHSS.

VEGF has emerged as one of the mediators intrinsic to the development of OHSS. The inhibition of vascular permeability appears to be an attractive and novel therapeutic approach to preventing and treating OHSS. Antiangiogenesis agents, such as VEGF antagonists or doxycycline, could offer theoretical advantages, but are still remote from clinical applications. Recently, DR-2 agonists have been shown to counteract VEGF-induced vascular permeability. The lack of toxic or teratogenic effects could make cabergoline or quinagolide an effective and safe etiological approach for OHSS prevention/treatment. Further studies are needed to establish protocols for OHSS prevention and treatment using these compounds.

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