

Victoria Fertility Centre.

Ovarian Hyperstimulation syndrome.

The following factors increase the risk independently for developing ovarian hyperstimulation syndrome (OHSS):

- Young age
- Low body weight
- Polycystic ovary syndrome (PCOS)
- Higher doses of exogenous gonadotropins
- High absolute or rapidly rising serum estradiol levels
- Previous episodes of OHSS

In addition, risk rises with the number of developing ovarian follicles, and the number of oocytes retrieved in assisted reproductive technology (ART) cycles. Risk increases when higher or repeated doses of exogenous human chorionic gonadotropin (hCG) are administered in superovulation and ART cycles (for ovulation induction or luteal phase support) and decreases when exogenous progesterone, rather than hCG, is used to support the luteal phase. Pregnancy increases the likelihood, duration, and severity of OHSS symptoms.

Clinical Features

The OHSS has traditionally been classified as mild, moderate, or severe. However, the clinical symptoms and signs of OHSS exhibit a continuum of scope and severity that defies attempts at specific classification or staging.

Mild manifestations of OHSS are relatively common and include:

- Transient lower abdominal discomfort
- Mild nausea
- Vomiting
- Diarrhea
- Abdominal distention (observed in up to a third of superovulation cycles)

Onset of symptoms typically occurs soon after ovulation (in superovulation cycles) or after oocyte retrieval in ART cycles, but it may be delayed.

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 exists when pain is accompanied by one or more of the following:

- Rapid weight gain
- Tense ascites
- Hemodynamic instability (orthostatic hypotension, tachycardia)

- Respiratory difficulty (tachypnea)
- Progressive oliguria
- Laboratory abnormalities

Hypotension results from extravasation of protein-rich fluid and contraction of the vascular volume, oliguria/anuria from reduced renal perfusion due to decreased vascular volume and/or tense ascites, and pulmonary compromise from an elevated diaphragm and/or hydrothorax. Risk of thromboembolism is increased as a result of hemoconcentration, diminished peripheral blood flow, and inactivity due to abdominal distension and pain. Life-threatening complications of OHSS include renal failure, adult respiratory distress syndrome (ARDS), hemorrhage from ovarian rupture, and thromboembolism.

Management

Outpatient Management

Patients with mild manifestations of OHSS can be managed on an outpatient basis. Treatment usually requires only oral analgesics and counseling regarding the signs and symptoms of progressing illness. Intercourse is best avoided as it may be painful and may increase the risk of ovarian rupture.

Treatment of worsening OHSS typically requires antiemetics and more potent analgesics. Most patients still can be effectively managed and monitored on an outpatient basis, but they require more careful evaluation including frequent physical and ultrasound examinations (to detect increasing ascites), daily weight measurements, and serial laboratory determinations of hematocrit, electrolytes, and serum creatinine. Careful monitoring is essential and should include at least daily communication, if not examination, to ensure that progression to more severe disease is promptly recognized.

Recommendations for the outpatient management of persistent and worsening OHSS include:

- Oral fluid intake should be maintained at no less than 1 L per day; any of the commercially available electrolyte-supplemented drinks is preferable to other beverages.
- Strenuous physical activity should be avoided as risk of ovarian torsion increases when the ovaries are significantly enlarged. Light physical activity should be maintained to the extent possible. Strict bed rest is unwarranted and may increase risk of thromboembolism.
- Weight should be recorded daily, as well as the frequency and/or volume of urine output. Weight gain of ≥ 2 pounds per day or decreasing urinary frequency should prompt repeated physical examination, ultrasound, and laboratory evaluation to include hematocrit, electrolytes, and serum creatinine.

- Pregnant patients with OHSS must be monitored very closely because risk of progressing to severe disease is particularly high for those further stimulated by rapidly rising serum concentrations of hCG.
- In ART cycles, it may be necessary to consider cryopreserving all embryos and deferring transfer to a subsequent cycle after symptoms have completely resolved. Although pregnancy rates in frozen embryo transfer cycles are generally lower than in fresh cycles, this approach may reduce the risk for developing severe OHSS without a marked decrease in pregnancy rates per cycle.

Hospitalization

Serious illness requiring hospitalization is relatively uncommon but by no means rare. Hospitalization may be required based on severity of symptoms, analgesic requirements, and other social considerations (availability of responsible adult supervision, support, and assistance with child care).

Given the scope and severity of symptoms and the potential for complications, most women with OHSS who are seriously ill merit hospitalization for more careful monitoring and aggressive treatment. No one symptom or sign is an absolute indication, but hospitalization should be considered when one or more of the following are present:

- Severe abdominal pain or peritoneal signs
- Intractable nausea and vomiting that prevents ingestion of food and adequate fluids
- Severe oliguria or anuria
- Tense ascites
- Dyspnea or tachypnea
- Hypotension (relative to baseline), dizziness, or syncope
- Severe electrolyte imbalance (hyponatremia, hyperkalemia)
- Hemoconcentration
- Abnormal liver function tests

Laboratory findings in women with serious illness resulting from OHSS include:

- Hemoconcentration (hematocrit >45%)
- Leukocytosis (white blood cell count >15,000)
- Electrolyte imbalances (hyponatremia: sodium <135 mEq/L; hyperkalemia: potassium >5.0 mEq/L)
- Elevated liver enzymes
- Decreased creatinine clearance (serum creatinine >1.2; creatinine clearance <50 mL/min)

Recommendations for the evaluation and monitoring of hospitalized patients with OHSS include the following:

- Vital signs (every 2–8 hours, according to clinical status)

- Weight (recorded daily)
- Complete physical examination (daily, avoiding bimanual examination of the ovaries due to risk of ovarian rupture)
- Abdominal circumference (at the navel, recorded daily)
- Monitoring of fluid intake and output (daily, or more often as needed)
- Ultrasound examination (ascites, ovarian size), repeated as necessary to guide management or paracentesis (see below)
- Chest x-ray and echocardiogram (when pleural or pericardial effusion is suspected), repeated as necessary
- Pulse oximetry (for patients with symptoms of pulmonary compromise)
- Complete blood count (daily, or more often as needed to guide fluid management)
- Electrolytes (daily)
- Serum creatinine or creatinine clearance, urine specific gravity, repeated as necessary
- Liver enzymes, repeated as necessary

Careful and frequent reevaluation of the hospitalized patient with severe OHSS is essential. Complaints of increasing abdominal pain and distension demand immediate attention, remaining mindful that pain and ascites can easily mask ovarian rupture and acute intra-abdominal hemorrhage. Serial clinical and laboratory evaluations provide the means to monitor progression of illness, to judge the response to treatment, and to recognize evidence of resolution.

Fluid Management

Hospitalized patients require intravenous (IV) fluid management to address the acute need for volume expansion while also considering the marked increase in vascular permeability that accompanies severe OHSS. Renal and pulmonary function must be carefully monitored. Guidelines for fluid management for patients hospitalized with severe illness relating to OHSS include the following:

- Strict monitoring of fluid intake and urine output is essential until symptoms improve or diuresis begins.
- Oral fluid intake should be carefully recorded and limited to those amounts necessary to maintain the patient's comfort.
- Rapid initial hydration may be accomplished with a bolus of IV fluid (500–1,000 mL). Thereafter, fluids should be administered judiciously, in the volumes necessary to maintain adequate urine output (>20–30 mL/h) and reverse hemoconcentration. Five percent dextrose in normal saline is preferable to lactated Ringer's solution, given the tendency to hyponatremia. Correction of hypovolemia, hypotension, and oliguria has highest priority, accepting that fluid administration may contribute to the accumulation of ascites.
- Albumin (25%) in doses of 50–100 g, infused over 4 hours and repeated at 4- to 12-hour intervals as necessary, is an effective plasma expander when infusion of normal saline fails to achieve or maintain hemodynamic stability and adequate urine output. In general, albumin is the preferred plasma expander, although

- others (e.g., mannitol, fresh frozen plasma) may be used. Dextran has been associated with development of adult respiratory distress syndrome (ARDS) and is best avoided. Albumin can also be given in a 5 % concentration. 5 % albumin comes in 250 cc bottles. A suggested protocol for patients with low albumin and also needing fluid supplementation would be 5 % albumin (which comes in normal saline) at 50 - 100 cc per hour – with a CBC/albumin/creatinine and electrolytes every 12 - 24 hours to check the hemoconcentration.
- Treatment with diuretics (e.g., furosemide, 20 mg IV) may be considered after an adequate intravascular volume has been restored (hematocrit <38%). Premature or overzealous use of diuretics will aggravate hypovolemia, and hemoconcentration, thereby increasing risk of thromboembolism.
 - Intravenous fluid administration should be sharply curtailed and oral fluid intake increased when there is evidence that the syndrome is resolving, generally heralded by improving symptoms and onset of a brisk diuresis.
 - Hyperkalemia is associated with risk of cardiac dysrhythmias. Acute management involves treatments that move potassium into the intracellular space (insulin and glucose, sodium bicarbonate, albuterol/salbutamol) or protect the heart from the effects of elevated potassium levels (calcium gluconate). Electrocardiographic manifestations of hyperkalemia (prolonged PR and QRS intervals, ST segment depression, tall peaked T waves) indicate the need for immediate treatment with calcium gluconate. Kayexalate is a cation exchange resin that removes potassium from the body but works more slowly (onset of action 1–2 hours); it may be administered orally or rectally as a retention enema.

Paracentesis

Ultrasound-guided paracentesis may be indicated for patients with ascites that causes pain, compromised pulmonary function (e.g., tachypnea, hypoxia, hydrothorax), or oliguria/anuria that does not improve with appropriate fluid management. A transvaginal or transabdominal approach may be used, under gentle ultrasound guidance. The optimal volume of fluid that should be removed on any one occasion, and over what interval of time, is not well established. Whereas rapid removal of large volumes of ascitic fluid has been observed to trigger dangerous compensatory fluid shifts in elderly patients with malignant ascites, the risk of such complications in young, otherwise healthy women with OHSS is generally small. Nevertheless, it is prudent to remove fluid at a deliberate pace until the desired effect is achieved, while carefully monitoring the patient's response. Serial paracentesis may be required to maintain adequate renal and pulmonary function. Severe ascites may be associated with hydrothorax, most commonly on the right, resulting from transfer of abdominal fluid to the chest via the thoracic duct. Paracentesis will generally be effective in resolving hydrothorax and thoracentesis may be reserved for those with bilateral or severe pleural effusions that persist.

Thromboembolism is a life-threatening complication of severe OHSS, and prophylactic measures are warranted. Full-length venous support stockings are recommended, and prophylactic heparin therapy (5,000 U subcutaneously [SC], every 12 hours) should be seriously considered. The use of an intermittent pneumatic compression device is prudent

when symptoms prevent ambulation and confine the patient to bed. Signs and symptoms suggesting thromboembolism demand prompt additional diagnostic measures (arterial blood gas measurements, ventilation/perfusion scan) and therapeutic anticoagulation when the diagnosis is confirmed or strongly suspected.

Intensive care may be required for management of thromboembolic complications, renal failure, or pulmonary compromise that does not respond to supportive care and paracentesis. Renal failure will often respond to low-dose dopamine therapy (0.18 mg/kg/h) that will dilate renal vessels and increase renal blood flow. Invasive monitoring of central venous pressure or pulmonary capillary wedge pressure and even short-term dialysis may be required. Pulmonary intensive care may involve oxygen supplementation, thoracentesis, and assisted ventilation when more conservative measures fail. Patients with severe OHSS who may require surgery for a ruptured ovarian cyst with hemorrhage, torsion, or an ectopic pregnancy present a unique challenge for the anesthesiologist who is unlikely to be familiar with the pathophysiology of the syndrome and must be quickly educated to minimize the additional risks involved.

Prevention

The keys to preventing OHSS are experience with ovulation induction therapy and recognition of risk factors for OHSS. Ovulation induction regimens should be highly individualized, carefully monitored, and use the minimum dose and duration of gonadotropin therapy necessary to achieve the therapeutic goal.

Caution is indicated when any of the following indicators for increasing risk of OHSS are present:

- Rapidly rising serum estradiol levels
- An estradiol concentration in excess of 10,000 pmol
- The emergence of a large number (more than 20 – 30) of intermediate sized follicles (10–14 mm)

Withholding further gonadotropin stimulation and delaying hCG administration until estradiol levels plateau or decrease significantly can reduce risks of OHSS. Available evidence suggests that such "coasting" does not adversely affect outcome in in vitro fertilization (IVF) cycles unless it is prolonged (>3 days).

Given the evidence suggesting that hCG may play a pivotal role in the development of OHSS, a lower dose of hCG (e.g., 5,000 IU vs. the standard 10,000 IU dosage) may be prudent for patients judged to be at high risk for OHSS. Alternatively, a GnRH agonist (e.g., leuprolide 0.5–1.0 mg SC) rather than hCG might be used to stimulate an endogenous LH surge to promote final oocyte maturation and induce ovulation. This approach would be useful only in cycles not involving previous down-regulation with longer term agonist treatment or use of a GnRH antagonist (e.g., ganirelix, cetrorelix).

Regardless whether hCG or a GnRH agonist is administered at midcycle, the use of exogenous progesterone (e.g., 50 mg progesterone in oil IM, 100 mg progesterone vaginal suppositories, or 8% progesterone vaginal gel, daily) for luteal phase support rather than supplemental doses of hCG, may further reduce risks of OHSS. When symptoms of OHSS emerge even before administration of hCG, cycle cancellation and less aggressive stimulation in a subsequent cycle should be seriously considered.

Although evidence indicates that meticulous follicle aspiration will reduce corpus luteum P production, it cannot be relied on to prevent development or progression of OHSS in ART cycles.

Summary

- Experience with ovulation induction therapy and knowledge of ovarian hyperstimulation syndrome (OHSS) pathophysiology, risk factors, and clinical features are key to preventing and managing OHSS.
- Mild manifestations of OHSS are fairly common, occurring in up to a third of exogenous gonadotropin-induced superovulation cycles.
- Worsening symptoms of OHSS can still usually be managed on an outpatient basis, but frequent monitoring and evaluation are essential.
- Serious illness resulting from OHSS is much less common, but it can be life-threatening.
- Hospitalization may be necessary for patients with serious illness resulting from OHSS.