Chapter 18
Ovarian Hyperstimulation Syndrome (OHSS)

Robert L. Barbieri

Précis

1. Clinical setting: Abdominal bloating and distention, intravascular volume depletion, ascites, hemoconcentration, and oliguria *following a fertility intervention involving the administration of exogenous follicle stimulating hormone (FSH).*
2. Diagnosis:
   (a) History: Abdominal bloating, distention, abdominal and/or pelvic pain, acute weight gain, and shortness of breath. A recent fertility intervention involving the administration of exogenous FSH. Young age, polycystic ovary syndrome, or low body mass. A previous history of OHSS.
   (b) Physical examination: Abdominal distention, weight gain, evidence for ascites (flank dullness), or pleural effusion (dullness to percussion, decreased breath sounds).
   (c) Laboratory values: Hemoconcentration (Hct >50%), elevated BUN and creatinine, elevated liver function tests.
   (d) Imaging: Bilateral ovarian enlargement, peritoneal fluid or ascites on ultrasound, pleural effusions on ultrasound.
   (e) Treatment: Close monitoring of hemodynamic status and renal function. Paracentesis to resolve the abdominal compartment syndrome. Administration of albumin or hydroxyethyl starch to improve renal function and urine output. Treatment with cabergoline to reduce ovarian vascular endothelial growth factor (VEGF) production. Thrombosis prophylaxis to reduce the risk of thromboembolism.

R. L. Barbieri (✉)
Department of Obstetrics and Gynecology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
e-mail: rbarbieri@partners.org

L. Loriaux, C. Vanek (eds.), *Endocrine Emergencies*, Contemporary Endocrinology,
https://doi.org/10.1007/978-3-030-67455-7_18

The most dangerous complications of OHSS are renal failure, hypovolemic shock, thrombosis, stroke, acute respiratory distress, ovarian torsion, ovarian rupture, and death.

Ovarian hyperstimulation syndrome (OHSS) is the presence of the combination of *ovarian enlargement* due to hormone-secreting *luteinized ovarian cysts* and an associated vascular dysfunction manifested by *increased capillary permeability*, resulting in the accumulation of fluid in the peritoneal and pleural cavity, and hemoconcentration.

Definition and Staging of OHSS There is no established uniform definition of OHSS [1]. One staging system for OHSS is presented in Table 18.1 [2]. Most staging systems regard *mild* OHSS, which includes abdominal discomfort and distention, along with variably enlarged ovaries, as a normal physiological consequence of ovarian hyperstimulation regimens that stimulate the growth of multiple ovarian follicles. *Severe* OHSS is a serious problem characterized by marked fluid shifts into the extravascular compartment and renal dysfunction. Mathur and colleagues have championed the division of OHSS into early and late cases. Early cases of OHSS present 3–7 days after follicle luteinization [3]. Late cases of OHSS present 12–17 days after luteinization. Early cases of OHSS are associated with excessive ovarian stimulation and the events surround luteinization. Late cases of OHSS are associated with singleton and multiple gestations with continuing stimulation of the ovary by rising levels of hCG from the trophoblast tissue. Late cases of OHSS are more severe and difficult to anticipate based on events during the follicular phase of the stimulated cycle [3].

Table 18.1 Ovarian hyperstimulation syndrome staging system

Category	Description
Mild	
Grade 1	Abdominal distention and discomfort, abdominal pain
Grade 2	Features of grade 1 *plus* nausea, vomiting, and diarrhea
	Ovaries are 5–12 cm in diameter
Moderate	
Grade 3	Features of *mild* OHSS *plus* sonographic evidence of ascites
Severe	
Grade 4	Features of *moderate* OHSS *plus* clinical evidence of ascites or hydrothorax or breathing difficulties
Grade 5	All of the above *plus* hemoconcentration or diminished renal perfusion and function or coagulation abnormalities

Adapted from Ovarian Hyperstimulation Syndrome Staging (Golan et al. [2])

Pathophysiology

In most cases of OHSS, the inciting cause is fertility treatment involving the sequential administration of exogenous FSH to stimulate multiple follicle growth followed by administration of a hormone to induce luteinization of the large follicles. Occasionally, OHSS may occur following clomiphene ovulation induction, during the agonist phase of GnRH agonist monotherapy [4, 5] or following monotherapy with an anti-estrogen such as tamoxifen [6]. Rarely a spontaneous pregnancy may cause OHSS [7].

A goal of many fertility treatments, such as in vitro fertilization (IVF) and FSH-intrauterine insemination (FSH-IUI), is to stimulate the growth and luteinization (IVF) or ovulation (FSH-IUI) of *multiple* follicles. In a typical IVF cycle, exogenous FSH is administered at a dose sufficient to stimulate the development of approximately ten or more large follicles. When the follicles are sufficiently mature, a luteinizing hormone is administered to cause luteinization of the granulosa and theca cells in the follicles. Hormones that can be used to trigger luteinization of mature follicles include recombinant human LH (rLH), human chorionic gonadotropin (hCG), or a GnRH agonist, which triggers the release of endogenous LH from the pituitary gland. These hormones trigger luteinization of the follicle, shifting the granulosa cells from estradiol production to progesterone and estradiol synthesis. They also stimulate the oocyte to resume meiotic division in order to prepare it for fertilization. The sequential ovarian stimulation regimen of FSH followed by a luteinization trigger is termed a controlled ovarian hyperstimulation (COH) or controlled ovarian stimulation (COS) cycle. In COH and COS cycles, hCG is the most commonly used hormone to trigger luteinization of the follicles.

Luteinized granulosa cells, stimulated by hCG or LH, secrete vascular endothelial growth factor (VEGF). In turn, VEGF increases endothelial permeability [8–10]. In model systems of ovarian hyperstimulation, increased capillary permeability caused by excessive VEGF secretion from luteinized follicles can be blocked by the administration of an inhibitor of VEGF, such as Flt-1 Fc [11].

In a COH cycle, the multiple luteinized cysts secrete large quantities of VEGF, which cause a marked increase in capillary permeability resulting in fluid shift from the intravascular to extravascular space. Circulating concentrations of VEGF are positively correlated with the risk of developing OHSS and the severity of the syndrome. Other proteins, which may play an auxiliary role in the development of OHSS, include interleukin-6, the renin-angiotensin system, the kinin-kallikrein system, selectins, IGF-1, epidermal growth factor, transforming growth factors alpha and beta, basic fibroblast growth factor, platelet-derived growth factor, and interleukin-1 beta.

During fertility treatment, OHSS most often occurs after luteinization triggered by hCG (early cases occur 3–7 days after the administration of the luteinization

trigger). Compared to endogenous or recombinant LH, hCG has a much longer half-life (>24 h for hCG versus <20 min for LH). Compared to LH, hCG has a higher affinity for the LH receptor and a longer duration of intracellular effect [12]. Interestingly, GnRH agonist stimulation of ovulatory events, by causing the endogenous pituitary release of LH, is associated with lower ovarian production of VEGF. In contrast, hCG administration is associated with greater ovarian production of VEGF [13]. As noted below, one approach to reducing the risk of developing OHSS, following the use of FSH to stimulate multiple follicle growth, is to trigger ovulation with a GnRH agonist or rLH rather than hCG.

Among women, there is great variability in the magnitude of ovarian follicle response to a fixed dose of FSH. The size of the woman's ovarian follicle pool is an important predictor of response to FSH. Women with large numbers of responsive antral follicles, such as young women and women with polycystic ovary syndrome (PCOS), respond more vigorously to a given dose of FSH than women with a small number of antral follicles, such as women >40 years of age and those with premature loss of ovarian follicles due to alkylating chemotherapy or multiple ovarian surgeries. Genetic mutations in proteins that regulate ovarian follicle growth may modulate the risk of developing OHSS by sensitizing the ovary to the stimulatory effects of FSH. Bone morphogenetic protein 15 (BMP15) is an important regulator of ovarian follicle development in sheep and mice. Certain alleles of BMP15 appear to be associated with increased ovarian response to FSH and an increased risk of OHSS [14, 15].

The ovary contains high concentrations of dopamine, and the theca-lutein cells of the corpus luteum contain dopamine receptors [16]. In human granulosa cells, cabergoline, a dopamine agonist, inhibits VEGF production. Women with PCOS are at increased risk for developing OHSS when treated with the sequential combination of FSH and a luteinizing hormone. Follicles from women with PCOS appear to have reduced ovarian dopamine concentration and decreased concentration of dopamine receptors suggesting that reduced dopamine tone permits increased VEGF secretion in these women [17]. As noted below, cabergoline treatment appears to have a beneficial effect on women with OHSS.

Rare causes of OHSS include an FSH secreting pituitary tumor or genetic mutations in the FSH receptor [18]. The most common FSH receptor mutation associated with OHSS (FSHR D567N) results in the expression of a permissive FSH receptor that binds not only FSH but also LH, hCG, and TSH. Women with FSH receptor mutations typically develop OHSS when they become pregnant due to excessive ovarian stimulation of the FSH receptor by placental hCG.

OHSS is associated with the accumulation of large amounts of fluid in the peritoneal cavity and occasionally in the pleural space. In women with OHSS, intra-abdominal pressure is often elevated, creating an *abdominal compartment syndrome*. In patients with mild and severe OHSS, the intra-abdominal pressure has been reported to be 13 and 40 mmHg, respectively [19]. Intra-abdominal pressure greater than 16 mmHg can cause reduced renal blood flow, decreased urine output, decreased cardiac output, increased systemic vascular resistance, and coagulopathy. Paracentesis performed early and often in the course of OHSS can reduce

intra-abdominal pressure and prevent the complications associated with the abdominal compartment syndrome.

Epidemiology Moderate and severe forms of OHSS have been reported to occur in approximately 4% and 0.5%, respectively, of women undergoing ovarian stimulation for IVF [20]. In a consecutive case series of 214,219 US women undergoing assisted reproductive treatment (ART), moderate and severe OHSS developed in 0.7% and 0.3% of the women, respectively, but under-reporting may have occurred [21]. Mild forms of OHSS occur in about 30% of ART cycles.

The most important pretreatment risk factors for developing OHSS include the following: (1) a previous history of OHSS, (2) age <30 years, and (3) diagnosis of polycystic ovary syndrome. The most important risk factors identified during an ovarian stimulation cycle include the following: (1) elevated circulating estradiol, >3500 pg/mL, (2) rapidly rising estradiol, (3) large number of follicles, for example >20 follicles, and (4) use of hCG to stimulate luteinization [22]. On a positive note, OHSS is more likely to occur in women who become pregnant during their fertility treatment, likely because of the continued stimulation of ovarian VEGF secretion by hCG secreted from trophoblast cells. Women who become pregnant with multiple gestations, which are associated with higher levels of circulating hCG, are also more likely to develop OHSS.

Clinical Presentation

Most cases of OHSS occur following ovarian stimulation with fertility medications. Women with mild OHSS typically present with lower abdominal pain, discomfort and distention, bloating, mild nausea, and occasionally vomiting. Women with moderate and severe forms of OHSS present with rapid weight gain, shortness of breath and tachypnea, reduced urine output, orthostatic hypotension, and tachycardia. The differential diagnosis includes ovarian hemorrhage, ovarian torsion, pelvic infection, intra-abdominal hemorrhage, ectopic pregnancy, and appendicitis.

Clinical examination should include sequential measurement of body weight, abdominal circumference, and pelvic ultrasound to measure ovarian size and check for the presence of ascites. Laboratory tests that are useful include hemoglobin/hematocrit concentration, creatinine, electrolytes, and liver function tests. Follow-up evaluation every 2–3 days is adequate to assess the progress of the condition. If a woman reports increasing and severe pain, abdominal distention, shortness of breath, and reduced urine output, immediate clinical reevaluation is warranted. Early cases of OHSS (3–7 days after administration of a luteinizing agent) tend to resolve within 1–2 weeks if pregnancy does not occur. Late cases of OHSS (presenting 12–17 days after administration of LH or hCG) are often associated with an ongoing pregnancy and may persist for weeks.

Women with severe OHSS should be considered for hospitalization. Specific conditions that may require intensive unit care include adult respiratory distress

syndrome, renal failure, or thromboembolism. Severe OHSS is associated with hematocrit >50% and hyponatremia in about 50% of cases. Oliguria is present in about 30% of women with severe OHSS. Abnormal liver function tests are present in about 30% of women with OHSS. Severe OHSS may occasionally be associated with pulmonary dysfunction including pneumonia, respiratory distress syndrome, and pulmonary embolism [23]. Chest X-ray is indicated to assess women for pleural effusion and coincident pulmonary infection.

Severe OHSS is associated with increased plasma levels of D-dimer, increased thrombin-antithrombin III complex, and decreased protein S activity [24]. Rarely, severe OHSS may cause arterial and venous thrombosis [25]. When the CNS is involved in the thrombotic process, the results can be devastating [26, 27]. Thrombosis can also occur in arteries supplying the limbs, rarely requiring amputation [28].

Prevention of OHSS

Selection of Stimulation Regimens Based on Risk Stratification

Prior to the initiation of a cycle of ovarian stimulation, higher circulating levels of antimullerian hormone (AMH) and a higher basal ovarian antral follicle count are associated with an increased risk of developing OHSS [29]. Therefore, it is possible to stratify women into high and low risk groups for the development of OHSS. It is known that certain ovarian stimulation protocols are associated with a higher risk of OHSS and other protocols with a lower risk of OHSS. For example, the risk of developing OHSS is lower with an ovarian stimulation protocol that uses FSH injections, GnRH antagonist to suppress a premature LH surge, and a GnRH agonist analog to trigger luteinization by stimulating the pituitary to release endogenous LH [30, 31]. In contrast, the risk of developing OHSS is greater with an ovarian stimulation protocol that uses a long downregulation regimen with GnRH agonist analog started in the luteal phase of the cycle preceding the treatment cycle (to suppress a premature LH surge), FSH injections, and hCG to trigger luteinization. Using this information, it has been proposed that women with high AMH (>29 pM), who are at higher risk of OHSS, receive the ovarian stimulation protocol that is associated with a lower risk of OHSS (FSH, GnRH antagonist, GnRH agonist) and women with normal AMH (16–29 pM), who are at a lower risk of developing OHSS receive a standard protocol (long-cycle downregulation GnRH agonist analog, FSH injections, hCG) [32].

Why not treat all women with the protocol associated with the lowest risk of OHSS? Many clinicians believe that the protocol with the lowest risk of OHSS, which utilizes a GnRH antagonist plus a GnRH agonist to trigger luteinization, is associated with lower pregnancy rates than the standard long downregulation protocol with a GnRH agonist or protocols that use a GnRH antagonist plus hCG to trigger luteinization [33]. Experienced clinicians are concerned that the stimulation protocols associated with a low risk of developing OHSS increase the risk of the "empty follicle syndrome," where no oocytes can be retrieved at the time of oocyte

harvest. Therefore, the use of the GnRH antagonist plus a GnRH agonist to trigger luteinization might best be limited to those women at the highest risk of OHSS and women who have experienced OHSS in a previous cycle.

Another option for reducing the risk of OHSS is to stratify women into high and low risk groups for OHSS and then give the women at high risk for OHSS, lower doses of FSH [34]. In a similar manner, if the treatment cycle appears to have resulted in excessive stimulation, the luteinization trigger can be switched from a standard dose of hCG to a low dose of hCG [35] or to switch, mid-cycle, to a GnRH antagonist plus GnRH agonist for luteinization protocol [36].

Coasting A very elevated level of estradiol (>3000 pg/mL) and/or the presence of a marked excess of growing antral follicles (>20 follicles >12 mm in diameter) are risk factors for developing OHSS. It is likely that the presence of a very elevated level of estradiol is a predictor for excessive ovarian production of VEGF following luteinization. Since estradiol levels are somewhat predictive of the risk of developing OHSS, one approach to prevention is to stop administering daily FSH when estradiol exceeds some predetermined threshold, such as 3000 pg/mL. Without continuing FSH stimulation, granulosa production of estradiol will decrease during the following days. When circulating estradiol reaches a lower level, such as 2000 pg/mL, a luteinizing stimulus is administered, and the cycle proceeds. A major advantage of coasting is that the treatment cycle is not abandoned, and for IVF cycles, in contrast to cryopreservation of all embryos, it allows the transfer of fresh embryos [37]. Coasting for more than 3 days may reduce oocyte quality and pregnancy rates. Some experts recommend that after 3 days coasting should be abandoned, and the cycle should proceed with cryopreservation of all the embryos [38]. In a systematic review of four randomized trials, there was no evidence that coasting reduced the risk of moderate or severe OHSS. However, in the review, coasting was associated with the retrieval of fewer oocytes [39].

Colloid Infusion at the Time of Oocyte Retrieval Women with an estradiol >3000 pg/mL on the day of triggering luteinization are at increased risk for OHSS. In one trial, women with an estradiol >3000 pg/mL, or >20 follicles on the day of hCG administration, were randomized to receive 500 mL of 6% hydroxyethyl starch or 50 mL of 20% human albumin or 500 mL of 0.9% NaCl at the time of oocyte retrieval [40]. The rate of moderate or severe OHSS was 19%, 10%, and 6% in the groups receiving saline, albumin, or hydroxyethyl starch, respectively.

Cryopreserving All Embryos and Delaying Embryo Transfer to Another Cycle

The goal of fertility treatments is to achieve a pregnancy. In programs involving the administration of FSH to stimulate multiple follicle development followed by the administration of an agent to trigger ovulation, the pregnancy rate is positively

correlated with the magnitude of the ovarian response. Within a corridor of safety, the greater the number of follicles stimulated, the greater the pregnancy rate. Clinicians who are highly focused on achieving a pregnancy recognize the increased risk of OHSS but want to achieve the highest pregnancy rate possible. Sometimes FSH stimulation results in the development of a great excess of mature ovarian follicles, thereby putting the patient at a risk of OHSS. One option to prevent OHSS in these cases is to retrieve the oocytes, fertilize the oocytes with sperm, and then freeze all the oocytes at an early embryonic stage [41], or after the embryos have developed for a few days in vitro. The embryo transfer is then cancelled for the stimulation cycle complicated by a high risk of OHSS.

The "freeze all" approach reduces the risk of severe and late onset OHSS, but mild or moderate early onset OHSS may still occur. In one study, women with circulating estradiol >3500 pg/mL had all their embryos cryopreserved after oocyte retrieval and fertilization. The outcomes in this experimental group were compared with a group of historical controls with a similar estradiol concentration, but who had their embryos transferred to the uterus. In this study, 60% of the historical controls with an estradiol >3500 pg/mL who had embryos transferred and became pregnant had OHSS compared to 6% of the women who had all their embryos cryopreserved [42]. Following a "freeze all" cycle, the patient is prepared for a cryopreserved embryo transfer in a subsequent cycle. In large IVF programs, this approach is used in about 2% of all initiated cycles [43]. In the "freeze all" cycle following oocyte retrieval, the patient may be treated with agents to reduce VEGF and estradiol production by the ovary (GnRH antagonist, dopamine agonist, and/or aromatase inhibitor) in order to further reduce the risk of OHSS [44].

Cabergoline As noted above, excess ovarian production of VEGF causes increased vascular permeability and plays a central role in the development of OHSS. Ovarian theca-lutein cells contain dopamine receptors, and the dopamine agonist, cabergoline, appears to reduce VEGF production from these cells [16]. Clinical trials report that cabergoline, initiated at the time of hCG administration, in women at high risk reduces the severity of OHSS. For example, in one trial, women with >20 growing follicles >12 mm in diameter were randomized to receive cabergoline 0.5 mg daily or a placebo daily for 8 days starting on the day of hCG administration. Hemoconcentration and ascites were significantly reduced by cabergoline compared to placebo. MRI scanning documented reduced vascular permeability in the women receiving cabergoline [45]. A meta-analysis reported that women at risk treated with cabergoline had a reduced incidence of OHSS (OR 0.41, 95% CI 0.25–0.66), and a trend to a reduced severity of OHSS. Cabergoline treatment did not reduce clinical pregnancy rate [46]. A standard prevention dose of cabergoline is to administer 0.5 mg daily for 8 days beginning on the day of hCG administration.

The dopamine agonist, quinagolide, when administered at doses of 50, 100, or 200 μg daily for 17–21 days starting on the day of hCG administration reduced the incidence and severity of OHSS in women at high risk of OHSS (≥20 follicles ≥110 mm in diameter) [47]. Quinagolide is not approved for use in the United States.

Treatment of OHSS

Women with mild OHSS and many women with moderate OHSS can be managed as ambulatory patients. Pain can be managed with narcotics. Nonsteroidal anti-inflammatory drugs should not be used to treat pain in women with OHSS because they can reduce renal function [48]. Nausea may be treated with agents consistent with the possibility of a developing pregnancy, such as prochlorperazine, metoclopramide, or cyclizine. Strenuous exercise and sexual intercourse should be avoided by women with OHSS because of the risk of torsion or ovarian rupture and hemorrhage. hCG injections to support the luteal phase should not be given to women with established OHSS.

Women with severe OHSS should be considered for hospitalization. Specific conditions that may require intensive unit care include adult respiratory distress syndrome, renal failure, or thromboembolism. Increasing abdominal pain, oliguria, weight gain, increased abdominal circumference, and shortness of breath suggest worsening OHSS. In the hospital, hydration and cardiopulmonary function should be assessed frequently. Abdominal examination should include an assessment for peritoneal signs, presence of ascites (flank dullness), and paralytic ileus. Diuretics should not be used in women with OHSS because they may further reduce intravascular volume unless hemodynamic monitoring is instituted. Women with hemoconcentration and oliguria may benefit from the administration of 6% hydroxyethylstarch or albumin (see below). Paracentesis (see below) may help reduce symptoms, reduce intra-abdominal pressure, and increase renal perfusion.

Thromboprophylaxis should be administered to all hospitalized women with OHSS. Compression stockings and prophylactic heparin (5000 unit sc twice daily) are commonly used because they permit the patient to ambulate. If the patient is at bed rest, an intermittent pneumatic compression device may be used.

Paracentesis As noted above, leaky vessels and the accumulation of fluid in the peritoneal cavity can result in an *abdominal compartment syndrome* causing decreased cardiac output, reduced renal blood flow, and decreased urine output. In non-randomized case series, aggressive and early paracentesis has been reported to be successful in the outpatient management of OHSS [49]. Based on modeling the cost-effectiveness of outpatient paracentesis versus in-patient management of OHSS, early aggressive outpatient paracentesis was reported to result in lower costs [50].

Paracentesis can be initiated for symptom control in patients with moderate or severe OHSS. Paracentesis can be performed either through a transvaginal route or through a standard lateral abdominal wall approach historically used to treat ascites caused by liver disease. In both cases, paracentesis is performed under ultrasound guidance. Gravity drainage or controlled vacuum suction can be used to remove the fluid. In most patients, 500–4500 mL of fluid is removed during a paracentesis over the course of 30–60 min. When massive pleural effusion occurs, pleurocentesis may be performed, or a chest tube inserted [51].

Anticoagulation Some experts recommend full anticoagulation when the hematocrit rises above 50%. Heparin or enoxaparin administered through subcutaneous

injection have both been utilized. If the patient is hospitalized, and not mobile, the use of an intermittent pneumatic compression device is recommended. If the patient is mobile, compression stockings may be preferred.

Colloid Infusion Colloid infusion may improve hemodynamic function in women with OHSS. In a systematic review of three trials, hydroxyethyl starch infusion was reported to be more effective in reducing the risk of developing severe OHSS than no treatment (OR 0.12, 95% CI 0.04–0.40) [52]. In a systematic review of eight trials, albumin infusion was reported to be modestly more effective than no treatment in reducing the risk of developing severe OHSS (OR 0.67, 95% CI 0.45–0.99) [52]. Building on these findings, investigators have reported that in cases of OHSS, hydroxyethyl starch 6% infusion is modestly more effective than albumin for increasing urine output, reducing the need for paracentesis, and reducing the length of hospitalization [53]. However, hydroxyethyl starch infusions have been reported to be associated with renal dysfunction and coagulopathy [54], causing some experts to prefer albumin infusions for the treatment of OHSS.

Recombinant Tissue Plasminogen Activator to Treat Thrombosis

Major arterial thrombosis is a devastating consequence of severe OHSS. In one case of OHSS causing thrombosis of the middle cerebral artery, intra-arterial infusion of recombinant tissue plasminogen activator was used to lyse the clot and facilitate neurological recovery [55].

Pregnancy Outcome

IVF pregnancy complicated by moderate or severe OHSS has an increased risk of spontaneous abortion, venous thrombosis, gestational diabetes, pregnancy-induced hypertension, placental abruption, premature delivery, and low birthweight compared to IVF pregnancy not associated with OHSS [56, 57]. A pregnancy occurring following an IVF cycle complicated by OHSS is a high-risk pregnancy and should be monitored closely during the antepartum period.

References

1. Golan A. A modern classification of OHSS. Reprod Biomed Online. 2009;19:28–32.
2. Golan A, Ron-el R, Herman A, Soffer Y, Weinraub Z, Caspi E. Ovarian hyperstimulation syndrome: an update review. Obstet Gynecol Surv. 1989;44:430–40.

3. Mathur RS, Akande AV, Keay S, Hunt LP, Jenkins JM. Distinction between early and late ovarian hyperstimulation syndrome. Fertil Steril. 2000;73:901–7.
4. Yeh J, Barbieri RL, Ravnikar VA. Ovarian hyperstimulation syndrome associated with leuprolide suppression: a case report. J In Vitro Fert Embryo Transf. 1989;6:261–3.
5. Droesch K, Barbieri RL. Ovarian hyperstimulation syndrome associated with the use of the gonadotropin releasing hormone agonist: leuprolide acetate. Fertil Steril. 1994;62:189–90.
6. Baigent A, Lashen H. Ovarian hyperstimulation syndrome in a patient treated with tamoxifen for breast cancer. Fertil Steril. 2011;95:2429.e5–7.
7. Ayhan A, Tuncer ZS, Aksu AT. Ovarian hyperstimulation syndrome associated with spontaneous pregnancy. Hum Reprod. 1996;11:1600–1.
8. Chen SU, Chen RJ, Shieh JY, Chou CH, Lin CW, Lu HF, et al. Human chorionic gonadotropin up- regulates expression of myeloid cell leukemia-1 protein in human granulosa-lutein cells: implication of corpus luteum rescue and ovarian hyperstimulation syndrome. J Clin Endocrinol Metab. 2010;95:3982–92.
9. Levin ER, Rosen GF, Cassidenti DL, Yee B, Meldrum D, Wisot A. Role of vascular endothelial cell growth factor in ovarian hyperstimulation syndrome. J Clin Invest. 1998;102:1978–85.
10. Neulen J, Yan Z, Raczek S, Weindel K, Keck C, Weich HA. Human chorionic gonadotropin-dependent expression of vascular endothelial growth factor/vascular permeability factor in human granulosa cells: importance in ovarian hyperstimulation syndrome. J Clin Endocrinol Metab. 1995;80:1967–71.
11. Rodewald M, Herr D, Duncan WC, Fraser HM, Hack G, Konrad R, et al. Molecular mechanisms of ovarian hyperstimulation syndrome: paracrine reduction of endothelial claudin T by hCG in vitro is associated with increased endothelial permeability. Hum Reprod. 2009;24:1191–9.
12. Casper RF. Ovarian hyperstimulation: effects of GnRH analogues. Does triggering ovulation with gonadotropin-releasing hormone analogue prevent severe ovarian hyperstimulation syndrome. Hum Reprod. 1996;11:1144–6.
13. Cerrillo M, Pacheco A, Rodriguez S, Gomez R, Delgado F, Pellicer A, et al. Effect of GnRH agonist and hCG treatment on VEGF, angiopoietin-2 and VE-cadherin: trying to explain the link to ovarian hyperstimulation syndrome. Fertil Steril. 2011;95:2517–9.
14. Moron FJ, de Castro F, Royo JL, Montor L, Mira E, Saez ME, et al. Bone morphogenetic protein 15 (BMP15) alleles predict over-response to recombinant follicle stimulating hormone and iatrogenic ovarian hyperstimulation syndrome (OHSS). Pharmacogenet Genomics. 2006;16:485–95.
15. Hanevik HI, Hilmarsen HT, Skjelbred CF, Tanbo T, Kahn JA. A single nucleotide polymorphism in BMP-15 is associated with high response to ovarian stimulation. Reprod Biomed Online. 2011;23:97–104.
16. Ferrero H, Gaytan F, Delgado-Rosas F, Gaytan M, Gomez R, Simon C, et al. Dopamine receptor 2 activation inhibits VEGF secretion in granulosa luteinized cells. Hum Reprod. 2010;25(S1):i56–8.
17. Gomez R, Ferrero H, Delgado-Rosas F, Gaytan M, Morales C, Zimmerman RC, et al. Evidence for the existence of a low dopaminergic tone in polycystic ovarian syndrome: implications for OHSS development and treatment. J Clin Endocrinol Metab. 2011;96:2484–92.
18. Rodien P, Beau I, Vasseur C. Ovarian hyperstimulation syndrome (OHSS) due to mutations in the follicle stimulating hormone receptor. Ann Endocrinol. 2010;71:206–9.
19. Grossman LC, Michalakis KG, Browne H, Payson MD, Segars JH. The pathophysiology of ovarian hyperstimulation syndrome: an unrecognized compartment syndrome. Fertil Steril. 2010;94:1392–8.
20. Delvigne A. Epidemiology of OHSS. Reprod Biomed Online. 2009;19:8–113.
21. Luke B, Brown MB, Morbeck DE, Hudson SB, Coddington CC, Stern JE. Factors associated with ovarian hyperstimulation syndrome (OHSS) and its effect on assisted reproductive technology treatment and outcome. Fertil Steril. 2010;94:1399–404.
22. Delvigne A, Rozenberg S. Epidemiology and prevention of ovarian hyperstimulation syndrome (OHSS): a review. Hum Reprod Update. 2002;8:559–77.

23. Abramov Y, Elchalal U, Schenker JG. Pulmonary manifestations of severe ovarian hyperstimulation syndrome: a multicenter study. Fertil Steril. 1999;71:645–51.
24. Yoshi F, Ooki N, Shinohara Y, Uehara K, Mochimaru F. Multiple cerebral infarctions associated with ovarian hyperstimulation syndrome. Neurology. 1999;53:225–30.
25. Chan WS. The ART, of thrombosis: a review of arterial and venous thrombosis in assisted reproductive technology. Curr Opin Obstet Gynecol. 2009;21:207–18.
26. Jing Z, Yanping L. Middle cerebral artery thrombosis after IVF and ovarian hyperstimulation: a case report. Fertil Steril. 2011;95:2435.e13–5.
27. Man BL, Hui AC. Cerebral venous thrombosis secondary to ovarian hyperstimulation syndrome. Hong Kong Med J. 2011;17:155–6.
28. Mancini A, Milrdi D, DiPietro ML, Giacchi E, Spagnolo AG, Donna VD, De Marinis L, Jensen L. A case of forearm amputation after ovarian stimulation for in vitro fertilization-embryo transfer. Fertil Steril. 2001;76:198–200.
29. Broer SL, Dolleman M, Opmeer BC, Fauser BC, Mol BW, Broekmans FJ. AMH and AFC as predictors of excessive response in controlled ovarian hyperstimulation: a meta-analysis. Hum Reprod Update. 2011;17:46–54.
30. Al-Inany HG, Yousssef MA, Aboulghar M, Broekmans F, Sterrenburg M, Smit J, et al. Gonadotropin-releasing hormone antagonists for assisted reproductive technology. Cochrane Database Syst Rev. 2011;(5):CD001750.
31. Humaidan P, et al. GnRH agonist for triggering the final oocyte maturation: time for a change in practice? Hum Reprod Update. 2011;17:51–24.
32. Yates AP, Rustamov O, Roberts SA, Lim HY, Pemberton PW, Smith A, et al. Anti-mullerian hormone-tailored stimulation protocols improve outcomes whilst reducing adverse effects and costs of IVF. Hum Reprod. 2011;26:2353–62.
33. Youssef MA, van der Veen F, Al-Inany HG, Griesinger G, Mochtar MH, Aboulfoutouh I, et al. Gonadotropin releasing hormone agonist versus hCG for oocyte triggering in antagonist assisted reproductive technology cycles. Cochrane Database Syst Rev. 2011;(10):CD008046.
34. Oliveness F, Howies CM, Borini A, Germond M, Tew G, Wikland M, et al. Individualizing FSH dose for assisted reproduction using a novel algorithm: the CONSORT study. Reprod Biomed Online. 2011;22(S1):S73–82.
35. Lin H, Wang W, Li Y, Chen X, Yang D, Zhang Q. Triggering final oocyte maturation with reduced doses of hCG or IVF/ICSI: a prospective randomized and controlled study. Eur J Obstet Gynecol Reprod Biol. 2011;159:143–7.
36. Martinez F, Rodriguez DB, Buxaderas R, Tur R, Mancini F, Coroleu B. GnRH antagonist rescue of a long-protocol IVF cycle and GnRH agonist trigger to avoid ovarian hyperstimulation syndrome: three case reports. Fertil Steril. 2011;95:2432.e17–9.
37. Delvigne A, Rozenberg S. Preventive attitude of physicians to avoid OHSS in IVF patients. Hum Reprod. 2001;16:2491–5.
38. Ulug U, Bahcecci M, Erden HF, Shalev E, Ben-Shlomo I. The significance of coasting duration during ovarian stimulation for conception in assisted fertilization cycles. Hum Reprod. 2002;17:310–3.
39. D'Angelo A, Brown J, Amso NN. Coasting for preventing ovarian hyperstimulation syndrome. Cochrane Database Syst Rev. 2011;(6):CD002811.
40. Gokmen O, Ugur M, Ekin M, Keles G, Turan C, Oral H. Intravenous albumin versus hydroxyethyl starch for the prevention of ovarian hyperstimulation in an in vitro fertilization programme: a prospective randomized controlled study. Eur J Obstet Gynecol Reprod Biol. 2001;96:187–92.
41. Griesinger G, Berndt H, Schultz L, Depenbusch M, Schultze-Mosgau A. Cumulative live birth rates after GnRH agonist triggering of final oocyte maturation in patients at risk of OHSS: a prospective clinical cohort study. Eur J Obstet Gynecol Reprod Biol. 2010;149:190–4.
42. Wada I, Matson PL, Troup SA, Morroll DR, Hunt L, Lieberman BA. Does elective cryopreservation of all embryos from women at risk of ovarian hyperstimulation syndrome reduce the incidence of this condition? BJOG. 1993;100:265–9.

43. Sills ES, McLoughlin LJ, Genton MG, Walsh DJ, Coull GD, Walsh AP. Ovarian hyperstimulation syndrome and prophylactic human embryo cryopreservation: analysis of reproductive outcome following thawed embryo transfer. J Ovarian Res. 2008;1:7.
44. Rollene NL, Amols MH, Hudson SB, Coddington CC. Treatment of ovarian hyperstimulation syndrome using a dopamine agonist and gonadotropin releasing hormone antagonist: a case series. Fertil Steril. 2009;92:1169.e15–7.
45. Alvarez C, Marti-Bonmati L, Novella-Maestre E, Sanz R, Gomez R, Fernandez-Sanchez M, Simon C, Pellicer A. Dopamine agonist cabergoline reduces hemoconcentration and ascites in hyperstimulated women undergoing assisted reproduction. J Clin Endocrinol Metab. 2007;92:2931–7.
46. Youssef MA, van Wely M, Hassan MA, Al-Inany HG, Mochtar M, Khattab S, van der Veen F. Can dopamine agonists reduce the incidence and severity of OHSS in IVF/ICSI treatment cycles? A systematic review and meta-analysis. Hum Reprod Update. 2010;16:459–66.
47. Busso C, Fernandez-Sanchez M, Garcia-Velasco JA, Landeras J, Ballesteros A, Munoz E, Gonzalez S, Simon C, Arce JC, Pellicer A. The non-ergot derived dopamine agonist quinagolide in prevention of early ovarian hyperstimulation syndrome in IVF patients: a randomized, double-blind placebo- controlled trial. Hum Reprod. 2010;25:995–1004.
48. Balasch J, Carmona F, Llach J, Arroyo V, Jove I, Vanrell JA. Acute prerenal failure and liver dysfunction in a patient with severe ovarian hyperstimulation syndrome. Hum Reprod. 1990;5:348–51.
49. Smith LP, Hacker MR, Alper MM. Patients with severe ovarian hyperstimulation syndrome can be managed safely with aggressive outpatient transvaginal paracentesis. Fertil Steril. 2009;92:1953–9.
50. Csokmay JM, Yauger BJ, Henne MB, Armstrong AY, Queenan JT, Segars JH. Cost analysis model of outpatient management of ovarian hyperstimulation syndrome with paracentesis: tap early and often versus hospitalization. Fertil Steril. 2010;93:167–73.
51. Ceyhan ST, Goktolga U, Karasahin E, Alanbay I, Duru NK. Continuous vaginal and bilateral thoracic fluid drainage for management of severe ovarian hyperstimulation syndrome. Gynecol Endocrinol. 2008;24:505–7.
52. Youssef AFM, Al-Inany HG, Evers LHJ, Aboulghar M. Intravenous fluids for the prevention of severe ovarian hyperstimulation syndrome. Cochrane Database Syst Rev. 2010;(2):CD001302.
53. Abramov Y, Fatum M, Abrahamov D, Schenker JG. Hydroxyethylstarch versus human albumin for the treatment of severe ovarian hyperstimulation syndrome: a preliminary report. Fertil Steril. 2001;75:1228–30.
54. Bayer O, Reinhart K, Sakr Y, Kabisch B, Kohl M, Riedermann NC, et al. Renal effects of synthetic colloids and crystalloids in patients with severe sepsis: a prospective sequential comparison. Crit Care Med. 2011;39:1335–42.
55. Elford K, Leader A, Wee R, Stys PK. Stroke in ovarian hyperstimulation syndrome in early pregnancy treated with intra-arterial rt-PA. Neurology. 2002;59:1270–2.
56. Abramov Y, Elchalal U, Schenker JG. Obstetric outcome of in-vitro fertilized pregnancies complicated by severe ovarian hyperstimulation syndrome: a multicenter study. Fertil Steril. 1998;70:1070–5.
57. Courbiere B, Oborski V, Braunstein D, Desparoir A, Noizet A, Gamerre M. Obstetric outcome of women with in vitro fertilization pregnancies hospitalized for ovarian hyperstimulation syndrome: a case–control study. Fertil Steril. 2011;95:1629–32.