CHAPTER 12

Prediction and prevention of ovarian hyperstimulation syndrome

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INTRODUCTION

Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic condition encountered in patients undergoing ovulation induction. The incidence of moderate to severe forms of OHSS occurs in 1–2% of assisted reproductive technology (ART) cycles. The clinical symptom complex of ovarian enlargement, abdominal distension, nausea/vomiting, ascites, and oliguria characterizes the syndrome. Although OHSS is almost exclusively observed in controlled ovarian hyperstimulation (COH) cycles using exogenous gonadotropins, rarely clomiphene citrate administration can cause similar clinical features. The existence of this syndrome was first reported in 1961[1]. Whereas transvaginal ultrasound and serum estradiol (E_2) determinations have made monitoring of the clinical response to gonadotropins far more precise, the incidence of OHSS per treatment cycle has not lessened in the past 30 years.

Although most cases of OHSS are considered mild and limited to tolerable gastrointestinal side-effects, serious complications such as ischemic stroke[2], acute myocardial infarction[3,4], forearm amputation[5], and death have been reported[6]. OHSS is a self-limiting entity in most cases over the course of a few days in non-conceptional cycles. However, worsening OHSS can be observed in conceptional cycles in which endogenous human chorionic gonadotropin (hCG) production continues and resolution of the syndrome is delayed. Since 1967, various investigators using both clinical and laboratory data have classified OHSS as mild, moderate, or severe, with various subgrades[1,7–10]. Although useful for study purposes, these schemes are unnecessarily complex. Firstly, comprehensive monitoring has revealed that many features found in 'mild' and 'moderate' OHSS are common in most patients with average response to gonadotropins and could probably be considered the upper limits of a normal spectrum of response[11]. Secondly, some criteria for severe OHSS, such as hydrothorax or hypercoagulability, can exist without other stigmata of the syndrome[12,13]. Lastly, for the purpose of management, only two categories of cases are important: cases that require hospitalization (severe) and cases that don't (mild) (Table 12.1).

PATHOPHYSIOLOGY

The underlying physiologic derangement primarily responsible for OHSS is increased vascular permeability. Capillary leakage leads to commonly observed ascites and pleural or

Table 12.1 Criteria for hospitalization

Abdominal pain requiring narcotic analgesics
Coagulopathy
Electrolyte imbalance
Hematocrit >45%
Hemorrhage
Oliguria/anuria
Respiratory distress (dyspnea, tachypnea)
Severe nausea and vomiting that prevents oral intake
Hemodynamic instability (hypotension, dizziness, syncope)

pericardial effusion. Simultaneously, decreased circulating blood volume gives rise to oliguria, which may result in electrolyte abnormalities and renal failure. Hyperviscosity of circulating blood, a result of low plasma volume, may predispose to thrombosis and embolization. However, there is evidence that hypercoagulability may be an independent process related to high estrogen levels[14].

The precise physiologic factor that mediates increased vascular permeability was initially unknown. Estrogens were initially thought to be the cause since estrone (E_1) and E_2 levels during ovarian stimulation were elevated and E_2 was known to have effects on vascular permeability in the uterus. However, Polishuk and Schenker were unable to induce OHSS in rabbits by administering high doses of E_1[15].

Histamine received considerable attention as a putative mediator after Knox was able to prevent ovarian enlargement and ascites by administering antihistamines to hyperstimulated rabbits[16]. However, subsequent research failed to reveal elevated plasma histamine levels or an increased number of ovarian mast cells in OHSS[17].

Serotonin, another vasomotor amine, was also studied in rabbits by using two antiserotonin drugs, both of which failed to prevent OHSS[18]. Because prostaglandins (PGs), specifically PGI_2, have been implicated in ovulation and increased follicle wall permeability, one may hypothesize that they cause or contribute to OHSS. However, no increases in levels of PGI_2 metabolites were noted in stimulated cycles compared with the normal luteal phase[19]. Furthermore, PG inhibition with indometacin was ineffective in decreasing ovarian size or ascites in rabbits[20].

Prolactin levels are elevated in OHSS[21]. Additionally, exogenous prolactin has been shown to increase ascites formation[22]. Elevated levels of testosterone, progesterone, interleukin-6 and interleukin-18, and inflammatory cytokines associated with increased vascular permeability, have also been described[21,23–25]. However, their putative role as a causative agent has not been substantiated.

Recent data have pointed to angiogenic factors in the ovary as potential agents responsible for the clinical syndrome of OHSS. These substances appear to be associated with neovascularization of the corpus luteum. In a hyperstimulated ovary, their levels are greatly increased and their normal physiologic role is magnified into the syndrome of OHSS. These substances include angiotensin II and vascular endothelial growth factor (VEGF), but there may be others.

Evidence supporting the role of angiotensin II is indirect but suggestive. Firstly, a complete prorenin–renin–angiotensin cascade exists within the ovary, and production of several components of this system appears to be enhanced by gonadotropins[26,27]. High levels of prorenin, renin, and angiotensin II have been found in follicular fluid, blood, and ascites of patients with the syndrome[26–30]. Secondly, angiotensin II has been found to increase vascular permeability in rabbits – probably by contraction of vascular endothelial cells[31].

If this hypothesis is substantiated by clinical data in humans, it may be possible to treat or prevent OHSS by inhibiting production or

action of angiotensin II. Angiotensin converting enzyme (ACE) inhibitors are currently used to treat hypertension and congestive heart failure. Moreover, recent evidence has suggested that ACE inhibitors help reduce vascular permeability in rabbit OHSS, as well as other abnormal vascular permeability syndromes.

In glomerular nephropathy (nephron protein leakage) and diabetic retinopathy (also a high prorenin state), ACE inhibition has been successfully used to reduce or prevent vascular leakage[32,33]. Moreover, in a controlled trial of the ACE inhibitor enalapril (Vasotec) in gonadotropin-stimulated rabbits, we were able to prevent OHSS completely in nearly half the treated animals[34]. In the remainder, weight gain was small or absent, and there was no hemoconcentration compared with controls.

However, while encouraging, these data need to be confirmed in humans before this form of therapy can be recommended. A recent report suggested for the first time in humans that the combination of an ACE inhibitor (alacepril) and an angiotensin II receptor blocker (candesartan cilexetil), in addition to cryopreservation, may prevent OHSS in patients at very high risk (E_2 levels ≥ 8000 pg/ml) for this syndrome[35]. It should be noted that ACE inhibitors have been associated with oligohydramnios and renal failure when used in later pregnancy.

VEGF is the other ovarian angiogenic factor thought to be involved in the pathogenesis of OHSS. VEGF stimulates endothelial cell proliferation and angiogenesis[36], and increases capillary permeability, which causes extravasation of protein-rich fluids, and these effects result in OHSS. VEGF levels are increased in serum, follicular, and peritoneal fluid of women who develop OHSS[37,38], and its levels correlate with the severity of the syndrome[39]. It has been reported that anti-VEGF antibodies can reverse the increased vascular permeability activity of the follicular fluid recovered from patients with OHSS[36]. These findings suggest that VEGF has a significant contribution to the pathogenesis of OHSS.

Leptin levels are elevated in patients with polycystic ovary syndrome, who are at a greater risk for OHSS during ART cycles. Whether leptin plays a role in OHSS is unclear, but levels of leptin were reported to be lower in patients with OHSS in one study[40] and were not associated in another[41].

More recently, spontaneous development of familial gestational OHSS has been described resulting from a mutation in the follicle-stimulating hormone (FSH) receptor. The mutation in the FSH receptor decreases the sensitivity of the receptor, thus allowing hCG and thyroid-stimulating hormone to stimulate it. Inappropriate stimulation of the FSH receptor results in clinical signs and symptoms of OHSS during gestation without a history of gonadotropin use for ovulation induction or in-vitro fertilization (IVF)[42–44]. Additionally, OHSS has been reported in women with FSH-secreting pituitary adenomas[45–47].

PREVENTION

Until adequate treatment is devised, prevention of OHSS remains the most effective way of avoiding serious sequelae. The most important prevention technique is identification of patients at high risk for severe disease, although even in this group such a development is relatively uncommon (Table 12.2).

Foremost among risk factors is luteal phase stimulation. The incidence of severe OHSS is significantly higher in patients who have either endogenous or exogenous hCG stimulation. It has been advocated that the ovulatory dose of hCG be withheld in 'high-risk' patients. While this measure is usually effective, it may not be necessary in patients receiving ovarian hyperstimulation for one of the ARTs. These women may undergo follicle aspiration followed by IVF and elective cryopreservation of all embryos, thus precluding the possibility of pregnancy and substantially reducing risk.

Table 12.2 Risk factors for severe ovarian hyperstimulation syndrome

Young age
Low body mass index
Known 'high responder'
High dose gonadotropins
High estradiol levels
Luteal phase stimulation with human chorionic gonadotropin
Polycystic appearance of ovaries on ultrasound
Polycystic ovary syndrome
Pregnancy

By contrast, in patients receiving gonadotropins for ovulation induction, withholding ovulatory hCG may be prudent. However, cases of OHSS have occurred both in spontaneous cycles and in stimulated cycles where hCG was withheld but in which the patient had a spontaneous luteinizing hormone surge and became pregnant[48,49]. Cancellation of a cycle may be avoided by conversion to an IVF cycle with cryopreservation[50]. A prospective randomized trial concluded that elective cryopreservation of zygotes in patients at risk for OHSS reduced the risk of the syndrome[51]. However, a recent Cochrane review suggested that there may be insufficient evidence to support routine cryopreservation of embryos[52].

Even though hCG may play a role in the development of OHSS, lowering the dose of hCG to trigger ovulation does not seem to reduce the risk of OHSS[53]. Reviews and studies suggesting such an improvement with the use of lower doses of hCG may be biased by other treatment modalities co-administered to prevent OHSS[54–56]. Additionally, when different recombinant hCG doses were compared with urinary hCG to trigger ovulation, the risk of OHSS was not reduced with lower doses[57].

It has been suggested previously that the number of gestational sacs could be predictive of OHSS 4 weeks after embryo transfer[58]. However, a recent report suggested that OHSS did not occur more frequently in twin than singleton pregnancies[59].

We retrospectively compared 133 cycles of COH consisting of 68 patients undergoing IVF and 67 oocyte donors, all of whom had extremely high degrees of ovarian response to COH (E_2 > 4000 pg/ml and more than 25 eggs collected)[60]. Donors, who received no luteal support and did not become pregnant, had no cases of severe OHSS. By contrast, among the IVF patients, there were six women with severe OHSS, four of whom later demonstrated clinical pregnancies. It is possible that pregnancy, even if subclinical, is a necessary condition for the development of severe OHSS.

Intravenous administration of albumin at the time of follicle aspiration has been advocated as a prophylactic measure for high-risk patients undergoing IVF[61]. Four prospective randomized trials supported this practice[62–65] and one study did not[66]. A meta-analysis of these five trials concluded that administration of intravenous albumin at the time of oocyte retrieval would be beneficial in patients at high risk for OHSS[67]. Based on the meta-analysis, in order to prevent one case of OHSS, 18 patients need to be treated with intravenous albumin. It should also be noted that the use of albumin was compared against similar volumes of crystalloid. It is possible that larger volumes of crystalloid, which would have a similar magnitude of effect on intravenous volume, may have matched the potential benefit of albumin. One conclusion from these data may be that volume expansion at the time of follicle aspiration is useful.

Repeated[68] and selective[69] follicle aspiration has been advocated as a possible means to reduce the number of preovulatory follicles and, thus, the risk of OHSS. Others have advocated a 'controlled drift', in which hyperresponding patients are maintained on gonadotropin-releasing hormone (GnRH) agonist therapy without gonadotropin stimulation for several days before

hCG administration[70,71]. This approach results in diminished E_2 levels, but ascites has been noted[71]. In a prospective randomized study, early unilateral follicle aspiration was compared with coasting for prevention of OHSS. There was no difference in the incidence of OHSS between the two groups[72]. Because the incidence of severe OHSS may be low even in so-called 'high-risk' patients, it is not valid to conclude that the absence of OHSS in a small group of patients receiving a particular treatment proves the efficacy of that treatment. A recent Cochrane review concluded that, as yet, there is lack of evidence to support the routine use of coasting to prevent OHSS[73].

Administration of methylprednisolone was reported to reduce the risk of OHSS in a retrospective study[74]. Prospective randomized trials have shown that glucocorticoids, GnRH agonists, or administration of ketoconazole do not prevent OHSS[75–77]. Additionally, a recent review of randomized controlled trials failed to demonstrate a reduction in the incidence of severe OHSS with the use of GnRH antagonists compared to GnRH agonists in IVF-embryo transfer cycles[78]. Low dose hCG alone or in combination with low dose FSH can stimulate the growth of antral follicles in the mid/late follicular phase and result in the demise of the smaller follicles[79]. Although not yet tested for the prevention of OHSS, selective growth of larger antral follicles and the failure of growth of smaller preovulatory follicles might have a beneficial effect against the development of OHSS.

TREATMENT

Once OHSS is diagnosed, a clinical decision should be made as to whether the patient needs to be treated as an inpatient or outpatient. Women with mild OHSS are generally managed as outpatients with oral analgesics and close clinical monitoring. Patients should be advised to refrain from intercourse and impacting exercise because this may worsen abdominal pain and possibly result in ovarian cyst rupture or even ovarian torsion. Although bed rest is commonly recommended as a part of the treatment algorithm, strict bed rest may actually increase the risk of thromboembolism and therefore light activity should be encouraged. Close surveillance with physical examinations (not pelvic), testing for complete blood count and electrolytes, monitoring urine output, ultrasound monitoring of ascites, measurement of weight, and frequent communication with the patient regarding the signs and symptoms of worsening OHSS are essential components of outpatient management. Early diagnosis of pregnancy is essential because the increasing hCG levels may worsen the clinical picture rapidly.

Severe OHSS requires hospitalization (Table 12.1) and careful hemodynamic and fluid monitoring. The goal of management is to maintain urine output and electrolyte homeostasis until spontaneous resolution (as indicated by diuresis) occurs. Close clinical assessment and laboratory testing allow monitoring of progression and response to the treatment modalities[80].

A recent report suggested that Dextran 40 infusion to inpatients with severe OHSS when compared to albumin infusion may result in a faster recovery from hemoconcentration and leukocytosis[81]. In a preliminary study, inpatients who initially had a poor response to albumin had improvement in clinical symptoms associated with ascites when treated with the oral dopamine prodrug docarpamine[82].

Prophylaxis against thrombosis is necessary because numerous cases of thromboembolic phenomena and their sequelae have been reported. Subcutaneous heparin (5000 IU twice a day) is typically used in severe OHSS cases to prevent thromboembolic phenomena. However, it is unclear at what point anticoagulation measures should be discontinued since thrombosis has been reported several weeks after resolution of other stigmata of severe OHSS[13]. Although relatively rare, signs and symptoms of acute

thrombus or embolism should prompt the clinician to obtain diagnostic testing immediately, initiate therapeutic anticoagulation, and provide appropriate supportive care.

Paracentesis, achieved by the abdominal[83] or transvaginal[84] route, offers substantial symptomatic relief of symptoms, especially if respiratory compromise is present. It is not clear if OHSS resolves more quickly after paracentesis than with conservative treatment, although one study[84] suggested that hospital stay might be shortened. Since the ascites fluid contains elevated levels of prorenin and angiotensin II[28,29] it is tempting to speculate that drainage of this fluid may provide symptomatic relief by more than just mechanical means. Paracentesis may also be beneficial in improving urine output by lowering the intra-abdominal pressure and decreasing renal arterial resistance[85]. One report[86] suggested that chest tube drainage of pleural effusion could reduce abdominal ascites.

SUMMARY

Severe OHSS is a rare but dangerous complication of gonadotropin therapy. Its stigmata are the result of fluid derangements caused by increased vascular permeability. Current evidence points to angiotensin II and VEGF as the most likely mediators. Prevention of the syndrome in IVF cycles for high-risk patients may include administration of intravenous albumin, avoidance of luteal stimulation by hCG, and, in selected cases, elective cryopreservation of all embryos. Lowering the hCG dose to trigger ovulation does not have a protective effect against OHSS in IVF cycles. However, in ovulation-induction cycles, consider withholding hCG in high-risk cycles or converting to an IVF cycle.

Since OHSS is self-limiting, treatment should be conservative. Hospitalization is necessary only in severe cases. Treatment goals should include maintenance of circulating volume, electrolyte balance, and urine output, and prophylaxis against thromboembolism. Abdominal paracentesis may provide substantial symptomatic relief in cases of OHSS and may be combined with drainage of pleural effusions in cases of respiratory distress. Patients who become pregnant are at an additional risk for developing severe illness and therefore should be more closely monitored.

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