Severe ovarian hyper stimulation syndrome

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INTRODUCTION

- Ovarian hyperstimulation syndrome (OHSS) is the gravest complication of controlled ovarian stimulation (COS) .
- In reproductive medicine in general and assisted reproduction technologies (ARTs) in particular, OHSS is second only to high-order multiple birth on the list of adverse outcomes that need to be minimized or completely eliminated.

- OHSS consists of ovarian enlargement accompanied by an overproduction of ovarian hormones and a host of other ovarian vasoactive substances, which alone or in concert may produce the hyperpermeability state responsible for the signs, symptoms, and complications of OHSS .

CLASSIFICATION

- Like many other diseases, OHSS exists in a clinical spectrum.
- Some patients, at one end of the spectrum, exhibit only mild signs and symptoms of the disease; others, at the other extreme, require intensive management and may even be at risk of death from the disease .

OHSS must be classified to help clinicians determine whether the patient should be managed supportively or intensively, medically or surgically, at home or in the hospital.

- Classification schemes by disease severity

Over the past 25 years, several classification systems have been suggested in order to better categorize OHSS and disseminate uniform guidelines for prevention and treatment.

Most of these classification systems are based on the severity of the disease, based on a combination of the severity of the patient's symptoms as well as the severity of the physical, laboratory, and radiologic signs of the disease.

CLASSIFICATION

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.

CLASSIFICATION BY DISEASE ONSET: EARLY AND LATE OHSS

- As a disease, OHSS seems to include these two distinct forms based on the timing of its onset, and can consequently be classified into early OHSS and late OHSS.
- Both forms of OHSS share a common pathophysiology; in both, hCG triggers granulosa cells to produce vasoactive substances that induce the capillary permeability that yields the clinical sequelae of OHSS. What distinguishes the early and late forms of the disease is the source of the hCG.
- In early OHSS, that occurs three to seven days after hCG triggering the exogenously injected hCG drives the granulosa directly to secrete sufficient vasoactive substances to produce the syndrome.
- In late OHSS, early pregnancy is responsible for the granulosa cell activity, as the implanting trophoblast produces increasing levels of endogenous hCG.

- Clinically, these two entities ought to be distinguished, because they are distinct.

Early OHSS, is dependent on ovarian stimulation; higher peak E2 levels and greater gonadotropin doses are correlated with an increased incidence of early OHSS, but not of late OHSS. Therefore, criteria related to ovarian response can be used to predict early OHSS, but not late OHSS. Early OHSS can occur in any stimulated cycle.

late OHSS only occurs in the setting of a pregnancy. Late OHSS is more likely to be severe; in fact, late OHSS may account for almost 70% of all cases of severe OHSS. Late OHSS can occur with either a singleton or multiple pregnancy. While some authors have suggested that multiple pregnancy has a stronger association with late OHSS than singleton pregnancy by virtue of higher trophoblastic hCG production.

ETIOLOGY

- The syndrome is known to be dependent on HCG. This HCG dependence underlies some of the major preventive strategies for the syndrome ,OHSS does not occur if HCG is withheld.
- More recently, numerous vasoactive substances have been implicated in the pathophysiology of the disease, including prorenin, renin, prostaglandins, angiotensin II, vascular endothelial growth factor (VEGF), tumor necrosis factor-α, insulin-like growth factor-1, epidermal growth factor, basic fibroblast growth factor, platelet-derived growth factor, transforming growth factors-α and -ß, and interleukins-1ß, -2, and -6 .

- Many of these substances are proangiogenic, and are probably responsible for the physiologic neovascularization that occurs during folliculogenesis and leutinization within the ovary.
- VEGF seems to play a particularly critical role in the pathophysiology of OHSS. Evidence for this critical role includes the facts that VEGF is secreted by granulosa cells, VEGF levels correlate with OHSS severity, recombinant VEGF has been shown to induce OHSS, and specific VEGF antiserum has been shown to reverse the effects of VEGF-induced OHSS. Furthermore, hCG has been shown to increase VEGF secretion by granulosa cells, and to increase serum levels of VEGF.

- OHSS has been reported in several women with spontaneous pregnancies , and the cause of this OHSS seems to be a familial mutation in the FSH receptor, increasing its sensitivity to trophoblastic hCG. The mutation allows for constitutive stimulation of the FSH receptor by hCG, triggering the ovarian cascade responsible for OHSS.

- Serum E2 also seems to play a role in the pathogenesis

of OHSS, but the nature of this role is not clear because a high serum E2 level, while a known risk factor for OHSS, seems to be neither necessary nor sufficient for the devel- opment of the disease.

- On the one hand, the fact that most patients with OHSS have high E2 levels may suggest that high E2 is necessary in the development of OHSS; but on the other hand, OHSS can occur in hypoestrogenic patients such as those with hypogonadotropic hypogonadism Similarly, the fact that a high serum E2 level is a definitive risk factor for OHSS may suggest that it is sufficient for the development of OHSS; but on the other hand, OHSS does not occur when hCG is withheld, despite high E2 levels .

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.

PREVENTION OF SEVERE OHSS

- As an iatrogenic condition resulting from elective ovarian stimulation in the quest for pregnancy, the need to completely prevent the syndrome is evident.
- In order to promulgate safe COS, it is essential to first define the “at-risk population.” .
- The single most important risk factor for OHSS is a polycystic appearance of the ovaries on transvaginal ultrasound, having a high antral follicle count and a “necklace sign” or “string of pearls” appearance (Figure 65.2).

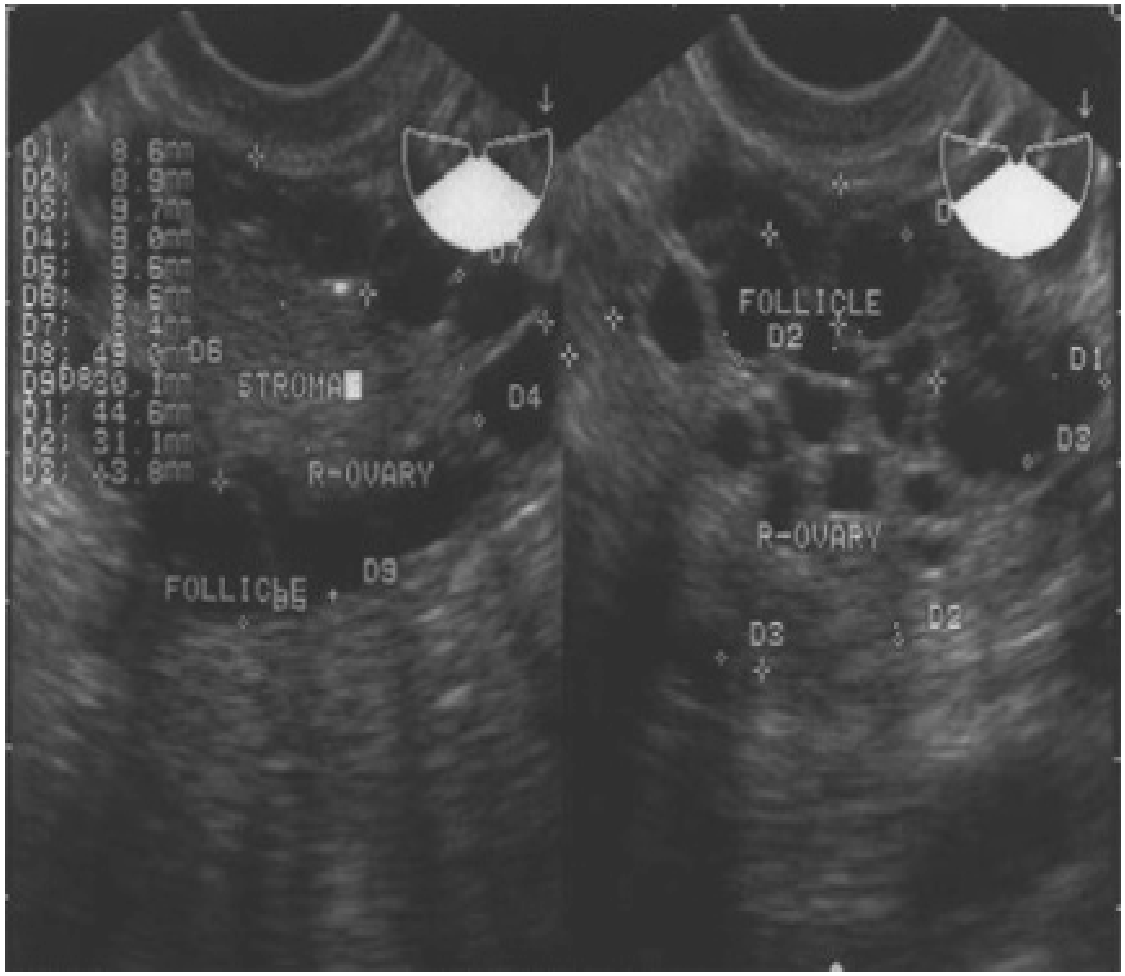

Figure 65.2 Transvaginal ultrasound depicting the right ovary of a 31-year-old woman with amenorrhea and polycystic ovary syndrome. The picture features major high-risk factors for the development of severe ovarian hyperstimulation syndrome: (1) "String of pearls" appearance of antral follicles on the left panel; (2) Dense stroma occupying the center of the ovary; (3) Enlarged ovary measuring 49 × 44.6 mm; (4) Total of 60 antral follicles in one ovary.

- Recently, serum concentrations of anti-Mullerian hormone (AMH) have been investigated as a risk factor for OHSS. AMH is secreted by ovarian granulosa cells in preantral and small antral follicles and can be used to estimate ovarian reserve and predict ovarian response to gonadotropin stimulation . In one study, all cycle cancelations due to OHSS occurred in patients who were in the highest AMH quartile of greater than 7 ng/ml.

- Early reports suggested a relationship between the type of gonadotropin preparation utilized and the risk of OHSS.
- More recent comparisons between recombinant FSH (rFSH) and human menopausal gonadotropins (hMGs) did not show significant differences among variable drug regimens.
- The rate of OHSS in this study was 3.2% versus 2.0% for rFSH and uFSH, respectively, and the difference was not statistically significant.
- The capacity of rFSH to enhance both follicular recruitment and serum E2 concentrations may indeed carry a slightly increased risk of OHSS. However, the seemingly increased risk in these studies may also be due to early inexperience with rFSH. With increased awareness and understanding of the unique features of rFSH, the actual rate of OHSS with rFSH use has since decreased.

- Indeed, numerous studies have shown that the method of stimulation (chronic low dose, step up, or step down) carries far more weight as a risk factor than the type of injectable gonadotropin used .
- Specifically, the socalled chronic low-dose regimen is more likely to result in a mono- or bi-follicular response and therefore a significantly lower rate of OHSS. Similarly, unlike a step-up protocol, which continuously rescues follicles from atresia, a step-down protocol will allow more follicles to undergo atresia, thus reducing the overall number of follicles capable of secretory activity by the time hCG is administered.

- An extension of the step-down concept is “coast-ing” or “controlled drift,” championed by Sher and colleagues , and later practiced widely by several other researchers with variable results.
- 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.

- The use of GnRHa in conjunction with COS, either as a "long" or "short" protocol, profoundly affects the risk of OHSS.
- GnRHas play a paradoxical role in OHSS by virtue of the control they afford, despite their overall suppressive effect on ovarian stimulation. Both the long and the short GnRH a protocols uniformly abolish the mid-cycle luteinizing hormone (LH) surge. This suppression of the LH surge allows continued stimulation by gonadotropins, which in turn will drive more follicles to either full or quasi-maturation with a consequent rise in serum E2 values and a markedly increased risk of OHSS.
- In contrast, during cycles without GnRHa suppression, either a significant LH surge or at least marked luteinization will limit continued gonadotropin stimulation and thus lead to a concomitantly lesser risk of OHSS.

The role of hCG and its substitutes

- exogenously administered or pregnancy-derived hCG is absolutely essential for the development of OHSS.
- In contrast, avoidance of hCG or substitution by a low-affinity, shorter-acting compound are the mainstays for the prevention of OHSS.
- Indeed, the acknowledgement of the role of hCG in OHSS has led to all but complete discontinuation of the foul habit of hCG administration for luteal supplementation.
- However, hCG as a surrogate for the mid-cycle LH surge is still universally used in COS for both ovulation induction and IVF. 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, thus exerting continuous ovarian stimulation up to the stage in which endogenous pregnancy-derived hCG is perceived.

- Because of these OHSS-promoting actions of hCG, 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.

Recombinant LH and OHSS

- The authors concluded that rLH may be safer than hCG as far as OHSS is concerned.
- Alternately, it is possible that a single peak of rLH is sufficient to induce final oocyte maturation as opposed to the 24-hour naturally occurring LH surge.

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 induces adequate ovulation while avoiding OHSS.

- The preponderance of evidence to date supports a decreased incidence of OHSS with GnRHa compared with hCG as the triggering agent for ovulation, although a small possibility of moderate OHSS remains, particularly in conception cycles. Most importantly, there have been no reports of severe or critical OHSS after triggering ovulation with mid-cycle GnRHa.
- Clinicians using GnRHa to trigger ovulation must realize that the ensuing luteal phase is dramatically deficient, and full luteal progesterone support must be employed.
- In oocyte donation cycles, in cycles using a gestational carrier, and in cycles in which all embryos or oocytes are expected to be cryopreserved, such as for purposes of pre-implantation genetic testing of embryos, luteal sufficiency is of no concern.

- Clinicians must also be aware that because of pituitary desensitization, 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

- GnRH-ants seem to be associated with a decreased risk of OHSS compared with the GnRHa long protocol in patients undergoing IVF.
- far more intriguing is the potential use of GnRH- ant in conjunction with either rLH or GnRHa to trigger ovulation.

- Because of the competitive nature of GnRH- ant suppression and lack of desensitization, it is possible to trigger ovulation with GnRHa during co-treatment with gonadotropins and GnRH-ant.
- Theoretically, a larger dose of GnRHa would be needed to induce an LH surge in cycles suppressed by a GnRH-ant than in cycles using gonadotropins alone without a GnRH-ant.
- It cannot be stressed enough that full progesterone support is mandatory throughout the luteal phase when GnRHa is used to trigger ovulation.

Embryology strategies

- Liberal application of embryo cryopreservation for patients showing early signs of hyperstimulation can be an important safety net in guarding against severe OHSS.

Prophylactic use of colloid agents to prevent 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

- 1.unilateral or bilateral follicular aspiration
- 2. ovarian diathermy : prior to initiation of COS Ovarian diathermy should, however, be reserved to young patients, with severe PCOS hyper stimulate on a Prolonged low-dose FSH regimen.
- 3. Metformin : the second-generation biguanide insulin sensitizer, has been advocated for the treatment of women with severe PCOS and insulin resistance. 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.

- 4. Aromatase inhibitors :administered in the luteal phase can be used to reduce luteal E2 concentrations, and thus may be a promising approach in preventing OHSS or minimizing its attendant hyperestrogenemia-related risks in patients such as oocyte donors whose luteal sufficiency is of no concern.
- 6. corticosteroids : The anti-inflammatory action of corticosteroids has also been hypothesized to be beneficial in preventing OHSS. Nevertheless, there may be a preventive role for corticosteroids used in conjunction with aspirin: one randomized trial demonstrated a decreased incidence of OHSS among women undergoing IVF who received a combination of aspirin and prednisolone from the beginning of COS through to the day of the pregnancy test , and another trial demonstrated a benefit to aspirin alone in the prevention of OHSS.

- 7.ASA

- 8. calcium gluconate 10%: Calcium infusion has also been hypothesized to prevent OHSS because of its inhibition of cyclic adenosine monophosphate (cAMP) synthesis and cAMP-dependent renin secretion from juxtaglomerular cells in the kidneys . Reduced renin secretion results in decreased angiotensin II production, with a consequent decrease in angiotensin II-mediated stimulation of VEGF synthesis.

IVF patients at risk for OHSS were infused intravenously with calcium gluconate 10%, 10 mL in 200 mL of normal saline, on the day of oocyte retrieval and for three days there after . This prevention modality carries little risk and potential benefit, but because of insufficient data cannot yet be routinely recommended.

- 9. Dopamine agonists: treatment with a VEGF receptor antagonist prevented the increase in capillary permeability seen in an OHSS. Cabergoline, a dopamine D2 receptor agonist, inactivates VEGF receptor 2 in animal models . 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.
- 10. kisspeptin: as a novel trigger of oocyte maturation for women at high risk of OHSS undergoing IVF.

TREATMENT OF SEVERE OHSS
Medical approach

- There are two possible approaches to the treatment of OHSS: one pathogenesis oriented and one empiric

Table 65.3 Pros and cons of various therapies of ovarian hyperstimulation syndrome

Therapy	Pros	Cons
Intravenous crystalloids	Alleviates hemoconcentration Improves renal perfusion	Lost immediately from vascular tree Aggravates ascites
Fluid restriction	Controls ascites	Reduces renal perfusion Promotes hemoconcentration
Albumin	Improves colloid-oncotic pressure Improves renal perfusion	Risks of human blood product
Furosemide	Reduces total body water	Further reduces intravascular volume
Indomethacin	May block prostanglandin-induced hyperpermeability	Implicated in renal failure
ACE inhibitors	May block angiotensin II-induced hyperpermeability	Teratogenic
Paracentesis	Alleviates tense ascites Improves renal perfusion	Risks of hemorrhage, infection, and leakage
Heparin	Decreases risk of thromboembolic phenomena	Increases risk of hemorrhage
Peritoneo-venous shunt	Replaces lost electrolytes and proteins	Risk of self-toxicity Elaborate setup and risk of infection
Dopamine drip	Improves renal perfusion	Need for Intensive Care Unit management

Abbreviation: ACE, angiotensin-converting enzyme.

- Individual treatment will depend on the severity of the syndrome. Mild forms of OHSS require little more than reassurance, since it is well established that mild symptoms usually resolve, in the absence of pregnancy, within two weeks of receiving hCG. If a pregnancy ensues, mild symptoms may progress, but rarely by more than one degree in severity.
- In patients with moderate ascites and mild hemoconcentration (hematocrit <45%), bed rest and abundant liquid intake should be prescribed. hyponatremia may be treated with oral isotonic electrolyte solutions, sports drinks.
- hematocrit >45%, or 30% increased over baseline, indicates that the condition has entered the category of severe OHSS and that hospitalization is required.

- The single most important variable that indicates the severity of the OHSS is hemoconcentration, as reflected in the hematocrit.
- An additional measure of hemoconcentration is the magnitude of leukocytosis.>25000.
- When oral isotonic fluid intake is insufficient to maintain plasma volume, intravenous fluid therapy becomes mandatory. Crystalloids alone, although seldom sufficient for restoring homeostasis because of massive protein loss through hyperpermeable capillaries, still remains the mainstay of treatment.

- 1.sodium chloride with or without glucose is the crystalloid of choice
- 2.fluid restriction
- 3.Whenever adequate fluid balance cannot be restored by crystalloid alone, plasma expanders should be utilized (albumin)
- **4.** paracentesis
- 5.albumin–furosemide
- 6. dopamine drip

Paracentesis

- The single most important treatment modality in lifethreatening OHSS that cannot be controlled by medical therapy is paracentesis. The indications for paracentesis include the need for symptomatic relief, tense ascites, oliguria, rising serum creatinine concentration or falling creatinine clearance, and hemoconcentration unresponsive to medical treatment. Paracentesis should be performed aseptically under ultrasound guidance

- Paracentesis is contraindicated in patients who are hemodynamically unstable or in the presence of suspected hemoperitoneum peritoneo-venous shunting

- although prophylactic treatment of women with OHSS with unfractionated or low-molecular-weight heparin is of some theoretical value, rapid alleviation of the patient’s hemoconcentration is far more important.

The GnRH antagonist protocol is recommended for PCOS women with regards to improved safety and equal efficacy.	Strong	⊕⊕OO

Recommendation

A GnRH agonist trigger is recommended for final oocyte maturation in women at risk of OHSS.	Strong	⊕OOO

A freeze-all strategy is recommended to eliminate the risk of late-onset OHSS and is applicable in both GnRH agonist and GnRH antagonist protocols.	GPP

Cabergoline or albumin as additional preventive measures for OHSS are not recommended when GnRH agonist is used for triggering final oocyte maturation.	GPP

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