ovarian hyperstimulation syndrome [created by Paul Young 02/10/07]

general

- Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic complication that is associated with modern techniques for in vitro fertilization (IVF).
- The syndrome typically is associated with regimens of exogenous gonadotrophins but also can be seen, albeit rarely, during administration of clomiphene citrate for ovulation induction or spontaneously during pregnancy
- Patients with the severe or life-threatening forms of OHSS can be critically ill and require aggressive medical intervention.
- This clinical situation is emotionally difficult because patients are often pregnant at the time of their acute illness.

pathogenesis

- IVF techniques include the use of gonadotropin-releasing-hormone (GnRH) agonists or antagonists and gonadotrophin drugs to stimulate the ovaries and human chorionic gonadotrophin (hCG) to initiate ovulation and sometimes maintain the luteal phase. Ovarian stimulation in these circumstances may result in an excessive ovarian response, which may lead to OHSS.
- This syndrome consists of ovarian enlargement accompanied by overproduction of ovarian hormones and a host of other ovarian vasoactive substances (eg, cytokines, angiotensin, vascular endothelial growth factor) producing a state of increased capillary hyperpermeability
- The clinical manifestations of OHSS are believed to be the result of increased capillary permeability, which in turn leads to a loss of protein-rich fluid from the intravascular compartment into the interstitial space
- OHSS produces a hyperdynamic circulatory dysfunction state, similar to that observed in other conditions associated with edema formation (eg, high-output heart failure, cirrhosis), that is characterized by arterial hypotension, increased cardiac output, reduced peripheral vascular resistance, and intense stimulation of the renin-angiotensin and sympathetic nervous systems and antidiuretic hormone.
- Although the development of OHSS usually is associated with the use of IVF techniques, the spontaneous occurrence of this entity has been reported in rare instances during pregnancy, most often when there is a supraphysiologic production of chorionic gonadotropin (eg, multiple gestations, molar pregnancies)

epidemiology & risk factors

- The prevalence of moderate to severe OHSS ranges from 1% to 10% in major IVF programs.

Risk factors associated with OHSS

High risk	Low risk
Young (<35 years)	Older (>36 years)
PCOS-like	Hypogonadotrophic
Asthenic habitus	Heavy build
High serum estradiol	Low serum estradiol
Multiple follicles	Few follicles
Necklace sign	Quiescent ovary
Pregnancy	Barren cycle
hCG luteal supplementation	Progesterone or no supplementation
GnRH-agonist protocol	Clomiphene citrate and/or HMG protocol

classification of severity

Criteria that define the severe and life-threatening stages of OHSS

Severe OHSS	Life-threatening OHSS
Variably enlarged ovary	Variably enlarged ovary
Massive ascites with or without hydrothorax	Tense ascites with or without hydrothorax
Hematocrit >45%	Hematocrit >55%
WBC count >15,000	WBC count >25,000
Oliguria	Oliguria
Creatinine level 1.0–1.5 mg/dL	Creatinine level ≥1.6 mg/dL
Creatinine clearance ≥50 mL/min	Creatinine clearance <50 mL/min
Liver dysfunction	Renal failure
Anasarca	Thromboembolic phenomena
	ARDS

clinical features

- Symptoms usually begin with a sensation of bloating and abdominal discomfort and proceed to nausea, vomiting, and diarrhea. The onset of vomiting or diarrhea within 48 hours of hCG administration, shortness of breath, or reduced urine output indicating accumulation of ascites suggest potentially severe disease.
- If patients present with acute abdominal pain, torsion of an adnexa should be considered as this is a rare but recognised complication of the syndrome.
- Fluid leakage into the interstitium manifests clinically as ascites, pleural or pericardial effusions, electrolyte imbalances, oliguria, hemoconcentration, or hypovolemia with or without hypovolemic shock.
- Physical examination of patients with OHSS may reveal weight gain, increased abdominal girth, oliguria or anuria, and signs of hypovolemia. The ovaries are enlarged greatly and are easily palpable in the abdomen.
- In severe cases, respiratory compromise or multiorgan failure can be seen, as can the sequelae of thromboembolic events
- In patients with moderate or severe OHSS, the pelvic examination must be avoided to decrease the likelihood of ovarian cyst rupture that may result in intraperitoneal hemorrhage.
- Respiratory distress in patients with OHSS most likely results from lung restriction caused by ascites, large cystic ovaries, or pleural or pericardial effusions . Pulmonary manifestations of severe OHSS include acute hydrothorax, ARDS, pulmonary embolism, pulmonary edema, atelectasis, and intra-alveolar hemorrhage. Pleural effusions develop in approximately 20% of patients with severe OHSS.
- OHSS can be accompanied by thromboembolic disease with both venous and arterial thrombosus seen. Central retinal artery occlusion with irreversible visual impairment has been described.
- Another complication seen in patients with OHSS is the presence of infections
- Laboratory data are characterized by electrolyte abnormalities, including hyperkalemia and dilutional hyponatremia. This reduction in the serum sodium level is associated with low serum osmolality.
- Hemoconcentration is frequently seen, and a hematocrit greater than 55% heralds a life-threatening situation. The white blood cell and platelet counts also are increased in OHSS, but the coagulation parameters are normal in most patients
- In severe and life-threatening OHSS, an elevated serum creatinine level can be seen; however, in most cases of OHSS, the creatinine levels are within normal limits.
- Abnormalities of liver function tests are seen in approximately 30% of patients with severe OHSS and are characterized by mild-to-moderate increases in transaminases, which are associated in some cases with increases in levels of GGT or ALP
- Hypoalbuminemia commonly is seen
- Serum IgG in patients with severe OHSS exudes into their peritoneal cavity, making them immunodeficient and at potential increased risk for infection

therapy

- There is no specific treatment for OHSS, and therapy is mainly supportive until the condition resolves.
- The syndrome is self-limiting, and resolution parallels the decline in serum hCG levels (about 7 days in nonpregnant patients and 10-20 days in pregnant patients).
- Medical treatment of severe OHSS should be directed to maintain circulatory function and to mobilize the intra-abdominal fluid by creating a net negative balance of sodium and water. Initially, the goal is to replace fluids in the vascular compartment sufficient to allow adequate urine production.
- echocardiography should be performed to exclude pericardial effusion
- administration of prophylactic anticoagulation should be part of routine care.
- The indications for paracentesis in patients with OHSS include the need for symptomatic relief, a tense ascites, oliguria, increasing creatinine or decreasing creatinine clearance, and hemoconcentration that is unresponsive to medical therapy . The use of ultrasound guidance during abdominal paracentesis to avoid ovarian puncture may be indicated.
- A low threshold to start empiric antibiotic therapy is suggested when the possibility of an infectious process is considered in patients who are critically ill and hemodynamically unstable.
- Empiric antibiotic therapy should be directed at the most likely pathogens involved in this type of infections, which are P mirabilis, K pneumoniae, P aeruginosa, E coli, and P vulgaris .
- The role of immunoglobulins is uncertain
- Nonsteroidal anti-inflammatory drugs (specifically indomethacin), antihistaminics, and ACE inhibitors have been mentioned in the medical literature as potential alternative therapeutic regimens for OHSS; however, most of the information regarding these drugs comes from animal studies or small, uncontrolled studies.
- In rare circumstances in which the syndrome increases in severity despite all interventions, termination of the pregnancy should be considered to decrease hCG levels.