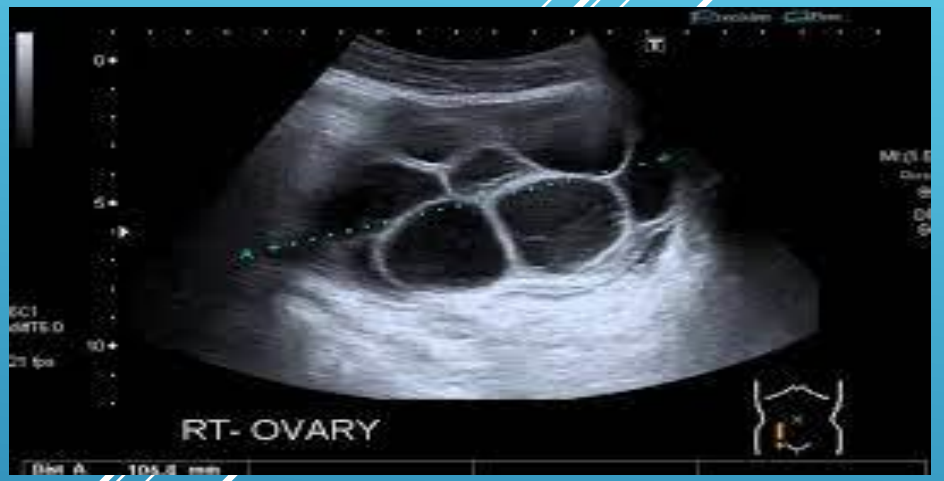
Management Of Ovarian Hyperstimulation Syndrome (OHSS)



E.Naghshineh MD

OB&GYN specialist

Infertility fellowship

IUMS

The pathophysiology of OHSS is not fully understood but increased capillary permeability with the resulting loss of fluid into the third space is its main feature.

In the susceptible patient, HCG administration for final follicular maturation and triggering of ovulation is the pivotal stimulus for OHSS, leading to overexpression of VEGF in the ovary, release of vasoactive-angiogenic substances, increased vascular permeability, loss of fluid to the third space

The early-onset form (occurring on the first eight days after exogenous hCG administration)

The late-onset form (occurring nine or more days after hCG administration, related to pregnancy-induced hCG production)

OHSS is a self-limited disease, although symptoms may be prolonged if pregnancy has occurred.

Prevention Of Severe OHSS

Table 65.2 Risk factors associated with ovarian hyperstimulation syndrome

High risk	Low risk
Young (<35 years of age)	Older (>35 years of age)
Polycystic-appearing ovaries	Hypogonadotropic
Asthenic habitus	Heavy build
High serum estradiol (ART >4000 pg/mL, OI >1700 pg/mL)	Low serum estradiol
Multiple stimulated follicles (ART >20, OI >6)	Poor response to gonadotropins
Necklace sign	Few antral follicles
Pregnancy	Elevated baseline FSH
hCG luteal supplementation	Progesterone or no luteal supplementation
GnRH agonist down-regulatory protocol	Clomiphene citrate and/or hMG protocol
High serum anti-Mullerian hormone	

Abbreviations: ART, assisted reproduction technology; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; hCG, human chorionic gonadotropin; hMG, human menopausal gonadotropin; OI, ovulation induction.

- More recent comparisons between recombinant FSH (rFSH) and human menopausal gonadotropins (hMGs) did not show significant differences among variable drug regimens.

- Coasting may work to prevent or reduce the severity of OHSS by altering the capacity of the granulosa cells to produce VEGF ,and seems to confer this benefit without compromising cycle outcomes.

- Coasting was continued until serum E2 levels fell below 3000 pg/ mL gonadotropins were withheld for an average of 2.2 days, showed that pregnancy rates in the coasting group were comparable to those in non-coasted control cycles.

- The standard dosage of HCG used to trigger ovulation is 5000–10,000 IU, or 250 µg of recombinant HCG (rHCG).
- HCG in these dosages takes six to nine days to clear from the circulation.
- one simple preventive strategy is to administer lower-dose HCG.
- As expected, triggering ovulation or oocyte maturation with lower-dose HCG on a sliding scale, with the administration of between 3300 and 5000 U depending on serum E2 concentration on the day of triggering, has been shown to decrease the risk of OHSS.

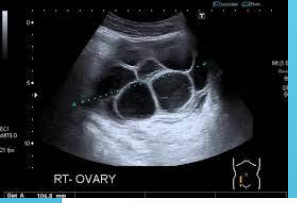
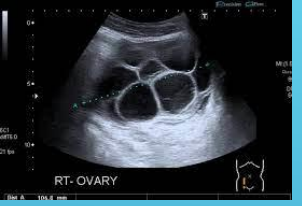


Table 65.1 Classification of ovarian hyperstimulation syndrome

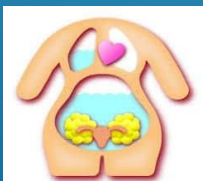
Mild	Moderate	Severe	Critical
• Bloating • Nausea • Abdominal distention • Ovaries ≤5 cm	• Vomiting • Abdominal pain • US evidence of ascites • Hct >41% • WBC count >10,000/mm^3 • Ovaries >5 cm	• Massive ascites • Hydrothorax • Hct >45% • WBC count >15,000/mm^3 • Oliguria • Creatinine 1–1.5 mg/dL • Creatinine clearance ≥50 mL/minute • Hepatic dysfunction • Anasarca • Ovaries variably enlarged	• Tense ascites • Hypoxemia • Pericardial effusion • Hct >55% • WBC count >25,000/mm^3 • Oliguria or anuria • Creatinine >1.5 mg/dL • Creatinine clearance <50 mL/minute • Renal failure • Thromboembolic phenomena • ARDS • Ovaries variably enlarged

Abbreviations: Hct, hematocrit; WBC, white blood cell; US, ultrasound; ARDS, acute respiratory distress syndrome.



MILD OHSS

- Most OHSS cases are mild or moderate and can be managed on an outpatient basis . normally, these cases are self-limited and can be managed conservatively, with a goal of relieving symptoms.
- Mild OHSS is seen in many women undergoing ovarian stimulation for assisted reproduction.



MILD OHSS

- For mild OHSS, analgesics (Acetaminophen rather than NSAIDS) and avoidance of heavy physical activity are usually enough. patients should be instructed to call for any signs or symptoms of worsening (oliguria, abdominal distention, shortness of breath, or weight gain)

- Mild OHSS can progress to become moderate or severe, particularly if pregnancy has occurred. therefore, women with mild disease should be observed for worsening abdominal pain, weight gain (>1 kg/day), and increasing abdominal girth for at least two weeks or until menstrual bleeding occurs

Moderate OHSS

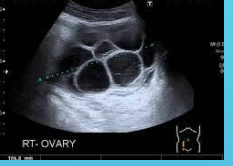
- Oral fluid intake of 1 to 2 liters per day.

Diuretics are contraindicated because they can worsen decreased intravascular volume.

- Ambulate, but avoid other physical activity.

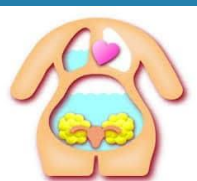
Avoid sexual intercourse.

- Daily weights, abdominal circumference measurements, and urinary output recordings.

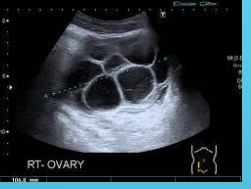


- Monitoring for signs of progression is performed at the time of initial presentation and every 48 hours thereafter (or daily if worsening symptoms develop):
  - physical examination
  - transvaginal ultrasound (TVUS)
  - laboratory testing (CBC, electrolytes, creatinine, serum albumin, and liver enzymes)

- daily communication with patient:
  - is hydration adequate?
  - Document weight, abdominal circumference, and urine output
  - report any signs or symptoms of worsening



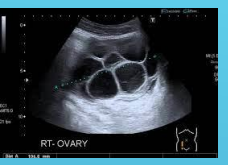
- Pregnant patients must be followed very closely as they are likely to worsen (or present with more severe symptoms) because of the rising levels of endogenous HCG. pregnant patients with severe OHSS take longer to recover than nonpregnant patients (who typically experience resolution of symptoms within 10 to 14 days).



- Ascites/culdocentesis : tense ascites, orthopnea, rapid increase of abdominal fluid, or any other sign that may indicate progression of illness .

removal of ascitic fluid provides symptomatic relief.

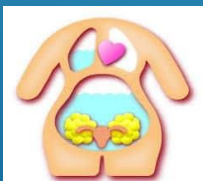
Women without other complications can then continue to be monitored as outpatients.

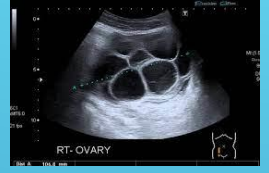


- The volume of fluid to be removed is not well established, but after aspiration of 500 ml of ascitic fluid, patients typically report resolution of abdominal discomfort. In one report of 19 women with OHSS, after aspiration of 2000 ml of ascites, a reduction in intra-abdominal pressure and renal artery resistance was seen, followed by an increase in urine output .

  removal of more than 4 liters of fluid is not recommended.

  Blind paracentesis should not be done, because of the potential risk of bowel or vessel puncture



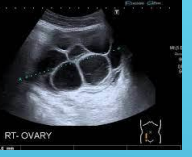


Dopamine agonists :

In women at high risk for OHSS undergoing ovarian stimulation, the rate of developing moderate and severe OHSS can be significantly reduced with cabergoline (0.5 mg/day orally), beginning on the day of HCG administration or oocyte retrieval. Less is known about the efficacy of Dopamine agonists for the treatment of OHSS once it is established. However, some small studies suggest it may diminish clinical symptoms and severity

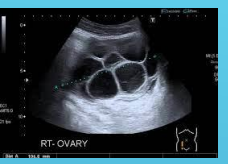
Severe and critical OHSS

- Hospitalization : Hospitalization is mandatory in women with severe OHSS and any of the following criteria:
- hematocrit >55 percent, leukocytes >25,000/L, and creatinine >1.6 mg/dL. Women with severe abdominal pain, intractable vomiting, severe oliguria/anuria, tense ascites, dyspnea or tachypnea, hypotension, dizziness or syncope, severe electrolyte imbalance, or abnormal liver function tests
- Medical treatment of severe OHSS is directed at maintaining intravascular blood volume. Although isotonic crystalloid solutions (eg, normal saline, Ringer's lactate) are typically used for intravenous hydration in patients with severe OHSS, some clinicians use intravenous albumin in critically ill, volume-depleted patients. However, available evidence suggests that intravenous albumin provides no additional benefit when compared with crystalloid solutions.
- thromboprophylaxis in all hospitalized patients with OHSS

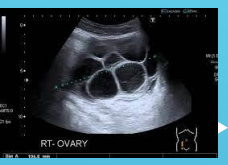


Critical OHSS :should be managed in an intensive care unit (ICU)

- ●Assessment of fluid balance (daily or more often)
- ●Weights and measurement of abdominal circumference
- ●CBC
- ●Electrolytes, BUN, creatinine
- ●Serum HCG measurements (to determine if patient has conceived)
- ●Invasive monitoring of central venous pressure
- ●Pelvic ultrasound as needed to evaluate ovarian size and ascites
- ●Chest radiograph and echocardiogram when pleural or pericardial effusion is suspected (as often as needed)

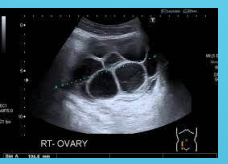


- Prophylaxis for thromboembolic event suggest prophylaxis for thromboembolism in the following settings:
- 1-All hospitalized patients with OHSS
- 2-Women with OHSS being managed as outpatients with two to three additional risk factors (in addition to OHSS): age >35 years, obesity, immobility, elevated hematocrit, personal or family history of thrombosis, thrombophilia, and pregnancy.
- For those in complete bed rest is suggested, an intermittent pneumatic compression device
- use prophylactic LMWH, 20 mg SC every 12 hours, or heparin 5000 units SC every 12 hours

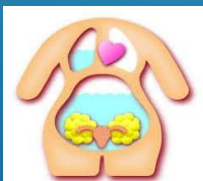


Resolution and prognosis:

- The pathophysiological process of OHSS is self-limited, and increased vascular permeability regresses spontaneously.
- Those who have not conceived recover over 10 to 14 days from the onset of initial symptoms. Third-space fluid begins to re-enter the intravascular space, hemoconcentration reverses, and natural diuresis ensues.
- Clinical evidence of resolution includes:
- Normalization of hematocrit
- Progressive reduction of ascites on ultrasound
- Alleviation of clinical symptoms



- If pregnancy occurs, resolution may take longer . As described above, OHSS may worsen initially as hCG levels rise.
- Uncontrolled studies suggested that OHSS pregnancies had a higher rate of miscarriage and later complications, such as gestational diabetes and pregnancy-associated hypertension .
- On the other hand, a controlled study did not shown increased fetal or maternal morbidity during the second and third trimesters among women who developed OHSS, compared with IVF control patients who had not developed the syndrome



▶ GnRHa trigger and OHSS:

Alternatively, final follicular maturation and ovulation may be triggered using a GnRHa to stimulate an endogenous LH surge in patients at risk for OHSS.

GnRHa cannot be used as an ovulation trigger for cycles in which GnRHa was previously used for down-regulation.
If a patient at high risk of OHSS is identified and GnRHa triggering is contemplated, a GnRH-ant protocol, rather than a long GnRHa protocol, should be used for suppression of the endogenous mid-cycle LH surge.

- **GnRH-ants and OHSS:**
- 0.25 mg of ganirelix or cetrorelix daily seems to be sufficient to eliminate the LH surge and seems to result in favorable clinical outcomes.
- Several investigators have administered intravenous colloidal agents such as albumin and hydroxyethyl starch at the time of oocyte retrieval as prophylactic intravascular volume and oncotic pressure enhancers to minimize the risk of developing OHSS.
- In contrast to the significant value of albumin for treatment of the fully developed syndrome, colloids are of questionable benefit as preventive measures

- **Miscellaneous techniques to prevent OHSS:**
- unilateral or bilateral follicular aspiration as a rescue for cycles not otherwise intended to undergo oocyte retrieval
- Ovarian diathermy prior to initiation of COS(young patients with severe PCOS who tend to hyperstimulate even on a prolonged low-dose FSH regimen)
- Metformin, Although a more favorable response to ovulation enhancement would be expected, it is unclear yet whether a reduction in the incidence of OHSS will follow
- The study showed more than a 50% reduction in the incidence of moderate OHSS with the use of cabergoline from the day of hCG administration through to six days post-oocyte retrieval.

TREATMENT OF SEVERE OHSS

- Treatment with high doses of cabergoline (1 mg daily), in conjunction with a GnRH-ant, seemed to facilitate a rapid resolution of even severe OHSS, with no side effects reported.
- In patients with moderate ascites and mild hemoconcentration (hematocrit <45%), bed rest, and abundant liquid intake should be prescribed.
- Towards intravascular volume depletion and hyponatremia may be treated with oral isotonic electrolyte solutions; sports drinks
- A hematocrit >45%, or 30% increased over baseline, indicates that the condition has entered the category of severe OHSS and that hospitalization is required.
- Dramatic clinical deterioration is most likely to manifest eight to nine days after HCG administration, when endogenous, pregnancy-derived HCG becomes perceptible.
- The single most important variable that indicates the severity of the OHSS is hemoconcentration, as reflected in the hematocrit

- Change of 2% in the hematocrit from 42% to 44% is four-times smaller than the actual 8% drop in plasma volume. One should therefore not be lulled into a false sense of security when only a small incremental rise in hematocrit between 40% and 45% is observed.
- An additional measure of hemoconcentration is the magnitude of leukocytosis; white blood cell counts higher than 25,000/mm3

- Crystalloids alone, although seldom sufficient for restoring homeostasis because of massive protein
- Loss through hyperpermeable capillaries, still remains the mainstay of treatment.
- The daily volume infused may vary from 1.5 L to greater than 3.0 L.
- Although some authors advocate fluid restriction to minimize the accumulation of ascites, one should rather deal with the discomfort of ascites than face the consequences of hemoconcentration with the attendant risks of thromboembolism and renal shutdown

- Albumin at doses of 50–100 g at 25% concentration should be administered intravenously and repeated every 2–12 hours until the hematocrit falls below 45% and urine output increases.
- When oliguria persists despite evidence of adequate hemodilution, intravenous furosemide at a 10–20-mg dose is often beneficial. In practice, an albumin–furosemide chase protocol seems to yield the best results. Two units of albumin, 50 g each, followed immediately by intravenous furosemide will often result in diuresis. In states of volume contraction, hemoconcentration, and hypotension, furosemide should be strictly avoided.
- OHSS, with impending renal failure, renal dose dopamine drip should be used for renal rescue.